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CLINICAL TRIALS: METHODOLOGY

P001- DESIGNING A TRIAL FOR LATE (LIMBIC-PREDOMINANT AGE-RELATED TDP-43 ENCEPHALOPATHY) WITH DONEPEZIL: DOUBLE-BLIND PARALLEL VS CROSSOVER METHODOLOGIES WITH AMYLOID STRATIFICATION.

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Background: Limbic-predominant age-related TDP-43 encephalopathy (LATE) is common in older adults but remains underdiagnosed. Amyloid co-pathology is frequent and may influence therapeutic response. We compared a double-blind parallel placebo-controlled design with a double-blind crossover design to evaluate for symptomatic treatment with donepezil in LATE with participants stratified by the presence or absence of amyloid co-pathology. **Methods:** We outline two potential frameworks for evaluating donepezil in LATE. A parallel placebo-controlled design would randomize participants 1:1 to donepezil or placebo for six months, stratified by the presence or absence of amyloid co-pathology, with a treatment by amyloid interaction as a pre-specified analysis. In contrast, a double-blind crossover design would administer donepezil and placebo in two eight-week treatment periods, separated by a blinded taper and a four-week washout. Alternative washout durations of two and eight weeks were modeled, with four weeks (~10 half-lives) proposed as the optimal compromise. The primary endpoint is change in ADAS-Cog13, with CDR-SB and progression to dementia as secondary outcomes. **Considerations:** Parallel trials provide unbiased estimates of treatment initiation and greater generalizability, but require larger samples (approximately 340–840 participants depending on effect size) and may involve six months off therapy for patients randomized to placebo. This prolonged discontinuation is particularly challenging for individuals already receiving donepezil. Crossover trials, by contrast, require only 100–140 participants across 8–12 sites, limit off-drug exposure to a single short placebo epoch, and improve feasibility and acceptability, while still allowing stratified analyses by amyloid co-pathology. **Conclusions:** Both approaches offer methodological strengths, but for an initial multi-site evaluation of donepezil in LATE, a crossover design with eight-week treatment periods and a four-week washout appears more pragmatic, particularly in patients already on therapy. Parallel trials remain important for confirmatory evidence once efficacy is suggested.
Key takeaway message: For LATE trials of donepezil, crossover designs reduce sample size requirements and time off therapy compared with parallel designs.

P002- INSTRUCTING EFFICIENT EARLY PHASE PRECLINICAL ALZHEIMER'S DISEASE TRIALS.

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Background: Preclinical Alzheimer's disease trials face substantial challenges including slow clinical progression rates, requiring long duration and large sample sizes. Identifying outcome measures that serve as early predictors of clinical progression could permit efficient early-phase studies that require smaller sample sizes and shorter durations. Despite failing to meet its primary endpoint with solanezumab, the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) Study (1) created a valuable dataset for exploring preclinical AD trial outcome measures. This analysis aimed to identify cognitive and functional measures at 48 weeks that can reliably predict Clinical Dementia Rating (CDR) progression at 240 weeks, potentially enabling more efficient proof-of-concept early-phase preclinical AD trial designs. **Methods:** We analyzed data from the placebo arm of the A4 Study (N=583) and the parallel LEARN Study (N=541). Participants were cognitively unimpaired adults aged 65-85 with elevated (A4) or not elevated brain amyloid levels (LEARN). Clinical progression was defined as CDR global score greater than 0 at Week 240. Twelve cognitive and functional measures were evaluated as potential Week 48 predictors of this outcome: Cognitive Function Index (CFI), Activities of Daily Living Prevention Questionnaire (ADL), Preclinical Alzheimer's Cognitive Composite (PACC), Mini-Mental State Examination, Logical Memory II Delayed Recall, Digit Symbol Substitution Test, Free and Cued Selective Reminding Test, and Computerized Cognitive Composite (C3). CFI and ADL were completed by both participants and study partners, with a

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third outcome created by combining total scores from these two sources. PACC is an objective cognitive composite comprising four component tests (Mini-Mental State Examination, Logical Memory II Delayed Recall, Digit Symbol Substitution Test, and Free and Cued Selective Reminding Test) administered by trained psychometrists. C3 is an independent computerized cognitive assessment. Binary logistic regression models quantified the association between CDR progression over 240 weeks of follow-up and standardized change-from-baseline scores over 48 weeks. Models were fitted with and without baseline score adjustment to isolate the effect of cognitive change from initial performance. We utilized the estimated associations between the changes in each candidate measure over 48 weeks and CDR progression over 240 weeks to rank possible outcomes for hypothetical Phase II trials. We then computed power and sample size requirements for these trials using the observed variation for each candidate measure in the A4 study. Power calculations were set for 80% power at α=0.05 using the standard formula for comparing two means, with hypothesized treatment effects ranging from no effect to an ideally effective treatment that completely halts cognitive decline (100% treatment effect). To compute this upper bound of a treatment effect, we used the LEARN study to estimate potential learning effects from test repetition in cognitively unimpaired individuals without elevated amyloid levels. The difference between this "natural aging" decline and that observed in the A4 placebo arm was then used to assess an ideal treatment effect and account for potential practice effects due to test repetition. **Results:** The A4 placebo arm (N=583) comprised cognitively unimpaired adults with a mean age of 71.9 years (SD=5.0), 60.4% female, highly educated (mean 16.6 years), predominantly White race (94.2%), with 58.7% carrying APOE ε4 and 77.0% having a family history of dementia. At Week 48, odds ratios for predicting CDR progression at Week 240, without baseline adjustment, ranged from 0.91 (95% CI: [0.70, 1.18]) for CFI Patient to 1.46 (95% CI: [1.13, 1.92]) for CFI Total. With baseline adjustment, odds ratios ranged from 1.05 (95% CI: [0.79, 1.38]) for CFI Patient to 2.30 (95% CI: [1.10, 4.91]) for C3. Baseline adjustment increased odds ratios for C3 (from 1.23 to 2.30), CFI Study Partner (from 1.16 to 2.09), and CFI Total (from 1.46 to 2.16). Study partner-reported measures showed higher odds ratios than participant-reported measures: CFI Study Partner (OR=2.09, 95% CI: [1.44, 3.14]) versus CFI Patient (OR=1.59, 95% CI: [1.43, 3.15]). Estimated Phase II trial sample sizes varied widely across measures. With learning effect adjustments applied, efficient endpoints identified were CFI Patient (n=65, AUC=0.68), CFI Total (n=85, AUC=0.74), Free and Cued Selective Reminding Test (n=265, AUC=0.69), PACC (n=296, AUC=0.72), CFI Study Partner (n=396, AUC=0.75), and C3 (n=545, AUC=0.64). The Free and Cued Selective Reminding Test was the most predictive individual PACC component (OR=1.62, 95% CI [1.23, 2.15]). Sample size calculations without learning effect adjustments showed larger requirements for measures with learning effects, with notable increases observed for CFI Patient (65 vs 113), CFI Total (85 vs 222), and C3 (545 vs 304), demonstrating the importance of accounting for practice effects in trial planning. **Conclusions:** Our findings suggest that optimized endpoint selection may enable feasible proof-of-concept early-phase preclinical AD trials with adequate statistical power. Limitations include the assumption that subtracting LEARN-derived practice effects accurately estimates true pathological decline for effect size calculations, and potential limited generalizability to populations with different demographic characteristics. **Keywords:** Preclinical Alzheimer's Disease, cognitive endpoints, sample size optimization, early-phase trials, learning effects.

Disclosures: The authors have no conflicts of interest to declare. This research utilized publicly available data from the A4 and LEARN studies. The A4 Study is a public-private partnership funded by the National Institute on Aging/NIH and Eli Lilly and Co. The LEARN Study was funded by the Alzheimer's Association, GHR Foundation,and other philanthropic donors. ClinicalTrials.gov: A4:NCT02008357 LEARN: NCT02488720. **References:** 1. Clinical Trial of Solanezumab in Preclinical Alzheimer's Disease. (The New England Journal of Medicine). Published July 17, 2023. doi: 10.1056/NEJMoa2305032.

Key takeaway message: Optimized endpoint selection may enable feasible and efficient proof-of-concept preclinical Alzheimer's disease trials.

P003- CSF CGMP LEVELS CORRELATES WITH ALZHEIMER'S DISEASE SEVERITY IN THE POLARIS-AD PHASE 3 TRIAL SCREENING COHORT.

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Background: Cyclic guanosine monophosphate (cGMP), a key mediator of neuronal signaling and synaptic plasticity, is dysregulated in Alzheimer's disease (AD), contributing to synaptic loss and cognitive decline. AR1001, a potent Phosphodiesterase 5 (PDE5) inhibitor, elevates cGMP levels in the brain and demonstrated neuroprotective effects in various AD animal models. The POLARIS-AD phase 3 trial for early AD, with 54% participants confirmed amyloid positivity based on CSF, provides a sample bank to analyze CSF cGMP and examine correlation with AD severity using Clinical Dementia Rating – Global Rating (CDR-GR) and CDR Sum of Boxes (CDR-SB) scores. **Methods:** CSF samples from 112 screened participants (aged 55–90 with mild cognitive impairment or mild dementia due to AD, NIA-AA Stage 3-4) were analyzed by LC-MS/MS (LLOQ 0.2 nM). Amyloid positivity was confirmed via PET or CSF assays. AD severity was assessed using CDR-GR (0.5 vs 1) and CDR-SB groups (0~2.5, 3~4.5, 5~9). Statistical analyses included Welch's t-test for CDR groups and Welch's ANOVA for CDR-SB groups, evaluating cGMP correlations with severity. **Results:** CSF cGMP levels showed a significant negative correlation with AD severity. Participants with CDR = 1 had significantly lower cGMP than those with CDR = 0.5 ($p = 0.0076$; mean difference = –0.6970; 95% CI = [–1.203, –0.1913]; $\eta^2 = 0.098$). Across CDR-SB strata, cGMP declined with increasing severity (Welch's ANOVA $p = 0.0337$; $F = 3.556$), with significant differences between low and high severity groups ($p = 0.0277$). **Conclusions:** This sub-analysis from POLARIS-AD screening highlights CSF cGMP as a potential marker of assessing disease severity in early AD, supporting AR1001's mechanism to elevate cGMP for neuroprotection. Results from the double-blind phase are expected in 2026 and will provide crucial evidence for AR1001's target engagement and potential of cGMP's role in monitoring disease progression. **Keywords:** Biomarker, disease severity, CSF, AR1001.

Disclosures: Authors are employees and/or equity holders of AriBio Co., Ltd., sponsor of AR1001 and the POLARIS-AD study. Members of AriBio's Senior Scientific Advisory Board receive consulting fees from AriBio. No other conflicts declared.

Key takeaway message: Baseline CSF cGMP levels are inversely associated with clinical severity in early Alzheimer's disease, supporting its potential as a biomarker for disease staging and pharmacodynamic response — and reinforcing AR1001's mechanism of action through cGMP elevation and neuroprotection.

P004- LEARNING FROM FAILURE: INVESTIGATING REASONS FOR FAILURE OF EFFECTIVE TREATMENTS IDENTIFIED IN A META-ANALYSIS OF ALZHEIMER'S DISEASE STUDIES.

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Background: Alzheimer's disease (AD) clinical trials have a long history of failure, and even the recent successes are struggling to reach patients. Each clinical development program requires significant investment to move treatments through the various phases of clinical research, so no promising treatment should be allowed to fail casually. After memantine was approved in 2003, almost 20 years passed before aducanumab, lecanemab, and donanemab were approved. Hundreds of treatments

have been investigated in the intervening years with all failing to make it to market. What caused these treatments to fail? Were they less effective than the approved treatments? Did they have greater safety issues? From a meta-analysis of over 200 clinical trials, we've selected several treatments with at least as much evidence for treatment efficacy as the approved treatments and present why they are not marketed today and what we can learn from them. **Methods:** We reviewed placebo/sham-controlled randomized clinical trials of treatments for patients with mild cognitive impairment due to AD or mild to moderate AD. Study results were included if at least two of the cognitive, function, and global domains were reported. A global statistical test (GST) combining cognitive, functional, and global domains assessed overall efficacy. All treatments that had at least as much evidence as any of the approved treatments across all reported clinical trials were investigated to determine why they were not approved. These results are summarized and interpreted. **Results:** Of the thirteen treatments that had at least as much evidence of efficacy as approved treatments, three treatments–linopirdine, metrifonate, and xanameline–were abandoned for safety concerns, and dimebon was discontinued because of clear failure in phase 3 due to suspected fraudulence in phase 2. Of the remaining seven treatments, Boswellic acids and ginkgo biloba are supplements with a less clear path for regulatory approval, and rTMS will be the subject of further investigation in planned late-phase trials. Based on these analyses, benzoate, choline alfoscerate, idebenone, rotigotine, gantenerumab, and solanezumab all had evidence as strong or stronger than approved treatments but are not marketed today because of differences in study design or analysis, shifting regulatory standards, an overemphasis on protecting against false positives while neglecting false negatives, and a lack of focus on the overall evidence for a treatment effect. **Conclusions:** Over half of the studies shown to have evidence of efficacy when combining evidence across outcomes have unsatisfying explanations for the failure. Many more would likely have risen to the same level of evidence if they had achieved similar sample sizes. Inherent variability in any single outcome assessment causes random chance to play an outsized role in AD clinical trials unless all evidence can be evaluated together. There are many costs associated with developing AD treatments, but some of the most difficult to pay are opportunity costs, especially those associated with promising treatments that have failed. Each failure that should have been a success moves the field away from what may be a critical component to the treatment of AD.

Key takeaway message: Treatments have failed despite being safe and efficacious due in part to a failure to evaluate all evidence effectively, which is worse for patients, caregivers, clinicians, sponsors, and the field in general.

P005- PHASE II CLINICAL TRIAL ON THE EFFECT OF UROLITHIN A IN ALZHEIMER'S DISEASE.

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Background: Mitochondrial dysfunction and impaired mitophagy are emerging as central contributors to the pathophysiology of Alzheimer's disease (AD), particularly in its early stages. Urolithin A (UA), a natural metabolite derived from dietary ellagitannins, enhances mitophagy, improves mitochondrial quality, and reduces oxidative stress in preclinical models. Phase I clinical trials have shown that UA improves mitochondrial function and muscle strength in older adults, supporting its therapeutic potential in disorders characterized by mitochondrial decline, such as AD. This Phase II double-blind, placebo-controlled clinical trial aims to evaluate the efficacy of UA in mitigating AD pathology and cognitive decline in individuals with mild cognitive impairment (MCI) due to AD. **Methods:** A total of 60 participants will be recruited and randomized in a 2:1 ratio to receive either oral UA softgels (1000 mg/day; manufactured by Amazentis SA, Lausanne, Switzerland; n = 40) or a matching placebo (n = 20) for 12 months. Randomization is computer-generated, with double-blinding of participants, investigators, and assessors. Clinical, cognitive, and biomarker assessments are conducted at baseline (week 0), 6 months (week 24), and study end (week 48). Functional and patient-centered outcomes (activities of daily living, quality of life, neuropsychiatric symptoms) are evaluated at baseline and every 12 weeks. The primary endpoint is the change in plasma phosphorylated tau 217 (p-tau217). Secondary endpoints include glial fibrillary acidic protein (GFAP). Exploratory endpoints include neurofilament light (NfL), mitophagy/autophagy-related biomarkers, oxidative stress markers, and inflammatory signatures. Multi-omic analyses (transcriptomics, proteomics, metabolomics) will be integrated to provide a systems-level understanding of UA's mechanisms. APOE genotyping will allow exploration of genotype-specific responses. **Results:** The findings from this study will elucidate the potential of UA as a therapeutic agent targeting mitochondrial dysfunction and its downstream effects on inflammation, lipid metabolism, and cognitive decline. APOE genotypes will provide critical insights into genotype-specific responses. Additionally, leveraging Phase I findings of UA's efficacy in improving mitochondrial function and muscle health, this Phase II study has the potential to extend its application to neurodegeneration. **Conclusions:** This is the first randomized clinical trial targeting mitophagy in prodromal AD. By combining clinical, functional, and molecular endpoints, this study will provide essential insights into the feasibility, safety, and potential efficacy of UA, laying the groundwork for larger multicenter studies.

Keywords: Alzheimer's disease, mild cognitive impairment, mitophagy, Urolithin A.

Disclosures: This trial is funded by the Alzheimer's Association Part the Cloud Challenge 2025. The authors report no other conflicts of interest.

Key takeaway message: This first randomized clinical trial targeting mitophagy in prodromal Alzheimer's disease evaluates the effects of Urolithin A on biomarkers and cognition, establishing its feasibility and supporting its potential as a novel disease-modifying therapy.

P006- CHARACTERIZING ENROLLMENT PATTERNS IN A PRECLINICAL ALZHEIMER'S DISEASE TRIAL.

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Background: Timely participant recruitment to Alzheimer's disease (AD) clinical trials is critical but largely understudied, particularly in preclinical AD trials. Results from an analysis of the recently completed Anti-Amyloid Treatment for Asymptomatic AD (A4) Study found that those who identify as being Black race, Asian race, and Hispanic ethnicity were more commonly recruited through local efforts compared to their non-Hispanic White counterparts who were recruited through more distributed sources (1). The current study aimed to further investigate whether recruitment sources and reasons for trial enrollment differed by participant sociodemographic characteristics in the ongoing AHEAD 3-45 study, a multi-center preclinical AD trial that recruited a higher proportion of historically underrepresented populations compared to the A4 Study. **Methods:** We utilized the AHEAD 3-45 Study screening data across 106 global sites. We first examined potential

differences in recruitment sources by participant sociodemographic factors including sex, educational attainment, race, ethnicity, rurality (Rural-Urban Commuting Area [RUCA] codes; limited to the US sites), and socioeconomic status (SES; Hollingshead Score). From 30 recruitment sources reported by sites, we a priori created seven categories, namely, site source, community-based recruitment, organization referral, media, national registry, and other. We then examined whether participants' self-reported reasons for participation (a priori categorized as altruism, personal benefit, and other from eight options) differed by sociodemographic factors. To address both questions, we used a multivariable logistic regression model controlling for site type (academic vs. non-academic) and site geographical region, using Holm's adjustments to account for multiple comparisons. **Results:** Screening data on 20720 participants were available. Overall, 42.1% of participants were recruited from a site source, 27.7% from media, 15.3% from community-based efforts, 12% from other sources, 5.4% from national registries, and 0.7% from organization referral. Compared to female participants, male participants had higher odds of being recruited through site sources (OR:1.21; CI:1.14, 1.29; $p<0.01$), but lower odds of being recruited through community-based efforts (OR:0.82; CI:0.75, 0.89 $p<0.001$) and media (OR:0.89; CI:0.84, 0.95; $p=0.002$). Compared to those with greater than high school education, participants with high school or less education had higher odds of being recruited through site sources (OR:1.37; CI:1.27, 1.49; $p<0.001$) but lower odds of being recruited through media (OR:0.88; CI:0.80, 0.96; $p=0.02$) and national registries (OR:0.68; CI:0.54,0.85; $p=0.003$). For racial groups, we found significant differences in recruitment sources. Compared to those who identified as being White race, those who identified as being Black race (OR:0.73; CI:0.65, 0.82) or more than one race (OR:0.66; CI:0.5, 0.87) had lower odds of being recruited from site sources ($p<0.001$). Participants identifying as being Asian race (OR:1.66; CI:1.26, 2.16), Black race (OR:3.09; CI:2.74, 3.48), more than one race (OR:2.08; CI:1.52,2.8), and other race (OR:1.57; CI:1.14, 2.12) had higher odds of being recruited through community-based efforts ($p<0.001$). Those who identified as being Asian race (OR:0.73; CI:0.57, 0.92) and Black race (OR:0.8; CI:0.7, 0.91) had lower odds of being recruited through media ($p<0.001$). We similarly observed differences by ethnicity. Compared to those identifying as being non-Hispanic ethnicity, Hispanic or Latino participants had higher odds of being recruited through site (OR:1.72; CI:1.58, 1.88; $p<0.001$) and other (OR:1.34; CI:1.17, 1.54; $p<0.001$) sources but lower odds of being recruited through national registries (OR:0.4; CI:0.28, 0.55; $p< 0.001$). Compared to those who live in non-rural areas, those who live in rural areas had lower odds of being recruited through site sources (OR:0.58; CI:0.49, 0.69; $p<0.001$), but higher odds of reporting community-based efforts (OR:1.72; CI:1.42, 2.07; $p<0.001$). Lastly, we observed that those with lower SES had higher odds of being recruited through site sources (OR:1.25; CI:1.16, 1.35; $p<0.001$) and community-based efforts (OR:1.19; CI:1.08; 1.31; $p=0.0024$), but lower odds of being recruited through media (OR:0.82; CI:0.75, 0.9; $p<0.001$) and national registries (OR:0.73; CI:0.58, 0.9) compared to those with higher SES. When examining reasons for enrollment, 85.8%, 21.7%, and 0.8% of participants selected altruistic motivations, personal benefit, and other reasons, respectively. Compared to those who identified as being White race, participants identifying as Asian (OR:0.68; CI 0.52, 0.92) and Black (OR: 0.84; CI: 0.72, 0.98) race had lower odds of reporting altruism (race: $p=0.023$), but higher odds of reporting personal benefit (race: $p=0.001$), though the results were not significant for the Asian participants (Asian [OR:1.17; CI:0.91, 1.49]; Black [OR:1.32; CI:1.16, 1.5]). Participants identifying as being Hispanic or Latino ethnicity (OR:0.86; CI:0.76, 0.98; $p=0.043$) also had lower odds of reporting altruism compared to non-Hispanic or Latino participants. No other significant differences by sociodemographic characteristics emerged. **Conclusions:** Our results support prior literature demonstrating that while individuals who identify as being White race are often recruited through distributed sources, community-based local efforts may be more effective for reaching participants belonging to underrepresented racial groups. We also extend these findings by revealing additional differences across ethnicity, sex, educational attainment, rurality, and SES. Furthermore, our results identifying racial and ethnic differences in reasons for enrollment may represent an important consideration for investigators designing recruitment strategies for future preclinical AD trials. Future research should incorporate more granular levels of recruitment sources to enable a better understanding of these observations across participant sociodemographic factors.

Keywords: Recruitment, preclinical Alzheimer's disease, clinical Trials.
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References: 1. Raman R, Quiroz YT, Langford O, et al. Disparities by Race and Ethnicity Among Adults Recruited for a Preclinical Alzheimer Disease Trial. JAMA Netw Open. 2021;4(7):e2114364. Published 2021 Jul 1. doi:10.1001/jamanetworkopen.2021.14364.
Key takeaway message: There are key differences across participant sociodemographic factors in recruitment source and reasons for enrollment that trialists should consider when conducting future preclinical AD trials.

P007- DOUBLE 6/18-MONTH PHASE III STUDY TO REPRODUCE SYMPTOMATIC AND POTENTIALLY SHOW DISEASE-MODIFYING EFFICACY OF BUNTANETAP IN TREATING ALZHEIMER'S DISEASE.

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Background: Neurotoxic aggregating proteins - amyloid precursor protein, tau, alpha-synuclein, and TDP43 etc. – precipitate a toxic cascade that starts with impairment of axonal transport and slowing of synaptic transmission, inflammation, and ends in nerve cell death. Buntanetap is an RNA-targeting molecule that interrupts this process by preventing the over-translation of these toxic proteins, effectively reversing the cascade. How does this translate into clinical benefit? The restoration of axonal transport and improvement in synaptic transmission are among the earliest responses to buntanetap, resulting in short-term symptomatic improvements. Over the longer term, reduced inflammation and preservation of neurons suggest a disease-modifying effect. Additionally, in preclinical models of Alzheimer's disease (AD), Parkinson's disease (PD), Down syndrome (DS), and frontotemporal dementia (FTD), buntanetap reversed the toxic cascade and exhibited disease-modifying effects. Our goal is to replicate the observed symptomatic benefits and further investigate buntanetap's potential for long-term disease modification in the clinic. In our phase II/III dose-ranging study, buntanetap improved cognition in mild AD patients after 3 months of treatment, a symptomatic improvement. Even though the study was only 3 months long, biomarker data confirmed the mechanisms of action and showed more insights into the molecular pathway, from neurotoxic proteins (Tau and TDP43), inflammatory responses (IL5, IL6, S100A12, IFN-Y, IGF1R), and neurodegeneration (NFL). **Method:** A double-blind, placebo-controlled Phase III trial is evaluating efficacy and safety of buntanetap in early AD. In alignment with the 2024 NIA-AA guidelines for AD diagnosis and staging, the study utilizes the plasma biomarker pTau217 for patient enrichment and diagnostic validation. The 760 early Alzheimer's patients are being recruited

according to their positive plasma pTau217 biomarker level and MMSE 21-28. The study consists of two parts one 6 months long (Part 1), and the other 18 months long (Part 2). Part 1 is designed to confirm buntanetap's symptomatic effects on cognitive improvement; Part 2 aims to assess the drug's potential disease-modifying effects. **Results:** At 6 months, co-primary endpoints ADAS-Cog13 and ADCS-iADL will be used to validate buntanetap's symptomatic treatment effects in improving patients' cognition and function. At 18 months, beyond the above co-primary endpoints, volumetric MRI and biomarker data will be incorporated to assess buntanetap's potential disease modifying effects. **Conclusions:** Based on clinical and biomarker data from our previous studies, we designed a novel Phase 3 study to validate symptomatic improvement and potentially show disease-modification effects of buntanetap in treating AD.

Key takeaway message: Based on clinical and biomarker data from our previous studies, we designed a novel Phase 3 study to validate symptomatic improvement and potentially show disease-modification effects of buntanetap in treating AD.

P008- ATTITUDES TOWARD THE STUDY PARTNER REQUIREMENT IN ALZHEIMER'S DISEASE PRECLINICAL TRIALS AMONG RACIALLY AND ETHNICALLY DIVERSE POPULATIONS.

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Background: Preclinical Alzheimer's disease (AD) trials require that participants enroll with a study partner. Study partners offer support for participants, can play a key role in retention, and provide valuable trial data. The requirement, however, may also be a barrier to trial participation and bring unique ethical considerations in potential unwanted disclosure of biomarker information. Previous preclinical AD trials have shown differences in study partner dyad types by racial and ethnic subgroups; why these patterns were observed is unknown. To address this gap in understanding, we investigated potential differences in attitudes towards the study partner requirement among a racially and ethnically diverse sample of older adults recruited through community outreach. **Methods:** Our study included N = 261 adults ages 55-85 who were free of major neurological or psychiatric disorders, did not take medications to treat AD, and were free of cancer for at least three years. Participants were screened with the Montreal Cognitive Assessment (MoCA) or telephone MoCA (T-MoCA). Recruitment was stratified by race and ethnicity across the following groups: non-Hispanic (NH) Asian, NH Black or African American, Hispanic ethnicity, and NH White. The study included a single mixed methods structured interview consisting of an educational primer and multiple sections, one of which focused on the study partner requirement. Using a 6-point Likert scale, participants were asked to rate their level of agreement from very strongly disagree to very strongly agree with 9 statements about the requirement as a facilitator or barrier to participation [1]. Sociodemographic variables collected included age, biological sex at birth, educational attainment, income needs, family history of AD, and study partner type. We analyzed the association between race and ethnicity and strong/very strong agreement that the study partner requirement was a barrier to participation. We also performed linear regression with participants' Likert-scale scores as the response. The predictor of interest for both models were participants' self-reported race and ethnicity. Other variables hypothesized to be associated with the response were included a priori as adjustment covariates. The final analysis included N = 250 participants with complete data. **Results:** The study cohort (those who completed all study partner questions) included N = 68, 73, 47, and 73 participants who were Hispanic, NH Asian, NH Black, and NH White, respectively. The most frequently reported likely study partner type was a spouse or a friend (39.5% and 28%, respectively). Approximately 13.4% of participants indicated that they strongly/very strongly agreed that the study partner requirement would be a barrier to participation. Among all participants, almost 36% cited not wanting to inconvenience their potential study partners as a barrier. NH Asian participants were most concerned with inconveniencing study partners compared to other groups (45.2%, compared to 35.6% overall) while Hispanic participants most frequently endorsed the concern of study partner availability (17.6%, compared to 13.4% overall). Among facilitators of participation, we found that 51.3% and 58.6% of participants strongly/very strongly agreed that they would want to be "accompanied by study partners to learn if they met biomarker criteria" and that "study partners would make them more comfortable about being in the study," respectively. We did not find evidence of a significant difference between racial and ethnic groups in the odds of strongly/very strongly agreeing with the requirement being a barrier. Additionally, among participants ten years older in age, and those without family history of AD (compared to those with family history), we estimated a 71% higher odds and 62% lower odds of strongly/very strongly agreeing that study partner was a barrier (OR: 1.71, 95% CI: (0.95, 3.08), p-value: 0.075) (OR: 0.38, 95% CI: (0.15, 0.98), p-value: 0.045), respectively. Study partner type was found to be a barrier to participation as well. Compared to those who indicated a spouse would be their potential study partner, those who indicated a friend had an estimated 3-fold higher odds of strongly/very strongly agreeing that the requirement was a barrier (OR: 3.08, 95% CI: (1.02, 9.37), p-value: 0.047). When modeling the mean Likert score response, NH White individuals reported 3.1 on average, with 3 being "somewhat disagree" and 4 "somewhat agree". Compared to NH White individuals, Hispanic individuals had 0.44 lower mean score (95% CI: (-1.04, 0.16), p-value: 0.153), NH Black individuals had 0.33 lower mean score (95% CI: (-0.88, 0.21), p-value: 0.233), while NH Asian individuals had 0.05 higher mean score (95% CI: (-0.43, 0.54), p-value: 0.836), in their agreement that the study partner requirement was a barrier. **Conclusions:** These data suggest a nuanced relationship between race and ethnicity and the study partner requirement in preclinical AD trials. We did not find significant differences between racial and ethnic groups and the odds of reporting that the study partner requirement represents a barrier to trial participation. Participants commonly agreed that study partners brought comfort in the process of a study and when learning biomarker criteria. Future studies may consider adjusting the study partner requirement to reduce inconvenience or decreasing study partner burden by allowing remote partner visits, for example. Trialists may benefit from understanding the social and cultural influences that contribute to observed differences among groups in study partner types.

Keywords: Preclinical trials, recruitment science, study partner, race and ethnicity.

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References: 1. Cox, C. G., Ryan, M. M., Gillen, D. L., & Grill, J. D. (2021). Is reluctance to share Alzheimer's disease biomarker status with a study partner a barrier to preclinical trial recruitment?. The journal of prevention of Alzheimer's disease, 8(1), 52-58. https://doi.org/10.14283/jpad.2020.36. **Key takeaway message:** Potential participants generally did not find the AD preclinical trial study partner requirement to be a significant barrier to participation, with some differences across racial and ethnic groups in attitudes toward elements of the requirement.

P009- ALZHEIMER'S DISEASE PIVOTAL TRIAL DESIGN FOR ZERVIMESINE FOLLOWING AN END OF PHASE 2 MEETING WITH FDA.

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Background: Zervimesine (CT1812) is an oral, small molecule, therapeutic in development for Alzheimer's disease (AD) and dementia with Lewy bodies (DLB). Zervimesine is a sigma-2 receptor modulator that reduces the affinity of amyloid oligomers for their synaptic receptors on neurons. Zervimesine was studied in several small biomarker-oriented clinical studies (EEG, CSF catheter, PET/MRI) and one Phase 2 safety and exploratory efficacy study of 153 individuals with mild-to-moderate AD referred to as SHINE (COG0201; NCT03507790). Zervimesine was generally safe and well tolerated. Within the prespecified subgroup of participants defined by baseline plasma p-tau217 below the study median, there were trends for slowing progression across outcome measures including the ADAS-Cog, MMSE, ADCS-CGIC and ADCS-ADL. A strategy for pivotal trials was discussed with FDA; here we present a summary of this registrational pathway. **Methods:** Data from the SHINE Phase 2 study along with a proposed plan for registrational trials was prepared and submitted to FDA in preparation for an End of Phase 2 meeting (EOP2). Cognition Therapeutics proposed basic inclusion and exclusion criteria for individuals with mild-to-moderate AD with a specific enrichment of the population based on a baseline plasma p-tau217 level. Outcome measures, dose levels, study duration and adequacy of the total exposure durations were proposed and discussed. **Results:** Cognition Therapeutics and FDA agreed that zervimesine will be studied in Phase 3 trials in individuals with clinically evident Alzheimer's disease and confirmed brain amyloid pathology via PET imaging or approved fluid (CSF or plasma) biomarkers. Participants with a baseline plasma p-tau217 (AlzPath assay) less than approximately 1.0 pg/mL will be treated once daily with 100mg oral zervimesine for six months. While FDA confirmed continued endorsement of co-primary outcomes comprising the ADAS-Cog with either the ADCS-ADL or ADCS-CGIC, the FDA also indicated a willingness to accept the iADRS as a primary outcome with the stipulation that the results of iADRS components and other supporting efficacy measures would also be considered in any potential drug approval. With similar efficacy data in the 100 and 300 mg dose groups and the clear dose response with certain adverse events and laboratory values, the 100 mg dose can be studied alone in Phase 3 without the need to explore lower or higher dose levels. Participants will be eligible for open-label extension. FDA has agreed to waive the requirement for pediatric investigations and has agreed data from completed trials may obviate the need to complete a standalone thorough QT prolongation study. The planned studies together with the open-label extension phase will provide sufficient numbers and duration of exposure. **Conclusions:** Trial design for registration of AD therapeutics has evolved from six-month studies with first generation acetylcholine esterase inhibitors in mild-to-moderate AD over two decades ago to 18 months or longer with certain antibody therapies in early AD and MCI. The zervimesine EOP2 meeting confirmed that pivotal trials of six months are sufficient for registration provided that disease progression and therapeutic effect may be observed within this time frame. FDA and Cognition also aligned on an enrichment strategy consistent with FDA guidance that will likely increase the chance of study participants realizing a benefit from the study drug. In this case, plasma p-tau217 will be used to enrich the study population for those most likely to respond positively to zervimesine therapy. A single dose level of CT1812 verses placebo will be studied in Phase 3. In summary, a registrational path for zervimesine was endorsed that would include participants with amyloid confirmed, mild-to-moderate AD and baseline plasma p-tau217 of less than approximately 1.0 pg/mL treated once daily with 100 mg oral zervimesine for six months using either the iADRS or traditional co-primary outcome measures followed by an open-label extension.

Key takeaway message: Cognition Therapeutics and FDA have agreed upon six-month studies with an enriched population in Alzheimer's disease for pivotal trials of Zervimesine (CT1812)

P010- PHARMACOECONOMIC EVALUATION OF LECANEMAB FOR EARLY ALZHEIMER'S DISEASE IN THE NORTHEAST CHINESE POPULATION.

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Background: Lecanemab is a humanized monoclonal antibody, which can selectively target and neutralize amyloid-beta (Aβ) protein aggregates that cause Alzheimer's disease (AD). Lecanemab is a humanized monoclonal antibody designed to selectively target and neutralize amyloid-beta (Aβ) protein aggregates that contribute to Alzheimer's disease (AD). However, its high cost and requirement for frequent intravenous infusions pose significant challenges to patient adherence and healthcare systems. There is a lack of pharmacoeconomic evidence from middle- and low-income countries. Specifically, Northeast China faces severe population aging and significant economic transitions, with limited patient affordability, underscoring the urgent need for a regional evaluation of the cost-effectiveness and real-world adherence to lecanemab.Notably, Northeast China faces significant population ageing and substantial economic changes, with limited affordability for patients, underscoring the urgent need for a regional assessment of the cost-effectiveness and real-world adherence to lecanemab. This study aims to establish a research framework to assess the cost-utility and treatment compliance of lecanemab in the real-world clinical setting of Northeast China. **Methods:** This observational cohort study enrolled early AD (MCI due to AD or mild AD dementia) who were confirmed amyloid pathology andpatients who had confirmed amyloid pathology and were eligible for anti-amyloid treatments. Participants were divided into two groups: an intervention group (receiving lecanemab in addition to standard of carecommon medication) and a control group (receiving standard of care aloonly common medicationne), with a follow-up period of one year. In addition to efficacy and safety, health utilities were assessed using a regression function based on the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Activity of Daily Living Scale (ADL) at baseline, 3, 6, 9, and 12 months to calculate quality-adjusted life years (QALYs). A Markov model was developed to simulate the long-term disease progression and cost-utility of lecanemab over a lifetime horizon. A Markov model was developed to simulate the long-term progression of disease and the cost-utility of lecanemab over a lifetime horizon. Costs and treatment compliance, including completion, discontinuation, or withdrawal (particularly due to economic reasons or adverse events), were recorded. The incremental cost-utility ratio (ICUR) was calculated, and multivariate regression analysis was employed to identify key factors influencing treatment adherence, such as insurance coverage, household income, and the occurrence of adverse reactions. The incremental cost-utility ratio (ICUR) was calculated, and multivariate regression analysis was employed to identify key factors influencing treatment adherence, such as insurance coverage, household income, and occurrence of adverse reactions. **Results:** The study aimed to enroll 120 patients to obtain the first real-world adherence data and ICUR values for lecanemab in Northeast China.The study aimed to enrol 200 patients, including 100 participants in an intervention group and 100 in a control group, to obtain the first real-world adherence data and ICUR values for lecanemab in Northeast China. The findings are expected to clarify the economic burden of this treatment regimen in the region and pinpoint major barriers to treatment persistence. The findings are expected to clarify the economic burden of this treatment regimen in the region and identify major barriers to treatment persistence. **Conclusions:** The results will provide critical evidence regarding the economic impact of lecanemab therapy and the principal factors affecting treatment adherence in Northeast China. Based on the Markov model simulation, the incremental cost-effectiveness ratio (ICER) of lecanemab is expected to be less than or equal to three times the per capita GDP of China, indicating favourable cost-effectiveness. These findings will support

healthcare policy decisions and facilitate the development of cost-effective AD management strategies in the region.

Keywords: Lecanemab, Alzheimer's disease, pharmacoeconomic, cost-utility analysis, real-world study, treatment adherence.

P011- METABOTYPING REVEALS DISTINCT GUT–BRAIN RESPONSE PROFILES TO POSTBIOTIC AND MULTI-NUTRIENT INTERVENTION IN OLDER ADULTS.

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Background: Individual variability in gut-derived metabolites may influence response to nutritional interventions. This study applied metabotyping to identify metabolic responders to PoZibio® and Cerbella® supplementation and explore links to gut–brain function. Metabolomic analyses were conducted as part of two randomised controlled trials investigating the cognitive and physiological effects of these supplements in healthy older adults. PoZibio is an oral dietary supplement containing a heat killed strain of Lactobacillus paracasei. Cerbella is a combination of fish oil, panax ginseng extract and green tea extract. **Methods:** Metabolite profiling was performed on urine and plasma samples collected from participants in Trial 1 (N=57; PoZibio vs placebo over 60 days) and Trial 2 (N=54; four-arm design including dual active, PoZibio-only, Cerbella-only, and double placebo). Urine samples were analysed using flow-injection electrospray mass spectrometry (FIE-MS) and plasma samples with gas chromatography with flame ionisation detection (GC-FID). Changes in plasma short-chain fatty acids (SCFAs) and bioactive compounds were assessed, including acetic acid, propanoic acid, isobutyric and isovaleric acid. Responders were defined by $\geq$10% reduction in acetic acid. Cluster analysis was used to identify metabolic profiles across both trials. **Results:** In Trial 1, responders (n$\approx$12) exhibited coordinated reductions in acetic, propionic, isobutyric, and iso-valeric acids. Non-responders showed stable or increased SCFA levels. Trial 2 confirmed similar patterns, with additional shifts in hydroxy-leucine derivatives, acylcarnitines, bile acids, and indole compounds, implicating gut–liver and gut–kidney axes. Plasma analysis revealed changes in brain-relevant lipids, including plasmalogens and sphingomyelins, suggesting systemic effects that may be linked to cognitive outcomes. **Conclusions:** Metabotyping across two trials identified distinct metabolic response patterns to supplementation. These profiles may predict cognitive and physiological outcomes, supporting personalised nutrition strategies for healthy ageing.

Key takeaway message: Metabotyping enables personalised insights into gut–brain responses to postbiotic and multi-nutrient interventions.

P013- THE ALZHEIMER'S DISEASE DIAGNOSIS AND PLASMA P-TAU217 (ADAPT) RANDOMISED CONTROLLED TRIAL: PROTOCOL.

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Background: Accurate diagnosis of Alzheimer's disease (AD) remains challenging in community memory service care, where access to cerebrospinal fluid (CSF) biomarker testing or amyloid PET imaging is limited. Current consensus guidelines recommend use of AD blood-based biomarkers (BBM) to support diagnosis of AD in specialty settings; plasma p-tau217 has been shown across multiple cohorts to have high diagnostic accuracy for detecting the presence of amyloid and tau pathology in AD, but evidence for clinical utility in unselected, prospectively tested real-world memory clinic populations remains limited. The Alzheimer's Disease and Plasma p-Tau217 (ADAPT) Trial will address this gap. **Methods:** ADAPT is a prospective, pragmatic, two-arm randomised controlled trial that will compare disclosure of plasma p-tau217 results at three and 12 months after initial memory clinic assessment, in people for whom AD is a diagnostic consideration. It will be conducted across approximately 20 memory services in the UK-wide National Health Service (NHS) and coordinated by the Comprehensive Clinical Trials Unit at University College London (UCL). The trial will enrol 1,100 participants over two years. Eligible participants will be aged $\geq$50 years and attending their first memory clinic appointment with a cognitive complaint, which the assessing clinician judges to involve progressive decline with objective cognitive impairment (MMSE $<$28, MoCA $<$28, ACE-III $<$90, or RUDAS $<$28), and a clinical presentation consistent with mild cognitive impairment (MCI) or mild/moderate dementia, in which AD is a possible diagnosis. All participants must have capacity to provide informed consent for study involvement and must nominate a study partner who has at least weekly contact with them. Individuals with subjective complaints that are not confirmed by the results of cognitive testing, and those with prior availability of amyloid PET, CSF analysis or plasma biomarker results, will be excluded. Patients referred to memory clinics will be invited to participate at or before their first appointment. Consenting participants will provide a venous plasma sample and then be randomised 1:1 to receive biomarker results via their memory service clinician at 3 months (early disclosure) or 12 months (late disclosure) appointments. Both clinicians and participants will be blinded to allocation at baseline, and both will be unblinded at the 3-month timepoint. Face to face visits will be undertaken with memory service clinicians at baseline, 3 and 12 months, with telephone follow-up assessments with the research team at 6 and 15 months. Blood samples will be taken at the baseline visit, centrifuged at sites, stored at -20°C for up to 2 weeks, the transported in Bio-Freeze devices (Biopackaging Ltd) for plasma p-tau217 analysis at the University College London Hospital NHS Trust's Neuroimmunology and CSF Laboratory using the Lumipulse G plasma p-tau217 assay (Fujirebio). Participating study clinicians will all undergo training on a Decision-Support for Alzheimer's Blood Biomarker Result Tool (DART) and pass a multiple-choice assessment of their knowledge from this before being authorised to undertake pre-test counselling, result interpretation and communication of results to patients. The primary outcome will be the difference in the proportion of participants diagnosed with AD between early and late disclosure groups at the 3-month appointment. The trial sample size will provide ^{3}80% power to detect a ^{3}10% absolute increase in proportion of AD diagnoses following early biomarker disclosure (one-sided alpha=0.025), including a 10% allowance for loss to follow up and other methodological challenges. A secondary analysis at the 3-month timepoint will be difference in proprtion of AD diagnoses within the MCI and dementia groups. Secondary analyses at both the 3- and 12-

month timepoints will include change in clinician diagnostic confidence pre- vs post-disclosure, difference in proportion of participants with diagnosis changed either to or from AD post-disclosure, clinician actions consistent with an AD diagnosis (medication initiation, AD diagnostic counselling, research referral), and incremental cost-effectiveness ratio (difference in mean costs of health and social care resource use divided by difference in health-related quality of life indexed by the EQ-5D-5L, between p-tau217 early disclosure and late disclosure group). **Results:** ADAPT received a favourable ethical opinion (REC reference 24/NI/0149) in January 2025 and the trial is registered (ISRCTN16203689). Recruitment commenced in September 2025. Real-time unbiased recruitment monitoring will be undertaken, aiming for the trial sample to be representative of the UK memory clinic population (females 58%, non-white British/Irish >15%, semi-skilled or unskilled manual occupations >25%). **Conclusions:** ADAPT is a multi-centre diagnostic RCT evaluating impact of plasma p-tau217 on AD diagnosis in UK NHS memory services. It will provide robust evidence regarding the clinical utility, patient and carer experience and health economic impact of implementing plasma p-tau217 testing in this setting. Findings will inform UK regulatory and commissioning guidance and contribute to international implementation of BBM in dementia care.

Keywords: Alzheimer's disease, dementia diagnosis, blood-based biomarkers, plasma pTau217, randomised control trial, memory clinic, clinical implementation, National Health Service.

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Key takeaway message: ADAPT is a diagnostic RCT of plasma p-tau217 in UK memory clinics, evaluating its impact on Alzheimer's disease diagnosis, clinician confidence, patient experience, and cost-effectiveness to inform national guidance and international implementation of blood-based biomarkers.

P014- CLINICAL RESEARCH PROTOCOL OF LECANEMAB BASED ON SYNAPTIC PLASTICITY FOR THE TREATMENT OF EARLY ALZHEIMER'S DISEASE.

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Background: Lecanemab, a monoclonal antibody that targets β-amyloid protein (Aβ), selectively neutralizes and eliminates soluble and toxic Aβ aggregates. Currently, it has been approved for maintenance treatment of Alzheimer's disease (AD) with mild cognitive impairment (MCI) or mild dementia. Studies have shown that synaptic plasticity impairment is strongly correlated with cognitive deficits in AD. Animal experiments have demonstrated that Aβ antibodies could reverse synaptic dysfunction caused by soluble Aβ oligomers, improve synaptic plasticity, and thereby enhance learning ability. However, the intervention effect of Lecanemab on synaptic plasticity in patients with early AD has not been verified clinically yet. Therefore, this study was designed as a prospective cohort study to evaluate the intervention effect of Lecanemab on synaptic plasticity in patients with early AD. **Methods/design:** This study is a 12-month longitudinal, prospective cohort clinical trial, aiming to evaluate the regulatory effects of Lecanemab on the brain neural network function and synaptic plasticity of early AD patients from multiple dimensions, including neuroimaging, clinical neuropsychological scales, blood and cerebrospinal fluid biomarkers, and exosome transcriptomics. It is estimated that a total of 120 patients with early AD (MCI and mild dementia) will be included. The subject will be non-randomized in a 1:1 ratio to recruit either the Lecanemab treatment group (experimental group) or the conventional symptomatic treatment group (control group). All subjects are required to maintain a stable dose of conventional symptomatic treatment (donepezil). The clinical data is collected at the baseline, 3, 6, 9, and 12 months of treatment. The primary endpoint is the longitudinal change from baseline to 12 months in independent component analysis (ICA) indicators of the experimental group and the control group. The secondary indicators include ①changes from baseline to 12 months in functional connectivity (FC) indicators; ②changes from baseline to 12 months in clinical neuropsychological scales, where the scale assessment covers cognitive function, daily activities, neuropsychiatric symptoms, and care burden; ③changes from baseline to 12 months in plasma biomarkers, including Aβ42, Aβ42/Aβ40, P-tau231, P-tau217 and SV2A; ④changes from baseline to 12 months in cerebrospinal fluid synaptic function proteins and biomarkers, including glutamate, acetylcholine, brain-derived neurotrophic factor (BDNF), and cerebrospinal fluid synaptic markers (growth-associated protein 43 [GAP-43], synaptic body-related protein 25 [SNAP25], etc.); ⑤changes from baseline to 12 months in Aβ-PET centiloid values; ⑥changes from baseline to 12 months in synaptic transmitter spatial distribution correlation coefficient indicators in the experimental group and the control group. The exploratory indicator is the transcriptomics detection of exosomes derived from neurons in peripheral blood. **Discussion:** The latest real-world studies have shown that Lecanemab treatment for early AD patients is feasible and safe. If this research trial is successful, the targeting mechanism of Lecanemab in treating neurodegenerative diseases will be expanded, which may provide clinical benefits for more patients with neurodegenerative diseases in the future.

Trial registration: ClinicalTrials.gov, NCT06871839. Registration 7 March, 2025.

Keywords: Alzheimer's disease, lecanemab, synaptic plasticity, prospective cohort study.

P015- OPEN SCIENCE: BUILDING AN INTERNATIONAL DATA AND SPECIMEN SHARING INFRASTRUCTURE FOR ALZHEIMER'S DISEASE CLINICAL TRIALS.

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Background: A major goal of the National Institute on Aging (NIA)-funded Alzheimer's Clinical Trials Consortium (ACTC) is to provide an optimal infrastructure for clinical trials by leveraging centralized resources and shared expertise to accelerate the development and rigorous evaluation of interventions for Alzheimer's disease and related dementias (ADRD). ACTC includes 38 academic member sites across the United States, each with extensive experience in ADRD clinical trials. ACTC completed the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) and Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN) studies between 2014 and 2023, with enrollment finalized in 2017 and study results reported in 2023 (1). These studies were conducted at 67 clinical trial sites across the United States, Canada, Japan, and Australia. The A4 study screened 6,763 individuals and enrolled and randomized 1,169 participants aged 65 to 85, with a blinded follow-up period of 240 weeks followed by a variable-length open-label phase. The LEARN study enrolled 538 individuals who were ineligible for A4 due to amyloid levels that did not meet A4 inclusion criteria as determined by positron emission tomography (PET) imaging. In alignment with the NIH resource sharing policy and the principles of Open Science, the A4/LEARN study team prioritized broad and timely data and biofluid sharing while safeguarding participant privacy and the scientific integrity of the studies (2). **Methods:** We describe the approach, methods, and platforms used to share the A4 and LEARN pre-randomization and final longitudinal study data and biofluids for secondary research use. Preliminary results measuring the impact of these efforts are also summarized. We conclude with a discussion of lessons learned and next steps. **Results:** The pre-randomization and final longitudinal study data and biofluids from the A4 and LEARN trials were released in December 2018 and July 2024, respectively. The shared resources included de-identified quantitative data, re-faced neuroimaging data, analysis software, study instruments, comprehensive documentation, and de-identified biofluids (plasma, whole blood, and DNA). As of August 12, 2025, a total of 1996 requests for access to the pre-randomization dataset had been submitted by investigators and citizen scientists from over 60 countries, with 1826 requests (91.5%) approved. The final longitudinal dataset was requested 436 times, with 419 requests (96.1%) approved. For biofluids, over 40,000 specimens have been shared for biomarker discovery analyses. To date, over 101 peer-reviewed publications have cited and acknowledged the use of data and biofluids from the A4/LEARN studies. **Conclusions:** Our preliminary findings underscore both the feasibility and scientific value of sharing Alzheimer's disease clinical trial data and biofluids in a broad and timely manner. These insights will inform and strengthen future initiatives aimed at expanding access to trial data across the research community. Notably, we intend to apply these lessons to optimize our data and biospecimen sharing strategy for the AHEAD 3-45 study, which is scheduled for release in Fall 2025.

Keywords: Open Science, Alzheimer's disease, clinical trial, data sharing, secondary research, longitudinal data, neuroimaging, analysis, specimen sharing.

Disclosures: The authors report no relevant disclosures.

Declaration of generative AI and AI-assisted technologies in the writing process: Artificial intelligence (AI) tools were used during the preparation of this work to assist with tasks such as language refinement, formatting, and summarization. Specifically, Microsoft Copilot and Grammarly were employed to enhance clarity and coherence in written sections and to support the organization of content. All intellectual contributions, interpretations, and conclusions are solely those of the authors, who take full responsibility for the final content. The use of AI did not replace human judgment or expertise in any part of the research or writing process.

References: 1. Sperling RA, Donohue MC, Raman R, et al. Trial of Solanezumab in Preclinical Alzheimer's Disease. N Engl J Med. 2023;389(12):1096-1107. doi:10.1056/NEJMoa2305032. 2. Jimenez-Maggiora GA, Schulz AP, Donohue MC, et al. Maximizing the Utility of Alzheimer's Disease Trial Data: Sharing of Baseline A4 and LEARN Data. J Prev Alzheimers Dis. 2024;11(4):889-894. doi:10.14283/jpad.2024.120.

Key takeaway message: Broad and timely sharing of A4/LEARN clinical trial data and biofluids has proven feasible and impactful, enabling important secondary research and informing future data sharing strategies, including those planned for the AHEAD 3-45 study.

P016- TAU-PREDICTIVE FUNCTIONAL CONNECTOME PATTERNS PREDICT CLINICAL PROGRESSION AND SOLANEZUMAB RESPONSE IN PRECLINICAL ALZHEIMER'S DISEASE.

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Background: Solanezumab, an anti-monomeric amyloid antibody, failed to demonstrate benefit in symptomatic, dominantly inherited, and preclinical Alzheimer's disease (AD). However, it is possible that treatment effects might exist in specific subgroups. We previously generated functional connectome-based models predicting regional tau PET signal in preclinical AD (1). Here, we tested whether tau-predictive functional connectivity from these models could identify clinically meaningful subgroups in the Anti-Amyloid in Asymptomatic Alzheimer's (A4) study, with a particular interest in treatment effects. **Methods:** Hierarchical clustering was applied to amyloid-positive participants in the A4 study (n=1045, aged 65-85) (2). Tau-predictive functional connectivity features from tau connectome-based models were used as clustering inputs. Clustering parameters were supported by metrics of stability (adjusted rand index, ARI) and cohesion/separation (silhouette score). We compared clusters on baseline demographics, biomarkers, and A4-study-defined primary endpoint (Preclinical Alzheimer's Cognitive Composite, PACC). Longitudinal outcomes were modeled with spline-based generalized linear models in placebo and solanezumab arms. Cluster differences were estimated as the marginal mean difference at study end (week 455), with significance tested using permutation models (n=5000) or bootstrap resampling (n=5000). 95% confidence intervals are defined by 2.5th and 97.5th percentiles of bootstrap distributions. PACC was the primary endpoint of A4 and therefore not FDR-adjusted; secondary endpoints were FDR-corrected by the Benjamini-Hochberg procedure. **Results:** The two-cluster solution was optimal in 96% of model-combination evaluations; the final clustering showed high stability, cohesion, and separation (mean silhouette = 0.72; mean ARI = 0.83). Of amyloid-positive participants, 68% were assigned to Cluster 1 (n = 618) and 32% to Cluster 2 (n = 427). Clusters did not differ at baseline in age, sex, ethnicity, APOE ε4 status, cortical amyloid burden, plasma biomarkers, or PACC scores. Race was modestly different and adjusted for in all models. Comparing clusters in the placebo group, one

cluster (Cluster 2) scored on average 3.3 points lower on the Preclinical Alzheimer's Cognitive Composite (PACC) than the other (Cluster 1) by the end of the study (95% CI: -0.8 to -6.0; p<0.001). Cluster 2 also showed greater functional decline (CDR-SB: +1.6, 95% CI: 0.4 to 2.9; p<0.001), lower activities of daily living (ADL: –8.7, 95% CI: –16.1 to –2.1; p=0.001), and higher subjective cognitive decline (CFI: +4.6, 95% CI: 1.3 to 8.0; p<0.001). Plasma pTau-217 trajectories did not differ between clusters (–0.03; 95% CI: –0.16 to 0.08; p=0.61). Comparing solanezumab and placebo participants within each cluster, Cluster 2 solanezumab participants had an associated difference in primary endpoint (PACC) compared to placebo counterparts (+3.2; 95% CI: 0.4 to 6.15; p=0.02), corresponding to a 48% decrease in cognitive decline and 103 weeks of estimated cognitive difference. Cluster 2 solanezumab patients also had associated reductions in plasma pTau-217 compared to placebo (–0.29; 95% CI: –0.48 to –0.11; p<0.001). Cluster 1 showed no difference in PACC (–0.03; 95% CI: –2.0 to 2.0; p=0.96) or pTau-217 (–0.058; 95% CI: –0.20 to 0.07; p=0.40) between solanezumab and placebo groups. Change in cortical amyloid burden between solanezumab and placebo groups was similar across clusters (Cluster 1: ΔSUVR: –0.058; 95% CI: –0.079 to –0.036; p<0.001; Cluster 2 ΔSUVR: –0.046; 95% CI: –0.075 to –0.017; p=0.002). **Conclusions:** We identified a subgroup of amyloid-positive, cognitively unimpaired individuals, defined by their tau-predictive functional connectivity, who had an associated reduction in cognitive decline on solanezumab, despite the overall negative results of the A4 study. In this group, treatment was associated with a 48% decrease of cognitive decline and an estimated two-year cognitive difference compared to placebo over nine years. These findings suggest that such functional connectivity-based techniques can identify preclinical AD patients at increased risk for decline and most likely to benefit from an anti-monomeric therapy. Incorporating this biomarker into trial design could reduce heterogeneity, improve power, and enable targeted interventions in clinically meaningful subgroups.

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Key takeaway message: Tau-predictive functional connectivity features identified a subgroup in preclinical AD with worse clinical outcomes and associated improvements in PACC scores for those on solanezumab.

P018- IMPROVING INSIGHTS ON DISEASE MODIFICATION IN ALZHEIMER'S DISEASE BY INCLUDING SEQUENTIAL GSTS IN THE ANALYSIS HIERARCHY.

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Background: Background: Complex neurodegenerative diseases like Alzheimer's Disease (AD) manifest symptoms across a wide variety of cognitive and functional domains. For disease modifying treatments the research question of interest is whether the treatment will affect the disease progression of the overall disease. If the underlying disease is improved, symptoms across all domains are expected to improve as a result, though not necessarily on the same time frame or by the same magnitude. Methods accounting for multivariate relationships among outcomes are needed to assist stakeholders in accurately assessing the evidence of an overall treatment effect among different combinations of endpoints. A global statistical test (GST) formally quantifies evidence of efficacy of a treatment across multiple endpoints, providing objective interpretation that accounts for aspects of the data that are harder to account for informally, like correlation between endpoints (1-4). **Methods:** We use sequential GSTs and cumulative p-values to provide objective assessment of the combined evidence for a disease modifying treatment effect from relevant subsets of outcomes in simulated clinical trials. Sequential GSTs are GSTs in which successive endpoints in a prespecified hierarchy of outcomes are added to the GST in order. Cumulative p-values are p-values taken from the steps of a sequential GST. Family-wise type I error rates are controlled using hierarchical gatekeeping strategies defined by the prespecified order of the outcomes. We use sequential GSTs and cumulative p-values with various orders of hierarchical gatekeeping to show how this method can improve interpretability without changing target statistical properties or other study design aspects. In addition to discussing general characteristics of the methodology, we highlighted its performance in two key scenarios of interest. Both of the main scenarios included primary endpoints with a test statistic of 2.2 and a p-value of 0.0278. In one scenario, four secondary endpoints included in the sequential GST hierarchy showed effects of a similar magnitude. In the other scenario the 4 secondary endpoints showed no effect. We also show how positive results from outcomes higher in the order affect the result required from each subsequent outcome in order to maintain significance at the next step of the sequential GST. In all scenarios an average pairwise correlation of 0.3 was assumed between the outcomes. **Results:** Sequential GSTs with hierarchical gatekeeping improve the interpretability of trial results without inflating type I error or decreasing power. When included in a gatekeeping hierarchy with individual endpoints the results for the original endpoints remain unchanged, since it can be shown that GSTs will always be significant when all contributing outcomes are significant. Sequential GSTs indicate overall synthesis of evidence for treatment across primary and secondary endpoints, while individual tests indicate results on specific symptoms or domains of the disease. Different hierarchical arrangements of outcomes allow for emphasis of different domains or combinations of domains in a way that is flexible to the stakeholders input. In the first scenario of interest (one primary outcome and four secondary outcomes showing equal significant effects) the sequential GST resulted in test statistics of 2.20, 2.73, 3.01, 3.19, and 3.32 with corresponding cumulative p-values of 0.0278, 0.0064, 0.0026, 0.0014, and 0.0009. This shows that consistent results add to the overall body of evidence as expected. In the second scenario where the secondary endpoint showed no effect the test statistics were 2.20, 1.36, 1.00, 0.80, and 0.66 with p-values of 0.0278, 0.1724, 0.3153, 0.4249, and 0.5071, demonstrating that significance immediately vanishes when endpoints do not show any positive trends. The p-values required to maintain significance at each step of a 5-step cumulative p-value are 0.0500, 0.2300, 0.2569, 0.2674, and 0.2725. Here we see that if we show significance in the primary endpoint then directionally consistent trends from the secondary endpoints are sufficient to provide supporting evidence and maintain significance. **Conclusions:** The proposed methodology provides more accurate assessment of total evidence than intuitive synthesis without creating statistical problems or increasing the burden on sponsors or regulatory stakeholders. Using a gatekeeping strategy that intersperses steps in a sequential GST with the component parts maintains the same conclusions and results for individual endpoints in isolation while providing added context on how to view the endpoints as a whole.

Keywords: Clinical trials, interpretation, global statistical tests.

Disclosures: All authors are employees of Pentara Corporation, a statistical consulting firm specializing in neurodegenerative diseases that provides services to pharmaceutical companies and academic institutions. **References:** S. P. Dickson et al., J. Prev. Alzheimers Dis., vol. 10, no. 3, pp. 595–599, 2023, doi: 10.14283/jpad.2023.50. S. P. Dickson et al., J. Prev. Alzheimers Dis., vol. 11, no. 3, pp. 529–536, 2024, doi: 10.14283/jpad.2024.64. S. P. Dickson et al., J. Prev. Alzheimers Dis., vol. 11, no. 4, pp. 992–997, Aug. 2024, doi: 10.14283/jpad.2024.55. S. P. Dickson et al., Alzheimers Res Ther. 2023 May 24;15(1):98. doi: 10.1186/s13195-023-01238-1.

Key takeaway message: Sequential GSTs and cumulative p-values

provide logically consistent tools for interpretation and decision-making in the context of multiple hierarchically organized outcomes which commonly occurs in clinical trials of complex diseases with disease modifying treatments.

P019- ALTITUDE-AD: RECRUITMENT STRATEGIES FOR A GLOBAL PHASE 2 TRIAL OF SABIRNETUG IN EARLY ALZHEIMER'S DISEASE.

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Background: Successful recruitment is critical for Alzheimer's disease (AD) clinical trials, yet identifying eligible participants remains a challenge. This study analyzed recruitment data from a global phase 2 trial in early AD, categorizing recruitment sources to evaluate their effectiveness in both screening and randomization. **Methods:** ALTITUDE-AD is an ongoing phase 2 randomized, double-blind study of sabirnetug in mild cognitive impairment or mild dementia due to AD. Participants were classified into six recruitment categories, all of which were led by study sites: site database, digital outreach (social media, web, search engines), physician referral, family/friend referral, community engagement, and traditional advertising. Recruitment patterns were analyzed by country, sex, education level, and age to determine trends and screen fail rates. **Results:** The study screened a total of 2,362 participants across 76 sites in five countries and 542 were enrolled in the study. Recruitment for the study began in February 2024 and enrollment was completed in March 2025. Recruitment source effectiveness varied from a 11% to 30% enrollment rate. Site database was the most effective recruitment source, accounting for 51.3% of screened participants and 61.5% of randomized participants, indicating a relatively low screen fail rate. Similarly, physician referrals (13.4% of total screened, 17.4% of total randomized) showed strong conversion to enrollment. In contrast, digital outreach, responsible for 15.7% of screened participants, contributed only 7.6% of randomized participants, highlighting a higher screen fail rate than the other recruitment methods. The other three sources similarly had low conversion rates: family/friend referral (7.2%, 4.4%), community engagement (5.7%, 3.7%) and traditional advertising (4.4%, 3.9%). Recruitment trends varied by country—sites outside the U.S. relied more heavily on site databases (64.1% vs. 46.9%), while the U.S. demonstrated a more balanced distribution across sources. Digital outreach was more often used in the U.K. (37.6% of screened), while physician referrals were more prominent in the U.S. (15.3%) and Canada (17%). Females were most likely to be recruited via digital ads (females 17.7% vs. males 13.7%), whereas males were most likely to come from physician referrals (males 15.9% vs. females 11.7%). Recruitment through digital sources declined with age (50s: 31.4%, 60s: 19.4%, 70s: 12.3%, 80s: 10.9%), whereas physician referrals increased with age (50s: 5%, 60s: 10%, 70s: 16%, 80s: 17%). Recruitment trends also varied by education level: participants whose highest level of education was an undergraduate degree were most likely to enroll via digital ads (19.7%), whereas those with primary/elementary-level education were most likely to be referred by a physician (25.8%). Recruitment using traditional advertising increased with level of education (elementary: 0%, secondary: 2.7%, high school: 3.8%, undergrad: 4.8%, graduate+: 5.1%). **Conclusions:** A tailored, multi-channel recruitment approach is essential for optimizing early AD trial enrollment. Site databases and physician referrals were the most reliable sources, yielding higher randomization rates. This may be attributed to the established trust and familiarity with the research team since the participants are usually known to the sites, and to pre-existing signals of eligibility, which are often lacking in broader digital campaigns. Digital ads, while effective for generating interest, had a higher screen-fail rate, underscoring the need for strategic pre-screening. Understanding demographic and regional recruitment trends can inform future trial designs, potentially improving efficiency and representation in AD research.

Keywords: Sabirnetug; recruitment; clinical trial eligibility; Alzheimer's disease.

Clinical Trial Registry: NCT06335173 https://www.clinicaltrials.gov/study/NCT06335173.

Data Deposition: not applicable.

Disclosures: RM, TF, AC, MH, KMP, STG and ES are employees and minor stockholders of Acumen Pharmaceuticals. DT is a study site investigator for the ALTITUDE-AD trial.

References: none.

Key takeaway message: Successful recruitment in AD trials hinges on trust, prequalification, and participant engagement. In ALTITUDE-AD, site databases and physician referrals yielded the highest enrollment percentages, while digital outreach generated interest but had higher screen-fail rates.

P020- STUDY DESIGN OF A MULTIPLE ASCENDING INTRAVENOUS DOSE STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS OF VY7523 IN PARTICIPANTS WITH EARLY ALZHEIMER'S DISEASE.

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Background: Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive cognitive and functional decline and accumulation of brain amyloid and pathological tau. Tau spreading across brain regions correlates with cognitive decline and disease progression. No tau targeting therapies are currently approved. VY7523 is a C-terminal targeting humanized immunoglobulin gamma 4 (IgG4) monoclonal antibody designed to inhibit the spread of human pathological tau protein and potentially leading to the prevention of AD progression. A single ascending dose study in healthy adult participants was recently completed and supports continued development of VY7523. **Objectives:** To describe the design of a multiple ascending dose study evaluating safety, tolerability, pharmacokinetics (PK) and preliminary efficacy of VY7523 administered by monthly intravenously infusions in participants affected by mild cognitive impairment due to AD and mild AD dementia. **Methods:** Multicenter, randomized, placebo-controlled, double-blind, 6-month (Cohorts 1 and 2) and 12-month (Cohort 3) study (NCT06874621), including 3 sequential cohorts with 8 participants each enrolled in Cohort 1 and Cohort 2 (treatment-to-placebo randomization of 3:1), and approximately 36 participants enrolled in Cohort 3 (randomization ratio 1:1). Participants aged 50-90 years with MCI-AD or mild AD dementia defined by amyloid positivity, global Clinical Dementia Rating (CDR) score of 0.5 – 1, CDR Memory Box sub-score $\geq$ 0.5, Mini-Mental State Examination (MMSE) range 18-30 in Cohort 1-2 and 22-30 as well as tau-positron emission tomography (PET) positivity in Cohort 3 will be enrolled. Serial tau PET, blood and CSF samples will be collected to evaluate VY7523 PK and effect on AD disease biomarkers. The primary objective of the study is to evaluate the safety and tolerability of VY7523 in AD as measured by the incidence of treatment-emergent adverse events and clinically significant changes in safety assessments. Secondary objectives include evaluation of serum and cerebrospinal fluid (CSF) PK parameters, immunogenicity and ability of VY7523 to prevent spread of pathological tau as measured by changes from baseline in standardized uptake value ratio (SUVR) using tau PET. The study is being conducted in the United States and Canada. **Results:** Study is ongoing and recruiting. **Conclusions:** This study will inform on the preliminary safety profile, PK, immunogenicity and potential early efficacy data related to the ability of VY7523 to prevent the spread of pathological tau in MCI-AD and mild AD dementia.

Keywords: Alzheimer's disease, tau, clinical trial, monoclonal antibody.

Clinical Trial Registry: NCT06874621, https://clinicaltrials.gov.
Disclosures: 1. Voyager Therapeutics employees and shareholders. 2. Voyager Therapeutics contractors.
Key takeaway message: This ongoing Phase 1 multiple ascending dose study evaluates monthly IV VY7523 in early Alzheimer's, assessing safety, PK, and tau PET to explore its potential to slow tau spread and disease progression.

P021- THE PRIMUS-AD STUDY: DESIGN OF THE PHASE 2 STUDY TREATING PATIENTS WITH MCI OR MILD DEMENTIA DUE TO ALZHEIMER'S DISEASE (AD) WITH THE ORALLY AVAILABLE PRI-002.

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Background: The drug candidate PRI-002 is an all-D-enantiomeric peptide that was developed to disassemble toxic Aβ oligomers into harmless Aβ monomers. It is anticipated that PRI-002 reduces neurotoxicity and restores synaptic functionality and plasticity in early stages of AD. In studies in healthy volunteers and in patients with mild cognitive impairment (MCI) and mild dementia due to AD (EudraCT 2020-003416-27) the orally administered PRI-002 has demonstrated to be safe and well tolerable (1,2). **Methods:** The PRImus-AD study (EU clinical trial number 2022-503148-41) is a randomized, double-blind, placebo-controlled study to assess safety and efficacy of PRI-002 in patients with MCI or mild dementia due to Alzheimer's Disease (AD). CSF or Amyloid-PET is used to confirm AD pathology The trial is conducted in six European counties at 40 study sites. The trial is registered at euclinicaltrials.eu/search-for-clinical-trials/?lang=en&EUCT=2022-503148-41-00 and clinicaltrials.gov/study/NCT06182085. Eligible patients were randomly assigned (1:1:1) to receive 300 or 600 mg PRI-002 per day or placebo following an adaptive design for 48 to 96 weeks of treatment duration. Stratification factors are disease state (MCI or mild dementia) and APOE e4 status. A follow-up assessment is planned 12 weeks after the end of treatment. Besides to the endpoint of primary safety objectives the efficacy will be assessed by the change from baseline to week 48 in global outcome as measured by CDR-SB. **Results:** 540 patients in total were screened. Screening was accomplished three months ahead of the original schedule. A Screening Failure Rate of 42 % resulted in 304 eligible patients randomly assigned to 300 or 600 mg PRI-002 per day or placebo. A blinded sample size recalculation confirmed the initial calculation of subjects to be enrolled. Although PRI-002 is not expected to induce ARIAs, ARIA monitoring is closely performed for the first 90 patients until week 24. **Conclusions:** The PRIMUS-AD phase 2 study has enrolled 304 patients with MCI and mild dementia due to AD to assess safety and therapeutic benefit of PRI-002. Results are expected mid-2026.
Keywords: Anti-prionic mode of action, phase II clinical trial.
Clinical Trial Registry: EudraCT 2020-003416-27; NCT04711486; EudraCT 2022-503148-41; NCT06182085. **Disclosures:** DW is co-inventor on patents related to the work described and co-owner of Priavoid GmbH, which holds the related patents. This did not influence evaluation or interpretation of the data.
References: 1. Kutzsche et al., Alzheimers Dement (N Y) 6, e12001 (2020). 2. Kutzsche et al., Nat. Commun. 16, 4180 (2025)
Key takeaway message: PRI-002 is an orally available drug that is designed to disassemble toxic Abeta oligomers into harmless monomers. PRI-002 has been demonstrated in phase I studies to be safe and well tolerable - with interesting signs of efficacy in MCI and mild AD patients. PRI-002 is now tested in a PoC phase 2 study for efficacy and safety.

P022- A PHASE 3 CLINICAL PROTOCOL: PLACEBO-CONTROLLED, DOUBLE-BLIND, PARALLEL-GROUP TO EVALUATE SAFETY AND EFFICACY OF NA-831 AS MONOTHERAPY AND IN COMBINATION WITH DONANEMAB IN SUBJECTS WITH EARLY ALZHEIMER'S DISEASE.

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1. Biomed Industries, Inc. - San Jose (United States)

Background: Donanemab (Kisunla) is a humanized IgG1 monoclonal antibody that binds with high affinity to Aβ soluble protofibrils, and has been approved by the FDA for patients with early Alzheimer's disease (AD). NA-831 is an oral experimental drug that has showed a proof of safety and efficacy in Phase 2 clinical trial for patients with early Alzheimer's disease. Monoclonal antibodies directed against aggregated forms of beta amyloid, including donanemab, can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). AD patients are treated with a number of comedications not only to address cognitive impairment (standard-of-care) but also other comorbidities. There is room for additional therapeutics to improve patient quality of life. **Aims:** The phase 3 study consists of a Core and Open Label Extension (OLE) Phase will be conducted to evaluate the efficacy and safety of NA-831 as monotherapy and in combination with donanemab with patients with Early Alzheimer's Disease (EAD). The Core is an 18-month treatment, multi-centers, double blind, placebo controlled parallel group study. **Methods:** Core Study: Participants will be divided in 3 groups, randomly assigned in a 1:1 ratio to receive a drug or a combination of two drugs or placebo. Group 1: will receive one 30 mg of NA-831 capsule orally once a day or placebo. Group 2: will receive and intravenous donanemab (700 mg administered as an intravenous infusion over approximately 30 minutes every four weeks for the first three doses, followed by 1400 mg every four weeks.) or placebo. Group 3: will receive one 30 mg of NA-831 capsule orally once a day and intravenous donanemab (350 mg administered as an intravenous infusion over approximately 30 minutes every four weeks for the first three doses, followed by 700 mg every four weeks) or placebo. The core study will be double blinded. Open Label Extension Phase: Participants completing the core study will receive one 30 milligram (mg) NA-31capsule orally once a day, and intravenous donanemab (700 mg administered as an intravenous infusion over approximately 30 minutes every four weeks). ENROLMENT: 550 participants. Ages: 50 to 90 Years. All sexes are eligible for study. Key Inclusion Criteria: Diagnosis: Mild Cognitive Impairment (MCI) due to Alzheimer's disease - intermediate likelihood: Meet the National Institute of Aging - Alzheimer's Association (NIA-AA) core clinical criteria for MCI due to Alzheimer's disease - intermediate likelihood. Have a global Clinical Dementia Rating (CDR) score of 0.5 and CDR Memory Box score of 0.5 or greater at Screening and Baseline. Report a history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; must be corroborated by an informant. Mild Alzheimer's disease dementia: Meet the NIA-AA core clinical criteria for probable Alzheimer's disease dementia. Have a global CDR score of 0.5 to 1.0 and a CDR Memory Box score of 0.5 or greater at Screening and Baseline. Key Exclusion Criteria: Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the participant's Alzheimer's disease. History of transient ischemic attacks (TIA), stroke, or seizures within 12 months of Screening. Any psychiatric diagnosis or symptoms (example, hallucinations, major depression, or delusions) that could interfere with study procedures in the participant. **Results to be presented:** I. Key Outcome Measures: Core Study: Change from Baseline in the CDR-SB at 18 Months [Time Frame: Baseline, 18 months]. Extension Phase: Number of Participants Reporting One or More Treatment-emergent Adverse Events (TEAEs) [Time Frame: From first dose of study drug up to approximately 24 months (including 3

months follow up) for the extension phase]. II. Secondary Outcome Measures: Core Study: Change from Baseline in Alzheimer Disease Assessment Scale - Cognitive Subscale 14 (ADAS-cog14) at 18 Months [Time Frame: Baseline, 18 months]. Core Phase: Change from Baseline in Alzheimer's Disease Composite Score (ADCOMS) at 18 Months [Time Frame: Baseline, 18 months]. Core Study: Change from Baseline in Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL) at 18 Months [Time Frame: Baseline, 18 months]. Additional study will include (a) complex PK-PK interaction studies, or (c) providing evidence that the combination has a synergistic effect. **Conclusions:** The Phase 3 clinical trial will be conducted more than 25 sites in the US and internationally. Detailed study methodology, rationale, and protocol design will be presented.
Key takeaway message: To study the efficacy and safety of NA-831 as monotherapy and in combination with donanemab with patients with Early Alzheimer's Disease (EAD). The Core is an 18-month treatment followed by Open Label Extension

P023- VHB937, A TREM2 STABILIZING AND ACTIVATING FULLY HUMAN MONOCLONAL ANTIBODY: A PHASE 2 STUDY DESIGN IN ALZHEIMER'S DISEASE AND RATIONALE.

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Background: Microglia are dynamic immune cells that maintain central nervous system (CNS) health by performing key neuroprotective functions (1). During an immune response, microglia become activated and dynamically adapt their activation states based on signals from their microenvironment (2). In neurodegenerative diseases, sustained environmental insults drive microglia into maladaptive pro-inflammatory and neurotoxic states which exacerbate pathology and disrupt the neuroprotective immune response (2,3). Signaling through TREM2, a key regulator of microglia, is pivotal in shifting microglia to a neuroprotective state (4,5). Over 40 hypomorphic TREM2 mutations in humans provide a strong genetic link to Alzheimer's disease (AD) pathophysiology and for example in R47H mutation carriers the microglia barrier around plaques is impaired (6,7). With sustained activation in neurodegenerative conditions like AD and chronic pain, microglia might become neurotoxic and pro-inflammatory (8). Activation of TREM2 might reduce the appearance of pro-inflammatory microglia and support microglial survival, chemotaxis, phagocytosis, improve metabolic fitness and skew microglia towards a neuroprotective and anti-inflammatory phenotype (9,10). VHB937 is a highly selective, IgSF-binding, Fc-silenced, human monoclonal TREM2 antibody that enters CNS. VHB937 selectively binds, stabilizes, and activates TREM2, shifting the microglial population to be more neuroprotective, less neurotoxic and pro-inflammatory, potentially enhancing microglial response to neuron damage and slowing disease progression (11). In vitro, within a microglia population, VHB937 increased a subcluster associated with phagocytosis and neuroprotection and reduced the subcluster associated with pro-inflammatory signaling (12). In vivo, VHB937 reduced pathology in a broad range of neurodegenerative/neuroinflammatory animal models (MPTP, cuprizone, tau and amyloidosis); after VHB937 treatment, a neuroprotective microglia phenotype emerged which promoted neuronal health (reduction of dystrophic neurites), reduced tau pathology and ameliorated astrogliosis (12,13). In the first-in-human study in healthy participants,11 VHB937 showed favorable safety and tolerability profile after single i.v. dosing. VHB937 was detected in the cerebrospinal fluid (CSF) and induced a clear decrease in the CSF concentration of neuroinflammatory biomarkers (SPP1, CSF1R, CCL3), indicating pharmacodynamic response. VHB937 has been shown to exhibit a unique mechanism of action (MoA) versus other TREM2-targeting therapies. The MoA of VHB937 could potentially reinstate a neuroprotective response from microglia and slow AD progression. **Methods:** VHB937 is being evaluated in a multicenter, randomized, double-blind, placebo-controlled, parallel group Phase II study in early AD. The duration of the double-blind treatment in the study will be 72 weeks, followed by an extension for at least 96 weeks. About 407 people living with early AD will be randomized to receive VHB937 (high/low dose) or placebo. Inclusion criteria are as follows: participants aged 50 to 85 years, with diagnosis of mild cognitive impairment (MCI) due to AD or mild AD, a clinical dementia rating (CDR) global score between 0.5 and 1.0, and confirmed early AD diagnosis based on CSF biomarkers or amyloid PET imaging. Participants must either not receive or be on a stable dose of acetylcholinesterase inhibitors or memantine. Efficacy endpoints will be assessed at the end of double-blind treatment period (Week 72). The primary efficacy endpoint is change from baseline in clinical dementia rating scale – sum of boxes (CDR-SB). Secondary efficacy endpoints include Alzheimer's disease Assessment Scale-Cognitive (ADAS-Cog14), instrumental activities of daily living (iADL) on the Alzheimers Disease Cooperative Study - Activities of Daily Living (ADCS-ADL) scale, pharmacokinetic parameters and safety. Safety will be assessed throughout the study period. **Conclusions:** Based on this positive pre-clinical and clinical data, stabilizing and activating TREM2 with VHB937 to enhance neuroprotective microglia function is being evaluated in the Phase 2 study for its potential to slow AD progression.
Keywords: Alzheimer's disease, CCL3, CSF1R, microglia, neuroinflammation, SPP1, TREM2, VHB937.
Clinical Trial Registry: Protocol submitted for registration.
Disclosures: All authors are employees and may hold stocks and/or stock options in Novartis.
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Key takeaway message: Preclinical studies indicate that VHB937, a TREM2 stabilizing and activating fully human monoclonal antibody, can reduce neuroinflammatory pathology and promote neuronal health, which was followed by expected pharmacodynamic response in healthy volunteers. The Phase 2 study will assess efficacy and safety of VHB937 in early Alzheimer's disease.

P025- HAS ALZHEIMER'S BEEN DEFINED AS A WHITE PERSON'S DISEASE? HOW BIOMARKER-BASED INCLUSION CRITERIA MAY LEAD TO DIFFERENTIAL ACCESS TO CLINICAL TRIALS ACROSS RACIAL AND ETHNIC GROUPS, AN ANALYSIS OF THE BIO-HERMES STUDY.

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Background: With the publication of "NIA-AA Research Framework: Towards a Biological Definition of Alzheimer's Disease" in 2018, the definition of Alzheimer's Disease in clinical research has shifted from symptom-focused to pathology-focused. Alzheimer's diagnosis in clinical research is now commonly confirmed using the AT(N) biomarker

system. In this system biomarkers related to amyloid beta pathology (A), tau pathology (T), and neurodegeneration (N) are used to determine if there is enough evidence of underlying pathologies to conclude that a participant likely has Alzheimer's disease. While the shift to pathology-based diagnoses allows for more specificity in diagnosing Alzheimer's compared to other dementias, it introduces the need to determine what levels of pathology expression are sufficient for diagnosis and subsequent inclusion in clinical trials. This question can be complicated further if there is differential pathology expression across subpopulations within a clinical trial's target population. There is evidence from the AHEAD 3-45 study and the Bio-Hermes study that racial and ethnic subpopulations with similar clinical symptoms exhibit different levels of amyloid and tau pathology expression. In the AHEAD 3-45 study this differential expression was linked to higher rates of screen failure due to biomarker levels in all racial and ethnic subgroups compared to the non-Hispanic white subgroup. The A4 study also showed lower inclusion rates in most racial groups compared to the white group and in Hispanics compared to non-Hispanics. **Methods:** Using data from the Bio-Hermes biomarker database we evaluated how the use of a single cutoff for a biomarker could affect inclusion and exclusion of subpopulations in a theoretical study enrolling from the MCI and probable AD cohorts of the Bio-Hermes study. A cutoff was chosen for each biomarker such that the hypothetical inclusion rate for non-Hispanic whites was 40%. Because inclusion rates are discrete in finite samples we required that the actual hypothetical inclusion rate be greater than or equal to 40%. 40% was chosen by taking the inclusion for this subgroup in the AHEAD 3-45 study (38.9%) and rounding. We then evaluated the hypothetical inclusion rates among other subpopulations using the same cutoff. Finally, we calculated a cutoff for each of the other subpopulations that would have resulted in the original inclusion rate (40%) and compared these new cutoffs to the original cutoff. We performed this analysis for multiple biomarkers used to screen for clinical trials. **Results:** For the standardized uptake value ratio for one of the vendors in the database, the cutoff used for the white population was 1.24. Using this cutoff resulted in 40% of non-Hispanic whites being included in the study compared to 21.1% of non-Hispanic Blacks, and 35.9% of Hispanics. In order to achieve 40% inclusion in the other race/ethnicity subgroups a cutoff of 1.07 would be required for non-Hispanic Blacks, and a cutoff of 1.20 would be required for Hispanics. For plasma pTau 217 for one of the vendors, the cutoff used for the white-population was 0.291. This cutoff results in 20.8% of non-Hispanic Blacks and 31.7% of Hispanics being included in the study. Results across other biomarkers and multiple vendors showed comparable disparities and will be presented in full in the poster. **Conclusions:** Pathology-driven inclusion in Alzheimer's Disease clinical trials may result in including white non-Hispanics at a greater rate than other racial and ethnic subpopulations. Adjusting cutoffs for different racial and ethnic groups may provide a way to include subpopulations at similar rates. More research is required to determine why different subpopulations exhibit different levels of biomarker expression and how those differences relate to symptoms of Alzheimer's Disease.

Keywords: Clinical trials, biomarkers, diversity, inclusion/exclusion.

Disclosures: All authors are employees of Pentara Corporation, a statistical consulting firm specializing in neurodegenerative diseases that provides services to pharmaceutical companies and academic institutions. **References:** 1. Alzheimer's Disease Redefined: New Research Framework Defines Alzheimer's by Brain Changes, Not Symptoms. Alzheimer's Association. April 10, 2018. Accessed September 30, 2025. https://www.alz.org/news/2018/alzheimer-s-disease-redefined-new-research-framework-defines-alzheimer-s-by-brain-changes-not-symp. 2. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. doi:10.1016/j.jalz.2018.02.018. 3. Mohs RC, Beauregard D, Dwyer J, et al. The Bio-Hermes Study: Biomarker database developed to investigate blood-based and digital biomarkers in community-based, diverse populations clinically screened for Alzheimer's disease. Alzheimers Dement. 2024;20(4):2752-2765. doi:10.1002/alz.13722. 4. LeBlanc L. USC study links lack of diversity in Alzheimer's disease clinical trials to differences in amyloid levels. Newsroom. April 17, 2024. Accessed September 30, 2025. https://keck.usc.edu/news/usc-study-links-lack-of-diversity-in-alzheimers-disease-clinical-trials-to-differences-in-amyloid-levels/. 5. Sperling RA, Donohue MC, Raman R, et al. Trial of Solanezumab in Preclinical Alzheimer's Disease. New England Journal of Medicine. Published online September 21, 2023. doi:10.1056/NEJMoa2305032.

Key takeaway message: Pathology-driven inclusion in Alzheimer's Disease clinical trials may result in including white non-Hispanics at a greater rate than other racial and ethnic subpopulations if racial/ethnic differences in biomarker expression are not taken into account.

P026- UTILITY OF HIGH THROUGHPUT BLOOD-BASED P-TAU217, GFAP, NFL AND APOEε4 IMMUNOASSAYS FOR CLINICAL TRIALS OF ALZHEIMER'S DISEASE.

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Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder with distinct molecular pathology. Plasma biomarkers—pTau217, GFAP, NfL, and APOE ε4—are increasingly recognized for their value in AD research and clinical assessment. pTau217 reflects tau phosphorylation, a hallmark of AD neurofibrillary tangles, and demonstrates strong diagnostic performance for distinguishing AD from other neurodegenerative conditions. GFAP, an astrocytic marker, is elevated in response to neuroinflammation and astrocyte activation commonly observed in AD. NfL, a marker of neuronal injury, correlates with axonal degeneration and disease progression. APOE ε4 is the most significant genetic risk factor for late-onset AD, influencing amyloid deposition, tau pathology, and neuroinflammatory processes. Collectively, these biomarkers provide complementary insights into AD pathophysiology and support early detection, disease monitoring, and therapeutic development. Recent advances in blood-based biomarker technology are transforming AD clinical research and patient care by enabling earlier, more accessible, and less invasive detection. These assays are scalable, cost-effective, and suitable for routine screening, helping to close the diagnostic gap left by traditional methods such as CSF collection and PET imaging. Industry collaborations, such as the partnership between Navigate BioPharma Services and Beckman Coulter Diagnostics, are accelerating the translation of research assays into clinical practice and supporting broader inclusion in clinical trials (1). **Methods & Analytical results:** To support investigational clinical trials, fit-for-purpose analytical validation of immunoassays for pTau217, GFAP, NfL, and APOE ε4 were performed in human K2 EDTA plasma using Beckman Coulter's sensitive, high-throughput DxI 9000 immuoassay analyzer. These validations included precision studies—encompassing intra-assay, inter-assay, and inter-operator variability—which yielded coefficients of variation (CV) of 13.3% for all analytes, at the limit of quantitation (LOQ). Quantitation limits were verified at Navigate Biopharma Services utilizing diluent fortified with recombinant protein demonstrating a broad dynamic range. For pTau217 the ULOQ and LOQ were 6.968 pg/mL and 0.101 pg/mL, respectively; for GFAP the ULOQ and LOQ were 572.2 pg/mL and 0.3 pg/mL; for NfL the ULOQ and LOQ were 9329.0 pg/mL and 6.2 pg/mL. Linearity experiments confirmed recovery rates within ±30% (2% to 20%) of nominal concentrations for GFAP, NfL, and pTau217. Stability testing showed all analytes remained stable at room temperature for up to four hours and through three freeze-thaw cycles. **Results in Disease specimens:** To evaluate real world performance of the validated immunoassays, a cohort of healthy donors ($n = 34$) and neurological disease patients, namely, Alzheimer's ($n = 25$), Parkinson's ($n = 12$) and Multiple Sclerosis ($n = 12$) were studied. Statistical analysis of neurological disease patients revealed strong correlation between Alzheimer's disease and protein levels of pTau217 ($p < 0.0006$) and

APOE ε4 ($p < 0.0012$), while GFAP and NfL levels correlated robustly with Alzheimer's ($p < 0.0001$) and Parkinson's disease ($p < 0.0050$ and $p < 0.0001$, respectively). **Conclusions:** The validated panel of plasma biomarkers—pTau217, GFAP, NfL, and APOE ε4—demonstrates high analytical precision, stability, and disease relevance. Our results support their utility of these validated immunoassays as reliable pharmacodynamic markers for assessing therapeutic efficacy and for early detection and monitoring of Alzheimer's disease. This panel advances research and clinical applications in neurodegenerative disease by enabling robust evaluation of novel therapeutics and facilitating timely diagnosis.
Keywords: Alzheimer's disease (AD), plasma biomarkers, analytical validation, pharmacodynamic markers, early detection, neurodegenerative disease.
Disclosures: The authors declared on competing interests.
References: 1. Nick Culshaw, In Vivo Citeline Commercial, September 2025; How Blood-Based Biomarkers AreTransforming Alzheimer's Clinical ResearchAnd Patient Care.
Key takeaway message: Validated plasma biomarkers—pTau217, GFAP, NfL, and APOE ε4—enable reliable pharmacodynamic monitoring and early detection in AD, supporting therapeutic development and advancing clinical research in neurodegenerative diseases.

P027- INCORPORATING AUXILIARY INFORMATION INTO A CONTINUATION DECISION ONCE A GROUP SEQUENTIAL BOUNDARY HAS CROSSED INTO AN INTERIM FUTILITY STOPPING SET.

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Background: While randomized clinical trials are the gold standard for evaluating the safety and efficacy profiles of new investigational treatments, they entail several administrative, economic, and ethical considerations. Statistical experimental designs that prioritize ethical and efficient studies, such as group sequential methods, are essential for rigorous and responsible science. In group sequential settings, data is analyzed intermittently. Time-varying treatment effects, however, commonly violate the assumptions made in parametric or semi-parametric models used in a clinical trial setting. For example, in the case of a delayed treatment effect, an interim analysis may have insufficient information on the clinical endpoint as the treatment effect may have yet to manifest. Subsequently, potentially leading to an erroneous decision to terminate a trial early for futility. Auxiliary information, such as biomarkers, may provide valuable insight into the eventual primary outcome to justify further data collection. **Methods:** To maximize information on treatment effects, we introduce a novel information-based weighting scheme to balance the clinical endpoint and auxiliary measure. At an interim analysis, we propose utilizing the auxiliary information in a decision to continue the trial when a group sequential boundary statistic falls into the futility stopping set. Our use of auxiliary data may lead to a violation of the independent increments assumption commonly made in group sequential designs. To maintain frequentist operating characteristics, we utilize resampling methods to estimate the correlation structure of our proposed test statistic. **Results:** We consider the operating characteristics of incorporating auxiliary information into futility decisions with a special emphasis on stopping probabilities, power, and type I error. These results will be drawn from on the ongoing simulation studies meant to mimic a clinical trial with no treatment effect, immediate treatment effect, and delayed treatment effects. We illustrate situations where the use of auxiliary information from a surrogate endpoint can improve power, particularly when a delayed treatment effect on the primary clinical endpoint exists. **Conclusions:** Our method gives trialists the flexibility to continue a trial when there is a potential delayed treatment effect to avoid an erroneous decision of terminating the trial early, while maintaining trial integrity.
Keywords: Clinical trial, interim futility analysis, time-varying treatment effect.
Disclosures: The authors declared no competing interests.
Declaration of generative AI and AI-assisted technologies in the writing process: Statement: During the preparation of this work the author(s) used ChatGPT to make the writing more concise and clear. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.
Key takeaway message: We leverage auxiliary information into futility decisions to avoid potential erroneous conclusions at interim analyses.

P028- IMPACT OF A MULTIMODAL LIFESTYLE INTERVENTION ON DEMENTIA RISK FACTORS AND ATTITUDE RELATED TO DEMENTIA RISK: A LOGISTICAL PILOT STUDY.

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Background: Many individuals develop dementia, and dementia has multiple causes, yet we currently have limited treatment options. A critical observation of the effectiveness of the available dementia treatments is that they tend to be more effective when started early. Previous studies have shown that multimodal lifestyle interventions can significantly delay the onset of Alzheimer's dementia in individuals with high risk for Alzheimer's or with Mild Cognitive Impairment (MCI). These interventions may be less effective when initiated after dementia has already been diagnosed or is more advanced. This study has two primary goals. The first goal is to assess attitudes around dementia risk for participants throughout the study as they learn of their personalized risk and possible lifestyle factors that may modify that risk. The second goal is to serve as a logistical pilot for the implementation of data collection and processing and multimodal lifestyle intervention to reduce the risk factors of dementia in individuals without current cognitive impairment but who are at high risk of progression to dementia. Secondary goals of this study include better defining what factors contribute the most risk to dementia and identifying sub-types of dementia defined by different genetic and molecular risk factors. **Methods:** We are enrolling individuals 65–75 with a first degree relative that has or had dementia. Within this group, we are identifying individuals at particularly high risk based our study-defined rubric taking family history, APOE genotype, AD PRS, mCAIDE score, lifestyle score described by Dhana and colleauges (see references section), MoCA, self-reported race/ethnicity, and pTau217 level into account. Individuals in this group will be offered a multimodal lifestyle intervention targeting the prevention of cognitive decline based on previous studies of lifestyle interventions for the prevention or delay of dementia as described in previous studies. All participants will be offered a survey about perception of and attitudes toward dementia risk using the scaling strategy described by Kasparian and colleagues and dementia questions from Kim and colleagues (see references). Participants identified as high risk (multimodal lifestyle intervention arm) will be asked to complete the REVEAL (Risk Evaluation and Education for Alzheimer's Disease) Impact of Genetics Testing in Alzheimer's Disease (IGT-AD) Distress Subscale. The scale is 12 items on a Likert scale, with higher scores indicating more distress. **Results:** As of September 30, 2025 we have enrolled 128 individuals and identified 43 individuals at high risk according to our risk rubric. Preliminary results indicate a correlation between self-reported and rubric-measured risk ($p=0.04$). Return of results (APOE, PRS, and pTau217) to all participants, as well as measurements of attitudes and distress, is ongoing. **Conclusions:** This logistical pilot study provides a framework for screening for AD risk in the general population based on a rubric taking genetics, lifestyle, and biomarkers into account.
Keywords: pTau217, APOE, PRS, lifestyle.
Clinical Trial Registry: NCT07146412; https://clinicaltrials.gov.
Disclosures: The authors declared no competing interests.

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Key takeaway message: This logistical pilot study provides a framework for screening for AD risk in the general population based on a rubric taking genetics, lifestyle, and biomarkers into account.

P029- ANNUAL SITE COORDINATOR MEETINGS AS A CATALYST FOR RETENTION STRATEGY DEVELOPMENT IN ALZHEIMER'S DISEASE LONGITUDINAL COHORT STUDIES.

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Background: Participant retention in longitudinal Alzheimer's disease (AD) observational and interventional studies is essential to ensuring study integrity and validity of results over time. Despite this importance, the literature reports limited strategies for effective participant retention, especially in AD research studies. The Alzheimer's Therapeutic Research Institute's (ATRI's) Recruitment, Engagement, and Retention (RER) team implements a multi-dimensional framework to address this gap prioritizing strategies around site engagement. An important initiative within this strategy is the in-person Annual Site Coordinator Retention Meeting which invites site coordinators, recruitment specialists and other site personnel who directly interface with study participants across the observational cohort studies and clinical trials centrally coordinated by the ATRI RER team. These meetings, with study specific agendas developed and delivered across 3-days, provide a unique forum for cross-collaboration across sites and central teams, networking, and gathering critical and actionable insights from participant-facing personnel to inform the tactical development of retention approaches. Here, we describe the structure, content and outcomes of the inaugural Site Coordinator Retention Meeting and its role in establishing retention strategy development across sites participating in the multi-center, non-randomized, natural history, non-treatment Alzheimer's Disease Neuroimaging Initiative 4 (ADNI4) Study (1). **Methods:** ADNI4, the latest phase of ADNI, builds on prior phases (ADNI1, GO, 2, and 3) by continuing longitudinal assessments of cognition, imaging, and fluid biomarkers while incorporating remote digital screening and a more diverse cohort. It includes both participants who have continued from prior phases of ADNI and newly enrolled individuals. ADNI4 completed enrollment in 2025 and is currently in the retention phase. Meeting attendees included only the RER personnel from the ADNI4 Clinical Core and Engagement Core, and the site coordinators and related personnel who are directly responsible for study participant retention. The meeting was exclusively in-person, to enable a high level of meeting participant interaction, and the agenda focused on maximizing participant retention and engagement, including: a study-wide update on data and contemporary retention resources, an expert panel discussion comprised of site personnel, and breakout groups addressing observations, barriers, and strategies for longitudinal retention. Participant insights were collected through written observations, verbal contributions during the discussion session, and a post-meeting survey comprising both quantitative satisfaction ratings (based on agenda topics) and qualitative free-text responses focused on retention-related considerations. Quantitative responses were scored for attendee satisfaction ratings via cumulative averages. Written free-text responses, and notes from verbal responses were analyzed using a combination of an AI-driven tool (University of Southern California Information Technology Microsoft Copilot. 2025, September 27) for initial processing to enable efficient and consistent thematic extraction across the various text data sources and RER team experts for refinement and final critical interpretation. **Results:** The meeting was attended by 59 coordinators across 37 of 62 (60%) ADNI4 Study sites. Of the 59 meeting participants, 59% completed the post-meeting survey with responses indicating high levels of satisfaction from attendees at the ADNI4 inaugural in-person meeting, including 100% satisfaction with agenda topics and the overall event. Analysis of participant insights and responses identified four central themes. They include: (a) novel strategies to mitigate participant burden and logistical barriers to continued participation, such as ensuring that study visits fall on the same day as clinical visits tests to minimize repeated travel to research site; (b) long-term engagement plans for building and maintaining rapport between site staff, study participants, and their study partners, such as expanding study partner support strategies for younger, busier partners; (c) development and standardization of retention strategies that prioritize community engagement, with an emphasis on under-studied research populations in AD clinical research, such as study-wide site coordinator trainings tailored to establish standards of communication with under-studied research population participants and their communities; and (d) strategies for centrally provided participant retention resources, such as a

webinar series and expansions of centrally offered transportation support. **Conclusions:** In-person site coordinator meetings can serve as a critical infrastructure strategy within coordinating center-led retention-related site engagement frameworks for identifying and addressing participant retention challenges in longitudinal cohort studies such as ADNI4. The experience from this initial meeting highlighted the value of centrally organized in-person forums in fostering collaboration and active discussion among study sites and central RER teams, empowering site coordinators, and identifying actionable insights to enhance study retention planning. Importantly, the themes and strategies identified in this instance were consistent with those observed in our clinical trials settings, thereby confirming the relevance of this approach for both observational and interventional AD studies.

Keywords: Alzheimer's, longitudinal, observational, retention, engagement, collaboration, participant.

Clinical Trial Registry: NCT05617014

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Key takeaway message: In-person site coordinator meetings foster collaboration and yield actionable insights that enhance participant retention strategies in Alzheimer's studies, confirming their value across longitudinal observational research protocols like ADNI4.

P030- A SINGLE-CENTER, RETROSPECTIVE, RATER-BLINDED, CROSSOVER STUDY TO EVALUATE THE CLINICAL UTILITY OF A MEDICAL IMAGE ANALYSIS SOFTWARE FOR QUANTITATIVE ANALYSIS OF BRAIN PET IMAGES IN PATIENTS WITH ALZHEIMER'S DISEASE.

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Background & Objective: The prevalence of Alzheimer's disease (AD), a leading cause of dementia, has been rapidly increasing, and the importance of accurate diagnosis has been consistently emphasized, spurring the development of various diagnostic approaches. Amyloid positron emission tomography (PET) scan is a key technique for diagnosis of AD. Amyloid PET evaluates the quantity and distribution of amyloid beta (Aβ) protein, which accumulates abnormally in the brain, forming plaques and damaging neurons. Aβ is one of the earliest biomarkers of AD, and its visualization and quantification through PET imaging play a key role in diagnosis and disease monitoring (1). Visual interpretation of brain PET images is widely used but is inherently subjective due to its dependence on the reader's experience and training, which can lead to inconsistencies and variability in diagnostic accuracy (2). This subjectivity can compromise diagnostic consistency, as the precision and uniformity of interpretation may differ among readers. For instance, in amyloid PET imaging, while a scoring method exists to determine positivity by summing regional scores, its application in clinical practice is challenging, resulting in 10–15% of cases being equivocal (3,4). Employing voxel-based quantitative data offers a more objective approach to evaluating tracer uptake, thereby reducing variability among readers (5). Quantitative metrics, such as the Standardized Uptake Value Ratio (SUVR) and the centiloid scale, provide consistent and reproducible measurements that can enhance diagnostic confidence, particularly in ambiguous cases (6,7). This study aims to determine if clinicians' diagnostic accuracy improves when using software that provides quantitative analysis of brain PET images, as opposed to relying solely on visual assessment. **Methods:** This is a single-center, retrospective, rater-blinded, cross-over design, incorporating 204 retrospective datasets: 10 for reader training and 194 for primary analysis. Cases were chosen from Ajou University Hospital and the Alzheimer' Disease Neuroimaging Initiative (ADNI) open-source database, based on specific inclusion and exclusion criteria. The collected data included clinical information such as age, sex, education, diagnosis, and cognitive assessments, as well as imaging data (Brain 3D T1 MR, amyloid PET). Two independent investigators established the reference standard, resolving any disagreements through consensus. The imaging data underwent processing via 'Neurophet SCALE PET', yielding quantitative reports for each case. Before the primary reader study, all readers received training in a simulated trial environment to ensure procedural familiarity. Four readers were divided into two groups and tasked with evaluating all 194 cases across two sessions, with a 4-week washout period separating them. Employing a crossover design, Group A analyzed cases with software assistance in Session 1 and without it in Session 2, while Group B followed the inverse order. Each group maintained an approximate 1:1 ratio of Aβ-positive to Aβ-negative cases. Readers assessed amyloid PET scans using a 5-point scale, where 1 indicated «Definitely negative» and 5 indicated «Definitely positive,» and rated diagnostic confidence on a 3-point scale. A score of 3 or higher was designated as positive. Utilizing both reader data and the reference standard, sensitivity and specificity were compared as primary outcomes, while inter-reader agreement and confidence levels were examined as secondary outcomes. **Results:** The principal outcomes of this study are the distinctions in readers' sensitivity and specificity for identifying Aβ positivity when comparing software-assisted and unassisted interpretations. Secondary outcomes encompass variations in the number of equivocal case ratings, differences in diagnostic confidence levels, and the inter-rater agreement observed across both reading conditions. These outcomes will be evaluated through statistical analyses. **Conclusions:** This rater-blinded crossover study presents a pragmatic methodology for assessing the clinical utility of artificial intelligence (AI)-based PET analysis software in AD. The direct comparison between assisted and unassisted interpretations within the study highlights the software's potential to enhance diagnostic consistency. Despite being constrained by its retrospective, single-center design, this approach establishes a basis for subsequent prospective, multi-center trials aimed at further validating software-assisted interpretation across varied clinical environments.

Keywords: Alzheimer's disease, amyloid PET, quantitative imaging, AI-assisted interpretation.

Clinical trial registry: N/A.

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Key takeaway message: Quantitative PET analysis using AI software may support more consistent and confident diagnosis of Alzheimer's disease, highlighting its potential clinical utility in routine imaging interpretation.

P031- MANY EXCITING NEW TARGETS FOR AD… BUT DO MORE MOAS MEAN MORE DUPLICATE SUBJECTS?

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Objectives: To identify and examine the use of a subject registry on the identification of duplicate, professional or otherwise inappropriate subjects in Alzheimer's Disease studies, expanding upon findings published in a prior JPAD study to look at trends over time. **Methods:** We looked at pooled study data for all subjects that presented for memory or Alzheimer's Disease Studies utilizing a subject registry between May 31, 2019 and August 13, 2025. This was compared with an earlier analysis done in 2019. A secondary analysis calculated the number of AD patients disqualified from studies due to findings in their history. The subject registry used was CTSdatabase, one of several commercially available subject databases. **Results:** Of the 5,412 memory/AD subjects who prescreened or screened, 597 (11%) had at least one match from a different site in their history. These matches were more often for non-memory indications (most commonly MDD or healthy normal) than for memory indications, a pattern consistent with our earlier JPAD analysis (10.8% of subjects, most commonly MDD or schizophrenia). In the secondary analysis (n=2,909 subjects), 136 exclusionary matches were identified, representing a 4.7% exclusionary match rate. **Conclusions:** Use of a centralized subject registry can identify AD and memory study participants who have previously presented at other sites or for other indications, allowing ineligible subjects to be detected before screening begins. In this analysis, 11% of memory study subjects had at least one visit in their history from a site they hadn't visited before, most often for non-memory indications. Among studies where the registry was in use, 4.7% of AD subjects were flagged for reasons that would make them ineligible per study protocol. These findings highlight that duplicate and ineligible subjects remain a concern in AD research and underscore the importance of early registry checks, particularly as the number of novel mechanism trials continues to expand.

Key takeaway message: Subjects in AD studies may be in/may have been in other studies that affect data integrity and patient safety in the current study. Use of a subject registry may help mitigate these risks.

P032- ADVANCING ALZHEIMER'S RESEARCH THROUGH COMMUNITY-BASED NEUROLOGY TRIALS: A PROFOUND RESEARCH MODEL.

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Background: Alzheimer's disease remains a critical public health issue, with less than 10% of eligible patients participating in clinical trials and even lower rates among underserved and minority populations (Grill & Karlawish, 2010). Community-based neurology practices are key to increasing diverse trial participation through patient-centric designs and trusted partnerships. Alzheimer's clinical trials face low enrollment due to barriers like limited access, stigma, and lack of culturally competent outreach. For minorities, distrust, logistical issues, and few referrals worsen the problem, delaying therapeutic progress. **Methods:** Profound Research's Approach: A Community-Embedded Model. Profound Research integrates clinical trials into local neurology practices, memory care centers, and health systems. This approach reduces patient disruption, boosts provider participation, and enhances accessibility, bridging the gap between patients and research. Key elements of the model include: - EMR-Based Pre-Screening. - Centralized Operational Support. - Point-of-Care Tools. Community Outreach: Building Trust and Awareness. To combat stigma and improve awareness, Profound prioritizes community engagement. Tactics include: Walk to End Alzheimer's & Awareness Events. - Support Group Collaboration. - Educational Seminars. Provider Engagement: Empowering Neurologists to Champion Trials. Neurologists endorsement of trials significantly influences patient willingness to participate. Profound supports providers by: Conducting regular research rounds and case reviews. - Offering trial summaries and tools that integrate with EMR workflows. Sharing real-time updates on enrollment targets and protocol changes. **Results:** In a 12-month evaluation, sites in the Profound network experienced a 95% increase in screened patients and a 39% increase in randomized patients in Alzheimer's trial enrollment compared to traditional methods. The datasets exhibit a near-balanced gender distribution, with approximately 60% female and 40% male participants, aligning with the epidemiology of Alzheimer's and Mild Cognitive Impairment (MCI), where women are more frequently affected, particularly in older age groups. This gender ratio is consistently maintained across different trial phases, indicating deliberate and stable recruitment strategies rather than random variation. Importantly, enrollment of underrepresented minorities rose significantly as follows: Improved Hispanic Representation. • Hispanic participants accounted for 11.84% of the Trial 1 cohort, exceeding national Alzheimer's trial averages, where Hispanic enrollment typically falls below 6%. • Indicates successful outreach and engagement strategies in Hispanic communities. Inclusion of Underrepresented Populations.
• Participants identifying as Black (6.06% in Trial 1, 1.32% in Trial 2), American Indian, and Asian were represented. • Reflects intentional efforts to include racially diverse populations often underrepresented in neurodegenerative disease trials. Diverse Self-Identification Captured. • An additional 7.89% (Trial 1) and 9.09% (Trial 2) of participants were categorized as "Other" or "Other, not of Hispanic origin." • Suggests flexibility in classification and inclusivity of participants beyond rigid ethnic labels. High Data Integrity on Race/Ethnicity. • 0% of participants were categorized as "Unknown" or "Unclassified." • Demonstrates strong data collection practices, enabling meaningful diversity analysis. Balanced White, Non-Hispanic Representation. • "White, not of Hispanic origin" participants made up 76.32% (Trial 1) and 81.82% (Trial 2) of enrolled patients. • This represents a notable improvement over industry norms, which often report 85–90 %+ White enrollment in Alzheimer's trials. Balanced Gender Participation Across Cohorts. • Both datasets demonstrate a near-balanced gender split, with female participants representing ~60% and male participants ~40%. • This distribution reflects the epidemiology of Alzheimer's and Mild Cognitive Impairment (MCI), where women are more commonly affected, especially in older populations. Consistent Representation Across Trial Phases. • The gender ratio remains consistent across collected datasets, suggesting stable and intentional recruitment practices rather than random variance. A significant majority of participating neurologists reported increased confidence in discussing trials with patients. This aligns with findings by Massett et al. (2021), who identified provider recommendation, awareness, and logistical ease as key drivers of enrollment. Profound's model not only accelerates recruitment speed and scale but also improves data quality by ensuring real-world diversity. As the demand for Alzheimer's therapies grows, these models become crucial for accelerating research and inclusivity. The infrastructure is designed for scalability, allowing expansion into rural, suburban, and urban settings with consistent performance metrics. Its success in Alzheimer's trials positions the model for broader application in other neurodegenerative

diseases, such as Parkinson's and frontotemporal dementia. Key future strategies include: Further integration of AI-driven EMR tools for predictive pre-screening.- Expanding bilingual recruitment materials and culturally adapted consent processes. - Deepening partnerships with geriatric and long-term care providers. **Conclusions:** Alzheimer's research must evolve to meet the realities of a diverse and aging population. By integrating trials into community practices, empowering physicians, and engaging communities, this model ensures that breakthroughs in Alzheimer's therapy reach a broader range of populations. As it continues to scale, this model sets a new standard for community-rooted, patient-centered research for Alzheimer's disease.

Keywords: clinical trial design, recruitment, Alzheimer's disease, mild cognitive impairment.

Disclosures: All three authors are employed by Profound Research.

References: J.D. Grill, J. Karlawish. Addressing the challenges to successful recruitment and retention in Alzheimer's disease clinical trials. Alzheimer's Res Ther. 2010 Dec 21;2(6):34. DOI: 10.1186/alzrt58. H.A. Massett et al. Facilitators, Challenges, and Messaging Strategies for Hispanic/Latino Populations Participating in Alzheimer's Disease and Related Dementias Clinical Research: A Literature Review". J Alzheimer's Dis. 2021;82(1):107-127. DOI: 10.3233/JAD-201463.

Key takeaway message: Alzheimer's research must evolve to be inclusive and efficient. Profound Research's community-based trials empower physicians and engage communities, ensuring breakthroughs reach those in need, setting a new standard for patient-centered research.

P033- LESSONS FROM REAL-WORLD CLINICAL IMPLEMENTATION OF ANTI-AMYLOIDβANTIBODIES: BRIDGING THE GAP TO CLINICAL TRIALS.

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Background: Two anti-amyloid β (Aβ) antibodies, lecanemab and donanemab, are now in clinical practice for the treatment of early symptomatic Alzheimer's disease in Japan. Our experience over nearly two years highlights a significant gap between clinical trials and real-world clinical practice regarding patient eligibility and treatment decision-making. To improve future treatment strategies, it is crucial to understand and address these real-world findings. **Method:** We established a specialized DMT clinic and implemented two-step screening process for patients seeking anti-amyloid therapy. The initial screening at the memory or neurology clinic assesses clinical severity assessments and differential diagnosis. The second screening at the DMT clinic includes detailed informed consent, followed by CDR, MRI, amyloid testing and optional APOE genetic testing. We collected demographic data of patients and reasons for exclusion at each step from December 2023 to July 2025. **Results:** A total of 540 patients sought anti-amyloid therapy. 282 (52.2%) patients were excluded at the initial screening. The most common reason for exclusion at this step was more advanced disease stage (n = 113, 40.1%). Combined with referred patients who attended the memory clinic without specific interest in anti-amyloid therapy and met eligibility criteria, a total of 353 patients attended the DMT clinic. Among them, 102 patients (28.9%) declined the treatment during the informed consent session, with the most common reason being concerns about side effects (n = 35, 34.3%), followed by lack of willingness for unspecified reasons (n = 23, 22.5%). After 89 patients were excluded by remaining eligibility assessments and 11 withdrew consent, 139 (39.3% of those who attended the DMT clinic) initiated anti-amyloid therapy. The proportion of female patients among those who initiated treatment was 73.4%, which is notably higher than the approximately 50% observed in clinical trials. The proportion of patients who initiated anti-amyloid therapy after attending the DMT clinic tended to be lower among male patients than female patients (32.7% vs 42.5%, $p = 0.09$), primarily due to a higher proportion of exclusions based on MRI findings. Furthermore, patients with an MMSE score ≥ 27 were less likely to seek anti-amyloid therapy and less likely to initiate treatment compared to those with a score of 20-26 (27.8% vs. 45.6%, $p < 0.001$), mainly because the proportion of negative Aβ accumulation was higher in this group. **Conclusions:** Our data reveal a substantial discrepancy between clinical trial participants and real-world patients. Patient Demographics: The patient cohort in our real-world setting, particularly the higher proportion of female patients, differs significantly from that of clinical trials. This suggests female participants may be underrepresented in clinical trials, highlighting the need for targeted outreach to address barriers to treatment access in different populations. Patient Selection and Treatment Perception: The low proportion of patients with higher MMSE scores (27–30) who would benefit more from anti-amyloid therapy seeking or initiating treatment suggests a public perception in Japan that dementia is synonymous with more advanced stages. This contrasts with the focus of clinical trials on very early-stage disease. Furthermore, many patients refrain from anti-amyloid therapy due to concerns about safety. A perception that differs from the high motivation and lower safety concerns typically observed in clinical trial and study participants. This underscores the need for safer and more convenient treatment options, such as subcutaneous formulations, to increase broader acceptance. Future Directions: Real-world experiences like this, including the critical role of patient education and shared decision-making, must be integrated into future research designs and clinical trial protocols to ensure broader applicability and patient acceptance of new therapies. A more thorough understanding of these gaps will be vital for developing more effective and widely adopted treatments.

Keywords: Anti-amyloid therapy, real-world data, sex differences, perception.

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Key takeaway message: Real-world data reveals significant gaps between trial and practice. Patient concerns about safety, later disease perception, and a higher female cohort underscore the need for safer, convenient treatments and targeted awareness campaigns.

P034- SUCCESSFUL STRATEGIES FOR RECRUITMENT AND RETENTION AS A FOUNDATION FOR ADRD-FOCUSED CLINICAL TRIALS IN A RURAL COHORT.

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Background: Older adults in the U.S. are increasingly likely to reside in rural areas (1). Rural residents are also steadily becoming more racially/ethnically diverse (2). Unfortunately, rural and multicultural groups are more likely to experience conditions that contribute to ADRD risk (3), but they are not well-represented in clinical trials. Our study participants from five rural communities surrounding the second largest freshwater lake in the contiguous U.S. (Lake Okeechobee, FL) experience all 14 potentially modifiable ADRD risk factors (4). These health and healthcare disparities are related to a high burden of chronic illness and low healthcare access (5). **Method:** A faith-based approach to increase ADRD awareness, early detection, and interventions to diminish

risk, which was launched eight years ago, continues to ground dementia prevention research in this rural and 89-81% racially/ethnically diverse cohort (6-13). In this NIA-funded R01 longitudinal study (14), we are examining prevalence and relationships between the preventable ADRD risk factors to inform next steps for prevention trials. All study activities are led by trained local church members serving as community research assistants (CRAs) who contact ministerial and civic leaders to establish recruitment dates, conduct data collection, and schedule participants for follow-up. They serve as both the community-facing representatives and the operational drivers of the study. Eligible participants are rural residents aged 45 and older who score ≥12 on the mini-MoCA (15). Exclusion criteria are persons who have been previously diagnosed with dementia, score below 12 on the mini-MoCA, or do not live in the target areas. Our primary outcome, cognitive function, is being measured by the MoCA (16), the computerized adaptive test Cogstate (17), the mCAIDE (18), subjective memory decline, and the n-back test delivered through smartwatches (19) in biannual subsamples. The modifiable ADRD risk factors are being measured through biomarkers and patient self-report data. Non-modifiable measured risk factors include age, sex, ethnicity, and years lived in a rural area. Neighborhood vulnerability and air quality is also being measured with subsamples for other environmental influences, including citizen science measures of PM2.5 levels and ecological momentary assessment. **Results:** Recruitment: Of the 902 residents screened to date, 808 (90%) were eligible based on the study criteria. Retention: Nearly 700 participants completed the T1 visit in the first year of this five-year study (n=684; 86%). These first follow-up assessments FY1 included the MoCA, mCAIDE, memory self-report, and demographic information. Most identified as female (287/72%). Ethnic group membership included Black (311/78%), White (74/19%), Hispanic/Latino (61/15%), Afro-Caribbean (12/3%) and other races (14/4%). Median age was 64±10.3 years, with 11.9±3. years of education, and rurality of 44.6±22.6 years. Over a third (38%) scored below the education-adjusted cut-off of 26 for no cognitive risk. No covariates predicted subjective memory decline, $p>.05$, suggesting persons may not be aware of or reluctant to report memory loss. Of the 374 participants with relevant data, education and Hispanic/Latino ethnicity were significant and positive predictors of MoCA scores ($p<.001$), while age, gender, or years in study communities, were not significant predictors ($p>.05$). Age ($p<.001$) and education ($p=.007$) were significant and positive predictors of mCAIDE scores, while gender, Hispanic/Latino ethnicity, years lived rural were not significant ($p>.05$). In the first year of the smartwatch sample, two groups totaling 33 participants wore the watch for 8 weeks, during which they were prompted daily to complete the 45-second n-back shape test delivered over the smartwatch. We calculated each participant's mean n-back score, variance, first score (y-intercept), and improvement over time (slope). From the 30 participants with completed n-back scores, mean n-back score significantly predicted MoCA ($p<.001$), which supports the use of the shape test for cognitive assessment. English language predicted mean score ($p<.001$), first score ($p<.001$), score variance ($p<.001$), and slope ($p=.022$). Age and years living in rural communities negatively influenced n-back slope and years of education predicted variance. **Discussion:** This resident-led research achieved high percentages of recruitment and retention (90% and 86% respectively). A key facet of recruitment/retention success has been the level of trust established by employing local residents to serve as project directors and research assistants. Of note is the heightened interest in smartwatch use; over 200 participants are on the waiting list, which suggests that persons are interested in technological assessments. However, one barrier to data collection was the numerous failed attempts to reach participants by telephone for the T1 data collection. Therefore, 140 letters were mailed to the addresses provided by residents during enrollment. Ten percent of those envelopes were returned for "no longer available" or "no such address existed." Consequently, we conducted "drive-bys" and succeeded in connecting with 102 (73%) of the missing residents with valid physical addresses, completing the T1 data collection in their home. Currently, overall retention has increased to 90%. Our long-range goal is to apply these findings when constructing a patient-preference randomized control trial (20,21) to address the salient dementia risk factors for which real-world interventions can be introduced, and which matter most to participants.

Keywords: Rural, faith-based, recruitment, Retention, multicultural, Alzheimer's disease.

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Key takeaway message: Rural residents often face twice the risk of ADRD as urban counterparts but are not represented adequately in clinical trials. Faith-based, resident-led approaches are strategies to increase engagement in dementia prevention research in rural settings.

P035- EFFECT OF CONSENTING CLINICIAN DEGREE ON SCREEN FAIL RATE IN ALZHEIMER'S DISEASE CLINICAL TRIALS.

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Background: Clinical trials on Alzheimer's Disease (AD) face exceptionally high screen failure rates, ranging from 88% in preclinical to 78% in prodromal AD clinical trials (Langbaum). These high screen fail rates can significantly impact trial timelines, costs, and ultimately slow the development of potential treatments for AD. Irvine Clinical Research is a commercial site network in California that specializes in Alzheimer's Disease clinical trials at 5 sites. In order to accelerate the recruitment process, Irvine uses multiple clinicians of varying degrees of advanced education to consent and screen participants into trials. In this study, we examine the relationship between the type of degree of the consenting clinician (PhD, PsyD, or MD/PA) and subsequent screen failure rates. **Methods:** We examined screening data for all 272 participants who screened into one of two clinical trials on Alzheimer's Disease conducted in 2023-2024. These two trials were separate but shared some similarities; they both were testing an anti-amyloid monoclonal antibody, they both were recruiting individuals who had mild cognitive impairment or mild AD, and both required certain scores on cognitive testing and positive amyloid PET. Of these 272 participants, 138 participants had consent obtained by a PsyD, 80 participants had consent obtained by a PhD in a relevant field, and the remaining 54 participants had consent obtained by an MD or PA. **Results:** A logistic regression analysis controlling for participant age, race, and trial was conducted on the collected data. Inclusion of the degree of the consenting clinician reduced the model deviance by 2= 3.59 on two degrees of freedom, yielding a p-value of 0.166. When looking at the individual effects of the specific degrees, participants who went through the consenting process with a PhD-level consenting clinician were very slightly more likely to screen fail ($\beta = 0.759$, p=0.09). **Conclusions:** While there was no material difference in screen fail rate for consenting clinicians of different degrees, screen fail rate should not be the only consideration. For the purposes of collecting participant consent, the primary consideration should be proper and thorough understanding of the risks so that they can ethically consent. Beyond obtaining thorough consent, consent success rate - the percentage of eligible participants that a clinician is able to get into screening - should be considered and evaluated. Study adherence / attrition rate or consent withdrawal rate could also be other measures to consider when delegating responsibilities at a research clinic.

Keywords: Informed consent, clinical research, Amyloid treatment.

Disclosures: All presenters are employees of Irvine Clinical Research, an independent clinical research site network that conducts industry-sponsored pharmaceutical trials in neurology and psychiatry.

References: Langbaum JB, Zissimopoulos J, Au R, Bose N, Edgar CJ, Ehrenberg E, Fillit H, Hill CV, Hughes L, Irizarry M, Kremen S, Lakdawalla D, Lynn N, Malzbender K, Maruyama T, Massett HA, Patel D, Peneva D, Reiman EM, Romero K, Routledge C, Weiner MW, Weninger S, Aisen PS. Recommendations to address key recruitment challenges of Alzheimer's disease clinical trials. Alzheimers Dement. 2023 Feb;19(2):696-707. doi: 10.1002/alz.12737. Epub 2022 Aug 10. PMID: 35946590; PMCID: PMC9911558.

Key takeaway message: There was no material difference between education of clinician (PsyD, PhD, and MD/PA) on screen fail rate in these Phase 3 clinical trials on Alzheimer's Disease.

P036- CLICK OR CLINIC? COMPARING REFERRAL-TO-PRE-SCREEN ATTENDANCE RATES BETWEEN DIGITAL ADVERTISEMENTS AND HCP REFERRALS IN ALZHEIMER'S CLINICAL TRIALS.

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Background: Recruitment remains one of the most significant operational challenges in Alzheimer's disease clinical trials. While digital advertisements offer the ability to generate high referral volumes rapidly, healthcare provider (HCP) referrals are often perceived as higher quality, albeit lower in quantity. However, few real-world analyses have directly compared these two strategies across the full referral-to-pre-screen pipeline. This study evaluated the performance of digital ads versus HCP referrals in terms of contactability, pre-screen scheduling, and attendance within three Alzheimer's disease clinical trials. **Methods:** Data were collected prospectively from three Alzheimer's trials conducted at Global Medical Institutes between March 2024 and March 2025. Referrals were categorized into two groups: (1) digital advertisements (via Meta and Google), and (2) HCP referrals from primary care physicians, neurologists, and geriatricians. Digital ad referrals were required to complete a short phone-based screener at the time of inquiry. Those who failed were excluded from follow-up. Those who passed were eligible for outreach by the recruitment team to schedule a pre-screen visit. HCP referrals bypassed the self-screen and were contacted directly, as the referring provider had typically reviewed eligibility criteria. All participants aged 50+ with subjective or caregiver-observed cognitive decline were included. Referrals were evenly distributed across all days of the week. Key metrics included contact success rate, pre-screen scheduling rate, and in-person pre-screen attendance. **Results:** Out of 1,284 total referrals, 912 (71%) came from digital ads and 372 (29%) from HCPs. Digital ads yielded a lower pre-screen attendance rate (17.4%) compared to HCP referrals (69.9%). Of the 912 digital referrals, 584 (64%) passed the initial screener. 298 (51%) of those were successfully contacted. 221 (74%) of contacted individuals were scheduled for a pre-screen, and 159 (72%) of those attended. Contact success was strongly influenced by time-to-contact. On weekdays, 44% of leads were reached within 3 minutes, achieving a 70% success rate. Leads not contacted within 3 minutes — including all weekend leads — had a contact success rate of only 33%. Among the 372 HCP referrals, 331 (89%) were successfully contacted. 271 (82%) of those were scheduled for a pre-screen appointment after undergoing the same phone-based mini screener used for digital referrals — but this time administered over the phone by a member of the recruitment staff. The remaining 60 individuals (18%) were either ineligible or were no longer interested. 260 (96%) of those scheduled attended their pre-

screen visit. HCP referrals consistently demonstrated higher engagement across all funnel stages, regardless of time-to-contact. **Conclusions:** While digital advertisements generate high referral volume and expand outreach rapidly, they often produce lower-quality leads and require immediate follow-up to convert interest into engagement. Without near-instant contact, many leads are either unreachable or quickly disengage, making digital recruitment highly sensitive to both operational speed and screening efficiency. In contrast, HCP referrals, though fewer in number, consistently yield higher-quality leads with strong contact, scheduling, and attendance rates—regardless of time-to-contact. This is likely due to the credibility and clinical framing provided by the referring provider. These findings support a hybrid recruitment strategy: one that leverages the scalability of digital platforms while relying on provider networks to ensure consistency, trust, and higher conversion.

Keywords: Alzheimer's disease, patient recruitment, digital advertising, healthcare providers.

Key takeaway message: With limited real-world data on recruitment strategies, this analysis highlights how HCP referrals yield higher-quality leads, while digital ads—though higher in volume—require speed and precision to convert interest into engagement.

P037- MINIMAL CLINICALLY IMPORTANT DIFFERENCES ARE OFTEN MISAPPLIED AND MISINTERPRETED AND SHOULD BE USED WITH CAUTION.

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1. Pentara - Millcreek (United States)

Background: Without the requirement that a drug or device effect be clinically meaningful, approval would merely hinge on sample size and a positive effect. Many outcomes have clear clinical relevance (e.g., time to onset of dementia), however, these endpoints may be difficult to attain within the timeframe needed for drug development. In such cases, a surrogate endpoint may be used (e.g., p-Tau 217), that is more sensitive to disease progression over time, is linked to the ultimate outcome of interest, but lacks a clear clinical interpretation. To compensate for the lack of clear clinical interpretations of these kinds of endpoints, regulators frequently encourage the use of minimum clinically important differences. The purpose of the MCID is to provide an easily interpretable scale for more esoteric measures: clinical relevance. There are two common methods to calculate MCIDs: anchor-based methods and distribution-based methods. Here we focus on anchor-based methods, which, in their simplest form, utilize some secondary measure that is clinically interpretable. A group experiencing a clinically meaningful difference on the anchor item is found and their difference on the outcome of interest (e.g., p-Tau 217) is estimated. This difference is the MCID, but MCIDs should be applied with caution. MCIDs, when based on less-correlated outcomes underestimate the value of the MCID, which has led to their use in more severe populations where correlations between outcomes are stronger. This means that MCIDs are inherently suited for large effects like those seen with symptomatic treatment. This leads many to minimize the importance of disease-modifying effects in early stage populations. **Methods:** We present a natural history study demonstrating a real world example of anchor based MCID calculations, which illustrates the statistical difficulties inherent in the method. Using publicly available ADNI data, the CDR-Global, CDR-SB, and CSF pTau-181, we calculate the MCID for CDR-SB anchored to the CDR-Global and CSF pTau-181, anchored to the CDR-Global. Changes were evaluated at 12 months. **Results:** For the CDR-SB and CDR-Global there were 186 subjects with a change from baseline at 12 months on the CDR-Global of 0.5. The average CDR-SB change from baseline among those subjects was 2.05. Forty-six subjects had both CSF pTau 181 data at 12 months and a CDR-Global, change from baseline greater than or equal to 0.5. The estimated MCID for pTau 181 anchored to a minimum 0.5 point worsening (a half point increase) on the CDR-Global, was -0.66 pg/ml. Among the 1,722 subjects with change data on both the CDR-Global and the CDR-SB, the correlation of the change scores was 0.76. Among the 297 subjects with change scores on both the CDR-Global and pTau 181, the correlation between the two change scores was -0.04. **Conclusions:** MCIDs are supposed to provide a clear clinical interpretation to guide the use of outcomes; however, there are complications in their use, both when the outcome is highly correlated with the anchor, as they are supposed to be, and when they have low correlation. The low correlation case often produces an MCID that leads to almost the entire population crossing into "clinically meaningful" changes (in the present case, this manifests as a negative MCID on a progressive variable), while the high correlation case leads to an MCID where the disease itself is not meaningful. In the example of the CDR-SB, the average progression in a mild population doesn't reach the MCID at the time point used in the calculation (12 months) and would require nearly 100% slowing of a disease-modifying treatment at 18 months. Given these examples, caution is advised in the application of MCIDs to interpret clinical trial results in general. In a progressive disease, the meaningfulness should align with the progressive nature of the disease. This can be done simply and clearly by using estimates of time savings to convey meaningfulness in a way all stakeholders can understand.

Key takeaway message: MCIDs estimated using anchor based methods have poor statisical properties. This is particularly likely when MCIDs are estimated for biological based measures.

P038- RETHINKING INTERIM ANALYSES: WHEN AND WHY TO AVOID THEM.

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Background: Interim analyses are commonly used in clinical trials to reduce the risk of costly failures and to generate early signals that can support investor confidence or funding decisions. However, interim analyses also introduce additional costs, including operational complexity, statistical penalties, and the potential for incorrect early stopping decisions. A thorough evaluation is needed to better understand the trade-offs involved and to determine when interim analyses are truly beneficial. **Methods:** Simulations were used to evaluate the impact of interim analyses on trial efficiency and decision-making in an 18-month, parallel-group clinical trial enrolling 76, 192, and 1200 participants depending on effect size. An interim analysis was conducted when 50% of participants had completed up to the timepoint of the interim analysis. Three interim analysis strategies were compared: (1) an interim analysis based on a biomarker with a 30% correlation to the final clinical outcome, (2) an interim analysis based directly on the 6-month clinical outcome with an assumed 60% correlation the final clinical endpoint, and (3) an interim analysis based directly on the 18-month clinical outcome. For each scenario, simulations were run under assumptions of small (Cohen's D of 0.2, n=1200), medium (Cohen's D of 0.5, n=192), large (Cohen's D of 0.8, n=76), and no treatment effects. Each of these scenarios were run 200 times, and followed up with 10,000 iterations. Outcomes of interest included the proportion of trials terminated early and the proportion of trials incorrectly declared unsuccessful due to alpha spending. These metrics were used to assess the practical value of implementing interim analyses under different conditions. **Results:** Interim analyses were classified as helpful if they stopped a study early for overwhelming efficacy given they went on to succeed or for futility in trials that ultimately failed. They were considered harmful if they continued trials that ultimately failed or stopped trials that would have been successful. An interim analysis was deemed neutral if it continued a trial that went on to succeed but did not meaningfully inform decision-making while still incurring additional cost. The interim strategy using a surrogate biomarker (30% correlation with the final clinical outcome) was never helpful, regardless of effect size. In contrast, the interim analysis using the 6-month clinical outcome showed limited benefit, being helpful in

only 2.5% and 0.5% of simulations under small and medium effect sizes, respectively, with no benefit in the large effect size scenario. The interim analysis based on the 18-month clinical outcome demonstrated utility in 0.5%, 19%, 18%, and 14% of cases for null, small (d = 0.2), medium (d = 0.5), and large (d = 0.8) effect sizes, respectively. These findings highlight that while interim analyses may offer theoretical benefits, their practical value is limited and often does not justify the additional operational complexity, cost, or potential regulatory implications. **Conclusions:** Interim analyses are commonly viewed as tools to reduce time and cost in unsuccessful trials. However, simulation results highlight key limitations of this approach. Specifically, interim analyses often fail to reliably stop trials for futility and carry the risk of prematurely halting trials that would have ultimately demonstrated a treatment benefit. When accounting for these risks along with the operational and statistical costs of conducting an interim analysis as well as the additional doubt that an interim analysis brings to final results based on partial data, this strategy may paradoxically lead to increased time and resource expenditure compared to trials without interim analyses.

Keywords: Clinical trials, study design, interim analysis, surrogate.

Disclosure: All authors are employees of Pentara Corporation, a statistical consulting firm specializing in neurodegenerative diseases that provides services to pharmaceutical companies and academic institutions. **References:** Mintun MA, Lo AC, Duggan Evans C, et al. N Engl J Med. 2021;384(18):1691-1704. doi:10.1056/NEJMoa2100708. Sims, J. R. et al. JAMA 330, 512–527 (2023). van Dyck CH, Swanson CJ, Aisen P, et al. N Engl J Med. 2023;388(1):9-21. doi:10.1056/NEJMoa2212948. Budd Haeberlein S, Aisen PS, Barkhof F, et al. J Prev Alzheimers Dis. 2022;9(2):197-210. doi:10.14283/jpad.2022.30. Bateman, R. J. et al. N. Engl. J. Med. 389, 1862–1876 (2023).

Key takeaway message: Interim analyses are often viewed as cost-saving tools, but simulations show they rarely stop futile trials, risk halting effective ones, add uncertainty, and are often viewed unfavorably by regulators, ultimately increasing time and cost.

P039- IMPROVING STUDY POWER THROUGH CONTINUOUS MODELING OF A GLOBAL TREATMENT EFFECT VERSUS COMPOSITE RESPONDER ANALYSIS.

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Background: Assessing the progression of Alzheimer's disease requires evaluating various aspects of the disease progression. However, most common outcome measures often focus on a single disease domain. To address this limitation, Global Statistical Tests (GSTs), first proposed by O'Brien in 1984, offer a method to integrate findings from multiple endpoints into a single assessment while accounting for correlation between outcomes, a complex statistical task that requires analytical methods beyond the scope of human intuition. This yields an objective overall estimate and probability for evaluating simultaneous outcomes. Given that clinical trials routinely collect data on several efficacy measures, GSTs provide a valuable and objective approach to synthesize this information and determine the overall evidence supporting a treatment's effect. Some have considered the use of responder analyses, either based on each separate outcome, based on a GST, or as a combination of response on a combination of separate outcomes, in an effort to address clinical meaningfulness. Here responders are defined as those that achieve a threshold level of response for a given outcome, either individually or in the GST, hypothesizing that such an analysis will be a powerful way to detect a disease modifying treatment effect. **Methods:** Three outcomes were simulated with 0.4 correlation between each pair, and an effect size of 30% slowing across sample sizes of 105 and 180 completers per arm. The results of a t-test were compared to a responder analysis using a chi-squared test for each outcome individually and for the GST. Additionally, the sum of the individual responder analyses was tested as a continuous outcome. Power was compared across 10,000 simulations of each scenario. **Results:** With 105 completers per arm each individual outcome had a power of 58%. The equivalent responder analysis on the outcome had a power of 35%. In comparison, the GST on the continuous endpoint (t-test) achieved 80% power while the responder analysis GST had a power of only 55%. The sum of the individual responder analyses tested as a continuous outcome had a power of 67%. When the responder definition on the responder analysis GST was poorly defined for the population, such as a cutoff of 0 in the given scenarios, the power decreased to 34%. In the scenario including 180 completers per arm, the single outcomes were each powered at 81% while the responder analysis showed approximately 58% power. The responder analysis GST also had 80% power, while the continuous GST had a power of 96% and the combination responder analyses tested as a continuous summed statistic had a power of 88%. **Conclusions:** Continuous outcome analyses are generally more powerful than binary outcome analyses like responder analyses. When there is consistency across the outcomes, as would occur with a disease-modifying treatment, GSTs are generally more powerful than individual outcomes. The responder analysis is highly dependent on the cutoffs chosen to define a responder and the standard continuous GST shows much higher power than even the most powerful responder analysis GST with optimized cut offs. Responder analysis results may be more interpretable for clinicians and patients than a mean score on an outcome, but should be used as a follow up analysis, not as the primary or secondary analysis for determining whether a treatment works. Because so many Alzheimer's disease clinical trials have failed, choosing the most powerful analysis for statistical decision-making is an important consideration in the design and analysis of clinical trials.

Keywords: Global statistical test, responder analysis, simulation, power, sample size, treatment effect, disease modifying.

Disclosures: All authors are employees of Pentara Corporation, a statistical consulting firm specializing in neurodegenerative diseases that provides services to pharmaceutical companies and academic institutions. **References:** O'Brien PC. Procedures for Comparing Samples with Multiple Endpoints. Biometrics 1984; 40(4): 1079 – 1087.

Key takeaway message: A global statistical test (GST) is a powerful way to estimate a treatment effect across aspects of the disease. A continuous GST is more powerful than a responder analysis GST.

P040- FEASIBILITY OF PARTICIPANTS WITH SYMPTOMATIC ALZHEIMER'S DISEASE TO SELF-ADMINISTER REMTERNETUG SUBCUTANEOUSLY: RESULTS FROM THE TRAILRUNNER-ALZ 1 PHASE 3 TRIAL.

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Background: Relative to an infusion, subcutaneous (SC) administration can reduce drug delivery-related healthcare costs and resources and is largely preferred by both patients and healthcare professionals (HCP) (1). SC administration may be performed by the patient, care partner, or HCP in an office or home setting offering potential flexibility, lower burden and improved access. It is unclear, however, whether patients with Alzheimer's disease (AD) can feasibly self-administer SC medications or would be dependent on care partners or HCPs. SC self-administration of AD participants is being permitted in two ongoing Phase 3 trials investigating remternetug, a monoclonal antibody directed at deposited amyloid plaques. In this analysis, we present data on the feasibility of SC self-administration in TRAILRUNNER-1-ALZ 1, which enrolled participants with mild cognitive impairment (MCI) due to AD and mild AD corresponding to AD Stages 3 and 4 (2-4). These analyses are informative for the recently initiated TRAILRUNNER-ALZ 3, which is enrolling participants with preclinical AD and MCI due to AD corresponding to AD Stages 1 through 3. **Methods:** TRAILRUNNER-ALZ 1 is a multicenter, randomized, double-blind Phase 3 study investigating remternetug versus placebo in participants with AD. Eligible

participants had a history of decline in cognitive function ≥6 months prior to screening, a Mini-Mental State Examination (MMSE) score of 20 to 28, an amyloid positron emission tomography scan result consistent with amyloid pathology, and a reliable study partner. The stable use of symptomatic treatments (memantine/acetylcholinesterase inhibitors) for at least 30 days prior to randomization was allowed. Participants received SC remternetug or placebo (3:1) over 52 weeks. Site personnel trained participants and their study partners on administering SC injections into the abdomen, thigh, and/or upper arm with at least the first 3 injections performed at the investigative site. Subsequently, participants could opt to inject off-site, such as their home, or return to the site for future injections. The study partner had to provide oversight for administration of at- home SC injections and be willing and able to administer the injections if the participant was unwilling or unable. For off-site dosing, information on timing of administration, who administered the injection, and anatomic location of the injection were collected with a participant diary. **Results:** In TRAILRUNNER-ALZ 1, the mean age of participants was 74 years, 53% of participants were female, 91% were White, and 16% were Hispanic or Latino. At baseline, 41% of participants were taking symptomatic AD treatments, 31% had MMSE scores > 27, mean (SD) MMSE score was 25 (2.6), and mean (SD) amyloid centiloids was 91(35.7). After the protocol-mandated on-site dosing, 28% of subsequent doses were administered by participants, 29% by study partners, and 37% by an HCP. Approximately 30% (n=60) of participants self-administered at least one injection. Relative to participants who never self-administered an injection (n=137), participants who self-administered at least one injection were less likely to be taking symptomatic AD treatments at baseline (32% vs 45%) and had higher MMSE scores (47% vs 24% of participants had MMSE>27). Of the participants who identified as Hispanic or Latino (n=31), 1 participant self-administered. No meaningful differences were identified in other baseline characteristics including age, sex, or amyloid burden. **Conclusions:** In TRAILRUNNER-ALZ 1, the feasibility of SC self-administration in participants with MCI and mild AD was investigated. Over half of all off-site SC doses were administered either by the participant or their study partner. Participants with less cognitive impairment, based on MMSE scores and symptomatic AD treatment use, were associated with greater likelihood to self-administer. This supports the ability of participants with earlier stages of AD, currently enrolled in the ongoing Phase 3 trial TRAILRUNNER-ALZ 3 (AD stages 1-3 with MMSE≥27), to self-administer SC remternetug.

Keywords: Remternetug, subcutaneous, phase 3, patient reported outcomes.

Clinical Trial Registry: NCT05463731; https://clinicaltrials.gov.

Disclosures: All authors are employees and shareholders of Eli Lilly and Company.

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Key takeaway message: The feasibility of subcutaneous self-administration in participants with mild cognitive impairment and mild Alzheimer's disease was investigated in a Phase 3 trial. Over a quarter of participants self-administered, particularly amongst those with less cognitive impairment.

P041- BREAKING DOWN THE INFLUENCES OF PLACEBO PROGRESSION AND PERCENT SLOWING IN THE CONTEXT OF TIME SAVED IN ALZHEIMER'S DISEASE CLINICAL TRIALS FOR POPULATIONS IN DIFFERENT DISEASE STAGES.

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1. Pentara Corporation - Millcreek (United States)

Background: Clinical trials aim to address three critical questions in terms of efficacy: the statistical significance of a treatment effect, the magnitude of that effect, and whether that effect is clinically meaningful. Symptomatic treatment effects can be assessed with actual point changes, or standardized changes (Cohen's D) on clinical scales. Directly comparing point differences on a scale across disease stages, and especially comparing to clinically meaningful thresholds implies that disease stages are comparable. However, in the context of progressive diseases like Alzheimer's Disease (AD), using the amount of time saved in a patient's progression provides a much more interpretable and meaningful result across all stages of the disease. This metric assesses the rate of disease progression observed in the placebo arm and the extent to which treatment slows that progression. **Method:** We extracted placebo progression data from early, mild, and moderate AD studies for ADAS-Cog scores up to 18 months. Theoretical percent slowing effects were applied to the observed progression rates. This allowed us to evaluate the amount of time saved within each population for similar disease slowing, highlighting how the magnitude of these effects varies depending on disease stage. **Results:** Using time saved provides a much more interpretable and consistent framework across different levels of disease. Despite seeing much larger raw point differences (170% larger) when comparing the moderate AD to the early AD population, the time saved proves to be much more similar when using an equal percent slowing across all three populations. At 12 months, with a 30% slowing, we observe an estimated time savings of 3.7 months in the early AD population and 4.4 months in the moderate AD population. **Conclusions:** Observed treatment effects must always be interpreted in the context of the specific population in which they are measured or they may be misinterpreted. Using the rate of placebo progression and the amount of time saved to standardize a treatment effect allows evaluation of disease slowing effects in early disease. Clinical meaningfulness needs to be assessed based on time savings instead of using points on a clinical scale in order to fairly value disease slowing effects. Without this change of perspective, we are likely to undervalue disease-modifying treatment effects that may significantly improve the lives of patients in an early stage by maintaining their functionality and life quality for a longer period of time, and overvalue symptomatic effects that are often observed in later stages.

Keywords: Time saved, placebo progression, clinical meaningfulness.

Disclosures: All authors are employees of Pentara Corporation.

References: Hendrix, Suzanne B., et al. «Time saved in disease progression for treatments in AD (including 3 monoclonal antibodies and 2 other promising treatments).» Alzheimer's & Dementia 19 (2023): e083240. Dickson, Samuel P., et al. «"Time Saved" Calculations to Improve Decision-Making in Proof-of-Concept Studies as Illustrated with a Post-hoc Analysis of IMM-AD04 Phase 2 Data in Patients with Early Alzheimer's Disease.» (2023).

Key takeaway message: By using time saved as a measurement of clinical meaningfulness in progressive diseases such as Alzheimer's Disease, studies can provide a much more interpretable and meaningful result across all stages of the disease.

P042- THE EFFECT OF CORTICOSTEROID PRE-TREATMENT WITH MODIFIED TITRATION OF DONANEMAB ON AMYLOID REDUCTION AND SAFETY: TRAILBLAZER-ALZ 6 ADDENDUM DESIGN.

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1. Eli Lilly and Company - Indianapolis (United States), 2. Huashan Hospital - Shanghai (China), 3. The First Affiliated Hospital of University of Science and Technology of China - Hefei (China)

Background: Corticosteroid use has emerged as a supportive strategy in amyloid-targeting therapeutic paradigms, primarily due to its potential to mitigate treatment-emergent adverse events. The TRAILBLAZER-ALZ 6 addendum study is designed to evaluate the impact of corticosteroid

pretreatment on amyloid reduction and safety outcomes [including amyloid-related imaging abnormalities (ARIA) and infusion-related reactions (IRR)]. **Methods:** Approximately 300 adults with early symptomatic AD and confirmed amyloid pathology will be randomly assigned to placebo or 10 mg dexamethasone in a 1:2 ratio. Participants will receive this double-blinded pretreatment before each of their first 6 donanemab monthly infusions. All donanemab infusions will be open label following the modified titration dosing regimen: a first dose of 350 mg, then 700 mg, 1050 mg, followed by 1400 mg every 4 weeks thereafter. The primary outcome, change in brain amyloid plaque deposition as measured by amyloid positron-emission tomography scan from baseline through Week 24, will be assessed using an analysis of covariance (ANCOVA) model with fixed factors of pretreatment, and covariates of baseline amyloid level and baseline age. To quantify the clinical significance of ARIA edema/effusions (ARIA-E) reduction, a Bayesian logistic regression model will compare frequencies at Week 24, incorporating pretreatment, Apolipoprotein E $\varepsilon 4$ status, and baseline amyloid levels as fixed effects. Safety profiles including IRR frequencies will be characterized. **Results:** The trial design will be presented. **Conclusions:** This study will advance understanding of the effect of corticosteroid pretreatment on donanemab-mediated amyloid reduction and ARIA-E.

Keywords: Corticosteroid, TRAILBLAZER-ALZ 6, donanemab, ARIA.

Disclosures: ESMN, HW, PA, RK, DS, SS, WX, PH, DB, EC, MM, and JS are employees and minor shareholders of Eli Lilly and Company. JY and JS have declared no competing interests.

Key takeaway message: The TRAILBLAZER-ALZ 6 addendum design will be presented.

P043- STUDY INSIGHT ANALYTICS (SIA) ALGORITHMS VALIDATION FOR SMART INDEPENDENT REVIEW OF THE ADAS-COG SCALE.

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Background: Although the ADAS-Cog is a commonly used primary endpoint in AD trials, its ability to identify subtle cognitive changes, particularly at early stages of the disease, is limited by ceiling effects and imprecision in measurements (1). The SIA methodology leverages algorithms that detect inconsistencies indicative of scale administration and/or scoring errors. The algorithms can also help identify potentially problematic assessments for a targeted, smart independent review, thereby reducing cost and improving data quality (2). The goal of this study was to validate the utility of SIA algorithms for ADAS-Cog scale by evaluating incidence rates and association with scoring errors. **Methods:** ADAS-Cog assessments aggregated from eleven double-blind, multinational trials of early symptomatic AD were analyzed. Algorithms indicative of scoring errors on the basis of clinical judgement were developed. These were then subjected to a validation procedure to determine both the rates flag trigger, and the degree to which each flag was associated with increased scoring errors. Algorithms that fire relatively infrequently (to minimize false positives), independently (indicating increased probability of scoring errors), and associated with increased error rates were identified. Generalized linear model was conducted to evaluate the association between number of flags triggered and scoring error rates. **Results:** Twelve flags emerged from the validation process to meet criteria of relatively low firing rate ($\leq$10%). The flags also showed increased rate of scoring errors when triggered than not, having relatively orthogonal relationships with each other. Consistent with this, there was a significant linear relationship between number of flags triggered and scoring error rate, such that as the number of flags triggered increased, the mean error rate was significantly elevated (estimate = 0.30, SE = 0.003; $p < 0.0001$). **Conclusions:** The present study demonstrated the utility of SIA algorithms in identifying potentially problematic assessments, as evidenced by the very strong association between flags triggered and error rates. This suggests that the algorithms can serve as a proxy for identifying assessments that are predictive of scoring errors; the assessments can then be submitted to a targeted and enhanced review/remediation to help reduce clinician burden and improve data quality.

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Key takeaway message: SIA algorithms can serve as a proxy for identifying assessments that are predictive of scoring errors; the assessments can then be submitted to a targeted and enhanced review/remediation to help reduce clinician burden and improve data quality.

P044- REACHED – A PILOT STUDY EXPLORING ELECTRONIC HEALTH RECORDS AND DIGITAL ASSESSMENTS TO IDENTIFY POTENTIAL PARTICIPANTS FROM UNDERSTUDIED POPULATIONS FOR CLINICAL STUDIES IN ALZHEIMER'S DISEASE.

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Background: Reaching people at different stages of Alzheimer's disease (AD) for clinical research poses many challenges, including the identification of participants representative of understudied populations. This historically has been difficult due to factors such as limited access to specialist care, logistical barriers, and issues that have impacted trust in clinical research (1-4). The FDA has provided recommendations to develop and implement strategies that facilitate the inclusion of representative participants into clinical trials (5). The primary objective of the REACHED study is to evaluate the feasibility and efficiency of novel participant identification methods for AD clinical trials, using Electronic Medical Record (EMR) real-world databases, remote consenting, and remote administration of simple cognitive tests. **Methods:** REACHED is an observational prospective study conducted from December 2024 to April 2025. A total of 60 individuals with early symptomatic AD (i.e. mild cognitive impairment (MCI) due to AD or mild AD dementia), including 50 from historically understudied populations, defined as individuals who are either non-White or of Hispanic ethnicity, were planned to be enrolled in the REACHED study along with an additional 10 non-Hispanic White individuals as reference group. The identification of eligible individuals was based on specific International Classification of Disease billing codes ICD-9 (331, 331.83, 331.2, 780.93 and 290) or ICD-10 (G30.1, G30.9, G30.8, G31.84, F03.90, R41.3) and meeting protocol-specified inclusion and exclusion criteria within the past year, as extracted from the EMR database. Participants had to be aged 50-90 years, capable of completing the remote eligibility questionnaire and giving informed consent (remote electronic consent), and needed access to a smartphone or tablet. Potential study participants meeting eligibility criteria were identified using artificial intelligence (AI) assisted search in a US real-world database, derived from patient EMR. Individuals whose treating physicians recommended the REACHED study for consideration were presented with a Health Insurance Portability and Accountability Act (HIPAA) release of information authorization (ROI). Participants who signed the ROI were invited by e-mail to proceed with a web-based eligibility questionnaire. The Principal Investigator reviewed the eligibility survey and medical records, and eligible participants received the informed consent form (eICF) electronically for remote review and electronic signature. Participants who signed the eICF were enrolled in the study. Study assessments

included the collection of demographics and social determinants of health (including year of birth, sex, primary language, years and highest level of education, employment status, self-reported race and ethnicity, living alone or with others, reliable transportation for medical appointments, meetings, things needed for daily living or work), a medical and medication history questionnaire, remote administration of two neurocognitive tests, followed by an exit survey. All data was collected remotely via the internet, App or telephone. The neurocognitive tests included a Speech Biomarker for Cognition administered by phone and a Self-Administered Smartphone-based List Learning and Memory Assessment. The protocol specified that the eligibility questionnaire and eICF were to be finalized within 2 weeks from the initial email contact with information about the study. Medical and medication history, demographic data and social determinants of health, digital cognitive tests and exit survey were to be completed within 2 weeks from the time the participant signed the eICF. The participant level study milestones included initial identification, completion of the eligibility questionnaire and eICF signature, completion of remote cognitive assessments, remote collection of demographics and Social Determinants of Health, and study completion (defined as time of completion of the exit questionnaire). **Results:** Based on AI assisted review of EMR, more than 900 people with early symptomatic AD were identified and recommended to their treating physicians for potential participation in REACHED. After further review, the physicians approved > 500 individuals, of which 151 signed HIPAA ROIs for research. A total of 115 potential participants completed the eligibility questionnaire, of which 47 screen-failed due to self-reported answers leading to exclusion. At this point, 61 participants (35 female, 26 male) signed the eICF and were enrolled. Participants had primary ICD10 codes for MCI (26), AD (16), other amnesia (15) or unspecified dementia (4) and the age range was 53 to 89 years. As specified by the protocol, 10 self-reported White participants were enrolled and the self-reported race/ethnicity status of the 51 participants from understudied populations were Black/African American (27), Hispanic/Latino (17), Asian (4), and Native American (3). A total of 49 participants completed all protocol-specified assessments. **Conclusions:** AI assisted review of a real-world electronic medical record database identified potential participants qualifying for research studies that otherwise may not have been within the reach of traditional research study sites. Pre-qualifying candidates through electronic medical records, along with remote assessments and outreach via their treating physicians, may enhance eligibility rates while significantly reducing site burden and screen failures. The identification of people with early symptomatic AD to support scientifically representative research and ensure generalizable safety and efficacy data for AD clinical research using electronic medical records, remote consent, and digital assessments is feasible and may be an efficient approach to improve access to clinical trials.

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Key takeaway message: Identification of people with early symptomatic Alzheimer's disease for scientifically representative research using AI assisted review of electronic medical records, remote consent, and digital assessments is feasible and may reduce site burden and screen failures.

P045- WEB-BASED PRESCREENING SURVEY FOR ALZHEIMER'S DISEASE CLINICAL TRIALS: ENHANCING EFFICIENCY AND DIVERSITY.

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Background: Prescreening for Alzheimer's disease (AD (1) clinical trials is an integral part of recruitment and retention and is essential for ensuring protocol adherence, subject safety, and resource efficiency (2). It enables early identification of exclusionary medical conditions and promotes equity in study enrollment. As the field increasingly adopts prescreening methods such as blood-based biomarkers and prioritizes diversity, sites must balance scientific rigor with operational practicality (3). Historically, our site's prescreening involved manual chart reviews following initial interest via a basic webform. This method, while thorough, was time-consuming and lacked systematic collection of sociodemographic data. Our goal was to develop a more efficient, informative, and cost-neutral prescreening process that would also enhance underrepresented group (URG) representation. **Methods:** We implemented an IRB-approved, web-based survey via REDCap, a secure data platform hosted by our university health system. The survey collects self-reported medical history, cognitive status, and sociodemographic data, referral source, and includes consent for EMR review. If selected by the respondent, certain medical conditions (e.g. cancer in the past 3 years) will result in prescreen failure (PSF), which ends the survey and prevents identifiable information from being collected. Access is provided through a QR-coded flyer distributed in clinic, at community events, and on our website. Completed surveys are imported into our clinical trial database (StudyTeam) twice weekly, and all respondents are contacted within 7 business days. Prior prescreening counts (May 2021–September 2024) were derived manually from email contacts initiated via a basic webform. Post-implementation data were compiled using Power Query and PowerBI. URG status is defined as either non-White and/or Hispanic. **Results:** From September 20, 2024 to May 20, 2024, 123 valid records were obtained after excluding eight erroneous, duplicate, or PSF entries. This represents an 83.3% increase in the rate of response compared to the 302 manual contacts over the previous three years. Among the 111 respondents who provided a referral source, 37 learned about the survey through a healthcare provider, 23 through other methods such as flyers and emails, 22 from the Byrd website, 16 from friends or family, 7 from social media, 4 from community events, and 1 each from newspaper/magazine and television. Twelve participants left the referral field blank. Over 26% (n=29) of respondents reported discovering the survey through community-facing channels, indicating strong outreach potential. Of the 123 respondents, 104 identified as White/Caucasian, of those 10 identified as ethnically Hispanic, 4 as Asian with 1 of those identifying as ethnically Hispanic, 4 as Black/African American with 1 of those identifying as also being racially White and another also identifying as mixed White and Other, 3 as Other which all identified as Hispanic, 3 preferred not to disclose race but identified as ethnically Hispanic, and 1 left the race question blank but identified as Hispanic. Regarding ethnicity, 18 identified as Spanish/Hispanic/Latino, 93 as not Hispanic, and 12 did not respond. Overall, 25 participants (20.3%) were from URGs. Cognitive status was reported across the disease spectrum. Of the 38 respondents interested in AD prevention without cognitive impairment, 11 were from URGs (1 indicated both Black/AA and White/Caucasian, 3 ethnically Hispanic White/Caucasian, 3 Asian with one ethnically Hispanic, 1 Black/African American, 2 Other/ethnically Hispanic, and 1 who preferred not to answer race but indicated Hispanic for ethnicity); 30 reported memory

concerns without a diagnosis, including 5 from URGs (1 Asian, 1 Black/African American and White/Caucasian, and 2 ethnically Hispanic White/Caucasian, and 1 who marked prefer not to answer for race but indicated Hispanic for ethnicity); 27 reported a diagnosis of Alzheimer's disease dementia, with 4 from URGs (3 ethnically Hispanic White/Caucasian and 1 Hispanic who preferred not to answer race); 21 reported mild cognitive impairment, with 4 from URGs (2 ethnically Hispanic White/Caucasian, 1 Black/African American, 1 Other/ ethnically Hispanic), and 7 reported dementia of unknown type, all of whom were White/Caucasian. In total, 24 of 123 respondents (19.5%) with known cognitive status were from URGs. **Conclusions:** The implementation of a web-based prescreening survey has significantly increased our contact volume, improved workflow efficiency, and added strategic value without incurring additional costs. Importantly, it has enabled more comprehensive collection of medical and sociodemographic data, which are critical for trial eligibility and equity tracking. This tool has also enhanced our ability to identify and engage participants from URGs, who are often underrepresented in AD research despite experiencing a disproportionate disease burden (Alzheimer's Association, 2025). Slightly over 20% of respondents were from URGs, and cognitive status analysis revealed engagement across the entire disease spectrum—from prevention to diagnosis. Notably, URGs comprised 28.0% of those interested in prevention, demonstrating reach into historically underrepresented populations. The robust representation of URGs in those interested in early intervention trials is an encouraging signal. Use of community-centric referral pathways such as social media, family networks, and local events has proven effective, underscoring the importance of diverse recruitment strategies. We conclude that this prescreening approach promotes efficiency, inclusivity, and alignment with current clinical trial priorities in AD. The project and data collection is ongoing and future directions include incorporating web-based cognitive assessments and expanding community outreach using this framework. **Keywords:** Alzheimer's disease, clinical trials, prescreening, underrepresented groups, REDCap, web-based survey, cognitive status, recruitment, StudyTeam, diversity in research.

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Key takeaway message: A web-based prescreening survey significantly improved recruitment efficiency, data quality, and diversity in Alzheimer's clinical trials, enabling broader outreach and better representation of underrepresented groups across the cognitive impairment spectrum.

P046- TRENDS ON PATIENTS' RECRUITMENT AND RETENTION IN ALZHEIMER'S DISEASE MODIFICATION TRIALS.

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Objective: To report rates and identify the most common causes of patients' screen failure (SF) and drop-out (DO) in Disease Modification Therapy (DMT) trials in Alzheimer's Disease (AD) over the last 10 years. **Background:** Numerous AD trials face delays due to high screening SF and DO. Identifying common causes of SF and DO would significantly optimize future trial designs. **Methods:** Data on Phase 1, 2 and 3 Industry-sponsored, interventional AD DMT trials completed within the last decade were identified and extracted from published literature, supplementary materials, protocols, abstracts and CT.gov. Trials lacking sufficient data were omitted from analysis. **Results:** 31 eligible AD DMT trials were analyzed. Most trials were in early-stage AD (83%). Average trial duration was 76 weeks. Mean screen failure rate (SFR) was 55% (median 63%). Mean dropout rate (DOR) was 24% (median 27%). Most common SF cause was failure to meet eligibility criteria related to evidence of amyloid pathology based on Positron Emission Tomography (PET) scan or Cerebrospinal Fluid (CSF) analysis and Mini-Mental State Examination (MMSE) score being outside the predefined range. Most common DO reasons were consent withdrawal by patient or care partner and adverse events, mostly amyloid related imaging abnormalities (ARIA). **Conclusions:** SFR in AD DMT trials is high, primarily influenced by failure to meet eligibility criteria. High SF might lead to recruitment delays. Mitigation strategies to reduce SF might include pre-screening, eligibility criteria optimisation, hierarchical screening approach and site selection and training optimization. DOR are mainly driven by patient or care partner consent withdrawal. Enhancing patient education on trials and investigational agents through consistent investigator-patient communication will help boost patient confidence on trial participation. Strategies to enhance subject retention should also prioritize reducing patient and care partner burden, by optimising the schedule of assessments through decentralisation.

Keywords: Alzheimer's disease, clinical trials, screening failure, drop out. **Disclosures:** authors are Parexel employees and have nothing to disclose.

CLINICAL TRIALS: RESULTS

P047- TRANSCRANIAL VIBROACOUSTIC STIMULATION ENHANCES COGNITIVE FUNCTION AND NEURAL PLASTICITY IN OLDER ADULTS: A DOUBLE-BLIND RANDOMIZED TRIAL.

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Background: Cognitive impairments in older adults remain a significant public health concern. While non-invasive neuromodulation methods like transcranial direct-current stimulation (tDCS) and transcranial magnetic stimulation (TMS) show some promise, limitations in precision, depth of stimulation, and durability of effects persist, necessitating use under expert guidance and in clinical settings due to potential hazards. Transcranial vibroacoustic stimulation (tVAS) is a novel modality leveraging low-frequency mechanical vibration to stimulate neural circuits through mechanotransduction. This study evaluated the cognitive, affective, and neurophysiological effects of 20 Hz and 40 Hz tVAS in healthy older adults. **Methods:** In this double-blind, randomized, comparative trial, 30 cognitively healthy participants aged 55–85 were assigned to receive either 20 Hz or 40 Hz tVAS (n=15 per each group) using a head-worn device targeting the frontal and temporal lobes. Participants self-administered 15 minutes of tVAS twice daily, 5 days per week, for 8 weeks. Primary outcomes included cognitive performance via CERAD-K, executive function via TMT-B&W, and depressive symptoms via CES-D. Salivary cortisol was measured for stress levels. Resting-state EEG and auditory event-related potentials (ERP; N100 and P200) were analyzed pre- and post-intervention, focusing on changes in Peak Power and the Individual Alpha Peak Frequency (IAPF). **Results:** Primary Cognitive Outcomes (CERAD-K). Within-group: Both 20 Hz and 40 Hz showed significant improvements in TS I and TS II versus baseline ($p<0.05$). Between-group: Attention favored 40 Hz at week 8 ($p=0.015$). Memory and language improved within the 20 Hz group; baseline imbalances likely contributed. Executive Function (TMT-B&W). No significant pre/post change in Part A or Part B for either frequency. Mood & Stress Biomarkers. CES-D: 40 Hz showed a significant reduction from baseline ($p=0.045$); 20 Hz showed a non-significant trend. Salivary cortisol: No significant change in either group (baseline in normal range). Resting-State EEG (Neural Oscillations). 40 Hz: Significant increases in absolute power across delta, theta, alpha, beta, gamma (all $p<0.01$), with the largest gains in beta/gamma; peak power increased ($p<0.01$); IAPF unchanged. Relative alpha decreased ($p<0.05$), consistent with proportionally larger rises in other bands. 20 Hz: No significant absolute/relative power changes. Between-group (difference-of-differences): Gamma showed the strongest group effect, followed by beta and alpha (all $p<0.05$), indicating successful gamma entrainment at 40 Hz. Auditory ERP (Early Sensory Processing & Attention). 40 Hz (within-group): N100 amplitude increased (more negative) for all- and low-frequency stimuli ($p<0.05$); P200 amplitude increased across all frequency bands (all $p<0.01$). Latencies unchanged. 20 Hz: No robust amplitude effects; isolated N100 latency change to high-frequency stimuli only. Between-group: P200 amplitude difference favored 40 Hz for high-frequency stimuli ($p<0.05$), suggesting enhanced sensitivity/attentional allocation to higher-frequency auditory input. Safety, Tolerability, and Adherence. Adverse events: 4/30 (13.3%) mild events (intermittent headache, dizziness, transient temple discomfort); no serious events or discontinuations. Adherence: Supported by use logs and contact checks; devices indistinguishable across arms. Frequency-Specificity & Mechanistic Signal. 40 Hz, but not 20 Hz, yielded convergent effects across behavioral (attention, mood) and physiological markers (gamma/beta power increases; larger N100/P200), consistent with gamma-range entrainment, network synchronization, and enhanced early sensory processing/attentional gating. **Conclusions:** tVAS at 40 Hz significantly improved cognitive performance, enhanced EEG gamma activity, and increased sensory ERP responsiveness in older adults. These findings suggest that 40 Hz tVAS induces gamma entrainment, enhances neural plasticity, and modulates attentional and sensory processing circuits. Compared to other non-invasive approaches, tVAS offers practical advantages for home and clinical use, including user comfort, safety and compliance. Larger studies are warranted to confirm efficacy and explore applications in neurodegenerative and affective disorders.

Keywords: Transcranial vibroacoustic stimulation, cognitive aging, gamma entrainment, EEG.

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Key takeaway message: Forty-hertz tVAS improved cognitive function, reduced depressive symptoms, and induced gamma-band entrainment with stronger N100/P200 responses, supporting frequency-specific neural plasticity and a practical, well-tolerated non-invasive approach for cognitive aging.

P049- STABILITY AND IMPROVEMENT IN EARLY ALZHEIMER'S DISEASE WITH LECANEMAB: SUB-ANALYSIS FROM A UNITED STATES MULTICENTER, RETROSPECTIVE REAL-WORLD STUDY.

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Background: Lecanemab is indicated for the treatment of patients with Alzheimer's disease (AD) in the mild cognitive impairment (MCI) or mild dementia stage. The efficacy and safety of lecanemab were demonstrated in a Phase 3 randomized controlled trial (1); however, real-world data are needed to understand clinical outcomes beyond controlled settings. We conducted a retrospective, multicenter, observational study to evaluate real world utilization of lecanemab, practice patterns, and clinical outcomes in the US. This abstract reports a sub-analysis of baseline characteristics and clinical outcomes of patients with early AD treated with lecanemab, characterized by those who were improved, stable, or progressed from baseline to chart abstraction. **Methods:** This retrospective, multicenter, observational study was conducted at 15 geographically diverse neurology clinics in the US. Each site contributed deidentified medical chart data via case report forms for up to 25 patients treated with lecanemab ($\geq$7 infusions). This interim sub-analysis includes data from 9 sites collected through July 1, 2025; site enrolment is ongoing. Baseline demographics, clinical characteristics, and lecanemab exposure, were extracted from patient charts. We descriptively analyzed patient characteristics and treatment outcomes with lecanemab as determined by change from baseline in disease stage to time of chart abstraction. Disease stage (improved, stable, progressed) was determined by clinician judgment based on chart review. Available cognitive (Montreal Cognitive Assessment [MoCA]) and functional (functional activities questionnaire [FAQ]) scores from chart data were provided by sites. MoCA and FAQ scores were then analyzed within these groups to explore potential correlations with cognitive and functional outcomes. The use of cognitive and functional assessments varied by site; therefore, MoCA and FAQ scores are reported for the subgroup of patients with both baseline and follow-up data. Descriptive statistics were used to summarize sociodemographic, clinical, and safety

variables. For all results, mean and standard deviation are reported unless otherwise stated. **Results:** A total of 178 patients were included in this sub-analysis; 57.6% had MCI due to AD and 42.4% mild AD dementia at baseline. The mean age was 74.2±6.6 years; 55.5% were female; 90.4% Caucasian; 14.5%Hispanic/Latinx. APOE ε4 status was 32.5% non-carriers, 49.4% heterozygous, and 18.1% homozygous. The mean lecanemab treatment duration was 375.4±182.8 days, and mean ±SD number of doses was 24.8±11.5. At last available follow-up, 6.7% of patients improved (n=12), 76.9% remained stable (n=137), and 15.7% progressed (n=28). Patients who improved had a longer mean duration of treatment (411.7±174.0 days, n=11) and received a higher mean number of doses (27.6±11.6, n=12) compared to those who were stable (369.3±183.4 days, n=135; 24.6±11.6 doses, n=137) or progressed (390.9±187.2 days, n=28; 24.6±11.4 doses, n=28). The improved group also had fewer comorbidities (2.3±1.4, n=12) and concomitant medications (2.3±1.8, n=12) than the stable (4.0±2.7, n=130; 4.2±3.6), or progressed groups (3.3±2.3, n=24; 3.2±2.1). No differences in sociodemographic or clinical characteristics were detected between groups. APOE ε4 status and amyloid-related imaging abnormalities (ARIA) were not associated with outcomes. Among the subgroup with cognitive and functional data, the overall mean MoCA cognitive score was 21.8±2.9 at baseline and 20.9±4.7 at last available follow-up (n=36); the overall mean FAQ score was 3.7±4.2 at baseline and 5.9±5.7 at last available follow-up (n=38). For cognitive status, patients in the improved group had a mean baseline MoCA score of 22.5 ±4.9, which increased to 23.5±2.1 at last follow-up (n=2). The stable group started with a mean baseline MoCA score of 21.8±3.0, and had a score of 21.2±4.7 at last follow-up (n=30), while the progressed group had a baseline score of 21.5±1.7 that declined to 17.5±5.1 at last follow-up (n=4). For functional status, patients in the improved group had a mean baseline FAQ score of 2.3±0.6 (n=3), which remained unchanged at last follow-up (2.3±0.6; mean change 0.0). In the stable group, baseline FAQ score was 3.6±4.6 (n=29) and increased to 6.1±5.7 at last follow-up (mean change +2.5). In the progressed group, baseline FAQ score was 5.0±3.2 (n=6) and increased to 7.0±1.1 at last follow-up (mean change +2.0). Patients that progressed had a higher mean FAQ score at baseline suggesting greater difficulty in activities of daily living than the stable and improved groups. Amyloid-related imaging abnormalities (ARIA; all) occurred in 23 patients. APOE ε4 status and ARIA among responder groups was not associated with clinical outcomes; of the 12 patients that improved on lecanemab two were APOE ε4 homozygous and four were heterozygous. Real-world evidence studies can provide valuable insights, but do have several limitations, including potential bias and lack of control group. **Conclusions:** Lecanemab has been shown to slow the progression of AD in a clinical trial1, and in this real-world study, ~84% of patients remained stable or improved after a mean of 375 days of treatment. Among 178 patients treated with lecanemab, 6.7% improved, 77.0% remained stable, and 15.7% progressed. Patients who improved had longer treatment duration, received more doses, and had lower baseline functional impairment compared to those who were stable or progressed (small sample size). These findings support the potential of lecanemab to help patients remain in the earlier stages of AD for longer.

Keywords: Real-world evidence, retrospective case series.

References: 1. van Dyck CH, et al. N Engl J Med. 2023;388(1):9–21.

Disclosures: C.S. has participated in advisory panels for Eisai, Eli Lilly, and C2N Diagnostics, and serves on the FDA PCNS Advisory Committee. C.S. has given talks for Eisai, Eli Lilly, Pfizer, and C2N Diagnostics, and received trial support from Eisai, Eli Lilly, Novartis, Roche, and Genentech. D.W. has served on advisory panels for Biogen, Eisai, Novartis, Lantheus, and the American Stroke Association, and is a member of the FDA PCNS Advisory Committee. D.W. has spoken for Eisai and Lilly, and received trial support from Eisai, Cognition, Acumen, Alnylam, Cereval, Sage, Acadia, the Alzheimer's Association, Lilly, Novartis, Ventus, Sanofi, Roche, and Serono. M.S. has provided advisory services to Anavex, Eisai, Signant, J&J, Neurotherapia, GSK, Cognito, Alshon, Athira, Novo Nordisk, AbbVie, and Fujirebio. M.S. is part of the speaker's bureau for Eisai and Lilly and serves on the Board of Directors for Cervomed. M.R. has received honoraria from Eisai, Johnson & Johnson, Eli Lilly, and CME Outfitters. J.S-L. has acted as a consultant or advisory panel member for Arrowhead Pharmaceuticals, Biogen, Eisai Inc., Merck, and Genentech. J.S.-L. has received grant and research support from the Alzheimer's Association, Aribio, Biogen, Eli Lilly, Karuna/BMS, NIH-NIA, Novartis, and Annovis Bio, and has participated in speaker bureaus or received non-CME honoraria from Biogen, Eisai Inc., Eli Lilly, and the Global Learning Collaborative. G.C.'s institution receives research funding from Lilly, Eisai, Novartis, and the Davos Alzheimer's Collaborative. G.C. serves on advisory panels for Eisai and Lilly and has recently been appointed to the HHS NAPA ASPE committee. S.G. serves on advisory panels for Eisai and Lilly, has been appointed to the HHS NAPA ASPE committee, and also holds an appointment to the Florida ADAC. C.L. has spoken for Eisai Inc., served as a consultant or advisory board member for Biogen, Eisai Inc., Eli Lilly, and Neurogen Biomarking, and received non-CME speaker bureau honoraria from Eisai Inc. and Eli Lilly. P.E.S. has participated in clinical trials sponsored by Acadia, Alnylam, Alzheon, the American College of Radiology, Eisai, Eli Lilly, Novo Nordisk, Passage Bio, and UCB Biopharma, as well as single-site trials with the Weston Brain Institute, MD Anderson Cancer Center Foundation, and the Fronto Temporal Lobar Disease Association. P.E.S. has received research support from the NIH through 15 grants related to AD/ADRD, served on Data Safety Monitoring Committees for stem cell trials in psychiatric disorders (Chair) and Vigil Neurosciences (pending), and sits on the Board of Directors for The Alzheimer's Association of Houston and The FTLDA of San Antonio. P.E.S. has also spoken for Acadia, Eisai, and Lilly. C.C. has no relevant disclosures to report. B.A. conducts clinical trials as a principal investigator in Alzheimer's disease for Eisai, Eli Lilly, Bristol Myers Squibb, Cassava, and Novo Nordisk. F. F., C.A., and D.R.J. are employees of Eisai Inc., US.

Key takeaway message: In this retrospective real-world sub-analysis of 178 cases of patients on lecanemab, most patients (>75%) remained stable or improved. Patients who improved received a higher mean number of doses and were on treatment for longer.

P050- A PHASE 1B STUDY OF THE SAFETY AND TOLERABILITY OF ALX-001 (BMS-984923) IN ALZHEIMER'S DISEASE WITH A PILOT STUDY OF SYNAPTIC IMAGING.

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Background: Brain synapse loss in Alzheimer's disease (AD) is strongly linked with cognitive symptoms, and developing drugs that preserve or restore synapses is an important therapeutic goal. Because synaptic toxicity involves soluble Aβ oligomers (Aβo) binding to the cellular prion protein (PRPc) and metabotropic glutamate receptor subtype 5 (mGluR5) receptor complex, mGluR5 is a potential target to interrupt AD related synaptic toxicity. We have identified a highly potent and orally bioavailable mGluR5 silent allosteric modulator (SAM), ALX-001 (formerly BMS-984923), that does not alter basal or glutamate activity while blocking Aβo/PrPC activation of mGluR5. In studies using multiple preclinical mouse AD models, treatment with ALX-001 recovers synapse density, restores long term potentiation and returns memory performance to wild-type levels. ALX-001 was advanced to early-phase human studies and was tolerated in a single ascending dose study that included 36 older adults with healthy cognition. A positron emission tomography (PET) receptor occupancy study indicated that 80% receptor occupancy of brain mGluR5 is achieved at plasma drug concentrations of 136 ng/mL (IC80). With these results, ALX-001 was advanced to a two-stage Phase 1b study with Stage 1 consisting of a multiple ascending placebo-controlled trial in older adults with healthy cognition

where oral doses ranged from 50 to 150 mg twice daily. Treatment was well tolerated, steady state was reached at about 14 days of treatment, and all doses achieved average steady state plasma drug concentrations above the IC80 with an adequate safety margin. We now report the results of the Phase 1b double-blind, placebo-controlled, parallel design study in participants with early-stage clinical AD. **Methods:** Eighteen participants between the ages of 60 to 82 years old with mild cognitive impairment or mild dementia due to AD were enrolled in a double-blind, placebo-controlled study and randomized to receive ALX-001 (50 mg, 100 mg) or placebo orally, twice daily in a 1:1:1 ratio for 28 days. Participants were monitored with weekly clinical safety assessments, laboratory testing, and plasma collection for pharmacokinetic analysis. The primary outcomes were safety and tolerability as assessed by treatment emergent adverse events (TEAE). Secondary outcomes included changes in brain synaptic density measured with [18F] SynVesT-1 PET, brain gray matter volume changes measured with magnetic resonance imaging (MRI) and cognitive changes assessed with ADAS-Cog14. Chi-squared tests were used to determine if TEAE differed between treatment groups. To assess the effect of treatment on synaptic PET (DVR), volumetric MRI, and cognition (ADAS-Cog14), separate general linear models were fit for each outcome with treatment group as the predictor, change in each measure from baseline to 28 days as the outcome, and the baseline value of each measure as a covariate. Statistical outcomes were considered significant if $P < 0.05$. **Results:** Twenty-one participants were screened and eighteen (6 female, 12 male, average age = 74 years) were randomized to ALX-001 50 mg, ALX-001 100 mg, or placebo twice daily (six per treatment group). Sixteen participants identified as White and non-Hispanic, one as White and Hispanic, and one as Asian. Nine total participants (50%) experienced a TEAE of which all were either mild or moderate in severity. The proportion of participants who experienced at least one TEAE was not significantly different between treatment groups (placebo - 16.7%, 50 mg - 50%, 100 mg - 83.3%, $\chi 2 = 5.3$, $P = 0.07$). All TEAEs were mild or moderate in severity and there were no serious adverse events. All adverse events were resolved by the end of study participation. Plasma drug concentration indicated that steady state was achieved by day 15 and the average trough plasma concentration of ALX-001 was above the IC80 in both the 50 mg and 100 mg twice daily dose group. Drug concentrations were undetectable 7 days after completion of dosing. Pharmacokinetic analysis indicated similar plasma exposure when compared to the previous multiple ascending dose study in cognitively healthy older adults. For the combined treatment groups compared to placebo, there were no significant differences in change from baseline to day 28 for synaptic density ($\beta = -0.046$, $P = 0.32$), brain gray matter volume ($\beta = 0.227$, $P = 0.93$), or ADAS-Cog14 ($\beta = -1.87$, $P = 0.33$). **Conclusions:** ALX-001 (BMS-984923) is safe and tolerable when dosing up to 28 days in participants with AD. Plasma concentrations were high enough to achieve significant target engagement with a robust safety margin. These results support continued development of ALX-001 for the treatment of AD and advancement to Phase 2 clinical trials.

Keywords: ALX-001, BMS-984923, mGluR5, [18F]SynVest-1.
Clinical Trial Registry: NCT05804383, https://clinicaltrials.gov.
Disclosures: TRS, PS, SMS and Yale University have financial interest in Allyx Therapeutics, a company developing ALX-001 for commercial use. Other authors do not have any conflicts of interest related to this study.
Key takeaway message: ALX-001(BMS-984923), a silent allosteric modulator of mGluR5, is safe and tolerable at doses achieving significant target engagement. Results of early-phase human studies support continued development for the treatment of Alzheimer's disease.

P051- POLARIS-AD: RECORD-BREAKING GLOBAL ENROLLMENT IN THE LARGEST PHASE 3 TRIAL OF AN ORAL MULTI-MECHANISTIC PDE5 INHIBITOR FOR EARLY AD USING BIOMARKER-AGNOSTIC MODALITIES FOR AMYLOID CONFIRMATION.

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Background: AR1001, a novel oral phosphodiesterase-5 (PDE5) inhibitor with multi-mechanistic effects (neuroprotection, tau phosphorylation reduction, anti-inflammatory effects, and improved cerebral perfusion), has shown promising preclinical results and early clinical signals at the 30 mg dose in mild-to-moderate Alzheimer's disease (AD) (1,2). Building on these findings previously presented at CTAD, this pivotal global Phase 3 registration study, POLARIS-AD, was launched in December 2022 to evaluate efficacy and safety of AR1001 in participants with mild cognitive impairment (MCI) or mild dementia due to AD. **Methods:** Polaris-AD is a global, multicenter, double-blind, placebo-controlled, 52-week treatment, parallel group trial with a 52-week extension phase in people with early AD. Eligible individuals were 55–90 years old with MCI or mild dementia due to AD, defined by stage 3 to 4 according to the National Institute on Aging and Alzheimer's Association (NIA-AA) 2018 criteria.3 Amyloid positivity, agnostic to biomarker modality, was confirmed via either visual and quantitative positron emission tomography (PET), with a centiloid value >30 CL14, where available, or cerebrospinal fluid (CSF) assays including the FDA cleared Lumipulse® G b-amyloid (1-42/1-40) ratio and Roche Elecsys® assay ratios of t-tau/b-amyloid (1-42) and p-tau181/b-amyloid (1-42). Participants were required to have cognitive and memory decline within 5 years, MMSE > 20, CDR global rating 0.5 or 1 and RBANS ≤ 85. The primary endpoint is change on the CDR-SB, and secondary endpoints are change on the ADAS-Cog13, A-IADL-Q-SV, GDS-15 and MMSE all from Baseline to Week 52. Safety is assessed by physical examination, laboratory assessments, and adverse events (AE), including incidents of unwanted sexual behavior (USB) reported by both the participant and caregiver. Enrollment took place from Dec. 2022 through June 2025. **Results:** A total of 4,025 participants were screened, and 1,535 (62%) were successfully enrolled across five global regions: North America (n=658), Republic of South Korea (n=200), United Kingdom (n=49), European Union (n=502), and China (n=126). The enrolled population was 55% female, with a mean age of 73 years. Racial composition was 72.3% White (including 11.7% Hispanic or Latino), 22% Asian, and 2.7% Black or African American. APOE-ε4 carriage was common, with 937 (65.9%) participants carrying at least one ε4 allele: ε3/ε4 652 (45.9%), and ε4/ε4 252 (17.7%) and ε2/ε4 33 (2.3%). Most participants were classified as NIA-AA Stage 3 (76.4%), with the remainder Stage 4 (22.8%). Baseline cognitive and functional scores were as follows (mean ± SD): Primary endpoint: CDR-SB 3.45 ± 1.70. Secondary endpoints: ADAS-Cog13 27.75 ± 8.02, A-IADL 72 ± 20.72, GDS 1.6 ± 1.81 and MMSE 24.01 ± 2.70. Biomarker confirmation was modality-agnostic as presented: CSF-based enrollment: 819 participants (53.6%), including 560 (36.5%) with Lumipulse® G β-amyloid (1-42/1-40) ratios <0.058, 132 (8.6%) with ratios between 0.058 and 0.073, 55 (3.6%) using Roche Elecsys® assays, and 16 (1.0%) other CSF-based results and 56 (3.7%) "other," representing the largest CSF collection trial to date. PET-based enrollment: 571 participants (37.2%), including 315 (20.5%) with PET results and 256 (16.7%) with historic PET results. For participants with PET analysis 279 (18.2%) had quantitative reads mean CL 89.99 ± 30.87, 28 (1.8%) visual reads and 8 "other." Comparatively, baseline AD clinical disease severity was generally greater in POLARIS-AD than in

the ENGAGE (CDR-SB 2.41 ± 1.01; ADAS-Cog13 22.46 ± 6.48) and EMERGE (CDR-SB 2.48 ± 1.02; ADAS-Cog13 22.2 ± 6.85) trials, and comparable to Clarity AD (CDR-SB 3.2 ± 1.34) and TRAILBLAZER-ALZ 2 (CDR-SB 3.70 ± 2.1; ADAS-Cog13 27.7 ± 8.45). Safety: To date, 2412 adverse events (AEs) have been reported in 844 participants (55.0%), for an average of 1.57 events per participant. The most common AEs (>2%) were diarrhea (4.9%), urinary tract infection (4.9%), falls (4.8%), headache (3.8%), and dizziness (3.1%). The vast majority of events are mild to moderate and not related to the investigational product. No cases of ocular neuropathy have been reported, though 24 ocular AEs of other types occurred. Systematic queries for USB were conducted over 13,000 times across participants and caregivers, with only 31 (0.002%) events reported, including 16 by caretakers and 14 by participants. Retention has been excellent: 410 participants have completed the Week 52 treatment phase, with 95.1% (n=390) entering the extension phase. To date, 140 participants (9.1%) have discontinued from the study. **Conclusions:** POLARIS-AD achieved one of the largest global enrollments for an oral multi-mechanistic agent for a phase 3 trial in early AD. Its unique biomarker-agnostic approach broadened access, accelerated recruitment and contributed to the largest CSF sample bank. Baseline demographics and cognitive profiles align with other landmark trials, supporting generalizability. Safety data thus far show no new signals. Results from the double-blind phase are expected Q3 2026 and will provide crucial evidence for the potential of this innovative therapeutic strategy. Updated metrics will be reported at CTAD2025.

Key takeaway message: POLARIS-AD successfully recruited one of the largest and most diverse early AD cohorts using a medley of biomarker in this global Phase 3 trial, with strong representation across regions, AD robust biomarker confirmation of disease, and excellent retention—positioning the study to deliver conclusive and highly generalizable results.

P052- LONG-TERM BENEFIT OF LECANEMAB IN PATIENTS WITH LOW BASELINE AMYLOID: ESTIMATION OF TIME SAVED.

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Background: Monoclonal antibodies (mAbs) against amyloid-b have been shown to slow the rate of cognitive and functional decline in Alzheimer's disease (AD) clinical trials. The primary endpoint of the CLARITY-AD trial was the change in CDR-SB over 18 months in participants treated with lecanemab. Interpreting the slowing of decline based on mean changes on continuous outcome scales are particularly challenging in early stages of disease, when pathology is not yet abundant and progression rates in the absence of treatment are relatively slow in many patients. Therefore, clinical progression was further contextualized by using the open label extension (OLE) phase of CLARITY-AD to estimate the time saved with up to 48 months of treatment, providing a more intuitive and clinically meaningful metric for clinicians. This calculation can be performed using a Time Component Test (TCT). Although treatment benefit is believed to be more difficult to show in patients who are earlier in the disease course, this population may experience greater benefit when treated early. This additional benefit can be captured by focusing on a sub-group of participants in CLARITY-AD who were in the earliest stages of disease, represented by low levels of amyloid plaques at baseline. **Methods:** Data from the OLE of the CLARITY AD study was used to estimate the time savings with 36-48 months of treatment, and specifically to identify whether the treatment benefit continued to accumulate after brain amyloid plaque is expected to have been cleared. Both the full population (data available for up to 48 months of treatment) and the low amyloid sub-group (defined as <60 Centiloids at baseline; data available for up to 36 months of treatment in this group) were analyzed. Treated participants were compared to the placebo group during the first 18 months, and to a historical, matched external control population from ADNI and BioFinder1 during the OLE phase. A sub-group of participants from ADNI with <60 Centiloids at baseline was used for comparisons with the low-amyloid population of CLARITY-AD. **Results:** During the first 18 months, the placebo group and matched external populations declined similarly but lecanemab treatment led to 5.5 months of time saved over those 18 months, as evaluated by the CDR-SB. After 36 months of treatment, time savings increased to 7.3 months when compared to ADNI and 7.8 months compared to BioFinder1. After 48 months of treatment, time saved increased to 11.0 months compared to ADNI and 13.1 months compared to BioFinder1, demonstrating greater time-savings benefit over time. This data was similar to what was presented at AAIC 2025 and validates our model. In the low-amyloid sub-group compared to a historical, matched low-amyloid group from ADNI, time savings with lecanemab at 18 months was 12 months, and at 36 months this increased to 17.4 months of time saved. When the low-amyloid group was compared to the ADNI and BioFinder1 groups that were matched to the full population, the estimated time savings with lecanemab at 36 months was 20.6 months compared to ADNI and 21.2 months compared to BioFinder1. **Conclusions:** The CLARITY AD OLE study demonstrates that lecanemab's treatment benefit continues to meaningfully accumulate with ongoing therapy beyond the initial 18-month trial period. This finding shows that lecanemab's ability to slow disease progression with ongoing treatment persists even after amyloid plaques are expected to have been cleared, perhaps due to its action on protofibrils, which are highly toxic but not visible on amyloid PET. The greater time savings in the low-amyloid group compared to the full population over 36 months suggests that treating at an earlier disease stage with lecanemab leads to even greater treatment benefit, highlighting the importance of timely diagnosis and treatment initiation.

Keywords: Amyloid, Protofibrils, Time Savings, Lecanemab, Alzheimer's.

Disclosures: John Whetten, Suzanne Hendrix and Sam Dickson received consulting fees from Eisai Inc. Katherine Youmans-Kidder and Daryl Rhys Jones are employees of Eisai Inc.

Key takeaway message: Lecanemab's ability to slow disease progression with ongoing treatment persists even after amyloid plaques are expected to have been cleared, particularly when treatment begins in early stages of disease.

P053- PATIENT, CARE PARTNER, AND HEALTH CARE PROFESSIONAL ACCEPTABILITY OF THE AUTOINJECTOR FOR THE SUBCUTANEOUS DELIVERY OF LECANEMAB IN PATIENTS WITH EARLY ALZHEIMER'S DISEASE IN THE US.

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Background: Lecanemab is an amyloid-targeting monoclonal antibody indicated for the treatment of patients with Alzheimer's disease (AD) in the mild cognitive impairment (MCI) or mild AD dementia stage (early AD). Lecanemab is approved in 50 countries as an intravenous formulation requiring bi-weekly administration; and in the US, patients may transition to maintenance therapy at 18 months every 4 weeks intravenously or weekly subcutaneous dosing administered via autoinjector. The aim of maintenance dosing is to continue to clear toxic soluble amyloid beta (oligomers and protofibrils) that continues to be formed even after amyloid plaque clearance, and to sustain favorable responses of biomarkers of AD and neurodegeneration, and maintain clinical benefit while reducing burden to patients, care partners, and health care

systems. Weekly subcutaneous administration using autoinjectors can be administered by patients, care partners, or health care professionals (HCPs) in convenient settings. In human factors studies, the autoinjector can be used under the expected use environments for maintenance and initiation. The objective of this present study is to examine patient, care partner, and HCP opinion of the lecanemab autoinjector. **Methods:** This US study, conducted in 12 cities (across 11 states), was designed to evaluate the acceptability of the lecanemab autoinjector device across several validated domains. In-person interviews were completed with participants divided into 3 sample groups: patients diagnosed with MCI due to AD or mild AD dementia; care partners currently caring for patients diagnosed with MCI due to AD or mild AD dementia; and HCPs (eg, nurses) experienced with training patients and care partners to perform self-injections. During in-person sessions, participants were trained on appropriate use of the autoinjector and practiced on an injection pad and were then asked to answer computer-based surveys about their experience on several measures of acceptability and feasibility, including the Self-Injection Assessment Questionnaire (SIAQ), Acceptability of Intervention Measure, and Feasibility of Intervention Measure. The overall survey had 3 main areas of focus: ease of use; satisfaction; and confidence with the autoinjector device. **Results:** In the full analysis set, 151 participants completed the interviews (50 patients, 50 care partners, and 51 HCPs). Data are reported for all participants. Mean (SD) age of patients was 68.8 (9.7) years; mean age of care partners was 53.2 (10.6) years and mean age of HCPs was 48.4 (11.4) years. Most care partners and HCPs were female (78% and 86%, respectively), while sex was balanced in patients (52% female). Over half of patients and care partners were White (56% and 57%); 36% and 26% were Black; and 12% and 9% were Hispanic or Latinx, respectively; 40% of HCPs were White, 36% were Black, 13% were Asian, and 8% were Hispanic or Latinx. Of patients interviewed, 76% had MCI due to AD, 24% had mild AD. Over half (58%) of patients were currently receiving treatment for AD, and all (100%) were managing their own medications. Care partners were either a son or daughter (54%), other relative (26%), spouse (12%), friend or neighbor (4%), or homecare professional (4%). Most HCPs were registered nurses (65%); 27% were physician assistants and 8% were nurse practitioners. HCPs resided mostly in hospital/outpatient clinics (69%), with a mean (SD) of 21.8 (11.0) years in clinical practice. On the SIAQ, 88% of patients, 98% of care partners, and 94% of HCPs reported that it was “easy” or “very easy” to use the autoinjector, while 14% of patients found it “somewhat easy” and 4% of patients found it “somewhat difficult”. Moreover, 100% of care partners and HCPs found it “easy” or “very easy” to use the autoinjector without any help, and 82% of patients found it “very easy” or “easy”, with 8% finding it “somewhat easy”. 90% of patients, 98% of care partners, and 96% of HCPs reported that they were “satisfied” or “very satisfied” with the autoinjector. Finally, after this study, 90% of patients, 98% of care partners, and 100% of HCPs reported that they were “very” or “extremely” confident about using the autoinjector at home. **Conclusions:** Patients, care partners, and HCPs found the autoinjector easy to use, expressing high levels of satisfaction and confidence. The weekly subcutaneous administration of lecanemab via the autoinjector provides a patient-focused approach to lecanemab treatment.

Disclosures: LZ is a consultant for Eisai. RST reports grant support to Georgetown University from Cognition Therapeutics, Eisai, Janssen, Lilly, and BMS. He serves on the Speakers Bureau for Lilly and as a consultant to Re:Cognition Health. DRJ and CA are both employees of Eisai Inc., US.

Keywords: Alzheimer’s disease, mild cognitive impairment, patient care.

Key takeaway message: In this US study, participants (patients, care partners, and health care professionals) found the lecanemab autoinjector device easy to use, expressing high levels of satisfaction and confidence.

P054- EFFECTS OF ORAL VALILTRAMIPROSATE ON CLINICAL EFFICACY, SAFETY AND BRAIN VOLUME OUTCOMES IN APOE4/4 HOMOZYGOTES WITH EARLY AD: TOPLINE RESULTS OF APOLLOE4 RANDOMIZED, PLACEBO-CONTROLLED 78-WEEK MULTICENTER TRIAL.

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Background: Valiltramiprosate (ALZ-801) is an oral anti-amyloid agent in clinical development for Alzheimer’s disease (AD). Valiltramiprosate is a valine-conjugated prodrug of tramiprosate with improved pharmacokinetic profile and gastrointestinal tolerability compared to its active agent (tramiprosate). Valiltramiprosate prevents the misfolding and aggregation of amyloid-beta (Aβ) monomers into toxic oligomers, an early and central driver of Alzheimer’s disease pathology (Kocis, 2017; Hey 2018, Muramatsu, 2025). Tramiprosate had shown promising efficacy with favorable safety in ~1300 APOE4 carriers with AD, with no observed ARIA-E (Abushakra 2016, 2017). Apolipoprotein ε4 (APOE4) is a major risk factor for AD and is associated with early and accelerated deposition of amyloid and tau pathologies, accelerated hippocampal atrophy and faster clinical decline (Martins 2005, Abushakra 2020, Fortea 2024). Valiltramiprosate clinical efficacy, brain volume effects and safety were evaluated in a Phase 3 randomized, double-blind, placebo-controlled, 78-week trial in APOE4/4 homozygotes with Early AD. **Methods:** This 78-week double-blind, placebo-controlled, two-arm trial was conducted at 77 sites in North America and EU countries (NCT# 04770220). The trial randomized APOE4/4 homozygotes with Early AD (MMSE 22-30) in 1:1 ratio to valiltramiprosate 265mg BID or matched placebo. The trial was stratified by disease stage, MCI (MMSE 27-30) or Mild AD (MMSE 22-26). Subjects with any number of microhemorrhages and up to 3 siderosis lesions were allowed. The primary outcome was ADAS-Cog13 (primary), with the CDR-SB (key secondary) and the DAD (disability assessment for dementia) as secondary outcome. The primary efficacy analysis was the LS means of drug-placebo difference on the change from baseline at 78 weeks. Hippocampal volume (HV) was the main imaging outcome. Data were analyzed using Mixed-Effect Model with Repeated Measures (MMRM) in the Full Analysis Set. defined as all participants who provided baseline, received at least one dose of study drug and provided postbaseline efficacy measures. All subjects were required to have serial MRIs, except for small number who could not undergo MRIs and had CT scans for screening and follow-up. Volumetric and safety MRIs (1.5/3 Tesla) were conducted every 26 weeks and were centrally assessed by expert neuroradiologists (Clario Inc). The study included diffusion MRI (dMRI) to assess microstructural integrity and serial plasma biomarkers of AD, which will be reported separately. **Results:** The safety population (N=325) was 51% females, 90% Caucasian, mean age 68 years, MMSE 25.6, 39% with MCI and 61% with Mild AD; and ~30% had baseline microhemorrhages and/or siderosis. In the overall efficacy population (N=320), ADAS-Cog13 placebo-adjusted effect (LS means of difference between drug-placebo) favored drug but was non-significant (delta= -0.5, 11% less decline, p=0.61) and the secondary clinical outcomes were nonsignificant. However, in the overall population, the HV favored drug significantly (18% less atrophy compared to placebo, p=0.017). Prespecified Mild AD effects favored

the placebo but they were small and not significant. In the prespecified MCI group, all clinical outcomes favored drug over placebo (nominal p-values): ADAS-Cog13 (delta= -2.14, p=0.042; 52% less decline compared to placebo); CDR-SB (delta= -0.65, p=0.053, 102%); DAD (delta= +6.1, p=0.016, 96%). HV showed significant slowing of atrophy compared to placebo (delta= 108 mm3, 26% less atrophy, p= 0.004), with 35% and 22% less cortical and whole brain atrophy. The most common treatment-emergent adverse event that occurred at rate >10% and double the placebo rate were: nausea (mostly mild), weight loss, appetite change and vomiting. ARIA-E incidence was the same as placebo, there were no reports of symptomatic ARIA-E or ARIA-H, and no deaths in the study. **Conclusions:** In the overall Early AD population, the ADAS-Cog13 primary outcome and secondary clinical outcomes (CDR-SB, DAD) did not achieve significance, but the hippocampus showed significant slowing of atrophy on valiltramiprosate (18% compared to placebo). The pre-specified MCI group showed nominally significant positive treatment effects on the cognitive and functional outcomes. In the prespecified MCI group, HV showed significant 26% slowing of atrophy that translated to clinical benefits with 52% less cognitive decline. This group also showed significant positive effects on all other brain compartments (cortical thickness, whole brain volume) and stabilization of function over 78 weeks (CDR-SB, DAD). The Mild AD group also showed slowing of HV atrophy compared to placebo but that was not significant (12%, p=0.12, versus placebo) and did not translate to significant clinical benefits. Overall safety was favorable with no increased ARIA-E or ARIA-H. In the high-risk APOE4/4 population, this positive benefit-risk profile supports valiltramiprosate's potential as an oral disease-modifying treatment for APOE4/4 homozygotes with MCI. These results will guide the design of future MCI and prevention trials.

Keywords: Valiltramiprosate, APOE4, mild cognitive impairment, early AD.

Clinical Trial Registry: (NCT# 04770220).

Disclosures: Drs Abushakra, Hey, Kesslak, Liang, Power and Tolar & Mr Albayrak and Ms Flint are employees of Alzheon, Inc. and hold stock or stock options of Alzheon, Inc. Drs Boada, Cohen, MacSweeney, Ousset and Watson are principal investigators of the Phase 3 ALZ-801-301 study. Drs Porsteinsson and Sabbah are consultants for Alzheon.

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Key takeaway message: This 78-week double-blind, placebo-controlled, two-arm trial enrolled 325 early AD subjects. The overall population did not achieve significance, but prespecified MCI group showed nominally significant positive treatment effects on cognitive, functional and brain volume outcomes.

P055- BASELINE CHARACTERISTICS AND PRELIMINARY SAFETY FROM A MULTICENTER, SAFETY SURVEILLANCE STUDY OF LECANEMAB TREATMENT FOR ALZHEIMER'S DISEASE IN REAL-WORLD CLINICAL PRACTICE USING ALZHEIMER'S NETWORK FOR TREATMENT AND DIAGNOSTICS (ALZ-NET) REGISTRY.

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Background: Lecanemab is an antibody directed against aggregated soluble and insoluble forms of amyloid beta (Aβ), a defining pathophysiological feature of Alzheimer's disease (AD). Lecanemab has shown marked amyloid reduction and slowing of cognitive decline as measured by cognitive and functional outcome measures in multiple clinical studies. In the US, lecanemab is indicated for the treatment of AD, with initiation in the mild cognitive impairment or mild dementia stage of disease. Lecanemab is also approved as a maintenance therapy of either once-monthly IV infusion or a weekly self-administered subcutaneous injection after completing the initial 18-month intravenous (IV) treatment in the US. Following the initial approval of lecanemab in the United States, post-marketing, multicenter, safety surveillance study was implemented to gather data for 10 years on the use of commercial lecanemab in real-world clinical practice. The baseline characteristics and preliminary safety data from participants enrolled through the data cutoff date of 23 May 2025 are presented. **Methods:** This is a post-marketing, multicenter, safety surveillance study of commercial lecanemab for the treatment of participants with AD in real-world clinical practice using Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) registry that will last 10 years. Physicians participating in the ALZ-NET registry prescribe lecanemab at their discretion and based on the approved United States Prescribing Information (USPI). Participants are monitored by the treating clinician according to participant needs and local standard of care. Data collection for the ALZ-NET registry consists of participant demographics, diagnosis, medical conditions, comorbidities, copathologies, concomitant medications, and safety outcomes. Data are collected from participants by ALZ-NET investigator sites every 6 months for the first 2 years of enrollment into the registry and annually thereafter. The primary objective of the study is to evaluate the safety of lecanemab in the real-world clinical setting with a focus on amyloid-related imaging abnormality (ARIA) events. **Results:** At the time of data cut off (23 May 2025), 742 participants were treated with commercial lecanemab, with a mean age 74 years. A majority of participants were female (55.4%) and Caucasian (87.1%). Overall, 56.6% of patients were ApoE ε4 carriers (47.3% heterozygotes; 8.2% homozygotes). Mean duration of lecanemab exposure was 8.4 months. The incidence of ARIA with edema/effusion (ARIA-E) was 5% (1.1% symptomatic ARIA-E), with all cases observed within the first 6 months of treatment. ARIA with microhemorrhages or superficial siderosis (ARIA-H) occurred in 7% of participants (1.3% symptomatic ARIA-H). Severity of ARIA events were 97.3% and 96.2% mild-to-moderate in ARIA-E and ARIA-H respectively. ARIA-E and ARIA-H events both led to discontinuation of lecanemab in 1.6% of participants. Intracerebral hemorrhage (ICH) greater than 1 cm in diameter occurred in 2 participants (0.3%). Two deaths were reported (pulmonary embolism; bile duct cancer), with one considered by the investigator as possibly related to commercial lecanemab (pulmonary embolism). **Conclusions:** The first interim safety results from a multicenter, safety surveillance study from patients with AD in a real-world clinical practice setting are consistent with the known lecanemab profile. No new safety signals were observed.

Disclosures: MS: Consulting: Roche-Genentech, Eisai, Lilly, Synaptogenix, NeuroTherapia, Signant Health, Novo Nordisk, Prothena, Anavex, Cognito Therapeutics, GSK, Abbvie, Athira, Alzheon; Board of Director: EIP Pharma/CervoMed. All other authors are employees of Eisai.

Keywords: Safety, lecanemab, Alzheimer's Disease, Real-World Clinical Practice, ALZ-NET, registry.

Key takeaway message: In an interim analysis from a multicenter, safety surveillance study from patients with Alzheimer's disease in a real-world clinical practice setting, results were consistent with the known lecanemab profile, with no new safety signals observed.

P056- CLINICAL STABILIZATION IN APOE4 CARRIERS WITH MCI OVER 3 YEARS CORRELATES WITH REDUCED HIPPOCAMPAL ATROPHY IN A PHASE 2 LONG TERM EXTENSION STUDY WITH ORAL VALILTRAMIPROSATE.

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Background: Valiltramiprosate/ALZ-801 is an oral, small molecule inhibitor of beta-amyloid oligomer formation in development as a disease-modifying treatment for Alzheimer's disease (AD). Whereas APOLLOE4 Phase 3 trial did not meet the primary endpoint in the overall APOE4/4 Early AD population, valiltramiprosate produced meaningful cognitive and functional improvement in the prespecified Mild Cognitive Impairment (MCI) subjects. Valiltramiprosate also significantly reduced atrophy in the hippocampus and other brain regions. In the Phase 2 open label trial, a total of 84 APOE4 carriers were enrolled and 75 completed 52 weeks. Baseline demographics were mean age 69 years, 51% female, MMSE 26.0, 70% MCI and 30% Mild AD. An interim analysis was conducted at 52 weeks and reported (Abushakra, CTAD 2022). Plasma p-tau181 showed significant reduction from baseline at 13 and 26 weeks, reaching -41% at 52 weeks (p=0.016). Plasma Aβ42 and Aβ40 showed 5% reductions at 52 weeks (p=0.002 & p=0.005). Composite cognitive test (RAVLT + DSST) Z-scores improved at 13 and 26 weeks (p=0.002, 26 weeks), remaining above baseline at 52 weeks (Abushakra, CTAD 2023). We hereby report the 3-year results in APOE4 carriers with MCI (N=36) from the Phase 2 long-term extension (LTE) study, showing sustained cognitive benefit that correlates with hippocampal volume (HV) changes over 3 years. **Methods:** The Phase 2 trial was conducted at 7 European sites in 84 APOE4 carriers (MMSE 22-30) with positive CSF amyloid/p-tau biomarkers who received oral valiltramiprosate tablet 265 mg BID over 208 weeks in the LTE. This included 31 homozygotes and 53 heterozygotes of the APOE4 gene. Cognitive (RAVLT+DSST composite score) and HV changes at 156 weeks were compared to matched external control AD subjects from Alzheimer's Disease Neuroimaging Initiative. Pearson correlations of cognitive vs. HV effects were analyzed. **Results:** RAVLT+DSST cognitive outcome remained stable in APOE4 carriers and homozygotes over 3 years relative to baseline in MCI subjects. Compared to the matched external ADNI control, there was 78% (delta=20.7, $p \leq 0.001$) and 84% (delta=21.0, p=0.002) reduction in cognitive decline in APOE4 carriers and homozygotes at 156 weeks, respectively. Cognitive benefits correlated significantly with reduction of neurodegeneration (HV effects; r=0.75, p=0.0001 in APOE4 carriers) at 156 weeks. Valiltramiprosate exhibited favorable safety without ARIA. **Conclusions:** Valiltramiprosate showed cognitive stabilization over 3 years in APOE4 carriers and homozygotes with MCI, similar to the prespecified MCI benefit in APOLLOE4 Phase 3 trial in APOE4 homozygotes. The clinical effects are supported by positive correlation between cognitive benefit and HV effects over 3 years in MCI subjects. These clinical benefits, together with favorable safety profiles, support evaluation of oral valiltramiprosate as a potential therapy for APOE4 carriers with early symptomatic AD.

Key takeaway message: Valiltramiprosate showed cognitive stabilization (RAVLT + DSST) over 3 years in APOE4 carriers and homozygotes with MCI. These results match the prespecified MCI benefit in APOLLOE4 Phase 3 trial in APOE4 homozygotes.

P057- XPRO1595, A SELECTIVE SOLUBLE TNF NEUTRALIZER, IN EARLY ALZHEIMER'S DISEASE WITH INFLAMMATION (ADI): RESULTS FROM THE PHASE 2 MINDFUL TRIAL.

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Background: Alzheimer's disease (AD) pathophysiology involves chronic neuroinflammation driven by tumor necrosis factor (TNF). XPro1595 selectively neutralizes pathological soluble TNF while preserving neuroprotective transmembrane TNF signaling, offering a mechanistically distinct approach from current amyloid-targeting therapies. **Methods:** The MINDFuL trial was a Phase 2, multicenter, randomized, double-blind, placebo-controlled study conducted across 35 centers in eight countries. Participants aged 50-85 years with Early AD (mild cognitive impairment or mild dementia) and elevated inflammatory biomarkers received weekly subcutaneous injections of XPro1595 (1.0 mg/kg) or placebo for 24 weeks. The primary endpoint was the Early Mild Alzheimer's Cognitive Composite (EMACC). A prospectively defined biomarker-enriched population included amyloid-positive participants with a high inflammatory burden (ADi), defined by the presence of $\geq$2 inflammatory markers. **Results:** Of 206 randomized participants, 200 comprised the modified intent-to-treat (mITT) population and 100 comprised the ADi population. In the mITT analysis, no significant difference was observed in the EMACC (p=0.672). However, the ADi population showed promising signals across multiple clinical endpoints favoring XPro1595, including the EMACC (Cohen's d = 0.27), Neuropsychiatric Inventory (NPI, d = 0.23), particularly the subfactor agitation / hyperactivity (d = 0.37), and a patient-reported outcome: Goal Attainment Scale (GAS, d = 0.18). These results were consistent with biomarker changes that favored XPro1595, as plasma pTau217 (d = -0.18) and GFAP (d = -0.19) were attenuated in the ADi population. In addition, many effect sizes were larger when assessing participants with higher drug exposure. Notably, no amyloid-related imaging abnormalities (ARIA) were observed, even though ~70% of the participants were APOE ε4 carriers, and one-third had baseline microbleeds. Although the initial data from MINDFuL has been presented, we will focus on additional new results from novel analyses (ongoing at the time of abstract submission), of which some are included above, and will be expanded upon in the presentation. **Conclusions:** While XPro1595 did not meet the primary endpoint in the overall population, participants with biologically-defined AD and high inflammatory burden demonstrated consistent trends toward cognitive benefit and neuropsychiatric improvement. The complete absence of ARIA distinguishes XPro1595 from amyloid-targeting therapies and supports its potential for use in combination strategies and potentially for those at a higher risk of ARIA. These findings support selective TNF inhibition as a promising therapeutic approach for persons with AD and elevated inflammatory burden.

Keywords: Alzheimer's disease, disease-modification, clinical trial, soluble TNF inhibition, biomarkers, cognition, inflammation, immune dysfunction, XPro1595, EMACC, CDR-SB.

Clinical Trial: NCT05318976.

Disclosures: KAS and CJB are employed by INmune Bio and hold shares. JJ and SB receive consultancy fees from INmune Bio. SC was a site investigator for the MINDFuL study and has no financial interests. MGT is a co-inventor of XPro1595, is an advisor to INmune Bio, and holds financial stake in INmune Bio.

Key takeaway message: The results from MINDFuL show favorable benefits of XPro1595 treatment on cognition, neuropsychiatric symptoms and disease-relevant biology in a subpopulation, thereby supporting soluble TNF inhibition as a promising therapeutic approach for persons with AD and elevated inflammatory burden.

P058- CORRELATIONS OF VALILTRAMIPROSATE EFFECTS ON HIPPOCAMPAL VOLUME AND CORTICAL THICKNESS WITH CLINICAL OUTCOMES IN APOE4/4 SUBJECTS WITH MCI: PRESPECIFIED ANALYSIS OF MCI GROUP IN THE 78-WEEK APOLLOE4 PHASE 3 TRIAL.

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Background: Valiltramiprosate (ALZ-801) is a valine-conjugated prodrug of tramiprosate that prevents amyloid-beta (Aβ) monomer aggregation into toxic oligomers, an early and central driver of Alzheimer's disease (AD) pathology (Kocis, 2017; Muramatsu, 2025). Apolipoprotein ε4 (APOE4), a major risk factor for AD with early & accelerated deposition of amyloid and tau pathologies (Fortea 2024), and frequently shows early and accelerated hippocampal atrophy and more rapid cognitive decline (Martin 2005, Abushakra 2020). Valiltramiprosate was evaluated in APOE4/4 homozygotes with Early AD (topline results presented at this meeting (Abushakra, 2025). In a Phase 3 trial in APOE4/4 Early AD subjects, the overall population did not show significant clinical benefits, but showed significantly less hippocampal volume loss (HV atrophy). The pre-specified analysis of MCI subgroup showed significant clinical benefits. Correlations between treatment effects on clinical and several pre-specified volumetric MRI outcomes were analyzed. **Methods:** A total of 325 homozygotes (placebo, 265 mg BID, randomized 1:1) stratified by MCI (MMSE 27-30) or Mild AD (MMSE 22-26),were enrolled in this 78-week placebo-controlled study (NCT# 04770220). The primary and key secondary outcomes were ADAS-Cog13 and CDR-SB respectively, and DAD (disability assessment for dementia) was a secondary outcome. MRI images were collected every 26 weeks and centrally analyzed (Clario, Inc) for safety and quantitative measures. Hippocampal volume (HV) was the main imaging outcome, with secondary measures of cortical thickness (CT) and whole brain volume (WBV). Analyses by disease stage were prespecified using baseline severity as covariate in the MMRM model; drug-effect correlations utilized Spearman's correlations. **Results:** The overall study did not achieve significance on the primary and secondary clinical outcomes, but all vMRI outcomes showed significant atrophy slowing versus placebo (HV, 18% less atrophy, p=0.017). The MCI subgroup (MMSE 27-30) included 125 subjects (58 placebo, 67 active); with balanced baseline characteristics except for cholinesterase-inhibitors (placebo 31%, active 19%). Imaging population included 52 placebo, 61 active subjects. The prespecified, MCI group analysis showed positive effects/trends on ADAS-Cog13 (52%, p=0.041), DAD (96%, p=0.016) and CDR-SB (102%, p=0.053); with significant atrophy slowing in HV (26%), CT (35%), both p< 0.01, and in WBV (22%, p=0.027). In the active arm, subject-level correlations between HV-ADAS (r=-0.40), HV-CDR (r=-0.45) were both significant (p<0.005); clinical correlations for CT, WBV were also significant (coefficients 0.34-0.49). **Conclusions:** In APOLLOE4 pre-specified MCI group, valiltramiprosate showed nominally significant cognitive and functional benefits with significant atrophy slowing in all brain compartments (HV 26%, WBV 22%). Hippocampal and whole-brain volume effects showed significant subject-level correlations with cognitive and functional benefits over 78 weeks (correlations 0.45-0.49). These strong correlations between structural preservation and clinical benefits of valiltramiprosate at the MCI stage are consistent with its proposed mechanism of inhibiting amyloid oligomer formation, thereby potentially protecting neurons from synaptic dysfunction and neurodegeneration. By inhibiting amyloid oligomer formation, valiltramiprosate can directly protect neurons from synaptic dystrophy and neuronal loss thus slowing neurodegeneration; this translates to cognitive and functional benefits. Given the accelerated neurodegeneration in APOE4/4 patients, these findings suggest that intervention at the early stages of AD when neuronal reserve is higher, may be critical for valiltramiprosate to exert meaningful clinical benefits with preservation of brain volumes. These strong subject-level imaging-clinical correlations support the efficacy of valiltramiprosate in APOE4/4 MCI subjects.

Keywords: Valiltramiprosate, APOE4, Hippocampus, MCI, early AD.

Disclosures: Drs Abushakra, Bray, Hey, Kesslak, Liang, Power and Tolar and Ms Flint are employees of Alzheon, Inc. and hold stock or stock options of Alzheon, Inc. Drs. MacSweeney and Watson are principal investigators of the Phase 3 ALZ-801-301 study. Mr. Bracoud is an employees of Clario, Inc. Drs Porsteinsson, Sabbah and Tosun are consultants for Alzheon. ALZ-801 is an investigational agent being evaluated as a potential disease-modifying treatment in an ongoing Early Phase 3 trial in N. America and Europe. **References:** Abushakra S, Portsteinsson AP, Sabbagh M, et al., Alzheimers Dement. 2020 Dec 4;6(1):e12117. Fortea J, Pegueroles J, Alcolea D, et al. CNS Drugs. 2017, 31(6):495-509. Kocis P, Tolar M, Yu J, et al. CNS Drugs. 2017, 31(6):495-509. Muramatsu D, Watanabe-Nakayama T, Tsuji M, et al. FASEB J. 2025 Feb 15;39(3):e70382.

Key takeaway message: In this Phase 3 placebo-controlled trial in APOE4/4 Early AD subjects, oral valiltramiprosate showed significant effects on slowing brain atrophy that correlated significantly with its clinical benefits in MCI subjects treated over 78 weeks.

P059- BASELINE ANTIHYPERTENSIVE MEDICATION USE IS ASSOCIATED WITH LOWER FREQUENCY OF AMYLOID-RELATED IMAGING ABNORMALITIES-EDEMA WITH DONANEMAB TREATMENT EVEN AFTER CONTROLLING FOR MEAN ARTERIAL BLOOD PRESSURE: ANALYSIS FROM TRAILBLAZER-ALZ RANDOMIZED CLINICAL TRIALS.

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Background: Amyloid-related imaging abnormalities-edema/effusions (ARIA-E) are a key risk with amyloid-targeting immunotherapies. Higher mean arterial pressure (MAP) at baseline has been associated with a higher risk of ARIA-E. Antihypertensives are common medications used in Alzheimer's disease patients. An exploratory post hoc analysis of randomized trials of donanemab showed a decreased risk of ARIA-E among participants using antihypertensive agents at baseline and during treatment compared to those not using any antihypertensive medications.1 We aimed to further evaluate the effect of baseline antihypertensive use on frequency of ARIA-E events among participants receiving donanemab using data from TRAILBLAZER-ALZ clinical studies. **Methods:** This post hoc exploratory analysis included a pooled sample of 2,721 donanemab-treated participants. Participants were from studies: TRAILBLAZER-ALZ (NCT03367403), TRAILBLAZER-EXT (NCT04640077), TRAILBLAZER-ALZ 2 (NCT04437511), and an open-label addendum to TRAILBLAZER-ALZ 2. Participants were 60–85 years of age with early symptomatic Alzheimer's disease. A logistic regression model was used to estimate odds ratios (OR) with 95% confidence intervals (CI). The model controlled for the number of APOE E4 alleles, number of microhemorrhages, presence of superficial siderosis, amyloid load, diabetes medications, and mean arterial pressure (MAP) at baseline. Participants were considered to have baseline antihypertensive use if they had medicine exposure in the first 7 days and for ≥30 days during the conduct of the respective study. **Results:** Baseline use of any antihypertensive agent was significantly associated with a 35% reduced odds of overall ARIA-E (OR 0.65, 95% CI 0.53–0.79; p<0.001) and a 50% reduced odds of symptomatic ARIA-E (OR 0.50, 95% CI 0.34–0.73; p<0.001). Significant reductions in both overall and symptomatic ARIA-E frequency were consistently observed across major classes of antihypertensive agents, including beta blockers, diuretics, and calcium channel blockers. Participants with MAP in both the normal and hypertensive range at baseline had reduced odds of ARIA-E with use of any antihypertensive agent, with numerically greater reduction in the hypertensive group. While hypertension at baseline is associated with increased ARIA-E risk and antihypertensive use is associated with decreased risk, the interaction between MAP status and antihypertensive use was not statistically significant (OR for interaction = 0.90, 95% CI 0.61–1.35; p=0.618). The presence or absence of other commonly prescribed medications was assessed to determine if this influenced the impact of antihypertensive use on ARIA-E. Patients on antihypertensive

agents are commonly also on diabetes medications. When participants taking diabetic medications were excluded from the analysis, baseline use of any antihypertensive was still significantly associated with reduced risk of overall ARIA-E (OR 0.66, 95% CI 0.54–0.82; p<0.001). **Conclusions:** Among clinical trial participants who received donanemab, baseline antihypertensive use was associated with reduced incidence of overall and symptomatic ARIA-E. This reduction in ARIA-E was consistent across MAP levels and even after controlling for MAP. The reduction in ARIA-E incidence with antihypertensive use did not depend on concomitant treatment with diabetes medications.

Reference: 1. Zimmer J.A., et al. Amyloid-Related Imaging Abnormalities with Donanemab in Early Symptomatic Alzheimer Disease Secondary Analysis of the TRAILBLAZER-ALZ and ALZ 2 Randomized Clinical Trials. JAMA Neurol. 2025 Mar 10:e250065.

Key takeaway message: Among clinical trial participants who received donanemab, baseline antihypertensive use was associated with reduced incidence of overall and symptomatic ARIA-E.

P060- EFFECTS OF THE ORAL ANTI-AMYLOID AGENT VALILTRAMIPROSATE ON MEASURES OF MICROSTRUCTURAL INTEGRITY: DIFFUSION MRI RESULTS OF THE PHASE 3 APOLLOE4 TRIAL IN APOE4/4 HOMOZYGOTES WITH EARLY AD.

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Background: Valiltramiprosate (ALZ-801) is an anti-amyloid oral agent in late-stage development for the treatment of Early Alzheimer's disease (AD). Valiltramiprosate is a valine-conjugated prodrug of tramiprosate that prevents amyloid-beta (Aβ) monomer aggregation into toxic oligomers, an early and central driver of AD pathology (Kocis, 2017; Muramatsu, 2025). Tramiprosate (active agent in ALZ-801), had shown promising efficacy signals with favorable safety in ~1300 APOE4 carriers with AD, with no observed ARIA-E (Abushakra 2016). Apolipoprotein ε4 (APOE4) is a major risk factor for AD with early and accelerated deposition of amyloid and tau pathologies (Fortea 2024), accelerated hippocampal atrophy, and frequently more rapid cognitive decline (Abushakra 2020, Martins 2005). Valiltramiprosate was evaluated in 325 APOE4/4 Early AD subjects in a Phase 3, 78-week placebo-controlled multi-center trial (APOLLOE4). Although the overall population did not show significant effects on the primary cognitive outcome, it did show significant slowing of hippocampal atrophy (Abushakra, CTAD 2025). The trial included diffusion MRI (dMRI) to complement the MRI volumetric analyses and assess microstructural integrity of the grey and white matter. We herein present the results of the dMRI analyses over 78 weeks. **Methods:** This Phase 3 randomized, double-blind, placebo-controlled multi-center trial was conducted at 77 sites in North America and the EU (NCT# 04770220). The study randomized APOE4/4 homozygotes with Early AD (MMSE 22-30) in 1:1 ratio to valiltramiprosate 265mg BID or matching placebo. The trial was stratified by disease stage with MCI (MMSE 27-30) or Mild AD (MMSE 22-26). The primary outcome was ADAS-Cog13 (primary), with CDR-SB (key secondary) and DAD (disability assessment for dementia) as secondary outcome. Hippocampal volume (HV) on volumetric MRI (vMRI) was the main imaging outcome with cortical thickness as secondary outcome. Additional imaging outcomes were mean water diffusivity (MD) on dMRI to assess microstructural integrity of grey and white matter. Most sites was able to obtain single-shell dMRI sequences. All vMRI and dMRI were conducted by Clario Inc. MMRM was main analysis model. Drug effects on the % change from baseline on MD are shown, with lower MD on drug indicating preservation of microstructure. Correlations of drug effects on the clinical and dMRI outcomes over 78 weeks were analyzed with Pearson's correlations. **Results:** In the overall population, the clinical/vMRI datasets included 320/290 subjects respectively; dMRI population included 208 subjects (85 MCI, 123 Mild AD subjects). In overall population, valiltramiprosate effects on MD showed positive trends favoring drug in 4 GM regions (p<0.1), and significant WM effects favoring drug [corpus callosum genu (GCC) (p<0.001), fornix (p=0.007), corpus callosum (p=0.023), and corona radiata (p=0.037)]. The prespecified MCI group showed positive GM effects in caudate (p=0.0095) and cingulate cortex (p=0.015); with positive WM effects in GCC/whole CC/splenium CC (p=0.003/0.014/0.037), fornix (p=0.032), and corona radiata (p=0.042). In the MCI active arm, the MD effects in several GM/WM areas correlated significantly with positive clinical effects on ADAS (correlation 0.33, p=0.04) and CDR-SB (0.48, p=0.002); and with positive hippocampal volume effects (0.47, p=0.002) at 78 weeks. These lower MD on drug correlated with less decline on ADAS and CDR and less hippocampal atrophy. **Conclusions:** In the overall Phase 3 study population, valiltramiprosate showed significantly lower mean water diffusivity in the subcortical white matter suggesting preservation of its microstructure. In the prespecified MCI group that showed promising clinical benefits and significant slowing of brain atrophy, valiltramiprosate showed significant positive effects on both grey and white matter. These effects were most significant in the cingulate cortex and major hippocampal outflow tracts (fornix and corpus callosum), that are areas affected early with AD pathology. In the MCI group, this microstructural preservation correlated significantly with preservation of hippocampal volume and with clinical benefits. These dMRI findings support proposed mechanism of action of valiltramiprosate, namely inhibiting toxic oligomer formation and preserving synapses/axons, thus slowing neurodegeneration. These microstructural effects and their significant correlations with clinical benefit also support the meaningful efficacy of oral valiltramiprosate in APOE4/4 homozygotes with MCI.

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Keywords: Valiltramiprosate, APOE4, volumetric MRI, diffusion tensor imaging (DTI), early AD.

Disclosures: Drs Liang, Abushakra, Hey, Kesslak, Power and Tolar & Ms Flint are employees of Alzheon, Inc. and hold stock or stock options of Alzheon, Inc. Dr D Tosun is a consultant for Alzheon. Drs Cohen, MacSweeney and Watson are principal investigators of the Phase 3 ALZ-801-301 study. Drs Conklin and Ingalhalikar are employees of Clario (Philadelphia, CA). ALZ-801 is an investigational agent evaluated as a potential disease-modifying treatment in Early AD.

Key takeaway message: In this phase 3 placebo-controlled study of oral valiltramiprosate (N=325), in APOE4/4 early AD subjects the prespecified MCI population showed significant effect on both grey/white matter microstructure that correlated with clinical and volumetric benefits (N=85).

P061- EFFECTS OF TRANSCRANIAL PHOTOBIOMODU-LATION (TPBM) ON COGNITIVE FUNCTION AND BRAIN FUNCTIONAL CONNECTIVITY: A PRELIMINARY CLINICAL STUDY.

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Background: According to the WHO (2021), over 55 million people were living with dementia globally as of 2019, and this number is

projected to reach 139 million by 2050. Since Alzheimer's disease accounts for 60–70% of dementia cases, the global burden of Alzheimer's is expected to rise significantly in the coming decades (1). Current FDA-approved medications (cholinesterase inhibitors, memantine, and recent antibody therapies) demonstrate limited efficacy with considerable adverse effects, highlighting the urgent need for effective non-invasive therapeutic interventions, particularly in early-stage disease (2). Photobiomodulation (tPBM) is a therapeutic modality utilizing near-infrared light at wavelengths of 600-1100nm to activate mitochondrial cytochrome c oxidase, thereby enhancing ATP production and reducing oxidative stress[3]. Previous studies have demonstrated that tPBM reduces amyloid-beta aggregation, inhibits tau phosphorylation, and enhances synaptic plasticity (4,5). Cognitive impairment during progression of neurodegenerative disorders is characterized by distinctive electroencephalographic changes, including increased slow-wave activity (delta, theta), decreased fast-wave activity (alpha, beta), reduced alpha peak frequency, and diminished functional connectivity (6). Notably, the loss of small-world network properties and disruption of the Default Mode Network are closely associated with cognitive decline (7). Therefore, comprehensive analysis of these neurophysiological markers is essential when evaluating therapeutic efficacy. This study aimed to comprehensively evaluate the effects of tPBM therapy on cognitive function, electroencephalographic activity, functional connectivity, and brain network topology. We particularly focused on detailed ROI-based analysis of AD-related core brain regions (entorhinal cortex, posterior cingulate cortex, precuneus) to elucidate the neurophysiological mechanisms and therapeutic effects of tPBM. **Methods:** Eighteen participants (12 females, 6 males; mean age 66.9±5.23 years, range 60-79 years) underwent 4-week tPBM therapy. tPBM was administered using the iSyncWave system (iMediSync Inc., Korea) with 850nm wavelength stimulation at 12Hz frequency across the entire head region, three times weekly for 15 minutes per session. Pre- and post-treatment assessments included: 1) Cognitive function evaluation using Montreal Cognitive Assessment (MoCA), 2) Quantitative electroencephalography (QEEG) using the iSyncWave dry-electrode system following the international 10/20 system with FPz as ground and left earlobe as reference at 250Hz sampling rate, 3) Frequency band-specific power spectrum analysis and 68 region-of-interest (ROI) based detailed analysis, 4) Inter-regional functional connectivity analysis, and 5) Brain network analysis (Global Efficiency, Clustering Coefficient, Small Worldness). EEG data underwent preprocessing with 1Hz high-pass filter, 45.5Hz low-pass filter, and 60Hz notch filter to remove AC power line noise, followed by Common Average Reference (CAR) application. Subsequently, automatic bad epoch rejection, Independent Component Analysis (ICA), and manual artifact removal were performed sequentially. Statistical analyses employed paired t-tests and Wilcoxon signed-rank tests. **Results:** MoCA scores increased from 26.0±2.66 to 27.8 ±1.36, representing a mean improvement of 1.8 points with significant increase by Wilcoxon signed-rank test (one-tailed $p=0.029$). Sixteen of eighteen participants (89%) demonstrated improvement, with meaningful improvement (≥6 points) in 2 participants (11%), moderate improvement (3-5 points) in 5 participants (28%), and mild improvement (1-2 points) in 9 participants (50%). Brain regions showing high correlation with MoCA score improvement included memory-related areas (inferior parietal lobule, entorhinal cortex, parahippocampal areas, temporal pole, posterior cingulate cortex, fusiform gyrus) and executive function-related areas (superior frontal gyrus, middle frontal gyrus, precentral gyrus, paracentral lobule, orbitofrontal cortex, inferior frontal gyrus, insula). QEEG analysis revealed widespread Beta3 power increase in frontal regions (F3, Fz, F4, F8; $p<0.05$), with Beta2 showing significant increase at F8. Alpha peak frequency demonstrated overall upward tendency. Left hemispheric frontal Delta-Alpha Ratio (DAR) consistently decreased, suggesting executive function and arousal improvement. Sixty-eight ROI analysis demonstrated consistent improvement patterns in AD core regions: Precuneus and posterior cingulate cortex showed marked Beta(1-3) and Gamma power increases, with widespread Beta activity elevation across lateral parietal cortex. Frontal regions (superior frontal, caudal anterior cingulate) exhibited normalization patterns with decreased pathological markers (Delta power, TBR) alongside increased Beta3 and Gamma. These changes represent improvement patterns directly opposite to AD pathological progression. Overall brain functional connectivity increased from 41.5 to 49.6, representing 19.5% enhancement ($p=0.342$). Regional analysis revealed significant improvement in left temporal lobe connectivity ($p=0.039$), particularly in Banks of Superior Temporal Sulcus (social cognition), Middle Temporal Gyrus (semantic memory), and Transverse Temporal Gyrus (auditory processing). Inter-hemispheric connectivity showed increasing tendency ($dz=0.283$), with significant increases in occipito-parietal Alpha1 and Beta2 connectivity. Brain network analysis demonstrated Clustering Coefficient increase of 0.162 in superior frontal regions ($dz=0.76$, $p=0.005$), Global Efficiency increase of 0.067 in posterior cingulate cortex ($dz=0.67$, $p=0.011$), and Global Efficiency increase of 0.060 in entorhinal cortex, the early AD pathological site ($dz=0.61$, $p=0.020$). Small Worldness increased by 0.174, indicating more efficient and integrated network structure ($p_t=0.007$, $p_w=0.003$), with positive correlation confirmed between Small Worldness and MoCA scores. **Conclusions:** Four-week 850nm tPBM therapy significantly improved cognitive function, with electroencephalographic analysis demonstrating increased neural activity in AD pathology-related core brain regions. Furthermore, inter-regional functional connectivity, particularly left temporal and inter-hemispheric connectivity, showed enhancement, with improved brain network integration and efficiency. These findings suggest tPBM's potential as a non-invasive therapeutic modality for neurodegenerative disorders. Large-scale randomized controlled trials including placebo controls are warranted for further validation.

Keywords: Photobiomodulation, quantitative electroencephalography (QEEG), Alzheimer's disease, Montreal cognitive assessment (MoCA).

Disclosures: No conflicts of interest.

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Key takeaway message: A four-week 850nm photobiomodulation therapy improved cognitive function and enhanced brain network efficiency in Alzheimer's-related regions, suggesting its potential as a non-invasive treatment for neurodegenerative disorders.

P062- SAFETY OUTCOMES OF LECANEMAB IN KOREAN REAL-WORLD CLINICAL PRACTICE: A MULTICENTER OBSERVATIONAL STUDY.

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Background: Lecanemab, a monoclonal antibody targeting amyloid-β protofibrils, has shown an overall manageable safety profile in clinical trials. The most common concerns are infusion-associated adverse events (IRAEs), followed by amyloid-related imaging abnormalities (ARIA), both of which typically occur within the first three months of treatment. However, trial participants are highly selected, whereas real-world patients are more heterogeneous and may exhibit different patterns of adverse events. Given that most safety events emerge early in the treatment course, we analyzed adverse events up to three months after lecanemab initiation in a multicenter observational cohort across seven memory clinics in South Korea to delineate its real-world safety profile. **Methods:** This multicenter observational study included consecutive patients with amyloid PET-confirmed Alzheimer's disease who initiated lecanemab between October 2024 and June 2025 at seven memory clinics in South Korea: HappyMind Clinic (n=117), Samsung Medical Center (n=89), Asan Medical Center (n=76), Chonnam National University Hospital (n=22), Yongin Severance Hospital (n=13), Inje University Haeundae Paik Hospital (n=13), and Kyung Hee University Medical Center (n=8). IRAEs were monitored during and after each infusion, with manifestations recorded using standardized checklists in two centers (n=165) and patient/caregiver reports in the remaining five centers (n=174). To detect ARIA, MRI was performed at baseline and prior to the 5th and 7th infusions, with acquisition protocols varying across hospitals (1.5T or 3T; GRE or SWI). Clinical protocols also differed with respect to premedication and titration strategies, reflecting heterogeneity in real-world practice. **Results:** A total of 339 AD patients were enrolled: 193 with MCI (56.9%), 130 with mild dementia (38.3%), and 16 classified as others (4.7%), comprising cognitively unimpaired individuals and those with moderate dementia (CDR $\geq$2). The mean age was 71.1 $\pm$ 8.6 years, and 224 patients (66.1%) were female. Average years of education were 13.3 $\pm$ 3.8. APOE ε4 genotypes included 133 non-carriers (39.2%), 164 heterozygotes (48.4%), and 42 homozygotes (12.4%). IRAEs occurred in 100 patients (29.5%), most frequently during the first infusion (67 cases, 67% of IRAEs). Reporting rates differed significantly between centers using standardized checklists versus patient/caregiver reports (61/165 [36.9%] vs. 39/174 [22.5%]; p=0.003). Discontinuation due to IRAEs was rare (4 patients, 1.2% overall; 4.0% of those with IRAEs). ARIA was observed in 41 patients (12.1%), including 10 with ARIA-E with/without ARIA-H (2.9%) and 31 with isolated ARIA-H (9.1%). Symptomatic ARIA occurred in 3 patients (0.9%), including 2 with macrohemorrhage. Eight patients (2.4%) discontinued treatment due to ARIA, and no deaths were reported. Compared with Clarity AD, the incidences of ARIA were significantly lower (any ARIA 12.1% vs. 22.6%, p<0.001; ARIA-E 2.9% vs. 13.6%, p<0.001; ARIA-H 11.2% vs. 18.5%, p=0.001; withdrawal 3.5% vs. 7.7%, p=0.006). IRAE and solitary ARIA-H rates were not significantly different. Subgroup analyses revealed higher ARIA frequencies among APOE ε4 carriers, although the magnitude of this association was notably attenuated compared with prior reports. Importantly, patients receiving an initial dose-escalation regimen tended to experience fewer ARIA events. Imaging analyses from Samsung Medical Center localized ARIA-E and ARIA-H predominantly to the occipital and parietal lobes. **Conclusions:** In this Korean real-world cohort of amyloid PET-positive patients, lecanemab demonstrated a favorable safety profile, with overall and symptomatic ARIA rates—particularly ARIA-E—substantially lower than those reported in Clarity AD. IRAEs were relatively common but rarely led to treatment discontinuation. The lower incidence and attenuated progression of ARIA among APOE ε4 carriers may be attributable to initial dose-escalation regimens or ethnic differences. These findings provide real-world evidence of lecanemab safety in heterogeneous clinical settings, suggest potential ethnic or practice-related differences in ARIA susceptibility, and underscore the importance of tailored monitoring strategies during the early treatment period.

Key takeaway message: In a multicenter Korean real-world cohort, lecanemab showed a favorable safety profile with lower ARIA incidence than Clarity AD. IRAEs were frequent but rarely led to discontinuation, and dose-escalation regimens appeared to reduce ARIA risk.

P063- COGNITIVE AND ELECTROPHYSIOLOGICAL EFFECTS OF POSTBIOTIC DIETARY SUPPLEMENTATION IN OLDER ADULTS: RESULTS FROM A RANDOMISED DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL.

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Background: Age-related cognitive decline is linked to changes in attention, memory, and executive function. Postbiotic interventions have shown promise in modulating gut–brain signalling, yet their impact on neurocognitive performance remains uncertain. This study aimed to evaluate the effects of PoZibio® supplementation on cognitive control and brain activity in healthy older adults. PoZibio is an oral dietary supplement containing a heat killed strain of Lactobacillus paracasei. **Methods:** The trial was a randomised, double-blind, placebo-controlled study conducted between September 2024 and January 2025. Participants (N=57; mean age 67) were assigned to PoZibio (n=28) or placebo (n=29) for 60 days. EEG recordings were collected during Stroop and NBack tasks. ERP components (N200, P300, LPC) and spectral power (delta, theta, alpha) were analysed across frontal, central, and parietal regions. **Results:** The Stroop task revealed a significant increase in P300 amplitude in the PoZibio group (p<.001), indicating enhanced attentional engagement. N200 amplitude increased significantly in both groups (p=.003), with a greater effect size (F=31.66) for the PoZibio group, suggesting possible improvements in conflict detection. LPC amplitude increased across both groups (p<.001). NBack task showed no significant ERP changes after correction, although placebo participants exhibited more pronounced raw ERP shifts. Spectral power increased in both groups, with larger gains in placebo, suggesting natural time-related changes. **Conclusions:** PoZibio supplementation improved early cognitive control markers during the Stroop task but did not produce reliable effects in working memory tasks. EEG findings suggest selective benefits for inhibitory control, with broader changes potentially driven by practice effects.

Key takeaway message: Postbiotic supplementation may enhance cognitive control in older adults.

P064- VALACYCLOVIR TREATMENT OF MILD COGNITIVE IMPAIRMENT WITH HERPES SIMPLEX SEROPOSITIVITY: THE VALMCI TRIAL.

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Background: Evidence from neuroscience, epidemiology, and electronic health records studies implicates herpes simplex viruses (HSV) as potentially etiologic for Alzheimer's disease (AD). In our recent randomized, double-blind, placebo-controlled clinical trial of 120 participants with early symptomatic Alzheimer's disease (VALAD trial), the anti-herpetic drug valacyclovir was not efficacious. **Methods:** This preliminary proof of concept, randomized, double-blind, placebo-controlled, 12-month trial, which was independent of the VALAD trial, was conducted in a single U.S research clinic specializing in memory disorders. The efficacy and side effects of valacyclovir 4 g/day were compared to placebo in participants with mild cognitive impairment (MCI, sample included early or eMCI and late or lMCI) who had seropositivity (IgG or IgM) to HSV1 or HSV2, Folstein Mini Mental State Exam score 23 to 30 and an AD biomarker positive 18F-Florbetapir PET scan that was conducted at screening to determine eligibility (mean SUVR $\geq$ 1.15 for six brain regions was required). Cholinesterase inhibitors or memantine were permitted if doses were stable for at least one month. Major neurological or psychiatric disorders and alcohol or substance use disorder within the previous 6 months were exclusion criteria. Randomized participants who took at least one study pill were included in the intention-to-treat analytic sample. The timeframe for outcomes was change from baseline to 52 weeks. The prespecified primary outcome was the composite z-score for the Preclinical Alzheimer Cognitive Composite (PACC) scale. Prespecified secondary outcomes were the Alzheimer's Disease Cooperative Study-Activities of Daily Living-Prevention Instrument (ADCS-ADL-PI) scale and 18F-Florbetapir PET SUVR (mean of six brain regions: medial orbitofrontal, anterior cingulate, parietal lobe, posterior cingulate, temporal lobe, and precuneus regions, all normalized to cerebellar gray matter). Change in plasma ptau-217 was an exploratory outcome. **Results:** In 50 randomized participants, 24 were assigned to valacyclovir and 26 to placebo. Participants in the two treatment groups did not differ significantly in age (valacyclovir: mean 69.29 SD 9.40; placebo: mean 68.35 SD 8.85), race (valacyclovir 58.3% white and placebo 53.8% white; minorities comprised 44% of the sample), Folstein MMSE scores (valacyclovir: mean 26.79 SD 1.38; placebo: 26.27 SD 1.73), proportion with eMCI (valacyclovir 54.2%, placebo 50%), and frequency of apolipoprotein E e4 genotype (valacyclovir: 45.8%; placebo: 58.3%). In linear mixed-effects model analyses, the least-squares mean (LSM) change in PACC composite at 52 weeks was 0.30 (95% CI, 0.04 to 0.56) on valacyclovir and 0.03 (95% CI, -0.24 to 0.30) on placebo, a non-significant difference (p=0.16). LSM change in ADCS-ADL-PI participant report at 52 weeks was 3.22 (95% CI, 1.68 to 4.75) on valacyclovir and 0.24 (95% CI, -1.36 to 1.85) on placebo ($p < 0.01$). LSM change in ADCS-ADL-PI study partner report at 52 weeks was 2.47 (95% CI, -0.08 to 5.02) on valacyclovir and -1.59 (95% CI, -4.20 to 1.02) on placebo ($p < 0.03$). Changes in ADCS-ADL-PI at 12 and 26 weeks, however, were not significantly different between valacyclovir and placebo. In linear regression analyses, change in 18F-Florbetapir PET SUVR was not significantly different between valacyclovir (LSM 0.07; 95% CI -0.001 to 0.14) and placebo (LSM 0.09; 95% CI 0.01 to 0.16). Change in plasma ptau-217 was not significantly different between valacyclovir (0.02; 95% CI -0.05 to 0.09) and placebo (0.09; 95% CI 0.01 to 0.17). Inclusion of age, sex and apolipoprotein E e4 genotype as covariates in analyses, and per-protocol analyses of study completers, led to similar results with the PACC composite showing no significant treatment group differences and change in ADCS-ADL-PI participant and study partner reports showing a significant advantage for valacyclovir over placebo. Common adverse events were diarrhea (4 on valacyclovir, 3 on placebo), fatigue (2 on valacyclovir, 3 on placebo), headache (4 on valacyclovir, 1 on placebo). **Conclusions:** Valacyclovir was not efficacious on the primary cognitive outcome, but the secondary outcome of functional ability showed improvement. Analyses were limited by low statistical power and there was no correction for multiple comparisons. In the context of lack of efficacy for valacyclovir in early symptomatic AD in the VALAD trial, these preliminary findings of valacyclovir treatment being associated with improvement in the secondary outcome of functional ability in MCI in the VALMCI trial indirectly suggest that larger intervention or prevention trials with antiherpetic medications at the pre-MCI or MCI stage may be warranted.

Keywords: Mild cognitive impairment, herpes simplex virus, valacyclovir.
Clinical Trial Registry: clinicaltrials.gov NCT 04710030.
Data Deposition: Data can be requested from the Principal Investigator, Dr. Devanand, 12 months after the primary outcome results are published.
Disclosures: Dr. Devanand is a scientific adviser to Acadia, Eisai and GSK, and serves on a Data Safety Monitoring Board for Cybin. Dr. Goldberg serves on a Data Safety Monitoring Board for BMS.
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Key takeaway message: In a clinical trial of 50 participants with MCI and positive AD biomarkers and HSV seropositivity, valacyclovir was not efficacious on the primary cognitive outcome but was associated with improvement on the secondary outcome of functional ability.

P065- RESULTS FROM A PHASE 1B TRIAL ON ANTI-Aβ OLIGOMER VACCINE ALZ-101 IN EARLY ALZHEIMER'S DISEASE.

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Background: ALZ-101 is an active vaccine eliciting an immune response targeting toxic oligomeric Aβ42. A Phase 1b trial (ALZ-C-001; NCT05328115) was undertaken to assess the safety, tolerability and immunogenicity of ALZ-101 in subjects with early AD. **Methods:** Twenty-six subjects (77% mild AD; 23% MCI) were randomized to receive placebo (n=6), 125 µg (n=10), or 250 µg (n=10) doses of ALZ-101 at weeks 0, 4, 8, and 16. Of these, 23 subjects entered an open-label extension (OLE) phase where those previously on active treatment received 250 µg ALZ-101 at weeks 0 and 16, and those previously on placebo received 250 µg ALZ-101 at weeks 0, 4, 8, and 16. Another six subjects (83% mild AD; 17% MCI) were also recruited to an open-label arm assessing 400 µg doses of ALZ-101 at weeks 0, 4, 8, and 16. Primary endpoint safety parameters, including brain MRI scans, were assessed at baseline and before each injection. Secondary endpoints included immunogenicity assessments. Exploratory endpoints included CSF levels of biomarkers and cognitive/functional tests. **Results:** The vaccine was

generally well tolerated. Sixteen asymptomatic ARIA-H events, of which two were superficial siderosis, occurred in nine patients: two subjects randomized to placebo (33%), six subjects randomized to 125 μg (60%), and one subject randomized to 250 μg (10%) with no cases in the 400 μg group. One asymptomatic ARIA-E occurred in the OLE in a subject initially randomized to placebo. The vaccine induced strong Th2 activity and sustained oligomer-specific antibody titers. Across the treatment groups, no statistically significant differences were observed in exploratory cognition/function assessments and CSF biomarker concentrations. However, patients randomized to 125 μg or 250 μg appeared to show a lower rate of neuronal damage, as measured by CSF neurofilament light (NFL), at the end of the two-year trial compared to those initially receiving placebo. Notably, this same group exhibited no meaningful clinical decline on ADCOMS over an average study duration of more than 100 weeks. **Conclusions:** ALZ-101 was well tolerated and immunogenic at all three tested dose levels. Most subjects enrolled were in the dementia stage (78% mild AD and 22% MCI). Stable ADCOMS scores and CSF NFL levels over two years in vaccinated individuals suggest slower disease progression compared to historical data for this population. Larger studies are needed to confirm the promising potential of anti-Aβ oligomer vaccination.

Keywords: Clinical Phase 1, vaccine, anti-Amyloid, oligomeric Aβ42.
Clinical Trial Registry: NCT05328115.

Key takeaway message: ALZ-101 targeting oligomeric Aβ42 was well tolerated and immunogenic in early AD. Vaccinated subjects showed slower ADCOMS decline and lower CSF NFL than expected, suggesting potentially reduced disease progression versus historical data.

P067- EFFECTS OF POZIBIO® AND CERBELLA® SUPPLEMENTATION ON BRAIN FUNCTION AND WELLBEING IN OLDER ADULTS.

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Background: Multi-nutrient strategies targeting the gut–brain axis may offer additive benefits for cognitive and emotional health. This study investigated the combined effects of PoZibio® and Cerbella® supplementation on EEG markers and wellbeing in older adults. PoZibio is an oral dietary supplement containing a heat killed strain of Lactobacillus paracasei. Cerbella is a combination of fish oil, panax ginseng extract and green tea extract. **Methods:** This trial was a randomised, placebo-controlled study (March–July 2025) with four arms (N=54): dual active, PoZibio -only, Cerbella-only, and double placebo. EEG and questionnaire data were collected at baseline and Day 60. ERP components and spectral power were analysed during Stroop and NBack tasks. **Results:** A significant condition*day interaction (p=.048) was observed for N200 amplitude in the NBack task. Estimated marginal means showed that for the Cerbella active + PoZibio Placebo cohort, N200 amplitude increased from day 0 to day 60. Additionally, enhanced P300 responses to distractors and novel stimuli were observed for Cerbella active + PoZibio Placebo cohort versus Cerbella placebo + PoZibio Placebo (diff ≈ +0.8 μV, t ≈ 3.0), suggesting improved conflict monitoring and novelty processing following Cerbella intervention. All groups showed increases in delta and theta power (p<.05), consistent with practice effects. Questionnaire data revealed improved sleep efficiency, energy, and mental wellbeing in PoZibio -active groups, especially PoZibio active + Cerbella placebo. **Conclusions:** Cerbella supplementation may enhance attentional and novelty processing, while PoZibio appears to support subjective wellbeing. Combined interventions may offer complementary benefits for cognitive and emotional health in ageing.

Key takeaway message: Dual supplementation may yield benefits for brain function and wellbeing

P069- COMPUTERISED COGNITIVE TRAINING BENEFITS COGNITION IN OLDER ADULTS WITH COGNITIVE IMPAIRMENT IN LONG COVID: OUTCOMES FROM THE BEACON RANDOMISED CONTROLLED TRIAL.

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Background: One of the public health legacies of the Covid-19 pandemic is the widespread prevalence of Long Covid, usually with cognitive manifestations. The precise aetiology of this post-SARS-CoV-2 infection remains undefined but cognitive deficits have been widely reported across the breadth of cognitive domains, with 81% of patients reporting brain fog. Cognitive impairment is a major public health issue, predominantly due to its association with increased risk for development of clinically significant cognitive decline and dementia in later life (1), with the potential to cause significant concerns for individuals and place further burden on primary and secondary care settings. Long Covid affects between 100 and 400million people worldwide, meaning that these cognitive symptoms are likely to be affecting over 100million people globally. There is therefore an urgent need to address this key symptom of Long Covid. Given the national and global scale of the issue, it is imperative that any intervention be affordable, widely accessible, and easily administered by health professionals. Cognitive training has proven effectiveness in maintaining cognition in older adults, and can be delivered online, thus addressing the need for scalability and affordability (2,3). The BEACON trial aimed to establish the impact of a computerised cognitive training programme, ReaCT, on cognition in patients with Long Covid. **Methods:** This study is a two-arm double-blind randomised controlled trial of the ReaCT cognitive training programme in 670 adults with cognitive impairment following infection with SARS-CoV-2. The trial was delivered remotely to individuals in the community. The primary population of interest was adults aged 50 and above, with a secondary population of adults aged 18-49. Eligible participants had a history of SARS-CoV-2 infection and subjective cognitive impairment and had access to a device with the internet. Participants were recruited across the UK through primary care settings, publicity and existing cohorts and signposted to access the BEACON trial on their device. Participants were randomised to either the active ReaCT training programme of six cognitive training games with a ratchet-model training mechanism or to an active control which contained identical games without the training mechanism. The primary outcome measure was executive function measured by the Verbal Reasoning cognitive test at six months. Additional cognitive outcomes were measured as secondary outcomes at six weeks and six months using the PROTECT Cognitive Test System (4). An initial analysis was conducted as a modified intention-to-treat approach in participants completing at least one session of cognitive training, controlling for age, gender and educational attainment level, using an ANOVA general linear model. **Results:** 667 participants were included in the MITT analysis, with 467 completing the six-month timepoint. The cohort had an age range of 50-84 years old and was well balanced for age, sex, educational attainment level and baseline cognitive performance. Analysis showed significant benefit to the primary outcome measure of executive function in adults over 50 in the ReaCT treatment group at six months (Cohen's d effect size (ES) 0.316, P=0.04). Significant benefit was also seen in measures of numerical working memory (ES 0.13, P=0.041), episodic memory (ES 0.215, P=0.036) and speed of attention (ES 0.208, P=0.038). No significant benefit was seen in measures of attentional accuracy (P=0.419). **Discussion:** This trial has shown that computerised cognitive training

confers benefit to cognition in older adults who are experiencing cognitive impairment following Covid-19 infection. The impact on cognition is seen across multiple cognitive domains, indicating a generalised benefit. Given the large-scale public health issue presented by Long Covid, and the imperative to deliver interventions to support long-term health in this group, these findings suggest that this training programme could provide a valuable intervention for brain health. Its online delivery format means it is scalable and accessible to large numbers of patients.

Keywords: Long Covid, cognition, cognitive training, clinical trial.

Disclosures: Clive Ballard has received consulting fees from Acadia pharmaceutical company, AARP, Addex pharmaceutical company, Eli Lily, Enterin pharmaceutical company, GWPharm, H.Lundbeck pharmaceutical company, Novartis pharmaceutical company, Janssen Pharmaceuticals, Johnson and Johnson pharmaceuticals, Novo Nordisk pharmaceutical company, Orion Corp pharmaceutical company, Otsuka America Pharm Inc, Sunovion Pharm. Inc, Suven pharmaceutical company, Roche pharmaceutical company, Biogen pharmaceutical company, Synexus clinical research organization and tauX pharmaceutical company and research funding from Synexus clinical research organization, Roche pharmaceutical company, Novo Nordisk pharmaceutical company and Novartis pharmaceutical company. Anne Corbett discloses financial relationships with Suven and Janssen pharmaceutical companies for consultancy work.

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Key takeaway message: Computerised cognitive training confers benefit to cognition in older adults with Long Covid and could offer a scalable, affordable intervention to address cognitive impairment in this large patient group

P070- ANTI-ABETA TREATMENT WITHOUT ARIA-E USING THE OLIGOMER DISASSEMBLING COMPOUND PRI-002 IN AN ONGOING PHASE 2 TRIAL.

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Aims: Amyloid related imaging abnormalities (ARIA) are a common side effect of monoclonal anti-amyloid antibodies and limit the benefit risk ratio. Here we investigate the safety and efficacy of the anti-oligomeric all-D-peptide PRI-002 in early AD. PRI-002 is an orally available, first in class compound developed to disassemble neurotoxic and synaptotoxic Aβ oligomers into harmless Aβ monomers. In a phase 1 B study PRI-002 has been shown to improve learning and memory function in early AD patients after 4 weeks of once-daily oral treatment and 4 weeks follow-up (Kutzsche et al., Nat. Commun. 2025). A phase 2 study is investigating safety and efficacy in a larger patient cohort. **Methods:** PRImus-AD (NCT06182085) is an ongoing randomized, double-blind, placebo-controlled phase 2 study of PRI-002 in early symptomatic AD. Primary efficacy outcome is CDR-SB. MRI monitoring to detect ARIA events is performed. **Results:** 304 patients 70.4±6.5 years on age, with a MMSE of 25.2±2.2, 155 with MCI (51.0%) and 149 (49.0%) with mild dementia were randomized. CDR-SB at baseline was 3.3±1.4 and RBANS-DMI 54.8±12.7. 208 patients have at least one APOE4 allele (68.4%). After 90 patients, irrespective of the treatment arm, had passed the first 24 weeks of treatment, the incidence of ARIA was evaluated. Within these 90 patients ARIA-E occurred in 4 (4.4%) and ARIA-H were detected in 13 (14.4%) subjects. An unblinded DSMB reviewed the ARIA incidence in all three study arms and recommended to terminate repetitive ARIA monitoring. **Conclusions:** In an ongoing phase 2 trial with oral PRI-002 that was designed to disassemble synaptotoxic Aβ aggregates into harmless Aβ monomers, the study drug is well tolerated and the safety profile favorable. Clinical efficacy data are expected in 2026.

Key takeaway message: PRI-002 is an orally available drug that is designed to disassemble toxic Abeta oligomers into harmless monomers. PRI-002 has been demonstrated in phase I studies to be safe and well tolerable - with interesting signs of efficacy in MCI and mild AD patients.

P071- NEFLAMAPIMOD SIGNIFICANTLY LOWERS PLASMA GFAP AND CORRELATES WITH CLINICAL BENEFIT IN DEMENTIA WITH LEWY BODIES: RESULTS FROM THE REWIND-LB TRIAL.

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Background: There is an urgent need for validated biomarkers that reflect disease processes in dementia with Lewy bodies (DLB). Plasma glial fibrillary acidic protein (GFAP) is a promising candidate: it rises in the prodromal stage of Lewy body disease, predicts cognitive decline in DLB, but is not associated with CSF Aβ42, suggesting it captures DLB-specific mechanisms. Autopsy data support this, showing plasma GFAP correlates with atrophy and tau but not amyloid pathology. Neflamapimod, an oral p38α kinase inhibitor, targets molecular drivers of cholinergic degeneration and rescues basal forebrain cholinergic neurons in preclinical models. In a retrospective analysis of phase 2a clinical data (CTAD 2024), neflamapimod reduced plasma GFAP versus placebo, with reductions correlating to CDR-SB benefit. Based on these findings, plasma GFAP was prospectively defined as the primary biomarker endpoint in the phase 2b RewinD-LB trial (NCT05869669), at study that otherwise showed significant and clinically meaningful effects on clinical progression, assessed by CDR-SB and ADCS-CGIC (Gomperts et al., AD/PD 2025; Honig et al., AAIC 2025). Here, we report the plasma biomarker results. **Methods:** A total of 159 participants meeting consensus clinical criteria were enrolled in a 16-week randomized, placebo-controlled period, followed by a 32-week neflamapimod-only extension. The population was enriched for those without AD co-pathology (plasma ptau181 <27.2 pg/mL, Quanterix® v2.1). Two drug batches were used: NFMD/A, which did not achieve target plasma concentrations (used only during the randomized phase), and NFMD/B, which achieved target concentrations (introduced progressively during the extension). During the first 16 weeks of the extension, 94 participants received NFMD/B and 55 received NFMD/A (most of whom switched to NFMD/B thereafter). Plasma GFAP and neurofilament light chain (NfL) were measured at Amsterdam Medical Center using the Simoa NF4PE kit, with all values reported in pg/mL. Reference is made to the results from Doeke et al (Alzheimers & Dementia, 2025), in which the same assay was utilized in the same laboratory to measure plasma various biomarkers, including GFAP and NfL, in patients with DLB (and other patients with AD and non-AD dementia) and healthy controls. **Results:** At baseline, mean plasma GFAP was 150 (SD 90), similar to the published value in DLB (154 [83]) and elevated versus controls (104 [45]). Mean baseline NfL was 21.9 (15.9), intermediate between DLB (26 [13.6]) and controls (17.5 [9.0]) in the reference publication. During the randomized phase, both placebo and NFMD/A groups showed

small, similar increases in GFAP (placebo median +5.8; NFMD/A +1.9) and NfL (placebo +0.25; NFMD/A +1.8). In contrast, during the extension, participants receiving NFMD/B at any point in the Extension showed significant GFAP reductions (N=107; median −16.0, IQR −35 to +6.7; p<0.00001 for change from start to week 32 of Extension), whereas no reduction occurred in those receiving NFMD/A for the entire Extension (N=12; median −0.1). In a within-subject comparison in participants who received placebo during the randomized period and then NMFD/B during the Extension, change in plasma GFAP over 32 weeks was significantly lower during treatment with NFMD/B compared to change over 16 weeks in the same participants during placebo administration over 16 weeks (-16.7 with NFMD/B, +5.8 with placebo; median difference = -23.5 pg/mL, p=0.016, paired Wilcoxon test). In this group, GFAP change correlated with CDR-SB change (r=0.35, p=0.036). NfL did not decline with NFMD/B (median +0.97 over 32 weeks, IQR −1.6 to +3.2). **Conclusions:** Neflamapimod in the Rewind-LB study markedly reduced plasma GFAP levels in patients with DLB when target plasma drug concentrations are achieved, confirming the preliminary findings from phase 2a. The magnitude of the effect appears to be substantial, with reductions relative to placebo corresponding to 40-50% of the disease-specific elevation in plasma GFAP (i.e., the increase observed in DLB compared with healthy controls). Importantly, this reduction appears clinically meaningful, as it correlates with treatment response as measured by CDR-SB. These findings also further support plasma GFAP as a validated biomarker for monitoring neurodegenerative processes in DLB.

Keywords: Plasma GFAP, dementia with Lewy bodies, clinical trial, neflamapimod.

Disclosures: Neflamapimod is an investigational drug. J. Alam, A. Gardner, and K. Blackburn are employees of, and H-M Chu is a consultant to CervoMed Inc, the company developing neflamapimod. C.E. Teunissen has no disclosures to declare. After the abstract draft was finalized, ChatGPT was utilized, with human oversight, solely for the purpose of improving readability of the manuscript.

Clinical Trial Registry: NCT05869669; https://clinicaltrials.gov.

Key takeaway message: Neflamapimod reduced plasma GFAP in DLB patients when target plasma concentrations were achieved. The reduction was substantial — corresponding to ~40–50% of the disease-specific elevation in plasma GFAP — and clinically meaningful, correlating with CDR-SB benefit.

P072- REAL-WORLD CLINICAL, SAFETY AND PATIENT-REPORTED OUTCOMES OF TREATMENT WITH LECANEMAB IN A NEW ENGLAND ALZHEIMER'S DISEASE CENTER.

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Background: The development of Alzheimer's disease (AD) involves pathologies, including those of amyloid beta (Aβ) peptide and tau processing, inflammation, oxidative stress, and vascular risk factors. AD has a non-linear progression over time that begins slowly during the initial phase of disease and then rapidly increases as patients transition from mild cognitive impairment (MCI) to AD. The humanized IgG1 monoclonal antibody lecanemab binds with high affinity to protofibrils of Ab protein. In clinical studies, lecanemab 10 mg/kg biweekly has been shown to reduce a complex group of protein interactions associated with early symptomatic AD and slow decline on clinical endpoints of cognition and function for up to 48 months to date. Lecanemab was well tolerated in clinical trials, with common adverse events including amyloid-related imaging abnormalities (ARIA) and infusion reactions. The objective of this retrospective case series is to provide an update on our real-world experience with the treatment of individuals with early AD treated with lecanemab. **Methods:** This analysis includes individuals with a diagnosis of early AD who were treated with lecanemab at the Infusion Center of New England in Foxboro, Massachusetts. Data collection included patient demographic characteristics, clinical history, lecanemab treatment exposure, and time from diagnosis to treatment. Assessments included Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) Test for Dementia, and safety measures. Clinician perspectives from our real-world experience with lecanemab and feedback from a patient survey were collected. Data were summarized descriptively. **Results:** A total of 47 patients with early AD were included in the data analysis (33 and 29 patients with 6-month follow-up along with 20 and 19 patients with 12-month follow-up MMSE and MoCA results, respectively; 45 patients who had at least one dose of lecanemab were included in safety analysis). Most of the patients were Caucasian (85%) and female (63%), with a mean age of 74 years. The most common diagnosis was mild AD (68%), and 66% of patients were ApoE4 carriers (51% heterozygotes; 15% homozygotes). Eight patients were initially on aducanumab and successfully transitioned to lecanemab. At 6 and 12 months, mean MMSE (baseline:23.8; 6-months:23.5; 12-months:23.4) and mean MoCA scores (baseline:18.7; 6-months:19.0; 12-months:18.2) were generally maintained or improved. The overall safety profile for lecanemab was similar to that observed in published clinical trials. One asymptomatic ARIA-E (2.2%) case, 2 asymptomatic ARIA-H (4.4%) cases, one symptomatic ARIA-E case (resolved), and 14 infusion-site reactions (31.1%) were observed. No new long-term safety signals were identified. Of the survey responders, 93.5% (n=31, mean follow-up 298 days) reported feeling 'very satisfied' (20/31) or 'satisfied' (9/31) with lecanemab treatment and experiencing stabilization or slowing of disease progression on lecanemab. **Conclusions:** Real-world evidence of the lecanemab safety and tolerability profile in our infusion center experience were consistent with published clinical trials, which demonstrated that lecanemab slowed disease progression in early-stage AD. Patient-reported outcomes gathered from patients who had been on lecanemab for almost a year were consistently positive.

Key takeaway message: In our infusion center, lecanemab slowed disease progression in indivdidual with early AD, with a tolerability profile consistent with published clinical trials. Individuals receiving lecanemab treatment at our center consistently reported positive feedback in patient-reported assessments.

P073- AMYLOID CO-PATHOLOGY AND COGNITIVE DECLINE IN BUNTANETAP TREATED PARKINSON'S DISEASE DEMENTIA PATIENTS.

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Background: Neurotoxic aggregating proteins—such as alpha-synuclein, amyloid-beta, and tau—are known to disrupt axonal transport, trigger inflammation, and lead to neuronal death and subsequent functional decline (1-4). Mixed proteinopathies are commonly observed in neurodegenerative disorders, including Parkinson's disease (PD) and Alzheimer's disease (AD) (5,6). Buntanetap (also known as Posiphen) has been shown to regulate the translation of multiple neurotoxic proteins, thereby potentially interrupting the pathological cascade they initiate (7,10). Here we investigated whether the presence of amyloid co-pathology influences cognitive outcomes in PD patients and assessed the efficacy of buntanetap in individuals with and without amyloid co-pathology. **Method:** To test the amyloid co-pathology, pTau217 plasma biomarker was tested in PD patients who had mild dementia and mild cognitive impairment (MCI, MMSE 20-28) at screening. **Results:** In our recent Phase 3 study in early PD patients (NCT05357989), buntanetap demonstrated cognitive improvement across the intent-to-treat population, with particularly notable effects in individuals with MCI or mild dementia. Amyloid co-pathology has been reported in approximately 30–50% of PD patients (5,6). Consistent with prior findings, our study confirmed that about 30% of participants with MCI or mild dementia exhibited amyloid co-pathology. Importantly, although these

patients all had MCI or mild dementia at screening, those with amyloid co-pathology experienced significantly greater cognitive decline over the 6-month study period. In the placebo group, patients with amyloid co-pathology showed a marked reduction in MMSE scores (-2.84 ± 1.054 points from baseline), while those without amyloid co-pathology exhibited minimal decline (-0.16 ± 1.25 points). Buntanetap at 20 mg daily significantly improved cognition in patients with amyloid co-pathology. MMSE scores in this subgroup increased by 1.91 ± 1.227 points from baseline and by 4.75 ± 1.595 points compared to placebo ($p < 0.05$). Similarly, WAIS Coding scores improved by 8.75 ± 5.121 points versus placebo. Additionally, buntanetap treatment led to improvements in MDS-UPDRS total scores in both amyloid-positive and amyloid-negative subgroups. **Conclusions:** Biomarker data revealed distinct patterns of cognitive decline over the 6-month study period between PD patients with and without amyloid co-pathology. Buntanetap treatment significantly improved cognitive function in the subgroup with amyloid co-pathology and improved MDS-UPDRS total scores regardless of amyloid burden. These findings are critical for informing the design of future studies and for further stratifying patient populations to optimize treatment outcomes.

Disclosures: Cheng Fang, Hui Liu, Melissa Gaines, and Maria Maccecchini are employees of Annovis Bio. David Feng is an employee of TCM, contracted for this project. The authors declared no competing interests.

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P074- COMPARING THE EFFECTS OF A MULTI-COMPONENT BEHAVIORAL INTERVENTION FOR PEOPLE WITH MILD COGNITIVE IMPAIRMENT BY CARE PARTNER TYPE.

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Introduction: Multicomponent nonpharmacological interventions, such as the HABIT Healthy Action to Benefit Independence & Thinking® program, have shown promise for improving emotional well-being, functioning, and self-efficacy in people with mild cognitive impairment (pwMCI) and their care partners. However, limited research has examined whether outcomes differ based on care partner type. **Methods:** We analyzed data from 875 pwMCI–care partner dyads who completed the HABIT program. Multivariate linear mixed-effects regression models evaluated differences in clinical outcomes by care partner type (spouse vs. non-spouse) at post-intervention, 6 months, and 12 months. **Results:** Compared with baseline, pwMCI cared for by spousal care partners demonstrated significant improvements in all seven outcomes at post-intervention, whereas those in the non-spousal group showed significant improvements in five outcomes. In the spousal group, reductions (mean changes) in anxiety were sustained across follow-ups—post-intervention (mean change: −2.0; 95% CI: −2.4 to −1.7), 6 months (−0.9; 95% CI: −1.4 to −0.5), and 12 months (−0.9; 95% CI: −1.3 to −0.5. Among care partners, those in the spousal group reported reductions in anxiety (−1.2; 95% CI: −1.6 to −0.9) and depression (−1.3; 95% CI: −1.7 to −0.8) at post-intervention. However, by 12 months, they experienced increases in burden, anxiety and depression relative to baseline. **Conclusions:** The HABIT intervention may have more favorable outcomes at post-intervention for pwMCI and care partners in spousal dyads compared to non-spousal ones. These findings highlight the importance of care partner context in intervention effectiveness. Further research is needed to assess long-term impacts by care partner type.

Key takeaway message: Nonpharmacological interventions for individuals with mild cognitive impairment should account for the influence of care partner type in their implementation.

P075- JOY-ALZ: FIRST NATIONWIDE REAL-WORLD DATA REGISTRY FOR ALZHEIMER'S DISEASE IN KOREA.

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Background: The advent of anti-amyloid disease-modifying therapies (DMTs) has shifted Alzheimer's disease (AD) care toward targeted interventions. Real-world data (RWD) from East Asians are scarce due to trial underrepresentation, healthcare variations, and possible ethnic safety differences. Preliminary findings suggest lower amyloid-related imaging abnormality (ARIA) rates in East Asians, highlighting the need for Korean-specific RWD. **Objectives:** To establish a nationwide RWD registry for AD in Korea, track safety/effectiveness of new anti-amyloid therapies, and harmonize data with ALZ-NET for global comparisons. **Methods:** JOY-ALZ, launched in 2024 by the Korean Dementia Association, is a prospective observational registry in 44 memory clinics. Patients with AD, mild cognitive impairment (MCI), or related

syndromes are enrolled. The Minimum Dataset (MDS) covers demographics, cognition, function, MRI, amyloid PET, treatment, and safety; the Extended Dataset (EDS) adds biomarkers/imaging. Coding (LOINC, ICD-10) and ALZ-NET-compatible formats enable interoperability. Follow-up is every 6 months for 18 months, then annually (NCT06889818). **Results:** As of July 2025, 251 participants have been enrolled (199 with analyzed baseline data). Mean age was 71.2 ± 8.4 years; 73.9% were female; mean education 11.5 ± 4.8 years. Baseline cognitive scores: MMSE 22.4 ± 4.7; MoCA 17.5 ± 5.9; Global CDR 0.7 ± 0.3; CDR-SB 3.5 ± 2.5. Diagnostic distribution: dementia (61.8%), MCI (35.8%), cognitively unimpaired/SCD and others (2.4%). At baseline, 83.3% had received anti-amyloid therapy, and 92.0% were on AChEI/memantine. Among participants who received anti-amyloid therapy (n = 166), safety monitoring identified 11 infusion-related reactions (6.6%) and 9 cases of ARIA (5.4%). **Conclusions:** JOY-ALZ demonstrates the feasibility of a nationwide, standardized RWD platform for AD in Korea, addressing a critical evidence gap in East Asian populations. Early findings provide valuable insights into treatment uptake, safety profiles, and patient characteristics in real-world settings. Ongoing harmonization with ALZ-NET will enable cross-national analyses to inform clinical practice and policy globally.

Key takeaway message: JOY-ALZ, Korea's first nationwide Alzheimer's real-world data registry, fills critical evidence gaps for East Asians, enabling safety and effectiveness monitoring of anti-amyloid therapies and harmonization with ALZ-NET for global clinical and policy impact.

P076- ORAL BLARCAMESINE COMPARISON TO NORMAL COGNITIVE AGING: DEMONSTRATING ALIGNMENT WITH PRODROMAL COGNITIVE AGING TRAJECTORIES IN PRECISION MEDICINE PATIENT POPULATION PHASE IIB/III TRIAL–FOR EARLY ALZHEIMER'S DISEASE PATIENTS.

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Background: There are no approved oral disease-modifying treatments for Alzheimer's disease (AD) with the ability to prolong time in a stable disease state and with clinically meaningful outcomes clear to patients and caregivers. **Methods:** Blarcamesine, for which Market Authorisation Application (MAA) is currently under review by EMA, underwent a randomized, double-blind, placebo-controlled, 48-week Phase IIb/III ANAVEX2-73-AD-004 trial with prespecified gene or GWAS identified genetic variant populations related to the mechanism of the pharmacological intervention. **Results:** Treatment of blarcamesine demonstrated significant clinical benefit in all primary, secondary and exploratory clinical endpoints in the Precision Medicine population ABCLEAR3 with the 30 mg cohort demonstrating cognitive outcomes approximating healthy aging patterns across key standardized assessment scales. Blarcamesine 48-Week clinical outcomes vs. healthy aging benchmarks: • ADAS-Cog13: Blarcamesine showed a change from baseline of 0.853 (±1.423) compared to ~1 point typical annual decline in aging adults. • CDR-SB: Blarcamesine demonstrated a change from baseline of 0.465 (±0.344), aligning with the 0-0.5 point annual range seen in normal aging. • MMSE: Blarcamesine showed a change from baseline of -1.285 (±0.626) compared to ~1 point typical annual decline in aging adults. These data are similar to referenced barely detectable prodromal AD decline (1). **Conclusions:** Oral blarcamesine treatment over 48 weeks in a Precision Medicine population, including up to ~70% of the global population, indicate the ability to shift the cognitive decline of a MCI or mild AD patient population to a prodromal AD population. This is consistent with the 84.7% reduction in decline at 48 weeks of blarcamesine treatment vs placebo on the prespecified co-primary cognitive endpoint ADAS-Cog13 in the ABCLEAR3 population as well as significant absolute improvement in Quality of Life2 (QoL-AD) scores indicating a reversal of negative trajectory for Alzheimer's disease patients from baseline to end of trial. Hence, coupled with a convenient once daily, oral pill administration, blarcamesine restoring impaired autophagy could represent a novel treatment option for up to ~70% of early AD patients benefiting from further improved outcomes using directed Precision Medicine to alleviate significant medical and economic burden. **Keywords:** Blarcamesine, precision medicine, autophagy, randomized clinical trial, GWAS, ADAS-Cog, CDR-SB, MMSE, QoL-AD.

Clinical Trial Registry: NCT03790709; https://clinicaltrials.gov.

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References: 1. McDougall, F et al. "Psychometric Properties of the Clinical Dementia Rating - Sum of Boxes and Other Cognitive and Functional Outcomes in a Prodromal Alzheimer's Disease Population." JPAD. vol. 8,2 (2021): 151-160.

Key takeaway message: In the ABCLEAR3 population, 48-week oral blarcamesine treatment indicate the ability to shift the cognitive decline from MCI or mild AD patient population to a prodromal AD population.

P077- A PHASE 1 CLINICAL TRIAL OF BDNF GENE THERAPY FOR AD AND MCI: UPDATE.

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We are conducting a first-in-human clinical trial of BDNF Gene Therapy in early stage Alzheimer's Disease and Mild Cognitive Impairment. In animal models of AD, including APP tg mice, lesioned rats, aged rats, lesioned monkeys and aged monkeys, AAV2-BDNF gene delivery to the entorhinal cortex prevents neuronal death, enhances neuronal function, restores synaptic density and improves learning and memory. BDNF also reduces Tau phosphorylation. In patients we are administering AAV2-BDNF to the entorhinal cortex under MRI guidance; BDNF is locally produced by neurons and is also anterogradely trafficked down axons to the hippocampus to influence memory circuits of the brain. A total of 7 of 12 patients have been treated to date. The first 6 patients have mild-stage AD (MMSE 21-28) and the next 6 have MCI. Treatment has been well tolerated in all treated patients to date, with the longest patient now 24 months post-treatment. Improvements in FDG PET scans after 6-24 months have been observed in all 3 patients who have been imaged to date. CSF biomarkers, memory function and global cognition will be reported at the meeting. BDNF has the potential to reduce disease progression and restore lost neural function. To date, FDG PET findings are consistent with metabolic recovery of function in memory circuits in treated patients.

Key takeaway message: Early results from a clincial trial of BDNF gene therapy in early stage AD and MCI suggests recovery of brain metabolic activity. Cognitive and biomarker outcome data are pending.

P078- RANDOMISED CONTROLLED TRIAL OF EXTENDED-RELEASE GUANFACINE IN ALZHEIMER'S DISEASE DEMENTIA (NORAD).

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Background: Noradrenaline is a key neurotransmitter that is critical, alongside acetyl choline, in regulation of attentional processes. The locus coeruleus, the brain's source of noradrenergic pathways, is affected very early by the pathology of Alzheimer's disease (AD), resulting in disruption of noradrenergic transmission. We hypothesised that the combination of a noradrenergic agent and cholinergic treatments may have a synergistic symptomatic treatment effect in AD. **Methods:** In the single-center, Phase 3, randomised, double-blind, placebo-controlled NorAD trial, we evaluated the effects of extended-release guanfacine (GXR), an α2A adrenergic receptor agonist approved for treating attention deficit hyperactivity disorder (ADHD), as an add-on symptomatic treatment for individuals with mild and moderate Alzheimer's Disease (MMSE: 10-30). GXR and placebo were supplied by Takeda (previously Shire) Pharmaceuticals, and the trial was funded by the UK National Institute for Health and Care Research. Participants were randomised to receive either daily GXR or placebo in combination with approved cholinesterase treatment for 12 weeks. Active treatment consisted of 1 mg of GXR daily for 1 week followed by 2mg GXR daily for 11 weeks or 1mg GXR daily for 12 weeks if dose increase was not tolerated. Eligible participants had been on a stable dose of donepezil, galantamine or rivastigmine for 12 weeks prior to entering the trial. The primary outcome was the change in cognition, as measured by the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), from baseline to 12-weeks in the GXR treatment group compared to placebo. The trial was powered to detect a mean difference of 3 points on ADAS-Cog at 12 weeks. Secondary outcomes included change in additional measures of attention (Trails A and B, digit-symbol substitution, Test of Everyday Attention and CANTAB-RVP), neuropsychiatric symptoms (Neuropsychiatric Inventory), caregiver burden (Zarit Burden Interview) and activities of daily living (Alzheimer's Disease Co-operative Study - Activities of Daily Living Inventory). **Results:** Following an interim analysis, the recruitment target was reduced from 160 to 148. 148 participants (91 female) were recruited, 72 randomised to placebo (Mean MMSE 18.53) and 76 to GXR (Mean MMSE 19.08). 133 participants (63 placebo; 70 GXR) completed 12 weeks of treatment. 20 patients (36%) randomised to placebo (17 mild, 3 moderate) and 13 (17%) of those randomised to GXR (11 mild, 2 moderate) experienced adverse events during treatment. There was no significant effect of GXR on the primary outcome (ADAS-Cog) or any of the secondary outcomes at 12 weeks. Further pre-specified analyses (type of cholinesterase inhibitor; mild versus moderate severity) revealed no subgroup-specific treatment effect. Three serious adverse events were reported, all in the GXR group. These were all judged to be unlikely to be related to study drug. **Conclusions:** This randomised, double-blind, placebo-controlled, phase 3 trial found no evidence of efficacy on cognition, neuropsychiatric symptoms, activities of daily living, or targeted measures of attention for extended-release guanfacine in patients with a clinical diagnosis of Alzheimer's disease who were taking a concomitant acetylcholinesterase inhibitor. There is meta-analytic evidence that noradrenergic treatments have a small positive effect on cognition in AD, and a more pronounced effect on apathy (doi: 10.1136/jnnp-2022-3291360). However, it should be noted that these effects appeared to be most pronounced for combined noradrenergic/dopaminergic agents, while guanfacine's effects are more specific to the noradrenergic system. There is also phase 2 evidence of a potential neuroprotective effect of another noradrenergic treatment, atomoxetine, in mild cognitive impairment and on this basis, evaluation of longer-term treatment with noradrenergic agents may be warranted.

Keywords: Phase 3, Alzheimer's' Disease, Noradrenaline, Guanfacine, clinical trial registry.
ClinicalTrials.gov: NCT03116126.
Disclosures: Active drug and placebo were provided via an investigator initiated 'drugs only' grant from Takeda (formerly Shire) Pharmaceuticals. PM is a member of the independent data monitoring committee for Johnson and Johnson.
Key takeaway message: This randomised, double-blind, placebo-controlled, phase 3 trial found no evidence of efficacy on cognition, neuropsychiatric symptoms, activities of daily living, or targeted measures of attention for extended-release guanfacine in patients with a clinical diagnosis of Alzheimer's disease after 12 weeks' treatment.

P079- RESULTS OF A «FIRST-IN-HUMAN» OPEN LABEL, PHASE 1 CLINICAL STUDY OF INTRACEREBROVENTRICULAR INJECTIONS OF EX VIVO EXPANDED, AUTOLOGOUS, WNT¬ ACTIVATED, ADIPOSE-DERIVED STEM CELLS IN 6 PARTICIPANTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE (AD).

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Background: There is very little human experience with cell therapy for AD. The current experience with monoclonal antibodies has failed to show cognitive improvement while at the same time reporting significant adverse events. We test the safety of using Wnt-activated adipose tissue-derived stem cells (ADSCs) injected directly into the ventricles of the brain to address the multifactorial etiologies of Alzheimer's disease. **Method:** Three subjects received 2 million, and 3 subjects received 5 million Wnt-expressing, ADSCs («low-dose and medium-dose») of a Phase 1 FDA clinical trial using escalating doses. Participants had age <80 years, FAST stages 4 and 5, cognitive, amyloid PET centiloid scores, and CSF analyses consistent with AD. The participants underwent: 1) lipoaspiration and test product preparation, 2) Ommaya intraventricular reservoir implantation, and 3) infusion of a single dose of the test product via Ommaya reservoir. The primary endpoint was safety. Secondary endpoints included improvements in cognitive testing scores, and phosphorylated tau (p-Tau) and amyloid beta levels. **Results:** Adverse events (AEs) from preinjection surgical procedures included mild bruising and discomfort. Test product injection, showed no AEs (range: 1-62 weeks) including headache or nausea. At 12 weeks post-injection, CSF phosphorylated tau (p-Tau) improved in 80% of the evaluable participants from a median of 60.2 pg/ml (range: 46.9 - 76.1) to a median of 36.8 (range 15.0 – 66.6) amyloid PET scan centiloid scores decreased in 60% of evaluable participants from a pre-injection median of 137.2 (range: 55.33 – 155.47) to a median of 100.53 (range: 55.58 – 168.1). ADAS-cog scores improved in 80% of evaluable participants by week 12 from a pre-injection median of 53 (range: 40 – 69) to a median of 38 (range: 20 – 69, Fig. 4), MMSE scores improved in 60% of evaluable participants by week 12 from a pre-injection median of 16 (range: 14 – 19) to a median of 18 (range: 12 – 20, Fig. 5.) Of the patients reaching 28 weeks of followup after the single dose, all went from cognitive improvement to showing expected signs of disease progression. **Conclusions:** This «first-in-human» trial of intracerebroventricular injection of expanded autologous, Wnt-expressing, adipose tissue-derived stem cells proved well-tolerated and safe for the low-dose and medium dose cohorts. Secondaryendpoints showed promising improvements, however these findings must be considered preliminary as there was a very small sample size and no control group. FDA submission for a Phase 2 trial is pending, and will also include separate trials for Parkinson's disease, ALS, MS and CTE.
Key takeaway message: Alternative approaches to the treatment of neurodegenerative diseases are necessary going forward. Our novel,

«first-in-human» approach is showing safety and signs of efficacy at this early stage.

P080- RESULTS OF A PHASE II RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF S-ADENOSYL METHIONINE IN PARTICIPANTS WITH MILD COGNITIVE IMPAIRMENT OR DEMENTIA DUE TO ALZHEIMER'S DISEASE.

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Background: S-adenosyl methionine is a key metabolite in diverse metabolic pathways on which neuronal homeostasis depends. The AD brain is known to be pathologically deficient in SAMe, with contributing factors including B12 and folate deficiency, hyperhomocysteinaemia, and excessive SAMe consumption in the setting of chronic neuroinflammation. Irrespective of cause, this SAMe deficiency exacerbates several processes that drive AD pathophysiology. Lack of SAMe drives hyperphosphorylated tau accumulation owing to impaired phosphatase function, increases the expression of genes involved in increased Aβ production, hinders acetylcholine production and retention, and promotes a neuroinflammatory state by compromising the quenching of reactive oxygen species by glutathione. Multiple animal models of neurodegenerative conditions, including the 3xTg mouse model of AD, demonstrate that SAMe supplementation improves cognition (1,2,3). Among humans with AD, SAMe has only been tested as a component of a multi-ingredient nutraceutical supplement, rather than as a stand-alone treatment. In these small phase I (4,5) and II (6) trials, SAMe administration was well-tolerated and demonstrated improvements in both cognitive function and dementia symptom severity. Currently, SAMe is widely available as a relatively affordable, non-prescription oral supplement. **Methods:** This phase II, randomized, multi-center, double-blind, placebo-controlled trial was conducted among 60 community-dwelling adults with either mild cognitive impairment (MCI-AD) or dementia due to AD according to NIA-AA 2011 criteria (7). Key inclusion criteria were age over 60 and a standardised mini mental state examination (MMSE) score of at least 18 out of 30 at the time of screening. Exclusion criteria included antidepressant use or a history of bipolar affective disorder. Participants were randomized in a 1:1 ratio to receive either SAMe (400 milligrams) or matching placebo, to be taken orally once daily for 180 days. The primary outcome was change in plasma p-tau217 concentration between baseline and following 180 days of treatment, compared between the active and placebo group. Secondary outcomes included the safety of SAMe administration (serious adverse event frequency) and change in cognitive performance measured by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). **Results:** A total of 63 participants (52% female, n=33) were randomized; 59 completed the trial. Balanced representation was achieved of participants with MCI-AD (46%, n=29) and dementia due to AD (54%, n=34). Participants' median age was 77 years (IQR 72.0-80.5). The majority of participants were APOE4 heterozygotes (n=40, 63.5%); 5 were homozygous for the ε4 allele (7.9%) and 18 were non-carriers (28.6%). At baseline, median results include a global Clinical Dementia Rating score of 0.5 (IQR 0.5-1), MMSE score of 24 (IQR 22-27), and RBANS total score of 68 (IQR 57.25-77.75). Results of primary and key secondary endpoints will be presented at CTAD. **Conclusions:** The AD treatment landscape would be transformed by the identification of an effective, cheap, well-tolerated, orally administered disease-modifying drug. Demonstration of safe and effective lowering of plasma p-tau217 with SAMe supplementation in this phase II trial would represent a significant step towards this endpoint, and would warrant exploration in larger phase III trials.

Keywords: Phase II clinical trial, S-adenosyl methionine; anti-tau, disease-modifying drugs.

Clinical Trial Registry: ACTRN12620000506998; http://www.anzctr.org.au.

Disclosures: This trial is funded by the Alzheimer's Association (US), National Health and Medical Research Council (NHMRC) of Australia, and by grants from the Yulgilbar Alzheimer's Research Program and Besen Family Foundation. The trial is sponsored by the University of Melbourne. S.H. is supported by an NHMRC Postgraduate Scholarship and the Australian and New Zealand Association of Neurologists Gwen James Dementia Fellowship. P.Y: Paid consultancy/presentation fees from Eisai, Eli Lilly, Novo Nordisk. N.Y. is supported by an NHMRC Investigator Grant (GNT2009843) and received honoraria for educational activities from Eli Lilly and Novo Nordisk. **References:**

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Key takeaway message: Demonstration of safe and effective lowering of plasma p-tau217 with SAMe supplementation in this phase II trial would represent a significant breakthrough and would warrant exploration in larger phase III trials.

P081- ABVAC40 VACCINE IS ASSOCIATED WITH REDUCED CORTICAL PERFUSION DECLINE IN EARLY-STAGE ALZHEIMER'S DISEASE: RESULTS FROM THE AB1601 PHASE 2 STUDY.

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Background: ABvac40 is an in-development vaccine targeting Aβ40 for the treatment of Alzheimer's disease (AD). Aβ40 plays a significant role in several pathological processes of AD, especially concerning amyloid deposition in blood vessels. The AB1601 phase 2 clinical trial of ABvac40 showed positive results with a favourable safety profile, robust immunogenicity, and promising trends in cognition and brain atrophy. We have conducted a quantitative analysis of cortical brain perfusion using the perfusion image obtained from the early acquisition phase of the amyloid PET scan, conducted within the framework of the AB1601 study. **Methods:** Perfusion PET images were quantified at baseline, 12-month, and 24-month visits of the AB1601 phase 2 study (NCT03461276), a multicenter, randomized, double-blind, placebo-controlled trial. All analyses were performed blinded by a team of nuclear medicine experts. Volumetric regions of interest (VOIs) were defined using the automatic anatomical labelling atlas. Twenty cortical VOIs (10 per hemisphere) and the cerebellum as the reference region were selected. Mean uptake values (kBq/cc) were extracted from each spatially normalized image, and VOI-to-cerebellum uptake ratios were calculated. Changes from baseline in perfusion of individual brain regions were analyzed using a Mixed-Model Repeated Measures approach. Additionally, a voxel-wise analysis was performed using Statistical Parametric Mapping (SPM) to explore regional perfusion differences at 12 months in patients with available data at both baseline and 12-month visits. **Results:** Positive trends favoring ABvac40 were observed in perfusion changes across multiple individual brain regions, compared to placebo. Statistically significant differences between groups were found at 12 months in the right parietal cortex (P=0.0447), right occipital cortex (P=0.0476), and left posterior cingulate (P=0.0346), with less perfusion decline in the ABvac40 group. Voxel-wise analysis using SPM revealed a more pronounced and widespread perfusion decline in the placebo group compared to the ABvac40 group. **Conclusions:** Preliminary findings suggest a favorable trend in regional perfusion in the ABvac40 group, particularly in cortical areas relevant to CAA. These differences, supported by voxel-wise SPM analysis, may reflect a vascular-related effect of the vaccine, consistent with its proposed mechanism of action targeting Aβ40 and reducing amyloid deposition in cerebral vessels. While exploratory, these results provide encouraging signals of a potential treatment effect and highlight the need for future studies to confirm these findings and further investigate the underlying mechanisms.

Keywords: ABvac40, vaccine, Aβ40, brain perfusion, CAA, immunotherapy, Phase 2, Immunotherapy.

Disclosures: MPL, AML, MM, JC and JL are full-time employees of Araclon Biotech-Grifols. JT is a full-time employee of Grifols. EP, KH, and JA received financial compensation for their work on this project, which was conducted under a service agreement.

Key takeaway message: ABvac40 showed favorable trends on cortical brain perfusion, with less decline compared to placebo. These exploratory findings support its vascular mechanism and suggest potential as a disease-modifying therapy for Alzheimer's disease and/or cerebral amyloid angiopathy.

P082- THE ORCHID STUDY: OPTIMIZING RURAL COMMUNITY HEALTH THROUGH INTERDISCIPLINARY DETECTION AND CARE.

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Background: Early dementia detection is imperative in rural areas, which experience multiple conditions that can lead to increased cognitive risk, e.g. high rates of diabetes and hypertension, low education levels, and less access to providers (1). However, dementia diagnosis rates in rural settings remain low, which suggests a need for innovative models of dementia detection, diagnosis, and care in rural areas, beginning with dementia-focused education (2). The ORCHID (Optimizing Rural Community Health to Increase Dementia Detection and Diagnosis) clinical trial presented here tested a model to increase dementia awareness, diagnosis, detection, and management in a rural and racially/ethnically diverse region of south Florida. **Methods:** A total of 294 residents, providers (n=14), health educators (n=8) and nursing students (n=23) collaborated in a quasi-experimental study comprising two community-based research interventions to increase local management of Alzheimer's disease and related dementias (ADRD): 1) one-group community brain health education intervention, and 2) clustered non-randomized Primary Care Provider (PCP) training intervention vs usual care, designed to foster new ADRD diagnoses and treatment. Resident education included a picture graphic brochure, also available in Spanish and Haitian Creole, based on the Alzheimer's Association ten healthy brain habits (3) designed primarily by a local nun who had served the community for over 20 years (4). Providers in the intervention group (n=4) received University of Washington's online Cognition in Primary Care Program (5). Providers in the control group (n=10) continued with their usual model of care. All providers were offered a manual consisting of novel and culturally relevant ADRD information and community resources. Pre-post analytic methods were used to assess changes in dementia knowledge (Basic Knowledge of Alzheimer's Disease (BKAD) (6) in residents, Alzheimer's Disease Knowledge Scale (7) in providers), mood (CES-D) (8), health literacy (REALM-SV) (9), dementia literacy (Dementia Literacy Assessment) (10) in residents, and rates of dementia screening (Mini-Cog©) (11) diagnosis, and treatment in residents and patients in participating PCP offices. **Results:** Most residents participating in the community intervention were African American (81.7%), aged 70.6±8.5yrs, lived in the study rural area for 31.0±19.3yr, and reported 10.2±4.7yrs of education. They had the health literacy equivalent of a 4-6th grade reading level (average REALM SV of 3.3) and showed a combination of lower levels of subjective cognitive impairment and depressive symptoms but poorer cognitive performance. Fifty residents (36%) screened positively for cognitive impairment based on a Mini-Cog© score of ≤3 and were recommended follow-up cognitive assessments. Of these, 44% received in-depth evaluations and most (72%) were started on new ADRD medications. Pre-post AD knowledge (BKAD) increased from 22.7±5.1 to 26.1 ±3.7, especially in Whites vs Blacks (p=0.031). In addition, dementia literacy (DELA) increased from 7.6±2.1 to 9.0±2.0 (p<0.001), with greater improvement in Whites vs Blacks (p=0.014). In the provider intervention group, 36% of patients identified as cognitively impaired were diagnosed and treated in-house, while in the control group, 19% of patients who screened positively for cognitive impairment were referred to a neurology clinic 30 miles away. Group differences were significant at p<0.001. Of interest is that provider confidence in managing ADRD (GPACS-D) (12) increased pre-post intervention by 9.4±3.1 vs 13.0±2.2 in the control and intervention group, respectively (p=0.057). In addition, pre-post provider AD knowledge (ADKS) increased by 1.2±2.7 points in the control group and by 6.5±5.8 in the intervention group (p=0.03). **Conclusions:** The ORCHID study revealed limitations and benefits to methods for community-based, provider-driven dementia diagnoses and treatments. Offering education to providers and their staff regarding cognitive screening led to higher rates of ADRD diagnosis and treatment by trained rural primary care providers. Barriers identified in the pre-trial provider qualitative interviews prevailed in limiting new diagnoses. These were 1) lack of time for training and managing ADRD in office, 2) lack of support for individuals living alone with dementia, 3) lack of community-based dementia specialists, 4) disbelief that treatment would make a difference, or 5) that patients/families would have access to effective treatments. To achieve sustainable increases in dementia detection, diagnosis, and management in rural settings, the ORCHID model can be successful. However, it is imperative to co-create with community stakeholders and local providers the most feasible options for establishing community algorithms for dementia diagnosis and management. Pathways could include the use of dementia-trained adult gerontological nurse practitioners to conduct detailed neuropsychological testing and provide findings with recommendations back to the PCP

(previously successful in this population) (13) or a telehealth approach with the support of local navigators in patient homes or local clinics to connect rural residents with neurology-trained providers (14). Designing the pathways is particularly important considering forthcoming advances in ADRD detection and treatment, such as remote blood biomarker testing (15).

Keywords: Rural, primary care provider training, ADRD diagnosis and treatment, nursing.

Clinical Trial Registry: NCT05760521.

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Key takeaway message: A clinical trial to test the interdisciplinary ORCHID model (Optimizing Rural Community Health to Increase Dementia Detection and Diagnosis) in a rural and racially/ethnically diverse region of south Florida revealed unexpected study strengths and limitations.

P083- VNA-318, A FIRST-IN-CLASS SMALL MOLECULE WITH A UNIQUE DUAL MODE OF ACTION, EXHIBITS PROPERTIES IN THE FIRST-IN-HUMAN TRIAL IDEAL FOR BECOMING A NOVEL COMBINATION PARTNER IN THE TREATMENT OF PATIENTS WITH ALZHEIMER'S DISEASE.

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Background: Despite the recent approval of the first disease-modifying therapies for Alzheimer's disease (AD) in the United States, these treatments provide only modest clinical benefit and carry significant safety concerns. This underscores a continued need for innovative therapeutics that can be used alone or in combination to more effectively and safely slow the progression of cognitive decline. In addition to hallmark amyloid and tau pathologies, AD is strongly associated with mitochondrial dysfunction, characterized by impaired oxidative phosphorylation and compromised cellular energy metabolism, features increasingly recognized as central to disease pathophysiology. We are developing first-in-class small molecules which flip a newly discovered master switch, reverting energy production towards the highly efficient mitochondrial oxidative phosphorylation. Our lead candidate, VNA-318, is an orally bioavailable, brain-penetrant compound that is highly potent and selective, with robust efficacy across multiple preclinical models. In vivo, VNA-318 significantly improved spatial memory in models of cognitive impairment including scopolamine-treated, LPS-challenged, and aged mice. In amyloid beta oligomer-injected aged mice and 5xFAD mice, VNA-318 demonstrated consistent neuroprotective and anti-neuroinflammatory effects. Chronic treatment further resulted in a marked reduction in amyloid beta plaque burden. Importantly, VNA-318 has successfully completed 28-day GLP toxicology studies, supporting its continued advancement toward clinical development. **Methods:** We are conducting a first-in-human, double-blind, placebo controlled clinical trial in healthy male volunteers. In the single-ascending dose (SAD) part of the trial, six cohorts of healthy trial participants were studied with six per cohort receiving 5 to 180 mg of VNA-318 via a liquid formulation, and two receiving matching placebo. In the multiple-ascending (MAD) dose part of the study, three cohorts of twelve healthy volunteers each (nine on VNA-318, three on placebo) are given 30 mg, 75 mg, and 180 mg of VNA-318, respectively. One cohort studied the effect of a standardized breakfast on VNA-318 exposure, whereas in all other cohorts subjects were fasting prior to administration. **Results:** At the time of abstract writing, 45 healthy volunteers have been administered VNA-318, and 15 subjects have been administered placebo. VNA-318 was very well tolerated. With the study still blinded, only two possibly related adverse events were reported, a grade 1 diarrhea, and a grade 1 nausea. There was a nearly dose-linear increase in exposure. At steady-state in the MAD cohort dosed 30 mg of VNA-318, variability of exposure was low with a coefficient of variation for Cmax of 20% and for AUC of 12%. The mean half-life of 16 hours strongly supports the target product profile of once-daily oral dosing. Biomarker data relating to target engagement will be presented and discussed. **Conclusions:** In a first-in-human trial, VNA-318 exhibited an ideal profile for a combination partner for the treatment of patients with Alzheimer's Disease, with excellent tolerability and once-daily oral dosing. Biomarker evidence will be presented to demonstrate the translation of the mode of action from pre-clinical models to humans. If the unique dual mode of action and the strong efficacy consistently demonstrated in pre-clinical models of Alzheimer's Disease can be confirmed in humans, VNA-318 will be a highly promising novel

treatment option for patients with Alzheimer's Disease.

Keywords: Clinical Trial Phase 1, mitochondrial function, dual mode of action, neuroinflammation.

Clinical Trial Registry: NCT06721091.

Disclosures: Klaus Dugi, Silke Kern, Tanes Imamura de Lima, Leila Mirmohamadsadeghi, and Penelope Andreux are employees of Vandria Ltd.

Key takeaway message: VNA-318 is a novel, first-in-class, oral pharmaceutical with a dual mode of action for the treatment of Alzheimer's Disease. Final results from the first-in-human trial including biomarkers will be presented.

P084- ADVANCING ALZHEIMER'S DISEASE CARE: CONVENIENCE FOR BOTH PATIENTS AND FAMILIES WITH ORAL BLARCAMESINE.

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Background: There are currently no new convenient patient-centric oral disease-modifying treatments approved for Alzheimer's disease (AD) which also prioritize patient perspectives that meet patients' needs without the requirement of complex logistical resources and added personnel for drug administration and expensive safety monitoring. **Methods:** Blarcamesine demonstrated in a randomized, double-blind, placebo-controlled, 48-week Phase IIb/III trial (ANAVEX2-73-AD-004) promising clinical results. The trial inclusion requirements were readily manageable for both the patients and the families with no mandatory invasive assessments required. The emphasis was on the National Institute on Aging (NIA) – Alzheimer's Association criteria for diagnosis of early-stage mild dementia due to AD or mild cognitive impairment due to AD. The same accommodating procedures would be followed upon potential market approval. Market Authorisation Application (MAA) is currently under review by EMA for Alzheimer's disease. **Results:** Treatment of Blarcamesine demonstrated significant clinical benefit with slowed clinical progression by 36.3% at 48 weeks for all patients as well as by 49.8% at 48 weeks for the prespecified patient group (~70% of population), as measured by the primary cognitive endpoint ADAS-Cog13 and also on predesignated biomarkers. Blarcamesine demonstrated a strong safety profile with no neuroimaging-related side effects. No ARIA events were reported. There were no deaths related to the study drug. **Conclusions:** Blarcamesine may provide advantages as there are no logistical barriers to treatment with no need to arrange or schedule complex, invasive PET scans, lumbar puncture (spinal tap) or repeated MRIs. This treatment option could be safer ¾ while allowing efficiency, accessibility, and ease for patients and families.

P085- BIOMARKER POSITIVE APOE4 CARRIERS WITH MCI SHOW STABILITY ON MMSE OVER 208-WEEKS OF TREATMENT WITH ORAL VALILTRAMIPROSATE IN A PHASE 2 MULTI-CENTER SINGLE-ARM TRIAL.

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Background: Valiltramiprosate (ALZ-801) is being developed as an oral disease-modifying treatment for APOE4 carriers with Alzheimer's disease (AD). Valiltramiprosate is a valine-conjugated prodrug of tramiprosate, the active agent in ALZ-801, that was shown to prevent amyloid-beta (Aβ) monomer aggregation into toxic oligomers, an early and central driver of AD pathology (Kocis, 2017; Muramatsu, 2025). Amyloid oligomers are reported to cause direct synaptic dysfunction with inhibition of long-term potentiation and neuronal injury, leading to cognitive dysfunction and to progressive hippocampal and cortical atrophy. Tramiprosate (active agent in ALZ-801), had shown promising efficacy signals with favorable safety in ~1300 APOE4 carriers with AD, with no observed ARIA-E (Abushakra 2016). Apolipoprotein ε4 (APOE4), a major risk factor for AD with early and accelerated deposition of amyloid and tau pathologies, rapid cognitive decline and accelerated hippocampal atrophy (Fortea, 2024, Martins 2005, Abushakra 2020). The effects of valiltramiprosate on plasma biomarkers, volumetric imaging and clinical outcomes were evaluated in a Phase 2 single-arm study in APOE4 carriers with Early AD (MMSE 22-30) over 208 weeks. We here report the long-term safety and MMSE effects of valiltramiprosate over 208 weeks. **Methods:** The Phase 2, single-arm, multi-center study of valiltramiprosate (NCT0493520) was conducted at 7 EU sites with AD expertise (Czech Republic and the Netherlands) and enrolled APOE4 carriers (APOE3/4 or APOE4/4 genotypes) with either MCI (MMSE >26) or Mild AD (MMSE 22-26) and CDR-G of 0.5 or 1. Subjects had positive CSF biomarkers at baseline (high p-tau181/Aβ42) or a historically positive amyloid-PET scan. Subjects received open-label treatment at dose of 265mg BID over 104 weeks, with a long-term extension of an additional 104 weeks for a total of 208 weeks (4 years). The primary outcome was reduction in plasma p-tau181 at 104 weeks. MMSE scores were collected throughout the study, including at weeks 104, 156 and 208. Results of the core study have been previously reported for the primary and key-secondary endpoints including plasma p-tau181, hippocampal volume, MMSE, Rey Auditory-Verbal-Learning-Test, and Digit-Symbol-Substitution-Test (Hey, 2024). The last-patient last-visit at 208 weeks was recently completed. Here we present a responder analysis based on MMSE scores, defined as MMSE decline from baseline by ≤4 points and as improvement from baseline by ≥ 1 point. **Results:** 84 subjects were enrolled (51% female, age 69 years, MMSE 26.0, 70%/30% had MCI/Mild AD; 70 completed 104-weeks, 65 had completed the third year (LTE Year 1), and 51 completed the fourth year (LTE Year 2). In the overall study, MMSE stability was high at week 104 (74% of subjects) and became 55% and 43% at weeks 156 and 208, respectively. Subjects with the APOE 3/4 and 4/4 genotypes showed similar response rates, and subjects with MCI had the best response rates. Improvement in MMSE scores of ≥1 was also noted at each timepoint, with 18 subjects showing improvement (26%; range 1-4 points) at week 104; with 8 (12%; range 1-5 points) at week 156, and 5 (10%; range 1-5 points) at week 208 showing improvement compared to their baseline. The majority of responders on MMSE had baseline MMSE scores of ≥25. Overall, valiltramiprosate was well tolerated with the most common adverse events reported in >10% if subjects being COVID-19 infection, nausea, urinary tract infection, decreased appetite, and decreased weight, each of which occurred in ≥10% of subjects; followed by vomiting, anxiety, fall, insomnia, back pain, headache and hypertension, which occurred in >5% of subjects. There were no ARIA-E events, and no symptomatic events of ARIA-H over 208 weeks. **Conclusions:** Amyloid positive, APOE4 carriers with early symptomatic AD treated with valiltramiprosate over 208 weeks (4 years) show stabilized MMSE scores, particularly in subject with MCI at baseline. With clinical stability defined as ≤4-point MMSE decline from baseline, approximately 74% and 43% of subjects had stabilized MMSE scores at 2 and 4 years, respectively. Subjects with MCI at baseline showed a high response rate with 84% and 58% showing MMSE stability at 2 and 4 years, respectively. Analyses of the other clinical outcomes, volumetric and biomarker effects are in progress. Long-term safety over 4 years of treatment was favorable with no ARIA-E and no symptomatic ARIA-H. The safety profile is consistent with prior tramiprosate and ALZ-801 data from >3000 AD patients. These results support the promising efficacy and favorable benefit risk profile of valiltramiprosate with long term treatment of APOE4 carriers.

Key takeaway message: This Phase 2, single-arm, multicenter study of

valiltramiprosate enrolled 84 APOE4 carriers (APOE3/4 or APOE4/4) with early AD. Subjects treated over 208 weeks (4 years) show stabilized MMSE scores, particularly those with MCI at baseline.

P086- THE SAFETY, TOERLABILITY AND ARIA EFFECTS OF THE ORAL ANTI-AMYLOID AGENT VALILTRAMIPROSATE FROM THE PHASE 3 APOLLOE4 TRIAL IN APOE4/4 HOMOZYGOTES WITH EARLY AD.

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Background: Valiltramiprosate (ALZ-801) is a valine-conjugated prodrug of tramiprosate that prevents amyloid-beta (Aβ) monomer aggregation into toxic oligomers, an early and central driver of Alzheimer's disease (AD) pathology (Kocis, 2017; Muramatsu, 2025). Valiltramiprosate/ALZ-801 was evaluated in APOE4/4 homozygotes with Early AD (topline results presented at this meeting, Abushakra et al., 2025). APOE4 is a major risk factor for AD, and for cerebral amlyloid angiopathy (CAA)which underlies the risk of ARIA, with increased risk for patients treated with amyloid antibodies (Sims 2023; van Dyck 2023; Whitington, 2022). Tramiprosate, the active agent in ALZ-801, had shown no ARIA-E in prior studies, allowing the APOLLOE4 trial to include subjects with any number of microhemorrhages (MH) and several siderosis lesions at baseline. **Methods:** This Phase 3, 78-week randomized, double-blind, placebo-controlled, multi-center two-arm trial randomized 325 APOE4/4 homozygotes with Early AD (162 to placebo, 163 to 265 mg BID), and was stratified by MCI (MMSE 27-30) or Mild AD (MMSE 22-26). In addition to standard safety assessments, MRIs were performed every 26 weeks and centrally evaluated (Clario Inc.) for occurance of ARIA with edema and/or microhemorrhage/siderosis (ARIA-E, ARIA-H, respectively). Subjects who had used anti-amyloid antibodies in prior 6 months, or who had lifetime use of anti-amyloid vaccines were excluded. The study allowed use of anti-platelets agents but anti-coagulants were exclusionary. **Results:** A total of 325 APOE4/4 subjects were randomized 1:1 to receive either ALZ-801 or placebo: 51% females, 89% Caucasian, mean age 68 years, MMSE 25.6; 298 had screening/baseline and 290 had post-treatment MRI. At baseline, ~31% of the enrolled population had at least 1 microhemorrhage, 24% had 1 to 4, and 8% had > 4 microhemorrhages; 10% had at least 1 siderosis lesion; with more males than females having microhemorrhages (63% vs. 37%) and siderosis (68% vs. 32%). During the study ARIA-E occurred in 5 subjects in each treatment arm (3%) and macrohemorrhages in 2 subjects/arm. All events were asymptomatic. Increase in MH from low to high category (0, 1-4, 5-9, ≥10 MH) occurred in 14% placebo and 9% in active arm. Radiographically all ARIA-E were mild except 1 severe (placebo) and 1 moderate (active arm). Treatment-emergent AEs with incidence >5% and >2x placebo rate were nausea (26%), weight decrease (14%), decreased appetite and vomiting (10% each); with lower headache, falls and dizziness rates in the active arm. **Conclusions:** In this Phase 3 placebo-controlled trial in 325 APOE4/4 subjects, valiltramiprosate was well tolerated with favorable safety and acceptable tolerability over 78 weeks of treatment consistent with prior tramiprosate/ALZ-801studies in >3000 AD patients. Gastrointestinal AEs were typically mild to moderate and transient; nausea and vomiting occurred early in the course of treatment and showed tolerance after several weeks. Weight loss occurred at later time points and either resolved or stabilized, with no drop-outs due to weight loss. ARIA-E rates were similar between valiltramiprosate and placebo arms (~3%), ARIA-H incidence was lower than placebo, and no ARIA events were symptomatic. In this high-risk APOE4/4 population with high prevalence of CAA, there was no increased risk of ARIA-E or ARIA-H. In the prespecified MCI group that showed promising clinical benefits, valiltramiprosate provides a favorable benefit-risk profile in APOE4/4 patients who have unmet need for safe and effective disease-modifying treatments.

Key takeaway message: In Phase 3 placebo-controlled trial in APOE4/4 Early AD subjects, oral valiltramiprosate showed favorable safety/tolerability with nausea as most common adverse event. There was no increased risk of ARIA, and no symptomatic events of ARIA.

P087- COGNITIVE EFFECTS OF POSTBIOTICS IN AGING AND COGNITION: STROOP PERFORMANCE BENEFITS IN A DOUBLE-BLIND STUDY.

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Background: The gut–brain axis has emerged as a promising target for interventions to support cognitive function in aging. Postbiotics, defined as inanimate microbial preparations conferring health benefits, may modulate cognitive control processes. This randomized, placebo-controlled trial examined the effects of a novel postbiotic intervention on cognitive performance and self-reported health in older adults. **Methods:** Fifty healthy participants aged 56–85 years (Intervention: n=26; Placebo: n=24) were randomized for 60 days. Cognitive outcomes included the Stroop Task (N=50) and N-back working memory task (N=43 after outlier removal). Self-reported outcomes included the Pittsburgh Sleep Quality Index (PSQI), Gastrointestinal Symptom Rating Scale (GSRS), Short Form Health Survey (SF-36), and Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS). Data were analyzed using repeated-measures ANOVA with Condition × Time interactions as the primary effect of interest. **Results:** In the Stroop task, significant main effects of Time ($p<.001$) and Congruency ($p<.001$) were observed, alongside a three-way interaction of Time × Congruency × Condition ($p<.001$, $\eta^2=.214$). The intervention group demonstrated reduced Stroop interference at Day 60, indicative of improved inhibitory control, whereas controls showed worsening performance. No significant effects were detected in the N-back task. Questionnaire data revealed no significant intervention effects on global scores across PSQI, GSRS, SF-36, or WEMWBS, though exploratory analyses indicated subtle trends in physical functioning (SF-36) and sleep subcomponents (PSQI). **Conclusions:** Sixty days of postbiotic supplementation selectively improved cognitive control in older adults, as evidenced by Stroop performance, without broad effects on working memory or self-reported wellbeing. These findings highlight the potential of postbiotics to enhance inhibitory control, a critical aspect of executive function, in healthy aging. Ongoing microbiota, biofluid, and EEG analyses may clarify the mechanisms underlying these observed cognitive effects.

Keywords: Gut–brain axis, postbiotic, aging, cognition, Stroop task.

Key takeaway message: Human-origin heat-inactivated probiotics (Postbiotics) intervention improves cognitive function in mid-aged older adults via modulating gut-brian axis.

P088- VIVA-MIND: PHARMACOKINETIC, PHARMACODYNAMIC, AND MRI EFFECTS IN A PHASE 2 STUDY EVALUATING VAROGLUTAMSTAT (PQ912) IN EARLY ALZHEIMER'S DISEASE.

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Background: VIVA-MIND was a seamless Phase 2A-B double-blind placebo-controlled randomized clinical trial evaluating the efficacy and safety of varoglutamstat (PQ912) as a treatment for early Alzheimer's disease (AD). PQ912 is an oral small molecule that inhibits glutaminyl cyclases (QC), which reduce the pyroglutamate formation of Aβ and CCL2. We have previously reported on the topline safety, tolerability, and clinical efficacy of VIVA-MIND, which was terminated prematurely (1). This follow-on report evaluates the pharmacokinetic (PK) and pharmacodynamic (PD) effects of PQ912 and its efficacy on CSF biomarker and brain volumetric MRI measures (vMRI). **Methods:** The design and methodology of VIVA-MIND has been previously published (2). PQ912 was titrated from 150 mg BID (for 4 weeks), to 300 mg BID (from weeks 5-8), and to 600 mg BID (from week 9 onwards). PK/PD data included steady-state trough (pre-dose) and 2 to <3 hours post-dose median plasma concentrations of PQ912, and serum QC enzyme activity, at weeks 4, 8, 16, 24, 48, and 72. Estimated Target Occupancy (TO) in CSF was calculated from plasma PQ912 levels and the previously ascertained relationship of CSF to plasma. CSF biomarkers, namely Aβ1-42, t-tau, p-tau181, YKL-40, neurogranin, and NfL, were assessed at screening, weeks 24 and 72. Effects on vMRI included assessment of change from screening to weeks 24 and 72 for whole brain, lateral ventricles, hippocampi, and entorhinal cortices. For biomarker and vMRI measures, change from baseline was analyzed using a mixed model for repeated measures (MMRM) with statistical significance reported at a two-sided 5% level. **Results:** There were 109 randomized and treated participants, 52 treated with PQ912 and 57 with placebo, with 73% completing week 24, and 30% week 72. There were no significant differences in baseline characteristics between the treatment groups. The median PQ912 plasma concentrations at trough levels were; 39 ng/mL (n=43) at week 4 on 150 mg BID, 91 ng/mL (n=50) at week 8 on 300 mg BID and 208 ng/mL (n=37) at week 24 on 600 mg BID. At 2 to <3 hours post-dose, median plasma concentrations were; 573 ng/mL (n=46) at week 4 on 150 mg BID, 1280 ng/mL (n=45) at week 8 on 300 mg BID, and 2790 ng/mL (n=24) at week 24 on 600 mg BID. These results are consistent with PK data obtained from earlier clinical studies (3,4). The mean QC activity (mU/L) in serum, at baseline and week 24 respectively, was 366.2 [SD 57.7] and 50.4 [SD 31.4] for the PQ912 arm, and 349.4 [SD 57.1] and 354.1 [SD 88.0] for the placebo arm, demonstrating effective QC inhibition in serum by active treatment of >85%. Treatment with 600 mg BID PQ912 resulted in a relative QC activity in serum 13.9% (SD 8.2), while QC activity was unchanged in the placebo arm (102.3%). The mean estimated TO (%) of PQ912 in CSF, at steady-state pre-dose and 2 to <3h post-dose respectively, was (22.1%, 77.1%) at week 4, (38.1%, 85.9%) at week 8, (51.6%, 93.3%) at week 16, (52.7%, 90.7%) at week 24, (60.2%, 94.6%) at week 48, and (47.3%, 89.0%) at week 72. For CSF biomarkers, no significant differences were found between PQ912 and placebo arms from baseline to week 24 or to week 72 in LS mean change via MMRM in Aβ1-42, t-tau, p-tau181, YKL-40, neurogranin, NfL, and p-tau181/ Aβ1-42 ratio. For vMRI, there were no significant differences between PQ912 and placebo in change from baseline to week 24 or to week 72 in whole brain, lateral ventricles, hippocampi, and entorhinal cortices. **Conclusions:** These analyses from VIVA-MIND illustrate that PK correlated with the targeted significant inhibition of QC activity in serum. After 600 mg BID dosing of PQ912, the calculated mean target occupancy in CSF was about 50% at trough levels and above 85% 2 to <3 hours post dosing. Although these results fell within the expected target ranges, corresponding changes in CSF biomarkers and brain volumes did not differ significantly between participants receiving PQ912 versus placebo. These findings indicate that the observed QC inhibition at the highest PQ912 dose level (600 mg BID) is not associated with or sufficient to achieve significant treatment effects in AD.

Keywords: Alzheimer's disease, varoglutamstat, PQ912, glutaminyl cyclase.

Clinical Trial Registry: NCT03919162; https://clinicaltrials.gov/study/NCT03919162.

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Key takeaway message: In VIVA-MIND, the confirmed PK correlates well with the significant and anticipated PD effects on QC inhibition. However, despite these expected PK/PD results, no significant treatment benefits on AD biomarkers and vMRI were achieved.

P089- REAL-WORLD EFFECTIVENESS AND SAFETY OF LECANEMAB IN JAPANESE PATIENTS WITH ALZHEIMER'S DISEASE: A SINGLE-CENTER STUDY.

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Background: Lecanemab, an anti-amyloid monoclonal antibody, has consistently demonstrated its ability to slow cognitive and functional decline in early Alzheimer's Disease (AD) (1,2). It received approval for reimbursement in Japan in December 2023. Despite expanding clinical use of lecanemab, real-world data on its effectiveness and safety is scarce. This study aimed to evaluate the clinical outcomes of lecanemab in Japanese patients from a single center, providing real-world evidence from routine clinical practice. **Methods:** A total of 86 patients who met the eligibility criteria for lecanemab therapy (3) and initiated treatment between December 2023 and October 2024 were enrolled, with a study period extending through October 2025. Baseline data included age, sex, symptom duration, amyloid PET or CSF Aβ42/40 ratio, APOE ε4 status, number of microhemorrhages on 3T MRI using susceptibility weighted imaging, plasma neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) levels, and concomitant use of symptomatic medication and antiplatelet agents. No patients were receiving

anticoagulant agents. The primary efficacy outcome was the 12-month change from baseline in the Clinical Dementia Rating (CDR) and its Sum of Boxes (CDR-SB). Safety assessments included infusion-related reactions (IRRs), amyloid-related imaging abnormalities (ARIA), and withdrawal from treatment. Statistical significance of differences between patients with and without ARIA was assessed using t-tests, Mantel-Haenszel tests, and Fisher's exact tests. **Results:** The 86 patients had the mean age of 73.8 ± 8.2 years, with 61 females (71%). A majority of patients (88%) had a baseline CDR of 0.5, and the mean CDR-SB score was 3.0 ± 1.3. Ten percent were APOE ε4 homozygotes and 28% were heterozygotes. At 12 months, among patients with baseline CDR 0.5, 51% remained at CDR 0.5. Among patients with baseline CDR 1, 10% improved to CDR 0.5, 60% remained at CDR 1. A total of 21% of patients showed a stable or improved CDR-SB score, with a mean change of +1.31. IRRs occurred in 28 patients (33%), all of which were mild or moderate. The most common symptom was fever (79%), emerging during the first infusion in 27 of 28 patients (96%). ARIA was observed in 18 patients (21%); ARIA-E ± ARIA-H in 3 patients (4%), and isolated ARIA-H occurred in 15 patients (17%). No patients experienced symptomatic ARIA. ARIA occurred more frequently in patients with higher baseline plasma GFAP levels ($p = 0.04$). In addition, APOE ε4 carriers exhibited a trend toward increased ARIA risk ($p = 0.15$). In contrast, the number of microhemorrhages at baseline and the use of antiplatelet agents were not associated with ARIA. Overall, a total of 14 patients (16%) discontinued treatment: due to disease progression ($n = 9$), due to ARIA ($n = 2$), due to unrelated medical conditions ($n = 2$), and due to safety-related anxiety ($n = 1$). **Conclusions:** In this Japanese AD cohort, lecanemab demonstrated a manageable safety profile in a real-world setting, supporting its feasibility in routine clinical practice. Baseline plasma GFAP levels and APOE ε4 status may influence ARIA risk, underscoring the importance of individualized risk assessment prior to therapy. Future analyses will compare CDR-SB changes between the patients treated with lecanemab and matched historical cohort.

Keywords: Alzheimer's disease, lecanemab, ARIA, japanese cohort, real-world data.

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Key takeaway message: In this Japanese AD cohort, treatment with lecanemab showed manageable safety in real-world practice.

P090- REAL-WORLD EXPERIENCE WITH LECANEMAB THERAPY FOR ALZHEIMER'S DISEASE IN THE INTERMOUNTAIN WEST.

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Background: Alzheimer's disease (AD) is a highly prevalent (1-3) and progressive neurodegenerative disorder (4,5) marked by early deficits in spatial processing (6) and memory. The pathological hallmark of the disease is amyloid plaques (7-10) and tangles of aggregated tau (11), which accumulate in the brains of individuals well before appreciable changes in cognition (12-15). Lecanemab is a monoclonal antibody directed against amyloid plaques that has been FDA approved for the treatment of Alzheimer's disease (AD). Data from pivotal clinical trials demonstrated that treatment with Lecanemab reduced amyloid plaque burden and slowed cognitive decline but also increased the incidence of potentially serious amyloid-related imaging abnormalities (ARIA) (7,16). However, there is relatively little real-world data on Lecanemab's efficacy and safety outside of a clinical trial environment. Here, we report on efforts at the University of Utah to administer amyloid-removal therapy in the Intermountain West (Utah, Wyoming, Idaho, and Nevada). **Methods:** This is a retrospective analysis of patients treated with Lecanemab between April 2023 and July 2025 at an academic medical center. Patients with biomarker-confirmed AD were screened in Cognitive Neurology or Geriatrics clinics at the University of Utah. Screening included neurological evaluations, MRI, lumbar puncture or amyloid PET, and multidisciplinary team consensus discussions. Safety monitoring included routine MRI scans for ARIA, per published guidelines. **Results:** Between April 1, 2023 and July 1, 2025, a total of 2372 patients were seen by prescribing providers. A total of 70 patients had received at least one Lecanemab infusion as of July 1, 2025. Patients were predominantly from Utah (53/70), but significant numbers of patients were from Idaho (8/70), Wyoming (4/70), Montana (1/70), Nevada (1/70), or Florida (1/70). The average distance to the University of Utah was 118.6 miles. For patient convenience, infusions were arranged locally; thus, only 55/70 patients received infusions at University of Utah infusion centers. In total, we observed 14 cases of ARIA, which was significantly associated with ApoE4 homozygosity. Zero cases of ARIA were symptomatic, and there was no association between geographical location and adverse effects. **Conclusions:** Our study examined the safety and tolerability of Lecanemab administration within the Intermountain West region of the United States, utilizing both centralized and distributed infusion sites. Although continued follow up is necessary to establish long-term efficacy and safety, our experience highlights that use of distributed infusion sites increases access to disease-modifying treatment without significant increase in risk to patients.

Keywords: Alzheimer's disease, amyloid-removal therapy, lecanemab, amyloid related imaging abnormalities, limbic predominant age associated TDP-43 encephalopathy.

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Key takeaway message: We report on the clinical outcomes of patients treated with Lecanemab at the University of Utah and observe similar ARIA incidence demonstrated in large-scale clinical trials.

P092- ANALYTICAL AND CLINICAL VALIDATION OF THE APOE GENOTYPING PCR TEST IN PATIENTS FROM THE PHASE III CLARITY AD TRIAL.

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Background: Anti-amyloid beta (Aβ) antibody drugs including lecanemab and donanemab have been recently regulatory approved and clinically administrated for the treatment of Alzheimer's disease (AD). ARIA (Amyloid Related Imaging Abnormalities) has been reported as an adverse reaction, and the risk of ARIA increases with APOE4 status. In Japan, the guidelines for an appropriate use of APOE genetic testing related to dementia states that the results of APOE genetic testing can be used for shared decision-making with patients and their families regarding one of the ARIA risk factors. Therefore, it is necessary to establish a robust and validated testing method in real clinical practice. In this study, we developed an APOE genotyping PCR test that allows for distinguishing six APOE genotypes and evaluated the analytical performance to determine accuracy and sensitivity of APOE genotyping. Additionally, we performed a clinical performance study using patient samples from the Phase III trial of lecanemab (Clarity AD) to evaluate clinical validity of this test. This APOE genotyping PCR test was submitted for regulatory approval in September 2024 in Japan and is currently under review. Our results suggest that the APOE genotyping PCR test is able to determine the APOE genotypes accurately. **Methods:** This PCR test consists of two assays, each designed to detect a single nucleotide polymorphism (SNP) at two different genomic positions to determine the APOE genotype (APOEε2*2, ε2*3, ε2*4, ε3*3, ε3*4, ε4*4). The genotyping function of the PCR device is used to determine the SNP in APOE in each assay. The combination of the SNPs of two positions will define one of six types of APOE genotypes. We evaluated the accuracy and sensitivity (limit of detection: LoD) of this PCR test by measuring synthetic DNA and clinical samples extracted from whole blood with known APOE genotypes. For accuracy, measurements were conducted for each APOE genotype sample (N=9/APOE genotype) using three different lots of the kit. For sensitivity, we tested these samples to determine the APOE genotypes. DNA concentration at which the APOE genotype is determined with 95% accuracy was calculated using the probit method. For the clinical performance study of this PCR test, we evaluated the concordance of APOE genotypes between the APOE genotyping test and the genetic test used in the phase III Clarity AD trial. We assessed the proportion of the samples from subjects who experienced ARIA by APOEε4 status and compared the results with those by genotype determined in Clarity AD. **Results:** We measured synthetic DNA and DNA samples extracted from whole blood with previously determined APOE genotypes using this PCR test. It shows that APOE genotype was determined with 100% accuracy across all APOE genotypes in all three different lots. Furthermore, the LoD for DNA sample concentration in this test was 4.89 ng/test. For patient samples from the Clarity AD trial (N=150), the APOE genotyping test showed 100% concordance to the reference method in determining three APOEε4 status: APOEε4 non-carriers, APOEε4 heterozygous carriers, and APOEε4 homozygous carriers. In addition, the concordance in five APOE genotypes status (APOEε2*3, ε2*4, ε3*3, ε3*4 and ε4*4) was also 100% between the APOE genotyping test and reference method. Furthermore, as a result of the 100% concordance in APOE genotypes, the proportion of the samples from subjects who experienced ARIA in each by APOEε4 status is same between the proposed method and the reference method. **Conclusions:** In this study, this APOE genotyping test was able to accurately determine the APOE genotypes. As a result of testing the synthetic DNA and clinical samples, it was suggested that this PCR test was able to test samples with clinically relevant DNA concentrations and could accurately determine APOE genotypes. This was especially notable when compared to serum proteotype blood tests, which are well known to be affected by high lipid concentrations. It was also confirmed that this test requires no complex steps of the PCR protocol from DNA extraction to reporting the APOE genotypes and could accurately determine the five APOE genotypes in patient samples from the Clarity AD study. Thus, we expect that APOE genotyping using this PCR test can be widely used in clinical practice and serve as a preliminary diagnostic tool prior to the administration of anti-Aβ antibody drugs.

Keywords: Alzheimer's disease, APOEε4, genotype, PCR test.

Disclosures: Authors in Group 1 are employees of Sysmex Corporation, Group 2 of Eisai Co., Ltd., and Group 3 of Eisai Inc.

Key takeaway message: This APOE genotyping PCR test accurately identifies six genotypes, demonstrates high analytical and clinical performance, and offers a reliable, simple method suitable for routine clinical use in Alzheimer's disease management.

P093- BREXPIPRAZOLE TREATMENT FOR AGITATION ASSOCIATED WITH DEMENTIA DUE TO ALZHEIMER'S DISEASE : POST HOC SUBGROUP ANALYSIS BASED ON CARE SETTING (INPATIENT/OUTPATIENT) IN BREXPIPRAZOLE FOR ALZHEIMER'S DISEASE PATIENTS WITH AGITATED SYMPTOMS (BRIDGE) STUDY.

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Background: Brexpiprazole is the first U.S. FDA approved drug indicated for agitation associated with dementia due to Alzheimer's disease and approved in Japan in 2024. The efficacy and safety of brexpiprazole have been demonstrated in the pivotal phase 2/3 (a multicenter, randomized, double-blind, placebo-controlled) BRIDGE study, which is the basis of the regulatory approval of brexpiprazole indicated for agitation associated with dementia due to Alzheimer's disease in Japan (1). The aim of this post hoc analysis in the BRIDGE study was to evaluate the efficacy of brexpiprazole treatment in different subgroups based on care setting (inpatient/outpatient) in Japanese patients with agitation associated with dementia due to Alzheimer's disease. Inpatient refers to patients in hospitals, while outpatient refers to patients at home or in care facilities. **Methods:** Patients were randomized to receive brexpiprazole 1 or 2mg/day, or placebo (3:4:4) for 10 weeks. Brexpiprazole was initiated at 0.5mg in Week 1, increased to 1mg in Week 2 (Day 8), and further increased to 2mg in Week 3 (Day 15) for the 2mg group in

the BRIDGE study. The mean change in Cohen-Mansfield Agitation Inventory (CMAI) total score from baseline to Week 10 was evaluated separately in different subgroups based on care setting (inpatient/outpatient). **Results:** The number of inpatients was 279 (1mg: 75, 2mg: 102, Placebo: 102), and the number of outpatients was 124 (1mg: 33, 2mg: 46, Placebo: 45). At Week 10, the mean change in CMAI total score for inpatients and outpatients in placebo group was –9.3 and -7.5, respectively. The mean change [Treatment difference (95% confidence interval)] for inpatients and outpatients in brexpiprazole treatment was -13.9 [-4.6 (-8.2, -0.9) $p<0.05$] and -8.0 [-0.5 (-6.1, 5.1) $p=0.8642$] for the 1mg group, and -16.7 [-7.4 (-10.8, -4.0) $p<0.001$] and -14.4 [-6.8 (-11.8, -1.9) $p<0.01$] for the 2mg group.
Key takeaway message: Brexpiprazole has demonstrated improvement in the treatment of agitation associated with dementia due to Alzheimer's disease in Japanese patients, regardless of care setting (inpatient/outpatient)

P094- ASSESSMENT OF ORTHOSTATIC TOLERANCE AND EFFICACY OF FIMASARTAN IN ELDERLY ALZHEIMER'S DISEASE PATIENTS WITH HYPERTENSION: A 16-WEEK OBSERVATIONAL STUDY.

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Background: Managing hypertension in patients with elderly Alzheimer's disease (eAD) requires careful consideration due to the high prevalence of autonomic dysfunction, including orthostatic hypotension (OH) and dizziness. These symptoms, combined with postural instability in AD, significantly increase the risk of falls and decrease quality of life. However the effect of ARB on blood pressure control and autonomic symptoms in elderly AD patients remains underexplored. **Objectives:** This study aimed to evaluate the effects of the ARB Fimasartan on blood pressure control, orthostatic stability, and cognitive function in hypertensive eAD patients, with a focus on safety and tolerability. **Methods:** A total of 35 participants with hypertension and AD were included, All patients were 90 years or younger and met the NIA-AA Criteria. They were on a stable dose of donepezil medication for at least 4weeks prior to the study. Fimasartan was administered at an average dose of 40mg (range: 30–60 mg) for a period of 16 weeks ($\pm$4 weeks). Assessments were conducted before and after treatment, including cognitive evaluation using the Korean version MMSE, and measurements of blood pressure and pulse rate in supine and sitting positions to assess the presence and severity of OH and dizziness. **Results:** The average participant age was 75 years (range: 65–85), with a mild to moderate AD. There were 16 males and 19 females. Baseline average blood pressure and pulse rate were 145/88 mmHg and 76/min. After 16 weeks of treatment with Fimasartan, there was a significant reduction in mean sitting blood pressure (systolic: -11 mmHg; diastolic: -8 mmHg; $P < 0.05$). However, no significant changes were observed in orthostatic blood pressure or pulse differences between the supine and sitting positions. The KMMSE scores showed no significant difference after treatment (mean change: -0.5; $P > 0.05$). Importantly, no new cases of OH, dizziness, or postural instability were reported during the study. Additionally, no severe adverse effects related to the study drug were observed. **Conclusions:** Fimasartan effectively reduced blood pressure in hypertensive elderly AD patients without worsening autonomic symptoms such as OH or dizziness. The medication was well tolerated, with no significant impact on cognitive function or new safety concerns. These findings suggest that Fimasartan may be a safe and viable option for managing hypertension in patients with eAD. However, further controlled studies with larger sample sizes and control groups are needed to confirm these results and explore potential cognitive enhancing benefits.

NEW THERAPIES AND CLINICAL TRIALS

P095- PRP-SIRNA: RATIONALE AND DESIGN FOR A FIRST-IN-HUMAN EVALUATION OF THE SAFETY AND PHARMACOLOGY OF INTRATHECALLY ADMINISTERED DIVALENT SMALL INTERFERING RNA (DI-SIRNA) TO REDUCE PRION PROTEIN (PRP) IN PATIENTS WITH PRION DISEASES.

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Background: Prion disease, including sporadic and hereditary Creutzfeldt–Jakob disease (CJD), fatal familial insomnia and Gerstmann-Straussler-Sheinker disease, is a rare, rapidly progressive, and uniformly fatal neurodegenerative disease with no effective treatments. It results from the misfolding of native prion protein (PrP) into misfolded conformers (PrPSc) that aggregate and propagate through the brain, rapidly inducing severe neurodegeneration. Human genetic data and preclinical disease models provide strong support for PrP reduction as a therapeutic strategy (1-3). Individuals with heterozygous loss-of-function variants in the PrP gene (PRNP) are healthy, while pathogenic gain-of-function PRNP mutations cause inherited prion disease. In animal models, lowering PrP consistently protects against disease. Heterozygous PRNP knockout mice are fully resistant to prion infection, and partial PrP reduction in mutant transgenic animals markedly delays disease onset and prolongs survival. Further, antisense oligonucleotides (ASOs) and RNA interference approaches targeting PRNP mRNA yield robust PrP knockdown, reduced neuropathology, and extended survival in prion-infected mice. Together, these findings provide strong rationale for testing PrP-lowering therapies both for disease modification in early stage symptomatic disease and prevention in at-risk PRNP mutation carriers. Di-siRNA is a next-generation RNA silencing oligonucleotide therapeutic engineered to achieve efficient and durable PrP knockdown. Like conventional siRNAs, di-siRNAs act through the endogenous RNA interference pathway: the guide strand is loaded into the RNA-induced silencing complex (RISC), where it directs Argonaute-mediated cleavage of complementary mRNA, resulting in potent and specific post-transcriptional gene silencing. The specific chemical configuration of this di-siRNA offers several potential advantages over other oligonucleotide modalities, including strong potency, long duration of silencing, and improved uptake into tissues, including the brain. These properties make di-siRNA an especially promising treatment modality for prion diseases (4). **Methods:** This study will enroll symptomatic adults with prion disease into two arms: Arm 1 is an observational natural history study with baseline, 4- and 8-week visits in which no drug treatment will occur. Participants will be offered the opportunity to enroll in this arm at any time when recruitment for Arm 2 is not open and they may transition into Arm 2 when open. Arm 2 is a first-in-human, open-label, single-ascending dose trial of intrathecal di-siRNA, with sequential cohorts planned for 50, 100, and 200 mg. Each participant will undergo baseline assessment and dosing with inpatient monitoring, followed by six visits over a 24-week follow-up period. Medical Safety Monitor reviews will guide dose escalation, with sentinel dosing in each cohort. Each arm will enroll up to 15 men or women over age 18. Key inclusion criteria include a diagnosis of probable prion disease per CDC diagnostic criteria, positive CSF RT-QuIC or a positive DNA test for a pathogenic PRNP mutation, and mild-stage disease with a Medical Research Council Prion Disease Severity Rating Scale («MRC Scale») score >15 at Screening. Key exclusion criteria include concomitant non-prion brain disease, suicidality, contraindications to lumbar punctures, pregnancy, and

acute, unstable or other excluded medical conditions or treatments. **Results:** The primary objective is to characterize the safety and tolerability of PrP-siRNA by tracking adverse events, physical, neurological and neuropsychiatric assessments, clinical laboratories, ECG, and MRI, with comparison to the observational arm participants. The secondary objectives are to characterize: 1) pharmacokinetics of single dose PrP-siRNA by measuring siRNA in CSF and blood using MS, 2) pharmacodynamics of PrP-si-RNA by comparing baseline and 4-week post-dose CSF PrP levels using ELISA (5), and 3) longitudinal change in CSF PrP in treated vs untreated participants. Exploratory objectives include to characterize and compare disease progression in untreated and treated participants at the three doses. Assessments will include MRC Scale, MoCA, NPI-Q, MRI signatures of prion disease and disease-related biomarkers in CSF (6). **Conclusions:** This first-in-human trial will determine the safety, pharmacokinetics, and target engagement of intrathecal di-siRNA therapy in prion disease. The findings will establish whether PrP lowering with di-siRNA is a viable therapeutic approach and lay the foundation for future trials aimed at altering the course of these otherwise untreatable, fatal neurodegenerative disorders.

Keywords: Prion disease, PRNP, RNA interference, intrathecal therapy, divalent siRNA, CSF biomarkers. **Acknowledgments:** This NeuroNEXT Network study NN112 is funded by NINDS (3OT2NS138339). The NeuroNEXT Network is supported by the NINDS (Clinical Coordinating Center: UO1NS077179, Data Coordinating Center: UO1NS077352). We also acknowledge the Mass General Brigham IRB (formerly Partners Human Research Affairs) for coordination and implementation of the single IRB model.

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Key takeaway message: This first-in-human trial will establish the safety, pharmacology, and target engagement of intrathecal di-siRNA therapy, laying the foundation for PrP-lowering strategies to alter the course of fatal prion diseases.

P096- COMPARISON OF AMYLOID-RELATED IMAGING ABNORMALITIES RISK FOR LECANEMAB VERSUS DONANEMAB AND THE POTENTIAL IMPLICATIONS.

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Background: Two anti-amyloid monoclonal antibodies, lecanemab and donanemab, have demonstrated efficacy in slowing disease progression in patients with mild cognitive impairment and mild dementia due to Alzheimer's disease (AD). Although both therapies target amyloid pathology, they target different amyloid species for removal, which may impact frequency of occurrence of amyloid related imaging abnormalities (ARIA). The primary objective of this study was to compare the incidence of ARIA and death outcomes using anchored Bucher indirect treatment comparisons (ITCs) based on aggregate data from Clarity AD for lecanemab and TRAILBLAZER-ALZ 2 for donanemab. Additionally, a network meta-analysis (NMA) was conducted to assess the impact of the modified regimen in TRAILBLAZER-ALZ 6 on the comparative risk of ARIA. **Methods:** The primary ITC comparing ARIA rates in Clarity AD and TRAILBLAZER-ALZ 2 utilized aggregate data available in FDA-approved labels, FDA review documents, or peer-reviewed publications. Anchored Bucher ITCs were used to compare rates of ARIA outcomes between lecanemab and donanemab, leveraging placebo as the common comparator. ARIA outcomes included ARIA with edema/effusions (ARIA-E), ARIA with microhemorrhage or superficial siderosis (ARIA-H), intracerebral hemorrhage (ICH, $\geq$1cm), APOE4 status, all-cause death, and other ARIA outcomes in the overall clinical trial population over 18 months. To further understand the modified titration dosing of donanemab, data extracted from the initial ITC was compared to available peer-reviewed data for TRAILBLAZER-ALZ 6. Specifically, the placebo arms served as an anchor between Clarity AD and TRAILBLAZER-ALZ 2, and the donanemab standard dosing arms served as an anchor between TRAILBLAZER-ALZ 2 and TRAILBLAZER-ALZ 6. Available outcomes included any ARIA, ARIA with edema/effusions (ARIA-E), and ARIA with microhemorrhage or superficial siderosis (ARIA-H) over 18 months. Risk difference-in-difference (RDD) with 95% confidence intervals and p-values were derived for all results. The study

populations included all patients assessed for safety outcomes within each trial. In addition to the treatment comparisons using clinical trial data, a combined analysis will be presented, incorporating results from a separate real-world survey study on the burden of ARIA, to compare healthcare resource utilization for managing ARIA events across treatments. **Results:** In the Clarity AD trial, a total of 898 participants received lecanemab and 897 received placebo, while in the TRAILBLAZER-ALZ 2 trial, 853 participants received donanemab and 874 received placebo. The mean age in Clarity AD was 71.4 years for participants receiving lecanemab and 71.0 years for those receiving placebo. In TRAILBLAZER-ALZ 2, the mean age was 73.0 years for both donanemab and placebo groups. The updated NMA included an additional n=207 patients (mean age 73.3 years) with donanemab standard dosing, and n=212 patients (mean age 74.3 years) with modified titration dosing from TRAILBLAZER-ALZ 6. The proportion of APOE ε4 homozygous patients in TRAILBLAZER-ALZ 6 (10%) is lower compared to TRAILBLAZER-ALZ 2 (17%) and Clarity AD (16%). In the primary ITC comparing lecanemab with donanemab standard dosing, lecanemab was associated with significantly lower risks of any ARIA (RDD [95% CI]: -10.1% [-15.3%, -5.0%]), ARIA-E (-10.7% [-14.5%, -6.9%], including symptomatic ARIA-E (3.3% [-5.2%,-1.4%], ARIA-H (-10.1% [-15.0%, -5.2%]), microhemorrhage (-7.5% [-12.1%, -2.9%]), and superficial siderosis (-8.8% [-12.0%, -5.6%]). In the updated NMA comparing lecanemab with donanemab modified titration dosing, results were directionally consistent, showing that lecanemab was associated with a 4.6% lower risk of any ARIA (95% CI: -14.9%, 5.7%), ARIA-E (-2.1% [-10.6%, 6.4%], including symptomatic ARIA-E -1.3% [-5.5%, 2.8%]), and ARIA-H (-8.1% [-17.8%, 1.7%], including microhemorrhage -8.9% [-18.1%, 0.3%] and superficial siderosis-2.8% [-9.7%, 4.2%]). The impact of the ARIA risk difference on healthcare resource utilization will be analyzed and discussed at the conference. **Conclusions:** In the primary Bucher ITCs and the updated NMA, lecanemab was associated with statistically lower risk of ARIA events compared with donanemab standard dosing and numerically lower risks of ARIA compared with donanemab modified titration dosing. Further research on comparative safety profiles in real-world settings may confirm and extend these observations and inform treatment decisions.

Key takeaway message: Indirect treatment comparisons demonstrate that lecanemab was associated with statistically lower risks of ARIA compared with donanemab standard dosing, and numerically lower risks of ARIA compared with donanemab modified titration dosing.

P097- OUTCOMES FROM A REAL-WORLD ACADEMIC ANTI-AMYLOID THERAPY ADJUDICATION BOARD.

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Background: Effective real-world use of anti-amyloid therapies (AATs) requires that clinicians balance disease-modifying benefits with the risk of amyloid-related imaging abnormalities (ARIA) and other adverse effects. Appropriate Use Criteria (AUC) (1,2) have been developed to guide clinicians in achieving this balance, although studies have suggested that a minority of patients actually meet treatment specifications (3). We applied the AUC in a formal monthly, multidisciplinary adjudication board meeting that discussed clinically complicated AAT candidates. Herein, we describe the outcomes from our real-world adjudication board. **Methods:** A multidisciplinary adjudication board was established consisting of four behavioral neurologists, a neuropsychiatrist, a geriatric psychiatrist, two neuropsychologists, two advanced practice providers, a neuroradiologist, a nuclear medicine radiologist, and a stroke specialist at a tertiary referral center in Seattle, WA as previously described (4). A shared document listed patient demographics, clinical information, and final treatment decisions for each month. Between June 2024 and September 2025, a total of 14 anti-amyloid adjudication meetings were conducted and outcomes in 101 patients were recorded. Categories were created for common factors associated with treatment denial. Descriptive statistics were used to determine rates of approval and reasons for AAT denial. **Results:** The adjudication board approved treatment in 53.5% of patients, denied treatment in 24.8%, and deferred treatment in 21.8%. The most common reasons for denial included: abnormal baseline 3T MRI (56%), suspected non-AD pathology (24%), low cognitive screening score (24%), history of prior poor AAT tolerance (4%), anticoagulation use (4%), active seizure disorder (4%), and active cancer (4%). The adjudication board had a 100% approval rate for AATs under the following circumstances: clinical history/data meeting AUC, presence of cardiac comorbidities, hypertension, mental health comorbidities, hypocoagulability, increased travel distance to infusion center, and increased potential need for anticoagulation (e.g., 2 prior paroxysmal atrial fibrillation patients and 1 with DVT). **Conclusions:** When applying the AUC, an academic adjudication board approved the majority of early-stage AD patients for AATs. Our findings contradict prior speculation that a minority of patients would be eligible for infusion therapy using AUC. The most common reasons for rejecting AAT therapy included abnormal baseline MRI findings and biomarkers indicating non-AD pathology, suggesting that these studies may be “rate-limiting steps” in determining AAT eligibility. In terms of chronic diseases, the board was more likely to approve AATs in patients with cardiac disease, hypertension, mental health comorbidities, hypocoagulability, and increased potential need for anticoagulation while rejecting treatment in those with cancer, seizure disorder, and on anticoagulation. Continued longitudinal follow-up of AAT-approved patients is necessary to determine whether real-world long-term outcomes support clinical judgment and application of AUC by an academic adjudication board.

Keywords: Real-world, donanemab, lecanemab, monoclonal antibody, anti-amyloid therapy.

Disclosures: Michael Rosenbloom has received honoraria from Eisai, Eli-Lilly, Johnson & Johnson, Medscape, and CME Outfitters.

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Key takeaway message: A majority of anti-amyloid therapy candidates were approved by a real-world adjudication board when applying Appropriate Use Criteria whereas abnormal baseline MRI findings and non-confirmatory biomarker results were the primary reasons for deferring treatment in early-stage AD patients.

P099- MULTICENTER CASE REGISTRY STUDY OF LECANEMAB IN EARLY ALZHEIMER’S DISEASE IN NORTHWEST CHINA.

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Background: Lecanemab (Leqembi®) is the first drug approved by FDA for the treatment of early Alzheimer’s disease (AD) (mild cognitive impairment due to AD or mild AD dementia) with confirmed brain amyloid pathology. However, the efficacy and safety of Lecanemab in China had not been reported. **Methods:** This is a multicenter case registry study conducted at 30 hospitals in Northwest China. All AD patients treated with Lecanemab were enrolled. The efficacy of Lecanemab was evaluated using Clinical Dementia Rating-Sum of Boxes (CDR-SB), Alzheimer’s Disease Assessment Scale (ADAS-cog), Alzheimer’s Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL) and

Minimal-Mental State Examination (MMSE) every 3 months. Amyloid-related imaging abnormalities (ARIA) were monitored via MRI-T2-FLAIR and MRI-SWI sequences. Blood samples were collected to evaluate the changes of plasma biomarkers (including Aβ42, Aβ40, Aβ42/40 and p-tau181). **Results:** There were 156 participants received Lecanemab treatment until September 20, 2025, all of whom were confirmed Aβ-positive by CSF or PET scans. The mean age was 67.3 years (range 37-88), with 101 (64.7%) female participants. The mean years of education was 12.0 years. Among the participants, 14 (9.0%) were homozygous for the ApoE ε4 allele, and 64 (41.1%) were heterozygous. At baseline, the CDR-SB score was 4.3±2.4, the MMSE score was 18.3±6.2, the ADAS-cog score was 19.0±10.4, and the ADCS-ADL score was 55.4 ±19.5. There were 79 participants completed the 3-month follow-up, 49 participants completed the 6-month follow-up, 23 participants completed the 9-month follow-up, and 6 participants completed the 12-month follow-up. The longest follow-up duration was 62 weeks. The change in CDR-SB at 6 months compare to baseline was 0.38 (95% CI -0.36 to 1.13, P=0.295), for the MMSE score was 0.62 (95% CI -0.47 to 1.70, P=0.253), for the ADAS-cog score was 1.28 (95% CI -0.92 to 3.47, P=0.240), and for the ADCS-ADL score was -2.56 (95% CI -5.29 to 0.16, P=0.063). The change in ADCS-ADL score for female patients at 6 months compare to baseline was -3.67 (95% CI -6.80 to -0.53, P=0.026), while male patients showed no significant changes from baseline on all scales. The plasma Aβ42/40 was increased 0.016 (95% CI 0.003- 0.030, P=0.039), while plasma p-Tau 181 was decreased 0.83 (95% CI 0.199 to 1.461, P=0.014) compared to baseline. Only 4 asymptomatic ARIAs (2. 56%, 1 ARIA-E and 3 ARIA-H) have been reported. Approximately 20% of patients reported treatment-related adverse events primarily involved infusion-related reactions, such as fever and chills, typically occurring within 24 hours post-infusion, which were alleviated with symptomatic treatment. **Conclusions:** This real-world study suggests that Lecanemab is well-tolerated in clinical use in Northwest China, with manageable adverse effects, and no severe adverse events have been reported to date. The neuropsychological scales remained stable during the 6-month follow-up, with males had higher benefit in Lecanemab treatment. Plasma biomarkers showed significant improvement after treatment, while a long-term follow-up and large sample are needed.

Key takeaway message: 1. Lecanemab is well-tolerated in clinical use in Northwest China. 2. Males had higher benefit in Lecanemab treatment. 3. Plasma biomarkers showed significant improvement after treatment.

P100- REPEATED THETA BURST STIMULATION TO BRAIN AREA 8AV TRANSIENTLY IMPROVES MEMORY RETENTION IN EARLY-STAGE ALZHEIMER'S DISEASE.

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Background: Alzheimer's disease (AD) is a progressive neurodegenerative condition characterized by central nervous system (CNS) deposition of amyloid plaques and neurofibrillary tangles, leading to decreased cognitive function through the disruption of large-scale brain networks (LSBNs). The default mode network (DMN) includes the hippocampus and other circuits involved in memory encoding and retrieval. Repeated theta burst stimulation (rTBS), a safe and effective FDA-approved treatment for Major Depressive Disorder (MDD), has been found to slow cognitive decline in AD (1) and intensive treatment (2), represents a potentially efficient way to ameliorate memory symptoms by inducing long-term synaptic plasticity in the network (3). Area 8AV, a subregion of the dorsal premotor cortex recently identified in the multimodal parcellation of the Human Connectome Project (4), is an anatomically accessible note to TMS within the DMN and prior investigations of non-invasive neurostimulation have demonstrated cognitive and behavioral benefits in patients (5-7). In contrast to cognitive screening assessments used in clinical practice, a model-based approach to evaluate memory retention that allows for repeated measurements without practice effects is an effective way to evaluate memory retention and DMN function. Hence, we applied the Seattle-Groningen Memory Assessment (SGMA (8) to assess longitudinal memory retention. In this clinical trial, we evaluated the impact of intensive rTBS to area 8AV (within the DMN) on memory in patients with early-stage AD as measured by SGMA. **Methods:** A single-arm, single-blind, crossover study with sham control was conducted in 8 early-stage Alzheimer's patient (mean age 76.3; 50% female; mean MOCA score 21.2) based on specified inclusion/exclusion criteria that included confirmed AD status with fluid or amyloid PET imaging biomarkers. Structural/functional MRI images, cognitive (MOCA), and mood assessments (GAD-7 and GDS) were collected one week before each stimulation session and four weeks after the final treatment session. Resting-state and task-based fMRI were used to localize the anatomical position of area 8AV and the right-hand primary motor cortex over each patient's individual neuroanatomical images. Functional and anatomical images were then applied to guide the application of rTBS via a dedicated neuro-navigation system. During each session, participants received six 10-min sessions of rTBS (3 pulses at 50 Hz in 5 Hz bursts at 80% of the resting motor threshold) or sham for five consecutive days. After a 4-week washout period, subjects receiving rTBS were switched to the sham regimen and vice-versa. The order of sham and active rTBS was balanced across participants. Memory performance was assessed at baseline and weekly during each treatment's washout period using the SGMA. The cognitive endpoint was the changes in SGMA score from the baseline. Weekly assessments were analyzed with a linear mixed-effect model, including rTBS condition (sham vs active), time after treatment (1-4 weeks), and their interaction as fixed effects. Anxiety and depression scores were included as covariates. Random intercepts and slopes over time were included for each patient to capture individual differences in response to treatment. **Results:** Intensive rTMS to area 8AV resulted in a mean 10.62% improvement in memory retention in the four weeks following treatment ($p = .02$). The effect of TMS declined over time (treatment by time interaction, $p = .06$): improvements were the largest (13.50%) in the week following TMS but returned to baseline by week 4. Sham had no effect on memory performance. Neither anxiety nor depression scores modulated the effect of TMS, nor were affected by treatment type ($p > .27$). Findings from fMRI studies were not analyzed at the time of publication. **Conclusions:** Intensive rTBS to the DMN via region 8AV is a safe and potentially promising treatment for memory loss in early stage-AD. Our preliminary findings suggest that benefits of this intervention are transient and further studies relating to the frequency and duration of non-invasive neurostimulation are necessary to determine the long-term efficacy of this treatment. Finally, fMRI outcomes when analyzed may provide additional insights into rTBS's mechanism of action in AD.

Keywords: Alzheimer's disease, long-term memory, transcranial magnetic stimulation, theta-burst stimulation;,default-mode network, area 8AV.

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Key takeaway message: Intensive rTBS to the DMN via brain region 8AV is a safe treatment that tranisently improves memory retention in early-stage AD.

P101- REAL-WORLD TREATMENT WITH LECANEMAB: MEDICALLY SIGNIFICANT AND INSIGNIFICANT ARIA, AND PSEUDO-ARIA.

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Background: Alzheimer's disease is now a treatable disease with the first proven disease-modifying medications avaialble to practitioners - the anti-amyloid monoclonal antibodies. While limitations to uptake of these new therapies have a variety of reasons, including their novelty, intravenous route of administration, need for amyloid confirmation, mandated MRI monitoring, recommendation to perform genetic counseling, and reluctance of payors to cover treatment, it is likely that the single greatest impediment is fear of side-effects. Amyloid related imaging abnormalities, ARIA-E and ARIA-H, may occur, and the risks of these brain side-effects can figure strongly in both reluctance of practitioners to prescribe, and concerns of patients and their familes to accept, therapy. **Methods:** At our center we have treated 235 patients with lecanemab. Patients have ranged in age from 35 to 90, and have had 1 to 51 infusions, with more tha 4000 infusions administered during the past two years. We describe here our experience with ARIA-E, and baseline and incident ARIA-H. **Results:** ARIA-E has occurred at our center in 11% of cases, more often in APOE4 homozygotes than heterozygotes or non-carriers. We report here the distribution of brian involvement and regional predilections. ARIA-E varies widely in degree of brain involvement from large portions of the brain affected to tiny punctate foci. And while overall, it is more likely that radiologically extensive ARIA is symptomatic, there are many cases in which it is asymptomatic. A new problem has evolved in that while early in the monoclonal antibody experience radiologists sometimes failed to identify minor ARIA-E, but now with increased sensitivity of radiologists to the issue of ARIA, increaseingly noted are cases of «pseudo-ARIA-E» in which a brain MRI is reported as showing ARIA-E, perhaps minor, but further analysis or additional imaging makes clear that the findings were not in fact ARIA. Suspicious regions may include white matter findings or sulci that are be reported abnormal due to comparison of imaging performed on different MRI machines, use of differing MRI techniques, issues of slice thickness and/or volume averaging, and FLAIR artifacts due to incomplete fluid suppression, which may give the the impression of sulcal effusions. Cases of pseudo-ARIA-E can cause distress to patients, families, and disruption to infusion schedules. Similarly, heightened sensitivity to ARIA-H has resulted in many reports of microhemes, and sometimes of superficial siderosis, some of which cases are pseudo-ARIA-H, in that additional imaging may reveal that these findings represent normal vessels. Marked variation in ARIA-H counts of microhemorrhages also results in fluctuating counts, and concerns as to whether continued anti-amyloid therapy is warranted. While pseudo-ARIA-H is an issue, also problematic are the wide variety of susceptibility weighted imaging sequences used, including variants of GRE T2* imaging and SWAN, SWIp, and SWI imaging, differing magnetic field strengths, differing slice thickness, and use or non-use of maximal intensity projections (MIP). **Conclusions:** Monitoring for ARIA-E and ARIA-H are important in the administration of anti-amyloid monoclonal antibodies. However, interpretation of MRI findings can be challenging. While «under-calls» of ARIA may result in individual patients with minor ARIA being infused without pause, this is permissible per product labeling. However, «over-calls» of ARIA are a separate challenge that may be disruptive to patients, families, practitioners, and smooth clinical care. In addition to increasing education, means of decreasing inaccuracy in identification of ARIA, includes use of the same MRI machine and sequences for each patient, when possible, and possibly the use of automated technology, including artificial intelligence. These may promote more uniformity and accuracy in ascertainment of brain side-effects of these useful therapies, and allow for their greater ease of use.

Keywords: Alzheimer disease, lecanemab, ARIA, neuroradiology.

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Key takeaway message: Administration of anti-amyloid therapies requires MRI monitoring for brain side-effects, ARIA-E and ARIA-H, but their identfication may be challenging. MRI findings may be reported as ARIA-E or ARIA-H, but represent pseudo-ARIA, not side-effects.

P102- REDUCED BRAIN NEUROINFLAMMATION AFTER LAROMESTROCEL TREATMENT IN MILD AD: RESULTS FROM THE CLEAR MIND STUDY.

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Background: A hallmark feature of Alzheimer's disease (AD) is neuroinflammation, which is a principal component of disease pathogenesis, gliosis, and neuronal death (1). In the CLEAR MIND study, we demonstrated that laromestrocel treatment improved clinical scores and reduced brain atrophy in multiple brain regions, including the hippocampus as well as the temporal and frontal lobes (2). To extend these findings, we sought mechanistic evidence of an effect on neuroinflammation in core AD-associated regions, particularly the hippocampal and parahippocampal regions. Here we examined the effects of laromestrocel treatment in patients of our CLEAR MIND Phase 2a trial (2,3) on inflammation in the AD brain using diffusion tensor imaging (DTI) and free water analysis. In DTI imaging, although mean diffusivity provides some indication of inflammation, free water is considered a more precise measure and is used in assessing hippocampal AD pathology, although no clinically meaningful difference in free water has yet been defined (4,5). Laromestrocel is a novel, bone marrow-derived, mesenchymal stem cell (MSC)-based investigational therapeutic that targets neuroinflammation, microvascular dysfunction, and has the potential to stimulate endogenous tissue regeneration, and has received RMAT and fast-track designations from the US FDA for mild AD. The CLEAR-MIND study (ClinicalTrials.gov: NCT05233774) was a 49-patient, randomized, placebo controlled, proof-of-concept study that tested 3 different dosing regimens of intravenous (IV) delivery of laromestrocel vs placebo in patients with mild AD dementia. The treatment groups were: four monthly IV infusions of Placebo (Group 1; N=12), 25 million (25M) cells once followed by 3 monthly infusions of placebo (Group 2; N=13); 25 million (25M) cells monthly for 4 months (Group 3; N=13), or 100 million (100M) cells monthly for 4 months (Group 4; N=11) (2). **Methods:** We extracted free water fraction data from the

MRI DTI dataset from nearly 150 brain regions. Sub-regions were grouped into 14 broad categories representing the major brain lobes and circuit systems, e.g. temporal, parietal, occipital, frontal, limbic, hippocampal etc. We focused on the core AD-associated brain regions for pathogenesis, particularly the hippocampal and parahippocampal regions, which include the entorhinal cortex, and which are among the first brain regions to show AD pathology and atrophy. Longitudinal data were collected using 3T MRI at baseline and weeks 16, 26, and 392. Diffusion MRI images were modeled using a single shell bitensor model that separates isotropic (free water) and anisotropic (tissue) diffusion components6. A linear mixed effects model with crossed random intercepts for subject and brain region was used to estimate longitudinal change in free water fraction (CFB) across treatment groups. **Results:** Patients receiving laromestrocel exhibited a durable reduction in free water fraction compared with placebo (N=11) at week 39 for several brain regions, including hippocampus (Group 4: p=0.004, N=8; Group 3: p=0.037, N=8), which showed a dose response, and also temporal cortex (Group 3: p=0.032, N=8), occipital cortex (Group 3: p=0.003, N=8), and parietal cortex (Group 3: p=0.038, N=8). This new result was accompanied by clinical benefit as wells as reduced brain atrophy, as demonstrated in our study2. Of the 14 brain regions, 13 (all but frontal) showed pooled treatment group responses (Groups 2, 3, and 4 combined) in the direction of improvement (reduction in free water) by week 39. **Conclusions:** Overall, treatment with laromestrocel was associated with a reduction in free water compared to placebo across multiple brain regions, including key AD-associated regions—most notably in the hippocampus. These findings suggest a sustained anti-inflammatory effect of laromestrocel, reinforcing its proposed mechanism of action in the treatment of mild Alzheimer's disease. This evidence supports continued clinical development of laromestrocel for this indication.

Keywords: Mesenchymal stem cell, cell therapy, DTI, atrophy, free water.

Clinical Trial Registry: NCT05233774.

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Key takeaway message: After laromestrocel treatment of mild AD, a free water fraction analysis of brain DTI imagery showed reduced neuroinflammation compared with placebo in the hippocampal, temporal, parietal, and occipital cortex after 39 weeks.

P103- A DELPHI PANEL EXPLORING THE BURDEN OF ARIA MANAGEMENT FROM THE PROVIDER'S PERSPECTIVE.

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Background: Amyloid-related imaging abnormalities (ARIA) are important adverse events associated with anti-amyloid monoclonal antibodies (mAbs) used in the treatment of early Alzheimer's disease (AD). ARIA is often asymptomatic, and may be identified and monitored using magnetic resonance imaging (MRI) scans. In some cases, ARIA is symptomatic and if presenting, symptoms may be non-specific or overlap with the symptoms of AD. Symptoms also do not always correspond with the severity of ARIA depicted on MRIs. Following initiation of anti-amyloid mAbs, post-treatment patient monitoring is focused on detecting ARIA and guiding patient management to minimize the likelihood of worsening or recurrence of ARIA. We aimed to describe resource requirements for the management of ARIA events from healthcare providers' perspectives in real-world settings. **Methods:** A modified Delphi panel was designed in consultation with expert clinicians in ARIA detection and management. The panel consisted of 26 healthcare providers ([HCPs], 22 physicians, 4 nurses), who were recruited to participate in two questionnaire rounds and a final consensus meeting. Eligibility criteria included being a United States-based healthcare professional involved in treating patients with early AD (mild cognitive impairment [MCI] due to AD and/or mild AD) with an anti-amyloid mAb in the prior 12 months and/or an understanding of the provider resource requirements for ARIA management associated with anti-amyloid mAbs. The first-round questionnaire was conducted during 18th March–30th April 2025 to gain general perspectives regarding provider resource requirements for ARIA management. The second round will further quantify the resource use and consensus (defined as $\geq$80% agreement) will be secured at the consensus meeting. The study sponsor, investigators, and panel participants remain blinded throughout the conduct of the study to mitigate bias. Interim results from the first-round questionnaire of the Delphi panel are presented in this abstract. Full results from both rounds of the survey will be presented at the congress. **Results:** The average number of patients with early AD treated by HCPs with anti-amyloid mAbs in the prior 12 months was 39. Within 12 months of initiating treatment with an anti-amyloid mAb, 19 out of the 26 HCP participants reported that 0–20% patients they observe developed any ARIA, and only 1 participant reported that over 30% (30–40%) patients developed any ARIA. Of the total cases of ARIA, a greater average number of cases were reported to be asymptomatic (72% [range: 2–100%]) versus symptomatic (28% [range: 0–98%]) across the 14 participants who responded to this question. APOE genotype was considered by 95% physicians (n=21/22) and all nurses as part of their evaluation for suitability for mAbs. The panel did not agree on whether APOE e4 allele status impacts provider resource use and therefore this will be explored further in the future rounds. The Delphi panel identified that ARIA events require additional HCP visits for follow-up. The average additional neurologist, primary care physician, and nurse visits for a patient with any ARIA events were 3.1, 1.5 and 1.0, respectively (ranges: 0–12, 0–10 and 0–6), within 12 months of initiating treatment with anti-amyloid mAbs. The average number of emergency department visits during this 12-month period were estimated to be higher for patients with "symptomatic ARIA" (2.12) and "severe ARIA" (2.15) versus patients with "asymptomatic ARIA" (0.35)", "moderate ARIA" (0.88) and "mild ARIA (0.41). MRIs, computed tomography (CT) scans, clinical exams and neurologist consultations were reportedly the most commonly used emergency department resources. The Delphi panel estimated that a patient with ARIA is likely to receive an average of 3.0 (range 1–6) additional MRI scans (excluding monitoring scans) within 12 months of initiating treatment with an anti-amyloid mAb. Most participants reported that these additional MRIs should be conducted monthly (n=14) or every three months (n=9). An average of 3 phone calls were estimated to be required to discuss MRI scan results with a patient with ARIA, up to 12 months following an episode of ARIA, with the approximate duration of each phone call being 13.4 minutes (range: 3–45 minutes). Overall, 20 out of the 26 participants reported that their healthcare system has the capacity for the additional MRI scans required to assess a patient with ARIA. In the second-round survey and consensus meeting of this Delphi panel, participants will consolidate their responses and reach more specific conclusions on ARIA-related provider resource use.

Conclusions: To our knowledge, this is the first Delphi panel to quantify ARIA-related provider resource use in clinical practice. These interim results provide real-world insights from physicians and nurses on their experiences managing ARIA events, by characterizing ARIA incidence and associated resource use in patients receiving anti-amyloid mAbs. The first-round survey examined HCP visits, emergency visits, MRI scans, and follow-up phone calls. Participants reported higher resource use in patients with severe ARIA and those with symptomatic ARIA. These findings help inform resource planning, patient counseling, and ARIA monitoring protocols as anti-amyloid therapies become more widely adopted.

Keywords: Alzheimer's, ARIA, resource utilization.

Disclosures: Marwan Sabbagh, Jerome Barakos, and Raymond Turner received consulting fees from Eisai. Feride Frech, Chenyue Zhao, and Hideki Toyosaki are employees of Eisai Inc., who provided funding for this study. Richard Perry, Medi Stone and Sophie Pope are employees of Adelphi Values PROVE. Adelphi Values PROVE received funding from Eisai Inc. for the conduct of the study and for manuscript development.

Key takeaway message: This Delphi panel of physicians and nurses characterizes ARIA incidence and quantifies ARIA-related provider resource use in clinical practice, among patients receiving anti-amyloid therapies. Findings will inform resource planning, patient counseling, and ARIA monitoring protocols.

P104- CLINICAL TRIALS (PHASES 1 & 2) OF TRANSDERMAL ALC919 PEPTIDE TO ACTIVATE BRAIN MITOCHONDRIAL COMPLEX I.

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Background: Alcadeins are transmembrane substrates for α- and γ-secretases. In CSF from subjects with presenilin mutations or with typical late-onset sporadic AD, misprocessed alcadein fragments shift to a pattern that resembles the γ-secretase misprocessing pattern for Aβ that is associated with cerebral Aβ amyloidosis (i.e., elevated Aβ42/40). This aberrant alcadein processing enhances the mitochondrial toxicity of amyloid β oligomers (Aβos). Transdermal delivery of alcadein 9-19 (ALC919) to mouse models of AD and aged nonhuman primates (NHPs) counteracted Aβo toxicity by activating brain mitochondrial complex I, as shown using [18F] BCPP-EF PET (Hata et al., 2023). We propose that ALC919 supplementation may delay, stabilize, or treat the cognitive decline of AD. Since Aβos are currently undetectable in the human brain in vivo, it is possible that amyloid fibril-depleting antibody therapies leave behind residual toxic Aβos that may be responsible (at least in part) for the incomplete clinical benefit associated with these therapies. **Methods:** We plan to conduct phase I SAD and MAD human clinical trials to establish safety and plasma/CSF pharmacokinetics of transdermal ALC919 in healthy young and elderly volunteers. We also propose to assess target engagement in subjects with early MCI or mild dementia due to AD using [18F] BCPP-EF PET, while in parallel, evaluating biofluid-based proteomic biomarkers seeking surrogates for the [18F] BCPP-EF PET activation that indicates the brain response to ALC919. **Results:** In CSF from patients with AD and MCI, levels of p3-Alcβ37 and p3-Alcβ40 (endogenously generated p3-Alcβ molecules) were altered, mirroring the increase in the Aβ42/40 ratio associated with mutant presenilins (Hata et al., 2009, 2011, 2019). This led us to propose that both increased amyloidogenic APP processing and p3-Alcβ deficiency might contribute to the molecular and clinical phenotypes of AD. To test this, we first assessed the effects of p3-Alcβ 9-19 supplementation on molecular, histological, and behavioral aspects of AD-related phenotypes in vitro. We discovered that the p3-Alcβ9-19 (ALC919) fragment of p3-Alcβ37 could enhance the mitochondrial activity of cultured neurons and protect cultured neurons against Aβo-induced toxicity (Hata et al., 2023). Turning to in vivo systems, ALC919 counteracted Aβo toxicity in mouse models of AD and in aged NHPs by activating brain mitochondrial complex I, as detected by [18F] BCPP-EF PET. In mouse models of AD, this complex I activation is accompanied by improvements in learning behavior. **Conclusions:** We are planning a phase I study aimed at establishing safety and tolerability and at assessing ALC919 pharmacokinetics and pharmacodynamics in humans. The presence or absence of adverse events, medically important changes (vital signs), and laboratory test results (hematological tests, blood biochemical tests, urine tests), and/or skin changes will be evaluated by comparing them with the baseline on the day before transdermal ALC919 administration. Using ELISA and LC-MS/MS assays established in the monkey PK study, we will evaluate blood ALC919 concentration changes before and after administration of ALC919. In addition, we will estimate the maximum plasma concentration (Cmax), time to reach maximum plasma concentration (Tmax), area under the plasma concentration-time curve (AUC), and elimination half-life (t 1/2) of ALC919. In single and multiple ascending dose studies (SAD, MAD), healthy young adult volunteers who meet certain inclusion and exclusion criteria will be randomly assigned to receive a placebo patch or a single patch of drug. For the phase 1 SAD, ten subjects will be assigned to each cohort, with 2 subjects receiving the drug and 8 receiving the placebo. The first 3 cohorts will be male only, since the nonhuman primate toxicology was limited to male monkeys. These cohorts of 10 subjects will contain 4 or more subjects who are APOEε4 carriers. For the MAD, subjects will receive a range of multiple patches per day over a period of 7 days with an optional extension to 14 days. In addition, an elderly cohort of 10 will have the same structure and dosing as the phase 1B MAD. The elderly cohort will receive 75% or 100% of the maximum tolerated dose used for the previous MAD cohorts. Pharmacokinetics, safety, and biomarkers will be assessed in both the SAD and MAD cohorts. A phase 2 trial in MCI and mild AD is planned following successful completion of the phase 1 SAD and MAD trials, wherein we will be seeking evidence of target engagement using [18F]BCPP-EF PET.

Keywords: Oligomer (Aβo), mitochondria, complex I, [18F] BCPP-EF (2-tert-butyl-4-chloro-5-{6-[2-(2[(18)F] fluoroethoxy)-ethoxy] -pyridin-3-ylmethoxy}-2H-pyridazin-3-one) PET.

Clinical Trial Registry: TBD.

Data Deposition: TBD.

Disclosures: Hokkaido University holds patent P6319912 (US, 10,206,979; EU, 2 987 496 B1) on the use of ALC919 to activate brain mitochondrial complex I activity and as a treatment or prophylaxis for MCI or dementia due to AD. S.G. is a consultant to Cognito Therapeutics, GLG Group, SVB Securities, Guidepoint, Third Bridge, MEDACORP, Altpep, Vigil Neurosciences, Memory Tree, Alzheon, and Eisai. He has received research support from Pfizer, Baxter, and Avid. H.A. is COO of Passport Technologies, San Diego, CA. E.A.R. is Executive VP, Head of Translational Applications, Perceptive Discovery, London, UK. M.W. is vice president for research and development at NeuroScios GmbH, Graz, Austria. M.S. is a consultant for Signant Health, Novo Nordisk, and Axsome.

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β-peptide. EMBO Mol Med. 2023;15(5):e17052. doi: 10.15252/emmm.202217052.

Key takeaway message: Transdermal alcadein 9-19 peptide counteracted Aβ oligomer toxicity by activating brain mitochondrial complex I, as shown by [18F] BCPP-EF PET. In mouse models, this complex I activation is accompanied by normalization of learning behavior.

P105- A REVIEW OF PATIENT DEMOGRAPHICS, CLINICAL CHARACTERISTICS, ELIGIBILITY, AND TREATMENT PLANNING FOR LECANEMAB IN AN ACADEMIC MEDICAL CENTER.

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Background: FDA-approved anti-amyloid therapies (AATs) show promise in slowing Alzheimer's disease (AD) progression. This study examines the demographics, clinical characteristics, eligibility, and treatment planning for patients evaluated for lecanemab at our academic medical center clinic. **Methods:** This retrospective chart review examines the real-world clinical use of lecanamab in our academic medical center. From an available pool of patients undergoing an initial evaluation within the Alzheimer Therapeutics Program (ATP) at Brigham and Women's Hospital (BWH) from October 2023 to February 2025, 200 were randomly selected for chart review. Collected data includes patient demographics, symptomatology, prior medical histories, functional assessment, cognitive performance, neurological examination findings, laboratory studies, brain MR imaging results, AD biomarker testing, diagnostic formulations related to staging, syndrome characterization, and underlying etiology, and information about eligibility status, patient treatment decision-making, and treatment initiation. Statistical analysis was performed in R. **Results:** Of the 200 randomly selected patients, 192 were included in the analysis after excluding those with undetermined eligibility status. Among these, 169 (88.0%) met eligibility criteria, with a treatment consent rate of 89.9% among eligible individuals. Mean age did not differ significantly ($p = .146$) between eligible (73.7 ± 7.61 years) and ineligible groups (76.0 ± 6.89 years). A majority (90.6%) of the sample was of self-reported White race, and individuals of White race were significantly over-represented among those eligible for AATs compared to those of non-White race ($p = .01$). Cognitive scores trended higher among eligible participants but were not statistically significant (median Mini-Mental State Examination (MMSE): 25 vs. 23, $p = .08$; median Montreal Cognitive Assessment (MoCA): 21 vs. 19, $p = .12$). Functional assessments showed that eligible individuals had significantly lower Quick Dementia Rating System (QDRS) scores (median = 4.5 vs. 6, $p = .03$), indicating lower functional impairment. This finding aligns with the appropriate use recommendations for lecanemab, which is intended for patients with mild impairment (excluding those with more advanced functional decline). Similarly, scores on the Functional Activities Questionnaire (FAQ) trended higher in ineligible participants (median = 9 vs 13.5, $p = .10$), though did not reach statistical significance. The white matter disease burden (measured by Fazekas scores) was similar (median = 1), with greater variability in eligible patients (IQR = 0 vs. 1, $p = .018$). Memory symptom presence (96.4% vs. 87.0%, $p = .38$), amnestic syndrome subtype (85.8% vs. 82.6%, $p = .75$), and use of cholinesterase inhibitors, SSRIs, and sleep aids did not differ significantly between the 2 groups. **Conclusions:** In this sample of patients evaluated for AATs, those found to be eligible vs ineligible were similar on several metrics. However, on QDRS, eligible patients showed significantly milder functional impairment, aligning with lecanemab's appropriate use recommendations. Additionally, observed racial disparities in eligibility highlight the need for further investigation to promote equitable access to emerging Alzheimer's disease therapies. **Keywords:** Lecanamab, Alzheimer's, Mild cognitive impairment, DMARD.

Disclosures: JRD has previously served on a scientific review board for I-Mab Biopharma. The authors declare no conflict of interest.

Key takeaway message: Eligible patients for lecanemab had significantly milder functional impairment and were disproportionately white, highlighting both alignment with appropriate use recommendations and the need to address racial disparities in access to Alzheimer's therapies.

P106- MTX46943, A NOVEL TREM2 SMALL MOLECULE AGONIST FOR THE TREATMENT OF EARLY-STAGE ALZHEIMER'S DISEASE.

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Background: Microglia function as CNS resident innate immune cells that maintain brain health and resolve Alzheimer's Disease (AD) pathology. Microglia also regulate neuronal networks by pruning synapses, clearing debris, and modulating neuroinflammation to maintain homeostasis and support neural plasticity. TREM2 detects neuropathogens and activates microglial responses to clear misfolded proteins like amyloid beta leading to neuroprotection. MTX46943 is a novel, potent, selective, safe and brain-penetrant TREM2 small molecule agonist developed for the treatment of early AD and currently in Ph1 studies. We show key features of MTX46943 mechanism of action, translational biomarkers and proof of efficacy in activating microglia and reducing AD pathology following chronic treatment in vivo. **Methods:** TREM2 agonist-induced receptor complex dynamics and downstream functional effects were assessed in vitro in various cell types including hIPSC derived microglia cells by nanoBiT, Western blot, alphaLISA, cell migration and phagocytosis assays. Differences in receptor activation between agonist modalities were studied by comparing MTX46943 with TREM2 agonist antibodies. Biomarker candidates were assessed through transcriptomic and proteomic analyses of brain, CSF and/or plasma samples from hTREM2 knock-in mice, 5xFAD / hTREM2 knock-in mice and non-human primates following acute and chronic dosing regimen with MTX46943. The impact of MTX46943 on amyloid pathology and microglia response patterns was tested in vivo by 3-month treatment of 5xFAD / hTREM2 knock-in mice followed by human microglia and brain tissue isolation for qPCR, single-cell RNA sequencing and immunostaining analyses. **Results:** MTX46943 activates TREM2 signaling through TREM2/DAP12 receptor complex formation and stabilizes surface location required for sustained microglia activation. These effects differentiate MTX46943 from TREM2 agonist antibodies and lead to functional re-programming of microglia as shown by facilitation of migration and phagocytosis in macrophages and human IPSC derived microglia in vitro. Acute and chronic treatment with MTX46943 in the presence or absence of pathology in mice and non-human primates reveal a pattern of biomarkers in brain and CSF demonstrating central target engagement, microglial activation and synaptic integrity. These pharmacological effects of MTX46943 in the brain correspond to biomarkers of neuroinflammation and neuronal function monitored in patients with amnestic MCI and mild AD. In the brain, human TREM2 is expressed by pathology-associated microglia and induced by amyloid plaques. In the presence of amyloid pathology, chronic and systemic treatment with MTX46943 induces re-programming of microglia transcriptomes in 5xFAD / hTREM2 mice. The differentiated response of microglia following treatment in the presence of pathology reveals a shift towards disease-associated, proliferating and migrating micrglia. This in turn leads to a reduction of neurotoxic amyloid beta species in the brain as well as protection of astrocytes as evidenced by lowered GFAP levels in plasma. **Conclusions:** MTX46943 is a selective, potent, safe and brain exposed small molecule TREM2 agonist currently being tested in Ph1 studies and developed for the treatment of early AD. We demonstrate here key aspects of the mechanism by which MTX46943 targets TREM2 and induces microglial re-programming via receptor complex formation and stabilization. Translational biomarkers of MTX46943 treatment allow monitoring of target engagement and

functional effects in the brain and are potential tools for patient population stratification in proof of concept trials. Chronic treatment of MTX46943 robustly and significantly reduces brain amyloid pathology at doses shown to promote peripheral and central biomarker responses. In summary, these data demonstrate the best-in-class therapeutic potential of MTX46943 for the treatment of Alzheimer's disease.
Disclosures: All authors are full-time employees of Muna Therapeutics.
Key takeaway message: MTX46943 is a novel, potent, selective, safe and brain-penetrant TREM2 small molecule agonist with best-in-class properties, developed for the treatment of early AD and currently in Ph1 studies.

P107- INTERNATIONAL REGISTRY FOR ALZHEIMER'S DISEASE AND OTHER DEMENTIAS (INRAD): DESIGN, DATA MODEL, AND INTEROPERABILITY.

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Background: Clinical trials in early Alzheimer's disease (AD) face numerous challenges, making it difficult to evaluate potential therapies. Some of the main challenges are associated with early disease detection, trial pre-screening, lack of run-in data, and trial population representativeness. Registries can be leveraged to accelerate the execution of clinical trials in early AD and improve its quality. The International Registry for Alzheimer's Disease and Other Dementias (InRAD) is designed as an international clinical practice-based disease registry aimed at collecting, organizing, and harmonizing real-world clinical data. Data registration includes patient history, clinical and biomarker outcomes, and safety profiles for AD and dementia care. InRAD is the first international registry initiative in the AD field and has an ongoing collaboration with US-based ALZ-NET International. To answer questions not addressed in clinical trials in AD - like the application of biomarkers for earlier diagnosis, the new natural history of early AD, the long-term effectiveness, safety and value of disease-modifying therapies (DMTs) - facilitating collaboration and data exchange between registries will be key. **Methods:** The InRAD Alzheimer's Disease Unified Data Model (AD-UDM) (1) forms the basis of the data captured in InRAD. The data model comprises a minimum dataset (MDS) and extended dataset (EDS) (2), and contains both single-point and longitudinal building blocks. This set-up allows for the capture of both observational data on natural disease course, as well as data on the efficacy of lifestyle- and DMT interventions. Multiple data entry methods are facilitated, including direct entry via a web-based portal and bulk data push. All building blocks and individual variables with the AD-UDM are, where possible, rooted in internationally recognized semantic standards such as MedDRA, ISO, Isced2011, SNOMED, and LOINC. Such standardization is key to ensure inter-operability between registry datasets. Here, we present a comparison between the data models of InRAD (1) and ALZ-NET (3). **Results:** The InRAD AD-UDM consists of 7 based objects and >50 linked local objects. Each object represents a set of variables pertaining to a common topic. In total, N=446 different variables can be captured per patient at a single time point. Clear overlap between the InRAD AD-UDM and the ALZ-NET case report form was identified in base objects of Diagnosis, Medical Events, and Treatment; whereas only partial or a lack of overlap was identified in base objects Patient Identification, Medical History, Visits, and Medical Tests. The InRAD AD-UDM contains N=19 elements that have affiliated semantic standard meta-data, whereas no such semantic standards could be identified within the ALZ-NET case report form based on the publicly available description. **Conclusions:** Optimizing interoperability across international AD registries is key to facilitate collaboration and data exchange. InRAD has taken important steps to optimize harmonization of data. Considerable overlap exists in building blocks between the InRAD AD-UDM and the case report form of ALZ-NET. However, interoperability on the level of individual variables between registries can be improved. Recommendations include mapping of as many individual variables as possible onto common semantic standards, as well as clear guidelines on the interpretation and conversion of variables from electronic patient records into a registry data entry form.
Keywords: Registry, real-world, data harmonization, interoperability.
References: 1. InRAD Alzheimer's Disease Unified Data Model (AD-UDM) v1.0 accessible https://www.inradnetwork.org/data-set. 2. Perneczky et al. J Prevent Alzheimers Dis 2025. https://doi.org/10.1016/j.tjpad.2025.100096. 3. ALZ-NET CRFs accessible https://www.alznet-providers.org/Network-Operations/ALZ-NET-Data.
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(Roche). All funding is paid to her institution. WF is member of the steering committee of PAVE, and Think Brain Health. WF is Chair of the Scientific Leadership Group of InRAD. WF was associate editor of Alzheimer, Research & Therapy in 2020/2021. WF is associate editor at Brain. WF is member of Supervisory Board (Raad van Toezicht) Trimbos Instituut. JLH has no competing interests. JLH is Deputy Chair of the Scientific Leadership Group of InRAD. FJ received a research grant from Roche, honoraria from Eisai, Lilly, Novo Nordisk and has provided consultancy services for Eisai, Lilly, Novo Nordisk, Abbvie & AC Immune. FJ is a founder Board Member of InRAD. RP has received research grants from Roche, Astra Zeneca, Bayer, Takeda and GE. He has received honoraria from Roche, Eisai, Biogen and Janssen-Cilag. RP provided consultancy services for Roche, Eisai, Biogen, Janssen-Cilag, Lilly, Astrazeneca, Grifols, Novo Nordisk, Abbvie and GSK. RP is a founder Board Member of InRAD.

Key takeaway message: InRAD, an international, practice-based registry, aims to enhance Alzheimer's disease research by harmonizing real-world data collection and defining a pathway for interoperability with other registries, enabling large studies to answer important questions for patient care.

P108- SAFETY, PHARMACOKINETICS AND CARDIODYNAMICS OF CMS121, A NOVEL SMALL MOLECULE FISETIN DERIVATIVE WITH NEUROPRO-TECTIVE PROPERTIES, IN PHASE 1 HEALTHY ADULT VOLUNTEERS.

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Background: Over the last few years, we and others have identified an association between the oxytosis/ferroptosis non-apoptotic regulated cell death pathway and Alzheimer's disease (AD). Activation of this pathway is characterized by changes in the redox balance leading to lethal lipid peroxidation. Growing evidence suggests that aging, the major risk factor for AD, predisposes the brain to activation of oxytosis/ferroptosis in AD. Thus, we believe that inhibition of this pathway offers the potential for developing an entirely new class of therapeutics for AD. Using phenotypic screening assays, CMS121 was identified as a potent and specific inhibitor of oxytosis/ferroptosis in nerve cells exposed to multiple, distinct inducers of this cell death pathway. CMS121 is also effective in multiple mouse models of AD where it maintains cognitive function and markers of synaptic and mitochondrial function and reduces markers of inflammation. **Methods:** This was a 4-part clinical study. Parts 1, 2, and 3 were randomized, double-blind, placebo-controlled investigations of CMS121 administered orally (po) with food. First, single ascending doses were administered to healthy adult subjects (SAD: Part 1, 50 to 1800 mg po single dose). Then, multiple ascending doses were administered to healthy adult subjects (MAD: Part 2, 150 to 900 mg po once daily [QD] for 7 days), and multiple doses were administered in healthy elderly subjects (Part 3, 600 mg po QD for 7 days). Part 4 was an open-label, 2 way crossover study to assess the effect of food on single oral doses of CMS121 (600 mg po after a period of fasting and 600 mg po after a high-fat/high-calorie meal) to healthy adult subjects. In total 100 healthy, adult male and female subjects were enrolled (8 per group (6 with CMS121 and 2 placebo) x 6 dose cohorts for SAD; 8 x 4 dose cohorts for MAD; 8 x 1 dose cohort for elderly and 12 subjects for the food effect study). Subjects participated in only one study part and in only one cohort. Pharmacokinetics were assessed by determining the levels of CMS121 and its three glucuronidated metabolites in plasma and urine using validated HPLC-MS/MS assays. Cardiodynamics were evaluated using 12-lead cardiodynamic ECGs. In addition, safety parameters, including physical examinations, vital signs, clinical laboratory parameters (including blood biochemistry, hematology, and urinalysis), 12-lead safety ECGs, and C-SSRS, were assessed throughout the study. **Results:** Single doses of up to 1800 mg or multiple doses up to 900 mg/day for 7 days were generally well tolerated with the majority of TEAEs mild in severity. The pharmacokinetics of CMS121 and its metabolites were well characterized and increased in a dose-proportional or slightly greater than dose-proportional manner across the range of doses assessed. Urinary excretion of CMS121 and its metabolites was minimal implying that urinary excretion may not be a major clearance route by which CMS121 is eliminated after oral dosing. There is a significant effect of age on the pharmacokinetics of CMS121 and its metabolites with higher systemic exposures to CMS121 and its metabolites and longer terminal elimination half-lives in elderly subjects. Systemic exposures to CMS121 also were higher in the fed state by approximately 50%. **Conclusions:** In summary, CMS121 showed excellent safety and tolerability in both healthy adult and elderly subjects in this Phase 1 study. In addition, the PK analyses indicated the acceptable dose ranges that can be utilised to further explore the safety, PK and potential for therapeutic effect of CMS121 in the management of AD in planned Phase 2 clinical studies. However, given the altered pharmacokinetics in elderly subjects, further investigation of multiple doses in this demographic appears warranted before advancement to Phase 2 trials.

Keywords: Phase 1 clinical trial; oxytosis/ferroptosis; Alzheimer's disease. Clinical Trial Registry: NCT05318040; https://clinicaltrials.gov.

Disclosures: This work was supported by the National Institute of Aging of the National Institutes of Health (R01AG074447).

Key takeaway message: The further development of CMS121, a novel inhibitor of oxytosis/ferroptosis and potential drug candidate for AD, is strongly supported by the results of this four part Phase 1 trial.

P109- STUDY DESIGN IN A PHASE 2A REGISTRATION TRIAL FOR OAB-14 IN THE TREATMENT OF MILD COGNITIVE IMPAIRMENT (MCI) OR MILD AND MODERATE DEMENTIA DUE TO ALZHEIMER'S DISEASE.

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Background: OAB-14 is a novel small-molecule designed with bexarotene as the lead compound. In preclinical studies, 3-month treatment with OAB-14 significantly alleviated cognitive impairment and markedly reduced the deposition of Aβ in APP/PS1 transgenic mice. A phase 1 clinical trial demonstrated that OAB-14 was safe following 14 consecutive days of oral administration in healthy participants. Consequently, a phase 2a registration trial was designed as a proof-of-concept study to evaluate efficacy and safety of OAB-14 in individuals with mild cognitive impairment (MCI) or mild and moderate dementia due to Alzheimer's disease (AD). The trial was launched in May. 2025, with enrollment expected to be completed by Q4 of 2025. **Methods:** This study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial with a 52-week treatment period. Eligible participants were aged 50–85 years, amyloid-positive (confirmed by CSF or PET), and diagnosed with mild cognitive impairment (MCI) or mild to moderate dementia due to Alzheimer's disease (AD), corresponding to stages 3 to 5 per the National Institute on Aging and Alzheimer's Association (NIA-AA) criteria at screening. Participants were also required to have an MMSE score of 14 to 26 (inclusive) and a CDR global score of 0.5, 1, or 2. A total of 90 participants were randomized in a 1:1:1 ratio to receive either 200 mg OAB-14, 400 mg OAB-14, or matching placebo under fed conditions. The primary efficacy endpoint was the mean change from baseline in the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) score over the 52-week treatment period. The key secondary endpoint was the mean change in the AD Composite Score (ADCOMS). Secondary endpoints included mean changes in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), the Alzheimer's Disease Cooperative Study-Activities of Daily Living scale (ADCS-ADL), and the Neuropsychiatric Inventory (NPI) score. Additionally, the effect of OAB-14 on amyloid-β (Aβ) deposition was evaluated via Aβ PET imaging at 26 and 52 weeks. The trial was conducted in China. **Results:** No

results are available. **Conclusions:** Although results are pending, this Phase 2a trial critically assesses OAB-14's efficacy, safety, and disease-modifying potential in AD patients with mild cognitive impairment or mild-moderate dementia. Employing robust biomarkers and clinical measures in a defined population, the trial seeks to evaluate its disease-modifying potential and thereby guide early intervention strategies and future trials.

Disclosures: Zhonghui Zheng, Yiyun Wang are employees of Shandong Xinhua Pharmaceutical Company Limited. The authors declared no competing interests.

Keywords: OAB-14, Alzheimer's disease, clinical trial, registration trial

P110- THN391 – A NOVEL, FIRST-IN-CLASS ANTI-FIBRIN ANTIBODY FOR TREATMENT OF INFLAMMATION IN ALZHEIMER'S DISEASE: AN ONGOING PHASE 1B STUDY FOR THE TREATMENT OF EARLY ALZHEIMER'S DISEASE.

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Background: Currently approved anti-amyloid treatments for Alzheimer's disease (AD) are modestly effective, and present safety risks, especially for patients who are ApoE4 homozygotes. Importantly, these agents do not target inflammation, an early and essential driver of disease. All trials to date targeting neuroinflammation in AD have failed. A large body of animal and clinical data has shown that fibrin is critical to the onset and progression of AD by triggering an inflammatory response that contributes to neuronal injury (1). THN391 is a first-in-class high-affinity humanized monoclonal antibody, targeting the inflammatory γ377–395 epitope on fibrin that binds complement receptors CD11b/c on microglia, macrophages, and dendritic cells. Cell binding to fibrin γ377–395 triggers an inflammatory response, resulting in neuronal damage and behavioral impairment in the 5XFAD mouse which is mediated by reactive oxidative stress and the upregulation of neurotoxic chemokines and cytokines. Anti-fibrin γ377–395 antibodies significantly reduce inflammation and neuronal damage in 5XFAD mice (2). THN391 was safe and well-tolerated in a randomized, first-in-human, double-blind, placebo-controlled single and multiple ascending dose (SAD and MAD) trial in healthy subjects (3). THN391 had no impact on coagulation and fibrinolysis, as measured by PT, aPTT, and rotational thromboelastometry (ROTEM). Population pharmacokinetic modeling shows that THN391 exhibits dose-proportional pharmacokinetics and a long terminal half-life supporting monthly or less frequent dosing. Based on these results, a Phase 1b study has been initiated in patients with early AD. **Methods:** THN391-NEU-102 is a double-blind, randomized, placebo-controlled, Phase 1b study designed to assess the safety, tolerability, and pharmacokinetics of multiple ascending doses of THN391 in early Alzheimer's disease subjects. The study includes individuals with mild cognitive impairment (MCI) due to AD and individuals with mild AD who show progressive decline in 1 or more cognitive domains. ApoE4 heterozygotes and homozygotes are allowed. Cohorts are randomized to placebo or THN391 and receive 3 intravenous doses starting at 20 mg/kg, every 4 weeks with subsequent dose cohorts escalating to at least 60 mg/kg. Primary objectives are safety and tolerability and THN391 pharmacokinetics. Secondary objectives are immunogenicity and impact of THN391 on coagulation. Exploratory objectives include:1) THN391 distribution in the CSF; 2) cognitive assessments including the Mini Mental State Examination (MMSE) and a digital battery of verbal, spatial memory and executive function, sensitive to change in response to treatment; 3) cerebral blood flow by arterial spin labeling MRI and blood-brain- barrier integrity by dynamic contrast-enhanced-MRI; and, 4) pharmacodynamic markers in the plasma and CSF, including fully validated assays for Aβ42/40, total Tau and p-Tau181, 217, 231 and exploratory NULISAseq for neurodegenerative and inflammatory markers. **Results:** THN391-NEU-102 , "A Double-Blind, Randomized, Placebo-Controlled, Phase 1b Study to Assess the Safety, Tolerability, and Pharmacokinetics of Multiple Ascending Doses of THN391 in Early Alzheimer's Disease Subjects," has been initiated in the Netherlands and the United Kingdom. Trial design, endpoints and progress will be discussed. **Conclusions:** THN391, a first-in-class antibody targeting fibrin-induced inflammation, was found to be safe and well-tolerated in a Phase 1a study, with a half-life supporting monthly intravenous dosing. A Phase 1b study is ongoing in patients with early AD with ApoE4 homozygotes included. The study will assess safety, pharmacokinetics, early signals of efficacy based on CSF and plasma biomarkers of inflammation and disease progression, brain MRI, and cognition.

Keywords: Clinical trial Phase 1b, Alzheimer's disease, therapeutic antibody, fibrin.

Clinical Trial Registry: NCT06814730, https://clinicaltrials.gov.

Data Deposition: TBD.

Disclosures: BN and ABK are employees of Therini Bio. TAMH and JK are consultants for Therini Bio. EGBV, CM, KA, HJMMM, FB, and CR are clinical investigators for the study.

References: 1 Kantor, A. B. et al., J Prev Alzheimers Dis 10, 647-660 (2023); 2. Ryu, J. K. et al,. Nat Immunol 19, 1212-1223 (2018); 3. Kantor, A. B. et al,. in AAIC 2025, Toronto (In Press).

Key takeaway message: THN391, a first-in-class monoclonal antibody targeting fibrin-induced inflammation, is being evaluated in a Phase 1b study in Early Alzheimer's disease patients.

P111- PNA5 FOR TREATMENT OF VASCULAR DEMENTIA: COMPOSITE SERUM BIOMARKERS FOR VCID PATIENTS ENROLLMENT STRATIFICATION.

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Background: Vascular cognitive impairment and dementia (VCID), particularly vascular dementia (VaD), represents a growing public health challenge, with no currently approved treatments. Among emerging therapeutic candidates, PNA5, a novel glycosylated Angiotensin-(1-7) Mas receptor agonist, is being developed to target the vascular and inflammatory pathways underlying vascular dementia (Hay et al. 2019),(Hoyer-Kimura et al.,2021), (Hoyer-Kimura et al.,2023). We are advancing PNA5 to Phase 1/2 clinical evaluation and there is need for biomarkers that can stratify at-risk individuals before the onset of overt cognitive decline, enabling early intervention and optimized clinical trial design. A key population of VICD patients are those with chronic cardiovascular disease. For example, of the estimated 6.7 million individuals living with heart failure (HF) in the United States, approximately 65% are at risk for developing VCID. Identifying patients in the prodromal phase of VCID prior to the development of clinical cognitive dysfunction is critical for early intervention. However, validated blood-based biomarkers for early neuronal injury and vascular inflammation for VCID remain an unmet need. The purpose of this pilot study was to determine if serum biomarkers of neurodegeneration and inflammatory cytokines are elevated in VCID-HF patients and whether a composite biomarker score could predict cognitive performance. **Methods:** A total of 23 HF subjects (mean age 68 years, 49% female) were recruited from Banner–University cardiology clinics in Tucson and Phoenix, alongside 26 healthy controls (mean age 66 years, 29% female). Education was not significantly different when comparing HF participants to controls and there were no significant differences in calculated GFR between the HF and control group. The average ejection fraction (EF) for all HF participants was 37.11%. HF

participants were stratified based on HF progression using NT-proBNP a biomarker indicative of HF progression and management. NT-proBNP levels, New York Heart Association (NHYA) status, ejection fraction (EF), medication relating to heart failure, comorbidities, and kidney function were obtained from the patient's clinical history. Cognitive function was assessed using a memory function composite score derived from the North American Adult Reading Test, Verbal Paired Associates Total, Face-Name Long Delay Test, and Cued Name Retrieval. Serum levels of neurofilament light chain (NfL), phosphorylated Tau (pTau181), and inflammatory cytokines (IL-6, IL-8, IL-12p40, TNFα) were measured using Quanterix Simoa and Milliplex assays, respectively. Cardiac disease severity was determined via plasma NT-proBNP levels. Data were analyzed using GraphPad Prism 10.1.0. **Results:** Compared to healthy controls, HF patients demonstrated significant cognitive impairment (composite z-score, p=0.0001) and elevated serum levels of NfL (p=0.028), pTau181 (p=0.042), IL-6 (p=0.008), IL-8 (p=0.014), IL-12p40 (p=0.0005), and TNFα (p=0.010). Importantly, higher levels of NfL, IL-6, and TNFα correlated negatively with cognitive performance. Of the circulating biomarkers that were significantly higher in HF compared to healthy control participants, NfL, IL-6, and TNFα significantly correlated to the composite cognitive score calculated from FNAME, VPA, and Keep track. With these biomarkers and NT-proBNP, we created a Calculated Biomarker Cognitive Score. The Calculated Biomarker Cognitive Score combines neurodegenerative serum biomarkers, NfL, proinflammatory serum cytokine, IL-6, and TNFα, and an HF biomarker NT-proBNP to predict an individual cognitive performance in HF individuals. A calculated composite cognitive score was significantly predictive of cognitive impairment (R^2 = 0.31, p=0.005) with excellent diagnostic accuracy (ROC area = 0.96, CI 0.91–1.0). Additional data from our longitudinal sub cohort from this same group (n=6) showed a decrease in cognitive performance over 12 months from baseline and a concomitant increase over from baseline for IFNγ for, TNFβ, TNFα and IL-6. Further details will be presented at the conference. **Conclusions:** These findings support the potential of a composite blood-based biomarker score that combines markers of cardiac function, neurodegeneration, and inflammation to predict cognitive impairment in patients with VCID. This biomarker strategy may serve as a critical tool for future VCID clinical trials. We plan on using this composite biomarker score to enable early patient identification, stratification, and enrollment into disease-modifying intervention studies with PNA5 to treat vascular dementia. Our extensive preclinical data with PNA5 in VCID models, IND-enabling translational research (NIA U01-AG066623), and successful chronic toxicology studies with PNA5 (NIA U01AG082617) resulting in our IND for PNA5 (IND #61,739) and our pilot de-risking studies with PNA1 in VCI patients with heart disease (IND #61,739, ClinicalTrials.gov ID NCT05336175, ClinicalTrials.gov ID NCT03252093, ClinicalTrials.gov ID NCT03159988), support the advancement of PNA5 to RCT Phase 1 Single and Multiple Ascending Dose, clinical trials in 2026 to be followed by Phase 2 RCT in VCID patients.

P112- PHASE 1 STUDIES OF MK-2214, A NOVEL ANTIBODY TARGETING PS413 TAU, FOR THE TREATMENT OF ALZHEIMER'S DISEASE.

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Background: Antibodies targeting extracellular tau have been proposed as a therapeutic strategy to reduce the spread of pathology and slow the progression of Alzheimer's disease (1,2). MK-2214 is a novel, highly potent, antibody targeting phosphorylated serine 413 (pS413) containing tau which is present in pathological forms of tau (3). In vitro and in vivo seeding studies showed robust reductions in tau pathology with antibodies targeting pS413 tau, suggesting that reducing extracellular pS413 tau can reduce the extracellular spread of tau seeds.3 Furthermore, studies in nonhuman primates demonstrated that MK-2214 has an extended half-life compared to traditional antibodies (3). Here we describe the clinical pharmacology of MK-2214 in humans. **Methods:** The safety, tolerability and serum pharmacokinetics of MK-2214 were evaluated in three randomized, double blind, placebo-controlled studies. Two of the studies (1 and 3) also assessed MK-2214 concentrations in the cerebrospinal fluid (CSF). Study 1 was a first-in-human single ascending dose study of MK-2214 IV (10 mg to 4200 mg) and SC (50 mg, 200 mg) in 64 healthy men and women age 18-55y (IV: N=36 MK-2214/N=12 placebo; SC: N=12 MK-2214/N=4 placebo). Study 2 was a single dose study of MK-2214 IV (700 mg, 2100 mg, 4200 mg IV) in 48 healthy Japanese men age 18-55y; the 4200 mg dose was also assessed in men age 56-75y (total N=36 MK-2214/N=12 placebo). Study 3 was a multiple ascending dose study of MK-2214 (4 mg to 500 mg IV; monthly dosing for 3 doses) in participants with mild-to-moderate cognitive impairment age 50-80y (N=23 MK-2214/N=7 placebo). This study also assessed MK-2214 effects on free pS413 tau levels in CSF. Participants in each study were followed-up for between 139 (Study 1) to 239 (Studies 2 and 3) days after dosing based on the projected long half-life of MK-2214. **Results:** Over the 3 studies, MK-2214 was generally well tolerated at all dose levels. There were no dose limiting tolerability issues and no pattern of drug-related events. In Study 1, in healthy participants (mean age 36y) maximum MK-2214 serum concentrations were observed at a median of 0.5 to 3 hours after end of IV infusion and 228 hours after SC administration. The geometric mean Cmax in serum following 1 hour IV infusion was found to be approximately dose-proportional and ranged from 1.70 μg/mL after 10 mg IV to 888 μg/mL after 4200 mg IV. Estimates based on data collected to 139 days postdose indicated a t½ of approximately 83 days. The estimated geometric mean absolute bioavailability of single SC doses of MK-2214 50-mg and 200-mg was 0.87 and 0.59, respectively. MK-2214 concentrations were assessed in CSF samples in a subset of participants at Day 4 (700 mg IV and 4200 mg IV), Day 7 (200 mg IV and 200 mg SC), and Day 28 (200 mg IV). The geometric mean CSF-to-serum concentration ratio on Day 28 was 0.26%, resulting in CSF concentrations of 19.6 ng/mL after a single dose of MK-2214 200 mg IV. In Study 2, in healthy Japanese men (mean age 42y) the observed median Tmax for the IV doses of MK-2214 ranged from 1 to 2 hours after the start of the 0.5-hour IV infusion. The geometric mean terminal t½ ranged from 76 days to 83 days. The observed Cmax exhibited an approximately dose proportional increase across the 700 to 4200 mg dose range. The pharmacokinetics of the 4200 mg IV dose in healthy older Japanese men (mean age 62y) were comparable to those in healthy younger Japanese men. The pharmacokinetics of MK-2214 in Japanese participants were generally similar to non-Japanese participants in Study 1. Analysis of pharmacokinetic data from Study 3 in participants with mild-to-moderate cognitive impairment age 50-80y is ongoing and will be presented at the meeting. Pharmacodynamics assessed in a subset of the participants in Study 3 showed that free pS413 tau in the CSF was reduced below the limit of quantitation at doses ≥20 mg IV on days 29 and 85 of the study, indicating a high level of target engagement. **Conclusions:** Single dose administration of MK-2214 in healthy participants, and multiple dose administration of MK-2214 in participants with mild-to-moderate cognitive impairment, was well tolerated at doses that produced near-saturating binding of free pS413 tau. MK-2214 had a long half-life of approximately 80 days. These findings indicate that MK-2214 has a favorable pharmacological profile as an antibody to slow the progression of Alzheimer's disease. An ongoing phase 2 trial is evaluating MK-2214 for slowing the progression of tau spreading in people with early Alzheimer's disease (NCT07033494).

Keywords: MK-2214, pS413 tau, Alzheimer's disease, phase 1.

Clinical Trial Registries: Study 1: EUDRACT 2021-003581-12, https://www.clinicaltrialsregister.eu; Study 2: JRCT 2031220627, https://jrct.mhlw.go.jp/en-top; Study 3: NCT05466422, https://clinicaltrials.gov.

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Key takeaway message: MK-2214 is a novel, highly potent, long half-life, antibody targeting phosphorylated serine 413 (pS413) containing tau that is being evaluated for slowing the progression of tau spreading in people with early AD.

P113- INCIDENCE, RISK FACTORS WITH CUT-OFF VALUES, AND MANAGEMENT OF LECANEMAB-RELATED INFUSION-RELATED REACTIONS IN CHINESE PATIENTS WITH EARLY ALZHEIMER'S DISEASE: A MULTICENTER RETROSPECTIVE STUDY.

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Background: Lecanemab, a US FDA-approved monoclonal antibody targeting amyloid-β protofibrils for the treatment of early Alzheimer's disease (AD), is associated with infusion-related reactions (IRR), which may affect its clinical utilization. Although Western clinical trials have reported an IRR incidence of 26.4%, real-world evidence on IRR in Chinese patients with early AD—characterized by distinct genetic backgrounds and comorbidity profiles—remains limited. This study aims to determine the incidence of lecanemab-related IRR in this population, identify clinically meaningful cut-off values for key risk factors, and validate the effectiveness of a standardized IRR management protocol. **Methods:** A retrospective multicenter study was conducted involving 509 patients with early Alzheimer's disease (AD), diagnosed according to the NIA-AA criteria and confirmed amyloid positivity, who initiated lecanemab therapy (10 mg/kg every two weeks, diluted in 250 mL of 0.9% sodium chloride) across 18 hospitals in China between June 2024 and March 2025. Infusion-related reactions (IRR) were assessed and graded using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Statistical analyses included univariate tests—Mann–Whitney U tests for continuous variables and chi-square tests for categorical variables—to screen potential risk factors, followed by multivariate logistic regression to identify independent predictors of IRR. Cut-off values for continuous variables were determined based on the distribution within our cohort using receiver operating characteristic (ROC) curve analysis where applicable, or median splits for preliminary risk stratification. The IRR management protocol encompassed standardized infusion procedures, including the use of a 0.2 μm low-protein-binding filter, an infusion pump rate of 250 mL/h, and pre- and post-infusion saline flushes, as well as symptomatic interventions such as ibuprofen for fever and loratadine for rash. **Results:** The overall incidence of lecanemab-related infusion-related reactions (IRR) was 16.5% (84/509), with the following severity distribution: 36.9% Grade 1 (mild, e.g., transient rash), 58.3% Grade 2 (moderate, e.g., persistent fever), and 4.8% Grade 3 (severe, e.g., hypotension requiring intervention); no Grade 4 or 5 events were reported. The majority of IRR (83.3%) occurred after the first infusion, with 45.2% of symptom onsets occurring within 1–5 hours post-infusion. The most common symptoms were fever (67.9%) and chills (42.9%). Multivariate logistic regression identified reduced pre-treatment serum albumin as the sole independent risk factor for IRR (OR = 0.951, 95% CI: 0.910–0.994, P = 0.011). Cut-off values for risk stratification were determined as follows: - Serum albumin ≤42.61 g/L (AUC = 0.610, 95% CI: 0.550–0.665, P = 0.001): IRR incidence was 21.6% in this group, significantly higher than the 9.2% observed in patients with albumin >42.61 g/L; - Body weight ≥59.55 kg: IRR incidence was 20.4%, compared to 11.8% in patients weighing <59.55kg (P = 0.010); - Total cholesterol ≤4.29 mmol/L: IRR incidence was 23.1%, versus 12.4% in patients with Total cholesterol >4.29 mmol/L(P = 0.002); - International standard ratio≤0.97, IRR incidence was 19.4%, compared to 11.9% in patients with International standard ratio >0.97(P = 0.028); All IRR cases resolved completely with the standardized management protocol, and only 1.2% (1/84) of affected patients discontinued lecanemab treatment due to IRR. **Conclusions:** Lecanemab-related infusion-related reactions (IRR) in Chinese patients with early Alzheimer's disease (AD) are predominantly mild to moderate in severity and occur at a lower incidence compared to those reported in Western clinical trials. Pre-treatment serum albumin ≤42.61 g/L emerges as a key predictor of IRR risk, while cut-off values for body weight (≥59.55 kg), total cholesterol (≤4.29 mmol/L) and international standard ratio (≤0.97) serve as supplementary tools for risk stratification. A standardized protocol combining optimized infusion procedures and prompt symptomatic management effectively mitigates IRR, enabling complete resolution of all events and maintaining high treatment adherence. These findings support the safe and feasible implementation of lecanemab therapy in Chinese patients with early AD.

Keywords: Lecanemab; infusion-related reaction, Alzheimer's disease, risk factor cut-off value, chinese population.

Disclosures: The authors declare no competing interests.

Key takeaway message: Lecanemab-related infusion-related reactions (IRR) in Chinese patients with early Alzheimer's disease are predominantly mild to moderate in severity and occur at a lower incidence. A standardized protocol effectively mitigates IRR.

P114- CLINICAL TRIALS WITH LAUGHTER INTERVENTIONS FOR ALZHEIMER'S DISEASE AND RELATED DISORDERS (ADRD) AND AT-RISK POPULATIONS.

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Background: Neuroimaging studies show that laughter engages brain regions involved in emotional regulation, social cognition, and executive function, areas commonly affected by Alzheimer's disease and related dementias (ADRD) (1). The involvement of these overlapping neural systems suggests that laughter-based therapies may support cognitive health and resilience to dementia. Over the past 15 years, laughter-based interventions conducted internationally have demonstrated therapeutic benefits across a wide range of medical and mental

health conditions (2,3). However, the application of laughter and humor in the context of cognitive health and ADRD remains relatively underexplored. Notably, many laughter interventions target conditions that correspond to potentially modifiable lifestyle and health-related risk factors that may enhance or maintain cognitive reserve, a central focus of dementia research and early intervention strategies (4). The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) is a global database that consolidates multiple national and regional trial registries (including ClinicalTrials.gov) and provides real-time insights into emerging practices in ADRD research. Healthcare agencies and providers who want to implement their own intervention programs rely on ICTRP to access timely trial information, especially given that there are often paywalls for access to journal articles and research study results are often published years after data collection. This review examined ICTRP registered clinical trials involving laughter- or humor-based interventions in ADRD or at-risk populations, as well as trials targeting health conditions aligned with potentially modifiable risk factors for dementia. **Methods:** A comprehensive search of the WHO ICTRP was conducted using keywords related to "laughter" and "humor," from database inception through August 2025. Inclusion criteria included laughter and/or humor intervention and therapies studies conducted world-wide. A subset of these clinical trials was further identified based on relevance to ADRD and/or potentially modifiable lifestyle and health risk factors aligned with the Lancet Commission Report on dementia prevention, intervention, and care (2024) (5). **Results:** Of 197 total trials identified, 53 met the inclusion criteria. Twelve trials directly targeted ADRD or high-risk populations, and interventions were often delivered to participants with varying cognitive ability: ADRD (41.7%), MCI or mild neurocognitive disorder (83.3%), and cognitively normal or at-risk individuals (50%). An analysis of outcome measures among these 12 trials showed that the interventions targeted improvements in cognitive ability and functioning (n=4, 33%), physical health (n=6, 50%), and mental health and well-being (n=12, 100%). An additional 25 clinical trials targeted potentially modifiable risk factors for dementia identified in the Lancet Commission Report (2024) including depression (n=12, 48%), hypertension (n=7, 28%), diabetes (n=6, 24%), social isolation (n=2, 8%), physical inactivity (n=2, 8%), high LDL cholesterol (n=1, 4%), social isolation (n=1, 4%), and vision impairment (n=1, 4%). These studies, along with the remaining 16, addressed additional risk factors considered by the Lancet Commission but not incorporated into their final list, including menopause (n=5), psychotic disorders, including schizophrenia (n=5), anxiety disorder (n=4), sleep disruption (n=3), systemic inflammation (n=3), multimorbidity or frailty (n=1), bipolar disorder (n=1), and PTSD (n=1). Clinical trials were geographically distributed around the globe: Asia (64.4%), Europe (17%), Middle East (17%) and the United States (5.7%). Laughter-based intervention models varied, with 74% using laughter-based interventions as stand-alone programs and 26% incorporating laughter and humor into multimodal therapeutic approaches, for example, a Longevity Program that included a Laughter Yoga component or a Cognitive Improvement Program featuring Laughter Therapy. **Conclusions:** This review reveals that a small but growing number of clinical trials directly target ADRD populations, while a substantial number of laughter-based interventions and therapies address conditions linked to increased dementia risk. Reframing these laughter interventions studies through a risk-reduction and dementia prevention lens provides a novel opportunity to broaden the range of non-pharmacological strategies to include laughter and humor. The global distribution and cultural adaptability of laughter-based interventions and therapies make them particularly promising as scalable, low-cost strategies for diverse populations. As interest in lifestyle-based risk-reduction and dementia prevention grows, laughter-based therapies may serve as a valuable and accessible tool in integrated care and community-based models.

Keywords: Laughter interventions, laughter therapy, ADRD, risk-reduction, modifiable risk factors, non-pharmacological interventions.

Disclosures: None.

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Key takeaway message: Laughter-based interventions may advance dementia prevention by supporting cognitive health and addressing modifiable risk factors; clinical trial data highlight their potential as low-cost, scalable, non-pharmacological strategies with global relevance for dementia and at-risk populations.

P116- TRANSCRANIAL DIRECT CURRENT STIMULATION–AUGMENTED COGNITIVE TRAINING IN MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE: PROTOCOL DESIGN AND PRELIMINARY FINDINGS.

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Background: Transcranial direct current stimulation (tDCS) has emerged as a promising non-invasive strategy for cognitive enhancement in patients with neurocognitive disorders (1,2). However, evidence regarding the combined use of tDCS and cognitive training (CT) remains limited. This study aims to establish a protocol for evaluating the efficacy of tDCS-augmented CT in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD), and to present preliminary findings from the CT component. **Methods:** We designed a randomized, double-blind, sham-controlled clinical trial. Participants with MCI or AD will be recruited from memory clinics and community-based dementia centers. A total of 40 participants per group is planned, based on an assumed mean difference of 1.6 and a standard deviation of 2.5. Participants will be randomly allocated (1:1) to either CT combined with active tDCS or CT with sham stimulation. Interventions consist of 10 weekly sessions. Active tDCS will be delivered at 2 mA for 30 minutes with the anode positioned over the left dorsolateral prefrontal cortex and the cathode over the right supraorbital area, concurrent with CT (3). CT will be administered using the Multi-strategic Memory Training program (10 sessions, 60 minutes each), incorporating educational content and metamemory-based strategies for memory enhancement (4). The Korean version of the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery (CERAD-K) (5) will be assessed at baseline and at 12 weeks. The primary outcome is the total CERAD-K score, analyzed using repeated-measures ANOVA. **Results:** To date, five patients with MCI and three with AD have completed the CT program. One MCI participant was excluded due to withdrawal of consent. Preliminary analyses indicate that CT significantly improved general cognition and executive function. Subgroup analyses suggest greater benefits in AD patients, particularly in memory and global cognition, whereas no significant improvements were observed in the MCI subgroup. **Conclusions:** This trial will establish an optimized protocol for investigating

tDCS as an augmentation strategy for CT in patients with neurocognitive disorders. Preliminary results highlight the potential cognitive benefits of structured CT, particularly among patients with AD.

Keywords: Transcranial direct current stimulation (tDCS), cognitive training (CT), mild cognitive impairment (MCI), Alzheimer's disease (AD).

Disclosures: The authors declare that they have no conflicts of interest.

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Key takeaway message: Transcranial direct current stimulation combined with cognitive training shows feasibility and potential cognitive benefits, supporting its role as a promising augmentation strategy.

P117- REGION-SPECIFIC EFFECTS OF 40HZ TRANSCRANIAL CURRENT STIMULATION (TACS) ON EEG ACTIVITY IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT.

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Background: Mild cognitive impairment (MCI) patients experience cognitive decline, necessitating the exploration of non-pharmacological interventions such as transcranial current stimulation (tCS), a non-invasive neuromodulation technique that has shown promise in improving cognitive function with minimal side effects. Among tCS methods, transcranial alternating current stimulation (tACS) modulates brain oscillations and has shown potential for cognitive enhancement, with gamma frequency tACS (>30Hz) being particularly effective in MCI patients. Despite the growing application of gamma-frequency tACS in individuals with MCI or Alzheimer's disease, the optimal cortical target region remains under debate. Some studies have stimulated the prefrontal cortex (e.g., dorsolateral prefrontal cortex, DLPFC), known for its association with executive and cognitive control, while others have targeted the temporal lobe, a region implicated in the pathophysiology of dementia. In this study, we aimed to explore which stimulation site—frontal, temporal, or both—elicits meaningful modulation of brain oscillatory activity in MCI patients, thereby providing insights into region-specific efficacy of gamma tACS. **Methods:** This study employed a double-blinded, counterbalanced within-subject crossover design involving 11 older adults (≥60 years, 4 males) clinically diagnosed with MCI based on DSM-5 or Petersen's criteria. Participants underwent four randomized stimulation conditions—Sham, Frontal (F3/F4), Temporal (T7/T8), and Mixed (F3/F4/T7/T8)—with one-week washout intervals between each condition. Online cognitive tasks (Corsi Block Tapping, Immediate Recall, Digit Span, TMT-A/B) were administered during stimulation, and offline resting-state QEEG was recorded post-intervention to assess neural activity. **Results:** No significant differences in cognitive task performance were observed across the four stimulation conditions. Friedman tests showed no statistical effects for any task, including Corsi Block Tapping, Immediate Recall, Digit Span (Forward/Backward), and TMT-A/B. This suggests that gamma-frequency tACS, regardless of stimulation site, did not alter online cognitive performance. EEG power analysis across brain regions and frequency bands revealed a significant reduction in high-beta (15–30 Hz) power in the right frontal region following both Frontal ($p = 0.010$) and Mixed (Frontal + Temporal) tACS ($p = 0.006$), compared to Sham. No other significant effects were found in other regions or frequency bands. These findings suggest a region- and frequency-specific neuromodulatory effect of gamma tACS, particularly in the right frontal cortex. **Conclusions:** Although gamma-frequency tACS did not affect cognitive performance, it significantly reduced high-beta activity in the right frontal cortex—particularly with frontal and frontal+temporal stimulation—suggesting cortical stabilization in MCI. This region-specific EEG modulation underscores the importance of targeting frontal areas like the DLPFC in neuromodulatory interventions. The absence of behavioral effects may reflect the limited sensitivity of brief cognitive tasks to detect real-time neural changes.

Keywords: Mild cognitive impairment, tACS (Transcranial alternating current stimulation), EEG.

Clinical Trial Registry: KCT0010158 (https://cris.nih.go.kr/).

Disclosures: The authors declared no competing interests.

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Key takeaway message: While cognitive performance remained unchanged, gamma-frequency tACS over the frontal cortex—especially the DLPFC—significantly reduced high-beta EEG activity in the right frontal region, suggesting potential cortical stabilization or reduced compensatory overactivation, which is commonly observed in MCI. This region-spcific neural modulation underscores the DLPFC as a key target for future tACS-based interventions.

P118- BARRIERS TO CURRENT ANTI-AMYLOID β INFUSION THERAPIES FOR ALZHEIMER'S DISEASE AND PREFERENCES FOR FUTURE TREATMENT: A QUANTITATIVE SURVEY.

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Objectives: The approval of disease-modifying anti-amyloid β therapies for Alzheimer's Disease (AD) has the potential to transform the treatment paradigm and offer slowed cognitive decline in patients with mild cognitive impairment (MCI) due to AD or mild AD dementia. However, early data has demonstrated limited uptake of therapies, which are currently only available for intravenous (IV) delivery. This study aimed to characterize the burden of IV therapies for AD and assess patient preferences for potential alternative treatment attributes. **Methods:** A quantitative survey was fielded between November 2023 - January 2024 among patients with MCI due to AD or mild AD dementia or their care partners in the United States (US). Care partner responses were evaluated as a proxy for patients and were reported accordingly. Recruited patients (and patients for whom care partners were responding) were diagnosed ≥1 year before survey participation and had not received anti-amyloid IV therapy. The survey included an assessment of blinded product profiles that represented FDA approved and investigational products. Product attributes for each profile were presented and included route of administration, frequency, administration time, and location of administration. **Results:** The study sample included N=404 participants (N=153 patients and N=251 care partners). Respondents were recruited from a range of US geographies (Northeast 26%, Midwest 19%, West 14%, South 42%) and settings (urban 30%, suburban 36%, rural 34%). Almost half of the respondents (45%, N=182) indicated they were unsure about or did not plan to seek treatment with anti-amyloid β

therapies, however, the potential availability of a subcutaneous therapy was reported to increase the likelihood of seeking treatment for 85% (N=342) of patients. Nearly two-thirds (72%, N=290) of respondents cited infusion-related challenges (including distance to an infusion center [N=110] and cost of traveling to an infusion center [N=106]) as barriers to accessing treatment. An at-home, subcutaneous, monthly dosing therapy was preferred by 62% (N=252) of respondents when asked to choose from four blinded product profiles. Across potential AD treatment attributes, subcutaneous injection, monthly dosing, rapid (<10 second) administration, and at-home administration were considered the least burdensome product characteristics by patients. **Conclusions:** This study revealed numerous challenges to accessing anti-amyloid β therapies for patients with AD, particularly surrounding barriers related to IV infusions. A large proportion of study respondents indicated that a therapy with a subcutaneous route of administration would change their willingness to seek treatment. Thus, an anti-amyloid β therapy offering at-home subcutaneous route of administration may help to reduce the considerable treatment burden for AD, increase the number of patients seeking therapy, and slow disease progression among those eligible for treatment.

Key takeaway message: This study revealed numerous challenges to accessing anti-amyloid β therapies, particularly surrounding barriers related to IV infusions. An anti-amyloid β therapy offering at-home subcutaneous route of administration may help to reduce the considerable treatment burden for AD, increase the number of patients seeking therapy, and slow disease progression among those eligible for treatment.

P119- DESIGN AND RATIONALE FOR A STUDY TO EVALUATE BLOOD AND IMAGING BIOMARKERS OF PERSONALIZED NEUROMODULATION THERAPY OF THE DEFAULT MODE NETWORK IN PATIENTS WITH ALZHEIMER'S DISEASE.

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Background: Altered cortical plasticity is considered a central neurophysiological feature of Alzheimer's Disease (AD) and non-invasive brain stimulation may represent a valid tool to restore altered cortical plasticity by promoting synaptic activity. Prior clinical trials have demonstrated the safety and feasibility of neuromodulation of the default mode network (nDMN) via the precuneus for the treatment of mild to moderate AD. These trials demonstrated that 24- and 52- weeks of treatment may slow down cognitive and functional decline in Alzheimer's disease representing a novel therapeutic approach in AD. However, a limitation of these earlier trials was the lack of comprehensive biomarker data. **Methods:** This study is designed as a prospective, multicenter, double-blind randomized sub-study of the larger RETAIN pivotal trial of nDMN via the precuneus for the treatment of mild to moderate AD. Key inclusion criteria include a clinical diagnosis of stage 4 or 5 AD with a positive biomarker profile, global CDR 0.5, 1.0 or 2.0 and memory decline over the prior 6 months. Key exclusions include significant neurological and cerebrovascular diseases, current memantine use, inability to tolerate the TMS-EEG procedure and lack of ability to elucidate a treatment evoked potential during screening. This study will further advance prior work by expanding clinical testing of this therapy to multiple US centers while expanding the prior data collection by focusing on obtaining blood biomarkers and imaging data to further evaluate neurobiological effects of this treatment. Patients will be studied clinically using a suite of standard clinical efficacy assessments (ADAS-Cog, CDR, ADCS-ADL) to correlate biomarkers with clinical outcome. Study visits will occur at Baseline, 12- and 24-weeks post randomization. In addition, we will collect plasma samples along with structural and functional MRI sequences during the study via central laboratories for both initial assessment and to create a repository of samples and images for future study. Finally we will gain CNS assessment data by combining neurophysiological monitoring (EEG) time-linked with a range of assessment tools. **Results:** Treatment evoked potentials (TEPs) data will be analyzed to determine its value as a predictive biomarker for clinical outcome. In addition we will assess the changes in TEPs and personalization parameters across time to further develop the treatment protocols. Biomarker samples, both blood and imaging (MRI), will be obtained during this study via central laboratories and will be analyzed to demonstrate the ability to obtain high quality samples and to provide data for both immediate analysis and future biomarker endpoints. These biomarkers will be analyzed to help identify responders to treatment and provide evidence of target engagement and downstream effects. The study will evaluate the plasma samples via a proteomic approach for CNS disease markers to include BDNF, GFAP, neurofilament (both heavy and light chain), neurogranin, SNAP25, alpha synuclein, Abeta 40 and 42, p-tau 181, 217 and 231. Data will be quality-controlled based on sample coefficient of variation (CV) and on the detection of sample outliers using principal component analysis. Normality will also be assessed. To investigate the differential expression of proteins between the groups a linear modeling analysis will be performed. The results will be visualized in volcano plots. Change over time for significant biomarkers will also be assessed. Additional samples will be stored as a resource for future work as the field of BBBMs for AD is a rapidly advancing area of research. We will analyze volumetric changes across time by group from the MRI images. Changes in local, inter-regional, and network-level functional connectivity can also be compared between groups using resting-state functional MRI. In addition we will be able to use the images obtained as part of this study to further investigate the preliminary findings of macro- and micro-structural preservation, correlated to an increase of functional connectivity within the precuneus to show the possibility to arrest atrophy progression by manipulating distributed network connectivity patterns. In addition, we will collect and assess the EEG synchronized digital assessment data with relevant ERP and qEEG components to add to the burden of evidence for treatment response and efficacy and correlations with other biomarkers and clinical outcome assessments. **Conclusions:** This trial is a unique opportunity to evaluate this new device and novel therapy to gain valuable insights into the neurobiological foundation of non-invasive brain stimulation for AD to increase the likelihood of success of our overall clinical program strategy to rapidly advance DMN-targeted repetitive Transcranial Magnetic Stimulation (rTMS) for AD through clinical trials while demonstrating target engagement. It will also build key partnerships for biomarker research in the AD field, a fast-growing area of research.

Key takeaway message: Understand the design and rationale for this study of biomarkers to demonstrate target engagement and mechanism of action of this new therapy for safely treating mild to moderate AD.

P120- EVALUATION OF AN ULTRA-HIGH-FREQUENCY VISUAL STIMULATION INTERVENTION ON MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE.

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Background: Patients suffering from neurodegenerative diseases such as Alzheimer's disease (AD) experience a marked decline in their cognitive abilities, especially in their ability to form and recall long-term memory. Whereas newly developed disease-modifying drugs target the neuropathology of AD and effectively reduce the accumulation of aggregated amyloid-beta in the brain, their effect on patients' cognitive symptoms is moderate (1). Building on current understanding of the

neural mechanisms of memory formation and memory recall, a different approach aims for a more precise intervention targeted at the cognitive abilities (2). Here, high-frequency neural oscillations, the so-called Sharp-Wave-Ripples (SWRs) play a prominent role: The SWR density tightly correlates with learning and memory capacity (3), and it was shown that artificially induced SWRs can improve memory (4). Established methods to induce SWRs in animals are invasive in nature, however, and hence not suitable for human application. In contrast, non-invasive brain stimulation could offer a safe way to induce SWRs. The effect of brain stimulation on the neural mechanisms of memory could represent a significant advancement in the therapy of memory impairment and offer the potential to address the high unmet need to delay or even prevent the onset of dementia in patients diagnosed with mild cognitive impairment (MCI), Alzheimer's disease or cognitive decline due to aging. **Methods:** The NIN-AD study, a registered, double-blind, placebo-controlled trial, will investigate the effect of a novel ultra-high-frequency visual stimulation (UHV-stimulation) in 36 patients diagnosed with MCI due to AD. The intervention comprises either active UHV-stimulation or control stimulation applied for one hour per day for a duration of six months. The active or control stimulation will be applied at home using augmented-reality glasses. The UHV-stimulation is based on a 120 Hz spatio-temporally organized flickering light stimulation, which is subjectively indistinguishable from the constant light control stimulation due to the UHV-stimulation's frequency exceeding the human visual flicker fusion threshold. The primary outcome measures will focus on the tolerability of stimulation and the adherence to the stimulation protocol. Secondary outcomes will evaluate the intervention's effectiveness on spatial and verbal memory, AD symptoms, sleep, and general wellbeing, as well as the caregiver assessment of daily functioning. Furthermore, exploratory analyses will comprise changes in brain structure and function assessed with resting state electroencephalography (EEG) and functional magnetic resonance imaging (fMRI), and AD biomarkers assessed from blood and cerebrospinal fluid (CSF) [5]. We hypothesize that all patients will tolerate stimulation and adhere to the trial protocol. Furthermore, we hypothesize that those participants with active stimulation will score better in memory tasks and display less severe AD symptoms than those who received the control stimulation, along with more intact brain structure and function and reduced AD biomarkers. **Results:** We have performed a series of pilot experiments on the mechanism of action of UHV-stimulation and the tolerability of stimulation. In N=8 patients suffering from epilepsy, we tested the safety of UHV-stimulation and the effectiveness on SWR induction. We found no side effects and no induction of epileptic seizures in this vulnerable population and could confirm that UHV stimulation increases the SWR density per second. In N=4 patients suffering from MCI, we tested the tolerability of UHV-stimulation and adherence to the trial protocol for four weeks. We found no side effects and patients adhered to the instructed stimulation protocol. Patient recruitment for the NIN-AD trial started on May 23rd 2025 and the data collection is still ongoing, with an intermediate read-out after 3 months, a post-intervention read out after 6 months and a follow-up read-out after 9 months. Results from the intermediate read-out will be reported. **Conclusions:** The NIN-AD trial investigates the feasibility of a long-duration, non-invasive, non-pharmacologic, symptomatic at home treatment targeted at the neural mechanisms of memory to improve the cognitive function of patients suffering from MCI due to AD. The intervention comprises UHV-stimulation applied with augmented-reality glasses, and outcomes cover tolerability, adherence, AD symptoms, brain structure and function, as well as AD biomarkers. Success of the trial could pave the way for safe and accessible therapies of AD and MCI and preventative treatments for age-related memory loss.

Keywords: Visual Stimulation, neuromodulation, non-invasive, digital drug, sharp-wave ripple, hippocampus. **Clinical Trial Registry:** EA1/205/24 Ethics Committee Charité - Universitätsmedizin Berlin, Berlin, Germany; DRKS00036848 German Register of Clinical Trials.

Data Deposition: Trial in progress.

Disclosures: Authors affiliated to Nuuron are employed by the company. SRS received support by the European Research Council (ERC) under the project BNCI2 (101088715) and the Einstein Foundation Berlin.

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Key takeaway message: This trial investigates a non-invasive at home treatment to improve cognition in MCI due to AD. The intervention comprises UHV-stimulation via augmented-reality glasses. Success could foster safe and accessible therapies and prevention for MCI.

P121- PHASE 1, MULTIPLE ASCENDING DOSE STUDY OF A NOVEL ORALLY ADMINISTERED MITOCHONDRIA-DIRECTED DRUG CANDIDATE (SUL-238) IN HEALTHY VOLUNTEERS.

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Background: Mitochondrial dysfunction and oxidative damage are implicated in the pathophysiology of Alzheimer's disease (AD) and Parkinson's disease (PD) (1,2). SUL-238 is a novel, investigational small molecule which improves mitochondrial function in animal models (3,4). Oral treatment with SUL-238 partially reduces amyloid plaque size/accumulation in an AD mouse model, resulting in enhancement of synaptic transmission and memory performance (3). These findings indicate that targeting mitochondrial dysfunction by SUL-238 may provide a promising approach for treatment of AD (3). **Methods:** This Phase 1 randomized, double-blind, placebo-controlled study evaluated the safety, tolerability, and pharmacokinetics (PK) after multiple-ascending doses (MAD) of orally administered SUL-238 in healthy men and women (aged $\geq$40 years). The study included two cohorts with a treatment period of 14 days and a safety follow-up through 14 days after the last dose. In the first cohort, 15 healthy adults were randomized in a 2:1 ratio to a total daily dose of 4000 mg (2000 mg b.i.d.) SUL-238 or placebo. In the second cohort, a total daily dose of 4500 mg (1500 mg t.i.d.) SUL-238 (n=10) or placebo (n=5) were administered. The first cohort completed the study, and the second cohort was in the safety follow-up period at the time of submission of this abstract. Safety and tolerability were assessed by physical and neurological exams, vital signs, ECG, clinical laboratory, and adverse events (AE). Blood samples were collected in all cohorts to characterize PK parameters. Cerebrospinal fluid (CSF)-to-plasma concentration ratio of SUL-238 was determined in participants who accepted to provide CSF sampling. The percentage of drug excreted in urine and feces was measured. **Results:** SUL-238 demonstrated a favorable safety and tolerability profile after multiple doses in both cohorts. No clinically significant changes were

observed in physical and neurological exams, vital signs, ECG and clinical laboratory parameters. AE rates were comparable between participants receiving SUL-238 and placebo and AEs were of mild intensity or considered not related to SUL-238. In the first cohort, SUL-238 was rapidly absorbed with a mean Tmax reached at 1.25(±0.54) and 1.50(±0.53) hours on day 1 and day 14, respectively. Mean t1/2 was 3.50(±1.06) hours on day 14. There was a 15% reduction in Cmax and a 29% reduction in AUC0-inf on day 14 as compared to day 1. Compared to day 1, SUL-238 CSF-to-plasma percentage at 8-hours post-last dose on day 14 was 75% (n=3, range 69%-85%), while CSF concentration of SUL-238 at 12-hours post-last dose was on or below the lower limit of quantification. The mean trough plasma concentration of SUL-238 was 39.23(±24.31) ng/mL on Day 8. The PK results of the second cohort and SUL-238 excretion in urine and feces in both cohorts will be presented at the meeting. **Conclusions:** In this Phase 1 study, 2000 mg b.i.d. and 1500 mg t.i.d. oral doses of SUL-238 were safe and well-tolerated. In the first cohort, 2000 mg b.i.d. demonstrated a favorable PK profile and a high CSF penetration. Results from this study support the further clinical development of SUL-238 for the treatment of AD.

Keywords: SUL-238, Phase 1 clinical study, mitochondrial dysfunction.
Clinical Trial Registry: NCT06277492; https://clinicaltrials.gov/.

Disclosures: NU and SK are full-time employees of Gen İlaç ve Sağlık Ürünleri A.Ş. DHS and ACvdG are full-time and and GK is part-time employees of Sulfateq B.V. ME and RHH chair the Scientific Advisory Boards of Gen İlaç ve Sağlık Ürünleri A.Ş. and Sulfateq B.V., respectively. All other authors declared no competing interests.

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Key takeaway message: Increasing evidence is supporting mitochondrial dysfunction in AD pathophysiology. SUL-238, targets mitochondrial dysfunction by preserving mitochondrial energy production. This study supports the further clinical development of SUL-238 for the treatment of AD.

P122- A FIRST-IN-HUMAN, SINGLE DOSE-ESCALATION STUDY OF CM383, A NOVEL ANTI- AMYLOID BETA ANTIBODY, IN HEALTHY VOLUNTEERS.

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Background: Amyloid-beta (Aβ) deposition plays a key role in the development and progression of Alzheimer's disease (AD), prompting the development of immunotherapies to reduce Aβ accumulation in the brain. CM383 is a novel humanized monoclonal antibody that targets Aβ protofibrils and plaques. In preclinical studies, CM383 demonstrated potent Aβ-binding and clearance activity by inhibiting Aβ1-42 aggregation and enhancing microglia-mediated clearance. **Methods:** This is a first-in-human, single dose-escalation, randomized, double-blinded, placebo-controlled phase I study (NCT06412185) to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity of CM383 in male healthy volunteers. Eligible participants aged 18-54 were randomized to receive a single, intravenous (IV) dose of CM383 (five dosing cohorts: 0.5, 1.5, 4.5, 10, 20 mg/kg) or placebo (3:1 or 4:1). Eligible participants aged 55-80 were administrated a single dose of 10mg/kg CM383 or placebo (8:4).**Results:** A total of 56 participants were enrolled and received CM383 (n=42) or placebo (n=14). The incidence of treatment emergent adverse events (TEAEs) was slightly lower in the CM383 than the placebo group (50.5% vs. 57.1%) and all events were mild in severity, with the most common being laboratory abnormalities. No amyloid-related imaging abnormalities were observed. Following a single IV infusion at doses from 0.5 to 20 mg/kg, CM383 demonstrated dose-proportional increases in exposure and linear elimination. The mean Cmax ranged from 10.4 to 415 μg/mL and the mean $t_{1/2}z$ was ~20 days across dose levels. At 10 mg/kg, PK profiles were similar between older (55–80 years) and younger (18–54 years) participants. Plasma Aβ1-42 and Aβ1-40 levels exhibited a dose-related increase, peaking 0.5 hours post-dose and almost returning to baseline by Day 85. No anti-drug antibodies (ADA) were detected across all dose groups. **Conclusions:** Following a single IV infusion, CM383 was well-tolerated up to 20mg/kg, and demonstrated a linear PK profile with a long half-life of ~20 days. No ADA was detected.

Keywords: Anti- amyloid beta, monoclonal antibody, phase 1 clinical trial, heathy volunteers.

Disclosures: L Zhang, Z Li, J Ma and B Chen are employees of Keymed Biosciences. Other authors declared no competing interests.

Key takeaway message: CM383 is novel anti-amyloid beta antibody, which may be a potential new therapy for Alzheimer's disease.

P123- MASUPIRDINE (A PURE 5-HT6 RECEPTOR ANTAGONIST): UPDATE ON THE PHASE-3 CLINICAL STUDY TARGETING AGITATION IN PATIENTS WITH DEMENTIA OF ALZHEIMER'S TYPE.

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Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder responsible for 60% to 80% of dementia. Neuropsychiatric symptoms (NPS) are common non-cognitive manifestations that emerge throughout the course of the disease. Managing NPS involves complex medical and nursing care and is linked to increased morbidity and mortality, as well as significant distress for both patients and caregivers. Among NPS, agitation is one of the most prevalent symptoms, affecting around 75% of individuals with AD, and its management typically includes psychosocial and pharmacological interventions. While psychosocial approaches are recommended as first-line treatment, severe agitation often necessitates pharmacological intervention. However, current pharmacological options offer modest efficacy and are associated with safety concerns. Therefore, there is a critical need for new, effective, and safe treatments for agitation in AD. Serotonin-6 (5-HT6) receptors are G-protein-coupled receptors with distinct localization and specific distribution in brain regions associated with mood and behavior regulation. Several clinically used psychotropic drugs exhibit high affinity for 5-HT6 receptors and act as antagonists, thereby inhibiting their function. This suggests that 5-HT6 receptor antagonists may hold therapeutic potential for the management of agitation.**Methods:** Masupirdine is a pure, potent, and orally active 5-HT6 receptor antagonist. Its effects on aggression have been studied using rodent behavioral models such as the resident-intruder task and the dominant-submissive assay. The impact of Masupirdine on neurotransmitter modulation was assessed in the cortex of rats, a brain region involved in behavioral regulation. Post hoc analyses from a Phase-2 study targeting cognition in AD patients suggested that Masupirdine may have potential in reducing agitation. Masupirdine is currently being evaluated in a Phase-3 pivotal global study (NCT05397639; EudraCT: 2021-003405-22) for the treatment of agitation in patients with dementia of the Alzheimer's type. This study will assess effect of Masupirdine at doses of 50 mg and 100 mg as compared to placebo, in approximately 375 patients recruited from the USA and Europe. The primary endpoint is the change in scores on the Cohen-Mansfield Agitation Inventory (CMAI) items that align with the International Psychogeriatric Association (IPA) agitation criteria domains. The key secondary efficacy endpoint is the Modified Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change (mADCS-CGIC) score related to agitation. **Results:** In animal models tested, Masupirdine reduces the aggressive behaviors and modulates neurotransmitters involved in agitation behaviors. The observations from animal models and AD patients in Phase-2 clinical trial, support the

beneficial effects of Masupirdine on agitation. The Phase-3 study is currently underway in the USA and Europe to confirm the effects Masupirdine on agitation. The demographic and baseline characteristics of the enrolled patients are consistent across regions and representative of the typical Alzheimer's disease population experiencing agitation. **Conclusions:** Results from the Phase-3 study will inform the utility of Masupirdine in treating agitation in patients with dementia of the Alzheimer's type. Phase-3 study data readout is anticipated in 2026.
Key takeaway message: Masupirdine a pure, potent, and orally active 5-HT6 receptor antagonist may have potential utility in treating agitation in patients with dementia of the Alzheimer's type

BEYOND AMYLOID AND TAU

P124- MODELING BRAIN HOMEOSTASIS FAILURE IN ALZHEIMER'S: A DIGITAL TWIN PLATFORM FOR TARGET DISCOVERY, BIOMARKERS, AND TRIAL DESIGN.

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Background: Despite decades of research and growing datasets, Alzheimer's disease (AD) remains without a unifying, mechanistically grounded framework for understanding disease heterogeneity, therapeutic failure, or personalized intervention. We have developed a computational platform that reframes AD not as a consequence of a single initiating lesion but as a destabilization of brain homeostasis: a systems-level collapse driven by the exhaustion of compensatory feedback loops responsible for cholesterol balance, glial debris processing, and neuronal energy support. **Methods:** Our Brain Health and Neurodegeneration (BHN) platform encodes a mechanistic model of brain homeostasis using nonlinear ordinary differential equations, built from the reconciliation of over 1,500 peer-reviewed publications. This dynamic framework tracks causal relationships between cholesterol trafficking, microglial flux capacity, astrocyte–neuron lactate shuttling, and metabolic stress, simulating disease emergence as a nonlinear transition from stable compensation to energetic collapse. We instantiate digital twins (patient-specific mechanistic hypotheses) from a probability-weighted digital population using Bayesian inference. These twins can simulate individual trajectories, identify upstream drivers of dysfunction, and predict the impact of multimodal interventions. **Results:** We have validated our platform by demonstrating its ability to simultaneously reproduce population-level outcomes across a range of Alzheimer's-relevant endpoints, including genotype-specific variation (e.g., APOE2, APOE4), cerebral perfusion dynamics, and longitudinal biomarker and cognitive trajectories. This validation confirms the internal consistency and external applicability of our mechanistic framework, which forms the foundation for four key translational applications. Target discovery is powered by our ability to correlate large-scale molecular datasets (proteomics, lipidomics, etc) with our digital twin framework. Using a method we call MOTIF (Multiomic Twin-Inferred Function), we correlate thousands of molecular analytes against the synthetic biological variables within our model. This allows us to infer likely functions for poorly understood proteins based on their alignment with known physiological processes. By embedding these correlations within a causal, systems-level framework, MOTIF enables biologically grounded, mechanism-informed target discovery that goes beyond traditional association studies. Our platform supports the target-specific design of biomarker strategies that confirm key causal paths from mechanism of action to clinical endpoints. Using digital twins, we can identify context-appropriate biomarkers that track engagement with the modeled biology and clarify how genetic and physiologic variability influences mechanistic response. Our platform enables a hybrid in vitro–in silico approach to experimental system design. Digital twins are used to define physiologic contexts relevant to disease mechanisms or therapeutic action, and these are then used to guide the design of in vitro protocols that replicate those conditions. Once in vitro data are generated, the responses are projected back through the digital twin framework to simulate full-system outcomes and predict therapeutic efficacy. This closed-loop design improves both the relevance and translatability of experimental systems for Alzheimer's research. Our platform supports clinical trial optimization by enabling simulation-informed patient selection to enhance response rates in early-stage studies. Digital twins can be generated for trial participants to interpret individual response trajectories and mechanistic patterns within the cohort. These insights can inform endpoint selection, dosing strategies, and subgroup refinement, ultimately improving the design and success probability of later-stage trials.
Key takeaway message: Our digital twin platform frames Alzheimer's as a systems-level failure of brain homeostasis, enabling mechanistic target discovery, biomarker strategy, experimental modeling, and trial design across genetically and physiologically diverse populations.

P125- ALZHEIMER'S AND LEWY BODY CO-PATHOLOGY: INTERACTIVE EFFECTS ON CLINICAL TRAJECTORIES IN PRECLINICAL DISEASE.

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Background: Alzheimer's disease (AD) and Lewy body disease (LBD) frequently co-occur, yet the extent to which these pathologies interact to influence clinical trajectories remains poorly understood. While AD pathology is a well-established driver of decline, the impact of concomitant LBD—particularly in individuals who are clinically unimpaired at baseline—has not been clearly defined. This uncertainty has important implications in the era of anti-amyloid therapies, as co-pathologies may alter treatment response. Understanding how AD and LBD interact to shape progression is therefore critical, not only for prognosis but also for the design and interpretation of clinical trials, where accounting for co-pathology may improve the evaluation of therapeutic efficacy. **Methods:** Data were obtained from the National Alzheimer's Coordinating Center (NACC). Participants who were CDR 0 at their initial visit and had available neuropathology data at autopsy were included. Neuropathology data were used to define amyloid pathology as Thal phase ≥ 4 or CERAD neuritic plaque score ≥ 2 (moderate or frequent) at the time of autopsy and were considered Alzheimer's pathology positive (AD+). Lewy body pathology was defined neuropathologically with four levels (none, brainstem, limbic, or neocortical) where participants with diffuse neocortical Lewy bodies were classified as LBD+ at the time of autopsy. Cognition was measured by Delayed Logical Memory, Trail Making Test Part B, Digit Symbol Substitution, Category Fluency, and the Boston Naming Test. Functional ability was measured by the Clinical Dementia Rating Sum of Boxes (CDRSB) and the Functional Activities Questionnaire (FAQ). Repeated measures of cognition and function were modeled using mixed-effects regression with subject-specific random intercepts and slopes. Departures from linear trajectories were modeled with natural cubic splines. Models were adjusted for age at baseline, sex, education, and time from baseline to autopsy. Interactions between AD and LBD over time were evaluated using likelihood ratio tests. **Results:** N=1202 participants were CDR 0 at baseline and had at least one measure of cognition or function. N=605 were classified as AD-/LBD-, N=23 were AD-/LBD+, N=526 were AD+/LBD-, and N=48 were AD+/LBD+. Pathology interactions between AD and Lewy body disease were examined in relation to longitudinal cognitive and functional outcomes. Pathology interactions between AD and LBD were examined in relation to longitudinal cognitive and

functional. Significant AD by LBD interactions were observed for Delayed Logical Memory (c=6.1, p=0.048), Trail Making Test B (c=6.6, p=0.037), CDR Sum of Boxes (c=34.7, p<0.001), and the Functional Activities Questionnaire (c=22.8, p<0.001). In these measures, participants with both AD and LBD pathology exhibited multiplicative decline, with steeper trajectories than expected from the additive effects of each pathology alone. **Conclusions:** In individuals who were cognitively unimpaired at baseline, the presence of both Alzheimer's disease and Lewy body pathology was associated with synergistic effects on clinical progression. Co-pathology produced multiplicative declines in memory, executive function, and was particularly strong in functional outcomes. These findings highlight the importance of considering co-existing pathologies in studies of preclinical Alzheimer's disease and suggest that stratification by Lewy body status may be critical for prognosis and for the design and interpretation of clinical trials targeting early disease stages. With the emergence of anti-amyloid treatments, it remains unclear what clinical benefit can be expected in individuals with concomitant Lewy body pathology, emphasizing the need for further study in this subgroup.

Keywords: Alzheimer's disease, Lewy body disease, co-pathology.
Disclosures: NM has been a paid consultant/speaker for Biogen, BioArctic, Eli Lilly, Novartis, Merck and Owkin. PI has nothing to disclose.
Key takeaway message: In clinically unimpaired older adults, co-existing Alzheimer's and Lewy body pathology accelerates memory, executive, and functional decline beyond either alone. These interactions may influence response to anti-amyloid therapies and highlight the importance of accounting for co-pathology in clinical trials.

P126- THE DNA DAMAGE REPAIR PATHWAY AS A POTENTIAL ROUTE FOR ALZHEIMER'S DISEASE TREATMENT.

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Background: In Alzheimer's disease (AD) the accumulation of DNA damage is frequently associated with the progression of the disease (1), and in and of itself has been associated with mitochondrial dysfunction, epigenetic alterations, and increased instability of the genome and telomeres (2). This accumulation of DNA damage is the end result of the reduced ability of the cells to perform DNA damage repair (DDR) (3,4). This makes the DDR pathway an attractive target for potential treatment of AD, as the restoration of the DDR will reduce the effects of the aging process on the cells. The DDR pathway is a complex system, thus, there are several potential routes through which treatments could be targeted. Firstly, it may be possible to restore functionality to inhibited parts of the DDR pathway. Secondly, the DDR response could be potentiated, which may also lead to the reversal of the effects of DNA damage. One of the critical proteins that controls it is the protein p53. Dubbed the 'Guardian of the genome', it is particularly famous in the cancer field as it is known to be disrupted in more than fifty percent of cancers (5). While it is known that, in neurodegenerative diseases, p53 expression is increased, likely leading to increased damage from stressors (6), it has not received as much attention as other proteins in AD research. Recently, it was reported that in AD patients, p53 aggregation could be detected, and that, moreover, the p53 protein interacted with tau (7). This suggests that the aggregation of p53 is a possible route for the impairment of the DDR, and thus a potential target for therapy (8). Thus, we are currently looking at developing anti-p53 aggregate antibodies that could potentially restore DDR functionality by removing the aggregated proteins. As mentioned, it may also be possible to increase the DDR. One potential method is the use of the NAT10 inhibitor remodelin, which has been shown to increase the lifespan and reduce apparent signs of aging in mice treated with it (9), and reduces the DNA damage observed in mice of the same model (10). Our hypothesis is that the DDR will be improved by the combination of both reducing the presence of p53 aggregates (thus restoring p53 function) and by increasing DDR through the addition of a NAT10 inhibitor. **Methods:** Initially, SH-SY5Y cells were cultured and used to determine the rate of uptake of the antibody into the cells. The antibody was bound to a fluorescent probe to allow for easy visualization of the antibody that was successfully internalized by the cells. We have then used primary neurons from mice to determine the effects that both anti-p53 aggrgate antibody and remodelin have on the expression of DNA damage repair proteins, and have evaluated the response of the primary neurons to DNA damage with and without both the p53 aggregate antibody and remodelin using both histochemistry, transcriptomics and proteomics. Finally, to confirm that the cells will survive treatment with both remodelin and with the anti-p53 aggregate antibody, a lactate dehydrogenase assay was used on the supernatant of the above primary neuron assays to measure the degree of cell death that the cells would undergo after 24 hours exposed to either or both compounds. **Results:** Our preliminary results have shown a strong degree of uptake of the anti-p53 aggregate antibody into the cells. Moreover, they have also shown changes in transcriptomics and proteomics with both the anti-p53 aggregate antibody and remodelin, particularly in terms of synapse-associated genes and proteins. Both the antibody and the remodelin were well-tolerated by the cells, suggesting that further treatments are possible and will not inflict undue damage on the cells. **Conclusions:** The treatments that we are implementing have been shown to be well-tolerated by cells, to be internalized by them, and moreover to have a biological effect, providing a good basis for future research into their effectiveness as an AD treatment.

Keywords: Small molecule inhibitors, p53, remodelin, proteomics, transcriptomics.
Disclosures: Funding for this project was received from the Pepper centre and the National Institute for Health. **References:** 1. Lin, X. et al. Contributions of DNA damage to Alzheimer's disease. International journal of molecular sciences 21, 1666 (2020). 2. Schumacher, B., Pothof, J., Vijg, J. & Hoeijmakers, J. H. The central role of DNA damage in the ageing process. Nature 592, 695-703 (2021). 3. Jones, S. et al. Decreased DNA repair in familial Alzheimer's disease. Mutation Research/DNAging 219, 247-255 (1989). 4. Thadathil, N. et al. DNA double-strand break accumulation in Alzheimer's disease: evidence from experimental models and postmortem human brains. Molecular Neurobiology 58, 118-131 (2021). 5. Levine, A. J. p53, the cellular gatekeeper for growth and division. cell 88, 323-331 (1997). 6. Szybińska, A. & Leśniak, W. P53 dysfunction in neurodegenerative diseases-the cause or effect of pathological changes? Aging and disease 8, 506 (2017). 7. Farmer, K. M. et al. P53 aggregation, interactions with tau, and impaired DNA damage response in Alzheimer's disease. Acta neuropathologica communications 8, 132 (2020). 8. Abuetabh, Y. et al. DNA damage response revisited: the p53 family and its regulators provide endless cancer therapy opportunities. Experimental & molecular medicine 54, 1658-1669 (2022). 9. Balmus, G. et al. Targeting of NAT10 enhances healthspan in a mouse model of human accelerated aging syndrome. Nature communications 9, 1700 (2018). 10. Larrieu, D., Britton, S., Demir, M., Rodriguez, R. & Jackson, S. P. Chemical inhibition of NAT10 corrects defects of laminopathic cells. Science 344, 527-532 (2014).
Key takeaway message: The use of anti-p53 aggregate antibodies and a NAT10 inhibitor are well-tolerated by neurons, and are of potential utility in Alzheimer's disease treatment.

P127- BONE AND SENESCENCE BIOMARKERS ASSESSED IN THE PLASMA OF MCI AND AD PATIENTS FROM THE ROSMAP COHORT.

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Objective: Alzheimer's disease (AD), characterized by progressive cognitive decline, frequently coexists with various comorbidities. Recent investigations have indicated a potential link between Alzheimer's pathology and alterations in bone health. This study aims to examine the presence of bone-related comorbidities across different cognitive states, specifically early, late-stage AD, and Mild Cognitive Impairment (MCI). **Methods:** The Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP), collectively known as ROSMAP, commenced in 1994 and 1997, respectively. As part of this collaboration, proteomic analyses using Somalogic were conducted on samples from 973 participants involved in the ROSMAP study. The breakdown of participants by disease state is as follows: No cognitive impairment (NCI): 507 participants, Mild cognitive impairment with no other contributing conditions (MCI): 262 participants, Mild cognitive impairment with another contributing condition (MCI+): 10 participants, Alzheimer's dementia with no other contributing conditions (AD): 167 participants, Alzheimer's dementia with other contributing conditions (AD+): 17 participants and Other dementia (otherdem): 10 participants, identified as having an alternative primary cause of dementia without any clinical evidence of Alzheimer's dementia. The analysis of proteins was carried out using an Ordinary Least Squares (OLS) regression model, to which a Benjamini-Hochberg correction was applied. Significance was established based on criteria that included whether the log2 fold change of a protein was $\geq$0.35 or $\leq$-0.4, alongside an adjusted p-value of less than 0.05. **Results:** YKL-40 and FGF-19 are significant in AD vs NCI for the bone pathway when the sexes are combined. YKL-40 and FGF-19 are significant bone markers in AD vs NCI females. In AD vs MCI females, YKL-40 is a significant bone marker. WISP-1 is a significant bone marker in AD females when compared against AD+. For AD vs OthrDem females, Ephrin-A2 is a significant bone marker. In AD+ vs NCI females, ON and WISP-1 are significant bone markers, and PAI-1 and DKK1 are significant senescence markers. In MCI vs AD+ females, ON and WISP-1 are significant bone markers, and DKK1 is a significant senescence marker. **Conclusions:** This study reports proteins related to bone and senescence metabolism altered in the plasma of AD, AD+, MCI, MCI+, revealing a potential link between neurodegeneration and bone health. **Clinical Trial Registry:** NA.
Data Deposition: The ROSMAP investigators are committed to timely data sharing of raw or processed data, which can be found on our Resource Sharing Hub with relevant links to the AMP-AD Knowledge Portal. Studies were approved by the IRB of Rush University Medical Center (no. L91020181, MAP IRB no. L86121802).
Disclosure: The authors declared no competing interests.
Keywords: MCI, AD, bone, senescence, proteomics.
Key takeaway message: Bone biomarkers are detected in the plasma of MCI and AD patients.

P128- DEVELOPMENT OF POTENT, SELECTIVE CPLA2 INHIBITORS FOR TARGETING NEUROINFLAMMATION IN ALZHEIMER'S DISEASE.

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Omega-3 supplements are not effective in patients with Alzheimer's disease (AD) despite a robust association between omega-3 tissue levels and lower AD risk observed across multiple cohorts. These findings support that tissue levels of omega-3s are more relevant to AD pathogenesis than omega-3 supplements. Our lab has been investigating the mechanisms of omega-3 brain metabolism and reported an upregulation of cytosolic calcium-dependent phospholipase A2 (cPLA2) brain enzyme activity in APOE4 AD human brains as a key regulator of brain omega-3 and omega-6 metabolism. Increased cPLA2 activity in APOE4 mouse models was associated with lower omega-3/ omega-6s in human APOE4 brain tissues and markers of neuroinflammation. Inhibiting brain cPLA2 expression in APOE4-TR mouse models is associated with greater omega3/omega6 ratios, less microglial activation, and better performance on water maze behavioral tests. To date, no potent and specific cPLA2 inhibitors capable of penetrating into the brain have been developed. By leveraging the giga-scale V-SYNTHES2.0 virtual screening in on-demand chemical space, followed by two rounds of chemical optimization for potency and selectivity, we have identified BRI analog-50054 and BRI-50460, with BRI analog-50460 achieving an IC50 of 0.88 nM using cPLA2 cellular assays. In vivo studies confirmed favorable brain-to-plasma (B/P), with 41% B/P after SQ administration, and 81% B/P after oral administration, highlighting the ability of BRI-50460 to penetrate the central nervous system, potentially modulating neuroinflammatory pathways and restoring lipid homeostasis. BRI analog-50054 reduced brain arachidonic acid (AA) levels and increased omega-3 fatty acids (DHA and EPA). In cultured neurons derived from human iPSCs, BRI-50460 mitigates the effects of amyloid-42 oligomers on cPLA2a activation, tau hyperphosphorylation, and synaptic and dendritic reduction. Our results suggest that small-molecule inhibitors of the cPLA2 enzyme can modulate the downstream inflammatory lipid signaling pathways as a promising therapeutic strategy for AD neuroinflammation.
Key takeaway message: How the brain uses omega-3s is likely more relevant to AD pathogenesis than taking omega-3 supplements. Targeting brain cPLA2 reverses omega-3 catabolism and neuroinflammation in preclinical AD models. We discovered potent and brain-penetrant cPLA2 inhibitors that warrant further drug development.

P129- MISFOLDING OF ALPHA-SYNUCLEIN AS A BLOOD BASED FLUID BIOMARKER FOR PARKINSON'S DISEASE.

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Background: We conducted discovery and validation studies for the investigation of the potential of alpha-synuclein-misfolding as fluid biomarker for Parkinson's disease (PD) and multiple system atrophy (MSA) (1). We have already shown that misfolding of amyloid-beta indicates the risk of Alzheimer's disease up to 17 years before clinical onset in plasma (2–5). **Methods:** For these studies, we analyzed CSF and blood samples from patients with idiopathic and atypical parkinsonian disorders as well as controls consisting mainly of individuals with headache or normal pressure hydrocephalus. Alpha-synuclein-misfolding was determined by the immuno-infrared-sensor (iRS) indicating protein-biomarker misfolding complementary to concentration change based biomarkers (1,5). **Results:** We achieved Sensitivity 92% and specificity of 96% in CSF by subdividing individuals into high, intermediate, and low misfolding like a traffic light scheme (1). This approach is now extended to bloodserum. Results of a larger discovery and validation study will be presented. **Conclusions:** We present for the first time a direct alpha-synuclein-misfolding-biomarker in CSF and blood which can discriminate synucleinopathies like PD and MSA from atypical syndromes and other controls. DLB samples are not yet analyzed and might also be indicated. This allows a precise stratification of early-stage-individuals for a precise symptomatic therapy today and a therapeutic intervention in the future.
Keywords: Body fluid, Alzheimer, Parkinson, ALS, biomarker.
Disclosures: Klaus Gerwert is founder and CEO of the betaSense GmbH.
References: 1. Martin Schuler et al. EMBO Mol Med 2025; doi: 10.1038/s44321-025-00229-z. 2. Nabers A, et al. J Biophotonics 2016;9 (3):224–34. 3. Nabers A, et al. EMBO Mol Med 2018;10(5). 4. Stockmann J, et al. Alzheimer's research & therapy 2020;12(1):1–13. 5. Beyer L, et al. Alzheimers Dement. 2022 Jul 19. doi: 10.1002/alz.12745.
Key takeaway message: We conducted a discovery and validation studies for the investigation of the potential of alpha-synuclein-misfolding as fluid biomarker for Parkinson's disease (PD) and multiple system atrophy (MSA).

P130- MICROBIOME–BRAIN VOLUME ASSOCIATIONS IN COGNITIVELY UNIMPAIRED ADULTS IN A COHORT ENRICHED FOR ALZHEIMER'S DISEASE RISK.

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Background: Alzheimer's disease (AD) is characterized by progressive neurodegeneration that begins years before symptom onset, with hippocampal atrophy often among the earliest imaging hallmarks. The gut microbiome has emerged as a potentially modifiable contributor to brain health through immune modulation, microbial metabolite signaling, and barrier signaling. Although microbiome compositional differences have been described in AD dementia and in individuals with AD pathology, less is known about how specific taxa relate to MRI markers of neurodegeneration in preclinical AD. We therefore tested whether microbial taxa are associated with regional and global brain volumes in cognitively unimpaired adults at risk for AD. We hypothesized that gut microbiome composition would be associated with MRI-derived markers of neurodegeneration in cognitively unimpaired adults at risk for AD, independent of age and AD biomarker status. **Methods:** T1-weighted MRI and 16S rRNA sequenced fecal samples were included in across-sectional analysis of 155 cognitively unimpaired participants enrolled in AD and microbiome studies at the Wisconsin Alzheimer's Disease Research Center (ADRC). Microbial taxa were regressed on brain volumes including gray matter (GM), white matter (WM), hippocampal volume (HIP), total brain volume (TBV), cerebrospinal fluid (CSF), and an atrophy index (CSF/TBV). Associations were modeled with Bayesian Inferential Regression for Differential Microbiome Analysis (BIRDMAn), adjusting for age, sex, total intracranial volume, amyloid and pTau biomarker positivity status, and time from MRI scan to fecal sample collection. Benjamini-Hochberg correction was used to adjust for inflated Type I error. **Results:** Microbiome analyses identified multiple associations with neurodegeneration markers (all $q<0.05$). Atrophy was negatively correlated with Anaerobutyricum hallii (β [95% highest density interval (HDI)] = −4.86, [−9.49, −1.51]), Streptococcus salivarius (β [95% HDI] = −4.65 [−9.14, −0.49]), Ruminiclostridium_E (−3.65 [−9.13, −0.16]), and Coriobacteriaceae (−4.73 [−10.78, −1.59]). HIP showed negative associations with S. salivarius (−1.26 [−1.92, −0.56]), Ruthenibacterium lactatiformis (−0.74 [−1.37, −0.12]), Anaerofilum (−1.30 [−2.37, −0.27]), Coriobacteriaceae (−1.13 [−2.69, −0.17]), and Streptococcaceae (−1.20 [−1.90, −0.54]), and positive associations with Roseburia hominis and Burkholderiaceae_A. GM volume was negatively associated with R. lactatiformis (−0.013 [−0.027, −0.004]) and Massilistercora (−0.028 [−0.053, −0.004]); WM volume was positively associated with Streptococcaceae (0.012 [0.004, 0.023]). CSF volume was negatively associated with Bifidobacterium breve (−0.013 [−0.021, −0.003]) and positively with Anaerofilum (0.011 [0.0001, 0.022]) and Limiplasma (0.013 [0.004, 0.023]). **Conclusions:** In this preclinical ADRC cohort, specific gut taxa were associated with MRI markers of neurodegeneration. Microbiota associated with butyrate production and bile acid metabolism were related to less atrophy, while abundance of oral taxa showed negative relationships with hippocampal volumes. Although we hypothesized that short-chain fatty acid producing taxa would be related to higher brain volume, potentially by maintaining gut barrier integrity, we unexpectedly found interesting patterns suggesting region-specific effects. For example, Streptococcus salivarius was negatively associated with hippocampal volume and inversely associated with the atrophy index (CSF/TBV), indicating smaller hippocampal volume alongside a lower global atrophy measure Longitudinal observation and mechanistic studies are needed to clarify whether these associations reflect causal effects or potential compensatory processes, which will inform microbiome-targeting interventions to mitigate or delay neurodegeneration in AD.

Key takeaway message: Specific gut taxa track MRI markers of neurodegeneration in preclinical Alzheimer's: SCFA producers associate with larger hippocampus and lower atrophy, while taxa show regional discordance. Findings support microbiome-based stratification and prevention targets to delay neurodegeneration.

P131- COMPARING THE EFFECTS OF DISCLOSURE OF MULTIPLE RISK FACTORS FOR ALZHEIMER'S DISEASE ON MOOD AND DISTRESS LEVELS IN COGNITIVELY HEALTHY INDIVIDUALS.

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Background: Alzheimer's Disease (AD) risk disclosure in cognitively unimpaired individuals is becoming increasingly common. Cognitively normal individuals can show abnormal AD risk markers years prior to functional impairment including the presence of apolipoprotein E (APOE) E4 allele, elevated brain amyloid levels, neuropsychological impairment. Disease modifying therapies are emerging that target these risk factors even prior to a clinical diagnosis of AD or Mild Cognitive Impairment. In contrast, not all individuals with these risk factors develop dementia. It is therefore crucial to assess the psychological and behavioral effects of disclosing AD risk to cognitively normal individuals. Studies involving the disclosure of genetic risk alone and the disclosure of amyloid risk alone have generally shown to not be associated with undue psychological distress or behaviors (such as suicidality). However, no study to our knowledge has examined if disclosing multiple risks (genetic, amyloid, and cognitive) in a single session is safe and tolerable. The purpose of this study is to compare depression, anxiety, and distress levels before and after disclosing individuals' APOE genotype, amyloid status, and cognitive status. **Methods:** The Brain Biomarker Brown (B3) study enrolled 67 cognitively healthy participants aged 50-80 with a Folstein Mini-Mental Status Examination (MMSE) score of 27 or greater for individuals under age 65 or a score of 26 or greater for individuals age 65 and older, for a 5-year observational trial. The study included APOE genotyping, amyloid PET imaging, and comprehensive cognitive assessment at baseline. A subgroup of participants opted into the disclosure of their AD risk factors. Three risk factors – APOE genotype, amyloid status, and cognitive results – were disclosed to participants at a personalized, in-person visit with a study partner. Disclosure occurred only after it was deemed that participants were psychologically ready by a trained clinician. Pre- and post-risk disclosure, the participants completed, among other measures, the six item State Anxiety Inventory Short Form (STAI), the 15 item Geriatric Depression Scale Short Form (GDS), and the Impact of Events Scale (IES). The IES assesses distress during the past week from 0 (not at all) to 5 (often), with two subscales, intrusion and avoidance, as well as a total subjective stress score. The IES intrusion questions capture thoughts related to nightmares, intrusive feelings and imagery, and dissociative-like re-experiencing, while the avoidance questions capture numbing of responsiveness and avoidance of feelings, situations, and ideas. Higher scores on the GDS, STAI-6, and IES reflected higher levels of depression,

anxiety, and distress. A series of Wilcoxon signed-rank test was conducted to compare depression, anxiety, and distress levels before and after the risk disclosure. Analysis was conducted in groups stratified by their risk factors , including (i) genotype (positive/negative); positive includes APOE4 allele homo- and heterozygotes, (ii) amyloid PET status (positive or negative) as confirmed by a neuroradiologist using standard algorithms, (iii) areas of relative cognitive weakness (present/absent); present includes performance below expectation for age and education in any domain (attention, memory, language, processing speed, executive function) based on normative scores and as confirmed by a neuropsychologist, and (iv) risk status (positive/negative) if either the genotype or the amyloid PET results were positive, or if low cognitive performance was present. **Results:** Participants were cognitively healthy older adults (N=24; M age =66.17, SD = 7.52; M education=17. 21 years, SD=2.21;75% female; 91.7% White; 87.5% Non-Hispanic) with an average MMSE score of 28.62 (SD = 7.52). The GDS, STAI, and IES were administered prior to the risk disclosure (average time interval from pretesting to disclosure=44 days; range 8-84) and after the disclosure (average time interval from disclosure to post testing = 7 days; range 1-18). In the genotype positive status group, individuals who were carriers of the APOE4 allele had significantly elevated avoidance scores on the IES post risk disclosure (Median = 0.5) compared to pretest disclosure (Median = 0), Z = 2.02, p = .042, r = .70, indicating a large effect size. No other significant differences in mood or distress levels were found in any of the other stratified groups for any of the AD risk markers. **Conclusions:** Findings reveal that cognitively healthy older adults can tolerate the disclosure of multiple risk factors in a single session. Approximately a week after disclosure, no significant changes in levels of anxiety and depression were observed as compared to prior to the disclosure for APOE, amyloid, and cognitive status for individuals with and without a positive risk-related status. In contrast, post disclosure, participants with at least one APOE4 allele showed increased avoidance thoughts indicating increased level of distress. No difference in avoidance thoughts was noted in those without an APOE4 allele. This may be due to APOE status being more well known in the community for increased risk of AD, therefore causing initial higher impact in avoidance related thoughts and behaviors. Limitations of this study include small and relatively homogenous sample with the analysis not adjusted for covariates. In future studies it would be beneficial to determine if avoidance thoughts are maintained over time and whether changes in mood emerge.

Keywords: Alzheimer's disease, disclosure, cognitive abilities, APOE, genetic risk, amyloid status, neuroimaging. **Disclosures:** None to disclose.

Key takeaway message: Cognitively normal individuals can tolerate disclosure of multiple risk factors for Alzheimer's Disease in a single session. Participants with an APOE4 allele show increased avoidance immediately after.

P132- EFFICACY AND SAFETY OF LEVETIRACETAM TO PREVENT SEIZURES IN DOWN SYNDROME ALZHEIMER'S DISEASE: THE PHASE III LESS-AD TRIAL.

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Background: Individuals with Down syndrome (DS) are at increased risk of Alzheimer's disease (AD) and epilepsy. Seizures become more frequent as dementia progresses, while epilepsy itself may accelerate cognitive decline. Preclinical studies suggest that suppression of neural hyperexcitability with levetiracetam (LEV) reduces epileptiform activity and improves synaptic and cognitive function. This trial aims to evaluate whether LEV can safely prevent seizures and potentially slow AD-related decline in DS. **Methods:** LESS-AD is a multi-center, randomized, double-blind, placebo-controlled phase III trial. A total of 120 participants with DS and symptomatic AD, but without epilepsy, will be randomized 1:1 to LEV (500 mg/12h) or placebo. The primary endpoint is safety (adverse events) and efficacy (incidence of bilateral tonic-clonic seizures). Secondary endpoints include time to first seizure, all-cause mortality, and changes in AD-related biomarkers (functionality, cognition, plasma biomarkers [pTau181, NfL], brain MRI, and EEG). Participants will be followed for two years. **Results:** The trial initiated recruitment in the last quarter of 2025. **Conclusions:** LESS-AD will test whether LEV is safe and effective in preventing seizures in DS-AD and whether it may secondarily slow neuronal damage and cognitive decline. This study addresses a critical unmet need in a population highly vulnerable to both AD and epilepsy.

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Key takeaway message: The LESS-AD trial will determine if levetiracetam can safely prevent seizures and potentially slow Alzheimer's-related decline in individuals with Down syndrome, addressing a critical unmet need in this vulnerable population.

P134- EARLY MICROGLIAL ACTIVATION AND ASTROCYTOSIS IN PRECLINICAL ALZHEIMER'S DISEASE.

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Background: The role of neuroinflammation in the asymptomatic stages of Alzheimer's disease (AD) remains unclear. We aimed to assess changes in microglial and astrocytic biomarkers in the preclinical Alzheimer's continuum in a well-characterized cohort of cognitively unimpaired (CU) individuals and investigate their relationships with early pathological events in the amyloid cascade. **Methods:** We included 211 CU volunteers older than 55 years from the Valdecilla Cohort for the study of memory and brain aging. Cerebrospinal fluid (CSF) soluble triggering-receptor expressed on myeloid cells 2 (sTREM2), Chitinase-3-like protein 1 (YKL-40), S-100 protein beta (S100β), and neurogranin were quantified using Luminex XMAP, while plasma and CSF glial fibrillary acidic protein (GFAP) and neurofilament light (NfL) were determined by SIMOA. CSF amyloid beta (Aβ) 40, Aβ42, phosphorylated tau 181 (p-tau181), and total tau (t-tau) were measured with Lumipulse. We analyzed correlations between glial biomarkers and CSF AD biomarkers, as well as differences in their levels according to the ATN group, AD status, and amyloid status. We used structural equation modeling to simultaneously analyze all relationships among microglia and astrocyte responses and AD pathological events. **Results:** Preclinical

AD showed increased plasma GFAP and CSF sTREM2 compared to normal subjects. Plasma GFAP correlated with CSF Aβ42/40, while CSF sTREM2 correlated with p-tau181. Plasma and CSF GFAP, CSF sTREM2, YKL-40, and S100β correlated with downstream neurodegeneration biomarkers. Our path model revealed an inverse bidirectional relationship between plasma GFAP and CSF Aβ42/40. CSF sTREM2 directly influenced CSF p-tau181 and neurogranin, and showed a bidirectional relationship with CSF S100β. CSF YKL-40 partially mediated the association between p-tau181 and t-tau, while CSF S100β and NfL showed mutual influence. **Conclusions:** Our findings suggest that microglial activation and reactive astrogliosis, measured through fluid biomarkers, occur early in the Alzheimer's continuum and impact the amyloid cascade in preclinical AD. Specifically, plasma GFAP influences amyloid accumulation, sTREM2 promotes tau pathology, and YKL-40 and S100β contribute to the progression of downstream neurodegenerative changes.

Keywords: Microglia, astrocyte, soluble triggering-receptor expressed on myeloid cells 2 (sTREM2), glial fibrillary acidic protein (GFAP), chitinase-3-like protein 1 (YKL-40), S-100 protein beta (S100β), biomarkers, preclinical Alzheimer's disease, structural equation modeling.

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Keywords: Microglia, astrocyte, soluble triggering-receptor expressed on myeloid cells 2 (sTREM2), glial fibrillary acidic protein (GFAP), chitinase-3-like protein 1 (YKL-40), S-100 protein beta (S100β), biomarkers, preclinical Alzheimer's disease, structural equation modeling.

P135- RELATIONSHIPS BETWEEN NEAR END-OF-LIFE PLASMA BIOMARKERS AND POSTMORTEM CEREBRAL AND VASCULAR AMYLOID, TAU, TDP-43, AND ALPHA-SYNUCLEIN MEASUREMENTS.

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Background: Alzheimer's disease (AD) is neuropathologically characterized by the accumulation of amyloid-β plaques, and the deposition of intracellular tau tangles. However, co-pathologies such as cerebral amyloid angiopathy (CAA), TDP-43, and alpha-synuclein are frequently observed in AD patients. The impact of these co-existing pathologies on disease progression and response to therapeutic interventions remains poorly understood, particularly given the lack of in vivo biomarkers to detect such co-pathologies. In this study, we analyze a panel of blood-based biomarkers in a unique cohort with diverse, neuropathologically confirmed diagnoses to determine whether surrogate indicators of co-pathologies can be identified. **Methods:** We measured 127 protein using NULISAseq CNS panel in an antemortem plasma samples <5 years prior to death (mean 1.76 years, SD= 1.3) from 253 participants including individuals with moderate-to-frequent neuritic plaques (n=150); elevated TDP-43+ (n=64) Lewy body (n=46) and CAA (n=142) pathology, alone or in combination, in the Brain and Body Donation Program at Banner Sun Health Research Institute. We evaluated the differential protein expression between pathology-defined groups using a linear regression model. We used Spearman correlations to test associations with neuropathology scores and ROC curves to evaluate plasma biomarker discriminative accuracy. We also trained an artificial neural network (ANN) model on the ~127 measured plasma biomarkers to predict mean Lewy body density at post-mortem. We used Spearman correlations to test associations with neuropathology scores and ROC curves to evaluate plasma biomarker discriminative accuracy. **Results:** In AD, and as expected, pTau-217 was the most upregulated protein (logFC= 0.77, padj < 0.001), correlated with postmortem cortical tau neurofibrillary tangles ($\rho = 0.51$, $p < 0.001$) with pTau-217/Aβ42 having the highest accuracy in classifying AD (AUC=0.93). Three proteins, including pTDP43-409, were significantly over-expressed in those with TDP-43 pathology and 16 proteins were differentially expressed in those with alpha-synuclein pathology. The ANN analysis demonstrated a strong correlation between predicted and observed postmortem Lewy body density values. Shapley value approximation identified 12 proteins, including SNCA and pSNCA129, as the main contributors to the model. Lastly, in participants with CAA, three proteins: CRP (logFC = 0.37, p = 0.002), IL4 (logFC = 0.42, p = 0.018), TEK (logFC = 0.93, p = 0.04) were upregulated; while four targets: CCL11 (logFC = -1.1, p = 0.002), PDLIM5 (logFC = -0.17, p = 0.02), NPY (logFC = -0.45, p = 0.03), GDNF (logFC = -0.17, p = 0.04) were downregulated. A refined multivariate analyte model demonstrated high accuracy (AUC = 0.90; 95%CI = 0.86-0.94) in identifying CAA. **Conclusions:** The lack of in vivo biomarkers for pathologies outside of the hallmarks of AD, limits our understanding of their role in disease progression and treatment response. Our findings show potential plasma biomarker combination that may act as surrogate indicators of TDP-43, alpha-synuclein and CAA–which warrants further investigation and validation.

Key takeaway message: AD patients have other existing comorbidities such as TDP-43, PD, CAA, that makes it difficult to diagnose and treat. We aim to find novel blood-based-biomarkers so that clinician can tailor the treatment regimen accordingly.

P136- FANNING THE FLAMES: DID COVID-19 ACCELERATE PROGRESSION OF ALZHEIMER'S DISEASE IN THE ADNI COHORT?

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Background: There is growing evidence that COVID-19 infection, caused by the SARS-CoV-2 virus, increases the risk of new onset dementia and accelerates cognitive decline in patients with dementia (1-3). Population-level data suggests that a COVID-19 diagnosis in older adults significantly increases the risk for a diagnosis of Alzheimer's disease (AD) within one year, suggesting that COVID-19 infection may accelerate the neurodegenerative process (4). We investigated the association of COVID-19 with dementia risk leveraging data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study cohort. The ADNI study collects data from over 60 sites in the USA and Canada to study the progression of Alzheimer's Disease (5). Participants are comprehensively evaluated with clinical history, cognitive status, and AD imaging and fluid biomarkers, allowing exploration of the clinical and cognitive trajectory of participants with and without a history of COVID-19 infection exposure. We hypothesized that participants reporting COVID-19 infection would have accelerated cognitive decline, decline in function and greater occurrence of neuropsychiatric symptoms between the visit prior to reporting COVID-19 and the visit after in comparison to matched controls who did not report an infection. **Methods:** This study is a secondary data analysis from ADNI cohort looking at participants with a diagnosis of MCI, mild dementia or cognitively normal. Data were collected over two visits at least 12 months apart. COVID-19 infection was reported in the ADNI adverse events log, recorded as "Related to COVID-19 illness," categorized as definitely (confirmed COVID-19 test), probably and possibly. We defined visit-1 as the visit occurring prior to their report of COVID-19 infection, and visit-2 occurring after their report of COVID-19 infection. We compared them to a matched group of participants who completed the same assessments but did not report a history of COVID-19 infection. To assess for global cognition the Mini Mental Status Exam (MMSE), Montreal Cognitive Assessment (MoCA), the Alzheimer's Disease Assessment Scale - Cognitive (ADAS-COG) total scores and The

Clinical Dementia Rating (CDR) global score and sum of boxes (6-9) were used. To assess different cognitive domains the Rey Auditory Verbal Learning Test (RAVLT) learning and immediate scores, Auditory Verbal Learning Test (AVLT) 30 minute delayed total score, Trail Making Test Part A and B, Clock Drawing, Category Fluency, the Multilingual Naming Test (MINT) and the Logical Memory Test (10-12) were assessed. The Functional Activities Questionnaire (FAQ) total score was used to assess activities of daily living (13). To assess for behavioral symptoms, the Neuropsychiatric Inventory (NPI) and the Geriatric Depression Scale (GDS) (14,15) were examined. Descriptive analyses were performed to summarize the study participants' characteristics. Continuous variables were reported as means with standard deviations, while categorical variables were presented as frequencies and percentages. Group comparisons were conducted using the Wilcoxon rank-sum test for continuous variables and Pearson's chi-squared test or Fisher's exact test for categorical variables. Changes in each outcome were evaluated between the COVID and control groups, with p-values derived from the Wilcoxon rank-sum test. All statistical analyses were performed using R version 4.4.1(R Foundation for Statistical Computing, Vienna, Austria), and statistical significance was set at $P < 0.05$. **Results:** By August 2022, 36 participants in the ADNI 3 cohort reported COVID-19 and had it recorded as an adverse event. 20 participants were excluded for having significant missing data. The remaining 16 participants were included as the COVID-19 cohort. The control population was selected to match by age, diagnosis at the time of enrollment (MCI, dementia and NC) and gender from the broader ADNI 3 population who did not report a history of COVID-19 infection. None of the participants in the COVID-19 cohort had a change of diagnosis between the time points. Regarding global cognition there was no significant change in MMSE (p=0.644), MoCA (p=0.757), ADAS-COG (p=0.793) total scores, the CDR global score (p=0.346), and sum of boxes (p=0.574) between the COVID-19 and control groups between both time points. Neither group exhibited cognitive decline between both time points. There was no significant change in RAVLT learning (p=0.529 or immediate scores (p=0.776), AVLT (p=0.841), Trail Making Test part A (p=0.793) or B (p=0.555), Clock Drawing (p=0.729), Category Fluency (p=0.878), MINT (p=0.872) and the Logical Memory Test (p=0.716). For level of functioning and behavioral symptoms there was no significant change in the FAQ (p=0.341), NPI (p=0.839) or GDS (p=0.478) scores between the COVID-19 and control groups between both time points. Overall GDS scores were low in both cohorts at both time points (range 0-7). **Conclusions:** There was no significant group difference in the cognitive, functionality and behavioral measures at study visits prior to and following COVID-19 infection comparing the COVID-19 cohort and the control group. While there is evidence that COVID-19 infection increases the risk for depression, cognitive changes and conversion to dementia, this examination of a well characterized cohort did not find evidence for this in the immediate post infection. Limitations include the small sample size and mild symptoms of infection in this cohort. Further work is needed to determine whether more severe infection, longer follow up, or different COVID-19 variants increase risk of accelerating cognitive decline and how is the risk differs with effective antiviral treatments.

Keywords: Cognitive impairment, COVID-19, dementia.

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Key takeaway message: While there is evidence that COVID-19 infection increases the risk for depression, cognitive changes and conversion to dementia, this examination of a well characterized cohort did not find evidence for this post infection.

P137- DEGENERATIVE PATHOLOGIES ON CORTICAL BIOPSY, DOPAMINERGIC DEPLETION, AND SHUNT EFFICACY IN INPH.

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Introduction: Coexisting degenerative pathologies may influence the efficacy of ventriculoperitoneal (VP) shunting in idiopathic normal pressure hydrocephalus (iNPH). **Methods:** We evaluated 58 iNPH patients who underwent VP shunting with cortical biopsy assessing b-amyloid, phosphorylated-tau, and a-synuclein. Concordance between biopsy-identified Alzheimer's pathology and amyloid-PET, and the influence of MRI-based iNPH indices, dopamine transporter (DAT) imaging, and biopsy pathologies on postoperative outcomes were examined. **Results:** b-amyloid pathology was detected in 23 patients (39.7%) and showed high concordance with amyloid-PET (95.2%). Both b-amyloid-positive and -negative groups showed functional and cognitive improvement after surgery, though b-amyloid-positive patients demonstrated attenuated functional improvement at two years. Lower anterior striatal DAT uptake was paradoxically associated with better postoperative outcomes, particularly in b-amyloid-positive or phosphorylated-tau-positive individuals. **Discussion:** Cortical biopsy provides information concordant with amyloid-PET, and biopsy-confirmed Alzheimer's pathology and dopaminergic status influence shunt efficacy. VP shunting remains beneficial in iNPH even with degenerative comorbidities.

Key takeaway message: VP shunting improves outcomes in iNPH even with coexisting AD pathology, and cortical biopsy plus DAT imaging

provides valuable prognostic insight, supporting personalized treatment decisions in this heterogeneous population.

P138- PERCEPTIONS OF AND ENGAGEMENT IN BRAIN HEALTH ACTIVITIES AMONG MIDDLE-AGED AND OLDER ADULTS: ASSOCIATIONS WITH LEVEL OF CONCERN, FAMILY HISTORY OF DEMENTIA, SUBJECTIVE MEMORY LOSS, AND DEMOGRAPHICS.

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Background: As cognitive decline and dementia become more prevalent in aging populations, maintaining brain health is a critical public health priority. Modifiable lifestyle factors—such as physical activity, cognitive stimulation, diet, and sleep—can influence cognitive aging and potentially delay dementia risk. While public health campaigns increasingly promote brain-healthy habits, little is known about how individuals perceive these activities or what predicts engagement. This study examined how concern about brain health, subjective memory loss, and family history of dementia relate to perceived usefulness of brain health activities and engagement. We also explored how demographic factors (age, gender, family history) influence participation. **Methods:** The sample included 758 individuals (mean age 52.6 years; 59% women), divided into three groups: early middle age (40–50 years, n = 380), late middle age (51–64 years, n = 265), and older adults (65+, n = 113). Participants completed an online questionnaire assessing perceived usefulness and regular engagement in 19 recommended brain health activities drawn from review articles and professional guidelines (e.g., aerobic exercise, cognitive training, social interaction, stress management, diet, supplements). Usefulness was rated on a Likert scale; engagement was binary («yes»/»no»). A composite «Doing» score represented the number of regularly performed activities. Predictors included self-reported concern about brain health, subjective memory loss, and family history of dementia. Demographics included age, gender, and family history. Linear regression models examined predictors of usefulness ratings and Doing scores. ANOVA with Tukey-corrected post hoc tests assessed group differences in Doing scores. **Results:** Greater concern about brain health was a strong, consistent predictor of higher usefulness ratings across most activities (e.g., aerobic exercise: $t[702] = 4.88$, $p < 0.001$; strength training: $t[653] = 4.80$, $p < 0.001$). Individuals with subjective memory loss tended to rate activities as more useful. Family history of dementia affected some ratings, especially for exercise, diet, and cognitive engagement, though it was generally a weaker predictor than concern or memory loss. A significant interaction between concern and memory loss emerged for several activities (e.g., mentally stimulating activities: $t[18] = 4.28$, $p < 0.001$), suggesting that concern may exert a stronger motivating effect among those experiencing cognitive changes. Regarding behavior, Doing scores varied widely, with many participants reporting engagement in 5–15 activities (mean = 12, SD = 4.53). Concern was again the strongest predictor of the Doing score ($t[728] = 4.93$, $p < 0.001$), while memory loss had a small but significant additive effect ($t[728] = 2.56$, $p = 0.01$). Family history of dementia also independently predicted Doing after controlling for concern and memory loss ($t[728] = 5.07$, $p < 0.001$). Group comparisons revealed that men (mean = 13.40, SD = 5.00) had significantly higher Doing scores than women (mean = 11.05, SD = 3.89; $F[757] = 11.01$, $p < 0.001$). Participants with a family history of dementia reported higher Doing scores (13.56 vs. 11.06). By age, the 51–64 group had the lowest Doing score (mean = 10.80), followed by the 65+ group (mean = 11.59), while the 40–50 group reported the highest engagement (mean = 12.97). Post-hoc comparisons indicated that adults aged 40–50 performed significantly more activities than older groups. **Conclusions:** These findings highlight the central roles of psychological concern, subjective experience of cognitive decline, and family history in shaping both beliefs about the value of brain health activities and actual behavior. Family history of dementia and subjective memory complaints also contribute to perceived usefulness, but concern (reflecting awareness of the possibility of change or perceived vulnerability) most robustly predicts engagement. The Doing score provides a simple measure of behavioral activation across domains, with associations by gender and age suggesting targets for tailored interventions. Specifically, late middle-aged and older adults may benefit from increased awareness of brain-healthy lifestyles. These results have key implications for brain health interventions, particularly digital ones. Interventions should assess and, if needed, elevate concern or perceived risk to enhance motivation. Tailoring content by gender or age may further improve effectiveness. Identifying concerned but inactive individuals may allow programs to better support the adoption of long-term brain-healthy behaviors.

Keywords: Brain health, lifestyle intervention, patient preference, exercise, diet, mentally stimulating activities.

Disclosures: The authors declared no competing interests.

Key takeaway message: Greater concern about brain health is the strongest predictor of both belief in the value of brain-healthy activities and actual engagement, highlighting the importance of psychological motivation in promoting cognitive health behaviors.

ARTIFICIAL INTELLIGENCE IN AD CLINICAL TRIALS

P140- FACILITATING PATIENT ELIGIBILITY MATCHING FOR RECRUITMENT WITH A RAG-LLM FRAMEWORK.

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Background: Patient recruitment into clinical trials is hindered by complex eligibility criteria and the predominance of unstructured data within electronic health records (EHRs) (1). Traditional recruitment process based on manual screening requires staff to review electronic health records (EHRs) against complex eligibility criteria, which is highly time-consuming (taking up to 1 hour per patient (1) and prone to subjective errors (2,3). The machine learning and natural language processing approaches lack generalizability and adaptability (2,3). There is another primary reason behind this limitation that many of the existing methods were initially designed to handle structured data, while in practice, the majority of EHRs are stored in unstructured form, such as free-text clinical notes, diagnostic reports, and medication histories (3,4). This mismatch between data type and methodological design significantly restricted the effectiveness and generalizability of traditional approaches. Consequently, it motivated researchers to explore more flexible solutions such as deep learning models for patient–trial matching. Large commercial language models (LLMs) show promise for handling clinical text (2,3), but raise concerns about accuracy, scalability, and leaking of patient records (privacy) (5,6). **Methods:** We propose a retrieval-augmented generation (RAG) framework that integrates locally deployed lightweight LLMs (3). The workflow encodes long EHRs and eligibility criteria into embeddings, retrieves the most relevant text segments, and leverages LLMs to generate semantic representations (3,7). A classifier is then trained on these embeddings to predict trial eligibility. Importantly, our approach incorporates multimodal EHR data, combining both structured and unstructured clinical information, thereby capturing richer patient profiles and improving prediction accuracy. We designed five sets of experiments, and the workflow is as follows: 1) Different Machine Learning Methods, frozen LLM embeddings were paired with different classifiers, including traditional machine learning methods (Random Forest, Decision Tree, SVM) and neural networks. 2) Different Large Language Models, we compared multiple backbone LLMs (Mistral-7B [8], LLaMA-3-8B [9], Falcon-7B [10]) under a frozen setting to assess robustness. 3) LLM fine-tuning or not, we investigated the effect of fine-tuning by jointly updating unfrozen LLMs with a neural network classification head, in contrast to frozen models. 4) Classification without

Classifier, we tested direct inference by using frozen LLMs without an added classifier, relying only on raw "Yes/No" outputs. 5) Enhanced Embedding with PCA, we enhanced embeddings through dimensionality reduction with PCA, feeding compressed representations into a neural network classifier to assess potential gains in efficiency and performance. **Results:** Experiments were conducted on four open-source datasets (N2C2 (11), SIGIR (12), TREC-2021 (13), TREC-2022 (14) and five AD/ADRD trials (MCT) conducted at Mayo Clinic. On the N2C2 dataset, our framework achieves a macro-F1 score of 0.8472, while on SIGIR, TREC-2021, and TREC-2022 it attains scores of 0.7803, 0.7829, and 0.8102, respectively, with an average AUROC of 0.7911. On MCT, classification heads combined with frozen embeddings outperformed traditional baselines, achieving macro-F1 up to 0.74 on structured data and 0.67 on mixed data. Across our five experiment settings, several consistent findings emerge. (Task 1: Different ML methods) Frozen LLMs paired with classification heads outperformed traditional ML baselines such as Random Forest, Decision Tree, and SVM, showing that LLM embeddings provide stronger inductive biases for structured EHRs. (Task 2: Different LLMs) While performance varied across Mistral-7B, LLaMA-3-8B, and Falcon-7B, all generally surpassed traditional methods, with Mistral-7B offering the most stable results. (Task 3: Fine-tuning vs. Frozen) Fine-tuning was indispensable for unstructured clinical notes and mixed data, consistently boosting performance, while frozen models were more effective for structured inputs. (Task 4: Different datasets) Fine-tuned variants consistently achieved state-of-the-art results on open-source datasets (N2C2, SIGIR, TREC-2021/2022), confirming the necessity of domain-specific adaptation. (Task 5: Cross-trials) Cross-trial experiments revealed sharp performance drops when entire trials were excluded from training, highlighting the challenge of generalization across heterogeneous clinical protocols. **Conclusions:** This study demonstrates that integrating retrieval-augmented generation (RAG) with lightweight, locally deployed LLMs offers an efficient and privacy-preserving framework for clinical trial patient matching. Compared with traditional ML and earlier NLP systems, the approach provides stronger robustness and adaptability while avoiding dependence on costly commercial APIs. Frozen LLMs work well for structured EHR data, and PCA enhances efficiency, but fine-tuning is indispensable for unstructured notes and mixed settings where free-text dominates. Nonetheless, limitations remain. RAG chunking can omit important details, lowering recall, and cross-trial experiments showed reduced performance when entire trials were excluded, highlighting generalization challenges. Large frozen LLMs like GPT-4 perform strongly in zero-shot settings but pose issues of cost, transparency, and feasibility for clinical use. A balanced solution is fine-tuning lightweight 7–10B parameter models locally, combining accuracy, scalability, and data security. In conclusion, RAG-LLM provides a promising path for patient–trial matching.

Keywords: Patient matching, retrieval-augmented generation, clinical trials, electronic health records.

Clinical Trial Registry: NA.

Data Deposition: NA.

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Declaration of generative AI and AI-assisted technologies in the writing process. Statement: During the preparation of this work the author(s) used ChatGPT in order to refine the language and polish the presentation. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

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Key takeaway message: RAG-LLM enables efficient, privacy-preserving patient matching for clinical trials by combining retrieval with lightweight local LLMs. This approach improves recruitment accuracy and equity, outperforms traditional baselines, and scales across structured and unstructured EHRs to accelerate trial enrollment.

P142- EFFICIENT CLINICAL DEVELOPMENT AND RESEARCH VIA AN AI-READY MULTIMODAL DATA PLATFORM.

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Background: Clinical drug development faces significant challenges in managing heterogeneous multimodal datasets across different studies and institutions. Traditional data lakes struggle with healthcare-specific needs, leading to prolonged data preparation phases that delay AI system development. This is particularly challenging in Alzheimer's disease research where multimodal data integration is crucial for drug development success. The AICURA Data Layer addresses this challenge by harmonizing complex multimodal clinical datasets with open-source datasets to lay the ground for accelerated drug development workflows, with particular focus on Alzheimer's disease. **Methods:** The AICURA Data Layer employs a scalable data model based on HL7 FHIR healthcare interoperability standards to integrate proprietary and open-source multimodal datasets. Once integrated the data can be served in an AI-ready form via the platform, eliminating time-consuming manual data engineering steps for repeated analyses. The employed data model integrates structured tabular data such as demographics, clinical scores and biomarker data, with raw 3D volumetric imaging data, into a unified, analysis-ready patient view. Core technical features include a patient-level access schema, streamlined quality control with signal-to-noise ratio analysis and artifact detection for imaging data, as well as replicable preprocessing workflows. The Query Builder enables rapid cohort definition across multiple datasets through a unified graphical user interface. An integrated Jupyter Hub environment allows users to conduct advanced analysis pipelines in a consistent and secure workspace. **Results:** We successfully integrated comprehensive multimodal data from two large-scale phase III trials investigating the monoclonal antibody aducanumab (221AD301, 221AD302) (n=12,930) and one open-source dataset from the Alzheimer's Disease Neuroimaging

Initiative (ADNI) [1] database (adni.loni.usc.edu) (ADNI; n=4,076). The integrated dataset encompasses diverse and longitudinal data types, including demographics, medical history, cognitive assessments (CDR, MMSE, ADAS-Cog13, MoCA), biofluid biomarkers (CSF t-tau, p-tau181, amyloid beta) as well as neuroimaging-derived measures such as brain regional volumetric data and SUVr values. We further integrated raw DICOM images, comprising of > 140,000 MRI and > 9,000 PET series from the phase III clinical trials, and > 35,000 MRI and > 7,000 PET series from ADNI. By providing pre-harmonized, AI-ready data, the platform reduces AI system development time by 6-12 months, enabling fast cohort identification and advanced analytics, thus eliminating traditional data engineering bottlenecks. **Conclusions:** This showcase demonstrates a paradigm shift from traditional data lakes and is offering superior healthcare-specific data integration capabilities by harmonizing multimodal datasets and enabling rapid AI system research and development. Leveraging advanced multimodal AI systems to accelerate clinical research becomes technically feasible and scalable with the potential to de-risk future trials and ultimately advance precision medicine approaches in clinical development.

Keywords: Multimodal AI-ready data, neuroimaging, data integration, phase III clinical trials. **Disclosures:** MK, AD, EM, EP, MU, AM, JR and KT are employees of AICURA medical GmbH (Berlin, Germany). SKW, MT, EV, CH, FB and RMN are employees of Neurimmune AG (Schlieren, Switzerland).

References: 1. The open-source dataset used in preparation of this article was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu).

Key takeaway message: A data layer is crucial for integrating and harmonizing clinical datasets across systems, offering AI-ready data that eliminates engineering bottlenecks. This enables scalable multimodal AI system development with potential to accelerate and de-risk clinical trials.

P143- EXPANDING PATIENT COVERAGE IN ALZHEIMER'S DISEASE STUDIES THROUGH ROBUST MULTIMODAL DATA INTEGRATION.

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Background: Recent advances in machine learning have produced predictive models that, in some cases, surpass physicians and pathologists in disease classification. In Alzheimer's Disease (AD), a highly complex brain disorder, AI-based approaches are now used to predict disease status and progression from multimodal data, while also identifying key predictive features. Clinically, AD diagnosis draws from diverse sources: cognitive assessments, medical history, genetics, and neuroimaging (1). Integrating such multimodal information offers a more holistic view of disease trajectory. However, many current studies are limited by requiring complete datasets, excluding participants missing data in any modality. This constraint is particularly problematic in real-world research and clinical trial settings where incomplete data is common, leading to the exclusion of valuable patient records. We address this limitation by introducing MOIRA (Multimodal Integration with Robustness to Absent modalities), a framework specifically designed to handle incomplete heterogeneous data. By leveraging available modalities while compensating for missing ones, MOIRA increases data coverage without compromising predictive performance. This is especially critical for AD research and clinical applications, as it enables inference even with partial records and broadens participant inclusion. **Methods:** We evaluated MOIRA on two widely used AD datasets. The first, Religious Order Study and Memory and Aging Project (ROSMAP) (2), contains five post-mortem omics modalities: mRNA expression, DNA methylation, microRNA expression, tandem mass tag proteomics, and HD4 metabolite quantification. Only 86 of 748 samples (11%) had all five modalities; most were missing at least one. The second dataset, the Alzheimer's Disease Neuroimaging Initiative (ADNI) (3), was organized into four modalities: Imaging, Clinical, Biospecimen, and Genomics. The Imaging modality comprised 3D T1-weighted MRI scans processed through a standardized pipeline with FSL library. The Clinical modality included demographics and medical history. The Biospecimen modality encompassed CSF biomarkers—amyloid-β, total tau, and phosphorylated tau—established measures for diagnosis and clinical-trial enrichment in AD (4), as well as the ApoE genotype, a major genetic risk factor frequently considered in trial design and drug development (5). Genomic data consisted of single nucleotide polymorphisms (SNPs) in PLINK format. Of the 2,380 participants, only 1,323 had complete data across all four modalities. MOIRA was designed to utilize incomplete cases, thereby expanding cohort coverage by approximately 80%. The architecture comprises three components: (1) modality-specific encoders that embed each modality into a latent representation, (2) a fusion module that integrates modality embeddings with learnable weights and redistributes contributions to present modalities by masking absent inputs, and (3) a predictor for classification. Feature selection reduced dimensionality while preserving signal. We used ANOVA F-tests for ROSMAP omics and ADNI Genomics. For ADNI Imaging, MRI scans were processed using a 3D convolutional neural network with three convolutional layers (16, 32, and 64 channels), LeakyReLU activations, 3D max pooling, and a final 128-dimensional flattened embedding. Other modalities were passed into encoders without additional preprocessing. The training objective combined prediction loss (cross-entropy on final outputs), auxiliary losses (cross-entropy on modality-specific embeddings to preserve discriminative capacity), and a contrastive loss (CLIP-style across modality pairs) to encourage alignment in the shared embedding space. **Results:** In ROSMAP, we conducted binary classification of cognitive diagnosis. MOIRA achieved an accuracy of 0.92, significantly outperforming previous methods. This gain was largely due to its ability to incorporate incomplete cases: earlier models were restricted to 391 fully observed samples, while MOIRA utilized 784 participants. Ablation studies confirmed that including all five modalities improved accuracy over three-modality models, and that union-based training (using all available samples) outperformed intersection-only approaches. These results demonstrate the clinical value of retaining partially observed data. In ADNI, MOIRA attained 0.91 accuracy in three-way classification among AD, mild cognitive impairment (MCI), and normal controls (NC). Other models that tolerate missing modalities often suffer reduced accuracy with larger, more incomplete cohorts. In contrast, MOIRA increased coverage from 1,323 to 2,380 participants while maintaining high performance—the best trade-off between accuracy and cohort size among models handling incomplete data. This is especially valuable for clinical trials, where maximizing patient inclusion without sacrificing diagnostic fidelity is essential. **Conclusions:** We present MOIRA, a robust multimodal integration framework that enables meaningful analysis of AD data even when modalities are missing. The inference under partial modality availability greatly expands usable cohort size without compromising prediction accuracy. In both ROSMAP and ADNI, it demonstrated that incomplete records can be leveraged effectively, increasing statistical power and avoiding unnecessary patient exclusion. By overcoming the constraints of requiring complete datasets, MOIRA makes predictive modeling more applicable to real-world clinical practice and research. Our findings underscore the importance of embracing incomplete yet informative data in AD studies. Our results suggest that future clinical studies and interventional trials in AD can benefit from adopting methods that explicitly accommodate missing modalities, improving both coverage and reliability. By bridging the gap between idealized complete datasets and the realities of clinical data collection, MOIRA offers a pathway toward more inclusive, accurate, and clinically meaningful applications of AI in AD.

Keywords: Incomplete multimodal learning, multi-omics integration, missing modality, machine learning.

Disclosures: This work was supported by LG AI Research. During the preparation of this work, the authors used ChatGPT to assist with

refining the manuscript's language and improving its readability. The authors declared no competing interests.

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Key takeaway message: To fully utilize multimodal data to facilitate clinical trials on Alzheimer's Disease, an integration that leverages incomplete data with missing modalities can enhance patient inclusion, improve prediction, and increase the real-world application.

P144- BRIDGING THE BIOMARKER–AI DIVIDE: REDESIGNING TRIALS AND INCENTIVES FOR DISEASE-MODIFYING SUCCESS IN ALZHEIMER'S DISEASE.

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Background: Recent advances in proteomics, transcriptomics, and AI-enhanced biomarker platforms hold immense promise for transforming Alzheimer's disease (AD) clinical trials—accelerating early detection, personalizing treatment, and improving endpoint sensitivity. However, the translation of these tools into trial design and real-world deployment remains hindered by economic, regulatory, and infrastructural misalignment. This presentation proposes an integrated framework that bridges the current disconnect between scientific capability and sustainable adoption by regulators, payers, and healthcare systems. We present insights from three complementary domains: 1. Omics and Trial-Ready Infrastructure: Multiomics platforms generate high-resolution data capable of identifying disease trajectories, reducing cohort heterogeneity, and stratifying patients by likely response. We describe actionable strategies to integrate proteomic and transcriptomic datasets into real-world trial infrastructure, focusing on metadata curation, harmonization standards, and use cases that demonstrate impact on personalized medicine and predictive modeling. 2. Payer Logic and Trial ROI Modeling: Designing trials for economic utility requires rethinking endpoints, time horizons, and sample selection. Drawing from actuarial science and experience across life insurance, CMS, and VA systems, we demonstrate how early detection tools—especially those driven by omics or AI—can be modeled for long-term return on investment (ROI). Concepts such as bundled payments, cross-sector pilot design, and actuarial valuation of delayed cognitive decline are explored as vehicles to secure real-world adoption. 3. AI-Enabled Trial Design and Regulatory Trust: AI/ML tools can address long-standing trial design challenges, such as placebo response and endpoint variability. We introduce the concept of "Trusted Model Zones" for deploying AI in adaptive protocols, including use of passive sensors, digital biomarkers, and real-world evidence (RWE). Ethical considerations and pathways for regulatory readiness are mapped, emphasizing the importance of transparent model evolution, auditability, and clinical relevance. Together, these domains offer a path forward for trials that are not only biomarker-informed and technologically advanced, but also financially viable and system-ready. By embedding commercial strategy and payer alignment into the earliest stages of trial design, we increase the likelihood of real-world adoption and reimbursement—critical outcomes for sustainable innovation in AD prevention and treatment.

Key takeaway message: To realize the promise of omics and AI in Alzheimer's trials, we must align discovery with payer logic, regulatory trust, and trial design—building studies that are not just approvable, but adoptable and investable.

P145- PRACTICAL IMPLEMENTATION OF A MACHINE LEARNING MODEL IN ALZHEIMER'S DISEASE TRIALS FOLLOWING THE RECENT FDA'S GUIDANCE ON THE USE OF AI TO SUPPORT REGULATORY DECISION MAKING.

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Background: FDA recently published the draft guidance "Considerations for the use of AI to support regulatory decision-making for drug and biological products", which outlines a risk-based credibility assessment framework for assessing the credibility of an Artificial Intelligence (AI-based) model. Here, we present a practical implementation of AI-generated digital twins following the seven-step assessment framework to support regulatory decision-making on the effectiveness of Alzheimer's disease (AD) trials. **Methods:** We trained a generative machine learning (ML) model using historical subject-level data of those with preclinical AD (N=5,730), MCI or early AD (N=13,919), and mild-to-moderate AD (N=10,903). Following the risk-based credibility assessment framework, we applied the AI model to each step of the framework on a completed Phase 2 trial (AWARE trial, N=453, NCT02880956), which tested tilavonemab, an anti-tau monoclonal antibody, in participants with early AD. The AI model generated digital twins of each participant in the AWARE trial, providing individual-level predictions of clinical outcome and biomarkers. **Results:** We demonstrate that this specific context of use of the model output establishes credibility in AD trials. Additionally, we discuss recommendations for best practice based on our experience including emphasis on transparency, pre-specification, rigorous validation, and interactions with regulatory agencies. The AWARE trial could have enrolled up to 15% fewer participants with digital twins to draw the same conclusions about treatment efficacy as previously reported, with minimal risk of introducing bias for the study's primary outcome and key secondary outcomes. **Conclusions:** As the use of AI/ML in clinical development expands to support regulatory decision-making on effectiveness, safety, and quality of drugs, a successful implementation depends on rigorous trial design, a well-defined context of use, and early, ongoing regulatory alignment. Digital twins methodology may be used throughout clinical development programs, including proof-of-concept and pivotal trials, to support effectiveness while establishing credibility based on the recent FDA guidance on the use of AI in drug development.

Keywords: Artificial intelligence, FDA, digital twins.

Key message: FDA recently published the draft guidance, which how to assess AI-based model. Digital twins methodology may be used throughout clinical development programs, while establishing credibility based on the recent FDA guidance on the use of AI in drug development.

Clinical Trial Registry: NCT02880956, https://clinicaltrials.gov/study/NCT02880956.

Disclosures: Run Zhuang, Coco Kusiak, Alyssa Vanderbeek and Jonathan R Walsh are equity-holding employees at Unlearn.AI. Deli Wang, Hana Florian, Yujie Zhao, Shau Yu Lynch, Weining Z Robieson and Ole Graff are employees of AbbVie and may hold AbbVie stock/options.

Key takeaway message: Digital twins, aligned with recent FDA guidance, can credibly support regulatory decisions and optimize clinical trial design in drug development, enhancing effectiveness and reducing participant numbers.

P146- BRAIN HEALTH DATA PILOT: A NATIONAL DATASET OF ROUTINE BRAIN IMAGING FOR ARTIFICIAL INTELLIGENCE AND EPIDEMIOLOGY.

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Background: Clinical trials in dementia and neurodegenerative diseases are often slow to recruit with limited tools to identify at risk participants at scale. Most prognostic models and AI tools are trained on small, highly selected cohorts with limited diversity. We established the brain health data pilot within Scottish Imaging Initiative to enable neurological research with clinical neuroimaging (CT and MRI) linked to national health records, with robust governance and privacy controls. We are implementing privacy preserving, federated methods to collaborate internationally without moving patient level data.Background: Clinical trials in dementia and neurodegenerative diseases are often slow to recruit with limited tools to identify at risk participants at scale. Most prognostic models and AI tools are trained on small, highly selected cohorts with limited diversity. We established the brain health data pilot within Scottish Imaging Initiative to enable neurological research with clinical neuroimaging (CT and MRI) linked to national health records, with robust governance and privacy controls. We are implementing privacy preserving, federated methods to collaborate internationally without moving patient level data. **Methods:** Resource and data: The dataset is a curated, research ready imaging and electronic health record resource within the Scottish National Safe Haven (NSH). It links CT and MRI brain scans within Scottish Medical Imaging (SMI), DICOM metadata and structured reports deterministically to outpatient, inpatient and day case, mental health, cancer, emergency care, prescribing, and deaths. Routine updates are planned as SMI receives new data. Curation and access: Data are pseudonymised. UK researchers can access data on successful application via a browser-based virtual desktop, and installation of custom analysis software is supported via container technologies; code and results are subject to disclosure checking. Adversarial testing of AI models is performed with experts from National Services Scotland (NSS) before any model egresses from the NHS. Federation: To support international collaboration, we are implementing containerised workflows and Swarm Learning (AI model parameter sharing only) over a VPN, with no transfer of patient level data. A Federated Data Sharing Appliance (FDSA) provided by the Alzheimer's Disease Data Initiative is in the final stages of security review. Governance and PPIE: The dataset has governance and ethics approval. International partners follow local information governance processes with no data export. Researcher access uses established Electronic Data Research and Innovation Service (eDRIS) processes. We engaged multiple Scottish patient and public participant panels to shape communications, scope, and acceptability. Compute: The NSH, hosted by EPCC, provides GPU enabled infrastructure; a major GPU cluster expansion is scheduled to be available in late 2025 to support training AI, including foundation models. Exemplars: There are three initial research projects: (i) comparing CT derived and MRI derived brain age for risk stratification; (ii) developing and evaluating imaging foundation models within the NSH and (iii) evaluating federated training (Swarm Learning) via an international exemplar with Helsinki and Bonn. **Results:** Research ready dataset spanning 2008 to 2018 including ~1.6M brain scans from ~800k individuals curated. A third (30.5%) were MRI, and two-thirds (69.5%) CT. Of the MRI population there were 16,819 (5.7%) people with a dementia diagnosis at any time, and of the CT population 116,121 (17.8%) at any time. Containerised solutions for supporting swarm learning and federated analysis for flagship linked brain health data asset in final stages of governance review and testing, ready to support international researcher analysis. **Conclusions:** A national, privacy preserving platform that links routine brain CT/MRI to comprehensive health records can accelerate dementia and neurodegeneration research and trial readiness by enabling risk prediction, automated pre screening, and rapid external validation. BHDP demonstrates feasibility within established trusted research environments, delivers a large, curated imaging–EHR resource and will operationalise federation for international collaboration without moving data. Next steps include international federated training, evaluation of CT vs MRI based predictors over multiple time horizons, and disclosure controlled release of foundation models and code to the community.

Keywords: Alzheimer's disease, clinical trials, electronic health records, federated learning.

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Key takeaway message: The Brain Health Data pilot links 1.6M Scottish brain scans with health records in a secure platform, enabling AI development whilst preserving privacy. We welcome discussion with new researchers who wish to use the resource.The Brain Health Data pilot links 1.6M Scottish brain scans with health records in a secure platform, enabling AI development whilst preserving privacy. We welcome discussion with new researchers who wish to use the resource.

P147- THE SANDBOX STUDY: AN NHS-EMBEDDED MULTIMODAL PLATFORM FOR AI-ENABLED DEMENTIA DIAGNOSTICS.

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Background: Artificial intelligence (AI) holds major promise for dementia diagnostics, but progress has been constrained by the absence of large, multimodal datasets collected in real-world settings. SANDBOX is a UK-wide study enrolling 1,000 participants across 15 NHS sites to create an AI-ready clinical infrastructure. By integrating blood-based biomarkers—including epigenetic signals from cell-free DNA (cfDNA), APOE genotyping, and proteomic measures such as pTau-217—with digital cognitive testing and speech analysis, SANDBOX is generating a comprehensive dataset designed to inform both immediate diagnostic practice and the training of next-generation AI foundation models. **Methods:** Participants referred to NHS Memory Clinics undergo APOE genotyping, plasma biomarker testing (pTau-217 and Aβ42/40 ratios; PrecivityAD2™), and CANTAB digital cognitive and speech assessments. A substudy evaluates Streck stabilised whole-blood tubes for room-temperature transport to enable biomarker scalability across diverse NHS settings. In parallel, plasma cfDNA is analysed with Pleiades, a novel epigenomic foundation model, to characterise disease-specific methylation signatures. Data are harmonised in a GDPR-compliant pipeline with rigorous quality control and linkage to clinical outcomes. **Results:** Early feasibility demonstrates successful integration of APOE and plasma biomarker testing into routine pathways and high adoption of digital cognitive assessments. Preliminary Streck analyses suggest preserved biomarker stability without cold-chain requirements. Pilot cfDNA analyses indicate that combining Pleiades-derived

epigenomic features with plasma biomarkers improves discrimination of Alzheimer's disease from controls (AUROC ~0.97). **Conclusions:** SANDBOX establishes one of the first real-world, NHS-embedded infrastructures for AI-ready dementia data generation. By integrating multimodal biomarkers with cfDNA epigenomics analysed through the Pleiades foundation model, alongside digital cognitive and speech assessments, SANDBOX provides a scalable platform for AI-enabled precision diagnostics. Pleiades outputs contribute novel epigenomic features that improve diagnostic performance, with early analyses indicating AUROC values approaching 0.97 when integrated with plasma pTau-217. These findings highlight the potential of cfDNA-based AI models to enhance diagnostic accuracy, support disease subtyping, and enable earlier identification of individuals at risk within routine clinical pathways.

Disclosures: I report no conflicts of interest. This work is supported by Prima Mente in collaboration with NHS Memory Clinics, C2N Diagnostics, and Streck.

Key takeaway message: SANDBOX combines blood-based biomarkers, cognition, and speech analysis within NHS memory clinics, delivering one of the first AI-ready multimodal dementia datasets while overcoming barriers to equitable implementation and advancing next-generation diagnostic tools for earlier, more accurate detection

P148- COMPARISON BETWEEN AUDITORY, TEXTUAL, AND LATE-FUSION TRANSFORMER MODELS FOR THE DISCRIMINATION OF PRODROMAL ALZHEIMER'S DISEASE BASED ON SPONTANEOUS SPEECH.

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Background: Interest in digital assessment of spontaneous speech for clinical trials is rising given its scalability, ecological validity, and the revolutionary progress in Natural Language Processing models. However, it remains unclear whether the auditory signal, the transcript, or a late fusion of both provides the most reliable basis for detecting prodromal Alzheimer's disease. **Methods:** The study population consisted of 53 memory-clinic recruited patients in NIA-AA stage 3 of Alzheimer's disease (biomarker-proven prodromal AD; mean MMSE 25.4 $\pm$ 3.1, range 20–30; mean CDR 0.55 $\pm$ 0.23, range 0–1), as well as 63 healthy age-, education- and sex-matched amyloid-negative participants from the Flemish Prevent AD Cohort KU Leuven. Spontaneous speech was elicited through semi-structured interviews comprising the Autobiographical Memory Interview and four additional tasks: recall of a recent news event, recall of a day from the past week, noun description, and the Cookie Theft picture description. The mean duration of recorded speech was 27.6 $\pm$ 9.4 minutes for prodromal AD interviews and 27.7 $\pm$ 10.4 minutes for controls. We compared the diagnostic accuracy of three cross-lingual models: XLS-R (operating on the auditory signal), XLM-R (operating on the transcript), and a late-fusion model combining both. The models were truncated by discarding the last layers (retaining layers 1-16 of XLS-R and 1-10 of XLM-R) to leverage intermediate representations, which have been shown to be more informative than the final layer output in many downstream tasks. To reduce the number of trainable parameters and mitigate overfitting, we only fine-tuned layers 11-16 of XLS-R and 7-10 of XLM-R with low-rank adapters, while a classification head was trained from scratch. To process full-length recordings, we employed chunking and merging, activation checkpointing, and gradient accumulation. For full-interview experiments, we additionally conditioned on the interview task using feature-wise linear modulation. Model performance was assessed with five-fold cross-validation at the participant level and evaluated using the area under the receiver operating characteristic curve (AUROC). We also evaluated ensembling by averaging predictions from 10 models trained with different random initializations. **Results:** The leading modality differed by task: text-based models were strongest for autobiographical recall (AUROC = 0.864) and day recall (0.805), whereas audio-based models led in object description (0.899), picture description (0.802) and news recall (0.785). A late-fusion model generally matched or modestly exceeded the stronger unimodal model within each section. When all sections were concatenated into a full-interview input, the text-only model (0.919) outperformed both audio (0.802) and fusion (0.905). Conditioning on the task further improved all three modalities in this setting, with the task-conditioned text-only configuration achieving the highest overall AUROC (0.927). Ensembling this configuration across 10 independently initialized models further increased performance to 0.939. Finally, ablation tests showed that truncating the models consistently improved performance compared to using all layers. **Conclusions:** Diagnostic performance depended on task: audio models were clearly superior in object and picture description and slightly ahead in news recall, whereas text models led in autobiographical and day recall. At the full-interview level, transcript-based models outperformed both audio and fusion, particularly when conditioned on the interview task and further boosted by ensembling, achieving the highest AUROC (0.939). This advantage likely reflects lexical and semantic alterations in prodromal AD, which transcript-based models can detect most effectively when sufficient speech material is available. The added value of audio was most evident in content-constrained descriptive tasks. Late fusion generally matched the strongest unimodal model within tasks, lending it greater generalizability across heterogeneous speech tasks, although it did not surpass text in the full-interview setting.

Key takeaway message: A late fusion model between auditory and transcript-based Transformer models has highest generalizability across spontaneous speech tasks for discriminating prodromal AD.

P149- AI+MRI IMAGING BIOMARKER FOR CLINICAL CHARACTERIZATION OF ALZHEIMER'S DISEASE BIOLOGICAL HETEROGENEITY.

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Background: Alzheimer's disease (AD) is a heterogeneous neurodegenerative disorder characterized by variability in its clinical manifestations and pathological progression. This heterogeneity is partly driven by differences in the distribution and severity of amyloid-β (Aβ) plaques and hyperphosphorylated tau tangles, which are recognized as core pathological features of AD. Among them, tau pathology plays a particularly important role in shaping individual heterogeneity of neurodegeneration patterns and cognitive decline profiles. Capturing this heterogeneity using imaging-based biomarkers that are independent of disease progression stages may complement existing plasma biomarkers and provide deeper clinical insights. **Methods:** In this study, we propose an intuitive, simple, and yet effective MRI-based imaging biomarker that captures level-independent regional contrast in tau accumulation. A total of 1173 datasets comprising MRI, tau PET, and cognitive scores were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). Regional tau SUVR values were normalized to z-scores using a Gaussian mixture model. We then defined five meta-Region-of-Interests (meta-ROIs) based on FreeSurfer lobe-level segmentations: medial temporal (MT), lateral temporal (LT), parietal (PA), frontal (FR), and occipital (OC) lobes. To identify the relative contrast of tau accumulation across these meta-ROIs, which contribute to diagnostic and prognostic characteristics of AD patients, we employed barycentric coordinates based on an intuitive pentagon space. The coordinates were further normalized by the global tau levels to emphasize level-independent regional contrast. Both PET-derived and AI-imputed MRI-derived tau patterns were projected onto the same space and then classified into five subgroups based on a concentration toward a specific vertex. For group comparison, patients were aligned based on the spatial

extent (SE) of the tau spreading, which was calculated as a weighted count of regions exceeding tau thresholds across multiple cutoffs. **Results:** Within each SE interval, subgroups exhibited distinct tau accumulation patterns. MT and LT groups showed typical Braak-like distributions, whereas PA, FR, and OC groups demonstrated atypical patterns. MT and OC groups were predominant in early disease stages with lower global tau extent (MT: 44.3%, OC: 29.1%, PA: 11.4%, FR: 7.9%, LT: 7.3%), while PA and LT groups dominated later stages (PA: 42.0%, LT: 42.0%, MT: 12.0%, OC: 4.0%, FR: 0%). Notably, the PA group primarily appeared at both ends of the SE spectrum, suggesting rapid tau propagation. In terms of cognitive decline, MT and LT groups showed significant MMSE score decreases from early to middle stages ($p<0.0001$ [MT], $p=0.0004$ [LT]), but not from middle to late stages ($p>0.05$ [MT], $p=0.032$ [LT]). Conversely, the PA group showed minimal early-stage decline but a sharp deterioration in later stages ($p<0.0001$). FR and OC groups showed no significant MMSE changes across disease stages. Regarding cognitive profiles for each subdomain, the median survival of memory function in MT and LT groups was shorter than other functions (median survival SE values: memory=48.6, executive=81.7, language=83.2, visuospatial=103.1), while PA and FR groups had similar median survival across domains (median survival SE values: memory=81.9, executive=89.6, language=93.1, visuospatial=93.3) with late rapid decline similar to MMSE scores. The OC group exhibited relatively slow progression but shoed the shortest median survival for visuospatial function compared to other groups (median survival SE values: visuospatial=81.0). The AI-imputed MRI-driven tau accumulation reproduced these trends well. The estimated MT and LT groups had the shortest median survival of memory functions (median survival SE values: memory=52.1), and the OC group had the shortest survival of visuospatial function (median survival SE values: visuospatial=70.3). The PA and FR groups also showed similar median survival SE across all cognitive domains (median survival SE values: memory=79.8, executive=84.1, language=88.9, visuospatial=97.7) as estimated from PET-derived tau accumulation. **Conclusions:** We propose a novel imaging biomarker based on level-independent regional contrast in tau accumulation that reveals heterogenous clinical characteristics of AD independent of global tau burden. MT and LT groups show an earlier increase of cognitive decline, especially in the memory domain, that proceeds slowly in later stages, while the PA group shows delayed but rapid deterioration across all domains. The OC group progresses slowly but shows early visuospatial impairment. This biomarker may enhance clinical characterization and prognostication by capturing tau-related heterogeneity beyond what global measures can provide. Moreover, the reproducibility of this representation using MRI-based AI models supports its potential for broader clinical application, especially where PET imaging is not feasible.

Keywords: Alzheimer's disease, amyloid-beta, tau, MRI, AI, imaging.
Disclosures: The authors declared no competing interests.

Key takeaway message: Level-independent regional tau contrast biomarkers reveal Alzheimer's heterogeneity in progression and cognitive decline, and can be imputed from MRI using AI, enabling subtype-specific prognosis without the need for PET.

P150- SIMULATING COGNITIVE DECLINE USING GENERATIVE AI MODEL.

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Background: It is well-known that the Amyloid-Tau-Neurodegeneration-Cognition (ATNC) axis encodes the information needed to characterize the complex model of Alzheimer's disease (AD) (1). Advances in machine learning and the availability of large public repositories of ATNC data enable researchers to understand this code and predict the natural progression of cognitive decline due to AD. Here, in this study, we propose a novel Generative-AI framework that enables the programmed generation of ATNC in response to user prompts and demonstrates versatility across a range of cognitive-decline-prediction and condition-prompted-generation tasks. As an example of the conditional generation of AD models, the proposed framework simulates various scenarios of AD clinical trials, including amyloid-lowering drugs, tau-targeting drugs, and their combinations. We further demonstrate that this simulation framework can optimize the clinical efficacy of different treatment strategies in terms of patient enrichment and companion diagnosis. **Methods:** Data pre-processing. We analyzed 1,967 participants who contributed 7,483 visits from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). Each visit provided (i) a T1-weighted MRI and cognitive scores for Memory, Language, and Executive function and (ii) follow-up scores for those domains ≈24 months later. Across all visits, Centiloid (CL) was acquired in 1,996 visits (955 amyloid-positive) and tau PET in 689 visits. MRIs were N4 bias-corrected, segmented into 95 regions of interest (ROIs) with FastSurfer, and converted to region-wise volume-to-area ratios that served as neuro-degeneration (ND) markers. Tau PET was co-registered for MRI, and partial volume was corrected and surface-mapped. Regional tau SUVRs (68 ROIs) and ND markers were each reduced to five principal components (PCs). The high-tau threshold was defined as the 70th%ile of neo-meta-ROI SUVR among neo-meta-ROI–positive participants (SUVR = 1.98) and mapped to tau-PC1 = 25. GenAI framework. Within the Generative-AI framework, we trained four conditional diffusion-based models (2): (i) an ATNC generator that learns the joint distribution of Amyloid, Tau, Neuro-degeneration, and Cognition while accommodating missing data, and (ii–iv) three C-FU models that draw 24-month Memory, Language or Executive scores conditional on current ATNC. Six hundred baseline ATNC samples were synthesized using the distribution of the donanemab phase-3 trial as prompt [3] and duplicated into active and placebo groups for three virtual-trial scenarios: amyloid-lowering (active –60 CL, placebo +10 CL), tau-lowering (active –60% global tau SUVR, placebo +5%) and combination-targeting (active –60 CL plus –60% tau; placebo +10 CL plus +5% tau). Slowing was defined as $1 - (\Delta_\text{active} / \Delta_\text{placebo})$. Distribution as prompt. Baseline summaries from the donanemab phase-3 trial (Inclusion criteria; the ratio of low/medium tau group versus high tau group; the ratio of age groups; the ratio of APOE ε4 status) were treated as marginal targets. These statistics were supplied to the ATNC generator, which then synthesized candidates from its learned distribution. Finally, 600 synthetic participants matched the prompt while retaining the multivariate structure learned from ADNI. Lobe-level meta-ROI subtyping. After synthesis, each participant was classified into one of five meta-ROI groups derived from FreeSurfer lobe-level segmentations: medial-temporal, lateral-temporal, parietal, frontal, and occipital. To capture the relative contrast of tau pathology across lobes, we mapped individual tau burdens into a barycentric pentagon space and normalized them with global tau. Then, we assigned each participant to the subgroup whose vertex showed the greatest concentration. **Results:** The 600 virtual participants reproduced the donanemab baseline distribution; 436 were in the low-medium-tau group and 164 in the high-tau group. After lobe-level stratification three response patterns became clear. First, amyloid-lowering was consistently more effective in low-tau brains. Twenty-four-month slowing Memory decline reached 39% in low-tau medial-temporal, 45% in low-tau lateral-temporal and 47% in low-tau parietal subgroups, whereas the corresponding high-tau strata showed 25% or less slowing in every cognitive domain. Second, tau-lowering produced its largest gains in high-tau individuals. In the high-tau medial-temporal subgroup, memory slowing was 61%, and executive slowing was 58%, compared with 43% and 27% in the low-tau subgroup. A similar pattern appeared in the occipital lobe, where Memory slowing was 68% in high-tau subjects versus 41% in low-tau subjects. Third, combination-targeting, defined as simultaneous 60% reductions in plaques and tau, delivered large and consistent benefits.

Memory slowing exceeded 70% in low-tau medial- and lateral-temporal groups and stayed above 60% in every high-tau group; Language and Executive did not fall below 56% and 59%, respectively, in any lobe–tau group. **Conclusions:** The Generative-AI framework converts brief, published baseline descriptions into complete ATNC profiles, then projects domain-specific cognition under amyloid-lowering, tau-lowering, and combination regimens. Simulations suggest that amyloid clearance benefits are greatest in low-tau subjects, tau reduction preferentially aids high-tau subjects, and the two mechanisms deliver the broadest and most uniform slowing of decline across tau subtypes. These findings, while model-based, illustrate how prompt-driven ATNC generation can inform early trial design, patient-enrichment thresholds, and companion-diagnostic strategies before real participants are enrolled. Confirmatory evidence from prospective combination studies will be essential to translate these in-silico insights into clinical practice.

Keywords: Generative AI framework, ATNC axis, virtual clinical trial, amyloid clearance, tau reduction, treatment combination.

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Key takeaway message: A prompt-based Generative-AI framework rapidly builds virtual AD trials and shows that amyloid, tau and combination therapies have distinct, subtype-dependent cognitive benefits.

P151- POST HOC DATA-DRIVEN SUBGROUP ANALYSIS OF THE A4 STUDY: SPATIOTEMPORAL ATROPHY PREDICTS DIFFERENTIAL TREATMENT RESPONSE TO SOLANEZUMAB.

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Background: The A4 Study was a Phase 3 secondary prevention trial of solanezumab in preclinical Alzheimer's disease. Subtype and Stage Inference (SuStaIn) is a biomarker clustering algorithm that uniquely disentangles severity from subtype, e.g., finding subtypes of AD having unique spatial profiles of atrophy. **Methods:** Experimental design: A post hoc subgroup analysis of outcomes in the A4 Study. Subgroups were data-driven: defined by a SuStaIn model of AD neurodegeneration subtypes pre-trained on MRI features from the ADNI observational study. SuStaIn training data (ADNI): N=1505 (190 CN, 951 MCI, 364 AD) amyloid-positive (A+) participants whose baseline T1w MRI successfully passed through automated processing using FreeSurfer 7.1.1. Model inputs: brain volumes (cortical and subcortical) adjusted for covariates (age, sex, education, head size) and z-scored relative to controls (N=435 A–, CN). A4 data: the modified intention to treat population (N=1147 A+, CN: 583 placebo, 564 solanezumab). Endpoint: the Preclinical Alzheimer Cognitive Composite, PACC. Statistical analyses: constrained longitudinal data analysis using natural cubic splines as in the clinical trial but stratified into our data-driven subgroups. **Results:** Analysis supported 4 longitudinally validated subgroups of spatial atrophy: Limbic (17% of A+ CN in ADNI / 9% in A4), Cortical (21% / 25%), Subcortical (4% / 7%), and Non-Atrophic (58% / 59%). The post hoc subgroup analysis revealed subgroup-specific treatment response and cognitive decline. The Subcortical subgroup favoured solanezumab over placebo: difference in means $\Delta PACC \approx 1$ at 240 weeks. The Limbic and Cortical subgroups showed more aggressive cognitive decline independent of treatment: $\Delta PACC \approx -2$ at 240 weeks. **Conclusions:** A computational model of spatiotemporal atrophy subtypes in AD, that was pre-trained on ADNI data using Subtype and Stage Inference, identified baseline biological heterogeneity in the Phase 3 A4 secondary prevention clinical trial. Post hoc subgroup analysis revealed that these subgroups have both predictive value (differential treatment response) and prognostic value (differential cognitive decline, independent of treatment). This supports two key outcomes: using data-driven disease progression modelling in trial design and treatment assignment; and openly sharing individual patient-level data from completed clinical trials.

Keywords: Heterogeneity, subtyping, disease progression modelling, solanezumab, phase 3, post hoc subgroups.

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Key takeaway message: The predictive and prognostic value of a pre-trained AI model of brain atrophy subtypes supports its use in future clinical trial design.

P152- SPEECH BIOMARKER FOR COGNITION AND CORRELATION WITH CLINICAL OUTCOME MEASURES OVER TIME IN PRECLINICAL ALZHEIMER'S DISEASE.

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Background: Early identification of cognitive decline in preclinical Alzheimer's disease (AD) remains a critical challenge for research and therapeutic development. The Speech Biomarker for Cognition (SB-C) is a clinically validated, AI-driven digital speech biomarker that offers a non-invasive, low-burden approach to capturing subtle cognitive changes in naturalistic, real-world contexts. **Objective:** To evaluate the utility of SB-C in tracking cognitive changes over time in individuals with subjective cognitive decline (SCD) to examine its correlation with established neuropsychological outcome measures. **Methods:** Participants were drawn from the longitudinal β-AARC cohort, all with biomarker characterization but no clinical diagnosis of cognitive impairment at baseline. Speech data were collected at baseline (T0) and after 12 months (T12) through structured cognitive tasks including semantic verbal fluency and a verbal memory test. Recordings were analyzed using a validated AI-driven speech analysis pipeline developed by ki:elements, yielding scores for overall cognition and specific domains: memory, executive function, and processing speed. Speech biomarker for Cognition (SB-C) scores were correlated with standard neuropsychological measures including the Free and Cued Selective Reminding Test (FCSRT) and Trail Making Test (TMT-A and TMT-B),

both cross-sectionally (T0, T12) and longitudinally using repeated measures correlation. **Results:** At both T0 and T12, SB-C domain scores captured clinically relevant cognitive variation and showed significant correlations with clinical outcome measures. For example, at T0, the SB-C cognition score correlated with TMT-B ($r = –0.427$, $p < 0.001$) and FCSRT delayed free recall ($r = –0.287$, $p = 0.006$). At T12, more and stronger correlations were found, particularly for memory scores (e.g., SB-C memory vs. FCSRT delayed free recall: $r = –0.338$, $p = 0.002$). Repeated measures correlation between SB-C executive function scores and TMT-B yielded $r = – 0.24$ ($p < 0.05$), supporting longitudinal sensitivity of the SB-C to changes in executive performance. These findings demonstrate that the speech-based assessments captured clinically meaningful variation in cognitive performance, even in individuals without a clinical diagnosis of impairment. **Conclusions:** Speech-based cognitive biomarkers are a promising objective, low-burden, and scalable solution for detection and monitoring cognitive trajectories in preclinical AD. The observed correlations with well-established clinical outcome measures—both cross-sectionally and over time—underscore the potential of integrating AI-driven speech biomarkers into clinical trials and large-scale observational studies targeting early-stage AD. This approach may enable earlier intervention and more precise tracking of cognitive decline in at-risk populations.

Key takeaway message: AI-driven speech biomarkers reliably detect and track subtle cognitive changes over time in preclinical Alzheimer's disease and correlate significantly with standard neuropsychological measures, offering a scalable tool for early detection and monitoring.

P153- DEVELOPMENT OF A COMMUNITY-BASED PREDICTIVE MODEL FOR MILD COGNITIVE IMPAIRMENT USING DIGITAL CLOCK DRAWING AND COMPLEX FIGURE TESTS.

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Objective: The Digital Clock Drawing Test (dCDT) and Digital Complex Figure Test (dCFT) have been utilized as more objective tools for assessing cognitive function. However, the effectiveness of either test alone or in combination for identifying mild cognitive impairment (MCI) among community-dwelling older adults remains uncertain. This study aims to develop an MCI prediction model based on these two digital tools to facilitate large-scale screening among community-dwelling older adults. **Methods:** From July to September 2023, a total of 413 participants aged 65 years or older were recruited from five community sites in Shanxi Province, including four rural and one urban location. Among them, 234 were classified as cognitively normal (NC), and 179 were diagnosed with MCI. Cognitive testing was conducted using proprietary dCDT and dCFT software developed by our team. Participants used a stylus to draw two figures on a 10.8-inch tablet. Upon completion, the system automatically captured dynamic drawing process parameters, such as stroke speed, stroke duration, number of strokes, and time in air. A community-based MCI prediction model was developed using the XGBoost algorithm with features extracted from both dCDT and dCFT. All participants completed the Mini-Mental State Examination (MMSE), Activities of Daily Living (ADL), and Clinical Dementia Rating (CDR) assessments to evaluate global cognitive function. Additionally, 95 participants underwent biomarker testing for plasma phosphorylated tau 217 (p-tau217) and glial fibrillary acidic protein (GFAP) levels. Pearson correlation analyses were conducted to examine associations between key digital features and the concentrations of plasma p-tau217 and GFAP. **Results:** A total of 67 digital features (including 18 from dCDT and 49 from dCFT) showed statistically significant differences between the two groups (all $p < 0.05$). The area under the curve (AUC) for distinguishing MCI from NC was 0.805 using dCDT and 0.833 using dCFT (a combination of three subtests). When dCDT and dCFT were combined, the AUC increased to 0.915, with an accuracy of 0.830. Additionally, the AUC of plasma p-tau217 for identifying MCI individuals was 0.761. When the two digital tools were combined with plasma p-tau217, the AUC reached 0.949, with a sensitivity of 0.889. Correlation analysis revealed that several digital features were significantly associated with plasma p-tau217 and GFAP levels (all $|r| > 0.3$, $p < 0.001$). **Conclusions:** The dCDT and dCFT demonstrated good performance in screening individuals with MCI in community settings. When combined, the two tools yielded an AUC of 0.915. The combination of two digital tools with plasma p-tau217 further improved diagnostic performance, achieving an AUC of 0.949. This study provides a novel digital approach for large-scale screening of community-dwelling individuals with MCI, offering potential to enhance early diagnosis and intervention for Alzheimer's disease (AD).

Keywords: Digital clock drawing test, digital complex Ffgure test, mild cognitive impairment, community-based screening model, machine learning algorithms.

Disclosures: The authors declared no competing interests.

Key takeaway message: This study aims to develop an MCI prediction model based on these two digital tools to facilitate large-scale screening among community-dwelling older adults. We also analyzed the associations between key digital features and plasma levels of p-tau217 and GFAP. The dCDT and dCFT demonstrated good performance in screening individuals with MCI in community settings. The combination of two digital tools with plasma p-tau217 further improved diagnostic performance, achieving an AUC of 0.949.

P154- TOWARD IN SILICO CLINICAL TRIAL EMULATION FOR ALZHEIMER'S DISEASE: THE THERAPEUTIC SIMULATION AGENT (TSA).

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Background: Clinical trials in Alzheimer's Disease (AD) face high failure rates, in part due to limited predictive power of animal and cellular models (1). Current preclinical systems often fail to anticipate biomarker trajectories in human participants, creating translational bottlenecks and costly late-stage attrition (2). To address this challenge, we developed the Therapeutic Simulation Agent (TSA), an AI-driven, modular framework that emulates trial-like conditions in silico. By integrating therapeutic proposal generation, biomarker response simulation, and retrospective validation, TSA is designed to prioritize interventions and dosing strategies that are more likely to succeed in human clinical trials. **Methods:** TSA is implemented as both a command-line tool and as an application interface service to support flexible use in research and clinical trial design contexts. The framework comprises five coordinated modules: (1) dataset availability and synthetic bootstrap initialization, (2) therapeutic proposal generation (target, dose, duration), (3) biomarker trajectory simulation with explicit uncertainty modeling, (4) critic agent for scoring and ranking interventions, and (5) retrospective validation using held-out datasets with error metrics such as RMSE. Demonstration runs focused on AD-relevant pathways (MAPT, APP), simulating dose-response profiles against available biomarker datasets. **Results:** In a representative test case with simulated data, TSA generated six therapeutic hypotheses, simulated biomarker trajectories, and ranked candidates by predicted efficacy and uncertainty. The top-ranked MAPT-directed perturbation achieved the most favorable composite score. Retrospective validation showed strong alignment with observed biomarker dynamics (RMSE = 0.189). Across bootstrap replications, TSA consistently generated biologically plausible predictions with interpretable uncertainty estimates. Importantly, TSA's modularity enables integration of patient-derived data streams, making it adaptable for trial emulation. These findings support the potential of TSA to inform early trial design and candidate prioritization in AD. **Conclusions:** TSA establishes proof-of-concept for in silico clinical trial emulation in AD. By uniting hypothesis generation,

biomarker simulation, and validation, TSA provides a reproducible framework to prioritize candidate interventions, optimize dose and duration, and quantify uncertainty before costly human studies. This approach can reduce translational risk and inform adaptive trial strategies. Future work will expand TSA to incorporate longitudinal biomarker datasets and multi-objective optimization, positioning it as a scalable platform to accelerate therapeutic discovery and trial readiness in AD.

Keywords: Artificial Intelligence, clinical trials, Alzheimer's disease, AI agent.

Disclosures: Authors have nothing to disclose.

References: 1. Cummings, Jeffrey, et al. «Alzheimer's disease drug development pipeline: 2024.» Alzheimer's & Dementia: Translational Research & Clinical Interventions 10.2 (2024): e12465. 2. Vaghari, Delshad, et al. «AI-guided patient stratification improves outcomes and efficiency in the AMARANTH Alzheimer's Disease clinical trial.» Nature Communications 16.1 (2025): 6244.

Key takeaway message: The Therapeutic Simulation Agent (TSA) enables in silico clinical trial emulation in Alzheimer's disease, prioritizing targets, doses, and biomarker trajectories to de-risk translation and accelerate therapeutic discovery.

P155- BRAIN-AGE PREDICTION IN ONE MINUTE FROM STRUCTURAL MRI USING ARTIFICIAL INTELLIGENCE: TOWARD A SCALABLE BIOMARKER.

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Background: Research on biomarkers for the early detection of cognitive decline and neurodegenerative diseases is rapidly advancing. Among these, brain age prediction based on T1-weighted structural MRI has emerged as a promising quantitative index that can capture subtle changes in brain structure. However, most existing brain-age models depend on preprocessing pipelines such as FreeSurfer or SPM, which require hours of processing for each scan. While such approaches achieve strong performance in research contexts, their reliance on time-consuming pipelines limits clinical applicability. To address this limitation, we developed an artificial intelligence (AI) based brain-age model using only freely available, fast preprocessing tools that are practically feasible in clinical settings. We then evaluated its potential as a biomarker by testing whether the brain-age gap (BAG: predicted age – chronological age) and its residualized form can (i) distinguish diagnostic groups, (ii) differentiate amyloid PET status, and (iii) predict near-term decline on the Mini-Mental State Examination (MMSE). **Methods:** We compiled a multi-site, multi-scanner dataset of healthy adults (n=4,346; HCP, OASIS-3, IXI, ADNI, 1000 Functional Connectomes, CamCAN, Narrative) and split it into training/validation/test sets (70/15/15). Preprocessing included HD-BET skull stripping (1), N4 bias-field correction, and ANTs spatial normalization, followed by cropping, Gaussian smoothing, and intensity normalization. From each axis, 40 slices with the fewest dark pixels were selected (2) and resized to form a $120\times120\times120$ tensor; end-to-end preprocessing per T1 took ~1 minute. A 3D EfficientNet-B1 was trained with Adam optimizer and Huber loss (delta = 3) with TorchIO augmentation (affine, noise, gamma, bias-field). Performance was evaluated on the test set (MAE, R^2) and externally validated in the Dallas Lifespan cohort (n=315). We then applied the model to the Biobank Innovations for chronic Cerebrovascular disease With ALZheimer's disease Study (BICWALZS) cohort to study group differences (cognitive normal (CN), mild cognitive impairment (MCI), vascular dementia (VD), and Alzheimer dementia (AD) and amyloid PET status using residualized BAG. BAG was calculated by predicted minus chronological age and residualized BAG was computed as the Ordinary Least Squares residuals of BAG on centered age (Age − μ_age; μ_age ≈ 46.9 y). Residualized BAG was analyzed using ANCOVA (Type II SS; covariates age, sex, site), with pairwise differences assessed by Welch's t-tests with Bonferroni correction and effect sizes (Hedges' g). Diagnostic discrimination was evaluated using ROC curves and AUC. Survival analysis was restricted to the MCI subgroup of BICWALZS, modeling time to fast MMSE decline defined as the earliest visit with a baseline-anchored annualized change $\leq$ c (c $\in$ {−0.8, −1.0, −1.2, −1.5, −1.8} points/year). Participants not meeting a threshold were right-censored. We fit site-stratified Cox models (ties=Efron; ridge penalty λ=0.1) with z-scored residualized BAG as exposure and age, sex, baseline MMSE as covariates, reporting HR per 1-SD (95% CI, p). All training, testing, and statistical analyses were performed in Python. **Results:** The 3D EfficientNet-B1 achieved strong performance on the held-out test set (R^2=0.95, MAE=3.76). External validation in Dallas Lifespan confirmed generalizability (R^2=0.90, MAE=4.82). In BICWALZS, the residual BAG showed robust group differences: CN vs MCI ($\Delta\approx+5.1$ years, $g\approx-0.67$, $p<1\times10^{-9}$), CN vs AD ($\Delta\approx+9.6$ years, $g\approx-1.47$, $p<1\times10^{-23}$), and CN vs VD ($\Delta\approx+10.8$ years, $g\approx-1.44$, $p<1\times10^{-19}$). ROC analyses indicated clinically meaningful discrimination, particularly with residual BAG (AUC/accuracy): CN vs MCI 0.69/0.61; CN vs AD 0.84/0.78; CN vs VD 0.87/0.80. Amyloid-positive participants showed higher BAG than amyloid-negative (+1.7 years, F=11.4, p<0.001), though effect size were modest; residual BAG also differed ($\Delta\approx+2.9$ years, $g\approx-0.38$, $p<1\times10^{-7}$). Survival analysis demonstrated that residual BAG independently predicted time to fast MMSE decline across multiple thresholds: at ≤ -1.0 points/year, HR=1.25 (95% CI 1.03–1.53; p=0.028); at ≤ -1.2, HR=1.26 (1.02–1.55; p=0.032); at ≤ -1.5 (primary), HR=1.28 (1.03–1.59; p=0.028); and at ≤ -1.8, HR=1.25 (1.00–1.57; p=0.049). Thus, each 1-SD increase in residual BAG conferred ~25–28% higher instantaneous risk of rapid MMSE decline. **Conclusions:** A fully open-source, rapid preprocessing (~1-minute per scan) and deep-learning pipeline achieved state-of-the-art brain-age accuracy with strong external generalizability. Residualized BAG robustly distinguished CN, MCI, AD, and VD with large effect sizes and clinically meaningful AUCs, whereas associations with amyloid status were modest. Critically, residualized BAG independently predicted the timing of accelerated MMSE decline in a real-world memory-clinic cohort. While individual-level diagnosis remains limited, consistent group-level effects support brain age as a scalable biomarker for progression risk stratification and trial enrichment. Future work will expand datasets, refine residualization (e.g., nonlinearity, demographics), and integrate residual BAG with cognitive and biomarker measures to improve individual-level prediction.

Keywords: Artificial intelligence, brain age, structural MRI, Alzheimer's disease.

Disclosures: This study used biospecimens and data from the Biobank Innovations for Chronic Cerebrovascular Disease with Alzheimer's Disease Study (BICWALZS) consortium funded by the National Institute of Health (NIH, Project No. 2024-ER0505-01). This work was supported by the GRRC program of Gyeonggi province (GRRCAjou2023-B02) and a research fund from Ajou University Medical Center (M2023C046000094, M2024C046000078). Additional support was provided by the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT (NRF-2019R1A5A2026045), the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health and Welfare (RS-2021-KH113821, RS-2022-KH125898, RS-2022-KH130303, RS-2023-00267453, RS-2024-00406876, RS-2025-25303051, RS-2025-25459402), the Korean ARPA-H Project through KHIDI (RS-2025-25455095), and the Korea Dementia Research Project through the Korea Dementia Research Center (KDRC) funded by the Ministry of Health and Welfare and the Ministry of Science and ICT (RS-2024-0339665). The funding sources had no role in study design, data collection, analysis, interpretation, or manuscript preparation.

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Key takeaway message: A rapid, open-source AI pipeline predicts brain

age in one minute, with residualized BAG distinguishing diagnostic groups and predicting cognitive decline, supporting brain age as a scalable biomarker for clinical translation.

P156- REGULATORY CONSIDERATIONS ON UTILIZING PROGNOSTIC MODELS FOR SAMPLE SIZE REDUCTION IN ALZHEIMER'S DISEASE CLINICAL TRIALS.

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Background: Artificial intelligence (AI) models of Alzheimer's Disease progression are valuable tools to understand disease course and predict standard of care outcomes of participants in clinical trials. Through the framework of prognostic covariate adjustment (PROCOVA), these models may be used to provide covariates that boost the power of clinical trials. In turn, this added power may be used prospectively to reduce the sample size required for a trial. Reducing sample size can be incredibly valuable for sponsors and patients, but it carries risk from a regulatory perspective and interfaces directly with the recent FDA guidance on AI applications in drug development. **Methods:** We explored the major considerations for context of use, risk, development, and implementation of AI-based models for sample size reduction using PROCOVA in AD clinical trials, formalizing these in terms of the 7-step plan for model credibility defined in the FDA guidance on AI applications in drug development. We evaluated the risk profile of this application and assessed various mitigation strategies to limit risk. Similarly, for the development of the model we defined validation strategies that can provide stronger evidence to justify the sample size reduction application, and built guidelines that can be generally applied to models. **Results:** The risk of sample size reduction is that the study is underpowered, and the magnitude of risk is variable depending on the amount of reduction. A few mitigation strategies can control this risk; these include interim analyses for sample size re-estimation, design considerations around the target study power, and validation choices to provide more robust evidence in selecting the amount of sample size reduction. The output is a framework for defining and implementing the 7-step plan for sample size reduction applications with PROCOVA. **Conclusions:** Applying AI models in novel applications such as sample size reduction requires thorough consideration of the context of use of the model. Confronting this risk is worth the effort given the benefit to patients and sponsors. FDA's guidance on AI provides a robust framework to define the context of use and evaluate the risk of a sample size reduction, and we detail the issues at play for the development and use of AI models to achieve faster clinical trials. This work serves as a practical guide to achieving this goal.

Keywords: Artificial intelligence, FDA, digital twins.

Disclosures: The authors are employees of Unlearn.AI and hold stock options in the company.

Key takeaway message: AI models can reduce sample size in Alzheimer's trials, but require careful risk mitigation and regulatory alignment using FDA's 7-step framework for credible AI in drug development.

P157- MACHINE LEARNING-BASED DIFFERENTIATION OF AMNESTIC AND NON-AMNESTIC MILD COGNITIVE IMPAIRMENT USING MULTIMODAL PHYSIOLOGICAL AND NEUROIMAGING BIOMARKERS.

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Background: Amnestic (aMCI) and non-amnestic mild cognitive impairment (naMCI) have distinct clinical trajectories and underlying mechanisms, with aMCI more often progressing to Alzheimer's disease and naMCI more frequently linked to vascular etiologies. Objective, non-invasive biomarkers could improve early subtype classification and facilitate targeted recruitment in clinical trials. This study aimed to develop and evaluate machine learning (ML) models integrating multimodal physiological and neuroimaging features to differentiate aMCI from naMCI. **Methods:** We prospectively recruited 80 participants with MCI (CDR 0.5; DSM-V criteria). Assessments included gait analysis (GAITRite®), body composition (DXA), polysomnography, and 3T brain MRI (gray matter morphometry, white matter hyperintensity quantification). Five unimodal and three multimodal datasets were generated. Dimensionality reduction was performed using independent component analysis and principal component analysis. Four supervised ML algorithms—support vector machine, random forest (RF), multi-layer perceptron (MLP), and convolutional neural network—were evaluated using 10-fold cross-validation.**Results:** In the combined health metrics dataset (gait, sleep, body composition), RF achieved an AUC of 0.89 and accuracy of 83%. In the health metrics + MRI dataset, MLP achieved the best performance (AUC 0.93, accuracy 80%). Top discriminative features included composite lean body mass and bone mineral content (BMC) of the right leg, total BMC, right arm bone mineral density, step length differential, cycle time differential, REM sleep proportion, and double step time variability. These features were associated with structural alterations in temporal (fusiform, lingual), frontal (precentral, frontal pole), and occipital (cuneus, pericalcarine) regions. **Conclusions:** Multimodal integration of gait, sleep, body composition, and neuroimaging biomarkers enables robust differentiation of aMCI from naMCI. Such approaches could support precision phenotyping in early cognitive impairment and improve trial readiness in Alzheimer's disease research.

Keywords: Amnestic mild cognitive impairment, non-amnestic mild cognitive impairment, machine learning, biomarkers.

Disclosures: The authors declare no competing interests.

Key takeaway message: Integrating gait, sleep, body composition, and MRI biomarkers via machine learning accurately differentiates aMCI from naMCI, supporting precision phenotyping and improving clinical trial cohort selection.

P158- ASSESSING VARIABILITY IN BRAIN SEGMENTATION ACROSS MULTIPLE RECENT AUTOMATED METHODS.

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Background: While FreeSurfer (1) is a well-established method commonly used in clinical trials to assess the volume of various brain structures, results are impacted by variability due to motion artifacts, partial volume effects as well as limitations of atlas-based methods in cases of high deformity. With successive iterations of the FreeSurfer algorithm and avenue of more robust deep learning AI-based segmentation methods, one can expect decreased variability and increased sensitivity to change over time. In this work, we seek to assess the variability of various automated segmentation methods in measuring the volume of several brain structures. **Methods:** 3D T1-weighted MRI scans were downloaded from ADNI. 100 ADNI2 subjects (22 CN, 6 SMC, 29 EMCI, 9 MCI, 19 LMCI and 15 AD) with test/re-test data, and 143 ADNI3 subjects (26 CN, 40 SMC, 55 LMCI and 22 AD) with good quality baseline and year 1 scans were selected. Each of the above MRI scans was processed using the following methods: FreeSurfer v6.0 (FS6), FreeSurfer v8.0 (FS8), SynthSeg (SS) (2), and Clario's AI model (CL) (3) (trained on FS6 data). In addition to whole brain, lateral ventricles and hippocampus, some cortical (entorhinal, precuneus, posterior cingulate (PC) and medial temporal lobe (MTL) and deep (caudate, pallidum,

putamen and thalamus) brain structures were assessed. Baseline and year 1 scans were processed cross-sectionally to estimate volume change over time. Tensor Based Morphometry (TBM) was also applied between year 1 and baseline scans to assess volume change longitudinally. For each segmentation method, variability was assessed using Intraclass Correlation Coefficient (ICC) and Percent Absolute Difference (PAD) between test and re-test data, while diagnostic sensitivity was estimated between CN+SMC and AD subjects using unpaired t-test and Cohen's d. Sensitivity to change was measured between baseline and year 1 using paired t-test and Cohen's d for CN, EMCI, LMCI and AD separately, looking at volume change across visits. **Results:** Test/re-rest results showed excellent agreement for all methods and locations, where CL method demonstrated the highest accuracy. ICC for FS6 ranged from 0.84 to 1.0, from 0.96 to 1.0 for FS8 and SS, and from 0.98 to 1.0 for CL. PAD for FS6 ranged from 0.78% to 7.30%, from 0.34% to 5.0% for FS8, from 0.19% to 2.66% for SS and from 0.27% to 2.54% for CL. Highest variability was seen in the pallidum and entorhinal cortex. All methods were able to successfully differentiate CN+SMC from AD at baseline for the entorhinal, hippocampus, MTL, posterior cingulate, precuneus, putamen and thalamus. AI-based methods were also able to differentiate caudate (SS only) and pallidum (both SS and CL) with $p < 0.05$. Top performers for effect size varied across location (FS6 for putamen, FS8 for entorhinal, hippocampus, MTL and thalamus, SS for caudate, LV and PC, and CL for pallidum, precuneus and whole brain). When comparing volumes between visits, all methods could detect significant changes at year 1 for lateral ventricles irrespective of disease severity. Looking at other structures, for CN individuals, TBM was able to detect significant changes for more regions than segmentation-based methods. When progressing towards disease continuum, all methods were able to detect changes for most regions. **Conclusions:** Our results show that while all methods exhibit very good test/re-test variability, AI-based methods outperform atlas-based methods in both reliability and measurement precision, particularly in AD-relevant regions such as the entorhinal cortex, hippocampus and posterior cingulate. When assessing volume change over time, AI-based methods are more sensitive cross-sectionally, although longitudinal registration-based TBM method remains the method of choice. More work is needed to expand this analysis over the entire ADNI3 and ADNI4 databases, to further inform about expected effect sizes depending on brain region and disease severity.

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Key takeaway message: Recent AI-based methods show lower variability than atlas-based FreeSurfer versions. Cross-sectional use to track volume changes becomes achievable with a sensitivity closer to registration-based methods.

P159- IMPROVING FREESURFER ROBUSTNESS BY INTEGRATING AUTOMATED FAILURE DETECTION USING ARTIFICIAL INTELLIGENCE FOR CONSISTENT QUANTITATIVE BIOMARKER EXTRACTION.

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Background: Accurate brain MRI segmentation is pivotal to the conduct of various quantitative analyses (atrophy assessment, DTI, fMRI, etc.) considered as exploratory endpoints in AD clinical trials. FreeSurfer (FS) (1) is a widely accepted algorithm used in many ongoing trials. Segmentation is however challenged in the presence of extensive brain atrophy, massively enlarged lateral ventricles or white matter (WM) disease, and may lead to processing failure or inaccuracies. Such issues may be resolved by re-running FS after manual intervention, but each round of re-processing implies up to 12 hours of additional time to improve segmentation output and may add variability. While switching to faster or more robust AI-based methods may be appealing, maximizing consistency with analyses conducted in past trials is essential, for comparability purposes. In this work, we present an AI-driven FS rescue workflow that automatically detects failures and gross segmentation inaccuracies and triggers built-in FS correction mechanisms to effectively resolve issues while preserving the underlying segmentation method used. **Methods:** 152 retrospectively acquired, aggregated and anonymized 3DT1 scans from past AD (N=70) and frontotemporal dementia (FTD, N=82) datasets were selected specifically for this work due to observed FS segmentation failure (55 total failures, 97 partial failures, see definitions below) caused by the presence of extensive disease. All cases had been prospectively processed with FS v6.0, visually reviewed and reprocessed as needed after use of FS "-bigventricle" option, brain and/or WM mask editing, and addition of WM seeds, when results were felt to be inaccurate. Such manual inputs are built into the FS pipeline and allow to improve accuracy without any direct editing of brain segmentation, which would be too labor-intensive. Besides, all cases were also automatically segmented using a previously validated AI method (2) which showed increased robustness. Segmentation consistency between the original FS segmentation (without visual review) and the fully-automated AI segmentation was estimated using the arithmetic mean of Dice similarity coefficients calculated independently for each anatomical FS region. The rescue method was designed as follows: - First, in the presence of very large ventricles, defined by a volume > 80 mL, FS "-bigventricle" option is set before FS is run. - Besides, for total failures (defined by empty FS brain masks) and partial failures (defined by Dice $< 80\%$ compared to AI-derived reference segmentation), AI-derived WM mask and if needed brain mask are leveraged. To assess the usefulness of the rescue method, segmentation accuracy was measured by calculating mean Dice against AI segmentation results, for the following approaches: - Fully Automated: FS segmentation without any human intervention. - Automated+Manual: FS segmentation followed by visual review and, if necessary, reprocessing based on manual input. - Automated+Rescue: FS segmentation without any human intervention but including automatic reprocessing within the rescue framework. Mean Dice was calculated for all FS regions, as well as for cortical regions alone, looking at all subjects, as well as subjects with partial failure (e.g. non-empty automated FS results). **Results:** Fully automated FS segmentation resulted in a mean Dice of 42.0% for all regions, and 49.3% for cortical regions only, when including all subjects. When restricting to partial failures, mean Dice was 65.8% and 77.3% respectively. After visual inspection and re-execution as needed (Automated+Manual), considering all subjects, Dice increased by +29.3 percentage points (pp) for all regions, and +31.4 pp for cortical regions. For partial failures alone, increase was +5.8 pp and +4.2 pp respectively. Finally, with the rescue method (Automated+Rescue), Dice for all subjects increased by +31.2 pp for all regions, and +33.9 pp for cortical regions. Looking at partial failures alone, increase was +8.4 pp and +7.0 pp respectively. **Conclusions:** The rescue method presented here successfully accomplishes what visual inspection and manual intervention by trained technicians could achieve in improving automated FS segmentation, at a similar to slightly superior level based on Dice similarity against robust AI-segmentation. While using AI-based segmentation may become the new norm in the coming years, maintaining consistent FreeSurfer-based analysis pipelines can be justified for comparability between compounds or trial phases. The proposed AI-integrated rescue method enables automatic FS failure detection and recovery within the established FS pipeline, allowing more reliable volumetric assessments in challenging populations without modifying the method used for analysis. By minimizing manual intervention and enhancing overall data quality, this approach has the potential for application in ongoing trials, particularly those in late-stage AD and FTD.

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Key takeaway message: AI can help increase FreeSurfer pipeline robustness, without modifying the core structure of the existing algorithm.

P160- LARGE LANGUAGE MODELS FOR CLINICAL DEMENTIA RATING SEVERITY ASSESSMENT: DOMAIN-SPECIFIC PERFORMANCE ANALYSIS.

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Background: The Clinical Dementia Rating (CDR) scale is the gold standard for staging dementia severity, with clinical implications for treatment planning and social support decisions (1). Distinguishing between CDR stages (0, 0.5, 1) is crucial for early intervention (2). While recent studies demonstrated diagnostic validity of large language models (LLMs) for binary dementia detection (77-91% accuracy) (3,)], severity validity—the ability to differentiate specific CDR stages—remains largely unexplored. The only prior severity assessment study achieved κ=0.83 but lacked domain-specific evaluation and direct clinician comparison, limiting clinical interpretability (3). This study aimed to establish the severity validity of LLM-based CDR assessment across all six domains, compare performance with clinical experts using identical text-based records, and identify documentation biases affecting cognitive evaluation accuracy. **Methods:** We analyzed 150 de-identified semi-structured clinical interview records from patients with memory complaints (Global CDR 0, 0.5, 1; n=50 each) at Seoul National University Boramae Medical Center (2020-2024). Three LLM approaches were evaluated: simple sequential processing (GPT-4.1), cost-efficient processing (GPT-4o-mini), and complex multi-stage processing with entity extraction and knowledge retrieva- augmentation-generation (RAG) (5). An independent clinical psychologist assessed identical text records without access to ground truth or model predictions. Performance metrics included accuracy, Cohen's kappa, confusion matrices, and Bonferroni-corrected comparisons across all six CDR domains (Memory, Orientation, Judgment, Social Activities, Home & Hobbies, Personal Care). Inter-rater reliability was assessed using Fleiss' kappa (6). **Results:** For global CDR severity, LLMs achieved 62.7-63.3% accuracy (κ=0.654-0.714) versus expert 72.7% (κ=0.794). Domain-specific analysis revealed striking disparities: functional domains demonstrated high accuracy—Personal Care (88.7-90.7%), Social Activities (79.3-81.3%), Home & Hobbies (78.7-80.0%)—while cognitive domains showed significant limitations—Memory (59.3-67.3%), Orientation (73.3-77.3%), Judgment (76.0-80.7%). LLMs systematically overestimated Memory impairment, failing to identify normal cognition (CDR=0), with confusion matrix analysis revealing consistent misclassification patterns. This reflects documentation bias where memory complaints, the primary referral reason, dominate clinical narratives (7). Both LLMs and experts struggled with CDR=0.5 identification across all domains, indicating fundamental limitations of text-based assessment for detecting mild impairment without objective testing (8). Simple architectures matched or exceeded complex processing across all metrics (p=0.001 for Judgment domain only after Bonferroni correction). Cost-efficient models performed equivalently to premium versions. **Conclusions:** This first comprehensive domain-specific CDR severity assessment reveals that aggregate performance metrics mask critical domain-level disparities. While functional domains (Personal Care, Social Activities, Home & Hobbies) achieved near-clinical accuracy suitable for automated monitoring, cognitive domains—particularly Memory—exposed fundamental LLM limitations and systematic documentation biases. The Memory overestimation pattern reflects how referral-driven clinical documentation creates inherent biases that LLMs amplify rather than correct (9). These findings support selective deployment strategies: functional domain assessment via automated tools for scalable monitoring, while cognitive evaluation requires multimodal clinical approaches integrating objective testing (10). Future LLM development for dementia assessment must address documentation biases through training on balanced datasets and incorporate mechanisms to recognize and adjust for referral-pattern biases in clinical texts.

Keywords: Clinical Dementia Rating, severity validity, domain-specific assessment, documentation bias.

Disclosures: The authors declared no competing interests.

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Key takeaway message: LLMs show near-clinical accuracy in functional CDR domains but systematically overestimate memory impairment, highlighting documentation bias and supporting selective use of automated tools with multimodal approaches for cognitive assessment.

P161- TRACKING COGNITIVE CHANGE OVER TIME USING A REMOTE TELEPHONE-BASED AI-DRIVEN DIGITAL COGNITIVE ASSESSMENT.

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Background: Remote, digital cognitive assessments enable more frequent cognitive monitoring and may detect changes more rapidly than traditional single-timepoint, in-clinic evaluations. The ki:elements Speech Biomarker for Cognition (SB-C) is a low-burden, remote, and cost-efficient tool designed to track cognitive changes across the Alzheimer's disease (AD) spectrum. The SB-C combines an automated landline telephone protocol with automated analysis of two established speech-based cognitive tasks: the Rey Auditory Verbal Learning Test (RAVLT) and Semantic Verbal Fluency (SVF). In this study, we investigated whether remote longitudinal administration of the SB-C over landline telephone calls could track cognitive changes over time in a multi-site Swedish-German memory clinic population. **Methods:** We evaluated whether longitudinal use of the SB-C could track cognitive change over time in two memory clinic populations enrolled in the PROSPECT-AD study: the Swedish BioFINDER-Primary Care cohort

(N=103, mean age=76.6 ± 6.4) and the German DESCRIBE-AD registry (N=177, mean age=72.9 ± 7.4). Participants completed assessments at baseline (t0) and at 3, 6, and 12 months (t3, t6, t12), with follow-up assessments conducted automatically via telephone. The SB-C score was extracted from SVF and RAVLT speech recordings using ki:elements' proprietary speech analysis pipeline including automatic speech recognition and feature extraction. The SB-C global cognition score is a z-score corrected for age and education. Participants were grouped according to their diagnosis at t0 either as participants that are healthy or have subjective cognitive impairment (HC/SCI) or patients with mild cognitive impairment (MCI). Over the four timepoints the following participants of both groups were assessed: t0 HC/SCI=169, MCI=111; t3 HC/SCI=115, MCI=52; t6 HC/SCI=147, MCI=75; t12 HC/SCI=109, MCI=50. Change in SB-C was calculated as the difference between baseline t0 and the respective time points t3, t6 and t12. Linear mixed effect (LME) models were used to test for effects in groups (HC/SCI vs. MCI), timepoints (t0, t3, t6, t12) as well as the interaction; we also report group comparisons for each timepoint separately. **Results:** We observed a significant group effect (F=11.13; p<.001), with the MCI group showing greater decline in cognitive performance compared to HC/SCI across timepoints. Group differences in absolute SB-C scores were significant at all timepoints except t3. A significant group-by-time interaction (F=4.78; p<.01) indicated that cognitive decline in the MCI group was more pronounced over time. No significant main effect of time was detected independently of the group. **Conclusions:** These findings demonstrate that the SB-C, administered remotely via automated telephone calls, is sensitive to longitudinal cognitive changes, particularly in individuals with MCI. The SB-C differentiates between clinical groups and captures progression over time, supporting its potential as a scalable, low-burden tool for remote cognitive monitoring in both research and clinical settings. This approach could facilitate future AD clinical trials by improving the efficiency of longitudinal tracking of cognitive changes.

Conflicts of Interest: EM, JT, AK, NL are employed by the digital biomarkers company ki elements GmbH. JT & NL hold shares in the digital biomarker company ki elements GmbH.

Key takeaway message: A remote telephone-based ai-driven digital cognitive assessment can track cognitive change over time in an MCI memeroy clinic population.

CLINICAL TRIALS: IMAGING

P162- CEREBRAL BLOOD FLOW RATIO OF THE DEFAULT MODE NETWORK TO THE CENTRAL EXECUTIVE NETWORK AS A PREDICTOR OF EXECUTIVE FUNCTION FOLLOWING N-ACETYLCYSTEINE SUPPLEMENTATION IN VASCULAR MILD COGNITIVE IMPAIRMENT PARTICIPANTS FROM THE MOVE-IT TRIAL.

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Background: Vascular mild cognitive impairment (vMCI) is characterized by executive dysfunction and may be an ideal stage for intervention while cognitive deficits are modest. The central executive network (CEN) is active during high-level cognitive processes, such as executive function, and is inversely related to the default mode network (DMN), which is active during rest. Neurovascular coupling describes the increase in cerebral blood flow (CBF) that occurs in response to increased neural activity, supporting the brain's metabolic demands. Individuals with vMCI may have impaired neurovascular coupling, where there may be a reduction in CBF to brain networks that are active during rest (e.g., DMN), or an increase in CBF to brain networks that are typically inactive during rest (e.g., CEN). As such, the regional CBF (rCBF) ratio of the DMN to the CEN (DMN/CEN-rCBF) may reflect impaired neurovascular coupling from a vascular imaging perspective. In vMCI, chronic hypoperfusion may lead to impaired neurovascular coupling and oxidative stress, exacerbating cognition. N-acetylcysteine (NAC), a precursor of the brain's major antioxidant, glutathione, may reduce oxidative stress and restore neurovascular coupling. We investigated whether baseline DMN/CEN-rCBF is a predictor of executive function outcome to NAC supplementation in vMCI. **Methods:** This secondary analysis utilized data from a recently completed randomized, double-blind, placebo-controlled, parallel-group phase 2 trial of oral NAC supplementation in individuals with vMCI undergoing cardiac rehabilitation (Efficacy and Safety of N-acetylcysteine in Patients with Mild Vascular Cognitive Impairment (MOVE-IT). Participants were classified with vMCI using a modified Gorelick criteria and were randomized to receive either NAC (2400 mg/day) or placebo (PLB) over the course of 24 weeks. Individuals with vMCI were included in this analysis if they had rCBF measures at week 0 and executive function assessed at weeks 0 and 24. Structural and pseudo-continuous arterial spin labelling images were acquired at 3 T. rCBF (mL of blood/100 g tissue/min) was quantified using the BASIL toolbox. rCBF from the core hubs of the DMN (medial prefrontal cortex, posterior cingulate cortex, precuneus, and angular gyrus) and the CEN (dorsolateral prefrontal cortex and posterior parietal cortex) were averaged to obtain rCBF values in the DMN and CEN, and a DMN to CEN rCBF ratio (DMN/CEN-rCBF) was obtained. Executive function was assessed with the Trail Making Test B (TMT-B) at weeks 0 and 24, where a shorter completion time corresponds to higher executive function. TMT-B scores were log-transformed prior to analyses to meet regression assumptions. Multiple linear regression models were used to examine 1) the relationship between baseline DMN/CEN-rCBF and baseline executive function; and 2) the interaction between baseline DMN/CEN-rCBF and treatment as a predictor of executive function at week 24 following 24 weeks of NAC or PLB supplementation, adjusting for baseline executive function, age, sex, and years of education. The latter model was bootstrapped with 10,000 iterations to account for the small sample size. **Results:** This analysis included 31 participants [16 randomized to NAC; 15 randomized to PLB; mean (SD) age: 68.5 (8.2) years; 65% male; years of education: 15.5 (3.2) years; DMN-rCBF: 38.0 (11.3) mL of blood/100 g tissue/min; CEN-rCBF: 36.0 (11.2) mL of blood/100 g tissue/min; DMN/CEN-rCBF: 1.1 (0.1); TMT-B: 121.7 (67.1) seconds]. Higher baseline DMN/CEN-rCBF was associated with lower baseline executive function, adjusting for age, sex, and education (B = 1.61, SE = 0.65, p = 0.0184). A significant DMN/CEN-rCBF by treatment interaction predicted executive function at week 24, adjusting for baseline executive function (B = -3.81, SE = 1.10, p = 0.0018), and remained significant after adjusting for age, sex, and education (B = -3.82, SE = 1.23, p = 0.0049). In the NAC group, higher DMN/CEN-rCBF predicted greater improvements in executive function (B = -2.92, SE = 1.00, p = 0.01), but not in the placebo group (B = 0.90, SE = 0.88, p = 0.32). The DMN/CEN-rCBF by treatment interaction remained significant in predicting executive function after bootstrapping with 10,000 iterations (B = -3.82, BCa 95% CI [-6.45, -1.05]). **Conclusions:** The DMN/CEN-rCBF ratio may be a predictor of NAC treatment response in individuals with vMCI, where those with higher DMN/CEN-rCBF may have greater cognitive benefits to NAC treatment due to higher baseline neurovascular coupling. Although higher neurovascular coupling was hypothesized to be associated with higher executive function at baseline, the inverse association between baseline DMN/CEN-rCBF and executive function observed in this analysis

suggests that individuals with vMCI may have an altered neurophysiological profile. Future studies should examine the association between DMN/CEN-rCBF and executive function in healthy controls. These findings also suggest that DMN/CEN-rCBF could be used to personalize NAC treatment. Individuals with vMCI with lower DMN/CEN-rCBF may be primed with interventions that may enhance neurovascular coupling, such as exercise and neurostimulation, which may lead to improved cognitive response to NAC.

Keywords: Antioxidant, cerebral blood flow, executive function, vascular mild cognitive impairment.

Clinical Trial Registry: NCT03306979; https://clinicaltrials.gov.

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Key takeaway message: Individuals with vascular mild cognitive impairment with higher cerebral blood flow ratio of the default mode network to the central executive network may have greater cognitive benefits to N-acetylcysteine treatment due to higher neurovascular coupling.

P163- AUTOMATED NEURODEGENERATION INDEX TO ENHANCE ALZHEIMER'S DISEASE TRIALS.

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Background: Alzheimer's disease (AD) clinical trials remain hampered by the lack of sensitive biomarkers to detect, quantify, and monitor neurodegeneration during the early clinical and biological stages of the disease. Diffusion magnetic resonance imaging (MRI) provides unparalleled insight into early microstructural changes and quantitative information on disease-specific neurodegeneration patterns in AD. However, its application in clinical trials is limited by complex data processing requirements, lack of standardization across sites and scanners, and insufficient integration into trial workflows. Automated Neurodegeneration Index for AD (ANDI-AD) is AI-powered imaging software designed to fill this critical void and provide a sensitive, scalable, and standardized approach to disease progression monitoring using an automated free-water analytical pipeline. This study examined whether ANDI-AD differentiated individuals along the AD continuum on the basis of clinical status and β-amyloid (Aβ) biomarker status. **Methods:** We analyzed diffusion MRI data from 122 participants enrolled in the 1Florida Alzheimer's Disease Research Center, recruited from both clinic and community settings. All scans were processed using the ANDI-AD pipeline to generate an individual-level, whole-brain neurodegeneration index score. Two primary analyses were conducted: (1) comparison of ANDI-AD scores across clinical groups (cognitively normal [CN; n=27], mild cognitive impairment [MCI; n=76], dementia [n=19]) and (2) comparison across Aβ biomarker groups defined by plasma Aβ42:40 (Quest AD-Detect®) and Aβ-PET concordance (concordant negative [plasma−/PET−; n=78], discordant [plasma+/PET−; n=25], concordant positive [plasma+/PET+; n=19]). In addition, conventional neurodegeneration markers, including plasma neurofilament light (NfL) and T1-derived volumetric measures of the bilateral hippocampus and total gray matter, were examined for comparison. Group differences were assessed using ANCOVA models adjusted for age and sex. **Results:** In the clinical comparison, ANDI-AD revealed a stepwise increase across groups (CN < MCI < dementia) ($p<0.01$), whereas higher plasma NfL and reduced T1-weighted hippocampal and grey matter volumes differentiated both CN and MCI from dementia ($p<0.01$). A similar pattern was observed in the Aβ status comparison. ANDI-AD revealed a stepwise increase across Aβ-defined biomarker groups (plasma−/PET− < plasma+/PET− < and plasma+/PET+) ($p<0.05$). In contrast, plasma NfL and T1-weighted volumes of the hippocampus and grey matter did not differentiate individuals with early Aβ biomarker evidence (plasma+/PET−) from their concordant negative (plasma−/PET−) counterparts. Plasma NfL was increased and hippocampal volumes were reduced in the concordant positive (plasma+/PET+) group compared to both the concordant negative and discordant groups ($p<0.05$). Total grey matter volume was reduced in the concordant positive group compared to concordant negative group ($p=0.001$). **Conclusions:** ANDI-AD differentiated individuals with CN, MCI, and dementia, as well as individuals with plasma−/PET−, plasma+/PET−, and plasma+/PET+ Aβ biomarker evidence. ANDI-AD, plasma NfL, and T1-weighted volumetric MRI provide independent information regarding the clinical and pathological staging of AD, with ANDI-AD being a more potent marker of early-stage disease processes in those with MCI and plasma Aβ biomarker evidence of AD. ANDI-AD is fully automated, highly scalable and cloud-based, providing seamless integration with clinical workflow systems to assess disease progression and treatment effects on neurodegeneration.

Keywords: Alzheimer's disease, clinical trials, neurodegeneration, biomarker. **Disclosures:** DEV, JCD, and AB claim intellectual property related to this abstract.

Key takeaway message: ANDI-AD is fully automated, highly scalable and cloud-based, providing seamless integration with clinical workflow systems to assess disease progression and treatment effects on neurodegeneration.

P166- BIODISTRIBUTION OF RADIOLABELED MAPT ANTISENSE OLIGONUCLEOTIDE BIIB080 FOLLOWING INTRATHECAL ADMINISTRATION IN HEALTHY ADULTS.

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Background: The brain accumulation of tau neurofibrillary tangles (NFTs) has been implicated in several neurodegenerative disorders including primary tauopathies like primary progressive supranuclear palsy and corticobasal degeneration, and in secondary tauopathies like Alzheimer's disease (AD). The regional distribution of tau pathology varies across disorders with clinical phenotype reflecting the brain regions impacted by the aggregation of NFTs. BIIB080 is an antisense oligonucleotide (ASO) that selectively reduces microtubule associated protein tau (MAPT) messenger RNA and thus reduces the synthesis of all forms of tau protein (1). Exploratory results from a Phase 1b study in participants with mild AD demonstrated that BIIB080 reduced aggregated tau pathology below baseline levels across the cortex (2). BIIB080 is currently being studied in a Phase 2 trial in early AD (CT05399888, CELIA). Translatability of these pharmacodynamic findings to other tauopathies with differing cortical and subcortical distributions of tau pathology remains unknown due to limited information regarding the biodistribution of BIIB080 in the brain. The present study

(NCT06454721) was designed to address this gap, with the primary goal of determining the biodistribution of a single dose of BIIB080 within the central nervous system over multiple days. **Methods:** Study participants will include 5 healthy adult volunteers aged 18 to 65 with a BMI between 18 to 30. A radiolabeled form of BIIB080 ([89Zr]Zr-DFO-BIIB080) has been developed which covalently links BIIB080 to deferoxamine (DFO) bound to zirconium-89. The radiolabeled BIIB080 tracer acts as a surrogate for the parent drug, allowing for estimation of BIIB080 distribution in vivo. Participants receive a single dose of up to 100 μg of [89Zr]Zr-DFO-BIIB080 co-administered with a high-dose of BIIB080 in a total of 20 mL of artificial cerebrospinal fluid (CSF) administered via intrathecal injection. Participants are scanned on a total body uEXPLORER PET/CT scanner at 4 hours, 24 hours, 5 days, and 8 days post-dose. Radiotracer activity is quantified as standard uptake values (SUVs) and as percent of injected tracer dose per gram of tissue (%ID/CC) at all PET imaging timepoints across multiple regions of interest in the brain. Enrollment is ongoing; at the time of submission three participants have completed the study. **Results:** Data from the first three volunteers have been evaluated. In all three study participants the [89Zr]Zr -DFO-BIIB080 tracer distributed up the spinal canal and into the cranial cavity. Signal at 4 hours post-dose was predominately in CSF, with subsequent timepoints showing high uptake across cortical grey matter, thalamus, brainstem, and cerebellum. The highest parenchymal signal for all brain regions was observed 24-hours post dose and remained relatively stable at days 5 and 8. Lower uptake was observed in the basal ganglia across all timepoints. No uptake was observed across timepoints in white matter or lateral ventricles. The relative uptake across brain regions was highly consistent across timepoints and across study participants. Peripheral clearance of the tracer is also seen through the kidneys, bladder, and liver. **Conclusions:** This study represents the first in vivo assessment of the distribution of an intrathecally administered ASO within the human central nervous system over multiple days. These preliminary (n = 3) findings with the tracer [89Zr]Zr -DFO-BIIB080 suggest that BIIB080 distributes in a stereotyped manner, with broad distribution throughout the cortical grey matter, brainstem, and cerebellum, with less distribution to deeper brain structures. These results are consistent with the previously observed effect of BIIB080 on tau PET across the cortex in patients with mild Alzheimer's disease (2). Additional forthcoming data will inform on the variability of BIIB080 distribution across individuals.

Keywords: BIIB080, biodistribution, Alzheimer's disease, tau.

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Key takeaway message: BIIB080 distributes in a stereotyped manner, with broad distribution throughout the cortical grey matter, brainstem, and cerebellum.

P167- MONITORING AND PREDICTING AMYLOID THERAPY RESPONSE USING ARTERIAL SPIN LABELLING PERFUSION MRI.

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Background: Treatment guidelines for the amyloid therapies lecanemab and donanemab mandate MRI scans to monitor for amyloid-related imaging abnormalities (ARIA) at regular intervals (1,2). However, no such mandate exists for monitoring treatment response. Arterial spin labelling (ASL) is a non-contrast MRI technique that measures cerebral perfusion (3), which can be readily included in existing ARIA monitoring sessions with little change to workflows. This abstract builds upon prior work (4) to demonstrate the suitability of ASL MRI to track and predict cognitive change during amyloid therapy. **Methods:** Data were collected from 13 patients (5M 8F, aged 73.4 ± 8.6 years, 11 on lecanemab, 2 on donanemab) undergoing amyloid therapy at Weill Cornell Medicine, New York, USA. T1-weighted structural and ASL images were acquired at baseline and during ARIA monitoring sessions on GE 3T scanners (SIGNA Architect, Discovery MR750). Pseudo-continuous (PCASL) was used with a 1.8s label duration, 2.025s post-label delay, 3D readout and TR/TE = 5.338s/53.6ms. Cognition was assessed using MOCA before and during treatment, with change in MOCA used to measure treatment response. MRI scans were paired with the closest cognitive exam; at baseline the mean time difference between an MRI scan and MOCA exam was 271 days, and at follow up 92 days. T1w images were processed using recon-all-clinical from FreeSurfer 7.4.1 to segment the cortex and subcortical structures according to the Desikan-Killiany-Tourville (DKT) atlas. ASL images were processed using the QASL pipeline (Quantified Imaging, UK), a derivative of FSL's BASIL to quantify cerebral blood flow (CBF) (5,6). To mitigate the effect of demographics on baseline CBF, each subject's map was normalised to a value of 60 units using a proprietary reference region method, analogous to normalising PET data to obtain SUVR using a "most-spared region" approach (7). Pearson's correlation was calculated between MOCA change and mean whole-brain cortical CBF change. To provide a comparator based on T1w structural MRI, the correlation was also calculated against change in cortical volume normalised by intracranial volume (NCV). Finally, baseline regional CBF or regional NCV was correlated against cognition change to assess the ability of each imaging technique to predict treatment response. For all correlations, statistical significance was set at $p = 0.01$ without correction for multiple comparisons. **Results:** Change in mean whole-brain cortical CBF correlated significantly with change in cognition ($r=0.90$, $p<0.001$), whereas the correlation with whole-brain NCV was insignificant ($r=0.11$, $p=0.726$). Among the 62 cortical structures in the DKT atlas, the right entorhinal cortex showed the strongest correlation between baseline CBF and change in MOCA ($r=0.75$, $p=0.003$). For baseline NCV, the strongest correlation was observed in the left insula cortex ($r=0.58$, $p=0.036$). **Conclusions:** In a small cohort receiving amyloid therapy, change in cortical CBF from ASL MRI showed excellent correlation with the change in MOCA during the course of treatment. Further, right entorhinal cortex CBF at baseline correlated well with future cognition change, demonstrating that ASL MRI may be used to predict treatment response. In both cases, CBF measures produced stronger correlations than structural measures, demonstrating the extra clinical value of ASL MRI compared to standard-of-care T1w structural imaging. Further work is needed to validate these findings on a larger cohort, with more regular scans and cognitive assessment, with a view to establishing ASL MRI as a valuable tool for monitoring and predicting treatment outcomes.

Conflicts of interest: The authors have no conflicts to disclose.

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Key takeaway message: Arterial spin labelling MRI was able to monitor cognitive change on amyloid therapy with a very high degree of correlation and to predict treatment response from baseline.

P171- DISCORDANCE BETWEEN VISUAL AND QUANTITATIVE AMYLOID PET IN NEARLY 500 REAL-WORLD CLINICAL CASES.

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Introduction: The Washington University Memory Diagnostic Center (MDC) in St. Louis, Missouri, sees ~3,500 patients annually with memory and thinking concerns. Testing for Alzheimer's disease (AD) pathology is performed via blood tests, cerebrospinal fluid tests, or amyloid PET. Discordance between amyloid PET visual read and quantitative methods (that yield a Centiloid value) is increasingly recognized as a clinically significant issue in AD diagnostics and therapeutic decision-making, particularly with the expansion of anti-amyloid therapies. Accurate identification and quantification of amyloid pathology is essential for patient selection and monitoring. Current guidelines recommend visual interpretation as the standard approach for interpreting amyloid PET scans, with quantitation considered an adjunct in cases that are challenging or equivocal. The present study aims to systematically evaluate the frequency, causes, and clinical significance of discordance between visual and quantitative amyloid PET interpretation in a large, real-world memory clinic cohort. **Methods:** Data on demographic, clinical information, visual interpretation, and biomarker results were retrospectively collected from electronic health records. Amyloid PET scans were interpreted visually by trained radiologists and quantified using the standardized Centiloid (CL) scale. Discordance was defined as cases where visual reads and CL-based classification using autopsy-validated thresholds did not agree (negative defined as <25 CL, positive defined as >25 CL). Patients with CL between 10 and 25 are considered an intermediate zone or "grey zone" of cerebral amyloid deposition. This group is clinically significant because discordance between clinical symptoms and biomarker status is a common phenomenon. A logistic regression analysis was performed, considering the visual read outcome (positive/negative) as the outcome with the CL status (<25 or >25 CL), age at PET scan, and sex as predictors. **Results:** Between July 2021 and March 2025, n=446 patients underwent an amyloid PET scan at MDC. Of these patients, n=99 subsequently initiated anti-amyloid therapy with lecanemab. The visual and CL-based status agreed in 424 of 446 patients (95%). Centiloid values above 25 were a highly significant predictor of positive visual amyloid PET reads (odds ratio 190.08, $p < 2e\text{-}16$). Age and sex were not independently associated with visual read outcome after adjustment for CL status. The causes of the 22 cases with discordant visual and quantification status include incorrect visual PET interpretation by the reader and a change of visual assessment when quantification was available (n=9). Technical quantification errors (n = 5) were attributed to incorrect region of interest placement, often due to prominent bone structure or parotid gland activity, head malpositioning, scalp shape, and marked ventriculomegaly. A combination of a low noise-to-image ratio and brain atrophy resulted in suboptimal scan images (n = 5). Discordant cases with CL in the intermediate amyloid pathology (CL 10–25) occurred in three cases. This intermediate or "gray zone" group is clinically important for identifying individuals at risk for progression, but borderline biomarker results increase diagnostic uncertainty due to asynchronous and heterogeneous biomarker trajectories in early Alzheimer's disease. Notably, this group may also have a higher rate of discordance with amyloid status, as determined by cerebrospinal fluid or blood-based tests. **Conclusions:** This study demonstrates high concordance between visual and quantitative (Centiloid-based) amyloid PET status in a large, real-world clinical cohort. Age and sex were not independently associated with visual read outcome after adjustment for CL status. This reinforces the clinical utility of adequate reader training for visual assessment of amyloid deposition PET, as high interrater agreement can be achieved among experienced readers. Quantification plays an adjunctive role in supporting visual assessment, particularly in cases with borderline or ambiguous findings, resulting in increased confidence for the reader and occasionally leading to changes in interpretation. Centiloid values above 25 were a highly significant predictor of positive visual amyloid PET reads. Despite the role of quantification methods, adequate visual training is required to identify potential quantification errors, including but not limited to in-region-of-interest placement, head shape, positioning, and marked atrophy. In summary, visual interpretation remains the clinical standard; however, the incorporation of quantitative analysis improves confidence and inter-reader agreement in equivocal cases, which is increasingly relevant as anti-amyloid therapies require the determination of amyloid status for eligibility and monitoring purposes.

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P173- HARMONIZATION VIA SMOOTHING TO A COMMON SPATIAL RESOLUTION YIELDS MODEST BENEFITS IN AMYLOID PET.

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Background: Harmonization of amyloid PET scans via smoothing to a common spatial resolution has been recommended for multi-centre Alzheimer's disease clinical trials, to reduce the variability of key eligibility or efficacy endpoints (1,2). This is typically achieved via scanning the Hoffman brain phantom (3), which entails significant financial and logistical burden. Moreover, computation of the site-specific smoothing kernels is non-trivial. There is limited evidence that this harmonization approach, when applied to real human PET data, justifies its considerable overhead. Our objective was to evaluate the effects of harmonization via smoothing to a common spatial resolution on SUVRs derived from humans, using AMYPAD's amyloid PET data (4,5). **Methods:** The available data comprised 632 [18F]florbetaben (FBB) scans (11% visual read 'positive') acquired across eleven sites from 368 participants (184 with follow-up); and 691 [18F]flutemetamol (FLUT) scans (27% 'positive') acquired across ten sites from 480 participants (211 with follow-up). Contemporaneous T1-weighted magnetic resonance imaging (T1w-MRI) was available for each participant. All had Clinical Dementia Rating (CDR) global score ≤0.5. The smoothing kernels required to yield common spatial resolution were provided by Shekari M, et al. (AMYPAD (2); 1.3–3.4 mm full-width at half maximum for FBB; 2.0–3.4 mm for FLUT). We computed composite cortical standardized uptake value ratios (SUVRs) via a T1w-MRI-guided analysis pipeline, using the whole cerebellum as reference region. Pipeline outputs were visually inspected to ensure quality. The analyses were applied separately to non-smoothed and harmonized (i.e., smoothed) PET scans. The SUVR threshold that best predicted visual read was calculated via maximal Youden's J statistic (sensitivity + specificity – 1; (6). We examined the influence of the 'Site', 'Smoothing', and their interaction on SUVR via separate linear mixed effects models

for each tracer, controlling for participant age, APOE4 status, CDR global score, Mini Mental State Examination (MMSE) total score, sex, and timepoint (e.g., 24-months' follow-up). We included a subject-level random intercept, and a 'Site'-by-'Smoothing' interaction effect to examine any changes in 'Site' effects by the employed harmonization. We tested the fixed effects for statistical significance using a Type II Wald chi-square test, and the semi-partial (marginal) R2 was computed as a measure of effect size. For each scan, we computed the absolute and percentage differences between SUVRs derived from harmonized and non-smoothed scans. We also computed the coefficient of variation (CoV) of ΔSUVR/year, and the percentage of longitudinal outliers (±1.5 x median ΔSUVR/year). **Results:** For FBB, there were significant main effects of 'Site' ($p=0.002$, $R2=0.009$) and 'Smoothing' ($p<0.001$; $R2=0.001$), and a significant interaction between these predictors ($p<0.001$; semi- $R2=0.004$). To examine the interaction effect, simple effects of 'Site' were tested within each level of the smoothing factor using joint F-tests on the 'Site' term. These revealed an effect of 'Site' on both the non-smoothed ($F=4.876$; $p<0.001$) and harmonized data ($F=2.502$; $p=0.012$), which was significantly smaller in the latter. The semi-partial R2 of 'APOE4 status', 'Age', 'CDR global', and 'Sex' were 0.130, 0.072, 0.002, and 0.001, respectively. For FLUT, there were significant main effects of 'Site' ($p<0.001$, $R2=0.026$) and 'Smoothing' ($p<0.001$; semi-partial $R2=0.001$), and a significant interaction between these predictors ($p<0.001$; $R2=0.004$). As for FBB, joint F-tests revealed an effect of site of both the unsmoothed ($F=6.713$; $p<0.001$) and harmonized ($F=5.302$; $p<0.001$) data that was smaller in the smoothed data. The semi-partial R2 of 'APOE4 status', 'Age', 'Sex', 'CDR global', and were 0.069, 0.078, 0.006, and 0.001, respectively. Harmonization increased the FBB SUVR by 0.04±0.03 (4.53±3.27%), i.e. approximately seven centiloids, and the FLUT SUVR by 0.03±0.04 (3.25±3.68%), i.e. approximately four centiloids. The SUVR thresholds that were most predictive of visual read were 1.130 (AUC=0.974) and 1.122 (AUC=0.949), respectively. 'Borderline' FBB SUVRs, i.e. those within the range threshold SUVR±2.5%, were increased by 0.029 ±0.0019, whereas 'borderline' FLUT SUVRs were increased by 0.026 ±0.016. Harmonization increased the CoV of ΔSUVR/year from 212% to 225% for FBB, but decreased it from 467% to 216% for FLUT. It reduced the percentage of longitudinal outliers from 12.50 to 10.87% for FBB, but increased it from 5.21 to 7.11% for FLUT. **Conclusions:** Our findings suggest harmonization via smoothing to a common spatial resolution reduces, but does not eliminate, site-related variability in amyloid PET. It may slightly increase statistical power in longitudinal trials, by reducing the CoV and/or prevalence of outliers. Investigators should be mindful of a potential impact on quantitative reads and thus eligibility. Future work will determine whether post-hoc statistical methods (7) yield greater benefit.

Keywords: Amyloid, harmonization, Hoffman Brain Phantom, Positron Emission Tomography, smoothing.

Clinical Trial Registry: 2018-002277-22 (www.clinicaltrialsregister.eu).

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Data Deposition: https://zenodo.org/records/7962925.

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Key takeaway message: Harmonization via smoothing to common spatial resolution reduces, but does not eliminate, site-related variability in amyloid PET. It may slightly increase statistical power in longitudinal trials, by reducing the CoV and/or prevalence of outliers.

P174- EXTENDING THE CENTAUR STANDARDIZATION FRAMEWORK TO THE VOXEL LEVEL: PRELIMINARY VALIDATION USING [^{18}F] FLORTAUCIPIR AND [^{18}F] MK-6240.

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Background: Tau PET imaging enables in vivo quantification of tau neurofibrillary tangle pathology in Alzheimer's disease (AD) and plays an increasingly important role in clinical trials for disease staging and outcome assessment. To facilitate cross-study comparisons, particularly in trials using different tau PET tracers, the Critical Path for Alzheimer's Disease (CPAD) Consortium introduced the CenTauR approach, an ROI-based standardization framework designed to harmonize quantitative tau PET metrics. While this method has shown promise for harmonizing tau PET standardized uptake value ratios (SUVR) measured in pre-specified regions of interest (ROI), the application of the CenTauR approach for voxel-based harmonization remains unexplored. In this study, we aim to extend the CenTauR framework to the voxel level and conduct a preliminary evaluation of its accuracy by using a head-to-head tau PET cohort of participants scanned with both [^{18}F]flortaucipir and [^{18}F]MK-6240. **Methods:** Fifteen participants—9 cognitively unimpaired individuals, 1 with mild cognitive impairment, and 5 with Alzheimer's disease dementia—were recruited from the University of Pittsburgh Alzheimer's Disease Research Center and affiliated studies. The included participants underwent both [^{18}F]flortaucipir and [^{18}F]MK-6240 PET imaging within an average interval of 26 days (maximum 54 days) between scans. Tau PET scans were converted to standardized uptake value ratio (SUVR) images using the inferior cerebellar cortex as the reference region. SUVR images were then transformed into the CenTauR scale using a Joint Propagation Model (JPM)-based conversion equation derived for the Universal CenTauR ROI (Leuzy et al., Alzheimer's Dement., 2024; Villemagne et al., Alzheimer's Dement. (Amst),

2023). This equation, originally defined for a specific ROI, was applied voxelwise to the entire spatially normalized tau PET image. The Universal ROI was selected for transformation because it is the largest among the CenTauR-defined regions, thereby averaging out potential variations in intercepts and slopes across regions and reducing bias in the resulting voxelwise harmonized images. To evaluate the accuracy of the transformation, we calculated the percent difference in cortical CenTauR values across the entire cortex and assessed the spatial similarity between binary maps of elevated tau burden. Elevated tau was defined as voxel values exceeding 20 CenTauRs, a threshold that corresponds to a visually positive [^{18}F]flortaucipir PET scan when applied to the Universal CenTauR ROI. **Results:** The mean difference in cortical voxelwise CenTauR values between head-to-head [^{18}F]flortaucipir and [^{18}F]MK-6240 was -16 CenTauRs ([^{18}F]flortaucipir − [^{18}F]MK-6240). After applying a global threshold of 20 CenTauRs, the resulting segmentations showed relatively good concordance, with an average Dice Similarity Coefficient of 0.73 (minimum: 0.32; maximum: 0.86). **Conclusions:** Voxelwise transformations demonstrated good concordance between [18F]flortaucipir and [18F]MK-6240 and preserved quantitative accuracy across multiple CenTauR-defined regions. These preliminary results support the feasibility of extending the CenTauR standardization framework to the voxel-level. Future work will include validation using additional head-to-head datasets with other tau PET radiotracers.

Key takeaway message: Extending the CenTauR framework to voxel-level tau PET data shows promising accuracy and concordance across tracers, supporting its potential for harmonized, ROI-independent analyses in Alzheimer's disease clinical trials and research.

P175- EVALUATING THE EFFECTS OF NON-LINEAR SUVR TRANSFORMATIONS FOR HARMONIZATION ON STATISTICAL POWER IN LONGITUDINAL TAU-PET STUDIES.

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Background: The increased availability of tau-PET radiotracers has supported their growing use in Alzheimer's disease (AD) clinical trials. To allow comparability of quantitative results across tracers, several harmonization techniques have been recently introduced, such as the CenTauR scale. The harmonization approaches vary in their mathematical modeling, with the CenTauR scale employing linear transformations, while others adopt non-linear mappings to better describe inter-tracer relationships. Although non-linear transformations may more accurately represent inter-tracer dependencies, they can also influence the statistical characteristics of the data, potentially affecting the ability to detect treatment effects in clinical trials using tau PET as an end point. In this work, we investigate how a previously proposed non-linear transformation affects statistical power in longitudinal tau-PET studies designed to detect a therapeutic impact on tau accumulation. **Methods:** We analyzed two distinct cohorts. The first cohort included 71 amyloid-β–positive (Centiloid >24), cognitively impaired participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) with available [^{18}F]flortaucipir tau-PET scans at baseline and 1-year follow-up (41 with mild cognitive impairment, 30 with mild Alzheimer's dementia). The second cohort consisted of 342 cognitively unimpaired, amyloid-β–positive individuals from the A4 Study—a clinical trial focused on preclinical Alzheimer's disease—with baseline and 72- or 84-week follow-up tau-PET scans. These cohorts were used to derive key parameters for power calculations, including baseline SUVR distributions, mean longitudinal SUVR change, and the correlation between baseline values and change. Using these empirical estimates, we performed simulations (N = 10,000 trials) to assess the statistical power to detect varying levels of treatment effect (50%, 75%, and 100% slowing of tau accumulation) in a hypothetical trial, comparing the performance of raw SUVR values against SUVR values transformed using a previously proposed non-linear function. **Results:** The average baseline SUVR was 1.66 in the ADNI cohort and 1.25 in the A4 study. Across both cohorts, applying the non-linear SUVR transformation led to a consistent reduction in statistical power compared to using raw SUVR. In the ADNI cohort, the difference in power was modest, with a maximum decrease of approximately 2%, whereas in the A4 study, the reduction was more pronounced, up to 25%. Correspondingly, estimated effect sizes were slightly diminished in ADNI when using the non-linear transformation (50% slowing: d = 0.0996 for SUVR vs d = 0.0979; 100% slowing: d = 0.1995 for SUVR vs d = 0.1956), while the drop in effect size was more substantial in the A4 study (50% slowing: d = 0.2518 for SUVR vs d = 0.2032; 100% slowing: d = 0.5010 for SUVR vs d = 0.4066). The non-linear transformation led to discordant statistical conclusions (i.e., p-value crossing the 0.05 threshold) in 4.5% of simulated trials based on ADNI and in 5.9% based on A4. **Conclusions:** Non-linear transformations of tau-PET SUVR data may reduce the statistical power to detect treatment effects, particularly in trials targeting preclinical Alzheimer's disease where baseline SUVR values fall within non-linear regions of the transformation. Future studies should further investigate the impact of these transformations across diverse trial populations and study designs.

Keywords: Alzheimer's disease, tau, PET, harmonization, longitudinal, non-linear, statistical power, clinical trials.

Disclosures: Alexis Moscoso is consultant for the Critical Path for Alzheimer's Disease (CPAD) Consortium. Antoine Leuzy is a consultant for CPAD and Enigma Biomedical Group. Hartmuth Kolb is a consultant for Enigma Biomedical Group. Victor L. Villemagne has received research grants from NHMRC (GNT2001320), the Aging Mind Foundation (DAF2255207), and NIH 2P01AG025204-16) and is and has been a consultant or paid speaker at sponsored conference sessions for Eli Lilly, Life Molecular Imaging, Ace Barcelona, BRI Japan, and AC Immune. Gregory Klein is a full-time employees of Hoffmann-La Roche Ltd. Diane Stephenson, Nadine Tatton, and Yashmin Karten reported that their organization (Critical Path Institute) received research funding via membership fees paid by members of the CPAD Consortium outside the submitted work. Christopher C Rowe has received research grants from the National Health and Medical Research Council, Enigma Australia, Biogen, Eisai and AbbVie. He is on the scientific advisory board for Enigma/Meilleur Technologies and has consulted for Prothena, Eisai, Roche and Biogen Australia. The other authors report no competing interests.

Key takeaway message: Non-linear transformations of tau PET SUVR data can reduce statistical power in clinical trials, particularly in preclinical Alzheimer's disease, highlighting the need to carefully evaluate harmonization methods when analyzing treatment effects.

P177- FUNCTIONAL NETWORK SEGREGATION AS A NEURAL CORRELATE OF COGNITIVE RESERVE IN ALZHEIMER'S DISEASE SPECTRUM.

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Background: Cognitive reserve (CR) refers to the phenomenon in which individuals demonstrate differing levels of cognitive performance despite similar degrees of underlying neuropathology. It is thought to reflect compensatory mechanisms that help mitigate clinical symptoms. Among proposed neural correlates of CR, functional network segregation—the degree to which brain networks maintain distinct within-network communication—has gained attention. This network property may support cognitive reserve by preserving efficient, specialized processing despite neurodegeneration. **Objective:** This study aimed to evaluate whether functional network segregation modulates the association between brain volume and cognitive function, and to determine whether this effect differs between cognitively unimpaired (CU) and impaired (CI) populations. **Methods:** A total of 413 participants in the BICWALZS cohort were included in the study, including 60 cognitively unimpaired (CU), 353 cognitively impaired (CI). Structural brain reserve was indexed by total brain volume (z-scored), and functional network segregation was computed from resting-state fMRI using the segregation index derived from within- and between-network connectivity. Cognitive performance was assessed using the Clinical Dementia Rating Sum of Boxes (CDR-SB), reflecting functional status, and the Mini-Mental State Examination (MMSE), representing global cognitive function. Participants were divided into high and low segregation groups based on a median split of the total segregation score. To examine whether functional network segregation moderates the relationship between structural brain reserve and cognition, we performed linear regression models including interaction terms between brain volume and segregation. All models were adjusted for age, sex, and years of education. Primary analyses were conducted in the total sample, and stratified analyses were additionally performed in CU and CI subgroups. **Results:** The high segregation group (average age: 71.6 $\pm$ 7.3 years) was younger than the low segregation group (average age: 74.1 $\pm$ 6.5 years) ($p < 0.001$). A higher level of education (8.1 $\pm$ 4.9 years) was reported by the high segregation group than by the low segregation group (7.2 $\pm$ 4.7 years) ($p < 0.05$). In the total sample, higher brain volume was significantly associated with better cognitive function as measured by both CDR-SB and MMSE ($\beta = –0.52$, $p = 0.001$ for CDR-SB; $\beta = 0.41$, $p = 0.010$ for MMSE). Functional segregation showed a marginal association with better CDR-SB ($p = 0.066$), and a significant interaction effect was observed between brain volume and segregation ($\beta = 0.13$, $p = 0.035$), indicating that the protective effect of brain volume was moderated by segregation. Subgroup analysis revealed that this interaction was significant in the CI group ($\beta = 0.17$, $p = 0.011$), where both brain volume ($\beta = –0.65$, $p < 0.001$) and segregation ($\beta = –0.17$, $p = 0.016$) were independently associated with better cognitive outcomes. No significant associations or interactions were observed in the CU group. For MMSE, brain volume remained a significant predictor in the CI group ($\beta = 0.48$, $p = 0.007$), but no significant interaction with segregation was observed ($p = 0.240$). **Conclusions:** Our results demonstrate that functional network segregation moderates the relationship between brain volume and functional outcome, as measured by the CDR-SB, specifically in individuals with cognitive impairment. In this group, both higher brain volume and higher segregation independently predicted better functional status, and their interaction revealed that segregation may buffer the clinical impact of brain atrophy. These findings support the role of functional network as a meaningful contributor to cognitive reserve, particularly for functional preservation in the cognitively impaired stage of the Alzheimer's disease spectrum.
Key takeaway message: Functional network segregation moderates the relationship between brain volume and cognition, suggesting it may serve as a neural substrate of reserve, particularly for functional preservation in cognitively impaired individuals.

P178- LOWER ANTEMORTEM [18F] FLORTAUCIPIR PET RETENTION IN MALES AND OLDER INDIVIDUALS IS EXPLAINED BY LOWER POSTMORTEM TAU TANGLE DENSITY.

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Background: Older age and male sex have been associated with lower Tau-PET uptake in symptomatic Alzheimer's disease. We investigated the PET-to-neuropathological correlates of age- and sex-effects on tau in independent PET (N=672), autopsy (N=945), and PET-to-autopsy (N=85) analyses. **Methods:** Tau-PET-analyses included amyloid-positive participants with MCI or dementia who underwent [18F] flortaucipir-PET. Autopsy-analyses included MCI or dementia cases with moderate-to-frequent CERAD scores and available Braak and tangle density data. PET-to-autopsy-analyses included cases who had undergone Tau-PET during life, died, and had undergone autopsy, including Braak staging (PET-to-post-mortem-interval: 9.3±15.4 months). In independent PET- and autopsy-analyses, we investigated age- and sex-effects on Tau-PET, Braak-V/VI-level tau neuropathology and tangle density. In PET-to-autopsy analyses, we assessed the correspondence of antemortem Tau-PET with postmortem Braak-V/VI neuropathology stratified for age (median-split at 83y) and sex, as well as associations between Tau-PET and tangle density according to age and sex. **Results:** In PET-analyses (age: 71.9±8.2, 52.8% male), older age and male sex were associated with a lower prevalence of Tau-PET-positivity (OR=0.94, p<0.001 and OR=0.43, p<0.001, respectively) and lower Tau-PET SUVr (β=-0.34, p<0.001 and β=-0.37, p<0.001). In autopsy-analyses (age: 82.7±7.9, 54.6% male), we replicated our Tau-PET results: older age and male sex were associated with a lower prevalence of Braak-V/VI neuropathology (OR=0.97, p<0.001 and OR=0.67, p=0.005). Among Braak-V/VI autopsy cases (n=598), older age (β=-0.32, p<0.001), but not male sex (β=-0.10, p=0.23), was associated with lower tangle density. In the PET-to-autopsy-analyses (age: 81.7 ±9.2, 52.9% male), the specificity of Tau-PET for detecting Braak-V/VI tau was excellent (100%) across age-stratified (stratified at the median age of 83 years) and sex-stratified groups. However, the sensitivity of Tau-PET for detecting Braak-V/VI tau decreased with age (sensitivity <83y: 92% versus ≥83y: 42%) and in males (sensitivity females: 85% versus males: 48%). Older and male participants with Braak-V/VI neuropathology showed lower Tau-PET SUVr (age: β=-0.46, p=0.003; sex: β=-0.97, p=0.001), and in the same individuals, older participants with Braak-V/VI neuropathology also showed trend-level lower tangle density (β=-0.31, p=0.053). The lack of age/sex-interactions indicate that the relationship between Tau-PET and tangle density is consistent across ages and sexes (p>0.05). **Conclusions:** Comprehensive and independent PET, autopsy, and PET-to-autopsy analyses demonstrate that the associations between older age and male sex with lower Tau-PET uptake and prevalence are explained by lower tangle densities at autopsy. Tau-PET closely reflects postmortem tangle density, which explains the lower sensitivity of Tau-PET to detect Braak-V/VI tau at lower densities frequently observed in older and male individuals.
Keywords: Tau, PET, Alzheimer's disease, age, sex.
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Key takeaway message: Tau-PET SUVr closely reflects postmortem tangle density, which explains the lower sensitivity of Tau-PET to detect low-density Braak-V/VI tau at older age and in males.

P179- TOWARDS CORRECTING FOR PSEUDO ATROPHY IN MONOCLONAL ANTIBODY CLINICAL TRIALS ON ALZHEIMER'S DISEASE: A MODEL OF AMYLOID-REMOVAL RELATED ATROPHY PREDICTS TREATMENT BENEFIT.

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Background: In clinical trials of monoclonal antibody (MAB) drugs for Alzheimer's Disease (AD), a phenomenon coined amyloid-removal related pseudo atrophy (ARPA) has been described where the active treatment arm apparently experiences more atrophy than the placebo arm. The biological mechanism behind this process is yet to be established, but current thinking is that excess apparent/pseudo atrophy in the active arm is caused by dissolution of amyloid plaques and their conjoining gliosis-related or inflammation-related supportive tissue. We present a mathematical model for atrophy biomarker outcomes in clinical trials as a function of the level of amyloid removal. **Methods:** We propose the following ordinary differential equation for brain volume: $dV(t)/dt=-\alpha(r+aC(t)V(t)$, where r is the rate of amyloid-independent atrophy, C(t) is brain amyloid load in Centiloids, a is the per-Centiloid increase in atrophy due to amyloid, and $\alpha=R_P/(r+aC_P$ (t) is a model calibration factor for specific clinical trial relative to observed placebo arm atrophy rate R_P in a clinical trial of interest. The parameters r and a are estimated from observational data (ADNI, N=395; A+ n=215, A− n=180) using the following linear mixed model for participant i and visit j: V_{ij} $(t)=V_0-rt_{ij}-aC(t_{ij})t_{ij}+\beta_{age}age_i+\beta_{sex}sex_i+\beta_{ICV}ICV_i+b_{0i}+b_{1i}t_{ij}+\varepsilon_{ij}$ which includes fixed effects for covariates (age, sex, intracranial volume ICV) and mixed effects for intercept and gradient (atrophy rate). On the timescale of a clinical trial, the exponential solution to our ODE is well-approximated by the first-order (linear) term. This can be expressed as the following equation for amyloid-dependent volume change at t weeks since baseline: $V(t)=V(t)-V_0=-\alpha(r+aC_{avg})t$ where mean Centiloid value over trial visits C_avg is a necessary approximation of C(t) because continuous amyloid PET monitoring is not possible and individual-level patient data is not available for these trials. This limitation may be removable in the future if replaced by fluid markers as a proxy for brain amyloid level. Experiments: We generate volumetric biomarker curves for whole brain volume V (t) in both placebo and active treatment arms in anti-amyloid trials from recent years where pseudo atrophy was reported: donanemab, lecanemab, aducanumab, gantenerumab. We report end of trial whole brain volume difference between active treatment and placebo. **Results:** Model parameters suggest that amyloid-independent whole-brain atrophy occurs at the rate of r=6.6 mL/year (approx 0.5%/year), and the presence of brain amyloid increases atrophy rate by a=0.063 mL/year per Centiloid, which is approximately 1% of r per Centiloid. These numbers are consistent with the literature. Our model-calculated end of trial volume difference (treatment minus placebo) and observed amyloid reduction in recent trials were: CLARITY-AD 2.5 mL (lecanemab; 78→19 CL); TRAILBLAZER-ALZ-2 5.5 mL (donanemab; 103→16 CL); EMERGE 3.8 mL (aducanumab; 76→14 CL); ENGAGE 3.2 mL (aducanumab; 77→23 CL); GRADUATE-I 5.8 mL (gantenerumab; 94→28 CL); GRADUATE-II 3.6 mL (gantenerumab; 96→40 CL). **Conclusions:** Our model of amyloid-dependent brain atrophy predicts treatment benefit on whole brain volume in key clinical trials of amyloid-removing monoclonal antibodies. We interpret this as "real atrophy" and an important step towards understanding and resolving the issue of amyloid-removal related pseudo atrophy.

Keywords: Pseudo atrophy, amyloid removal, disease progression modelling, phase 3, anti-amyloid.

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Key takeaway message: We present a model of amyloid-related atrophy that predicts treatment benefit on whole brain volume in monoclonal antibody trials that reported pseudo atrophy. This is a step towards understanding pseudo atrophy.

P180- RECOMMENDATIONS FOR DTI HARMONIZATION IN MULTICENTER CLINICAL TRIALS.

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Background: White matter (WM) degeneration is a feature of mild cognitive impairment (MCI) and Alzheimer's disease (AD) pathophysiology. Diffusion tensor imaging (DTI) characterizes WM integrity as well as microstructural changes occurring in the grey matter (GM). Elevated mean diffusivity (MD) and decreased fractional anisotropy (FA) in the WM is consistently observed in prodromal AD, and in cognitively normal elderly who progress to MCI (1). Large multi-site clinical trials are challenged to overcome variability induced by different MRI manufacturers and models to maximize the sensitivity of DTI as an endpoint. To mitigate these differences, ComBat (Correcting for Batch Effects in Multivariate Data) harmonization can be applied which uses empirical Bayes method to remove site and scanner differences, while preserving between-subject biological variability (2). However, ComBat parameters depend upon on the sample size, vary when new data is introduced, and require a representative dataset from each site for parameter estimation, ideally with a normal population distribution balanced for covariates such as age and gender. This complicates its utility in a

clinical trial setting where sites continuously acquire data for years and harmonization parameters could therefore not be finalized until study completion. To mitigate this issue, we tested the impact of defining a reference site with robust data to which all data from other sites can be harmonized, obviating the need for training a new model when data from new sites and timepoints is acquired. **Methods:** 3T DTI scans from ADNI3 and ADNI4 acquired on multiple Siemens (30 AD, 25 healthy controls (HC), GE (20 AD, 18 HC) and Philips (28 AD, 15 HC) scanners were used. A standard DTI processing pipeline was employed, involving eddy-current correction, skull stripping, tensor estimation using linear least square fit, followed by computation of fractional anisotropy (FA) and mean diffusivity (MD). The DTI FA maps were registered to JHU atlas (3) using ANTs (advanced normalization tools) SyN (symmetric normalization) deformable registration (4), and average values of FA and MD from each of the 48 regions defined on the atlas were computed. The neuro-harmonize tool (5) was used to compare the impact of various strategies of training ComBat parameters: training parameters on HC and applying to AD subjects (ideal situation), training on AD subjects only (applicable at end of study in a clinical trial setting), and training using a reference site and applying to all sites (most practical in a clinical trial setting). To verify the impact of ComBat harmonization, FA and MD in a sample region (genu and splenium of the corpus callosum (CC) were used and differences across sites were assessed using ANOVA, before harmonization and after harmonization. Besides, to verify whether such normalization may impact longitudinal sensitivity, means of difference from baseline was assessed using t-test between non-harmonized and harmonized data. **Results:** Non-harmonized data demonstrated an overall significant p-value ($p<0.05$) in CC FA and MD means between sites, suggesting that batch effects related to site/scanner did exist. Following harmonization on the AD group, CC means from different sites demonstrated non-significant p-value ($p>0.4$). When a reference site was employed for harmonization, a similar result was obtained ($p>0.8$). Moreover, longitudinal effects were not sacrificed as the change from baseline between non-harmonized and harmonized data was non-significant ($p >0.6$), for both harmonization strategies. In practice, while methodologically ideal, training of ComBat parameters based only on HC data was infeasible, as not all sites that scanned AD also scanned HCs. **Conclusions:** The utility of a reference site for harmonization, and illustrative parameters on reference datasets spanning multiple age groups have been released by a recent study (6). However, MRI acquisition protocols as well as processing pipelines for each study may not match these reference studies. Therefore, using a reference site within each study could be the way forward. We demonstrated that using a reference site can mitigate some issues currently faced while using ComBat, as iterative retraining of harmonization parameters is not required. Moreover, the harmonization parameters are not biased by noise otherwise induced from sites providing unreliable data. Future work will include investigating the impact of age, gender and clinical status on reference-site harmonization toward its broader application in clinical trials.

Keywords: Diffusion MRI, harmonization, ComBat. **Disclosures:** All authors are full-time employees of Clario.

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Key takeaway message: Iterative retraining of harmonization parameters can be eliminated by using a reference site in ComBat harmonization and is a step forward in harmoizing multi center clinical trial imaging data.

P181- ASSOCIATIONS OF AMYLOID-BETA WITH ENTORHINAL CORTICAL THICKNESS AND EPISODIC MEMORY AMONG A DIVERSE OLDEST-OLD COHORT: THE LIFE AFTER 90 STUDY.

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Background: While associations of amyloid-beta (Aβ) with regional cortical thickness and cognition have been well-documented among the aging population, little is known about these associations in the oldest-old (90+ year olds). Moreover, no previous studies examined the effects of Ab on neurodegeneration and memory in ethnoracially diverse oldest-old populations. The entorhinal cortex, an important structure for memory and a gateway to the hippocampus, is one of the earliest regions to show structural changes in Alzheimer's disease (AD). Here, we tested whether Aβ is associated with entorhinal cortical thickness and verbal episodic memory, and if these associations differ across racial/ethnic groups and by sex/gender. **Methods:** We included participants from LifeAfter90, a multiethnic cohort of individuals aged 90 years and older. T1-weighted images from 3T MRI were acquired to measure left, right, and average entorhinal cortical thickness. Global Aβ was assessed with amyloid-PET, using AV45 and a standard SUVR analysis with cerebellar gray matter as the reference region. We assessed verbal episodic memory with the Spanish and English Neuropsychological Scales. Using linear regressions, we tested the main effects of global Aβ on entorhinal cortical thickness and verbal episodic memory. We then tested these associations when stratified by race/ethnicity and by sex/gender. Linear regression models were adjusted for age at PET and sex/gender, or only by age at PET when stratified by sex/gender. Lastly, we tested whether entorhinal thickness mediates the association between global Aβ and verbal episodic memory. Models testing associations with verbal episodic memory were further adjusted for years of education and the time interval between PET acquisition and cognitive evaluation. **Results:** Participants (N=259) had a mean age of 93.1 + 2.04 (range: 90.4-101.02), 56.4% were women, and self-identified race/ethnicity were 26.3% Asian, 24.3% Black, 21.1% Latinx, and 28.2% White. Overall, higher Aβ was associated with lower right entorhinal cortical thickness (b=-0.376, b=-0.157, 95% CI [-0.698, -0.054], p=0.022). When stratified by race/ethnicity, only Black participants demonstrated an association between higher Aβ and lower average and right entorhinal cortical thickness (average: b=-0.665, b=-0.268, 95% CI [-1.326, -0.005], p=0.048; right: b=-1.185, b=-0.382, 95% CI [-2.001, -0.368], p=0.005). When stratified by sex/gender, only men showed an association between higher Aβ and lower right entorhinal cortical thickness (b=-0.677 b=-0.302, 95% CI [-1.107, -0.247], p=0.002). Overall, higher Aβ was associated with lower verbal episodic memory (b=-0.685, b=-0.149, 95% CI [-1.300, -0.071], p=0.029). When stratified by race/ethnicity, higher Aβ was associated with lower episodic memory only in Latinx participants (b=-1.266, b=-0.314, 95% CI [-2.529, -0.002], p=0.050). In a mediation model, there was an indirect effect where right entorhinal thickness fully mediated the relationship between global Aβ and verbal episodic memory (b=-0.157, 95% CI [-0.328, -0.020]). **Conclusions:** Higher Aβ was associated with lower entorhinal thickness, particularly among Black participants. The association between Aβ and verbal episodic memory is particularly evident in Latinx participants. Future work should investigate the mechanistic pathways through

which global and regional Aβ affect regional atrophy in the oldest-old. Another future direction is to examine the underlying factors that may modify Aβ-related associations, such as socioeconomic status, that may explain differences in the associations among groups.

Keywords: Amyloid-PET, aging, oldest-old, entorhinal cortex, race/ethnicity, sex/gender, memory.

Key takeaway message: In the oldest-old, higher Aβ was associated with lower entorhinal thickness and lower verbal episodic memory, and these associations were particularly evident in Black and Hispanic groups.

P183- ASSOCIATION BETWEEN THE INCIDENCE OF AMYLOID-RELATED IMAGING ABNORMALITIES AND AMYLOID PLAQUE CLEARANCE ON POSITRON EMISSION TOMOGRAPHY OF AMYLOID-TARGETING THERAPIES.

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Background: Amyloid-targeting therapies (ATTs) in the form of monoclonal antibodies are the first approved disease-modifying treatment for Alzheimer's disease. The risk of amyloid-related imaging abnormalities (ARIA) - a major complication of ATTs - has become a crucial part of clinical decision making. Two subtypes of ARIA have been described: ARIA with edema/effusion (ARIA-E) and ARIA with hemorrhage (ARIA-H). Interestingly, ARIA risk varies between ATTs. This pilot study aims to investigate whether differences in amyloid plaque clearance capacity on positron emission tomography (PET) between ATTs are associated with increased ARIA risk. We hypothesized that ATTs that clear amyloid from the brain more effectively in the long run cause more ARIA events in the short term, presumably by increasing vascular amyloid load before clearance mechanisms set in. To our knowledge, the relationship between amyloid clearance and ARIA risk has not been studied before. **Methods:** Data for this study were identified by searches of PubMed and references from relevant articles. The search terms "amyloid-related imaging abnormalities", "Alzheimer's disease", "lecanemab", "donanemab", "aducanumab", and "gantenerumab" were used. Based on the public availability of data on ARIA incidence and amyloid PET status, the following phase II and III trials were included: ENGAGE + EMERGE (aducanumab; n = 4), GRADUATE I + GRADUATE II (gantenerumab; n = 2), CLARITY AD + BAN 2401-201 (lecanemab; n = 6), and TRAILBLAZER ALZ + TRAILBLAZER ALZ2 (donanemab; n = 2). Statistical analysis was carried out using GraphPad Prism. Differences between ARIA rates and APOE4 carrier status of multiple ATTs were analyzed using one-way ANOVA with Bonferroni-adjusted post hoc correction. Amyloid clearance efficacy indicated as centiloid change from baseline, a parameter for amyloid plaque clearance on PET, was correlated with ARIA incidence across the indicated phase II and III clinical trials and their respective dosing regimens using linear regression analysis. Each analysis was done separately for ARIA-E and ARIA-H. **Results:** We first compared the incidence of ARIA-E and ARIA-H between ATTs. ARIA-E incidence of lecanemab was significantly lower compared to gantenerumab ($p < 0.01$), donanemab ($p < 0.01$) and aducanumab ($p < 0.0001$). Conversely, ARIA-H incidence of lecanemab was significantly decreased compared to gantenerumab ($p < 0.05$) and donanemab ($p < 0.01$), but not aducanumab. ARIA-H rates of aducanumab were also significantly lower than those of donanemab ($p < 0.05$). There was no significant difference between the percentage of APOE4 carriers per monoclonal antibody. Next, ARIA-E and ARIA-H incidence of different antibodies and dosages were correlated with PET centiloid change from baseline. For ARIA-E, an overall trend pointing to higher incidence with increased centiloid change across different antibodies and dosages was observed; however, this trend was not significant ($r2 = 0.17$; $p = 0.14$). For ARIA-H, linear regression analysis showed a significant correlation between incidence and increased centiloid change from baseline ($r2 = 0.43$; $p = 0.02$), suggesting a higher risk of ARIA-H with increased amyloid plaque removal from the brain. **Conclusions:** The first part of our study showed that ARIA incidence differed between ATTs, with lecanemab exhibiting significantly lower rates of ARIA-E and ARIA-H compared to gantenerumab, donanemab, and in the case of ARIA-E, aducanumab. Interestingly, lecanemab was the only antibody included in this study that prefers binding protofibrils (i.e. soluble amyloid) over fibrils, suggesting that differences in primary amyloid binding target may contribute to varying ARIA rates of ATTs. The second part of our study suggests a relationship between amyloid clearance capacity and risk of ARIA events. Interestingly, ARIA-H incidence showed a significant correlation with amyloid PET removal indicated by centiloid change while ARIA-E, despite exhibiting a similar trend, was not significantly correlated with amyloid PET clearence. This discrepancy might be due to multiple reasons, including different trial designs and patient populations. Under more comparable conditions, the trend between ARIA-E incidence and amyloid clearance may reach significance. Since ARIA-H frequently co-occurs with ARIA-E, the significant correlation between ARIA-H incidence and amyloid plaque clearance encompasses mostly ARIA-H in the context of ARIA-E and not isolated ARIA-H events. While preliminary and purely correlative, the results of our pilot study point to higher incidence of ARIA-E and ARIA-H with increased amyloid plaque clearance capacity. Since ARIA is thought to result from increased amyloid clearance along the perivascular drainage system, it appears pathophysiologically plausible that higher amyloid plaque removal, especially early after treatment initiation with ATTs, may lead to perivascular amyloid overload and hence elicit a perivascular and transmural immune response responsible for ARIA. It is important to note, however, that higher amyloid clearance capacity does not necessarily reflect the clinical effectiveness of the respective antibody and that future studies are needed to deepen our understanding of ARIA and its risk factors.

Key takeaway message: This pilot study provides preliminary results indicating that the risk of ARIA may be positively correlated with increased amyloid plaque clearance capacity of amyloid-targeting therapies.

P184- FLORBETABEN BINDING TO AMYLOID PLAQUES IS UNAFFECTED BY AMYLOID-TARGETING ANTIBODIES LECANEMAB AND DONANEMAB.

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Background: Amyloid PET imaging enables the in vivo visualization and quantification of amyloid-beta (Aβ) deposits in the brain (1). In research and clinical settings, it is further used to monitor amyloid burden as well as the biological response to disease-modifying therapies (2). Amyloid-targeting monoclonal antibodies (mAbs) such as lecanemab and donanemab were designed to reduce brain amyloid burden (3,4). If the PET tracer and the mAbs would bind to the same site, the PET signal may be impacted in patients undergoing therapy. Binding interaction studies were conducted to verify the reliability of PET readouts in this setting. The aim of this study was to investigate whether lecanemab or donanemab interfere with the binding of the amyloid PET tracer florbetaben (FBB) to aggregated Aβ deposits in vitro. **Methods:** Human Alzheimer's disease (AD) brain tissue from the FBB phase 3 study and from the Netherland Brain Bank was used to assess potential interactions between FBB and lecanemab or donanemab. Three complementary approaches were used to confirm target binding and to study

potential interactions: (1) competitive immunohistochemistry (IHC), (2) competitive autoradiography (ARG), and (3) ligand binding assays (LBA). **Results:** Across all three sets of experiments, no evidence of competition or inhibition of FBB binding to Aß deposits by lecanemab or donanemab was observed. Autoradiography demonstrated robust tracer binding to Aβ plaques that was unaffected by incubation with excess antibody. Similarly, IHC and LBA experiments confirmed that FBB and the tested mAbs target distinct binding sites on Aβ aggregates. **Conclusions:** These results demonstrate that neither lecanemab nor donanemab interfere with florbetaben binding to Aß plaques in vitro, which is further validating its use in this setting. While the current data are limited to in-vitro experiments, they further support the use of florbetaben PET for monitoring amyloid changes during treatment with amyloid-targeting therapies.

Keywords: Amyloid PET, disease modifying therapies, Alzheimer's disease, amyloid-targeting monoclonal antibodies.

Disclosures: MC, AM, AJ, JS, MR, EB, NKi, AS, NKo are all employees of Life Molecular Imaging. EM is the Co-Founder and CEO of Re:Cognition Health UK & USA.

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Key takeaway message: Florbetaben PET binding to amyloid plaques is not affected by lecanemab or donanemab, supporting its reliability for monitoring amyloid changes during treatment with disease-modifying therapies in Alzheimer's disease.

P186- METABOLIC SYNDROME RISK FACTORS ASSOCIATED WITH LOWER CEREBRAL BLOOD FLOW AND MOCA SCORES IN HEALTHY OLDER ADULTS.

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Background: Metabolic and vascular risk factors are increasingly understood as contributors to Alzheimer's Disease (AD). Arterial spin labeling (ASL) noninvasively quantifies cerebral blood flow (CBF), which reduces early in AD and may serve as a biomarker for vascular contributions to cognitive decline in AD. **Methods:** Out of 96 cognitively normal adults (ages 55–86) screened, 87 completed ASL MRI procedures and data from 82 participants were analyzed. ASL was used to quantify global and regional CBF in areas implicated in cognitive decline in AD (hippocampus, temporal lobe, angular gyrus, posterior cingulate). Presence of metabolic syndrome (MetS) risk factors (lipids, waist circumference, fasting glucose, blood pressure) were determined by laboratory values and clinical measurements and counted for each participant. Participants also underwent APOE genotyping and cognitive testing with the Montreal Cognitive Assessment (MoCA). Associations between individual variables were analyzed using linear regression in R. **Results:** Number of MetS risk factors was significantly associated with reduced global CBF (linear regression, p= 0.0039) and regional CBF (p= 0.0049, p= 0.0043, p= 0.027, p= 0.024 for hippocampus, temporal lobe, angular gyrus, and posterior cingulate cortex, respectively). CBF was positively associated with MoCA scores (p= 0.012), and MetS risk was negatively associated with MoCA scores (p= 0.011). We also observed a significant interaction between age and CBF (p= 0.032) such that the relationship between CBF and MetS risk was most pronounced in younger ages within the study sample. Results were unaffected by APOE status or sex. **Conclusions:** MetS risk factors were linked to reduced CBF. Global CBF was positively related to cognition as measured by the MoCA. The association between MetS and CBF was moderated by age, suggesting that vascular-cognitive relationships are stronger in younger participants, which may implicate younger ages as a particularly relevant window for MetS treatment and AD prevention. Our findings also support the potential of ASL as a noninvasive biomarker of vascular contributions to cognitive function and AD risk.

Keywords: Alzheimer's disease, cerebral blood flow, arterial spin labeling, metabolic syndrome.

Clinical Trial Registry: Lipid MRI Study, NCT04692441.

Disclosures: The authors have no conflict of interest. During the preparation of this work the authors consulted ChatGPT (OpenAI) for guidance on writing structure and formatting norms. The authors reviewed and edited the content independently and take full responsibility for the final abstract.

Key takeaway message: Metabolic and vascular risk factors are linked to reduced cerebral blood flow, which in turn correlates with global cognition, supporting ASL MRI as a biomarker of vascular influences on Alzheimer's disease risk.

P187- INTEGRATING VISUAL ASSESSMENTS AND QUANTIFICATION METHODS FOR TAU PET STAGING.

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Background: Tau positron emission tomography (PET) is increasingly used for disease staging in Alzheimer's disease, but optimal methods for interpretation remain debated. We aimed to compare visual assessments and quantitative approaches for tau PET staging, and to examine plasma biomarkers and cognitive trajectories across amyloid and tau (AT) stages. **Methods:** Tau PET scans from 289 participants in the Korea-Registries to Overcome Dementia and Accelerate Dementia Research (K-ROAD) were analyzed using both visual interpretation and multiple quantification pipelines. Findings were validated in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort (n = 870). Plasma biomarkers and longitudinal cognitive measures were evaluated across AT stages. **Results:** FreeSurfer without partial volume correction achieved the highest area under the curve (AUC) for tau positivity against visual interpretation (AUC = 0.918). The temporal meta-region showed the best performance for moderate tau staging (AUC = 0.856), while the temporoparietal region performed best for advanced staging (AUC = 0.828). Quantitative methods were more sensitive than visual reads in detecting phosphorylated tau217 changes during intermediate stage transitions (e.g., A+/T− to A+/Tmod+). Plasma biomarkers and cognitive measures showed progressive changes across AT stages, with consistent results between the K-ROAD and ADNI cohorts. **Conclusions:** Visual and quantitative tau PET methods provide complementary strengths for staging, with quantification offering higher sensitivity for biomarker transitions and visual interpretation providing robust clinical utility. Integrating both approaches enhances tau PET staging and better captures biomarker and cognitive trajectories across disease stages.

Key takeaway message: Quantification improves early tau detection and correlates with plasma biomarkers and cognition, while visual reads offer robust staging—together providing complementary strengths validated across K-ROAD and ADNI cohorts.

P188- ALLOPREGNANOLONE INCREASES HIPPOCAMPAL VOLUME IN EARLY ALZHEIMER'S DISEASE: IMPORTANCE OF SEGMENTATION METHOD AND BASELINE ATROPHY.

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Background: Regenerative therapeutics hold the promise of self-renewal and repair. Allopregnanolone (Allo) promoted neurogenesis, restored cognitive function and reduced AD pathology in earlier preclinical cell and animal models. We previously reported that Allo slowed or reversed hippocampal atrophy and preserved white matter structural integrity in major commissural and association pathways, and that white matter effects were independent of APOE genotype. The hippocampal analyses were based on Freesurfer's automatic subcortical segmentation (ASEG), which may overestimate hippocampal boundaries, reducing anatomical specificity and treatment effect specificity. Additionally, prior analyses did not account for individual differences in disease burden. To address these limitations, we reanalyzed hippocampal volume changes using Freesurfer's longitudinal hippocampal subfield segmentation approach, which offers better anatomical reliability and improved sensitivity to subtle volumetric changes. Our goals were threefold: (1) to determine whether Allo's hippocampal effects persist using this more conservative method, (2) to assess whether baseline hippocampal atrophy influences treatment response, and (3) to evaluate whether APOE genotype moderates these effects. **Methods:** A randomized, double-blind, placebo-controlled, multiple ascending dose trial was conducted. Intravenous placebo or Allo was administered once-per-week for 12 weeks. Participants with early AD (mild cognitive impairment due to AD or mild AD), a Mini-Mental State Examination score of 20-26 inclusive, and age $\geq$55 years were randomized (6:2 to three Allo dosing cohorts or one placebo cohort). Primary endpoints were safety and tolerability. The Phase1b/2a trial was powered only for safety and not for exploratory outcomes, including hippocampal volume. T1-weighted MRI data were preprocessed using the longitudinal pipeline in Freesurfer version 6.0. Hippocampal volume was estimated using both ASEG and the longitudinal subfield segmentation routines, the latter providing a more anatomically accurate reconstruction of hippocampal structure. Bilateral hippocampal volume was calculated as the sum of left and right segmentations for both methods. Change from baseline was expressed as percent volume change. Baseline scans were also processed using CorInsights® MRI to derive participant-specific Z-scores reflecting hippocampal atrophy relative to a normative aging population, adjusted for intracranial volume, age, sex, and scanner. A Z-score threshold of –1 was used to classify participants as having evidence of baseline atrophy. Treatment effects were quantified using Hedges' g to compare the 4 mg Allo group to placebo. We conducted sensitivity analyses stratifying participants by APOE genotype and baseline atrophy to assess potential treatment response moderators. We further estimated the sample size required to detect a statistically significant treatment effect under the observed effect size using standard power analysis assumptions ($\alpha = 0.05$; $1–\beta = 0.80$). **Results:** Visual inspection of the Freesurfer outputs confirmed that ASEG frequently overestimated the hippocampal boundaries, often incorporating surrounding non-hippocampal tissue. In contrast, subfield segmentation produced anatomically refined and consistent hippocampal delineations across timepoints. Among the three Allo dose groups, only the 4 mg group exhibited bilateral hippocampal volume increases, which were evident in both segmentation methods. However, subfield segmentation yielded a more conservative and precise estimate of this effect (mean percent change $\pm$ SD: $0.368 \pm 0.992\%$) compared to ASEG ($1.59 \pm 4.20\%$). When restricting the analysis to participants with baseline hippocampal atrophy ($Z \leq –1$), the evidence for a positive treatment effect in the 4 mg group was strengthened. In this subgroup, the observed mean volume change was $0.728 \pm 0.966\%$ (subfields) and $3.95 \pm 2.67\%$ (ASEG). APOE genotype effects could not be reliably assessed within the 4 mg dose group due to an insufficient number of ε3/ε3 homozygotes ($n = 1$), precluding stratified analysis for this cohort. Effect size estimates from subfield-derived volumes were moderate for the group comparison between 4mg Allo and placebo (Hedges' $g = 0.54$) and large within the baseline atrophy subgroup ($g = 1.15$). In contrast, ASEG-derived estimates were inflated ($g = 1.23$ overall; $g = 2.27$ in the atrophy subgroup), likely reflecting segmentation inaccuracies. Power analysis using the subfield-based effect size ($g = 0.565$) indicated that a sample size of 50 participants per group would be sufficient to detect a statistically significant difference in hippocampal volume change between 4mg Allo and placebo at standard significance thresholds. **Conclusions:** This reanalysis confirms and extends prior findings of the potential that Allo may promote hippocampal regeneration in early AD. The more conservative and robust subfield-based estimates suggest that Allo's regenerative effects may be most detectable in individuals with pre-existing hippocampal atrophy. These findings underscore the importance of rigorous imaging methodologies and suggest that screening for hippocampal atrophy may improve sensitivity to therapeutic effects in future trials. Although APOE genotype could not be fully evaluated in this analysis, its role in Allo's regenerative effect remains an important target for future study. Taken together, these results reinforce the therapeutic potential of Allo as a regenerative treatment for AD and underscore practical strategies for optimizing clinical trial design. The on-going Phase 2 REGEN-Brain clinical trial incorporates optimized MRI sequences for tissue segmentation, targeted screening for atrophy burden, and up-to-date improvements in subfield segmentation and longitudinal measurement to maximize our ability to detect Allo regenerative treatment effect in hippocampal volume.

Keywords: Allopregnanolone, hippocampal volume, subfield segmentation.

Clinical Trial Registry: NCT02221622 (https://clinicaltrials.gov/).

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Key takeaway message: The presence of neurodegeneration is a critical factor in Allopregnanolone's regenerative effect. These findings underscore the importance of imaging and analytic methodology and suggest that screening for hippocampal atrophy may improve sensitivity to therapeutic effect.

P189- LONGITUDINAL IMPACT OF SARCOPENIA ON AMYLOID DEPOSITION, BRAIN ATROPHY, AND COGNITIVE DECLINE: A

MULTI-MODAL LINEAR MIXED MODEL ANALYSIS.

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Background: Sarcopenia has emerged as a potential systemic risk factor for cognitive impairment and neurodegeneration. However, its longitudinal effect on brain structure, amyloid accumulation, and neuropsychological outcomes remains underexplored. **Methods:** We analyzed 390 older adults from a longitudinal cohort with repeated measures of MRI (n=378), amyloid PET (APET, n=74), and neuropsychological scores. Baseline sarcopenia was assessed by skeletal muscle index (SMI) measured by bioimpedance analysis, handgrip strength, and five-time sit-to-stand (5STS). Linear mixed models (LMM) were used to evaluate whether these measures influenced longitudinal changes in imaging biomarkers (e.g., global SUVR, centiloid, cortical volumes) and CERAD total scores. Interaction terms between time and baseline sarcopenia/physical function were tested. Age, sex, education years, and APOE ε4 carrier status were included as covariates. **Results:** The interaction between time and baseline sarcopenia diagnosis was significantly associated with increased global SUVR ($\beta = 0.010$, $p = 0.007$) and centiloid scale ($\beta = 5.376$, $p = 0.029$), suggesting accelerated amyloid accumulation. Similarly, handgrip strength moderated the trajectory of temporal lobe atrophy ($\beta = 0.182$, $p = 0.033$) and cognitive decline measured by CERAD ($\beta = 0.962$, $p = 0.001$). However, no significant interaction was observed for most cortical subregion volumes (e.g., frontal, occipital, cingulate) or for the SMI. Several models failed to converge or showed boundary estimates, warranting cautious interpretation. **Conclusions:** Baseline sarcopenia and impaired physical function were associated with accelerated amyloid pathology and cognitive decline in older adults, independent of demographic risk factors and APOE ε4 carrier states. These findings highlight the importance of sarcopenia measures as a systemic contributor to Alzheimer's disease prevention.

Key takeaway message: Baseline sarcopenia and poor physical function predicted faster amyloid accumulation and cognitive decline over time, highlighting their potential role as systemic contributors to Alzheimer's disease progression in older adults.

P190- EXPLORING INDIVIDUAL VARIATION IN TAU PET AND CDR-SB: A META-ANALYSIS OF PLACEBO ARM DATA.

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Background: There is a significant unmet need in early-stage Alzheimer's disease drug development for a surrogate endpoint biomarker that reliably predicts or correlates with clinical benefit. Such an endpoint would enable more efficient trials, enhance statistical power, and provide insights into underlying disease biology. While antibodies targeting the N-terminal of tau have not significantly affected tau PET signals, several mid- and C-terminal tau-directed antibodies, as well as tau-targeting vaccines and antisense oligomers, are currently in phase II trials. Tau removal may offer a higher dynamic range than amyloid removal, potentially improving correlations with clinical benefit. If validated, tau PET could facilitate robust group-level characterizations of treatment effects while also supporting individual-level assessments. A deeper understanding of individual variation in tau PET measurements could further refine these analyses and enhance its utility. **Methods:** This study evaluates the ability of tau PET to track disease progression over time, its sensitivity to changes in tau pathology, and its correlation with clinical outcomes. Longitudinal studies are essential to determine tau PET's predictive value for disease progression and its prognostic relevance to the final clinical endpoint (CDR-SB). This information could inform future analyses, including treatment evaluations, to assess tau PET as a potential surrogate endpoint in clinical trials for early Alzheimer's disease. **Results:** We analyzed data from the placebo arms of multiple randomized clinical trials where tau PET was measured longitudinally. To cover the full spectrum of tau aggregation from early to later affected areas, a universal and four additional subregion regions of interest (ROIs) were defined: mesial temporal, meta temporal, temporo-parietal, and frontal and regional SUVRs were converted to CenTauR, a standardized scale for tau PET (Leuzy et al., 2024). Clinical progression was assessed using the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB). Using ideas from the meta-analytic framework (Buyse et al., 2000), we jointly modeled the cognitive outcome (CDR-SB) and regional tau PET CenTauRs (CTRs) with a multivariate linear mixed model, including subject-specific random intercepts and slopes. The random effects for CDR-SB and for Tau PET uptake are jointly modelled with a multivariate distribution. The joint distribution of these random effects captures the association between Tau accumulation and cognitive decline. This analysis focuses on individual-level surrogacy, as only placebo arm data are available, and trial-level surrogacy cannot be assessed in the absence of treatment effects. To assess individual-level surrogacy, the $R_\lambda 2$ was computed for each ROI, which quantifies how well the variation in tau PET explains variation in cognitive decline (Buyse et al., 2005). **Conclusions:** Our findings offer insights into the potential of tau PET as an individual-level surrogate marker in Alzheimer's disease and may inform future clinical trial endpoint development.

Disclosures: Gregory Klein is an employee of F. Hoffmann-La Roche Ltd.

References: Buyse, M., Molenberghs, G., Burzykowski, T., Renard, D., & Geys, H. (2000). The validation of surrogate endpoints in meta-analyses of randomized experiments. Biostatistics, 1(1), 49-67. Buyse, M., & Molenberghs, G. (2005). The evaluation of surrogate endpoints (Vol. 427). T. Burzykowski (Ed.). New York: Springer. Leuzy A, Raket LL, Villemagne VL, et al. (2024) Harmonizing tau positron emission tomography in Alzheimer's disease: The CenTauR scale and the joint propagation model. Alzheimers Dement. 20(9).

Key takeaway message: This study evaluates the ability of tau PET to track disease progression over time, its sensitivity to changes in tau pathology, and its correlation with clinical outcomes.

P191- ADVANCING CLINICAL RESEARCH WITH PET IMAGING: EMERGING RADIOTRACERS AND EVOLVING ROLES IN ALZHEIMER'S DEMENTIA DIAGNOSIS.

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Background: Positron Emission Tomography (PET) has become a cornerstone in the clinical research of Alzheimer's disease (AD) and related dementias. Its ability to visualize molecular processes in vivo has led to significant advances in early diagnosis, disease staging, and therapeutic monitoring. Current imaging biomarkers include amyloid-targeting tracers such as 18F-florbetapir, flutemetamol, 11C-PiB, which detect β-amyloid plaque deposition, and tau-targeting tracers like flortaucipir, 18F-MK-6240 and 18F-PI2620, which visualize neurofibrillary tangles. These radiotracers are central to both clinical diagnostics and research trials, enabling more precise staging and monitoring of disease progression. Novel radiotracers are being developed to target neuroinflammation, synaptic density, and mitochondrial function, offering new insights into disease mechanisms. PET imaging is

increasingly used in longitudinal studies and therapeutic trials, supported by harmonization efforts across international research cohorts. **Methods:** To evaluate the current landscape of clinical research utilizing PET imaging in Alzheimer's, with a focus on the discovery and application of new radiotracers, and to assess the evolving role of PET as a primary imaging modality in clinical trials and diagnostic workflows in this therapeutic area, we performed a structured review of ongoing and completed clinical trials was conducted using ClinicalTrials.gov. Trials were selected based on their intent to: 1. Evaluate novel imaging biomarkers for Alzheimer's disease and related dementias, 2. Conduct comparative studies between PET imaging methods or clinical or cognitive assessment scales, and 3. Investigate imaging as a primary endpoint or objective, particularly in therapeutic or observational research settings. **Results:** As part of our review, we identified 210 clinical trials that met our inclusion criteria: 142 were interventional studies, 18 are currently enrolling participants, 7 are active but not recruiting, and 84 have been completed, while 68 trials were observational, 31 trials being open at the time of assessment. Each trial was assessed for the type of PET radiotracer used, its regulatory status, and the specific clinical indication being investigated. Notably, there is a current predominance of trials utilizing tau PET radiotracers in the interventional trials, reflecting a growing interest in tau pathology as a key target for both diagnostic and therapeutic strategies in Alzheimer's disease. **Conclusions:** The current clinical research landscape demonstrates the central role of PET imaging in advancing our understanding of Alzheimer's disease and related dementias. Through a targeted review of 210 clinical trials, we identified a strong emphasis on the development and evaluation of novel radiotracers, comparative imaging methodologies, and imaging-driven endpoints. These findings underscore the growing reliance on PET as a primary tool for both diagnostic refinement and therapeutic evaluation. As regulatory frameworks and biomarker technologies evolve, PET imaging is poised to remain a cornerstone of precision medicine in neurodegenerative research.

Key takeaway message: PET imaging, a cornerstone of precision medicine, is central to Alzheimer's research. Novel radiotracers - especially tau-targeting agents - highlight its growing role in diagnosis, monitoring, and as a primary endpoint in clinical trials.

CLINICAL TRIALS: BIOMARKERS INCLUDING PLASMA

P192- THE BEYONDD STUDY: PRELIMINARY PLASMA BIOMARKER FINDINGS WITHIN A COMMUNITY-BASED SAMPLE.

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Background: Early onset dementia (EOD) affects people at the peak of personal and professional responsibilities and economic productivity. Alzheimer's disease (AD) and Frontotemporal Dementia (FTD) are the most common EOD etiologies but are rarely detected and have not been studied in a sample representative of the general US population. Cardiovascular factors and socioeconomic stressors may lead to increased vulnerability and risk in adults from historically understudied communities. Multiple barriers impede research participation for individuals from these groups, but community-engaged research (CER) strategies to enhance recruitment may make research participation more accessible and convenient for all. BEYONDD is an NIH-funded, community-based study focused on understanding the etiology of EOD, uses CER strategies such as remote assessments and return of research results as tools for enhancing sample representativeness. These preliminary data demonstrate the feasibility of a decentralized, community-based screening approach and suggest that many individuals maybe eligible for current or planned prevention trials. **Methods:** The BEYONDD study (www.beyonddproject.org) aims to enroll individuals to evaluate the use of remote assessments and the impact of returning diagnostic information to participants as a more accessible research framework. Participants are recruited using a combination of social media advertisements and local in-person CER strategies and screened via an online platform for eligibility (age 40-64, with concerns about cognitive, language, or behavioral function). Remote completion of online questionnaires, smartphone app, cognitive testing, and an in-home blood draw for standard labs, plasma Aβ42/40 and p-tau217 ratios (C2N PrecivityAD2TM), and plasma neurofilament light chain (NfL; Quest) comprise the initial phase of the project. Upon completion of the remote blood draw, all participants are invited for a more comprehensive in-person evaluation at one of 7 BEYONDD in-clinic sites, followed by tailored referral to other NIH-funded research programs. Participants can learn their results remotely or in person. **Results:** BEYONDD has recruited over 660 individuals with self-reported changes in cognition, language, or behavior across the US and Puerto Rico. 284 (43%) of the eligible individuals indicated interest in receiving an in-home blood after completing their other remote procedures. To date, we have successfully completed blood draws in 21 states and Puerto Rico. Of the 149 participants that completed the in-home blood draw, most were women (n=120, 80.5%) with a mean age of 53.3 years (SD=6.514) and identified as Latino (n=60; 40%) or Black (n=57; 38%). Within this sample, the most prevalent routine lab abnormalities observed were lipids and hemoglobin A1c, which were observed in over 38% of the sample. Preliminary analyses have revealed abnormal Aβ42/40 (n=31; 21%), p-tau217 ratio (n=7; 5%), and NfL (n=19; 12.8%) levels in approximately 1/3 of the individuals in this community-based sample. An additional 57 individuals (38%) had borderline biomarker values (within 10% of cutoff value) suggesting that they may be at risk for having abnormal values. Participants with abnormal Aβ42/40, p-tau217 ratio, or NfL values comprised the plasma biomarker positive group. Participants with normal or borderline levels were considered plasma biomarker negative. While there were no significant differences in mean age, sex, ethnoracial makeup, or ApoE carrier between these two groups, we did observe that the biomarker positive group on average reported 2.6 (SD=0.6096) cognitive complaints compared to the plasma biomarker negative group (mean=2.2, SD=0.7288, p=0.0018). Additionally, individuals in the plasma biomarker positive group were more likely to have abnormal glucose (X2 (1, N=149)=4.165, p=0.0412) and eGFR (X2 (1, N=149)=4.952, p=0.0261) values. **Conclusions:** These preliminary data demonstrate that early neurogenerative plasma biomarker abnormalities are common in adults ages 40-64 and are associated with cognitive and behavioral complaints. Because individuals were enrolled in the study based on their cognitive and behavioral complaints and their experiences of how these changes affect their daily lives, plasma biomarkers may be useful for screening for clinically meaningful correlates of early neurodegenerative disease. More work is needed to better understand the associated risk factors and trajectory of biomarker abnormalities across time in this cohort to improve and optimally support recruitment and enrollment of a representative population in EOD studies and prevention trials.

Keywords: Aβ42/40, p-tau217, NfL, early onset dementia, plasma biomarkers.

Key takeaway message: Community based screening using

neurogenerative plasma biomarkers (Aβ42/40, p-tau217, NfL) can be used identify individuals with plasma biomarker abnormalities associated with cognitive and behavioral complaints in adults ages 40-64 in a representative US sample.

P193- IMPACT OF PLASMA COLLECTION TIME OF DAY ON PLASMA P-TAU217 MEASURES IN AUTONOMY AND RETAIN TRIALS.

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Background: Plasma biomarkers are a promising tool for detection and staging of patients with Alzheimer's disease (AD). Plasma levels of phosphorylated tau (p-tau217) have been shown to be upregulated in AD and can be used to identify people with amyloid and tau pathology (1,2). Recently, studies have shown conflicting data on the effect of sample collection time on plasma p-tau217 levels (3,4). **Methods:** Plasma samples were obtained from participants screened for Johnson & Johnson clinical trials Autonomy (NCT04619420; early AD; N=1820 screened) and Retain (NCT06544616; preclinical AD; N=14322 screened) with informed consent for use in scientific research to better understand AD or to develop tests for AD. Plasma p-tau217 levels were measured using the Lucent AD p-Tau 217 assay (aka Janssen p217+tau assay (1) at Quanterix, MA, USA. Data was combined and summarized according to sample collection time. Additionally, plasma p-tau217 levels were categorized as "Low" or "High" by applying an equivalent threshold of 110 fg/mL, based on the results from Feizpour et al. (1). Generalized linear models (GLM) were run to determine if collection time as well as other covariates (plasma p-tau217 level and age) had any effect on plasma p-tau217 concentrations. **Results:** Collection time was normally distributed, with most samples collected within a 10-hour range (8:00 and 18:00 local time). A generalized linear model (GLM) of the entire sample set showed that the cohort screened for the Autonomy study in early AD had higher levels of plasma p-tau217 relative to those who were screened for the Retain study in preclinical AD ($p<0.0001$). When examining the relationship between collection time and p-tau217 concentration, GLM models showed no significant relationship between p-tau217 concentration and collection time across all samples (P=0.321). When accounting for p-tau217 level and age as covariates in GLM models, we found no significant effect of collection time in the low p-tau217 cohort but a small effect in the high p217 cohort (P=0.04). The observed difference in average p-tau217 over a 10-hour period amounted to a ~7% decrease (0.0157 pg/mL, 95% CI: 0.0166-0.0148 pg/mL) from morning to evening in the high p-tau217 cohort. **Conclusions:** Findings in the Retain and Autonomy cohorts points to minimal effects of diurnal fluctuations in plasma p-tau217 concentrations, with concentration decreasing from morning to evening only in the high p-tau217 cohort. This small decrease differs from reports in previous studies of diurnal variation in p-tau217 concentration [3,4], and more data will be needed to confirm effect direction and magnitude. All together, we conclude that the impact of sampling time on measured p-tau217 concentrations is small and standardization of p-tau217 collection time in clinical trials is likely unnecessary.

Keywords: Alzheimer's disease, plasma p-tau217, fluid biomarkers, diurnal variation.

Clinical Trial Registry: NCT04619420, NCT06544616; https://clinicaltrials.gov.

Disclosures: SS, GTB, DH, TTW, JW, LS, MF, and ZSS are employees of Johnson & Johnson.

References: 1. Triana-Baltzer G, et al. Alzheimers Dement (Amst). 2021 May 27;13(1);e12204. http://doi.org/10.1002/dad2.12204. 2. Feizpour A, et al. Commun Med (Lond). 2025 Feb 27;5:53. http://doi.org/10.1038/s43856-025-00768-z. 3. della Monica C, et al. Transl Psychiatry. 2024 Sep 13;14(1):373. http://doi.org/10.1038/s41398-024-03084-7. 4. Dolado A, et al. Alzheimers Res Ther. 2024 Jun 22;16 (1):132. http://doi.org/10.1186/s13195-024-01503-x.

Key takeaway message: Minimal effects of diurnal fluctuations in plasma p-tau217 concentrations were observed in the Retain and Autonomy screened cohorts, pointing to a small impact of sample collection time on measured p-tau217 concentrations.

P194- AUTOMATED PLASMA IMMUNOASSAY FOR APOE E4 ZYGOSITY IDENTIFICATION IN ALZHEIMER'S DISEASE BIOMARKER RESEARCH.

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Background: Apolipoprotein E (APOE) is involved in lipid metabolism and has 3 primary isoforms (ε2, ε3, and ε4). The APOE ε4 isoform is a key genetic risk factor for developing Alzheimer's disease (AD), with higher risk for homozygous APOE ε4+/+ individuals. Currently, APOE status is assessed using molecular methods or mass spectrometry, requiring specialized equipment, expertise and different specimen workflows from other AD-associated biomarkers. We describe the performance of Access APOE ε4 (RUO), a high-throughput automated APOE proteotype assay on the Access family of immunoassay systems that informs APOE ε4 zygosity. **Methods:** The Access APOE ε4 RUO assay is a combination of 2 two-step sandwich assays using paramagnetic particles coated with anti-PanAPOE monoclonal antibody (MAb) and either (1) a complementary anti-PanAPOE MAb/alkaline phosphatase conjugate, or (2) an anti-APOE ε4 MAb/alkaline phosphatase conjugate. K2 EDTA plasma samples containing APOE protein isoforms and reactants are incubated and washed, followed by addition of a chemiluminescent substrate. An algorithm processes the light generated, providing a result indicating the APOE ε4 zygosity of the sample. This fully automated immunoassay was evaluated for concordance with polymerase chain reaction (PCR) genotyping in 460 K2 EDTA plasma samples from 3 independent cohorts. In addition, ε4 isoform specificity, interference, precision, and sample stability were evaluated. **Results:** Concordance of the Access APOE ε4 RUO immunoassay was 99.6% (95% confidence interval [CI] 98.9 – 100.0%) with PCR genotype results across the 3 cohorts. Concordance was 100.0% (95% CI 100.0 – 100.0%) in the AD subgroup (n=127) and 99.5% (95% CI 98.9 – 100.0%) in the non-AD subgroup (n = 333). We observed no cross reactivity to the APOE ε2 and ε3 isoforms in the APOE ε4-specific assay. Spiking common interferents showed no change in the results interpretation. Precision analysis showed a within-laboratory imprecision of 6.4-10.4 % coefficient of variation. Finally, stable results were obtained after storage of K2 EDTA plasma samples for up to 14 days at 4 °C or room temperature and after up to 5 freeze-thaw cycles. **Conclusions:** The Access APOE ε4 (RUO) immunoassay provides rapid and precise results with excellent concordance to PCR genotyping. This proteotype assay fits well within existing blood-based biomarker workflows, potentially reducing the cost and complexity of AD biomarker research. The Access family of immunoassay analyzers provides a true random-access solution for evaluation of APOE ε4 zygosity, offering significant advantages of performance, throughput, and ease-of-use compared with alternatives.

Keywords: Apolipoprotein E, biomarker, immunoassay, Alzheimer's disease.

Disclosures: Beckman Coulter is the developer and manufacturer of the Access APOE ε4 (RUO) zygosity immunoassay studied. BE, BS, KH, YEB,

MS, CC, and MH are employees of Beckman Coulter. SLevin and JH are employees of Danaher Diagnostics. Both Beckman Coulter and Danaher Diagnostics are wholly owned subsidiaries of Danaher Corporation. AA-S has participated in advisory boards for Roche Diagnostics, Fujirebio Diagnostics, and Siemens Healthineers, and has received speaker honoraria from Roche Diagnostics and Eli Lilly. DF has received speaker honoraria from Beckman Coulter. S Lehmann has served as a consultant or at advisory boards for Fujirebio-Europe, Roche Diagnostics, Lilly, Biogen, and Beckman Coulter. The remaining authors report no conflicts of interest.

Key takeaway message: The RUO Access APOE ε4 immunoassay offers rapid, precise, automated determination of APOE ε4 zygosity, showing excellent concordance with PCR genotyping. This proteotype immunoassay integrates well into existing biomarker workflows, potentially simplifying Alzheimer's disease research.

P195- ASSOCIATION OF PLASMA ALZHEIMER'S DISEASE AND NEURODEGENERATION BIOMARKERS WITH PERCEIVED STRESS, NEIGHBORHOOD DISADVANTAGE, AND SOCIOECONOMIC STATUS.

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Background: Social exposures (e.g., psychological stress, neighborhood disadvantage, socioeconomic position) have been associated with an increased risk of dementia. Yet, few studies have investigated associations between social exposures, Alzheimer's Disease (AD), and neurodegeneration-related plasma biomarkers, especially in heterogeneous, representative populations. **Objectives:** In this study, we examined the cross-sectional relationship between perceived and objective social exposures and AD and neurodegeneration-related plasma biomarkers in an ethnoculturally heterogeneous sample. **Methods:** We retrieved data (9/29/2025) from Alzheimer's Disease Neuroimaging Initiative (ADNI4) participants with baseline plasma biomarker data and self-reported measures of perceived and objective social exposures (n = 502). For perceived social exposure, the Perceived Stress Scale (PSS) total score was used. PSS scores range between 0-40, with higher scores indicating higher perceived stress. For objective social exposure, we used the national Area Deprivation Index (ADI), which represents neighborhood disadvantage, and the Hollingshead Index, which measures socioeconomic status (SES). For ADI calculation, self-reported residential addresses were linked to 2021 ADI scores. Scores are expressed as a percentile, ranging from 1-100, with 1 representing the lowest level of socioeconomic disadvantage. The 2-factor Hollingshead was calculated using self-reported education and occupation, using Rentz and colleagues coding revised in 2024. For the Hollingshead, scores range from 11-77, with lower scores indicating higher socioeconomic status. Plasma biomarkers included Aβ40, Aβ42, pTau-217 via Fujirebio Diagnostics Lumipulse assay and neurodegeneration (neurofilament light [NfL] and glial fibrillary acidic protein [GFAP]; via Quanterix Neurology 4-Plex E assays). Aβ40/Aβ42 and pTau-217/Aβ42 ratios were also calculated. For analysis, all biomarkers were log-transformed to allow for consistent log-linear interpretation of estimated parameters. A multivariate multiple regression model was fit to the data, with a response vector consisting of all measured biomarkers and independent variables consisting of PSS, ADI, Hollingshead Index, age, sex at birth, ethnocultural status, the presence of at least one apolipoprotein E (APOE) ε-4 allele, body mass index (BMI), and glomerular filtration rate (eGFR, a blood measure for kidney filtration that can affect blood biomarker concentration). A multivariate analysis of variance (MANOVA) test using Pillai's trace statistic was performed to assess the existence of an association between each covariate and the multivariate response vector. Regression coefficients associated with marginal responses were examined (equivalent to univariate regression). In addition to the multivariate model, univariate regression models with the two log-transformed biomarker ratios (Aβ40/Aβ42 and pTau-217/Aβ42) as dependent variables were fit, using the same set of covariates. **Results:** Median age was 74 (interquartile range (IQR) = 67-79), 58% were female, 74% reported having completed a Bachelor's degree or higher, 11% identified as Latino, 21% Non-Latino Black, 58% Non-Latino White, and 10% Non-Latino Other. The majority were cognitively unimpaired (58%), while 32% had mild cognitive impairment, and 10% had dementia. Overall, the sample had PSS scores indicative of low stress (m = 10, IQR = 5-15), were from relatively advantaged neighborhoods (median national ADI = 30, IQR = 12-50), and had a intermediate Hollingshead scores (m = 22, IQR = 15-33), indicating intermediate SES. In the sample, 25% were pTau-217 positive, 36% were pTau-217/Aβ42 positive, and 49% were Aβ42/40 positive. A MANOVA indicated that PSS was significantly associated with the combined set of biomarkers ($F(5, 490) = 2.0$, $p = .038$). Based on hypothesis tests performed on marginal coefficients ($\alpha = 0.05$): Higher PSS was associated with elevated pTau-217 ($\beta = 0.0099$, SE = 0.0046, $p = .032$), pTau-217/Aβ42 ($\beta = 0.0118$, SE = 0.005, $p = .019$) and NfL ($\beta = 0.0076$, SE = 0.0024, $p = .002$). Greater national ADI was associated with elevated pTau-217/Aβ42 ($\beta = 0.0033$, SE = 0.0014, $p = .019$) and elevated GFAP ($\beta = 0.0022$, SE = 0.0009, $p = .008$), as well as with lower Aβ42 ($\beta = -0.0007$, SE = 0.0003, $p = .025$) and Aβ42/40 ($\beta = -0.0006$, SE = 0.0003, $p = .024$). The Hollingshead Index was not associated with any of the plasma biomarkers. **Conclusions:** Taken together, perceived stress and ADI were associated with plasma biomarker levels in this sample of older, ethnoculturally heterogeneous ADNI4 participants. Specifically, higher perceived stress and greater neighborhood disadvantage were associated with the presence of AD neuropathology and higher levels of neurodegeneration. Our findings emphasize the importance of quantifying perceived and objective social exposure factors when interpreting plasma biomarker levels in the context of AD diagnosis, risk, and research. Our analyses are limited by a sample that is primarily cognitively unimpaired and has fewer adverse social exposures based on perceived stress, neighborhood disadvantage, and socioeconomic position.

Key takeaway message: In a sample of older ethnoculturally heterogeneous participants, higher perceived stress and greater neighborhood disadvantage were associated with plasma biomarkers, specifically the presence of Alzheimer's disease neuropathology biomarkers and higher levels of neurodegeneration.

P196- DIAGNOSTIC ACCURACY OF NOVEL PLASMA PTAU-217 AND P-TAU181 ASSAYS FOR ALZHEIMER'S DISEASE.

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Background: Phosphorylated tau (pTau) is a highly specific biomarker for detecting Alzheimer's disease (AD) pathology. Among plasma pTau biomarkers, pTau-217 has demonstrated superior diagnostic accuracy compared to pTau-181 biomarkers. However, the availability of pTau assays in standard clinical laboratory analyzers has been limited,

hindering their broader adoption in routine clinical practice. To date, there is one FDA-approved assay for the ptau-217/Aβ42 ratio. The introduction of pTau assays on commercially available in vitro diagnostics platforms widely used in clinical laboratories could significantly facilitate the adoption of biomarkers into clinical workflows. Establishing interpretative cut-offs with high sensitivity, specificity and predictive values is critical for maximizing their clinical utility.

Objective: This study aimed to establish and validate interpretative cut-offs for the Elecsys pTau-181 and pTau-217 assays to detect amyloid pathology in patients with symptoms of dementia or AD. **Methods:** The study was conducted in two phases. In the first phase, cut-offs for pTau-217 and pTau-181 were determined. EDTA plasma samples were collected from patients with amyloid PET scan data and cerebrospinal fluid (CSF), sourced from the Cleveland Alzheimer's Disease Research Center and the Cleveland Clinic Lou Ruvo Center for Brain Health, Aging, and Neurodegenerative Disease Biobank. A total of 69 plasma samples were analyzed for pTau-181 and pTau-217 using the Elecsys assays (Roche Diagnostics) and the cobas® e801 analytical analyzer. Corresponding CSF samples were assayed for amyloid-beta (Aβ42), total tau (tTau), and pTau-181, and the pTau181/Aβ42 and tTau/Aβ42 ratios were calculated. Biostatistical analyses were conducted to determine the optimal cutoffs for amyloid positivity, targeting an 85–90% concordance rate with amyloid-PET results. Additionally, a two-cutoff approach was explored to refine classification performance. In the second phase, the cutoffs established in Phase I were validated by comparing the qualitative classification of cerebrospinal fluid (CSF) and plasma samples from the same patients. A total of 187 matched CSF and EDTA plasma samples were included. Plasma samples were assayed for pTau-181 and pTau-217, while CSF samples were analyzed for pTau181/Aβ42 and tTau/Aβ42. Concordance between the plasma- and CSF-based classification was evaluated to validate the proposed cutoffs. **Results:** The receiver operating characteristics (ROC) curves demonstrated good concordance between plasma biomarkers and amyloid PET, with an area under the curve (AUC) of 0.876 (95% CI: 0.781-0.876) and 0.917 (95% CI: 0.830-0.917) for pTau-181 and pTau-217, respectively. Using Youden's J statistics, the optimal thresholds (95% CI) were 1.005 (0.821, 1.049) for pTau-181 and 0.249 (0.233-0.279) for pTau-217, with sensitivity/specificity values of 84%/92% for pTau-181 and 93%/92% for pTau-217. At a disease prevalence of 62.3%, the negative predictive value (NPV) and positive predictive value (PPV) were 0.791 and 0.947 for pTau-181, and 0.889 and 0.952 for pTau-217. These thresholds were consistent with those derived using CSF biomarker ratios. In an independent validation cohort of 187 matched CSF-plasma samples, using the pTau-181/Aβ42 ratio as the reference standard, pTau-181 achieved a sensitivity of 84% and specificity of 88%, and pTau-217 a sensitivity of 94% and specificity of 82%. A two-cut-off approach was also established for pTau-217. When applying the two cut-offs to the original cohort (n = 69) and comparing plasma pTau-217 to amyloid PET, the assay demonstrated a sensitivity of 98% (95% CI: 93%, 100%) and a specificity of 73% (95% CI: 54-88%) at a cutoff of 0.220. At a higher cutoff of 0.293, sensitivity decreased to 84% (95% CI: 72-93%), while specificity improved to 92% (95% CI: 81-100%). The proportion of cases classified as intermediate was 17.3%. In the validation cohort (n=187), using CSF-based classification as the reference, the pTau-217 assay demonstrated a sensitivity of 96% (95% CI: 92-99%) and a specificity of 80% (95% CI: 64-92%) at the 0.220 cutoff. At the 0.293 cutoff, sensitivity was slightly lower at 92% (95% CI: 88-96%), but specificity reached 100% (95% CI: 100-100%). The proportion of intermediate cases in the validation sample was reduced to 5.4%. **Conclusions:** These results confirm the robustness of the proposed plasma cutoffs for the Elecsys pTau-181 and pTau-217 assays in identifying amyloid pathology. The pTau-217 assay demonstrated strong diagnostic performance, with high sensitivity and specificity across the establishment and validation cohorts. The use of a two-cutoff approach effectively reduced the number of intermediate classifications. These findings support the clinical utility of plasma pTau-217 as a reliable and accessible biomarker for Alzheimer's disease, facilitating broader clinical adoption of blood-based biomarkers for detecting amyloid pathology.

Keywords: Blood-based biomarkers, cut-offs, pTau, amyloid pathology.
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Key takeaway message: The Elecsys pTau-217 assay demonstrated robust diagnostic performance for detecting amyloid pathology, with high sensitivity and specificity across both the discovery and validation cohorts, and the two-cutoff approach effectively minimized the proportion of intermediate classifications.

P197- HIGH DIAGNOSTIC PERFORMANCE OF THE RANDOM-ACCESS HISCL-5000 PTAU217, Aβ42 AND Aβ40 PLASMA ASSAYS FOR DETECTING AMYLOID PATHOLOGY ACROSS THE ALZHEIMER'S DISEASE CLINICAL CONTINUUM.

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Background: Alzheimer's disease (AD) blood biomarkers are now being implemented. Particularly plasma phosphorylated tau217 (pTau217) and the pTau217 over amyloid-beta (Aβ)42 ratio measured on high performing technologies are considered ready for use in clinical and trial settings to detect cerebral amyloid pathology (i.e., (Amyloid positive or negative (A+ or A-) status). To facilitate clinical uptake, robust assays on fully automated random-access instruments are required. Random-access technologies offer flexibility, accessibility and scalability in comparison to batch-based technologies, which are essential characteristics for use in a clinical and trial settings. Sysmex developed assays for pTau217, Aβ42 and Aβ40 quantification on their random-access Automated Immunoassay System HISCLTM-5000 / HISCL-800. Here, we sought to clinically validate these assays for their potential to detect amyloid pathology across the clinical AD continuum. **Methods:** We selected plasma samples from the Amsterdam Dementia Cohort of 50 subjects with subjective cognitive decline (SCD) who were A- (40% female, median age 65 [interquartile range (IQR); 61–69] years), 50 SCD A+ subjects (40% female, median age 66 [61–71] years), 50 mild cognitive impairment (MCI) A- subjects (40% female, median age 67 [61–72] years), 50 MCI A+ subjects (40% female, median age 68 [61–71] years), and 50 AD-dementia subjects (40% female, median age 67 [62–70] years). Amyloid status was based on cerebrospinal fluid analysis of core-1 AD biomarkers. Samples were measured on the HISCLTM-5000 platform in duplicates for the biomarkers pTau217, Aβ42 and Aβ40. As a benchmark, the same samples were also measured on the Lumipulse platform for the same biomarkers. All measurements were performed in the first freeze-thaw cycle and according to manufacturer's instructions. Mann-Whitney U tests with Benjamini-Hochberg correction for multiple testing and ROC AUC analyses were conducted. **Results:** Average coefficients of variation (CV) of duplicate measurements reflecting the repeatability precision of the HISCLTM-5000 assays were 3.3% for pTau217, 1.4% for Aβ42 and 1.4% for Aβ40 across all plasma samples. Plasma pTau217 levels measured on the HISCLTM-

5000 were significantly increased in all A+ subjects (SCD A+, MCI A+ and AD-dementia groups) when compared to A- subjects (SCD A- and MCI A- groups; all p<0.001FDR), with no difference between SCD A- and MCI A-. A stepwise increase in plasma pTau217 levels was observed across all A+ stages: from SCD A- to SCD A+ (%change of median: +188%, pFDR<0.001), from SCD A+ to MCI A+ (+43%, pFDR=0.001) and from MCI A+ to AD dementia (+114%, pFDR<0.001). Similar findings were obtained when pTau217 is measured with the Lumipulse platform, albeit with a slightly lower %change of the median in the comparison SCD A- to SCD A+ (i.e., +119% instead of +188%). The plasma Aβ42/40 ratio measured on HISCLTM-5000 was significantly decreased in the SCD A+, MCI A+ and AD dementia groups compared to the SCD A- and the MCI A- group (all: pFDR<0.001; range %change of median A+ versus A- groups: -7.8% – -10.2%), whereas there was no difference in plasma Aβ42/40 levels between the A+ groups. Similar findings were observed when Aβ42/40 ratio was measured on Lumipulse. HISCLTM-5000 group differences observed for pTau217 alone were highly similar to group differences observed for the pTau217/Aβ42 ratio, except that discrimination between A+ and A- in the SCD stage was enhanced (median %change 220% for the pTau217/Aβ42 ratio compared to +188% for pTau217 alone). HISCLTM-5000 pTau217 discriminated A+ from A- with an AUC of 0.92 (95%CI: 0.89 – 0.96), the HISCLTM-5000 pTau217/Aβ42 ratio discriminated A+ from A- with an AUC of 0.93 (95%CI: 0.89 – 0.96) and the HISCLTM-5000 Aβ42/A40 ratio discriminated A+ from A- with an AUC of 0.80 (95%CI: 0.74 – 0.86). ROC-AUCs for Lumipulse measurements were similar to those obtained for HISCLTM-5000 measurements for pTau217 and pTau217/Aβ42 ratio (both DeLong's p > 0.155), whereas ROC-AUC was higher for the HISCLTM-5000 Aβ42/40 ratio compared to the Lumipulse Aβ42/40 ratio (DeLong's p: 0.02, ΔAUC: 0.08). Zooming in on the SCD stage (SCD A- vs SCD A+), HISCL-5000 pTau217 yielded an AUC of 0.90 (95%CI: 0.84 – 0.96), pTau217/Aβ42 ratio an AUC of 0.91 (95%CI: 0.85 – 0.97) and the Aβ42/40 ratio an AUC of 0.74 (95%CI: 0.63 – 0.84). AUCs obtained with Lumipulse for these same markers were comparable (all DeLong's p>0.05), but AUC of pTau217/Aβ42 tended to be higher for HISCLTM-5000 compared to Lumipulse (DeLong's p=0.506; Δ0.05). **Conclusions:** We have clinically validated the HISCLTM-5000 / HISCL-800 pTau217, Aβ42 and Aβ40 plasma assays, and found them fit for purpose to detect amyloid pathology across the clinical AD continuum. Robust clinical assays on random-access instruments will streamline participant recruitment for clinical trials and diagnostic decision making in dementia care.

Key takeaway message: We have clinically validated the HISCLTM-5000 / HISCL-800 pTau217, Aβ42 and Aβ40 plasma assays and found excellent diagnostic accuracy to detect amyloid pathology, also in the earliest clinical stage, i.e., subjects presenting at memory clinics with subjective cognitive decline.

P198- MULTIOMICS BLOOD BIOMARKERS COMBINED WITH AMYLOID STATUS IMPROVE PREDICTION OF ALZHEIMER'S DEMENTIA IN COGNITIVELY UNIMPAIRED INDIVIDUALS.

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Background: Amyloid biomarkers lack the specificity to predict which cognitively normal individuals will progress to Alzheimer's disease (AD) dementia. Up to 70% of amyloid-positive individuals without cognitive impairment remain non-converters over their lifetime (1). With the advent of disease-modifying therapies, more specific biomarkers are urgently needed to optimize secondary prevention trials, as amyloid's limited accuracy undermines both efficiency and impact. **Methods:** We analyzed 258 cognitively unimpaired individuals from seven independent cohorts in the United States, Europe, and Australia, each with baseline plasma samples and longitudinal follow-up of up to 18 years. Over this period, 48 participants (18.6%) developed AD dementia symptoms (converters), while 210 (81.4%) remained cognitively stable (non-converters). Baseline amyloid status was available for 212 participants (82.2%), of whom 42.9% were amyloid-positive. ApoE genotype was available for all individuals, with 32.6% identified as ApoE4 carriers. A total of 81 blood biomarkers (45 proteins and 36 metabolites), initially identified in the AAV-AD rat model, were quantified using targeted mass spectrometry. Biomarker selection and predictive model training were performed on 70% of the dataset, with the remaining 30% reserved as an independent blind validation cohort. **Results:** The B-AHEAD predictive model, integrating 9 biomarkers (2 proteins and 7 metabolites) with ApoE genotype, achieved 83.3% specificity and 56.3% sensitivity in blind validation on the test dataset. 4 of the selected metabolites were linked to mitochondrial dysfunction, highlighting its role in the earliest stages of AD. Combining amyloid status with B-AHEAD further improved performance, yielding 98.2% specificity and 46.2% sensitivity. Among cognitively normal and amyloid-positive individuals, 42.9% converted to AD symptoms; this rate increased to 85.7% when participants were also B-AHEAD–ApoE positive. **Conclusions:** Incorporating amyloid status with multiomics blood biomarkers, particularly those reflecting mitochondrial dysfunction, improves prediction of which cognitively normal individuals will progress to AD dementia symptoms. This refinement reduces enrollment of non-converters and increases the efficiency and impact of preventive clinical trials.

Keywords: Blood-based biomarkers, asymptomatic Alzheimer's, animal model, machine learning, mass spectrometry, mitochondrial dysfunction.

Disclosures: BS, SS, BB and JB are AgenT employees.

References: 1. Brookmeyer R and Abdalla N., Alzheimers Dement. 2018;14(8):981-8.

Key takeaway message: Combining amyloid with a multiomic blood biomarker panel achieves high specificity in predicting progression to Alzheimer's dementia, reducing non-converter enrollment, to improve efficiency of preventive clinical trials.

P199- VERABIND TAU: A NOVEL PLASMA ASSAY REFLECTING TAU AGGREGATION IN ALZHEIMER'S DISEASE INCREASES OVER TIME IN INDIVIDUALS WITH POSITIVE TAU-PET SIGNAL.

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Background: Blood-based biomarkers are critical for clinical trials, not only for confirming Alzheimer's disease pathology, but also for monitoring drug efficacy. The concentration of tau hyperphosphorylated at specific epitopes (e.g., pTau217) is frequently elevated in the context of isolated amyloid-β pathology (A+). Plasma assays associated with tau aggregation (T+), as observed using tau PET imaging, are still in development. Here, we present results of the VeraBIND Tau, a plasma assay that isolates pathologically active hyperphosphorylated tau (HP-tau) from the plasma and uses normal tau with a recombinant tag for subsequent anti-tag conjugate chemiluminescence to evaluate whether HP-tau is able to bind to and aggregate normal tau, i.e., testing whether the isolated plasma HP-tau is pathologically active. **Methods:** Two hundred sixty-eight plasma samples were collected from 145 participants in an ongoing prospective study at UCLouvain, Belgium over an average 1.7±0.9 years [min: 0.4, max: 3.9]. A+ status was determined

using either CSF (Aβ42≤544pg/mL) or amyloid-PET (Centiloid≥20). F18MK6240 tau-PET status was determined visually as negative (Braak 0) or positive (Braak≥1). Plasma pTau217 was quantified using Lumipulse (Fujirebio). At the time of tau-PET, 79 participants were clinically normal (CN, 21A+) and 66 clinically impaired (MCI/AD, 52A+). **Results:** Using tau-PET as ground truth for tau in these 145 participants, VeraBIND Tau detected 58 of 60 A+T+ participants (sensitivity=96%) and excluded tauopathy in 59 of 62 A-Tparticipants (specificity=95%). Sensitivity was equivalent in low (Braak-like 1-3, 93%) and high (Braak-like 4-6, 95%) tau-PET stages. In contrast, pTau217 sensitivity was lower in Braak-like 1-3 (48%) vs. Braak-like 4-6 (93%) tau-PET stages. VeraBIND Tau was more often positive in A-T+ (7/9) than in A+T- (4/13) individuals, indicating higher association with tau aggregates than with amyloid plaques. In contrast, pTau217 was more often positive in A+T- (7/13) than in A-T+ (2/9) individuals. In longitudinal analyses of 207 EDTA plasma samples collected from 88 of these 145 participants at 2 to 5 different collection time points relative to their F18MK6240 tau-PET imaging dates (0.6±1.3 years; min: -2.5, max: 5.5), VeraBIND Tau demonstrated 93.8% sensitivity (95CI, 85.6-97.7), 97.6% specificity (95CI 92.7-99.4), and an overall accuracy of 96.1% (ROC-AUC 0.956) as compared against tau PET with accuracies of 97.2% (A-T-: N=106), 100% (A-T+: N=6), 100% (A+T-: N=20), and 93.3% (A+T+: N=75) based on both amyloidosis and tau pathology status. The annual change in VeraBIND Tau was associated with Braak stages (ageadjusted Spearman's rho=0.32, p=0.002), entorhinal tau-PET SUVr (rho=0.27, p=0.012), lower episodic memory z-scores (rho=-0.36, p=0.001), and lower MMSE scores (rho=- 0.41, p=0.0001), indicating that VeraBIND Tau measures (VeraBIND Tau Scores) increase with disease progression. Five individuals had initial negative VeraBIND Tau test while it became positive during follow-up. Of note, two had positive tau-PET with a retrospective negative sample; and three had negative tau-PET with a prospective positive sample. All positive VeraBIND tests retested positive after follow-up. **Conclusions:** Whereas pTau217 is more closely associated with amyloid than tau-PET results, VeraBIND Tau is highly sensitive to early tau-PET positivity, indicating active tau aggregation, with or without amyloidosis. The mismatch between pTau217 and VeraBIND results provides a plasma indication of discordant A/T PET-status that would provide useful information in clinical trial recruitment. The longitudinal analyses indicate >96% test-retest reliability and high correlation with disease progression, highlighting the potential of VeraBIND Tau for monitoring disease progression and drug efficacy.

Keywords: Alzheimer's disease, tau pathology, blood biomarker, diagnostics, clinical trials, patient stratification. **Disclosures:** J. Soldo is the Chief Scientific Officer and shareholder of Veravas, Inc., a co-inventor of the VeraBIND Tau assay. L. Quenon has nothing to disclose. K. Shamsundar is an employee and shareholder of Veravas, Inc. W. Pak is a paid consultant for Veravas, Inc. K. Iqbal is the Chief Scientific Officer of Phanes Biotech, Inc., and co-inventor of the VeraBIND Tau assay. B. Hanseeuw has served as a paid consultant for Biogen, Eisai, Lilly, and Roche over the past five years. These disclosures are unrelated to the present work. Funding for the presented work was provided by Veravas, Inc.

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Key takeaway message: VeraBIND Tau is a sensitive, specific, and accurate measure of hyperphosphorylated tau aggregation activity in plasma; it is highly correlated with disease progression, highlighting the potential for use in monitoring disease progression and drug efficacy.

P200- CHANGES OF BLOOD BIOMARKER IN ALZHEIMER'S DISEASE DURING LECANEMAB TREATMENT: A REAL-WORLD CLINICAL STUDY.

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Background: Alzheimer's disease (AD) is the most common age-related cognitive disorder, posing a substantial global public health and socio-economic burden. The advent of disease-modifying therapies like Lecanemab, a monoclonal antibody targeting amyloid-β (Aβ), has revolutionized Alzheimer's disease (AD) treatment. However, real-world dynamics of blood biomarkers across treatment timelines remain unclear. Molecular imaging (e.g., Aβ-PET, Tau-PET) examinations and cerebrospinal fluid (CSF) tests are limited for routine monitoring due to high cost, low accessibility, and invasiveness. In contrast, blood biomarkers offer minimal invasiveness, affordability, and repeatability, making them pivotal for assessing AD treatment efficacy -with advanced platforms (e.g., Lumipulse G 1200) enabling high-sensitivity, automated detection, facilitating clinical application. This study aimed to characterize dynamic, time-dependent changes in core blood biomarkers s (Aβ42, Aβ40, pTau217) in AD patients undergoing Lecanemab treatment , aligning with reported findings to validate their real-world utility in monitoring therapeutic response. **Methods:** In this multicenter, real-world study, patients with Alzheimer's disease (AD) confirmed by Aβ-PET and Tau-PET were enrolled from two clinical centers in China. All patients received a standardized regimen of Lecanemab (10 mg/kg bi-weekly IV infusion). Over a follow-up period of 3–8 months,serial peripheral blood samples were collected alongside clinical and cognitive assessments. Plasma levels of Aβ42, Aβ40, and pTau217 were quantified using the fully automated Lumipulse G1200 platform. The primary outcome measure was the change in blood biomarker concentrations from the baseline to the final follow-up. The secondary outcome included the longitudinal dynamic change characteristics and timing differences of blood biomarkers with treatment time. The Wilcoxon test was used to compare biomarker concentrations. The linear mixed - effects model was used to analyze the dynamic changes of biomarkers with treatment time. The local weighted scatterplot smoothing method was used to analyze the overall change trend and timing of biomarkers. All statistical analyses were performed using R software (version 4.4.1), and a two-tailed $P<0.05$ was considered statistically significant. **Results:** A total of 23 patients with PET-confirmed Alzheimer's disease were enrolled, with a median follow-up of 184 days (IQR: 175-202). Lecanemab treatment induced significant, opposing changes in key plasma biomarkers. Primary outcomes: levels of Aβ42 and Aβ40 were significantly elevated from baseline, with median fold changes of 9.41% and 10.64%, respectively ($P=0.003$, $P<0.001$). Aβ42/Aβ40 ratio: There was no significant difference at the end of follow-up compared with baseline ($P=0.665$). pTau217 and pTau217/Aβ42 ratio: At the end of follow - up, they were significantly lower than those at baseline, with median fold changes of - 11.79% and - 18.61%, respectively ($P=0.013$, $P=0.002$). Secondary outcomes: Biomarkers showed time-dependent changes during treatment. (1) Indicators with an increasing trend: Aβ42 increased by an average of 0.4115 pg/mL per month (monthly increase relative to baseline was 1.86%, $P<0.001$), Aβ40 increased by an average of 3.1099 pg/mL per month (monthly increase relative to baseline was 1.09%, $P=0.002$), and the Aβ42/Aβ40 ratio increased by an average of 0.0005 per month (monthly increase relative to baseline was 0.64%, $P=0.014$). (2) Indicators with a decreasing trend: pTau217 decreased by an average of 0.0176 pg/mL per month (monthly decrease relative to baseline was 2.24%, $P=0.031$), and the pTau217/Aβ42 ratio decreased by an average of 0.0011 per month (monthly decrease relative to baseline was 3.21%, $P=0.002$). (3) Differences in timing of change: Plasma Aβ42/40 showed a tendency to

stabilize earlier over the course of Lecanemab treatment, while pTau217 and the pTau217/Aβ42 ratio exhibited a later trend toward a stable pattern, with their dynamic trajectories reflecting a temporal change profile in response to the therapy. **Conclusions:** In this real-world study, Lecanemab treatment induced a reversal of core AD blood biomarker trajectories, characterized by rising Aβ42/Aβ40 and declining pTau217, with Aβ-pathway changes preceding pTau217 reduction, showed dynamic changes opposite to the natural course of AD.These results suggest that Lecanemab treatment may reverse the pathological damage process related to AD to a certain extent. At the same time, it indicates that blood biomarkers can effectively reflect the pathological changes of AD after antibody treatment and have the potential to be used as clinical efficacy monitoring indicators, providing a minimally invasive and convenient tool for individualized evaluation of AD treatment. This study has limitations, including its small sample size (n=23), relatively short follow-up (≤8 months), and the absence of a control group. Future larger-scale, longer-term multicenter studies are warranted to validate the consistency of these blood-based measures with established biomarkers (e.g., Aβ-PET) and to explore their utility as predictive biomarkers of treatment response.

Key takeaway message: Lecanemab treatment induced a reversal of core AD blood biomarker trajectories, characterized by rising Aβ42/Aβ40 and declining pTau217, with Aβ-pathway changes preceding pTau217 reduction.

P202- SPECTRISTM TREATMENT MAY MITIGATE THE NATURAL PROGRESSION OF RESTING STATE EEG IN ALZHEIMER'S DISEASE.

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Background: Pathological changes in neural activity associated with Alzheimer's disease (AD) can be revealed by electroencephalography (EEG). The most consistent findings are increased power in low-frequency bands (delta, theta) and decreased power in high-frequency bands (alpha, beta) compared with cognitively healthy age-matched subjects (1). These changes reflect inhibitory-excitatory imbalances and correlate with disease progression and cognitive decline. In the OVERTURE feasibility trial of the Spectris™ investigational device (NCT03556280), EEG recordings were obtained from participants with mild or moderate AD at baseline, 3-months, and 6-months during resting state and sensory stimulation (2). The current analysis assessed whether Spectris treatment modulated AD-related EEG changes. **Methods:** The OVERTURE randomized controlled trial (RCT) evaluated the safety, tolerability, and efficacy estimates of Spectris treatment, which induces 40 Hz steady-state oscillations through combined auditory and visual stimulation. Of 76 participants randomized, 53 completed the 6-month study. Resting-state EEG and sensory-evoked steady-state gamma oscillations were recorded from each participant at baseline, 3-months, and 6-months from a standard 10/20, 30-channel montage (ANT-Neuro). Resting-state EEG was collected under both eyes-closed and eyes-open conditions. In total, 172 eyes-closed and 167 eyes-open EEG recordings from 68 participants passed data quality checks and were analyzed. Recordings were band passed filtered, re-referenced to the average of all channels, had noisy epochs removed, and underwent independent component analysis to remove artifact components. Power spectral density (PSD) was calculated on the resulting clean data using the welch function with a 2-second window with 1-second overlap. Absolute and relative power were calculated for the delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta1 (12–18 Hz), and beta2 (18–25 Hz) frequency bands. In addition, peak alpha frequency (PAF) and the ratios of theta-to-alpha power and delta-to-alpha power were determined. Baseline EEG characteristics were compared to the Firefly Neuroscience Normative EEG Database of age-matched, cognitively healthy subjects. Statistical analysis of baseline recordings included z-score normalization and t-test comparisons to the normative database; changes in EEG parameters from baseline to 6-months between the sham and active treatments were analyzed using a linear mixed-effects model to measure visit x treatment interaction effects after controlling for age and sex. As this was an exploratory analysis, corrections for multiple comparisons were not performed. **Results:** Compared to the Firefly Normative EEG Database of age-matched, cognitively healthy subjects, participants in the OVERTURE trial showed significant differences in multiple EEG signals (n = 68, one-sample t-test). At baseline, resting-state, eyes-closed EEG recordings from OVERTURE participants revealed significantly higher theta and delta power, lower alpha and beta power, and a lower peak alpha frequency relative to normative data. In addition, both theta/alpha and delta/alpha power ratios were significantly higher. These differences were observed across all brain regions analyzed, including left/midline/right frontal, central, and occipitoparietal regions. None of these EEG measures differed significantly between the active (n = 41) and sham (n = 27) groups at baseline. Of the 53 participants who completed the 6-month trial, resting-state EEG was available from 34 participants (n=23, active; n = 11, sham). Significant group differences (interaction effect: visit × treatment) were detected almost exclusively in the occipitoparietal region. Specifically, significant differences between active and sham group participants were observed in relative alpha power ($p = 0.001$; Cohen's $f2 = 0.09$), and theta/alpha ($p = 0.002$; Cohen's $f2 = 0.1$) and delta/alpha ($p = 0.001$; Cohen's $f2 = 0.08$) power ratios during the eyes-closed condition, with active treatment associating with higher alpha power and lower theta/delta power. Significant differences were also found in relative power of beta1 band ($p = 0.025$; Cohen's $f2 = 0.04$) and theta/alpha ratio ($p = 0.002$; Cohen's $f2 = 0.08$) during the eyes-open condition. Overall, the sham group showed increasing theta/delta power with decreasing alpha power, consistent with typical AD progression, whereas the active group showed changes in the opposite direction. **Conclusions:** Spectris treatment altered the course of resting-state EEG progression over 6-month as compared with sham stimulation in mild or moderate AD participants in the OVERTURE study. At baseline, eyes-closed resting state EEG recordings revealed higher power in low-frequency bands and lower power in high-frequency bands when compared with healthy controls. After 6 months, changes in resting-state EEG from baseline revealed significant differences between active and sham group participants. These results provide initial neurophysiological evidence that Spectris treatment may attenuate AD-related EEG alterations, suggesting an improvement in pathological neuronal activity. Such neurophysiological improvements may be linked to preliminary efficacy data which showed a reduced decline in cognitive and functional abilities together with brain volume preservation in OVERTURE trial participants with AD2.

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Key takeaway message: SpectrisTM treatment altered the course of resting-state EEG progression over 6-months as compared with sham stimulation.

P203- NATURALLY OCCURRING IGG TARGETING NEUROTOXIC Aβ42 OLIGOMERS IN HEALTHY ELDERLY.

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Background: Naturally occurring antibodies (NAb), produced by B-1 cells of the innate immune system without prior antigen exposure, contribute to infection defense, clearance of cellular debris and misfolded proteins, and regulation of autoimmunity. Research on NAb in Alzheimer's disease dates back to 1993, yet results have been contradictory with some studies suggesting protective effects and others

pathogenic roles. These inconsistent findings may stem from the use of Aβ peptides or fragments that do not accurately represent the toxic species involved in disease. In this study, we investigated NAb reactive towards the oligomeric Aβ42 antigen used in vaccine ALZ-101, which presents a unique and immunogenic conformational epitope. This is the first clinical assessment of baseline NAb levels selective for the Aβ42 oligomer epitope, which was previously shown in non-clinical studies on brain-derived Aβ to be disease-relevant. **Methods:** Drug-naïve and post-ALZ-101 vaccination serum and CSF samples from 32 individuals (age 68.5±6.42 (SD) diagnosed with early AD (MMSE 24.1 (±3.03) were collected as part of clinical study ALZ-C-001 (NCT05328115). Sera from healthy young individuals (n=10; average age of 26.7 ± 1.5 (SD) and healthy elderly individuals (n=10; average age of 66.4 ± 3.6 (SD) were acquired from BioIVT. A follow-on confirmatory experiment assessed additional serum samples from human healthy individuals (n=3; average age of 52.7 ± 10.0 (SD) and non-human primate serum controls, also acquired from BioIVT. Samples were analyzed by ELISA for reactivity against the Aβ42CC oligomer antigen in vaccine ALZ-101. Sera were diluted in twofold (1:2) serial dilutions, starting with 1:10. Protein A or an anti-IgG were used for detection. **Results:** Unexpectedly high levels of naturally occurring IgG antibodies against the ALZ-101 epitope were detected in individuals without prior antigen exposure. In healthy elderly subjects, antibody signals were 1.6-fold higher than in young individuals ($P = 0.072$, pooled t-test) and 1.8-fold higher than in age-matched participants from study ALZ-C-001 ($P = 0.055$, Welch's t-test). A follow-on experiment confirmed that healthy individuals had significantly greater NAb amounts than early AD patients. Moreover, IgG titers in healthy individuals were comparable to those of ALZ-101-vaccinated AD patients. In clinical trial samples, anti-ALZ-101 antibodies were detectable in CSF only after vaccination, suggesting that NAb in healthy elderly may reach concentrations allowing CNS exposure comparable to post-vaccination levels. **Conclusions:** These findings support the hypothesis that ageing may increase exposure to brain-derived neurotoxic Aβ42 species driving production of protective antibody responses, whereas failure to respond may predispose to the development of AD. The predominance of the IgG isotype and the high levels of NAb in healthy elderly align with a potential protective role across the tightly regulated blood-brain-barrier. Restoration of these antibodies through ALZ-101 vaccination could therefore represent an attractive strategy to prevent disease progression.

Keywords: Naturally occuring antibodies, Aβ42 oligomer.

Key takeaway message: High levels of naturally occurring IgG antibodies against oligomeric Aβ42 were found in healthy elderly, suggesting a protective role; their restoration by ALZ-101 vaccination may offer a strategy to slow Alzheimer's progression.

P204- PLASMA GFAP IDENTIFIES A TRANSITIONAL PATHOPHYSIOLOGICAL STAGE FROM MISFOLDED PROTEIN ACCUMULATION TO NEURODEGENERATION IN ALZHEIMER'S DISEASE.

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Background: Plasma glial fibrillary acidic protein (GFAP) has recently attracted attention as a blood-based biomarker of astrocytic activation and neuroinflammation in Alzheimer's disease (AD) (1). While GFAP levels are known to increase with disease progression, its exact temporal positioning within the AD biomarker cascade—particularly in relation to amyloid-β (Aβ), tau pathology, and neurodegeneration—remains insufficiently defined. Clarifying this sequence is critical for interpreting GFAP changes and for understanding its potential role in disease staging. To address this gap, we applied causal mediation analysis and structural equation modeling (SEM) (2)across two large independent cohorts to delineate the temporal placement of plasma GFAP within the AD biomarker cascade. **Methods:** We analyzed 2,495 participants from the Korea-Registries to Overcome Dementia and Accelerate Dementia Research (K-ROAD) and 307 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Plasma biomarkers included GFAP, phosphorylated tau 217 (pTau217), and neurofilament light chain (NfL). Amyloid burden was quantified in Centiloid units from PET, and global cognition was assessed with MMSE. Mediation analyses were performed to test whether GFAP mediates the effects of APOE ε4 on AD-related biomarkers, and SEM was applied to evaluate alternative biomarker cascade models. All analyses were adjusted for age and sex. **Results:** Mediation analyses showed that GFAP elevations were downstream of Aβ and tau. In K-ROAD, the average causal mediation effect (ACME) was significant for both Aβ ($\beta = 0.08$, $p < 0.001$) and tau ($\beta = 0.06$, $p < 0.001$), with nonsignificant direct effects. Similar results were replicated in ADNI (Aβ: $\beta = 0.07$, $p = 0.002$; tau: $\beta = 0.05$, $p = 0.01$). Reverse models specifying GFAP as the mediator yielded weaker effects (proportion mediated < 10%). In contrast, associations of GFAP with NFL and cognition suggested bidirectional influences, but evidence was less robust across cohorts. Structural equation modeling further supported the positioning of GFAP between tau and neurodegeneration. The model in which GFAP was positioned between tau pathology and neurodegeneration (Aβ → tau → GFAP → NFL → cognition) showed the best fit in both cohorts (K-ROAD: CFI = 0.84, RMSEA = 0.14; ADNI: CFI = 0.83, RMSEA = 0.16), outperforming models that placed GFAP earlier or later in the cascade. Collectively, these findings highlight GFAP as an intermediate biomarker within the AD continuum, bridging tau pathology and subsequent neurodegeneration. **Conclusions:** Plasma GFAP is positioned downstream of Aβ and tau pathology, but prior to overt neurodegeneration, indicating its role as an intermediate biomarker in the AD cascade. These findings suggest that GFAP may serve as a stage-specific marker for disease monitoring and progression modeling, and provide further insight into the contribution of astrocytic activation in AD pathophysiology.

Keywords: Glial fibrillary acidic protein, plasma biomarkers, mediation analysis, structural sequation modeling. **Disclosures:** The authors declared no competing interests.

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Key takeaway message: Plasma GFAP reflects a transitional pathophysiological stage in Alzheimer's disease, positioned after misfolded protein accumulation but before neurodegeneration, highlighting its potential as a stage-specific biomarker for disease monitoring and progression assessment.Plasma GFAP reflects a transitional pathophysiological stage in Alzheimer's disease, positioned after misfolded protein accumulation but before neurodegeneration, highlighting its potential as a stage-specific biomarker for disease monitoring and progression assessment.

P205- ASSOCIATION OF NEIGHBORHOOD-LEVEL DISADVANTAGE WITH ALZHEIMER'S DISEASE BLOOD BASED BIOMARKERS.

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Background: The advent of anti-amyloid therapies has created a pressing need for accessible biomarkers to confirm amyloid pathology for clinical trial eligibility and treatment monitoring. Blood-based biomarkers (BBMs) offer a scalable solution, but for them to be broadly applicable in multi-site clinical trials, their performance must be consistent and reliable across diverse populations and geographies. Neighborhood-level factors, measured by the Area Deprivation Index

(ADI), are linked to health conditions (1-9) that might impact BBM performance (10-15). However, the direct relationship between neighborhood disadvantage and core Alzheimer's disease (AD) pathology remains unclear. This study investigates the relationship between neighborhood-level characteristics, as measured by ADI, and the prevalence of AD amyloid pathology and assesses whether the predictive performance of plasma BBMs for amyloid PET status is consistent across different levels of neighborhood disadvantage. **Methods:** This cross-sectional study utilized data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). The cohort included 755 participants with national ADI data and an amyloid PET scan. The primary analyses were conducted on a sub-cohort of 438 individuals who also had plasma BBM data (p-tau217, Aβ42, Aβ40) collected at a mean interval of 1.35 ± 2.73 months from their PET scan. Participants were stratified into three groups based on their national ADI percentile: least disadvantaged (G1, national ADI <20), intermediately disadvantaged (G2, national ADI of 20-40), and most disadvantaged (G3, national ADI > 40). Amyloid PET scans were acquired using either 18F-Florbetapir or 18F-Florbetaben, with results converted to the Centiloid scale. Plasma BBMs (p-tau217, Aβ42, and Aβ40) were measured using Fujirebio assays. We also collected data on key AD risk factors (age, sex, APOE e4 status, ethnoracial background, educational attainment), cognitive status (CDR-SB and MMSE), and comorbid health conditions (body mass index (BMI) and estimated glomerular filtration rate (eGFR). These variables were considered as covariates for the adjusted models based on their significance in ADI group differences and their established relevance to BBMs and amyloid PET imaging. First, the prevalence of amyloid PET positivity across ADI groups was assessed using logistic regression (unadjusted and adjusted for sex). Second, differences in BBM levels by ADI group were evaluated with Wilcoxon rank-sum tests and effect sizes in three models (unadjusted, adjusted for sex, adjusted for sex and BMI). The association between BBMs and Centiloid within ADI groups was assessed with correlation analyses and partial correlations adjusted for age and sex, as well as age, sex, BMI, and eGFR. Third, to evaluate the predictive performance of BBMs for amyloid PET positivity, we applied a two-cut point approach targeting ^{3} 90% sensitivity and ^{3} 90% specificity, classifying cases between the thresholds as "indeterminate". This analysis was conducted in an unadjusted model, a model adjusted for age, sex, and APOE e4 status, and a model adjusted for age, sex, APOE e4 status, BMI, and eGFR. Classification performance metrics were compared between ADI groups using Wilcoxon signed rank tests. Finally, a sensitivity analysis was performed on a sub-cohort of participants with mild cognitive impairment (MCI) or dementia. **Results:** The ADI groups differed significantly by sex, ethnoracial background, and MMSE scores. The intermediately disadvantaged group (G2) had higher odds of being amyloid PET positive (OR: 1.55, p=0.033) compared to the least disadvantaged group (G1). This difference in odds was not observed between G1 and G3. G2 also exhibited significantly higher plasma levels of p-tau217/Aβ42 and p-tau217 than both the least (G1; effect size of 0.21 and 0.23, respectively) and most disadvantaged (G3; effect size of -0.13 and -0.17, respectively) groups. Despite these differences, the strong correlations between all BBMs and amyloid PET Centiloid levels were consistent across all three ADI groups (p-tau217/Aβ42 r: 0.59 to 0.76; p-tau217 r: 0.56 to 0.73; Aβ42/40 r: -0.40 to -0.49). Crucially, there were no significant differences in the accuracy, sensitivity, or specificity of any BBMs in predicting amyloid PET positivity status between the ADI groups. BBMs perform across ADI groups equally well for predicting amyloid PET positivity status. The p-tau217/Aβ42 ratio performed best overall, with high accuracy (87-91%) and the fewest indeterminate cases (6.5-12%). These performance metrics remained stable across unadjusted and adjusted models. Similar results were found in the sensitivity analysis of cognitively impaired participants. **Conclusions:** Although neighborhood disadvantage is associated with differences in the prevalence of amyloid pathology and levels of some plasma biomarkers, the ability of BBMs to accurately predict brain amyloidosis is robust and not impacted by these factors. Plasma p-tau217/Aβ42, in particular, demonstrates high accuracy and a low rate of indeterminate results regardless of a participant's neighborhood characteristics. These findings strongly support the generalizable clinical utility of plasma p-tau217/Aβ42 for participant screening and stratification in AD clinical trials, confirming its reliability across diverse communities.

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Keywords: ADI, amyloid PET, p-tau217, Aβ42.

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Key takeaway message: Our findings support the generalizability and potential clinical utility of biomarkers like plasma p-tau217/Aβ42 for AD diagnosis, even in the presence of varying neighborhood characteristics.

P206- DIAGNOSTIC PERFORMANCE OF MULTI-ANALYTE ALGORITHMS AND %P-TAU217 USING HIGH RESOLUTION LC-MS/MS IN A MIXED MEMORY CLINIC COHORT.

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Background: Alzheimer's disease (AD) affects more than 55 million people worldwide with an expected increase in prevalence in the coming years. Advancements in blood-based biomarkers have positioned these as an alternative to cerebrospinal fluid and imaging-based biomarkers. In the present study we investigated the diagnostic accuracy of multi-analyte algorithms (MAA) and %p-tau217 that use high resolution liquid chromatography, tandem mass spectrometry (LC-MS/MS) in blood in a mixed memory clinic cohort of patients referred for diagnostic assessment for cognitive impairment. **Methods:** The cohort included patients referred to the Copenhagen Memory Clinic at Rigshospitalet for diagnostic workup in the period 2021-2023 who also gave informed consent to the Danish Dementia Biobank. Moreover, patients had assessment of amyloid through CSF analysis or amyloid PET. Plasma samples were sent to C2N Diagnostics' CAP/CLIA lab in St. Louis, USA for analysis using MAA's from the PrecivityAD® and PrecivityAD2™ blood tests, APS and APS2, respectively. Data on endogenous Microtubule Binding Region of tau243 (C2N eMTBR-tau243) is ongoing and will be presented at the conference. Standard reference tests included cerebrospinal fluid (CSF) AD biomarkers (beta-amyloid1-42, p-tau181 and total tau) and amyloid PET (11C-PiB-PET). **Results:** A total of 503 patients were included in the study. Of these 407 patients had CSF results and were classified as being amyloid positive (A+) (n=169) or amyloid negative (A-) (n=238) based on pTau181/AB1-42 ratio in CSF. Results from amyloid PET are undergoing analysis and will be presented at the conference. For the CSF cohort, mean age was for A+ 71.2 years (SD ± 7.48) and for A- 73.1 years (SD ± 7.54) ($p = 0.01$) with more females in the A+ group (A+ vs A-; 104 (61.5%) vs. 96 (40.3%), $p < 0.001$) and lower MMSE (A+ vs A-; 23.65 (SD ± 4.77) vs. 25.19 (SD ± 3.99, $p = 0.002$). Using the APS2 MAA cutoffs of 27.5 APS2 and 66.5 APS2, sensitivity was 76.1% (95% CI 67.3 – 83.5) and specificity 97.7 % (95% CI 94.8 – 99.3). **Conclusions:** A two-cut-off approach with the APS2 MAA yielded a very high specificity at the cost of a moderate sensitivity demonstrating the utility of this MAA that uses high resolution LC-MS/MS in blood to detect amyloid positivity in a real-world clinical population. Further data, including PRECIVITYAD® and C2N eMTBR-tau243 results will be presented at the conference.

Keywords: Blood-based biomarkers, PRECIVITYAD, PRECIVITYAD2, diagnostics.

Disclosures: This study was supported by an in kind contribution from C2N Diagnostics, LLC.

Key takeaway message: Multi-analyte algorithms and %p-tau217 measured via high-resolution LC-MS/MS in blood show high specificity and moderate sensitivity for detecting amyloid positivity in a real-world memory clinic cohort, supporting their diagnostic utility.

P207- CLINICAL EVALUATION OF BLOOD-BASED ASSAYS FOR RAPID DETECTION OF AMYLOID-β PATHOLOGY IN ALZHEIMER'S DISEASE (CLEAR-AD) —A PROSPECTIVE, DOUBLE-BLINDED HEAD-TO-HEAD COMPARISON STUDY OF BLOOD-BASED BIOMARKER.

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Background: Blood-based biomarkers (BBM) have been shown to predict Alzheimer's disease (AD) pathology and disease progression; however, standards for detecting AD biomarkers are inconsistent. Therefore, a head-to-head comparison of the performance of commercially available biomarkers would help to optimize the clinical pathway in screening and diagnosing AD. **Methods:** The CLEAR-AD study is a prospective, double-blinded, multicenter, head-to-head comparative study. A total of 431 participants were recruited from 10 tertiary medical centers in China, including 30 cognitively normal controls (CN), 99 mild cognitive impairment (MCI) patients with negative amyloid PET (Aβ), 131 MCI patients with positive amyloid PET (Aβ+), 144 AD dementia patients, and 27 non-AD dementia patients. All participants underwent Aβ-PET scans and blood sample collection. Blood samples, either fresh or previously stored (after January 1, 2024) in compliance with project quality standards, were analyzed at a central laboratory in a blind manner to assess the sensitivity and specificity of various BBM for predicting amyloid pathology confirmed by Aβ-PET. Nine commercial p-tau217 and p-tau217/Aβ42 assays (4 single-molecule immunoassay; 4 chemiluminescence and one flow luminescence assay, 9 assays were listed as P1-P9) were evaluated for their performance in predicting amyloid pathology (Aβ-PET status) and differentiating clinical diagnoses. **Results:** Among the 431 participants, the median age was 68 years (range: 55-75 years across groups), and 61.8% were female. Cognitive scores decline progressively from CN to AD groups (MMSE: 28 to 16; MoCA: 25 to 10). Of these, 276 (64%) participants were Aβ-PET positive and 155 participants (36%) were Aβ-PET negative. For predicting Aβ-PET positivity, all nine p-tau217 assays demonstrated substantial diagnostic accuracy, with AUC values ranging from 0.55 (P4) to 0.93 (P2, P6). The top-performing assays were P2 (AUC=0.93, 95%CI: 0.90-0.96, PPV=0.96, NPV=0.76), P6 (AUC=0.93, 95%CI: 0.90-0.96, PPV=0.94, NPV=0.81), and P7 (AUC=0.92, 95%CI: 0.89-0.95,

PPV=0.92, NPV=0.83). When evaluating p-tau217/Aβ1-42 ratios, performance was similar and remained clinically relevant, with AUCs ranging from 0.57 to 0.91. For differentiating AD dementia from CN, most assays achieved excellent performance with AUCs exceeding 0.95, notably P6 (AUC=0.98, 95%CI: 0.96-1.00) and P7 (AUC=0.97, 95%CI: 0.94-0.99). In the clinically challenging distinction between MCI Aβ+ and MCI Aβ-, P1, P2, and P6 showed strong performance (AUCs ≥0.91). For distinguishing AD from non-AD dementia, AUCs ranged from 0.58 to 0.90, with P7 and P9 achieving AUCs=0.90. Implementing a dual cut-off strategy with 95% sensitivity thresholds created clinically useful 'grey zones', allowing PET avoidance in 15.1% to 84.2% of cases across different assays. Assay P5 demonstrated the highest PET avoidance rate (84.2%), followed by assays P6 and P2 (78.4% and 78.6%, respectively). Inter-assay reliability analysis revealed excellent overall concordance for p-tau217 measurements (ICC=0.89, 95%CI: 0.88-0.91), with single-molecule assays showing higher consistency (ICC=0.92, 95%CI: 0.90-0.93) compared to electrochemical methods (ICC=0.78, 95%CI: 0.75-0.81). **Conclusions:** This large-scale, head-to-head comparison study demonstrates that multiple commercially available blood assays of p-tau217 can accurately predict cerebral amyloid pathology and differentiate AD from other cognitive states. These blood-based biomarkers hold great promise for optimizing the diagnostic workflow for AD in clinical practice, potentially reducing the need for more invasive and expensive tests.

Keywords: Alzheimer's disease, blood-based biomarkers, amyloid pathology, head-to-head comparison.

Clinical Trial Registry: NCT06889896; https://clinicaltrials.gov.

Disclosures: The authors declared no competing interests.

Key takeaway message: A landmark, head-to-head study shows blood p-tau217 tests accurately identify Alzheimer's and predict amyloid, streamlining diagnosis.

P209- CSF PROTEOMICS REVEALS SPECTRIS-INDUCED NEURITIN-1 UPREGULATION AND MODULATION OF BRAIN RESILIENCE PATHWAYS.

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Background: Neuritin-1 (NRN1/CPG15) is an activity-regulated, GPI-anchored neurotrophic factor that promotes dendritic branching, synapse stabilization, and neuroprotection. First identified as a light-inducible plasticity gene, NRN-1 has been linked to resilience in Alzheimer's disease (AD) through effects on PI3K/AKT signaling, anti-ferroptosis pathways, and suppression of Aβ-induced hyperexcitability. While preclinical data implicate NRN-1 as a mediator of activity-dependent resilience, its modulation in human CSF has not previously been shown. This analysis extends the previous published unbiased CSF proteomic observations (Hajos et al 2025) with supervised clustering and label free quantitation (LFQ). **Methods:** We conducted CSF proteomics in amyloid-positive MCI participants (n=10) enrolled in the FLICKER trial (NCT03543878). Participants used the investigational SPECTRIS gamma sensory stimulation device daily for 1 hour after confirmation of steady-state 40 Hz oscillation. CSF was collected at baseline, 4 weeks, and 8 weeks, and analyzed with label free quantitation (LFQ) mass spectrometry. In the delayed start design, 5 participants were treated for 8 weeks and 5 initiated treatment after 4 weeks. Treated participants at 4 and 8 weeks were combined (n=10) and compared to untreated participants at 4 weeks (N=5). Supervised clustering was performed using the six proteins most significantly altered in abundance post-treatment ($p<0.01$). Results were contrasted with ADNI proteomics (n=1104, Tandem Mass Tag (TMT) mass spectrometry). **Results:** SPECTRIS treatment increased CSF Neuritin-1 in contrast to reductions observed in ADNI AD patients. Other significantly altered proteins included reduced ADAMTS1 and OSCAR, and increased IGHV3-43, MASP1, and SELENBP1, mapping to pathways of extracellular matrix remodeling, immune modulation, complement activity, and oxidative stress regulation (all $p<0.01$). Supervised clustering using these proteins accurately predicted treatment arms at 4 and 8 weeks. Together, these changes suggest that SPECTRIS treatment may activate multiple brain resilience mechanisms. **Conclusions:** This study provides preliminary biomarker evidence that sensory gamma stimulation upregulates CSF Neuritin-1 in humans along with modulation of several proteins that may be associated with brain resilience mechanisms. Neuritin-1 emerges as both a candidate biomarker and mechanistic driver of cognitive resilience, supporting the hypothesis that SPECTRIS may engage activity-dependent neuroplasticity and neuroprotective pathways in Alzheimer's disease.

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Key takeaway message: This study provides preliminary biomarker evidence that sensory gamma stimulation upregulates CSF Neuritin-1 in humans along with modulation of several proteins that may be associated with brain resilience mechanisms.

P210- VALIDATION OF AN ALZHEIMER'S DISEASE CONFORMATION-SPECIFIC P53 ANTIBODY IN PATIENT SAMPLES.

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Background: It is estimated that Alzheimer's disease (AD) will have a cost of 16.9 trillion US dollars combined across all countries by 2050. Control of the disease is often limited by the how late in disease progression that an accurate diagnosis can be made. Therefore, high-performing biomarkers are vital to optimize clinical decision-making, in the context of AD. A specific unfolded version of p53 has been shown to be present in the blood of AD patients via the use of an antibody specific to it, U-p53AZ. The clinical data supports that this marker can be used for prognosis, even in individuals who are not yet cognitively impaired. Previously we have demonstrated that the U-p53AZ antibody will detect U-p53 in patient tissue and not in healthy control tissue. As the U-p53AZ has only a limited demonstration in patient tissue previously, we have expanded our work in this project to show further the correlation between U-p53 detection and other markers of AD, such as tau phosphorylation and protein oligomers. **Methods:** Control tissue from mouse models P301L and C57 was used to optimize U-p53AZ antibody staining with immunohistochemistry. Tissue samples from AD patients as well as age-matched controls were co-stained with U-p53AZ, phospho-tau and oligomer-specific antibodies. Tissue samples from the same cases were then co-stained to determine co-localisation of the U-p53 protein, tau neurofibrillary tangles, and amyloid oligomers. **Results:** Immunohistochemistry for the mouse models demonstrated that the P301L, a common AD model which had previously shown p53 aggregation, had positive staining for 2D3A8 staining, while the C57 mouse, commonly used as a control in AD studies, did not. The U-p53AZ antibody showed a very strong presence in Braak stage VI patients, while not in the age-matched Braak stage 0 controls. This was strongly associated with the presence of the phosphorylated tau and toxic oligomers also detected in the AD samples, but to a much lesser extent in the age-matched control. Finally, there is a degree of co-localisation between the NFTs and U-p53 proteins. **Conclusions**: The U-p53AZ antibody has demonstrated that it has a strong correlation with the pathology state of AD patients. Given that it has already been shown as a potential

prognostic tool for AD, this means that the U-p53AZ antibody strongly correlates with the pathological staging of AD as a disease. The antibody shows strong promise as a useful feature in future clinical assessments for AD, and should be moved towards a larger clinical study confirming it as such.

Key takeaway message: An AD-specific unfolded form of p53 is developed as a prognostic biomarker for AD. This histopathology study shows it colocalizes in the brain with pTau, in patients with AD and not present in healthy individuals.An AD-specific unfolded form of p53 is developed as a prognostic biomarker for AD. This histopathology study shows it colocalizes in the brain with pTau, in patients with AD and not present in healthy individuals.

P211- CONCORDANCE OF APOE PROTEOTYPE VS GENOTYPE ASSAYS: A LOW FRICTION METHOD FOR OBTAINING E4 CARRIER STATUS.

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Background: Apolipoprotein E (ApoE) haplotype (ε2 and ε4 carrier status) is the most predictive known genetic risk factor for onset and progression of Alzheimer's disease (AD) and for amyloid-related imaging abnormality (ARIA) risk with FDA-approved anti-amyloid therapies (1) and is therefore typically part of the work-up for AD in clinical practice and trials. ApoE haplotype is typically determined using genotyping which requires a whole blood collection, DNA extraction, and informed consent for genetic testing. In the era of plasma A-T-N-I biomarkers obtaining ApoE haplotype from the same sample (plasma) as these other markers can improve efficiencies in clinical diagnosis and trials. Mass spectrometry methods for assigning ApoE haplotype from plasma have recently been reported to be highly accurate (2,3) but are limited in availability. Here we confirm the mass spectrometry method accuracy and evaluate a new immunoassay which could enable greater access. **Methods:** We compared ApoE haplotype assigned by genotype (rtPCR) with proteotype (via C2N mass spectrometry method and/or immunoassay in 3 cohorts: 1) CHARIOT-PRO (REGISTRYALZ00001, NCT02114372 a non-interventional study comparing cognitively unimpaired (CU) participants with elevated brain amyloid compared to those without elevated brain amyloid (N=15 CU), 2) 42847922ALZ2001 (NCT05307692) a randomized, double-blind, placebo-controlled, multicenter study to investigate seltorexant (JNJ-42847922) on behavioral and psychological symptoms of dementia in participants with probable Alzheimer's Disease (N=52 MCI); and 3) Autonomy (63733657ALZ2002, NCT04619420), a randomized, double-blind, placebo-controlled, parallel-group, multicenter study to investigate posdinemab (JNJ-63733657), an anti-tau monoclonal antibody, in participants with Early Alzheimer's Disease (N=300 MCI). **Results:** ApoE proteotype determined by mass spectrometry had 100% concordance with genotype in CHARIOT-PRO (determined as Apo ε4 carrier status) and 42847922ALZ2001 (haplotype). Data from Autonomy (mass spectrometry and immunoassay) will be presented. **Conclusions:** ApoE haplotype measured by non-genotyping methods in standard plasma sample using mass spectrometry is highly accurate and therefore represents an efficient method for determining Apo ε4 carrier status in the same collection as standard A-T-N-I measures.

Keywords: ApoE, genotype, proteotype, Alzheimer's, plasma.

Disclosures: GTB, TV, SM, ZS, JW, DH, YF, GP, and SB are employees of Johnson and Johnson and receive salary &/or stock options.

References: Filippi M et al. Amyloid-Related Imaging Abnormalities and β-Amyloid-Targeting Antibodies: A Systematic Review. JAMA Neurol. 79(3):291-304. (2022) doi: 10.1001/jamaneurol.2021.5205. Kirmess KM et al. The PrecivityAD™ test: Accurate and reliable LC-MS/MS assays for quantifying plasma amyloid beta 40 and 42 and apolipoprotein E proteotype for the assessment of brain amyloidosis. Clin Chim Acta. 19:267-275 (2021). doi: 10.1016/j.cca.2021.05.011. Weber DM et al. New plasma LC-MS/MS assays for the quantitation of beta-amyloid peptides and identification of apolipoprotein E proteoforms for Alzheimer's disease risk assessment. J Investig Med. 72(5):465-474. (2024). doi: 10.1177/10815589241246537.

Key takeaway message: ApoE haplotype is a key measurement in AD clinical practice and trial can now be reliably measured in plasma with several non-genotyping methods.

P212- TARGETED PLASMA PROTEOMIC BIOMARKER PROFILING IN THE FINGER MULTIMODAL LIFESTYLE INTERVENTION TRIAL.

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Background: Plasma biomarkers are emerging as key tools to identify individuals at risk of Alzheimer's disease (AD) dementia, monitoring disease progression, and response to therapeutic interventions. Plasma biomarkers also open the opportunity to study AD-related mechanisms and longitudinal dynamics of pathophysiological pathways in randomized controlled trials (RCTs) with proven effects on clinical outcomes in instances where CSF-samples or PET-data are not available. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) previously demonstrated that a two-year multidomain lifestyle intervention can positively impact cognitive function in older adults at risk of cognitive decline. Elucidating the involved mechanisms could provide novel insights for precision prevention and new treatment targets. In the current study, we examined the levels of plasma biomarkers in FINGER over an extended 11-years period. **Methods:** FINGER included 1260 individuals, aged 60-77 years with an increased risk of dementia. The participants were randomized to receive either a multidomain intervention including dietary counselling, exercise training, cognitive training and social stimulation, and management of vascular risk factors (intervention), or regular health advice (control). The intervention lasted for 2 years and participants were invited to follow-up visits approximately 5, 7 and 11 years after the baseline visit. Plasma samples from the FINGER RCT were analyzed with the Nucleic Acid Linked Immuno-Sandwich Assay (NULISA) central nervous system panel (120 biomarkers) and the p-tau217 fully automated Lumipulse immunoassay that has previously been extensively studied in clinical cohorts. Samples were included from all FINGER participants when available which resulted in N=1221 at baseline, N=1105 at 2-year follow-up and N=871 with long-term follow-up (5-11 years). Core AD blood-based biomarkers assessed with Lumipulse (p-tau217) and NULISA (p-tau217, p-tau181, p-tau231, Glial fibrillary acidic protein (GFAP), Aß42/40) and 100+ exploratory markers (e.g. inflammatory, synaptic) were analyzed in relation to cognitive change over time, intervention effects and to other available, clinical data (e.g. PIB-PET in a subsample). For p-tau217 measured by Lumipulse, both lab- (from the memory clinic in Kuopio, Finland) and data-driven cut-offs were applied. **Results:** In total, 3197 samples collected at baseline and 2 years, and 5, 7 or 11 years follow-up were analysed. At baseline, a majority (81.8%) of the FINGER participants were shown to be in the

normal p-tau217 range (<0.19 pg/ml), 10.6% were in the intermediate (0.19-0.30 pg/ml) and 7.6% in the pathological range (>0.30 pg/ml) when using laboratory cut-offs. When applying logistic regression to a FINGER subsample with available PIB-PET data, the data-driven cut-off for p-tau217 to determine amyloid positivity was calculated to 0.162 pg/ml. Overall cognitive improvement from the lifestyle intervention was more prominent in participants who had p-tau217 levels below this cut-off. Further stratifying participants by ApoE4 genotype showed distinct trajectories over the 11-year follow-up period, with ApoE4 carriers having a significant increase in levels of several of the core AD blood-based biomarkers (by Lumipulse and Nulisa). **Conclusions:** This study intended to characterize the longitudinal molecular changes in a population at risk of dementia exposed to an extensive lifestyle intervention protocol. We aim to explore the interventions' differential biomarker responses in participants with normal versus pathological AD blood-based biomarker levels and clarify relationships between the treatment effects on biomarker and clinical outcomes. Finally, the goal is to advance the role of emerging AD blood-based biomarkers in risk-group assessment for precision prevention. Our preliminary data shows that individuals with lower levels of p-tau217 in plasma at baseline benefited more from the lifestyle intervention compared to those with higher levels. ApoE4 carriers were in the normal range of pathology at baseline but reached pathological levels at 11-years follow-up at a group level. The combination of different biomarkers may have the potential to establish molecular profiles associated to different cognitive trajectories in people at risk of dementia.

Keywords: Dementia, lifestyle, prevention, AD blood-based biomarkers.
Disclosures: The authors declared no competing interests for this work.
Key takeaway message: Multidomain lifestyle interventions shows positive effects on cognition in people at-risk of dementia. We analyzed plasma samples from the FINGER RCT using the NULISA CNS panel and Lumipulse p-tau217 to identify mediating pathways.

P213- DOES AMYLOID PLAQUE REDUCTION MEDIATE THE CLINICAL EFFECT OF AMYLOID-TARGETING ANTIBODIES?

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Background: Aducanumab and lecanemab received FDA marketing approval (accelerated approval) based on their effects on amyloid plaque lowering and not clinical efficacy. FDA's rationale was that plaque lowering established a likelihood for clinical benefit (Dunn et al 2021). Thus reduction of amyloid tracer uptake or plaque lowering was formally recognized as a surrogate endpoint for some Alzheimer therapies. (Lecanemab was subsequently recognized as showing statistically significant effects on its primary clinical endpoint, the CDR-SB, and given regular marketing approval). Regular FDA marketing approval for lecanemab and donanemab is uncontroversial from a regulatory point of view as both showed positive clinical outcomes in phase 3 trials, thus meeting 2019 FDA requirements for 'substantial evidence for effectiveness.' Despite the fact that clinical evidence for the effectiveness of amyloid plaque-targeting antibodies has been demonstrated, many clinical researchers, developers, and pharmaceutical company representatives argue that plaque reduction alone should be sufficient for an Alzheimer's drug to gain FDA regular approval and that a clinical endpoint is not necessary (Aisen et al 2025). Obvious advantages to this policy position would be faster, cheaper, development programs, and smaller, efficient clinical trials without the need to formally assess clinical outcomes. The validity of using amyloid-PET tracer uptake as a surrogate clinical marker from a mathematical – not regulatory – view requires that plaque lowering can be seen as a necessary mediator of the clinical effect of the antibodies. The FDA Office of Biostatistics previously reported that for aducanemab correlations between change in amyloid PET SUVR and CDR-SB was about $r = 0.09$ to about 0.15 depending on the clinical trials subsets used, suggesting that there may be little correlation between the biomarker and clinical endpoint. However, correlations do not necessarily imply that one measure has a mediating effect on the other. Thus, FDA approval of amyloid antibodies based on plaque lowering may not be valid. We performed mediation analysis to examine whether antibody treatment might influence the clinical endpoint of a trial through its effect on plaques. Such knowledge would aid in determining an underlying relationship between plaque reduction and the CDR-SB, suggesting (though not proving) potential pathways for understanding why the effect on the CDR-SB occurs. **Methods:** As patient-level data sets were not available, we conducted trials-level meta-analysis of the mediating effects of Aβ on CDR-SB scores across published phase 3 trials of aducanumab, lecanemab, donanemab, and gantenerumab. We simulated clinical trials based on the sample sizes, as well as mean and change in CDR-SB and amyloid PET from the original published studies. We modeled two-group trials (treatment vs placebo, using the high doses for aducanemab) with the collection of CDR-SB and PET centiloid data at the time points in the original trials. Due to the skewed distribution with underdispersion for CDR-SB scores, these were simulated based on a generalized Poisson distribution with the specified mean and standard deviation. Aβ centiloid values ('plaque levels') were simulated based on a normal distribution. We allowed correlations between the CDR-SB and Aβ centiloid scores to range from 0.1 to 0.5, representing a small to medium effect, and set the correlation between adjacent time points at 0.1. We used mixed effects models (random coefficients models) to estimate change in CDR-SB and plaques over time, and used bootstrap methods to estimate the indirect mediation effect of plaque level on the relationship between treatment and CDR-SB and the proportion mediated, along with 95% confidence intervals. Simulations were performed using the SimCorrMix package in R, with mixed effects models estimated using the lme4 package and mediation effects estimated using the mediation package. **Results:** Overall the mediation effect of amyloid plaque reduction on clinical outcome is not statistically significant. This, alone, suggests that lowering plaques is not predictive of a clinical effect (i.e., CDR-SB difference) that is observed with the FDA-approved antibodies in commonly anticipated clinical trial scenarios with low to medium correlations between CDR-SB and amyloid PET (generally, $r < 0.5$). However, we observed heterogeneity across trials, as the donanemab trial, which had a mean effect on the CDR-SB nominally larger than that of other antibodies (e.g., −0.70 vs. −0.45 for lecanemab), appeared to show a greater reduction in plaques and a small but significant mediation effect up to −0.23 for plaque-lowering at correlations greater than $r = 0.1$. Thus, while a mediation effect of amyloid is generally not statistically significant at low to medium correlations between CDR-SB and amyloid, exceptions might be observed with specific agents. **Conclusions:** Reducing plaque level generally does not appear to mediate clinical outcome with amyloid-targeting antibodies. The mediating effect with donanemab treatment is low and of uncertain significance. Notably, this is a simulation study and study-level meta-analysis and has limitations. It was performed because subject-level data was not available. Clearly, to develop evidence that plaque lowering mediates clinical benefit, or that amyloid PET could be used as a surrogate clinical endpoint, patient-level data must be made available for more detailed analysis.

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Key takeaway message: Reducing plaque levels generally does not appear to mediate clinical outcome with amyloid-targeting antibodies.

P214- AGE-RELATED CHANGES IN PLASMA P-TAU217 AND REFERENCE LEVELS IN COGNITIVELY UNIMPAIRED Aβ-NEGATIVE INDIVIDUALS.

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Background: Recent advances in blood-based biomarkers that detect core Alzheimer's disease (AD) pathology offer cost-effective, less-invasive, and scalable alternatives to PET or CSF testing. Phosphorylated tau at threonine 217 (p-tau217) has shown high accuracy identifying AD pathology even in cognitively unimpaired (CU) individuals1-3. Understanding the baseline level of p-tau217 in CU individuals and establishing a clinical reference range is critical, as clinical trials are increasingly using plasma p-tau217 for recruitment and evaluating early drug intervention. In this study, we investigate age-related changes in plasma p-tau217 among amyloid-PET negative (A−) CU individuals and examine how aging influences p-tau217 positivity rates within this population. **Methods:** We measured plasma p-tau217 in 360 CU, amyloid-PET negative participants from the Australian Imaging, Biomarkers & Lifestyle (AIBL) study. Plasma p-tau217 concentrations were measured using two immunoassays, ALZpath pTau217 SIMOA assay and Fujirebio Lumipulse pTau217. The reference range was determined based on clinical laboratory guidelines (CLSI) for establishing reference intervals. The proportions of negative, intermediate, and positive p-tau217 results were compared across age groups. Associations with sex, ApoE ε4, and cognitive scores (MMSE & CDR) were examined to determine their effect on the established reference range. **Results:** Plasma ALZpath p-tau217 concentration was normally distributed with a mean of 0.23 ± 0.09 pg/mL an upper reference range of 0.46 pg/mL based on 97.5th percentile. A significant age-related increase in p-tau217 levels was observed. The proportion of individuals with intermediate p-tau217 levels increased with age: 6.1% (60–69), 13.2% (70–79), and 32.5% (80+ years). However, the proportion of p-tau217 positive cases remained less than 5% for all age groups meeting the acceptance criteria of greater than 90% specificity. Sex, ApoE ε4 status, or MMSE score did not impact the reference range value. A similar age-related effect was observed for the lumipulse p-tau217 assay suggests that the effect is not method-dependent. **Conclusions:** Our results show a modest but significant age-related increase in p-tau217 among individuals CU A- despite the majority (> 95%) remaining below the established positivity threshold. These results underscore the critical importance of accounting for age when interpreting p-tau217 concentrations to avoid potential false-positive classifications, particularly in older populations. Incorporating age adjustments could improve the accuracy of identifying individuals at risk for Alzheimer's disease pathology, ensuring the utility of plasma p-tau217 as a screening biomarker in clinical trials and early intervention strategies.

Keywords: p-tau217, biomarkers, normal aging.

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Key takeaway message: Plasma p-tau217 shows a modest but significant age-related increase among CU amyloid-negative individuals. Suggesting that age is an important factor when using plasma p-tau217 as a screening tool for clinical trials and early intervention efforts.

P215- A COMPARATIVE ANALYSIS OF CREATININE- AND CYSTATIN C-BASED EGFR EQUATIONS FOR THE ASSESSMENT OF CHRONIC KIDNEY DISEASE INFLUENCE ON PLASMA P-TAU217 CONCENTRATIONS.

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Background: Alzheimer's disease (AD) blood-based biomarkers (BBMs) are noninvasive tools that can assist), in the evaluation of AD in patients presenting with cognitive impairment. Although these biomarkers can exhibit high diagnostic accuracy, the presence of chronic kidney disease (CKD) can result in elevations of renally cleared BBMs, such as pTau217. In previous work, we have demonstrated that this is particularly relevant in amyloid PET negative patients (A-) with creatinine based estimated glomerular filtration rates (eGFR) indicating stage CKD of stage 3B or higher (1). While creatinine based eGFR (eGFR cr) determinations are widely available, relatively inexpensive, and are often utilized in AD-related and other clinical studies, eGFR cr exhibits limitations in accuracy for the estimation of true GFR, as creatinine concentration can be affected by muscle mass. Alternatively, Cystatin C-based eGFR (eGFR cys) or combined creatinine-cystatin C eGFR (eGFR cr-cys) GFR estimates are an attractive option, in part due to reports of more accurate eGFR associations with true renal function (GFR). Differences between creatinine and cystatin C based eGFR determinations have been reported to potentially alter the significance of eGFR based associations/conclusions in some diseases. To our knowledge the potential impact of different eGFR equation determination methods has not been assessed for AD BBMs in regard to associations with positive bias of BBM concentrations in the presence of CKD. Here we undertake the first direct comparison of the impact of using Creatinine versus Cystatin C based eGFR determinations, as well as Creatinine versus combined Creatinine-Cystatin C based eGFR determinations, in an amyloid negative cohort on the relationship of plasma p-tau217 concentrations versus creatinine-based estimated glomerular filtration rate (eGFR) in individuals with CKD. **Methods:** p-tau217 was measured as previously described in EDTA plasma samples obtained from participants (N=202) in the Mayo Clinic Study of Aging or the Alzheimer's Disease Research Center cohorts who exhibited varying degrees of renal impairment (CKD) and amyloid pathology. In all, 88 of these individuals were categorized as A-based on amyloid-PET and a Centiloid of <25. p-tau217 concentrations were determined by an ALZpath Simoa p-tau217 immunoassay, and also, via an immunoprecipitation mass spectrometry (IP-MS) assay that simultaneously measured p-tau217 and non-phosphorylated-tau217 (np-tau217) to determine %p-tau217 ([p-tau217/non-phosphorylated-tau217]) x100%) (C2N Diagnostics). Log-log linear regression fits were used to quantitatively predict increases in plasma p-tau217 associated with decreasing eGFR. The three comparative eGFR equations utilized in this study were: (a) GFR calculated with the creatinine-based 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, (b) combined CKD-EPI Creatinine-Cystatin Equation (2021), and (c) the CKD-EPI Cystatin Equation (2012). Serum creatinine measurements were performed using the Roche Elecsys enzymatic method (Roche Diagnostics). Serum Cystatin C was measured via an immunoturbidimetric Cystatin C Gen 2 method (Roche Diagnostics). **Results:** Of the 88 A- individuals, 54 had eGFR cr values of ≥60 mL/min/1.73m2 (representing CKD stages 1-2), 22 had eGFR cr values of 45-59 mL/min/1.73m2 (representing CKD stage 3a), 10 had eGFR cr values of 30-44 mL/min/1.73m2 (representing CKD stage 3b), and 2 had eGFR cr values of 15-29 mL/min/1.73m2 (representing CKD stage 4). Both eGFR cys and eGFR cr-cys exhibited an absolute median difference of 5 eGFR

(in 60 mL/min/1.73m2) as compared to eGFR cr. Log-log linear regression quantitatively predicted increases in plasma p-tau217 associated with decreasing eGFR based on eGFR cr, eGFR cys, and eGFR cr-cys..For an eGFR cr of 45 vs 60, the calculated eGFR percentage changes were +31%, +55%, and +19%, for ALZpath p-tau217, C2N p-tau217, and C2N %p-tau217, respectively. For an eGFR cys of 45 vs 60, the calculated percentage changes were +24%, +39%, and +15%, for ALZpath p-tau217, C2N p-tau217, and C2N %p-tau217, respectively. For an eGFR cr-cys of 45 vs 60, the calculated percentage changes were +28%, +47%, and +17%, for ALZpath p-tau217, C2N p-tau217, and C2N %p-tau217, respectively. The predicted magnitude of increase in biomarker measurements attributable to a decrease in eGFR from 60 to 45 mL/min/1.73m2, was 23% reduced for eGFR cys versus eGFR cr for ALZpath p-tau217 (24% eGFR cys predicted increase as compared to a 31% eGFR cr predicted increase). Additionally, as a 29% and 21% reduced predicted relative increase, for C2N p-tau217 and C2N %p-tau217, respectively, was observed. The difference of predicted marker increases between eGFR cr-cys and eGFR cr at 60 versus 45 mL/min/1.73m2, followed a similar pattern with a smaller reduction in the estimated eGFR relative increase from 60 to 45 mL/min/1.73m2 versus eGFR cr, being 10%, 13%, and 11% for ALZpath p-tau217, C2N p-tau217, and C2N %p-tau217, respectively. **Conclusions:** This study represents the initial assessment of the effects of different eGFR determination equations (eGFR cr, eGFR cys, and eGFR cr-cys) on previously described effects of decreased kidney function on p-tau217 concentrations. The use of eGFR using cystatin C (eGFR cys or eGFR cr-cys) based equations somewhat reduced, but did not eliminate, observed increases in p-tau217 and %p-tau217 with decreasing kidney function. These results substantiate plasma p-tau217 concentration positive bias associated with CKD previously observed utilizing eGFR cr based kidney function estimates, to both eGFR cys, and eGFR cr-cys based CKD assessments.

Reference: 1 Bornhorst et al. Neurology vol. 104,3 (2025): https://doi.org/10.1212/WNL.0000000000210287.

Key takeaway message: This study substantiates the plasma p-tau217 concentration positive bias associated with CKD previously observed utilizing eGFR creatinine based kidney function estimates, to both eGFR cystatin C, and eGFR combined creatinine-cystatin C based CKD assessments.

P216- RESEARCH ON BIOMARKERS OF EARLY ALZHEIMER'S DISEASE IN CHINA IN THE PAST DECADE, A SCOPING REVIEW.

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Background: The diagnosis of Alzheimer's disease (AD) is shifting from symptom-based exclusion to biomarker-based inclusion, reflecting the underlying biology. Given differences in AD risk across diverse populations, generalizability of existing biomarker data, including fluid (plasma or CSF) and neuroimaging biomarkers, is not assured. Thus, it is important to validate the accuracy and diagnostic performance of these biomarkers within the Chinese population. There is already considerable published evidence on biomarkers for diagnosing AD in early-stage symptomatic patients (early AD) in China. However, a comprehensive review that depicts the distribution of evidence and assesses the diagnostic accuracy of existing biomarkers has not yet been conducted. This scoping review provides a comprehensive overview of clinical research on biomarkers for early AD in China from the past decade. **Methods:** The scoping review followed the Joanna Briggs Institute methodological framework (INPLASY registration number: 202460069) (1). Articles on early-stage symptomatic AD or early AD (NIA-AA Stages 2–4 or equivalent) in the Chinese population between 2013 and 2023 were searched in four English-language databases (PubMed, EMBASE, Cochrane, and Web of Science) and three Chinese databases (CNKI, Wanfang, and CQVIP) (2-6). Due to rapid advancements in early AD biomarker research in China, a supplementary search was conducted in the four English databases until April 30, 2025. Studies investigating AD biomarkers that include accuracy data, including AUC values, sensitivity, and specificity, were screened for data extraction and subsequent analysis. **Results:** A total of 15,824 articles related to early AD within the Chinese population were identified from 2013 to 2023. Among these, 354 articles focused on AD fluid or imaging biomarkers and included accuracy data, and 34 studies were conducted in biomarker-confirmed early-stage symptomatic AD patients with amyloid positive evidence (PET or approved CSF tests), rather than only clinically diagnosed AD patients. 13 additional articles from 2024 and 2025 meeting the same criteria were identified through the supplementary search. Most recent literature focuses on blood-based biomarkers; however, composite biomarkers including neuroimaging and machine learning-based biomarkers are also well-developed. Six single diagnostic biomarkers in plasma showed good performance (AUC>0.8) in distinguishing between amyloid positive and negative individuals with cognitive impairment (using PET or CSF as gold standard) and were validated in more than one Chinese cohort: p-tau217, p-tau181, p-tau217/Aβ42, p-tau181/Aβ42, Aβ40/42 and GFAP. Plasma p-tau217 alone and the p-tau217/Aβ42 and p-tau181/Aβ42 ratios also met the minimum acceptable criteria in the Chinese population for clinical use as confirmatory tests recommended by the Global CEO Initiative on AD, with a sensitivity and specificity of ≥90% and a PPV and NPV of ≥90% in detecting brain amyloid pathologies across both research and real-world clinical practice cohorts, when the Aβ prevalence is ~50%. **Conclusions:** The landscape of AD biomarker research in China is evolving rapidly, and studies on the accuracy of biomarkers in diagnosing patients with early AD have significantly increased. Plasma biomarkers, such as p-tau217 and the p-tau217/Aβ42 and p-tau181/Aβ42 ratios, show equivalent accuracy to CSF tests and therefore hold substantial potential for future clinical applications, but require further validation in real-world clinical settings.

Keywords: Scoping review, early Alzheimer's disease, biomarker, China.

Disclosures: Yang Yan and Wang Ying are employees of Novo Nordisk (China) Pharmaceuticals Co., Ltd, and Sagar Anil Chandekar is employee of Novo Nordisk A/S. All other authors declare no conflict of interest that may have influenced the work reported in this study.

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Key takeaway message: Plasma biomarkers, such as p-tau217, p-tau217/Aβ42 and p-tau181/Aβ42 ratios, show equivalent accuracy to CSF tests and therefore hold substantial potential for future clinical applications, but require further validation in real-world clinical settings in China.

P217- CLINICAL TRIAL PATIENT COHORT ENRICHMENT USING COST-EFFECTIVE BLOOD-BASED BIOMARKER SCREENING.

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Background: A critical success factor for any clinical trial is enrolling the right patients for the right trial. A strong cohort must not only meet the eligibility criteria of the trial but also include a sufficient number of disease-positive individuals to enable meaningful assessment of therapeutic efficacy. In Alzheimer's disease (AD), especially among individuals with mild cognitive impairment (MCI), accurate diagnosis remains challenging. Gold-standard methods such as CSF biomarker testing or PET imaging are too costly to scale for large trial screening populations, yet precise diagnosis is essential to ensure trial success. To significantly reduce costs and improve screening efficiency, we propose a blood-based biomarker (BBM) approach to enrich the pool of participants who proceed to PET imaging. This strategy identifies individuals more likely to meet amyloid-based inclusion criteria before undergoing PET. Those unlikely to qualify would be excluded prior to undergoing the expensive procedures. Given that amyloid PET scans can cost up to $8,000 per patient, a ~$200/sample BBM screening test could greatly reduce overall enrollment costs, reach a larger population eligible for the trial, and increase trial efficiency. More importantly, patients would avoid unnecessary lumbar punctures or radiation exposure if ineligible for trial inclusion. To enable this scalable screening approach, we present a benchtop, fully automated blood biomarker testing platform capable of analyzing 48 plasma samples in under four hours. Taudia has developed a prototype screening assay and tested age-matched AD+ and AD- samples to demonstrate this enrichment strategy's potential. **Methods:** Ninety patient plasma samples – consisting of 10 AD+ and 20 AD- samples per age group (60s, 70s, 80s) – were tested. Testing was performed using Taudia's automated platform with two cutoff thresholds used to classify samples as "High AD probability" or "Low AD probability." In a clinical trial context, a "High AD probability" would trigger PET confirmation of amyloid burden, while patients below the threshold would be excluded the patient from further diagnostic steps when the trial is looking to enroll AD+ patients. The Low AD probability cutoff is useful for when the trial is seeking to enroll healthy patients from a pool that potentially have elevated prevalence of Alzheimer's disease. Similar to how the High AD probability score is used, patients below the Low threshold can be tested further to confirm low amyloid burden. Based on known clinical status, we calculated an enrichment rate and compared it to the base case in which all patients undergo PET scans. **Results:** In this simulated trial cohort with a 1:2 AD+:AD− ratio, the baseline PET failure rate (i.e., percentage of patients excluded after PET) would be 67%, in line with published studies. Applying the BBM cutoff reduced the failure rate to approximately 11% (3 out of 30 passing samples). In other words, only 10% of patients who screened positive on the BBM test turned out to be amyloid-negative, indicating a substantial enrichment. Additionally, more than 65% (60 out of the 90 samples) of the total cohort would avoid PET scans all together, significantly reducing procedural burden and cost. For instance, at $8,000 per PET scan, excluding 125 patients could save at least $1 million in direct imaging costs. **Conclusions:** This preliminary study demonstrates that a cost-effective, fully automated blood biomarker platform can significantly reduce amyloid PET failure rates through pre-screening and cohort enrichment. The proposed strategy can lower overall clinical trial costs, improve enrollment efficiency, reduce burden on participants and staff, and ultimately accelerate Alzheimer's disease therapeutic development.

Keywords: Clinical trial, enrichment, recruitment, screening.

Disclosures: Robert Lin, Noah Elder, Hien Nguyen, Jason Wan and Paul Hung are employees of Taudia, Inc, the company that developed the technology and performed the testing reported.

Key takeaway message: A fully automated blood-based screening assay could reduced amyloid PET failure rates for trial patient recruitement, offering a scalable, cost-saving strategy to enrich Alzheimer's trial cohorts and minimize unnecessary procedures for participants.

P218- P-TAU217 TESTING IMPACT ON PATIENT MANAGEMENT IN A RACIALLY/ETHNICALLY DIVERSE POPULATION: SIX-MONTH FOLLOW UP IN A RANDOMIZED CLINICAL UTILITY STUDY.

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Background: Biomarker confirmation of amyloid pathology is required in the most recent diagnostic criteria for Alzheimer's disease (AD) and may be achieved by plasma testing. Few studies assess the clinical utility of plasma P-tau217 testing on initial evaluation of patients with cognitive impairment (CI). We previously reported the impact of the Lilly SP-X P-tau217 test on healthcare provider (HCP) intended patient management and working diagnosis (WDx) immediately after receiving test results. In this 6-month follow-up analysis, we assessed testing impact on actual patient management in comparison to patients who did not receive testing at baseline. **Methods:** This 6-month, open-label, randomized, 2-arm, multicenter, prospective, observational study enrolled 609 patients evaluated for initial presentation of CI and was conducted at 32 US-based sites. Patients were randomized to P-tau217 tested (n=391) and control (n=218) arms. Using questionnaires, intended patient management at baseline and at 4-week follow-up (immediately after result disclosure in the tested arm) and actual patient management at 6-month follow-up were obtained, as well as WDx (likely AD versus not likely AD) and confidence in WDx at all 3 timepoints. Differences in the frequency of AD diagnostic testing (blood, CSF, and/or PET measures of amyloid/tau, excluding study-provided test), WDx, and confidence in WDx were evaluated. **Results:** From the total study cohort, 10.1% of participants identified as Black/African American, 2.1% as Asian, and 22.4% as Hispanic. For AD diagnostic tests, a mean of 0.14 versus 0.27 of tests per patient were undertaken in the tested versus control arm (p=0.001). For aggregated, management changes at month 6 from baseline intended management, the percentage of patients was not significantly different between arms. Within the tested arm, 2.7%, 1.4% and 10.3% patients received additional HCP-ordered blood, CSF and PET evaluations for AD biomarkers, respectively, compared to 12.6%, 2.0% and 12.6% patients within the control arm, respectively. Within the tested arm, frequency of CSF and/or PET evaluations differed significantly by test result: 2.4% and 14.9% of patients with positive or indeterminate, versus 0% and 4.3% with negative results. Change in WDx (29.3% versus 15.6% patients in tested versus control arm) and increase in confidence in WDx (8.8% versus 1.7% in tested versus control arm) were significantly different between the two arms at 4-week follow-up. Additionally, between baseline and 6-month follow-up, change in WDx was observed in 31.2% of tested versus 20.2% of control patients while confidence in WDx increased by 12.1% in tested and 6.3% in the control arm. **Conclusions:** P-tau217 testing had an immediate impact on WDx and diagnostic confidence. Changes from baseline WDx and increases in diagnostic confidence were greater in the tested arm immediately after P-tau217 results compared to the control arm after 5-months of patient work-up. For the tested arm, additional AD diagnostic testing was mainly restricted to those with positive/indeterminate P-tau217 results. Overall, these findings indicate early P-tau217 testing increases diagnostic confidence earlier in patient evaluation and contributes to more focused patient management.

Conflict of interest: RCB, SCB, HH, YT, and AS are employees and shareholders of Eli Lilly & Company. MJP is a minor shareholder of Eli Lilly & Company and was an employee at the time this work was

performed before recently retiring. PES is a consultant and speaker for Eli Lilly, Eisai, and Acadia Pharmaceuticals. CPS receives grant support from Amgen, Genentech, Roche, Teva, and Lilly and is a speaker on the boards of Abbvie, Amgen, Biogen, C2N Diagnostics, Lilly, and Pfizer.
Key takeaway message: In this 6-month follow-up analysis, we show that early plasma P-tau217 testing contributes to more focused patient management by increasing diagnostic confidence earlier in patient evaluation and increasing efficiency of patient management.

P219- NOVEL BIOMARKERS DRIVE A DISTINCT PATTERN OF CLINICAL CHARACTERIZATION OF TWO COHORTS: A CHINESE AGING AND NEURODEGENERATIVE DISORDER INITIATIVE (CANDI) AND A HEFEI AGING STUDY URBAN COMMUNITY (HAS).
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Background: The previous studies about "A/T/N" biomarkers were mostly investigated in Caucasian populations. There was little systematic cohort study based on the "A/T/N" framework in a Chinese population, and it remains unclear whether biomarkers could reflect the brain pathologies within the Chinese population. Moreover, ageing is a major risk factor for Alzheimer's disease (AD), which is accompanied by cellular senescence and thousands of transcriptional changes in the brain. To identify the biomarkers in the cerebrospinal fluid (CSF) that could help differentiate healthy ageing from different types of neurodegenerative processes and monitor clinical trials. **Method:** A total of 700 participants were selected from CANDI cohort, including cognitively normal individuals (CN), patients with mild cognitive impairment (MCI) patients, patients with AD, and patients with non-AD dementia. Moreover, a total of 1000 urban community cohort were recruited from the Hefei Aging Study (HAS) cohort. Fluid biomarkers including ptau-217, Abeta 40, 42, certain types of inflammatory biomarkers were measured with single molecule array. Amyloid beta (Aβ) deposition was determined by 18F-Flobetapir positron emission tomography (PET), and brain atrophy was quantified using magnetic resonance imaging (MRI). Aging-and inflammatory related molecules were screened in primary astrocytes and postmortem brains with different types of brain disorders. The inflammatory molecules were further investigated in CSF from a CANDI cohort comprising individuals with CN, diagnosed with MCI, and AD patients. pTau and certain types of inflammatory biomarkers were mesureed. **Result:** We are the first to examine the core AD biomarkers from each arm of the "A/T/N" framework in CANDI, a Chinese cohort:
• CSF phosphorylated tau (p-tau) and plasma p-tau show high concordance in differentiating Aβ-positive individuals from the negative individuals. • Plasma p-tau, but not the Aβ42/Aβ40 ratio, is a reliable marker of brain atrophy. • Plasma p-tau combined with minimally invasive measurements, such as MRI and APOE genotype, are highly accurate in predicting Aβ burden in the brain. This study first investigated both fluid and imaging biomarkers in a well-designed Chinese dementia boutique cohort. These data reveal a consistent utility of the "A/T/N" framework in a Chinese population and emphasize universal applicability for AD diagnosis. Moreover, machine learning suggests that a combination of plasma phosphorylated tau (ptau), apolipoprotein E (APOE) genotype, and magnetic resonance imaging (MRI) measures, all of which are cost-effective and non-invasive approaches, is highly accurate in predicting AD dementia. Aging is a most risk factor for AD, we first screened and discovered the p16/p21-positive senescent "old" cells accumulated in AD brains, particularly in astrocytes and oligodendrocyte cells. Interestingly, we found that the level of YKL-40 and CCL2 were markedly elevated in CSF with healthy older individuals whereas HGF, MIF, and TSP2 levels were more susceptible to AD pathology. Moreover, YKL-40, TSP2 and/serpinA3 were identified as useful biomarkers for discriminating AD patients from CN individuals. Beside of aging markers, we extended our study to specific inflammatory molecules. Unexpectedly, we discovered that only interferon-β in CSF was significantly elevated in AD groups, while interferon-β, interferon-γ, TNFa, and IL-6 were significantly elevated in the serum of AD patients than that in cognitively normal. Moreover, interferon-β was significantly associated with AD core biomarkers (Aβ42, Aβ42/Aβ40 ratio, P-tau, and T-tau) and cognitive performance. CSF interferon-β levels were also significantly higher in APOE ε4 carriers than in non-carriers, while including the CSF Ptau, T-tau, and plasma P-tau as co-variables changed this difference, but not by the Aβ42/ Aβ40 ratio. **Conclusions:** Our findings are the first to demonstrate the different patterns of CSF biomarkers related to senescent glial cells between normal aging and AD, implicating these biomarkers could identify the road node in the healthy path off to neurodegeneration and improve the accuracy of clinical AD diagnosis. Moreover, our results also demonstrate that interferon-β levels, especially in the CSF, are significantly associated with the pathology and disease progression of AD, making it a potential therapeutic target and promising biomarker for AD. Moreover, our findings further demonstrated the different patterns of CSF biomarkers related to senescent glial cells between normal ageing and AD, implicating these biomarkers could identify the road node in healthy path off to neurodegeneration and improve the accuracy of clinical AD diagnosis, which would help promote healthy ageing.
Key takeaway message: Novel biomarkers from Asia elderly and asia AD patients. New pattern of biomarkers for two Chinese AD and community cohorts.

P220- MIGRATING THE USE OF PLASMA P-TAU217 FROM RESEARCH SETTING TO CLINICAL PRACTICE: A REAL-WORLD STUDY IN SUBJECTIVE COGNITIVE DECLINE AND MILD COGNITIVE IMPAIRMENT.
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Background: The Revised Criteria of Alzheimer's Association Workgroup proposed the use of blood-based biomarkers for diagnostic purpose, even in the early stages of Alzheimer's Disease (AD) (1). Plasma p-tau217 is becoming increasingly notable for its accuracy in detecting AD pathology even in preclinical stages (2). The aim of this study is to investigate the role of plasma p-tau217 as a potential biomarker for AD pathology in early stages of the disease in a real-world cohort of Subjective Cognitive Decline (SCD) and Mild Cognitive Impairment (MCI) patients. **Methods:** We included 50 SCD, 87 MCI and 50 AD-dementia (AD-d) patients, who self-referred to the Centre for Alzheimer's Disease of Careggi Hospital in Florence. Patients underwent plasma p-tau217 analysis with the fully automated Lumipulse G600II assay. Thirty-six SCD, 83 MCI and 50 AD-d patients underwent CSF biomarkers analysis (Aβ1-42, Aβ1-42/1-40, p-tau, t-tau); 25 SCD, 5 MCI and 4 AD-d underwent amyloid-PET. According to the Revised Criteria of Alzheimer's Association Workgroup, patients were classified as Core1+ or Core1-. **Results:** Plasma p-tau217 levels were significantly higher in SCD Core1+ than in SCD Core1- (0.50±04.7 vs 0.25±0.24, p=0.025), and in MCI Core1+ than in MCI Core1- (0.78±0.60, p<0.001). AD-d patients showed the highest plasma p-tau217 levels (1.66±1.70). In a multiple regression analysis, plasma p-tau217 levels were significantly influenced by both diagnostic category (B=0.39, p=0.002) and Core1 status (B=0.75, p<0.001). The ROC curve analysis showed an excellent accuracy of plasma p-tau217 in discriminating Core1+ from Core1- patients (AUC=0.92), with an optimal cut-off value of 0.274 pg/ml, revealing a good accuracy (86.29% [95%CI 81.20-91.39]), sensitivity (89.81% [95%CI 85.33-94.3]), specificity (80.60% [95%CI 77.44-84.46]), PPV (88.18% [95%CI 83.40-92.96]) and NPV (83.09% [95%

CI 77.52-88.63]). Plasma p-tau217 levels were dichotomized according to calculated cutoff and showed a good concordance with Core1 status (86.28%, Coehn's k=0.70, p<0.001). When applying a two cut-offs approach (0.229 pg/ml and 0.516 pg/ml), plasma p-tau217 showed higher accuracy (93.54% [95%CI 89.00-97.00]), sensitivity (93.90% [95%CI 89.69-98.11]), specificity (92.86% [95%CI 88.32-97.39]), PPV (96.25% [95%CI 92.91-99.59]) and NPV (88.64% [95%CI 85.05-98%]). **Conclusions:** Plasma p-tau217 showed a high accuracy in discriminating patients according to the underlying pathology (3), even in SCD and MCI patients in a real-world cohort, with a good concordance with the new Core1 biomarkers for AD diagnosis. Thanks to the use of two cut-offs approach, plasma p-tau217 might be a valid tool for the early identification of AD pathology, even in real-world settings, making it possible to transition from research to clinical practice.

Keywords: Plasma p-tau217, subjective cognitive decline, mild cognitive impairment, Alzheimer's disease. Disclosures: GG was a speaker for Eli Lilly at scientific meeting; the other authors have nothing to disclose.

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P221- IMPACT OF RECRUITMENT MODALITY ON PLASMA PTAU217 ELIGIBILITY IN CLINICAL TRIALS OF ALZHEIMER'S DISEASE.

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Background: Blood-based screening of phosphorylated tau (pTau) has emerged as a critical tool to accelerate the screening of participants in preclinical Alzheimer's Disease (AD) trials. Screening with plasma pTau can be a cheaper and less invasive alternative to traditional PET scans or CSF collection. However, despite these changes in study design, AD drug trials are still slower and more expensive to enroll because of the target population. Clinical research sites have increasingly turned to online advertising to speed up recruitment by reaching participants outside of traditional offline methods. In this study, we examine the relationship between recruitment modality and pTau eligibility in Alzheimer's Disease clinical trials. **Methods:** From 2024 to 2025, an independent commercial research site in California screened 527 participants into one of two Phase 3 multi-center clinical trials of anti-amyloid monoclonal antibodies for early or preclinical AD. Both trials used a plasma pTau217 blood test at the beginning of the screening process to rule out participants. Across both studies, 92 of the screened participants had eligible pTau217 results. The specific pTau217 level or thresholds for eligibility were not revealed by the study sponsors. However, eligibility rate did not appear to differ across the two studies (16.8% vs. 18.1%, p=0.70). These 527 participants were recruited either through online advertising (336) or some kind of offline modality (191) - community outreach event, database search, physician referral, or friend/family referral. **Results:** When examining pTau eligibility by recruitment modality, participants recruited online were less likely to be pTau eligible than participants recruited offline (15.3% vs. 21.7%) and this difference was significant (p=0.06). However, when controlling for demographic characteristics that are known to affect blood pTau217 levels - age, race/ethnicity (Molina-Henry 2025), and gender (Mielke 2022) - this effect largely goes away. A logistic regression analysis that controls for these characteristics yields a nonsignificant effect for recruitment modality ($\chi2(1) = 1.833$, p=0.18). **Conclusions:** While it might seem like online participant recruitment has a negative impact on pTau217 eligibility, the bulk of the effect can be explained by the observed demographic differences in the recruited participants when recruiting online instead of an offline modality. Controlling for these demographic differences reduced the effect of recruitment modality to a small, non statistically significant level. Controlling for additional factors such as body weight or other relevant comorbidities could further reduce or even eliminate this effect.

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Key takeaway message: Recruitment modality has no effect on pTau eligibility for preclinical AD trials when controlling for demographic attributes in the recruited populations.

P222- BASELINE GUT MICROBIOME COMPOSITION INFORMS ABOUT COGNITIVE CHANGES IN LIFESTYLE AND DIET INTERVENTIONS IN OLDER ADULTS: RESULTS FROM THE U.S. POINTER-MICROBIOME STUDY.

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Background: Multidomain lifestyle interventions are a promising approach to protect cognitive health in older adults, potentially through effects on the gut microbiome and metabolome. The POINTER-Microbiome ancillary study of U.S. POINTER (1), a large, multi-site randomized controlled clinical trial, investigates whether multidomain lifestyle interventions alter gut microbial and blood metabolomic profiles and how these changes relate to cognitive function over time. **Methods:** U.S. POINTER is a large randomized controlled two-year trial examining the effects of two multidomain lifestyle interventions on global cognitive function in 2,111 older adults (60-79 years) who were at risk for dementia due to well-established factors. Participants were

randomly assigned to either a structured or self-guided lifestyle intervention that targeted four lifestyle domains: physical activity, diet, social and intellectual challenge, and cardiometabolic risk factor monitoring, but that differed in structure, intensity, and accountability. The POINTER-Microbiome ancillary study examined the association between baseline gut microbiome composition and global cognitive function in a subset of parent trial participantsWe performed shotgun metagenomic sequencing on fecal samples from n = 654 participants at baseline. At Year 2, cognitive test scores were converted to z-scores relative to the mean and standard deviation at baseline to generate change score values (2). Taxonomic profiling and Bayesian-informed differential abundance testing were used to identify baseline microbes associated with cognitive improvement. Log-ratio features were then constructed from microbes that were positively versus negatively associated with cognitive function and correlated against the global cognitive composite scores. **Results:** Mean (SE) global cognitive function increased in both groups over time, more in the structured (0.564 +/- 0.028) versus the self-guided (0.498 +/- 0.028) group. Differential abundance analysis identified several opportunistic pathogens, including Clostridium perfringens, Enterococcus faecalis, Fusobacterium, Proteus mirabilis, Desulfovibrio desulfuricans, Klebsiella, and Streptococcus spp., as associated with lower cognition scores (3). Interestingly, taxa typically considered beneficial, such as Limosilactobacillus fermentum, Lactiplantibacillus plantarum, Bifidobacterium animalis, and certain Weissella and Ligilactobacillus species, were also associated with lower cognition in this analysis, despite prior reports linking them to protective effects via SCFA and antioxidant production (4). This suggests that the impact of gut microbes on cognition may be highly context-dependent, varying with host factors, strain-level differences, and overall community structure. Log-ratio features demonstrated a positive correlation with global cognitive composite z-scores ($r=0.254$, $p<0.001$). These log-ratios did not vary significantly by intervention group ($p=0.500$). **Conclusions:** Baseline gut microbial composition is associated with Year 2 global cognitive scores for both intervention groups. The resident gut microbiome and its metabolites may help explain individual variation in treatment response. **Keywords:** Microbiome, metabolome, cognition.
Clinical Trial Registry: NCT03688126; https://www.clinicaltrials.gov/.
Data Deposition: N/A.
Disclosures: L.P. is supported by the University of California San Diego Medical Scientist Training Program (NIH/NIGMS T32GM007198). R.K.-D. is an inventor on a series of patents on use of metabolomics for the diagnosis and treatment of CNS diseases and holds equity in Metabolon Inc., Chymia LLC, PsyProtix, and Metabosensor. R.K. is a scientific advisory board member, and consultant for BiomeSense, Inc., has equity and receives income. He is a scientific advisory board member and has equity in GenCirq. He is a consultant and scientific advisory board member for DayTwo, and receives income. He has equity in and acts as a consultant for Cybele. He is a co-founder of Biota, Inc., and has equity. He is a cofounder of Micronoma, and has equity and is a scientific advisory board member. The terms of these arrangements have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies. This project was enabled in part by the Alzheimer's Gut Microbiome Project (AGMP), supported by the National Institute on Aging grants: 1U19AG063744 and 3U19AG063744-04S1, awarded to Dr. Kaddurah-Daouk at Duke University in partnership with multiple academic institutions. As such, the investigators within the AGMP not listed in this publication's authors' list, provided analysis-ready data, but did not participate in designing the study, conducting the analyses or writing of this manuscript. A listing of AGMP Investigators can be found at https://alzheimergut.org/meet-the-team/. A complete listing of the AD Metabolomics Consortium (ADMC) investigators can be found at: https://sites.duke.edu/adnimetab/team/.
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Key takeaway message: Baseline gut microbiome composition is associated with cognitive performance after two years of lifestyle interventions, with opportunistic pathogens linked to worse outcomes. Microbiome profiles may help identify who responds best to cognitive protection strategies.

P223- MULTIPLE PLASMA BIOMARKER DIAGNOSTIC CASCADE: PERFORMANCE OF THE BECKMAN COULTER P-TAU217, Aβ42, AND NFL ASSAYS IN A COHORT OF INDIVIDUALS WITH COGNITIVE IMPAIRMENT.

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Background: Optimizing the use of plasma biomarkers for early detection of amyloid pathology provides critical support for diagnosis of Alzheimer's disease (AD). The plasma biomarker ratio p-Tau217 / Aβ42 has demonstrated improved diagnostic performance for detecting amyloid positivity (Aβ+) compared with individual biomarkers alone (1). Multiple interdependent pathologies characterize AD, making a multimarker approach likely needed for precision diagnosis. Recent literature suggests that neurofilament light chain (NfL) may provide additional diagnostic utility for differential diagnosis (2). **Methods:** Plasma samples from 188 participants receiving care at the Catholic Brain Health Center at Yeouido St. Mary's Hospital (Republic of Korea) under the DAVOS Alzheimer's collaborative (DAC) were analyzed. Biomarker concentrations of Access p-Tau217, Aβ42, NfL, and GFAP RUO assays were measured. APOE genotyping was also conducted for each participant. An amyloid positivity endpoint was determined by positron emission tomography (PET). Several multivariable modeling approaches (logistic regression, linear discriminant analysis, classification tree analysis, random forest) were applied to the combination of biomarkers (p-Tau217, Aβ42, NfL, GFAP) with APOE ε4 zygosity status and age for prediction of Aβ+. Diagnostic performance of multivariable outputs was compared to the performance of a recommended two-cutoff approach of the p-Tau217 / Aβ42 ratio and p-Tau217 standalone assays. **Results:** The 188 participants had a median age of 77 (interquartile range: 70 to 82), 127 (68%) were female, and 118 (63%) were Aβ+ spanning cognitive stages. While multivariable models out-performed individual markers, classification tree analyses revealed a simple, easily implementable cascading method. Classification tree analysis confirmed the recommended two-cutoff approach for the p-Tau217 / Aβ42 ratio as the primary discriminative performance for Aβ+ within the variable set. Cutoffs were aligned with the target 90% positive predictive value (PPV) and negative predictive value (NPV) cutoffs for the p-Tau217 / Aβ42 ratio (3). The analyses subsequently identified NfL to provide additional refinement for classifying individuals in the p-Tau217 / Aβ42 indeterminate prediction zone. Under these conditions prior analysis demonstrated the p-Tau217 / Aβ42 ratio reduced the indeterminate prediction zone to 13.6% compared with 40.8% for p-Tau217 standalone (3). Applying a single NfL cutoff to participants

within the p-Tau217 / Aβ42 ratio indeterminate zone further reduced this group to 6.9% while maintaining similar positive and negative predictive values. Those with NfL values below the cutoff were counterintuitively shifted to an Aβ+ predictive status. **Conclusions:** While the current study represents a limited number of participants for traditional application of statistical predictive modeling techniques, classification tree analysis identified a simple extension of the p-Tau217 / Aβ42 ratio two-cutoff approach that may be applied as a predictive cascade with NfL for subjects in the indeterminate prediction zone. This finding suggests that further studies are warranted to optimize the predictive utility of a multiple biomarker approach to identifying amyloid positivity to further reduce the intermediate prediction zone. providing the potential for earlier identification of individuals at risk or informing decision regarding confirmatory testing.

Keywords: AD diagnosis, plasma biomarkers.

Disclosures: The authors declared no competing interests beyond organization affiliation listed for each author.

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Key takeaway message: A multiple plasma biomarker approach beyond p-Tau217 and Aβ42 may further improve detection of amyloid positivity.

P224- COMPREHENSIVE BIOMARKER ASSESSMENT OF THE GAMMA-SECRETASE MODULATOR NIVEGACETOR IN PRESYMPTOMATIC CARRIER PARTICIPANTS OF THE PSEN1 E280A MUTATION.

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Background: Gamma-secretase modulators (GSMs) are a promising therapeutic approach to treat and/or delay the onset of Alzheimer's disease (AD) since they reduce the production of longer, amyloidogenic amyloid-beta (Aβ) peptides (such as Aβ42) and increase the production of shorter, non-amyloidogenic species (such as Aβ37 and Aβ38) (1-3). Nivegacetor (RO7269162) is a novel, potent, and selective oral GSM in clinical development for sporadic AD (4). Autosomal-dominant Alzheimer's disease (ADAD) accounts for < 1% of all AD cases and is the result of fully penetrant, autosomal-dominant mutations of genes coding for either gamma-secretase subunits (presenilin 1 [PSEN1] or presenilin 2 [PSEN2]) or the amyloid precursor protein (APP) (5). Since ADAD and sporadic AD have many clinical and neuropathological features in common, it is assumed that they would respond to the same treatments (5). However, since PSEN1 and PSEN2 are subunits of the gamma-secretase enzyme and APP is its substrate, mutations in these three genes could alter the enzyme's sensitivity to a small molecule modulator (6). This Phase Ib study was designed to investigate the pharmacokinetics (PK), pharmacodynamics (PD), and safety of nivegacetor and characterize the PK/PD relationship in carriers of the PSEN1 E280A mutation (ISRCTN identifier: ISRCTN75434529). As part of the study, a broad panel of AD-related fluid biomarkers was assessed to better understand the mechanism of action and the PD effects of nivegacetor. **Methods:** This Phase Ib, single-center, adaptive, repeated-dose study enrolled 15 presymptomatic mutation carrier participants and five cognitively unimpaired noncarrier participants aged 18–25 from the Colombian PSEN1 E280A kindred. Genotype status was kept unknown to participants and investigators by enrolling noncarrier family members. All participants received once-daily oral doses of nivegacetor for seven consecutive days in three sequential, dose-escalating cohorts (70 mg, 120 mg, and 230 mg). Plasma and cerebrospinal fluid (CSF) samples were collected to assess the PK and the effects of nivegacetor on Aβ isoforms (Aβ42, Aβ40, Aβ38, Aβ37), and safety data were recorded. A comprehensive panel of downstream AD-related biomarkers was assessed in plasma and/or CSF samples using Roche's NeuroToolKit prototype panel of immunoassays, which included phosphorylated tau protein (pTau) 217, pTau181, total tau (t-Tau), neurofilament light chain (NfL), chitinase-3-like 1 (YKL 40), glial fibrillary acidic protein (GFAP), triggering receptor expressed on myeloid cells 2 (TREM2), and neurogranin. **Results:** Consistent with its mechanism of action, oral administration of nivegacetor for seven days resulted in marked reductions in Aβ42 and Aβ40 levels (plasma and CSF) and pronounced increases in Aβ37 and Aβ38 levels (measured in CSF only). In PSEN1 E280 mutation carrier participants, after seven days of daily dosing of nivegacetor at the highest dose (230 mg), the maximum mean percentage change from baseline in plasma levels was 72% for Aβ42 and 43% for Aβ40. Similarly, CSF levels at the highest dose exhibited average reductions from baseline at predose of 53% for Aβ42 and 40% for Aβ40 in PSEN1 E280A mutation carrier participants. In CSF, there was a dose-dependent increase in the Aβ38/ Aβ42, Aβ37/ Aβ40, Aβ37/ Aβ42 ratios and a dose-dependent decrease in the Aβ42/ Aβ40 ratio. The magnitude of these relative Aβ changes was comparable between PSEN1 E280A mutation carrier participants and noncarrier participants. Consistent with the short treatment duration, no significant changes were observed in downstream biomarkers in either CSF (pTau181, GFAP, TREM2, YKL 40, and neurogranin) or plasma (YKL 40, pTau217, GFAP, NfL, and tTau), in both PSEN1 E280A mutation carrier and noncarrier participants. **Conclusions:** This study demonstrated that nivegacetor specifically and effectively modulates gamma-secretase processivity for Aβ monomers in presymptomatic PSEN1 E280A mutation carrier participants. Furthermore, the presence of the PSEN1 E280A mutation in the drug's target enzyme did not appear to alter its PD effects. As expected, given the short treatment duration, downstream biomarker levels were unchanged, reinforcing the need for long-term studies to assess the potential for meaningful biological and clinical effects in this specific ADAD population.

Keywords: Gamma-secretase modulator, Aβ peptides, autosomal-dominant Alzheimer's disease, biomarkers.

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Clinical Trial Registration: https://www.isrctn.com/ISRCTN75434529.

Key takeaway message: The gamma-secretase modulator nivegacetor demonstrated robust modulation of Aβ monomers in presymptomatic PSEN1 E280A carriers. The 7-day treatment did not alter downstream AD biomarkers, highlighting the need for longer studies to assess broader biological effects.

P225- DEVELOPING MICRORNA CLASSIFIERS ENRICHED IN BRAIN AND ASSOCIATED WITH INFLAMMATION IN PLASMA SAMPLES TO CLASSIFY COGNITIVELY UNIMPAIRED, MCI, AND AD STUDY PARTICIPANTS.

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Background: Developing minimally invasive blood-based diagnostic tools to better characterize heterogeneous cognitively unimpaired from mild cognitively impaired (MCI) and Alzheimer's disease (AD) subjects is critical for identifying neurodegeneration early and developing effective treatment regimens. Our approach is based on quantitative expression and machine learning analysis of circulating brain-enriched and inflammation-associated microRNAs (miRNAs) detectable in blood plasma. miRNAs are small non-coding regulatory molecules that control translation of proteins and, in the brain, are involved in processes associated with normal neuronal functioning, brain aging, and neurodegeneration. CogniMIR®, an analytically validated (1) panel of 24 miRNAs that have been selected based on promising data generated in our prior studies, interrogates expression ratios of miRNA pair biomarkers to distinguish patients in clinically relevant subgroups. A pair of two miRNAs is considered a single biomarker in our work. The following 24 miRNAs comprise CogniMIR®: let-7e-5p, miR-7-5p, miR-9-5p, miR-16-5p, miR-107, miR-125b-5p, miR-127-3p, miR-128-3p, miR-132-3p, miR-134-5p, miR-146a-5p, miR-155-5p, miR-181a-5p, miR-323-3p, miR-335-5p, miR-370-3p, miR-382-5p, miR-409-3p, miR-433-3p, miR-451a, miR-487b-3p, miR-491-5p, miR-874-3p, and miR-99b-5p. Here, we report the utilization of the CogniMIR® panel to differentiate cognitively unimpaired and cognitively impaired study participants based on the analysis of plasma samples collected at the Alzheimer's Disease Research Center of New York University (NYU). **Methods:** Plasma samples provided by NYU for this study were prospectively collected under the following protocol: blood was collected into K2EDTA BD vacutainers, placed on melting ice or refrigerated for no longer than 60 min, centrifuged at 4 °C for 15 min at 3,000xg, transferred into 0.5 ml aliquots into cryovials, and stored at -80 °C. miRNA levels were measured in a blinded fashion at the DiamiR Clinical Laboratory Improvement Amendments (CLIA) certified, College of American Pathologists (CAP) accredited laboratory. Demographics and clinical data, including clinical diagnosis, cognitive scores, and APOE genotype, were collected. Associated clinical data did not include amyloid status. This sample set of 95 plasma samples contained 63 cognitively unimpaired and 32 cognitively impaired study participants. The average participant age at blood draw was 75.13 years, and there were 23 male and 72 female participants in the cohort. Each of the cognitively impaired study participants was matched with a cognitively unimpaired participant having the same sex and race categories and an age at sample collection within 5 years. This formed a balanced group of 32 cognitively impaired and 32 cognitively unimpaired participants for further analysis. The matched subgroup had 10 male and 54 female participants and an average age at blood draw of 75.81 years. The RNA isolation from the plasma specimens was carried out using MagMAX mirVana extraction kit (ThermoFisher). Quantitative PCR-based miRNA expression analysis for the 24 miRNAs for each plasma isolated RNA sample was carried out using custom plates (Qiagen) pre-plated with lyophilized miRCURY LNA-based primers. A proprietary software program was used to select miRNA pair biomarkers and to evaluate their ability to distinguish groups with different cognitive status, as demographic confounders were minimized. For each biomarker, the software developed linear classifiers using individual miRNA pair biomarkers or combinations of biomarkers to distinguish between the subgroups. By evaluating individual miRNA pairs, biomarkers with an AUC above a 0.7 threshold were selected for further analysis. Multi-feature linear classifiers that combine up to three biomarkers from amongst those with an AUC above the threshold were then created for final classifications. **Results:** Our analysis yielded multi-feature classifiers with clinically relevant performance at distinguishing between the two subgroups without known amyloid status. The best multi-miRNA pair biomarker classifier made predictions with an AUC of 0.879 when distinguishing the cognitively unimpaired and cognitively impaired subgroups. These results were similar in nature to those generated with other cohorts in our prior and ongoing studies. miR-382-5p was present as a target (numerator) in multiple effective miRNA pair biomarkers. miR-382-5p is enriched in the hippocampus, frontal cortex, and pituitary gland, and is present in synapses. Further, let-7e-5p appeared four times in the top ten miRNA pair biomarkers. This miRNA is present at higher levels in the cerebellum, midbrain, and pituitary gland, and is present in synapses. **Conclusions:** These results further support the development of circulating brain-enriched and inflammation-associated miRNAs as epigenetic biomarkers for cognitive impairment. The work on combining additional risk factors and markers, such as amyloid status, with the CogniMIR® panel is ongoing.

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Disclosures: This work has been funded by SBIR Grant # R44AG044860 from the National Institute on Aging of the NIH; P30AG066512, NYU Alzheimer's Disease Research Center grant contributed to support patient recruitment. **Key takeaway message:** Brain enriched miRNA blood-based biomarkers are emerging tools in developing non-invasive clinical testing solutions for Neurodegeneration and Alzheimer's Disease.

P226- PERFORMANCE OF PLASMA PTAU217/Aβ42 RATIO AND PTAU217 TO PREDICT Aβ PATHOLOGY STATUS DEFINED BY CSF TESTING IN SPIN COHORT.

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Background and Objectives: Predicting the Amyloid status in brain by blood-based assays is useful for screening of Alzheimer's disease. Recent studies suggest that plasma phosphorylated tau at threonine 217 (p-Tau217) is currently promising blood biomarker for detecting amyloid pathology. In this study, we aimed to evaluate the performance of plasma p-Tau217 and p-Tau217/ Aβ42 measured by an Automated Immunoassay System HISCLTM-5000 / HISCL-800 (Sysmex Corporation, Kobe, Japan) to predict Aβ pathology defined by CSF testing in SPIN (Sant Pau Initiative on Neurodegeneration) cohort. **Methods:** This study included 199 participants: 50 cognitively unimpaired (CU), 49 mild-cognitive impairment (MCI) due to Alzheimer's disease (AD), 49 MCI due to non-AD and 51 AD dementia from the SPIN cohort which were enrolled at Hospital de la Santa Creu i Sant Pau from 2013 to 2022. The Aβ pathology was defined by CSF Aβ42/40 ratio measured by Lumipulse (Fujirebio-Europe). The plasma p-Tau217 and Aβ42 were measured by HISCL-5000. **Results:** Plasma p-Tau217 and the p-Tau217/ Aβ42 ratio predicted Aβ pathology as defined by the CSF Aβ42/40 ratio, with AUROC values of 0.947 (95% CI, 0.911–0.982) and 0.954 (95% CI, 0.920–0.987), respectively. The optimal thresholds determined by the Youden Index were 0.176 for p-Tau217 and 0.010 for the p-Tau217/ Aβ42 ratio. At the p-Tau217 threshold of 0.176, sensitivity, specificity, PPV, NPV, and overall accuracy were 93.0%, 90.9%, 91.2%, 92.8%, and 92.0%, respectively. At the p-Tau217/Aβ42 ratio threshold of 0.010, the corresponding values were 92.0%, 91.9%, 92.0%, 91.9%, and 92.0%. A two-threshold approach to achieve 95% sensitivity and specificity was also evaluated. Thresholds of 0.158 and 0.490 for p-Tau217 achieved a 94.2% accuracy with 16% of intermediate population, while thresholds of 0.007 and 0.024 for the p-tau217/Aβ42 ratio yielded 96.1% accuracy with 17% of intermediate population. These findings indicate that both single-threshold and two-threshold approaches can achieve >90% sensitivity, specificity, and accuracy. **Conclusions:** Plasma p-Tau217 and the p-tau217/Aβ42 ratio achieved high accuracy in predicting Aβ pathology determined by CSF testing.

Keywords: Alzheimer, amyloid, biomarkers, blood, plasma, tau, pTau 217, phosphorylated tau, HISCL. Disclosures: Daniel Alcolea participated in advisory boards from Fujirebio-Europe, Roche Diagnostics,

Grifols S.A. and Lilly, and received speaker honoraria from Fujirebio-Europe, Roche Diagnostics, Nutricia, Krka Farmacéutica S.L., Zambon S.A.U., Neuraxpharm, Alter Medica, Lilly and Esteve Pharmaceuticals S. A. DA declares holding a patent for markers of synaptopathy in neurodegenerative disease (licensed to ADx NeuroSciences N.V., WO2019175379 Markers of synaptopathy in neurodegenerative diseases).

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Key takeaway message: Plasma p-tau217 and the p-tau217/Aβ42 ratio accurately predict CSF-defined Aβ pathology with ≥90% sensitivity and specificity, aligning with clinical practice guideline recommendations for the use of blood-based biomarkers in Alzheimer's disease stratifications.

P227- DEVELOPMENT OF MTBR-TAU FRAGMENT ASSAY USING A FULLY AUTOMATED IMMUNOASSAY SYSTEM.

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Background: The Alzheimer's Association Workgroup has proposed a staging system that facilitates the characterization of disease progression in Alzheimer's disease dementia (AD) based on clinical and biological status determined by biomarkers (1). While amyloid-β has long been a primary therapeutic target, increasing attention is now being directed toward tau pathology as a critical driver of neurodegeneration in AD. In this context, there is a growing need for reliable tau biomarkers to support patient selection for emerging therapies, monitor treatment response, and evaluate therapeutic efficacy. To address this need, various candidate biomarkers such as the residue 243-containing microtubule-binding region of tau (e.g. MTBR-tau243), phosphorylated tau (e.g. p-tau205), and non-phosphorylated mid-region tau fragments have been proposed. MTBR-tau243 in cerebrospinal fluid (CSF), measured by immunoprecipitation-mass spectrometry (IP-MS), reported to correlate strongly with Tau-PET status and is a promising biomarker for insoluble tau aggregates (2,3). To facilitate the widespread adoption of such promising tau biomarkers in routine clinical practice, the development of simple, cost-effective, and fully automated immunoassays represents one potential approach. In this study, we developed a highly sensitive and simple immunoassay for the detection of a novel MTBR-tau fragment using a fully automated immunoassay system. Here, we report the analytical performance of the assay along with a preliminary evaluation of clinical specimens. **Methods:** Reagent for the detection of the MTBR-tau fragment was developed by selecting antibodies from various original and commercially available candidates based on their sensitivity and specificity. This assay was optimized for application on Automated Immunoassay System HISCLTM-5000 (Sysmex Corporation, Japan), which enables highly sensitive testing and provides rapid results within 17 minutes, requiring only 10 – 30 μL of sample. Analytical performance of the assay was evaluated by assessing parameters such as dynamic range, dilution linearity, within-run precision, and spike recovery. For quality control (QC) samples, pooled commercial CSF was diluted to prepare two levels, low and high. To confirm the basic clinical performance of the assay, MTBR-tau fragment levels in commercially available CSF samples were measured and compared between cognitively normal individuals (CN, n=18) and patients with clinically diagnosed AD (n=18). Group differences were assessed using the Mann-Whitney U test. Furthermore, several plasma samples from CN and AD were analyzed to evaluate the potential applicability of the assay to blood-based measurements. **Results:** This highly sensitive assay, requiring only 30 μL of sample per test, was developed with a dynamic range of 0.50 – 54.60 pg/mL. Sample dilutions within this range demonstrated 88–100% linearity compared to theoretical values. The assay showed high within-run precision, with coefficient of variation values of 3.7% or less for two QC samples. The spike recovery rate in CSF was 100% relative to the theoretical value. Among the 36 CSF samples, the median (interquartile range) concentrations of the MTBR-tau fragment in the CN group and the AD group were 0.35 (0.27 – 0.66) pg/mL and 4.11 (0.97 – 6.86) pg/mL, respectively. A significant increase in MTBR-tau fragment levels was observed in AD group compared to CN group ($p < 0.01$), with median values indicating an approximately ten-fold difference. Furthermore, fragments were successfully quantified within the assay's dynamic range in plasma samples, and similar to the CSF results, the AD group showed a trend towards higher levels compared to the CN group. **Conclusions:** This newly developed assay achieved high sensitivity with minimal sample volume requirements and can be easily operated on a fully automated platform. It also demonstrated excellent analytical performance, indicating that MTBR-tau fragment concentrations can be reliably measured in clinical samples. CSF levels of MTBR-tau fragment measured using this assay were significantly elevated in the AD group, suggesting that our assay may reflect the progression of AD tau pathology. Although the sample size was limited, this assay showed potential for application to plasma-based measurements. Additionally, the implementation of fully automated measurement systems for MTBR-tau fragment in clinical settings may contribute to the appropriate selection of eligible patients for future tau therapies.

Keywords: MTBR, tau, immunoassay.

Disclosures: SM, YH, SW, KI, KY, MM, and TS are full-time employees of Sysmex Corporation.

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Key takeaway message: Our novel, automated MTBR-tau immunoassay demonstrated excellent analytical performance enabling detection of significantly elevated MTBR-tau in AD patients in a pilot study. Our assay has potential to reflect progression of AD tau pathology.

P228- COMBINATION OF PLASMA Aβ42/40 AND P-TAU217 MEASURED USING FULLY AUTOMATED IMMUNOASSAY SYSTEM ACCURATELY PREDICTS AMYLOID PATHOLOGY DETERMINED BY AMYLOID PET.

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Background: Prior to initiating anti-amyloidβ (Aβ) antibodies for Alzheimer's disease (AD), confirmation of amyloid pathology in the brain is required. Currently, positron emission tomography (PET) or cerebrospinal fluid (CSF) testing are mainly used. These tests are also useful for the differential diagnosis of atypical cases. However, these methods have limitations on their costs, burden, and invasiveness. Therefore, blood-based biomarkers have been highly sought after in clinical

practice. Plasma Aβ42/40 ratio was first reported as candidate biomarkers, and more recently, p-tau217 has gained increasing attention. We previously reported that our plasma Aβ42/40, measured by a fully automated immunoassay system, can predict amyloid pathology as defined by amyloid PET (1). Recently, Alzheimer's Association Clinical Practice Guideline on the use of blood-based biomarkers has been published and they recommended that blood-based biomarker tests for triaging should have sensitivity of at least 90% and specificity of at least 75% (2). Although further validation may be required, our plasma Aβ42/40 met these criteria in previous studies (1). Measuring p-tau217 on the same platform may further improve diagnostic accuracy. On the other hand, in clinical practice, atypical cases may show exceptional values and affect accuracy. In this study, we evaluated the performance of our highly accurate Aβ42/40, p-tau217, and their combinations to predict amyloid pathology in a clinically heterogeneous cohort that includes atypical cases. **Methods:** Plasma samples from 45 Japanese patients registered in the TMIG Biobank were used in this study. All patients underwent amyloid PET using Pittsburgh Compound B (PiB) to support the differential diagnosis. PET positivity was determined by visual read. Plasma levels of Aβ40, Aβ42, and p-tau217 were measured using the Automated Immunoassay System HISCLTM-5000 (Sysmex Corporation, Japan). The predictive performance for amyloid PET positivity was evaluated using each biomarker, their ratios, and combinations of biomarkers based on logistic regression. Receiver operating characteristic analyses were conducted, and cohort specific cut-offs were determined using Youden index. **Results:** Among the 45 patients, 22 were amyloid PET positive and 23 were amyloid PET negative. The median (interquartile range) ages of amyloid PET–positive and amyloid PET–negative groups were 62 (55 – 68) and 70 (60 – 75) years, respectively. Two patients in the amyloid PET–positive group and one in the negative group were younger than 50 years of age, and the remaining were 50 years or older. Both groups included 14 male patients, and the remaining patients were female. Clinical diagnoses were mainly symptomatic AD in the amyloid PET–positive group and non-AD mild cognitive impairment or dementia in the negative group. The amyloid PET–positive group showed significantly lower plasma Aβ42/40 (0.098 [0.094 – 0.103] vs 0.118 [0.110 – 0.121]) and higher plasma p-tau217 (0.669 [0.459 – 1.114] vs 0.073 [0.050 – 0.119]). Plasma Aβ42/40 and p-tau217 predicted amyloid PET positivity with area under curves (AUCs) of 0.859 and 0.925, and cut-offs in this cohort calculated by Youden index were 0.105 and 0.179, respectively. Based on these cut-offs, there were two patients in the amyloid PET–positive group with extremely high Aβ42/40 values, leading to false negative results. Both patients had early onset AD and were younger than 50 years of age. One patient had a family history of early-onset dementia compatible with autosomal dominant AD. Both showed increased values above the cut-off and were correctly identified as positive by p-tau217. For p-tau217, we observed two patients in the amyloid-PET-negative group showing high values above the cut-off leading to "false-positive" results. One of them showed Aβ42/40 in the normal range in concordance with amyloid PET. Both patients were in their 60s and had no significant family history of dementia. Both patients were suspected to have positive tau pathology based on high neocortical tau PET uptake using MK6240. Amyloid PET showed mild local uptake that did not reach the threshold of a positive binary reading (equivocal results). Predictive performance of p-tau217/Aβ42 was also evaluated and the AUC was 0.936. The combination of Aβ42/40 and p-tau217 yielded a slightly higher AUC (0.941) and better separation in typical cases. **Conclusions:** We confirmed that plasma Aβ42/40 and p-tau217 measured using our fully automated immunoassay system demonstrated high accuracy in predicting amyloid PET positivity. Although each of these biomarkers showed false-positive or false-negative results against amyloid PET, the results of other biomarkers were often useful in clinical interpretation. A previous study also showed that plasma Aβ42/40 can be increased in patients with autosomal-dominant AD (3) and may warrant further investigation. Patients with low Aβ PET and high neocortical tau PET results are the focus of debate and may or may not have AD (4, 5). While combined biomarkers (i.e. p-tau217/Aβ42) can improve diagnostic performance, assessment of individual biomarkers may also be important in evaluating patients in a heterogenous cohort including rare but important cases such as those with early-onset familial AD or low Aβ and high neocortical tau PET cases.

Keywords: Blood-based biomarker, Aβ42/40, p-tau217, immunoassay.

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Key takeaway message: Plasma Aβ42/40 and p-tau217 measured using our immunoassay system can predict amyloid PET positivity. While their combination can improve diagnostic performance, assessment of individual biomarkers may also be important in heterogenous patient cohort.

P229- DIFFERENTIAL AGE EFFECTS ON PLASMA P-TAU217 BY AMYLOID STATUS, COGNITIVE STAGE, AND SEX IN ALZHEIMER'S DISEASE.

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Background: Plasma p-tau217 is a highly sensitive biomarker that reflects Alzheimer's disease (AD) pathology, including both amyloid-β and tau, even in cognitively unimpaired (CU) individuals. Age has a strong association with AD and represents its most important risk factor, and this relationship may differ across cognitive stages. Sex and APOE ε4 carrier status are also well-established risk factors for AD. The objective of this study was to investigate how the association between age and plasma p-tau217 differs according to cognitive stage, amyloid PET positivity, sex, and APOE ε4 carrier status. **Methods:** We analyzed 2,698 participants who underwent both amyloid PET and plasma p-tau217 measurement. The cohort included 666 cognitively unimpaired (CU), 1,402 mild cognitive impairment (MCI), and 630 dementia due to AD (DAT) individuals. Plasma p-tau217 was measured at the University of Gothenburg using the Simoa platform with the ALZpath antibody. Amyloid PET positivity was defined using a Centiloid threshold of 20. **Results:** In amyloid-positive groups, age correlated positively with p-tau217 in CU ($\beta = 0.029$, 95% CI 0.013–0.045, $p < 0.001$) but negatively in DAT ($\beta = -0.010$, 95% CI –0.016 to –0.004, $p < 0.05$), with no association in MCI. In amyloid-negative groups, CU ($\beta = 0.027$, 95% CI 0.021–0.033, $p < 0.0001$) and MCI ($\beta = 0.029$, 95% CI 0.022–0.035, $p < 0.0001$) showed significant positive associations, whereas DAT did not. When stratified by sex, amyloid-positive women demonstrated positive associations in CU and negative associations in DAT, while men showed positive associations in CU and MCI but no association in DAT. Similarly, APOE ε4 carriers exhibited stronger positive associations in CU and MCI compared with non-carriers. **Conclusions:** The relationship between age and plasma p-tau217 is shaped by cognitive stage, amyloid status,

sex, and APOE ε4 carrier status. These findings emphasize that plasma p-tau217 should not be interpreted in isolation, but rather within the clinical context of age, cognitive status, and genetic risk. Incorporating these factors may improve the accuracy of biomarker-based staging and enhance prognostic precision in Alzheimer's disease.

Keywords: Plasma Ptau217, age, cognitive status, differential age effects.

Disclosures: The authors declare no conflicts of interest relevant to this work.

Key takeaway message: The influence of age on plasma p-tau217 differs according to cognitive stage, amyloid status, sex, and APOE ε4, emphasizing that biomarker interpretation requires clinical and biological context.

P230- THE SPRING TRIAL: TREATMENT OF P. GINGIVALIS-POSITIVE MILD-TO-MODERATE ALZHEIMER'S DISEASE WITH THE SECOND-GENERATION GINGIPAIN INHIBITOR LHP588.

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Background: Gingipains are toxic protease virulence factors from the oral bacterial pathogen P. gingivalis (Pg) that were discovered in post-mortem brains of patients with Alzheimer's disease (AD) (1). Gingipain brain levels correlated with AD diagnosis and tau pathology, and oral infection of wild-type mice with Pg resulted in brain inflammation, neurodegeneration, and increased Ab42 production that was blocked by gingipain inhibitors (1). In a Phase 2/3 trial (GAIN) of the first-generation lysine-gingipain (Kgp) inhibitor atuzaginstat in mild-to-moderate probable AD (NCT03823404), the primary intent-to-treat prespecified endpoint was not met. However, prespecified subgroup analyses indicated efficacy in patients with Pg-positive saliva (Pg+) (N = 244), slowing cognitive decline compared with placebo on the ADAS-Cog11 by 57% in the high-dose group (p =0.020) (2). Changes in Pg DNA in saliva correlated significantly with changes on the ADAS-Cog, CDR-SB, and MMSE. In a prespecified exploratory analysis of AD biomarkers in CSF, atuzaginstat blocked an increase in CSF p-tau-181 levels compared to placebo. Atuzaginstat was generally well tolerated but development was discontinued because of liver transaminase elevations that demonstrated significant correlations with high levels of an inactive metabolite, M9. In response, a second-generation Kgp inhibitor was developed, LHP588, which doesn't create the M9 metabolite produced by atuzaginstat, for testing in mild-to-moderate AD patients with Pg+ saliva. The SPRING Trial is a 300-patient Phase-2 study of LHP588 in mild-to-moderate AD with biomarker evidence of Pg infection. We report here the Phase-1 results for LHP588, and the design of the ongoing Phase-2 for LHP588. The supportive data from the atuzaginstat trial informed critical learnings for the SPRING trial design, including optimization of dosing for target engagement, small-molecule safety, and testing methods for patient selection. The SPRING Trial is supported by a $49.2 million grant from the National Institute on Aging. **Methods:** The Phase-1 study of LHP588 enrolled 32 healthy volunteers in the SAD component with 4 cohorts and concurrent placebo (25 mg, 50 mg, 100 mg, 200 mg) and 24 healthy volunteers in the 10-day MAD portion, with 3 cohorts and concurrent placebo (50, 100 mg, and 200 mg). Food effects on LHP588 absorption were measured, and CSF levels of LHP588 were assessed to determine brain penetrance. **Results:** LHP588 was well-tolerated in the Phase-1 SAD and 10-day MAD study. Adverse events in the active arms were mild and sporadic and fewer than the placebo arm. PK with once-daily dosing achieved target concentrations predicted to be sufficient for reduction of systemic Pg infection at doses >25 mg of LHP588, and exposures equivalent or greater than those achieved with the high dose of atuzaginstat. LHP588 was also detected in the CSF. The dose of 200mg, 4x the highest dose planned for further development (50mg), achieved approximately 7x the exposure of the 50 mg dose, further supporting the overall safety index. **Conclusions:** LHP588 was well-tolerated in healthy volunteers without evidence of hepatic safety signals to date, and its PK profile was supportive of once-daily dosing. The Phase-2 trial of LHP588 is similar in design to the prior atuzaginstat study but is restricted to subjects with Pg+ saliva and high plasma p-tau-217 levels associated with AD and more reliable placebo-group decline. Saliva Pg load and plasma p-tau-217 level will also be measured at the end of treatment, since Pg infection has been shown to increase p-tau-217 in an AD animal model (3).

Keywords: Phase 2, LHP588, P. gingivalis, Alzheimer's.

Clinical Trial Registry: NCT04920903; https://clinicaltrials.gov/study/NCT04920903.

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Key takeaway message: The Phase-2 trial of LHP588 is similar in design to the prior atuzaginstat study but is restricted to subjects with Pg+ saliva and high plasma p-tau-217 levels associated with AD and more reliable placebo-group decline.

P231- PROGNOSTIC MODELS FOR DEVELOPMENT OF ELEVATED PLASMA P-TAU217 IN PRECLINICAL ALZHEIMER'S DISEASE: INSIGHTS FROM A4/LEARN.

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Background: Plasma phosphorylated tau217 (P-tau217) has emerged as a highly sensitive and specific biomarker of Alzheimer's disease (AD) pathology, with increasing evidence supporting its role in early detection and disease monitoring. Few studies have developed prognostic models that integrate demographic and clinical measures to estimate risk of developing elevated P-tau217. Improved prediction of this occurrence in cognitively unimpaired populations could help inform diagnostic testing in clinical practice, inform primary prevention trial enrichment strategies, and clarify the temporal sequence of AD pathophysiology. **Objectives:** To identify baseline demographic and clinical factors most strongly associated with development of elevated plasma P-tau217 in cognitively unimpaired adults, develop a five-year prognostic model for estimating risk of elevation, and evaluate model predictive performance using internal validation. **Methods:** This prognostic modeling study was based on secondary analysis of data from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) study and its companion study, Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN). Both studies enrolled cognitively unimpaired adults aged 65-85 years, with elevated amyloid on positron emission tomography (PET) (A4) and without elevated amyloid on PET (LEARN) at baseline. Plasma P-tau217 samples were quantified with analytically validated electrochemiluminescence immunoassay (1). The analytic sample included individuals with Mini-Mental State Examination of 27–30 and Clinical Dementia Rating Global score [CDR-GS] of 0 at index visit without elevated plasma P-tau217, and who had at least

one follow-up plasma assessment. The outcome was time to development of elevated plasma P-tau217 at any follow-up visit, defined as the highest tertile plasma P-tau217 level at baseline in A4 (2), indicating increased risk of clinical progression. Candidate predictors included demographics, clinical characteristics, genetics, and baseline plasma P-tau217. Categorical predictors with <10% missingness were imputed to the mode among non-missing values, and those with >10% missingness were coded as "Unknown". Random survival forests (RSF) were used as an initial screening method to estimate permutation-based variable importance, using nested k-fold cross validation. Variables with high importance were further assessed in Cox proportional hazards models with elastic net regularization, with selection informed by statistical significance, clinical relevance, and feasibility for real-world use. Predictor variables were categorized using clinically relevant thresholds when available, or optimal data-driven cut-points. Discrimination was quantified using Harrell's concordance index (C-index) (3) and time-dependent area under the receiver operating characteristic curve (AUC); calibration was assessed using Integrated Brier Score (IBS). Risk scores were derived from the final Cox models by multiplying model coefficients by a scaling constant and rescaling to a 0–100 range. Participants were stratified into risk groups based on predictor categories. Kaplan–Meier survival analyses were used to evaluate the ability of the models to meaningfully separate risk groups over five years. **Results:** Of 1,707 participants in the original studies (1,169 in A4 and 538 in LEARN), 881 met the criteria for the prognostic modeling sample (A4: 636 [54.4%], LEARN: 245 [45.5%]). Mean (standard deviation [SD]) age at index date was 70.6 years (4.3), and 62.0% of participants were female. Mean (SD) plasma P-tau217 was 0.179 (0.050) u/mL at baseline, and 47.1% of participants were carriers of at least one APOE ε4 allele. Median follow-up time was 4.2 years (minimum 0.2, maximum 5.5) years, and 194 participants (22.0%) developed elevated plasma P-tau217 during follow-up. RSF identified baseline plasma P-tau217 as having the highest permutation importance, followed by clinical measures (Logical Memory-Delayed Recall, Cognitive Function Index [CFI] combined participant and study partner total score, Preclinical Alzheimer Cognitive Composite score and subcomponents), age, education, and number of APOE ε4 alleles. Three multivariable Cox models were selected, all including age and education as predictors, and additional predictors as follows: Model A: baseline plasma P-tau217 (C-Index=0.822; AUC=0.759; IBS=0.069). Model B: number of APOE ε4 alleles [zero, one, or two] (C-Index=0.551; AUC=0.561; IBS=0.083). Model C: no other predictors (C-Index=0.502; AUC=0.560; IBS=0.084). Model A had the best performance, showing very good discrimination and calibration over 5 years. Model B showed significantly lower performance, offering an alternative prediction option where baseline plasma biomarker values are not available, but genetic information is available. Model C had the poorest prediction performance, yielding modest discrimination and calibration for settings where only basic demographics are available. Kaplan–Meier curves of out-of-fold risk groups demonstrated clear separation for all models. Across risk groups, the 5-year cumulative incidence of development of elevated plasma P-tau217 for the low-, intermediate-, and high-risk groups, respectively was 15%, 27%, and 67% in model A; 25%, 39%, and 67% in model B; and 31%, 41%, and 74% in Model C. **Conclusions:** Prognostic models using baseline demographic, genetic, and plasma P-tau217 measures stratified cognitively unimpaired individuals by 5-year risk of developing elevated plasma P-tau217. The best-performing model, incorporating baseline plasma P-tau217, age, and education, showed very good discrimination and calibration, with clear separation of risk groups. Simpler models relying on APOE ε4 genotype and demographics or demographics alone performed worse but provide feasible alternatives when plasma P-tau217 data are unavailable. These findings highlight the potential of prognostic modeling to identify individuals at high risk for near-term development of elevated plasma P-tau217, informing plasma P-tau217 diagnostic testing in clinical practice, supporting more efficient primary prevention trial enrichment strategies, and advancing prevention-focused research in AD.

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Funding: This study was sponsored by Eli Lilly and Company.

Key takeaway message: Prognostic models combining baseline demographic, genetic, and plasma P-tau217 measures can identify cognitively unimpaired individuals at high risk for near-term development of elevated plasma P-tau217, supporting early detection strategies and primary prevention trial enrichment.

P232- EVALUATION OF THE CLINICAL IMPACT OF BLOOD-BASED BIOMARKER ASSAYS ON DEMENTIA SPECIALISTS' DECISION-MAKING (CIMBBBA): PRELIMINARY REPORT FROM A REAL-WORLD DEMENTIA SUBSPECIALTY CLINIC STUDY.

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Background: The current workflow in the Massachusetts General Hospital and Brigham & Women's dementia subspecialty clinics (at MGH, the Memory Disorders Unit, the Frontotemporal Disorders Unit, and the Lewy Body Dementia Unit; and at BWH, the Center for Brain/Mind Medicine) for the diagnostic evaluation of a patient suspected of having MCI or mild dementia due to Alzheimer's disease (AD), Frontotemporal Lobar Degeneration, Lewy body disease, or another AD related disease (ADRD) follows 2024 Alzheimer's Association DETeCD-ADRD guidelines (Atri, Dickerson, et al., Alzheimers Dement, 2024). Typically, this includes 1) a comprehensive clinical assessment by a dementia subspecialist; 2) blood labs tailored to a patient's risk profile and chosen to rule out common comorbid or contributing medical conditions (often ordered immediately after an initial clinic visit), and then usually 3) structural brain imaging with MRI and sometimes 4) formal neuropsychological assessment. Patients may also have 5) an FDG PET to evaluate regional brain glucose metabolism. Depending on the level of concern for AD, many patients may then undergo 6) cerebrospinal fluid examination for amyloid-beta, total tau, and phospho-tau or 7) an amyloid PET scan, the two current gold standard tests for consideration for amyloid-targeted therapy. In many cases, additional diagnostic assessments and testing tailored to the individual may be indicated. As blood-based biomarkers (BBBs) become available for clinical use, we are working to follow the Alzheimer's Association appropriate use recommendations for plasma biomarkers (Hansson et al., Alzheimers Dement 2022) by obtaining them in conjunction with gold standard subspecialty imaging and biomarker testing. We developed this project because our clinicians sought to use BBBs in the diagnostic evaluation of individual

patients, but we had not yet validated them in our clinical practice setting, patient population, nor in our clinical workflow against gold standard tests. In this project, we evaluated two commercially available BBBs in the early stage of our diagnostic workflow (#2 above) to determine their role in clinicians' decision-making and with validation against gold standard testing. **Methods:** As part of the workflow above, clinicians were offered the opportunity to order the Lucent ptau217 assay and/or the more recently available LucentAD Complete panel as standard sendout labs for their clinic patients. The clinicians served as research subjects and each provided consent to participate. Prior to learning the results of the test(s), clinicians completed forms (similar to the procedures in the IDEAS study of amyloid PET) detailing their differential diagnoses and their plans for testing and treatment. The clinician then completed a follow up form after the BBB results were returned, capturing any changes in diagnostic considerations and further diagnostic evaluation plans and treatment plans based on those results. Last, an additional form was completed after gold-standard biomarker information was obtained to finalize the diagnostic formulation. **Results:** These preliminary results represent data from 131 patients (70 with MCI and 61 with dementia) who were being evaluated to determine the likely etiology of their cognitive impairment. Lucent ptau217 was obtained on 123 cases and LucentAD Complete on 47 cases; 39 cases had both. Compared against gold-standard biomarkers, plasma ptau217 demonstrated a true positive rate of 70/73 (96%) and a true negative rate of 18/23 (78%). Results were intermediate for 27 cases (21%). Plasma LucentAD Complete demonstrated a true positive rate of 24/26 (92%) and a true negative rate of 11/13 (85%). Results were intermediate for 8 cases (17%). For 24 cases in which both biomarkers were obtained and neither was intermediate, results were 100% convergent. For 15 cases in which ptau217 was intermediate, LucentAD Complete resolved 66%, producing a true negative or true positive result in 9, a false positive result in 1, and an intermediate result in 5. For 4 cases in which LucentAD Complete produced an intermediate result, ptau217 resolved 25%, producing a true negative in 1 and an intermediate result in 3. Clinician decision-making data are currently being analyzed. **Conclusions:** Consistent with published reports involving blood-based AD biomarkers, we found in our subspecialty clinical practice that both the Lucent ptau 217 assay and the LucentAD Complete panel were highly sensitive and specific for detecting likely AD pathologic changes when measured against widely accepted gold standard AD biomarkers. These results support the use of blood-based biomarkers in the early clinical workflow of dementia subspecialists, although they do not yet support their use as standalone tests capable of supplanting current gold standard assessments.

Key takeaway message: In our subspecialty clinic, we found that two blood-based biomarkers, the Lucent ptau 217 assay and the LucentAD Complete panel, were sensitive and specific for detecting AD pathologic changes when measured against gold-standard AD biomarkers.

P233- COMBINING COGNIVUE CLARITY AND LUCENT AD COMPLETE FOR A TIME AND COST EFFICIENT TWO STAGE SCREENING FOR ALZHEIMER'S DISEASE CLINICAL TRIAL RECRUITMENT ENRICHMENT AND TREATMENT PROTOCOLS.

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Background: For patients living with Alzheimer's disease and Mild Cognitive Impairment due to AD (MCI-AD), there can be a long delay in getting a correct diagnosis. This may reduce the window for treatment with amyloid-lowering therapies and missed opportunities for enrollment into clinical trials. The advent of sensitive computerized cognitive tests such as Cognivue Clarity and blood-based biomarkers of AD pathology such as LucentAD Complete offer unique opportunities to hasten screening and identification of patients with early-stage AD outside of specialty centers and expensive and invasive biomarkers. For individuals with preclinical Alzheimer's disease (pAD), defined by amyloid positivity in the absence of cognitive impairment, recognition in the clinical setting has been nearly impossible. With the advent of amyloid PET being used more frequently in clinical trials and longitudinal research, pAD is increasingly recognized in research participants enrolled in these studies but otherwise pAD is very difficult to identify in order to recruit in AD prevention studies. Cognivue Clarity is a 10-minute self-administered computerized cognitive assessment. A cut-off score of <69 can differentiate individuals with MCI from healthy controls. Cognivue Clarity is also sensitive to the presence of amyloid potentially allowing the rapid identification of early-stage AD and pAD (1-3). A machine learning paradigm to combine three Cognivue Clarity subtests and age was used to create the Cognivue Amyloid Risk Measure (CARM) as an added value metric for the likelihood of a positive amyloid PET scan (4). LucentAD Complete is a highly sensitive multi-biomarker blood test for assessing the presence of AD pathology using an algorithm to combine SIMOA ultrasensitive analysis of pTau217, Ab42/40 ratio, NfL, and GFAP into a single score ranging from 0-100 and uses a two threshold cutoff with 0-44 representing low risk, 45-70 representing intermediate risk, and 70-100 representing high risk of a positive amyloid PET scan (5). To increase the likelihood of screening for early-stage AD, we combined the Cognivue Clarity with LucentAD Complete in a two-stage screening approach to (a) identify individuals with early-stage AD, (b) differentiate AD from non-AD processes, and (c) screen for pAD among cognitive normal controls. **Methods:** The Bio-Hermes Study (6), funded by the Global Alzheimer's Platform Foundation, investigated the relationship between emerging blood-based and digital biomarkers and the presence of amyloid measured by PET scan in 1,001 participants were enrolled, of which 887 completed Cognivue Clarity, LucentAD Complete, and amyloid PET scans. Participants were stratified into three clinical cohorts (Cognitively Normal, MCI, probable AD) using National Institute on Aging-Alzheimer Association criteria for MCI-AD and AD. Participants underwent amyloid PET using 18F-Florbetapir as the Gold Standard.The clinical diagnosis was combined with amyloid status to develop clinicopathologic groups consisting of 297 True Controls, 91 pAD, 111 MCI-AD, 171 MCI due to a process other than AD (MCI-non-AD), 130 dementia due to AD, and 87 dementia due to a process other than AD (non-AD). Statistical analyses were conducted using IBM SPSS v29. Independent sample t-tests or one-way ANOVA with Tukey-Kramer post-hoc tests were used for continuous data, and Chi-square analyses were used for categorical data. **Results:** The sample had a mean age of 71.8+6.7y with 15.5+2.7y of education, 56.4% female, 37.3% ApoE e4 carriers, and 78.8% non-Hispanic White. Cognivue Clarity scores differentiated True Controls from all other clinicopathological groups, pAD from MCI and dementia groups, and MCI from dementia (all $p<0.001$). LucentAD Complete differentiated True Controls from amyloid positive group (pAD, MCI-AD, AD) and between amyloid positive (pAD, MCI-AD, AD) and amyloid negative (MCI-non-AD, non-AD) groups (all $p<0.001$). We tested the 2-stage screening paradigm to mimic how individuals might be evaluated in clinical practice. First, using screening cognition with Cognivue Clarity, the sample was divided into impaired (58%) and non-impaired individuals (42%). LucentAD Complete was then used to classify individuals as low, intermediate, or high probability of amyloid PET scans. Five classifications were derived matching 85% of BioHermes clinicopathological groups: True Controls (Cognitive Normal, Amyloid Negative), pAD (Cognitively Normal, Amyloid Positive), early-stage AD (Cognitive Impaired, Amyloid Positive), non-AD process (Cognitive Impaired, Amyloid Negative) and a small indeterminant group (15%) with mismatches between cognitive performance and amyloid status that would benefit from a confirmatory PET scan. **Conclusions:** Cognivue Clarity, a 10-minute computerized battery, can detect individuals with cognitive impairment and with the CARM can identify individuals likely to have amyloid positivity. Using the staged screening approach (Cognivue Clarity + LucentAD Complete), we classified 85% of the BioHermes sample into (a) True Controls who could be assured and reassessed at a later date, (b) non-AD

processes that would direct towards a different work-up, or (c) early-stage AD and pAD that could be entered into a treatment protocol or enrolled in a clinical trial. Only 15% of the sample would need a confirmatory amyloid PET scan. With many AD prevention and treatment trials on-going, screening for individuals with cognitive impairment and amyloid is an expensive and labor-intensive proposition since neuropsychological testing alone cannot detect amyloid, and biomarkers alone cannot characterize cognitive performance. Employment of a 2-stage screening strategy (Cognivue Clarity + LucentAD Complete) could increase the likelihood of identifying early AD for treatment or trial enrollment, avoiding the cost of expensive PET scans in a time- and cost-effective fashion.

Keywords: Cognivue clarity, lucentAD complete, Alzheimer's disease, mild cognitive impairment, preclinical Alzheimer's disease, amyloid, clinical trials. **Disclosures:** Dr Galvin is a full-time employee of the University of Miami and serves as Chief Scientific Officer for Cognivue, Inc. Ms Harris and Mr Estes are full-time employees of Cognivue, Inc. Ms Mette and Dr Wilson are full-time employees of Lucent Diagnostics.

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Key takeaway message: Employment of a 2-stage screening strategy (Cognivue Clarity + LucentAD Complete) could increase the likelihood of identifying early AD, potentially avoiding the cost of expensive PET scans in a time- and cost-effective fashion.

P234- PERFORMANCE TESTING OF THE NOVEL DDC XPLORER LUMIPULSE G1200 IMMUNOASSAY FOR MEASURING DOPA DECARBOXYLASE IN CEREBROSPINAL FLUID (CSF).

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Background: Dementia with Lewy Bodies (DLB) and Parkinson's Disease (PD) are characterized by aggregation of α-synuclein into Lewy bodies and neurites and by dopaminergic dysfunction, which can be measured by Dopamine transporter imaging with SPECT or PET (1,2,3). The α-synuclein Seed Amplification assay in CSF (CSF_synSAA) is widely accepted as a biomarker of synucleinopathy (4). Recently mass spectrometry and proteomics studies have indicated Dopamine Decarboxylase (DDC) as a novel promising fluid marker for DLB and PD (5,6). However, such technologies, require specialized expertise and are not easily implemented in verification and validation studies to fully assess the clinical potential of this candidate biomarker. We therefore developed and analytically validated an automated research use only (RUO) immunoassay to quantify DDC in CSF on the Lumipulse G1200 platform. This assay was tested in a cohort of patient CSF samples including AD, PD and controls. **Methods:** CSF samples were obtained in a retrospective cohort (Perugia University, Italy) consisting of 31 controls, 51 AD patients, and 24 PD patients diagnosed according to the 2018 NIA-AA (7) and MDS PD criteria (8), respectively. For all the patients CSF Aβ42/40, CSF pTau181, CSF t-tau were previously measured (9,10). The one-step immunoassay using 70 µL of neat CSF, was developed on the Fujirebio Lumipulse G1200 platform, employing a DDC-specific monoclonal antibody pair: a bead-conjugated IgG2b capture antibody (code# ADx412) and an alkaline phosphatase-conjugated Fab fragment derived from an IgG1 detector antibody (code# ADx411). A limited analytical performance study was done including intra- and inter-assay precision, accuracy, parallelism, and dilutional linearity. Lot-to-lot consistency was assessed using a QC panel of three neat CSF samples tested across two independently produced reagent lots. A Mann-Whitney test with post hoc Dunn test was used to compare levels across diagnostic groups and receiver-operator-curve analysis was performed using Delong method. **Results:** The DDC Xplorer assay demonstrated intra- and inter-assay precision of 3.8%CV and 7.2%CV, respectively, across five independent runs using CSF and recombinant DDC-spiked buffer. Parallelism and dilutional linearity were within acceptance criteria (80–120% recovery). All CSF samples were measurable above the LLOQ (0.5 pg/mL) and within the analytical measuring range (1.3–15.4 pg/mL). Lot-to-lot variation ranged from 96–111% across five runs. CSF DDC levels were significantly elevated in the group of PD patients compared to controls ($p < 0.0001$) and AD ($p = 0.0247$). No significant difference was observed between AD and controls ($p = 0.0814$). Diagnostic accuracy in this exploratory study was higher for PD versus controls (AUC = 0.80, 95%CI: 0.68–0.92) than for PD versus AD (AUC = 0.66, 95%CI: 0.54–0.78). **Conclusions:** A prototype LUMIPULSE G1200 RUO assay was developed for the quantification of DDC in CSF. Our findings indicate that this DDC Xplorer assay exhibits good analytical performance and detected elevated DDC levels in CSF of PD patients but not in AD or controls, which supports the potential use of DDC as a biomarker of dopaminergic dysfunction. Additional studies with larger sets of well-characterized samples, including CSF_synSAA, are needed to enhance our understanding of DDC as a CSF fluid biomarker in synucleinopathies. The DDC Xplorer assay offers a readily implementable, robust and scalable alternative for proteomics based technologies.

Key takeaway message: We present a novel immunoassay to quantify DDC in CSF. Increased levels in the group of PD patients compared to controls and AD suggests that DDC is a potential fluid biomarker of dopaminergic dysfunction.

P235- BLOOD BIOMARKER TESTING IN REAL-WORLD CARE SETTINGS: EARLY LEARNINGS FROM THE ACCURATE DIAGNOSIS IMPLEMENTATION PROJECT.

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Background: A timely and accurate diagnosis of Alzheimer's disease (AD) is needed for patients and families to access optimal care and supportive services, and to support their planning for the future. AD blood biomarker (BBM) tests are promising innovations; however, healthcare systems are not prepared to integrate BBM testing as part of the diagnostic workup for AD. In January 2024, the Davos Alzheimer's Collaborative Healthcare System Preparedness (DAC-SP) program launched the Accurate Diagnosis project in eight sites across five countries (Germany, Japan, Netherlands, UK, and US). This multi-site implementation study uses theories, methods, and frameworks from implementation science to identify best practices for real-world use of BBM tests in primary and specialty care settings. **Methods:** Program implementation process and outcomes will be evaluated using a concurrent mixed-methods design guided by the revised Consolidated Framework for Implementation Research (CFIR; Damschroder et al.,

2022), to identify real-world barriers and facilitators to BBM adoption and sustainability. DAC-SP convenes a monthly Accurate Diagnosis community of practice (CoP) for sites to discuss emerging learnings and collaborate on common implementation barriers. Sites independently developed study protocols for BBM implementation (e.g., clinical workflows and provider training) and to assess clinical outcomes important to their local systems. DAC-SP coordinated with sites on a harmonized dataset to assess the cross-site impacts of including BBM testing in the diagnostic process, including the effects on health services and clinical outcomes. Data will be triangulated across sources and sites to develop key learnings that will inform updated implementation guidance on the open access DAC-SP Early Detection Blueprint (www.dacblueprint.org) microsite. **Results:** The first ten months of the Accurate Diagnosis project was dedicated to workflow design and operational set-up, with the first site actively enrolling patients in October 2024. As of September 2025, 1,492 AD BBM tests have been ordered as part of this program. To facilitate healthcare system adoption of BBM care pathways, sites collaborated on content for the training and education of providers on Alzheimer's blood biomarkers and the diagnostic workup. Across sites, ADRD experts partnered with clinicians in primary and general specialty care settings to generate and launch site-specific training materials, tools, and resources to support the use of BBM tests in clinical decision-making. Training predominantly focused on promoting knowledge and confidence of healthcare providers on the benefits and limitations of AD BBMs and guidance on discussing the tests and results with patients, including appropriate follow-up and referral practices. To date, 242 healthcare providers have been trained on BBM care pathways across sites, including clinicians in primary (n=145), general specialty (n=36) and specialized memory (n=61) care settings. **Conclusions:** The DAC-SP Accurate Diagnosis project is the first global implementation study of the real-world use of Alzheimer's blood biomarker tests. Common site implementation challenges and learnings will be presented with practical guidance and case examples in the DAC-SP Early Detection Blueprint for other healthcare systems. Findings from this project will support broader global adoption of Alzheimer's disease BBMs, so that patients and families can benefit from a timely and accurate diagnosis.

Key takeaway message: The ongoing DAC-SP Accurate Diagnosis project launched in 2024 to support broader global adoption of Alzheimer's disease BBMs, so that patients and families can benefit from a timely and accurate diagnosis.

P236- ADXPLORER: FILLING THE GAP FOR EARLY-STAGE FLUID BIOMARKER RESEARCH ON THE FULLY AUTOMATED LUMIPULSE® G1200 PLATFORM.

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Background: There is a pressing need in the field of neurodegeneration for reliable early-stage, exploratory fluid biomarker tests, which play a key role in early decision-making in (pre-)clinical drug development programs (1,2,4). Homebrew assays are often used in this context, developed on a variety of research platforms that lack proper characterization for their analytical performance (1,3). Moreover, these assays are often limitedly made available to the field, which further hampers understanding of the new biomarker's potential value. The ADxPLORER portfolio, part of the Fujirebio Neuro Expert Toolbox (NExT), addresses this gap by making well characterized biomarker immunoassays available on the fully automated LUMIPULSE® G1200 platform, a technology with a track record in all stages of clinical programs. At this moment the ADxPLORER portfolio includes Neurogranin, VAMP2, NPTX2, BD-Tau, pTau231, DDC and Beta-synuclein of which the analytical qualification is presented in this work. **Methods:** Each Xplorer immunoassay is developed using a specific monoclonal antibody (mAb) pair: a bead conjugated capture antibody combined with an alkaline phosphatase conjugated Fab fragment of the detector antibody. Analytical qualification parameters include precision, accuracy, analytical measuring range (AMR), lower limit of quantification (LLOQ), parallelism, dilution linearity, specificity, and lot-to-lot consistency in line with Andreasson et al, 2015 (5). Assessments are carried out across multiple days and instruments. Inter- and intra-assay precision are determined from five independent test runs using a panel of remnant specimen samples (n=3) and run validation (RV) samples. Accuracy is reported as the percentage recovery of the back calculated values of the calibration curve. AMR is determined by measuring at least 15 remnant samples per compatible matrix. The LLOQ is established based on accuracy and precision profile of low-range calibrators. Specificity is confirmed by testing homologous analytes at concentrations within and above the calibration range using a synthetic peptide or recombinant protein approach. Parallelism and dilution linearity are assessed with remnant specimen samples (n=3) and spiked high-concentration samples. Lot consistency is evaluated using different lots of reagents including mAbs. Finally, we aim to provide a recommended dilution factor in the assays for cerebrospinal fluid (CSF), plasma and serum matrices, if applicable. **Results:** The Xplorer assays for Neurogranin, VAMP2, NPTX2, BD-Tau, pTau231, DDC and Beta-Synuclein demonstrate strong analytical performance for each of their compatible matrices (CSF and/or plasma/serum). The intra-assay precision ranges between 1.0–5.1% CV, inter-assay precision between 3.6–11.5% CV, and accuracy of 98.3–100%. A high analytical sensitivity to cover low analyte levels in serum and plasma is demonstrated by achieving low LLOQ values in the low pg/mL range which allow confident measurement (signal/noise (S/N) >2) of biological specimen samples based on the determined AMR (e.g. DDC Xplorer assay LLOQ 0.50 pg/mL, AMR: 1.33-15.3 pg/mL). Parallelism and dilutional linearity are within acceptance criteria (80–120% recovery) and specificity is confirmed by low S/N ratios for homologous analytes. For the current available assays, the lot variation across two lots is <20% using a remnant specimen panel (n=3) in five independent runs. **Conclusions:** The data shows that the currently available Xplorer assays can measure low abundant analytes with high precision and specificity and are well characterized for their analytical performance. The ADxPLORER concept fills the gap in the neurodegeneration field as it provides an accessible alternative for the less extensively documented homebrew assays. Promising biomarkers can ultimately move on through the NExT trajectory towards a globally available RUO, or even regulatory approved assay if needed by the field.

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Key takeaway message: Xplorer assays are well characterized biomarker immunoassays which can measure low abundant analytes with high precision and specificity and are well characterized for their analytical performance, available on the fully automated LUMIPULSE® G1200 platform.

P237- NOVEL HIGH-THROUGHPUT, FULLY AUTOMATED IMMUNOASSAY FOR CEREBROSPINAL FLUID TAU MICROTUBULE BINDING REGION (MTBR-TAU).

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Background: MTBR-tau refers to a specific domain of the tau protein that has been shown to play a crucial role in the development of neurofibrillary tangles (NFT), a hallmark of tauopathy. Measuring MTBR-tau in cerebrospinal fluid (CSF) may offer direct insight into the central nervous system tau pathology. MTBR-tau is a domain strongly implicated in tau aggregation and NFT formation, making it a promising and more pathology-specific biomarker compared to existing tau measures. However, because MTBR-tau is present at very low quantities, it undergoes extensive posttranslational modifications, and may experience epitope masking during aggregation, improvement in the sensitivity and specificity of MTBR-tau assays is needed. Here, we describe the performance of three highly sensitive proof-of-concept MTBR-tau assays on the Beckman Coulter Access DxI 9000 Immunoassay Analyzer. **Methods:** We developed three proof-of-concept MTBR-tau prototype assays targeting unique areas of the MTBR-tau domain. These assays are a one-step sandwich assay utilizing anti-MTBR-tau monoclonal antibodies (MAb)/alkaline phosphatase conjugate, and paramagnetic particles coated with a complementary anti-MTBR-tau MAb. Sample and reactants are incubated and washed, then a chemiluminescent substrate is added. The light generated is directly proportional to the MTBR-tau concentration in the samples. Samples were screened on the Access DxI 9000 Immunoassay Analyzer, capable of analyzing up to 450 tests/hour. For this study, CSF samples were collected from donors who were $\geq$55 years of age and had cognitive impairment evaluation using a mini-mental state examination (MMSE). Levels of total Tau, β-amyloid 1-42, and β-amyloid 1-40 were determined with the Lumipulse G1200 immunoassay analyzer. Two groups were defined based on the evaluations described above with the following study-specific thresholds (No standardized clinical cutoffs. Not a diagnostic criterion.): Group 1: tau negative (CSF total-tau $\leq$225 pg/mL); amyloid negative (CSF β-amyloid 1-42/1-40 ratio $\geq$0.072); and MMSE $\geq$28, or Group 2: tau positive (CSF total-tau $\geq$325 pg/mL); amyloid positive (CSF β-amyloid 1-42/1-40 ratio $\leq$0.072); and MMSE $\leq$20. **Results:** Each of the MTBR-tau proof-of-concept prototypes showed robust signal generation and were able to produce measurable signal in all CSF samples tested. None of the CSF samples had signal below blank sample background for each of the three MTBR-tau prototypes. We confirmed that all prototypes can detect MTBR-tau across a range of forms, though further work is needed to confirm recognition of specific oligomeric states. CSF sample discrimination between the two groups was >2-fold ($P < 0.05$) for each of the MTBR-tau prototype assays. Additionally, the prototypes showed strong correlation with CSF total-tau levels (R2 >0.92), but not with β-amyloid 1-42 (R2<0.36). **Conclusions:** Our results suggest that the three proof-of-concept MTBR-tau assays can measure MTBR-tau signal in all CSF samples, even in samples with low levels of amyloid and total-tau. Initial assessment of these MTBR-tau assay prototypes demonstrates their ability to distinguish between samples with high and low tau. This research is an exciting step towards high throughput, automated tauopathy quantification and NFT accumulation.

Keywords: Microtubule binding region, tau pathology, immunoassay biomarker, Alzheimer's disease.

Disclosures: All authors are employees and minor shareholders of Beckman Coulter/Danaher.

Key takeaway message: We have developed three novel proof-of-concept MTBR-tau assays that demonstrate high sensitivity and specificity in cerebrospinal fluid, offering a potential tool for automated, high-throughput quantification of tau pathology.

P238- HIGH FAT FEEDING EFFECTS ON PERIPHERAL AND CEREBROSPINAL MEASURES OF GLUCOSE, INSULIN AND APPETITE HORMONES.

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Background: High fat western-style diets are a risk factor for Alzheimer's disease (AD). However, this relationship is less strong in individuals with the AD risk gene APOE4 (E4 carrier) state. Previous research has demonstrated that E4 carriers performed better on cognitive tests following a high fat meal (HFM). The objective of this project is to investigate plasma and cerebrospinal fluid (CSF) levels and relationships of glucose, insulin and other appetite hormones in E4 carriers after high fat feeding. **Methods:** The Meal and Memory study (NCT#03070535), conducted at the University of Washington, enrolled 78 cognitively healthy older adults, half with E4 carrier status, who ingested a breakfast-style HFM after an overnight fast. Ages ranged from 55-84 years. Blood samples were taken at baseline and at 6 time points after meal provision, and CSF was collected 4 hours after meal provision. Measures of plasma glucose, lipids and insulin were performed through our university's CLIA-certified laboratory, and measures of CSF appetite hormones were performed using Meso Scale Discovery multiplex kit. Statistics including ANCOVA and Pearson correlation were performed in SAS Enterprise. **Results:** E4 carriers had lower glucose curves after HFM compared to non-carriers (ANCOVA F statistic 8.8, $p<0.01$, adjusted for BMI) whereas insulin and lipid curves did not statistically differ by E4 status. CSF glucose and appetite hormones did not differ by E4 group, and with the exception of GLP-1, correlated stronger with fasting rather than prandial levels of plasma glucose, insulin and triglycerides. Only about 60% of participants had detectable levels of active GLP-1 in CSF and GLP-1 levels positively correlated with max triglyceride post-HFM (CC +0.39, $p=0.009$). **Conclusions:** Despite significant peripheral glucose changes, CSF appetite hormones did not differ at 4 hours by E4 after high fat meal ingestion. GLP-1 was detectable in CSF in about 60% of the participants and correlated with prandial triglycerides. For CSF glucose and several other appetite hormones, fasting rather than prandial levels of nutrients more strongly predicted levels, suggesting these CSF measures are relatively impervious to single meal ingestions.

Key takeaway message: APOE4 carriers respond differently to acute high fat feeding in terms of peripheral glucose; these peripheral metabolic changes do not immediately translate into changes in CSF glucose, insulin or appetite hormones.

P240- CHARACTERIZATION OF STAGES OF NEURODEGENERATION USING CIRCULATING BRAIN-ENRICHED AND INFLAMMATION-ASSOCIATED MICRORNAS.

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Background: Minimally invasive blood-based diagnostic tools are crucial to characterize heterogeneous mild cognitive impairment (MCI),

pre-MCI, and Alzheimer's disease (AD) cohorts and individual patients. Our approach towards developing these tests is based on targeted selection and quantitative analysis of brain-enriched and inflammation-associated microRNAs (miRNAs) detectable in blood plasma. miRNAs are promising epigenetic markers reflective of pathophysiological processes at a cellular level. They are small non-coding regulatory molecules that are associated with normal neuronal functioning, as well as brain aging and the development of neurodegeneration. We have developed CogniMIR®, a panel of 24 miRNAs with possible connections to AD. Our panel interrogates ratios between miRNA pairs and uses these biomarkers to distinguish patients belonging to clinically relevant subgroups. Here, we report a comparative analysis using our pair-based approach and the CogniMIR® panel to investigate a set of 299 plasma samples with known cognitive impairment. **Methods:** Our study focuses on 299 plasma samples collected at UPenn's Alzheimer's Disease Research Center (ADRC) from patients with known cognitive impairment status: cognitively unimpaired (CU), mildly cognitively impaired (MCI), or AD. Blood samples were centrifuged at 3000 x g for 15 minutes at 4 °C and aliquoted into 2.0-ml polypropylene cryovials (Corning Life Sciences, Corning, NY, USA). The aliquots were stored at −80 °C. We isolated miRNAs from plasma samples using the MagMAX mirVana kit (ThermoFisher) and measured the expression of the 24 miRNAs in our CogniMIR® panel through qPCR using custom plates (Qiagen) preplated with lyophilized miRCURY LNA-based primers. The amyloid status (Ab+/-) and APOE genotype (APOE4 +/-) for each patient were also considered during our data analysis. We use a pair-based approach for our analysis in which we consider a single biomarker to be the ratio between the expression levels of two separate miRNAs. The numerator miRNA is the target to be investigated, while the denominator is a comparatively stable miRNA used for normalization. To investigate the diagnostic potential of such biomarkers, we divided patients into twelve subgroups based on cognitive status, amyloid and APOE risk factors, and gender. For each subgroup, we developed linear classifiers using individual miRNA pair biomarkers or combinations of biomarkers to distinguish between the subgroups. By evaluating individual miRNA pair biomarkers, self-validation metrics were developed, and biomarkers with an AUC above a 0.7 threshold were selected for additional analysis. We then constructed multi-feature linear classifiers that combine up to three biomarkers from amongst those with an AUC above the threshold to create final classifications. **Results:** We evaluated single-biomarker and multi-biomarker linear classifiers for 12 different subgroup classification tasks. While our largest subgroups, MCI irrespective of risk factors (n=122) vs CU irrespective of risk factors (n=123) did not provide classifiers with >0.7 AUC, inclusion of demographics and risk factors in our data analysis yielded more effective classifiers. For sex-based subgroup comparisons of MCI male (n=41) vs CU male (n=41) and MCI female (n=55) vs CU female (n=55), the better-performing classifiers were with AUC of 0.725 and 0.705, respectively. Consideration of other risk factors yielded similar results, with MCI amyloid positive (n=67) vs CU amyloid negative (n=67) classifier having AUC=0.710 and MCI amyloid positive/APOE4 positive (n=35) vs CU amyloid negative/APOE4 negative (n=35) having AUC of 0.801. Combining amyloid and APOE status with gender resulted in our most performant classifiers overall, with MCI amyloid positive male (n=25) vs CU amyloid negative male (n=25) and MCI amyloid positive female (n=30) vs CU amyloid negative female (n=30) having AUC of 0.873 and 0.832, respectively. When amyloid-positive MCI and AD specimens were combined into a single subgroup, the best AUC for MCI or AD amyloid-positive (n=79) vs CU amyloid-negative (n=79) was 0.744, while the best AUC for MCI or AD amyloid-positive/APOE4-positive (n=75) vs CU amyloid-negative (n=79) was determined to be 0.723. Importantly, miRNA-based classifiers were able to differentiate between the sets of cognitively unimpaired groups with the risk factors from those without the risk factors. For example, CU APOE4 positive (n=47) vs CU APOE4 negative (n=47) and CU amyloid positive (n=44) vs CU amyloid negative (n=44) were differentiated with the AUC of 0.721 and 0.735, respectively. CU amyloid positive/APOE4 positive (n=20) vs. CU amyloid negative/APOE4 negative (n=20) were differentiated with the AUC of 0.893. **Conclusions:** These results support the potential utility of circulating brain-enriched and inflammation-associated miRNAs for characterizing pre-MCI/MCI/AD patients and developing minimally invasive diagnostic tools, especially when combined with known risk factors and patient demographics. The ability to distinguish between cohorts with different cognitive impairment status using miRNA pair biomarkers suggests that these biomarkers are informative for understanding disease pathology. Conditioning on gender, amyloid status, and APOE genotype can improve the ability of our classifiers to distinguish between subgroups, indicating these are important characteristics for developing miRNA-based diagnostic tools. These encouraging results motivate our ongoing work, including analyses of larger cohorts, longitudinal data sets, and comorbidities.

Key takeaway message: microRNAs are effective diagnostic targets for developing non-invasive biomarker testing solutions for early identification of high-risk individuals for Alzheimer's disease.

P241- PERFORMING MULTIPLE BIOMARKER TESTS DELAYS INITIATION OF LECANEMAB TREATMENT.

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Background: With disease-modifying treatments now available, rapid and accurate biomarker-based diagnosis of Alzheimer's disease (AD) has become critically important. Three biomarker modalities (amyloid PET, CSF tests and blood tests) are currently clinically available. Some providers suggest confirming the results of blood tests with CSF tests or amyloid PET before initiating amyloid-targeted treatments, even in patients with clearly positive blood test results. At the Washington University Memory Diagnostic Center (MDC), we investigated the time from the MDC visit immediately before the first biomarker test, and the time from the first biomarker test until the first lecanemab infusion. Further, we examined how these time intervals compared in patients with different biomarker modalities and with one or multiple biomarker tests. **Methods:** Clinical data were retrospectively extracted from electronic health records. The usage of Florbetaben/Florbetapir amyloid PET (visual read), CSF Roche Elecsys p-tau181/Aβ42, and plasma PrecivityAD2 biomarker tests were examined. All MDC patients who underwent biomarker testing from 7/6/2023 to 3/1/2025 and who subsequently initiated lecanemab treatment (n=221) were included. For many patients, their initial MDC visit took place years ago, before disease-modifying treatments were available. Therefore, to understand the time required from ordering a biomarker test to undergoing the test, we selected the MDC visit date immediately before the first biomarker test. **Results:** Out of 221 patients who were treated with lecanemab, 84 (38%) underwent an amyloid PET scan only, 86 (39%) underwent a CSF test only, and 39 (18%) underwent a blood test only. A subset of patients (12 out of 221, 5%) underwent multiple biomarker tests (n=3 amyloid PET and blood test; n=4 CSF test and blood test; n=4 amyloid PET and CSF test; and n=1 amyloid PET, CSF test, and blood test). Of those patients who underwent multiple biomarker test modalities, the first test was the following: n=3 amyloid PET, n=7 CSF test, n=2 blood test. The median time interval between the MDC visit (immediately before the biomarker test) and first AD biomarker test was 1.1 months for amyloid PET, 1.8 months for CSF tests, and 1.2 months for blood tests ($p < 0.01$; Kruskal-Wallis-test). The median time between the first biomarker test

and first lecanemab infusion was 3.3 months for patients who underwent a single biomarker test and 6.1 months for patients who underwent multiple tests ($p < 0.001$; Mann-Whitney-U test). For patients who underwent testing with a single biomarker modality, the median time between biomarker testing and first lecanemab infusion was 2.9 months for amyloid PET, 3.7 months for CSF tests, and 3.7 months for blood tests. Amyloid PET results agreed with CSF test results in 2 out of 4 (50%) cases. Amyloid PET or CSF test results agreed with blood tests results in 8 out of 8 (100%) patients. The most common reason for multiple biomarker tests was a borderline or ambiguous CSF test result (7 out of 12 cases, 58%). Previous treatment with amyloid-targeted treatments, e.g. aducanumab or gantenerumab in research studies, represented another issue that complicated biomarker interpretation. Finally, the single patient who received all three biomarker modalities also presented with a parkinsonian syndrome and CSF was collected to additionally perform an alpha synuclein seeding assay. **Conclusions:** Performing a second biomarker test may delay initiation of disease-modifying therapy by ~3 months, potentially reducing the benefit of treatment. Given the generally consistent results between blood tests and traditional biomarker modalities (amyloid PET and CSF tests), confirmatory testing should be limited to selected cases. The modality of biomarker testing should be carefully selected based on diagnostic accuracy, individual patient factors (e.g., medical comorbidities), and practical considerations. For example, CSF testing should be used in a targeted manner considering the comparatively frequent occurrence of ambiguous results leading to additional biomarker testing, as well as constrained capacities for lumbar punctures. At institutions with a high capacity for PET scans, amyloid PET performance and interpretation may allow for a faster start of treatment compared to fluid biomarker modalities. However, once blood test workflows are optimized (i.e. performed immediately during the clinic visit, digitized and regularly reimbursed), they may be reported even faster (e.g., within days).

Keywords: Alzheimer (blood) biomarkers, lecanemab, timely treatment initiation.

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Key takeaway message: Performance of multiple instead of a single Alzheimer biomarker test (amyloid PET, CSF or blood) critically delays initiation of lecanemab treatment by ~3 months.

P242- A NOVEL APPROACH FOR RECRUITING PATIENTS FOR EARLY PHASE TRIALS IN ALZHEIMER'S DISEASE: FASTER, SIMPLER, AND WITH REDUCED PATIENT BURDEN.

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Background: Early phase clinical trials with patients on the Alzheimer's Disease (AD) continuum (1) can be very challenging to recruit. Strict inclusion/exclusion criteria, long inpatient stays, invasive study procedures, and no treatment benefit can result in low interest in study participation. In contrast, it is comparatively easy to recruit healthy elderly volunteers to participate in phase 1 studies, as these volunteers often have prior study experience, and are motivated by the financial and prosocial benefits of study participation, rather than the possibility of treatment benefit. The current study tested the hypothesis that AD-related plasma biomarkers and subtle cognitive changes, consistent with stages 2-3 of the AD continuum, were detectable in healthy older adults at levels significant enough to allow these individuals to serve as surrogates for AD patients in early phase studies evaluating safety, tolerability, and target engagement. The study objective was to create a database of healthy older adult research participants in stages 2-3 who have interest and/or experience in early phase clinical trial participation, for the purpose of facilitating recruitment timelines for phase 1 studies. **Methods:** Between 18 April 2023 and 05 June 2024 all volunteers aged 60+, screened to participate in a healthy elderly clinical trial at the California Clinical Trials Medical Group/Parexel Clinical Pharmacology Research Unit in Los Angeles, were invited to participate in this study. All volunteers received and passed a pre-screening assessment in which medical history was collected and reviewed against standard healthy elderly study eligibility criteria. Participants received a blood test for plasma pTau181, ab42 and ab40 and a cognitive screening test, the Montreal Cognitive Assessment (MoCA). Participants received no compensation for study participation but were informed that their results might qualify them for a future study. Participants were categorized as biomarker positive based on pTau181 >14.2pg/mL and MCI positive based on MoCA score at or below 26/30 with items missed consistent with AD as etiology and not attributable to other factors (e.g. low education, English as a second language). **Results:** Among the 73 individuals invited to participate, 52 individuals with mean age of 68 agreed to participate in this study. Among these, 21 were identified as biomarker positive and reported experiencing subtle cognitive changes consistent with Stage 2 of the AD continuum (40%). An additional 6 were biomarker positive with diagnosable MCI consistent with Stage 3 of AD continuum (22%). Among these 6, 2 participants were successfully recruited into a high-burden phase 1 study for a disease-modifying treatment for MCI due to AD and AD. **Conclusions:** The current study suggests that both subtle cognitive changes and biomarker evidence of AD brain pathology are ubiquitous in healthy elderly volunteers. Our data supports the use of these AD-biomarker positive healthy elderly research participants in early phase clinical trials as surrogates for patients with diagnosed MCI or AD, thus, reducing the need for AD patients in early phase studies and significantly speeding up study timelines.

Keywords: Early phase Alzheimer's clinical trials, plasma biomarkers, early detection. **Disclosures:** Study funded by Parexel International.

References: 1. Jack, C.R. et al (2024). Revised criteria for diagnosis and staging of Alzheimer's Disease: Alzheimer's Association Workgroup. https://doi.org/10.1002/alz.13859.

Key takeaway message: Subtle cognitive changes and biomarker evidence of AD brain pathology are ubiquitous in healthy elderly volunteers, supporting the use of these volunteers as surrogates for AD patients in early phase clinical trials.

P243- AMPLIFIED TAU AGGREGATES IN CEREBROSPINAL FLUID TRACK TAU PET AND COGNITIVE DECLINE IN ALZHEIMER'S DISEASE.

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Background: Tau aggregation is a core pathological hallmark of Alzheimer's disease (AD) and closely correlates with neurodegeneration and cognitive decline. Soluble, seed-competent tau aggregates—particularly oligomers and pre-fibrillar assemblies—are thought to drive tau pathology propagation, yet are challenging to detect in biofluids due to low abundance and structural heterogeneity. Existing CSF tau biomarkers primarily measure phosphorylated epitopes and may not fully capture dynamic aggregation processes. **Methods:** We developed a seeded amplification immunoassay that exploits secondary nucleation to selectively detect low-abundance tau aggregates in CSF. Recombinant full-length tau fibrils served as seeding substrate, with amplified products quantified on a digital immunoassay platform (Simoa). CSF was analyzed from a discovery cohort ($n = 40$) and an independent validation cohort ($n = 225$; TRIAD), including cognitively unimpaired individuals, amyloid-positive mild cognitive impairment (MCI+), AD dementia, and non-AD neurodegenerative disease controls.

We assessed associations between CSF tau aggregates and established fluid biomarkers (p-tau181, p-tau217, total tau, neurofilament light [NfL]), tau PET uptake (Braak staging), and longitudinal cognitive measures. **Results:** CSF tau aggregates were significantly elevated in MCI+ and AD dementia versus controls and increased progressively along the AD continuum. Levels correlated strongly with tau PET Braak stage, p-tau217, p-tau181, and NfL. In longitudinal analyses, tau aggregates tracked cognitive decline and disease progression more dynamically than phosphorylated tau alone. In amyloid-positive MCI, elevated tau aggregates identified individuals with higher baseline tau PET signal and faster cognitive deterioration. **Conclusions:** Amplified CSF tau aggregates provide a scalable, fluid-based biomarker that closely mirrors tau PET signal, supports disease staging, and offers dynamic tracking of progression in early and symptomatic AD. This assay's compatibility with high-throughput platforms and its ability to capture pathogenic tau species in vivo position it as a promising endpoint for clinical trials targeting tau pathology and a potential tool for early diagnosis and therapeutic monitoring.

Keywords: Alzheimer's disease, tau aggregates; cerebrospinal fluid, seeded amplification assay, tau PET, biomarkers.

P244- A COMPARISON OF LEVELS AND LONGITUDINAL TRENDS OF P-TAU 217 WITH MMSE, ADAS-COG, AND CDR IN A COHORT OF 113 COGNITIVELY NORMAL AND COGNITIVELY IMPAIRED INDIVIDUALS OVER 6 YEARS USING ADNI DATA SET.

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Background: FDA's approval of the plasma P-Tau217/ß-amyloid 1-42 ratio test has increased interest in blood-based biomarkers for Alzheimer's disease (AD), offering a less invasive alternative to PET imaging or lumbar punctures. While some literature shows high diagnostic accuracy for plasma P-Tau217 in detecting amyloid pathology (1), others caution against full adoption, citing limitations in reliability and clinical applicability (2). Moreover, despite the historical role of cognitive assessments, like MMSE, ADAS-Cog, and CDR, in tracking AD, few studies explore longitudinal relationships with plasma P-Tau217. This lack of data raises questions about whether P-Tau217 reflects functional cognitive decline or merely tracks underlying pathology without capturing symptom progression. As the use of plasma biomarkers expands in clinical and research settings, it is essential to investigate the correlation between P-Tau217 and cognitive decline. We hypothesized that in cognitively impaired individuals, longitudinal changes in plasma P-Tau217 levels would significantly correlate with cognitive and functional decline, as measured by cognitive assessment scores. **Methods:** We utilized open-source data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) from 2005-2013, including 121 participants with P-Tau217 data. For our current analysis, we included participants with reported plasma P-Tau217 values and corresponding cognitive assessments (MMSE, ADAS 11, ADAS 13, and CDR). Participants were stratified into Cognitively Normal (CN) and Cognitively Impaired (CI). CI includes, as defined by ADNI and board-certified psychiatrist evaluations, Subjective Memory Complaints, Early and Late Mild Cognitive Impairment, Mixed MCI, and AD (3). We calculated the means and standard deviations for P-Tau217 and cognitive scores at each time point, excluding months where only one patient had data. Data tabulation began at month 48, when P-Tau 217 was first collected in ADNI. Net changes in both biomarker and cognitive scores were calculated from the first to the final visit (month 120) for each group. Linear regression analyses were performed for both the CN and CI cohorts to examine longitudinal trends and assess the relationship between changes in P-Tau217 levels and MMSE. **Results:** Out of 121 participants, 113 were included in our analysis, with 40.71% females and 59.29% males. The mean age and median age were 71.9. At month 48 for each patient, P-Tau 217 data were available for 24 cognitively normal (CN) and 39 cognitively impaired (CI) participants. Throughout the study, an additional 12 CN and 38 CI participants joined the dataset. At month 120, 4 CN and 5 CI participants had available data for both P-Tau217 and cognitive assessments. The mean plasma P-Tau217 concentration at month 48 was 0.066 ± 0.053 pg/mL for CN and 0.078 ± 0.056 pg/mL for CI. By month 120, the CN group's average P-Tau217 increased by 0.003 ± 0.032 pg/mL, and CI's increased by 0.048 ± 0.033 pg/mL. At baseline, CN participants had average scores of 4.22 ± 2.23 on ADAS-Cog11, 6.56 ± 3.93 on ADAS-Cog13, 0.08 ± 0.25 on CDR, and 29.0 ± 1.44 on MMSE. These changed over time by +5.38, +10.19, +0.17, and −0.5 points, respectively. CI participants began with scores of 10.54 ± 8.46, 15.85 ± 12.13, 0.41 ± 0.4, and 26.74 ± 3.82, with corresponding changes of +14.79, +20.88, +0.39, and −6.74 points over the study period. Linear regression analyses for CN showed an increase in P-Tau217 (slope = $1.47e^{-4}$, $R^2 = 0.055$) and a decline in MMSE (slope = −0.0048, $R^2 = 0.012$); for CI, P-Tau217 also increased (slope = $2.47e^{-4}$, $R^2 = 0.008$) and MMSE declined (slope = −0.069, $R^2 = 0.108$). **Conclusions:** While plasma P-Tau217 is strongly associated with Alzheimer's pathology, our 6-year longitudinal analysis suggests it does not reliably reflect cognitive or functional decline. Although P-Tau217 levels were generally higher in CI participants than CN ones, these differences were not statistically significant. Across 9 visits, P-Tau217 trajectories showed inconsistent correlation with MMSE and other cognitive scores, especially in the CN group. Linear regression of P-Tau217 and MMSE slopes revealed an inverse relationship; biomarker levels rose as MMSE scores declined, but low R^2 values (≤ 0.108) indicated weak, non-predictive associations. Even at later timepoints, any observed differences lacked strong predictive value. These findings suggest that while P-Tau217 may indicate underlying pathology, it is limited as a standalone diagnostic or monitoring tool. Relying on it alone could risk excluding individuals with meaningful symptoms from care or trial eligibility. The study had limitations: the sample size declined over time, and averages at each wave reflected different individuals rather than a consistent cohort. Additionally, the ADNI dataset, drawn from a research setting, may not generalize well to the broader population. More research is needed to clarify P-Tau217's role and assess its longitudinal utility.

Keywords: Alzheimer's disease, plasma P-Tau181, blood-based biomarkers, diagnostic accuracy.

Disclosures: The authors declare no competing interests.

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Key takeaway message: This study examined 6-year longitudinal trends in plasma P-Tau217 and cognitive scores using ADNI data, finding weak correlations. Results suggest limited utility of P-Tau217 alone for tracking cognitive decline, warranting further research.

P245- REGIONAL AMYLOID POSITIVITY PREDICTS ALZHEIMER'S DISEASE PROGRESSION DESPITE LOW CENTILOID VALUES IN MILD COGNITIVE IMPAIRMENT.

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Purpose: With the advent of disease-modifying therapies (DMTs) for Alzheimer's disease (AD), the Centiloid (CL) scale has become crucial for

identifying treatment candidates and monitoring therapeutic efficacy. Since CL values depend on the extent and distribution of amyloid deposition, regionally positive scans may yield lower CL scores than globally positive ones despite visual positivity. This study evaluates the prognostic significance of regional amyloid uptake in amnestic mild cognitive impairment (aMCI) patients using CL scoring. **Methods:** We retrospectively analyzed florbetaben PET scans from 1,586 individuals across the AD spectrum acquired between March 2015 and April 2024 at Asan Medical Center. Standardized uptake value ratios (SUVRs) were calculated using frontal, parietal, lateral temporal, and precuneus/posterior cingulate (PPC) cortices as target regions, with whole cerebellum as reference. SUVRs were converted to CL values. A nuclear medicine physician performed visual interpretation, classifying scans as positive or negative based on cortical uptake relative to adjacent white matter. Positive scans were categorized as regionally positive (1-3 regions) or globally positive (all 4 regions). **Results:** Among 1,586 individuals across the AD spectrum (163 SMI, 905 aMCI, 518 AD), amyloid positivity rates increased progressively: 17.8% (SMI), 51.3% (aMCI), and 71.2% (AD). In aMCI patients, 51.3% showed amyloid positivity, with 14.3% demonstrating regional positivity (1-3 regions) and 37.0% showing global positivity. Critically, regional amyloid patterns demonstrated distinct prognostic profiles: single-region positivity (predominantly PPC involvement) showed a substantial 23.1% three-year AD conversion rate despite lower CL values (44.05 ± 19.7) compared to global positivity (87.54 ± 23.08). CL values increased progressively with regional extent: 44.05 ± 19.7 (1 region), 53.23 ± 20.46 (2 regions), 60.76 ± 21.03 (3 regions), reaching 87.54 ± 23.08 for global positivity. Notably, even patients with isolated PPC positivity—representing the earliest detectable amyloid pattern—demonstrated clinically meaningful progression risk, challenging conventional CL thresholds for treatment eligibility.
Conclusions: Although regional amyloid positivity showed lower SUVR and CL values compared to global positivity, even isolated single-region uptake—particularly in the PPC—was significantly associated with clinical progression to AD within three years. These findings suggest that both visual interpretation and CL quantification should be considered when selecting aMCI patients for DMT eligibility.
Key takeaway message: Regional amyloid positivity, despite showing lower SUVR and CL values than global positivity, particularly in isolated single-region uptake, notably in the PPC, significantly predicts clinical progression to AD within three years. These results indicate the importance of both visual interpretation and CL quantification in selecting aMCI patients for DMT eligibility.

P246- HEAD-TO-HEAD COMPARISON OF 4 CAPILLARY BLOOD SAMPLING DEVICES FOR MEASURING P217 TAU.

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Background: Blood based biomarkers for phosphorylated Tau (pTau) species and NFL using plasma have emerged in recent years as robust tools for assigning probable Alzheimer's Disease (AD) pathology and neurodegeneration via Amyloid, Tau, or Neurodegeneration (A-T-N) status. However, these tests have been designed for venipuncture-collected plasma, which requires patients to visit a phlebotomy site and obtain intravenous blood draw, which is not always feasible or desirable for patients. As an alternative there have been reports of using capillary blood (as fluid plasma or dried blood spots) for measuring these analytes (1,2), which could allow for remote &/or more frequent sampling with great value for prescreening in clinical trial. However, the reliability of these blood draw methods, and head-to-head comparison of the options have not been performed. **Methods:** We conducted a head-to-head evaluation of 4 capillary devices: Tasso+, TapMicro, Haiim, and SEP10, vs venipuncture using samples obtained from BioIVT/PrecisionMed (Carlsbad, CA, USA). All samples were processed immediately to plasma, with exception of Sep10 which were stored ambient per vendor instructions. We also included Sep10 controls 2 AD pools and 3 peptide-spiked Healthy Donor (HD) plasmas. **Analysis focused on:** Reliability of blood collection (ability to collect at least 0.5 mL blood or obtain a successful dried plasma collection (blue spot) for Sep10). Precision of p-tau217 concentrations in immediate repeated capillary blood collections. Correlation, and relative concentration, of p-tau217 levels in each capillary collection vs that obtained by venipuncture. Ability to distinguish HD from AD subjects (via clinical diagnosis only). The devices were compared in a 2-phase approach. Phase 1: Evaluation of all devices in 4 HD's. Phase 2: Evaluation of the devices that were promising in Ph1 in a cohort of 10 HD and 10 AD. **Results:** Reliability of collection. In Phase 1 the percentage of blood draws yielding a successful sample collection was Tasso: 75%, TapMicro: 60%, Haiim: 25%, SEP10: 0%. The poor blood collection with Haiim and Sep10 devices appeared due mostly to clotting before sufficient sample reached the collection reservoir. In Phase 2 the percentage of blood draws yielding a successful sample collection was: Tasso: 100%, TapMicro: 100%, SEP10: 42%. The poor blood collection with Sep10 devices appeared due mostly to clotting, as before.
Precision of measurement: Where multiple blood collections per device were collected the average precision (avg+/- SD) was: Tasso: (30 +/- 28.5; n=20), 11/20 donors had CV<20%, TapMicro: (30 +/- 28.8, n=19), 9/20 donors had CV<20%, SEP10: (115 +/- 20, n=4), 0/20 donors had CV<20%. **Association with venipuncture**: Tasso+ showed much higher p-tau217 concentrations than seen by venipuncture (avg of 0.450pg/ml vs 0.056 pg/ml), but with a positive correlation (r2=0.4564, p=0.0011, n=20). Tapmicro also exhibited much higher p-tau217 concentration than seen by venipuncture (avg of 0.495 vs 0.056pg/ml) and did not show any association with venipuncture (r2=0.0002, p=0.9506, n=19). Sep10 collections measured comparable concentration to venipuncture (avg of 0.054pg/ml vs 0.056 pg/ml and did not show any association with venipuncture (r2=0.0998, p=0.3169, n=12).
Diagnostic potential: Using clinical diagnosis as the gold standard venipuncture plasma identified AD subjects accurately (p=0.0266), while all microsampling devices did not (student t-test = 0.3858, 0.3936, and 0.9764 for Tasso+, Tapmicro, and Sep10, respectively). Using venipuncture p-tau217 concentration as the gold standard Tasso+ identified AD subjects accurately (student p=0.017), while all other devices did not (student t-test 0.7161 and 0.472 for Tapmicro and Sep10, respectively). **Sep10 controls**: Plasma from mild-moderate dementia subjects (pool 1= 0.342 pg/ml; pool2 = 0.200 pg/ml) exhibited substantially higher signal than seen in Ph2 sample (avg = 0.054 pg/ml). Plasma from HDs spiked with p-tau217 calibrant exhibited higher signal than Ph2 samples and good spike recovery (111 +/- 24%, 83 +/- 35%, 160+/-45% spike recovery for high, med, low concentrations respectively). **Conclusions:** The Haiim device may not be a suitable candidate for capillary blood collection for pre-screening candidates in clinical trials due to its low blood draw volume. The TapMicro device reliably collected sufficient sample volume, however the obtained p-tau217 concentrations did not associate with venipuncture p-tau217 concentrations or clinical Dx so its utility is unknown. The Tasso+ device reliably collected sufficient sample volume and showed some association with venipuncture p-tau217 concentrations, but not clinical diagnosis, so it may have utility. The Sep10 device proved challenging to get successful sample collection and showed no association with venipuncture p-tau217 concentrations or clinical diagnosis in the Ph2 samples, however mild-moderate dementia pool and spike controls showed expected patterns. Optimization of dried plasma spot collection and/or understanding of Tasso+/TapMicro's aberrant p217 concentrations is suggested prior to implementation in the field. Higher sensitivity/lower sample volume assay technologies such as NULISA may enable better

Sep10 association with disease. These results provide guidance for use of capillary blood collection devices for detecting AD pathology and neurodegeneration via A-T-N measurement, potentially allowing for a low friction initial step in clinical trial screening &/or clinical care.

Keywords: Tau, pTau217, NFL, Sep10, capillary device.

Disclosures: SM, AC, KH, and GTB are employees of Johnson and Johnson and receive salary &/or stock.

References: 1. Kolanko, M.A., et al. Quantification of neurofilament light and glial fibrillary acidic protein in finger-prick blood. Brain Commun 6, fcae151 (2024). doi: 10.1093/braincomms/fcae151. 2. Huber, H et al. Biomarkers of Alzheimer's disease and neurodegeneration in dried blood spots-A new collection method for remote settings. Alzheimers Dement 20(4): p2340-2352 (2024). doi: 10.1002/alz.13697.

Key takeaway message: Comparing 4 capillary blood devices to measure ptau217. Caplillary devices are less invasive, more patient friendly and cost-efficient making it a game changer for screening patients at home. We comapre 4 capillary blood sampling devices for their reliability,precision ,its diagnostic power and correlation with p217 measuremtns from venipuncture-collected plasma.

P247- LEVERAGING RECENT ADVANCES IN BIOMARKERS TO OPTIMIZE EARLY PHASE DRUG DEVELOPMENT IN ALZHEIMER'S DISEASE.

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Background: As the field shifts towards disease-modifying treatments that may be more effective when administered in earlier stages of disease, the importance of biomarkers as a primary outcome in an accelerated approval pathway or as supportive evidence of clinical effect is rising because they have lower variability and can indicate disease progression earlier than clinical outcomes. We investigated the performance of plasma pTau as a biomarker to predict clinical outcomes, with focus on its potential as a surrogate endpoint of early phase studies in AD. **Methods:** Published summary data from recent mAB studies with plasma pTau as a biomarkerwere analyzed to assess the relationships between plasma pT217, pT181 and clinical outcome. To explore the potential as a surrogate outcome, plasma pTau was run through each of the Prentice criteria (1) using mediation analysis and additional simulations constructed from the data.To explore the potential of plasma pTau as a primary outcome, power was evaluated in simulated data using dose-escalation, proof-of-concept study designs. The additional criteria needed to evaluate the merits of pTau as a biomarker from an individual clinical trial were specified and applied for illustration to a simulated data set. **Results:** The group-level correlation of plasma pT217, pT181 with CDR-SB was strong (0.786) and mean change from baseline in plasma pTau was a significant ($p=0.036$) predictor of mean change in CDR-sb. The effect size on pTau was predicted to be ~2.5-fold greater than the treatment effect size on CDR-sb. With a significant difference between treatments on the biomarker, Prentice Criteria 1 is met. Prentice criterias 2, 3, and 4 are reasonably met, citing strong correlations and a higher percent indirect effect. **Conclusions:** Based on these results, it is reasonable to propose plasma pTau at month 6 as a primary endpoint in a proof-of-concept AD clinical trial. When using pTau as a primary endpoint, trials with a few as 100 patients could be sufficient for adequate power if the anticipated effect size is similar to that observed for donanemab. Such early-phase trials should pre-specify analyses to assess relevant Prentice criteria from the individual patient data. Results on pTau, combined with the relationship between pTau and CDR-sb can be used to predict the Phase 3 effect size.

Keywords: plasma pTau, proof-of-concept study, surrogate endpoints.

Disclosure: All authors are employees of Pentara Corporation, a statistical consulting firm specializing in neurodegenerative diseases that provides services to pharmaceutical companies and academic institutions. **References:** 1. Prentice, R.L. (1989), Surrogate endpoints in clinical trials: Definition and operational criteria. Statist. Med., 8: 431-440. https://doi.org/10.1002/sim.4780080407.

Key takeaway message: Plasma pTau effect size at 6 months has a strong correlation with CDR-sb at 12 months and reasonably meets the Prentice Criteria as a surrogate endpoint.

P248- IDENTIFYING NEUROPSYCHOLOGICAL AND SOCIODEMOGRAPHIC PREDICTORS OF A BLOOD-BASED BIOMARKER OF ALZHEIMER'S DISEASE.

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Background: The current clinical diagnosis and staging model for Alzheimer's Disease (AD) present a biological pathology, beginning with an abnormal occurrence of core 1 biomarkers of AD neuropathological change (ADNC) (e.g., Aβ proteinopathy and phosphorylated and secreted AD tau) observed through biomarker testing (e.g., plasma pTau assays, amyloid PET). Validated as an AD biological diagnostic agent, the results of AD biomarker testing is utilized as a primary inclusion criterion and endpoint measurement in AD clinical trials (1). However, due to time, cost, and incidence of AD-nonrelated cognitive impairment, it is often not feasible nor appropriate to obtain AD biomarker testing from all screening participants in a clinical trial. This creates a screening strain on clinical trial sites to identify and implement the best strategies for assessing AD biomarker pathology potential. The Montreal Cognitive Assessment (MoCA), one of the most frequently used screening assessments in clinical research and practice, offers a cost-effective option for identifying individuals at risk for cognitive impairment (2), a symptomatic presentation of AD. The MoCA Memory Index Score (MoCA-MIS), a subcomponent of the MoCA that captures delayed free-recall and recognition memory, has been demonstrated to be a strong risk predictor of mild cognitive impairment conversion into AD (3). This, however, only reflects the symptomatic prognosis of AD. Previous research has not tested the utility of the MoCA or its subcomponents in predicting the likelihood of AD biomarker pathology. This study fills an important gap by testing the MoCA as a tool for predicting the presence of phosphorylated tau-217 (pTau-217) in a large sample of participants in an AD clinical research site. **Methods:** Participants were 752 individuals (52.3-80.8 years of age) who provided a blood sample for one of two enrolling AD medication clinical trials (one preclinical amyloid prevention trial and one anti-tau trial for individuals with mild cognitive impairment or mild AD). Participants were recruited through advertisements on Google and social media sites (e.g., Facebook) to participate in a pre-screening appointment to determine potential eligibility for an AD medication clinical trial. Potential eligibility was determined by a clinician interview and MoCA. Potentially eligible participants who signed informed consent to participate in screening for an AD medication clinical trial provided a blood sample to test for pTau-217. Data were aggregated across the two enrolling trials for the purposes of this study. Plasma pTau-217 test results (coded 0 as negative, 1 as positive) were regressed on total MoCA and MoCA-MIS scores. Demographic factors including participant age, education, race, and ethnicity were included as covariates. A dummy variable was included to control for differences in study eligibility criteria across the two enrolling medication trials. **Results:** Total MoCA scores were not significantly associated with the probability of having a positive pTau-217 test ($B = 0.00$, $p = .503$). However, higher scores on the delayed recall MIS were associated with a lower likelihood of a positive pTau-217 result ($B = -0.02$, $p = .003$). Older participants were more likely to have a positive pTau-217 result ($B = 0.01$, $p < .001$). **Conclusions:** With core 1 biomarkers of ADNC at the forefront of AD clinical research, identifying participants who are most at risk of exhibiting a positive AD biomarker test result is a critical consideration for initial intake procedures. These findings demonstrate that among a large set of participants screening for AD clinical trials, the MoCA-MIS score was an important predictor of a pTau-217 blood-based biomarker test result. Notably, MoCA-MIS predicted the presence of

pTau-217 across both a preclinical prevention trial and a trial for symptomatic AD in models that accounted for total MoCA performance and sociodemographic factors. In contrast to previous research suggesting an association between total MoCA scores and cognitive impairment related to AD [3], the total MoCA score was not significantly associated with the detection of plasma pTau-217. Additionally, age was positively predictive of this AD biomarker outcome. Overall, these findings novelly display an AD biomarker predictive capability of the MoCA, an expansion of its utility in AD clinical research beyond symptomatic evaluation. This method can be replicated and utilized by clinical trial sites to improve the screening selection and duration for AD clinical trials. To further investigate its predictive utility, future implementations of this method will explore other subcomponents of the MoCA as well as the outcomes of other AD biomarker tests. Moreover, sociodemographic and medical history covariates will continue to be identified. Finally, it is worth applying this method to other neuropsychological assessments relevant to AD to establish the best screening tools for predicting the presence of an AD biomarker.

Keywords: Phosphorylated tau-217 (pTau-217), MoCA Memory Index Score (MoCA-MIS), AD biomarker test, AD clinical trials.

Disclosures: The authors declare no competing interests.

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Key takeaway message: While primarily used to evaluate cognitive impairment in AD clinical research, a novel utility of the Montreal Cognitive Assessment was demonstrated to provide predictability over the presence of phosphorylated tau-217 detected through blood-based biomarker testing.

P249- MK-1167, A POSITIVE ALLOSTERIC MODULATOR OF α7 NICOTINIC CHOLINERGIC RECEPTORS: PROOF-OF-BIOLOGY, DOSE SELECTION, AND CLINICAL TRIAL DESIGN.

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Background: The α7 nicotinic acetylcholine receptor (α7 nAChR) is highly expressed in the cortex, hippocampus, and subcortical limbic regions of the brain (1). Substantial evidence from preclinical and clinical studies implicates the α7 nAChR in cognition (2,3). Significant reductions of α7 nAChR expression have been reported in people with Alzheimer's disease (4). The α7 nAChR elevates intracellular Ca2+ levels which increases the release of a number of neurotransmitters, including glutamate (5). Glutamate metabolism can be measured by 13C-magnetic resonance spectroscopy (13C-MRS) (6) as a proxy for glutamate release and this technique can be used as a pharmacodynamic marker for establishing activity of drugs targeting the α7 nAChR. Here we report on the use of Selective Proton-Observed, Carbon-Edited 13C-MRS (selPOCE-13C-MRS) to monitor pharmacodynamic modulation of glutamate metabolism by MK-1167, a positive allosteric modulator of the α7 nAChR, in healthy humans. Results from the study informed on the dose range for evaluation in an ongoing clinical trial in people with Alzheimer's disease dementia. **Methods:** A Phase 1 single-blind, placebo-controlled, 2-period, fixed-sequence study was conducted to assess the effect of oral MK-1167 doses of 1 mg and 6 mg on glutamate metabolism in the prefrontal cortex of healthy men. selPOCE-13C-MRS scans were used to measure MK-1167 induced changes in the fractional enrichment of 13C-glutamate in the prefrontal cortex relative to placebo (baseline) treatment. Each participant was scanned twice, once under baseline conditions (placebo treatment) and a second time ≥14 days after the first scan in the presence of MK-1167. Scans were conducted at 7 Tesla MRI using a [U-13C]-labeled glucose infusion. Data acquisition and post-processing were conducted as described previously (6). **Results:** In the 6 mg Panel of 8 participants, MK-1167 significantly increased glutamate metabolism by 31% compared to placebo, while in the 1 mg Panel of 8 participants there was an increase of 9%. The results suggest that MK-1167 can increase brain glutamate metabolism and there may be a dose-response relationship. Based on pharmacokinetic/pharmacodynamic modeling including data from this study, as well as the threshold established for proof of mechanism-driven pharmacology from preclinical experiments, the exposure target for MK-1167 in the Alzheimer's disease dementia trial was an average plasma concentration of 200 nM, which is expected to be achieved at a qd dose of ~1 mg. In order to evaluate possible dose-response, a lower (0.3 mg qd) and higher (3 mg qd) dose of MK-1167 are also included in the ongoing Phase 2 randomized, placebo-controlled, double-blind, parallel-group, 24-week trial in participants with mild to moderate Alzheimer's disease dementia on stable doses of acetylcholinesterase inhibitor therapy (NCT06721156). **Conclusions:** MK-1167 increased glutamate metabolism in the prefrontal cortex of healthy men as assessed by selPOCE-13C-MRS, indicating activation of the α7 nAChR. Results from the study helped inform dose selection for an ongoing Phase 2 trial of MK-1167 0.3 mg qd, 1 mg qd, and 3 mg qd in people with Alzheimer's disease dementia. Additional MK-1167-003 Clinical Study Team Members: Arie Struyk, Anthony Basile, Shawn Kim, Ilias Triantafyllou, Janita Patwardhan Hogan, Joseph Raybon, Ka Lai Yee, Tian Zhao, John Palcza, Wybe van der Kemp, Jeanine Prompers, Kevin Behar, Henk De Feyter, Robin de Graaf. **Keywords:** MK-1167, α7 nAChR, Alzheimer's disease, magnetic resonance spectroscopy.

Clinical Trial Registry: NCT06721156; https://clinicaltrials.gov.

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Key takeaway message: 13C magnetic resonance spectroscopy imaging of brain glutamate metabolism may be useful for assisting in dose selection for clinical trials of modulators of the α7 nicotinic

acetylcholine receptor in Alzheimer's disease

P250- OPTIMIZING PLASMA P-TAU217 CUTOFFS FOR AMYLOID PATHOLOGY ACCORDING TO KIDNEY FUNCTION, BODY WEIGHT, AND ANEMIA.

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Background: Plasma phosphorylated tau 217 (p-tau217) demonstrates high diagnostic efficacy for detecting amyloid-β positivity on positron emission tomography (PET) imaging; however, renal dysfunction, body mass index (BMI) variations, and anemia may influence biomarker concentrations. This study aimed to investigate the impact of estimated glomerular filtration rate (eGFR), BMI, and hemoglobin levels on plasma p-tau217 concentrations, determine optimal diagnostic cutoffs for amyloid-β positivity detection across these clinical subgroups, and evaluate diagnostic performance when applying reference-derived cutoffs. **Methods:** We enrolled 2,525 participants across the cognitive spectrum, including cognitively unimpaired individuals and those with mild cognitive impairment (MCI) or Alzheimer's-type dementia, who underwent amyloid-β PET imaging quantified using BeauBrain Amylo® and plasma p-tau217 biomarker assessment. Participants were stratified by cognitive status and further categorized into chronic kidney disease (CKD), underweight, obese, and anemic subgroups based on established clinical criteria. Optimal p-tau217 cutoffs were determined using maximum Youden index methodology, with diagnostic performance evaluated through sensitivity, specificity, positive and negative predictive values (PPV, NPV), and overall accuracy. **Results:** Locally weighted scatterplot smoothing (LOESS) curve analysis revealed that p-tau217 concentrations increased linearly when eGFR declined below approximately 70 mL/min/1.73m^2, with steeper increases observed below 45 mL/min/1.73m^2. P-tau217 levels were elevated in underweight individuals (BMI $<$18.5 kg/m^2) and when hemoglobin fell below 12 g/dL, with these associations more pronounced in cognitively unimpaired participants. Optimal cutoffs varied substantially across subgroups. In cognitively unimpaired individuals, the reference cutoff from the total group was 0.355 pg/mL, increasing to 0.720 pg/mL in CKD patients (+103%), 0.440 pg/mL in underweight participants (+24%), and 0.430 pg/mL in anemic individuals (+21%), while remaining stable in obese participants (0.345 pg/mL, -3%). In cognitively impaired individuals, the reference cutoff from the total group was 0.495 pg/mL, with corresponding increases to 0.675 pg/mL (+36%), 0.620 pg/mL (+25%), and 0.615 pg/mL (+24%) for CKD, underweight, and anemic subgroups, respectively, and a decrease to 0.440 pg/mL (-11%) in obese participants.However, despite changes in optimal cutoffs, applying reference cutoffs from the total group to underweight and obese subgroups showed relatively preserved accuracy (80.0% and 82.4% in cognitively unimpaired participants; 92.8% and 87.3% in cognitively impaired participants, respectively). When applying the total group-derived reference cutoffs, diagnostic accuracy was substantially compromised in CKD and anemic subgroups (56.3% and 78.4% in cognitively unimpaired; 74.6% and 80.2% in cognitively impaired participants). In contrast, underweight and obese subgroups maintained relatively preserved accuracy despite changes in optimal cutoffs (80.0% and 82.4% in cognitively unimpaired participants; 92.8% and 87.3% in cognitively impaired participants, respectively). Implementation of subgroup-specific optimized cutoffs markedly improved diagnostic accuracy to 87.5% and 94.1% in cognitively unimpaired CKD and anemic participants, and to 83.6% and 85.4% in corresponding cognitively impaired subgroups. **Conclusions:** Plasma p-tau217 concentrations are significantly influenced by renal function, nutritional status, and hematological parameters, necessitating subgroup-specific diagnostic thresholds. The substantial elevation in optimal cutoffs among individuals with CKD, underweight status, and anemia, combined with markedly improved diagnostic performance using tailored thresholds, underscores the clinical importance of personalized cutoff strategies for reliable amyloid-β detection in diverse patient populations.

Keywords: Plasma p-tau217, amyloid-β PET, chronic kidney disease.

Disclosures: The authors declared no competing interests.

Key takeaway message: Plasma p-tau217 detects Aβ positivity, but kidney dysfunction, BMI, and anemia influence levels and optimal cutoffs. Tailoring p-tau217 cutoffs, especially for CKD and anemic patients, is crucial for diagnostic accuracy.

P251- PREDICTING ALZHEIMER'S DISEASE PROGRESSION USING NEUROIMAGING AND GENETICS MARKERS.

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Background: We aimed to identify statistically significant associations between regional, diagnostic, and genetic effects, using multinomial linear modeling analysis. This paper examines late-onset dementia-related cognitive impairment utilizing Neuroimaging and genetics biomarkers. **Methods:** The participants included 266 cognitively normal (CN), 572 volunteers with mild cognitive impairment (MCI), and 188 Alzheimer's disease (AD) patients. The 1,026 ADNI participants included: 266 CN's (CDR=0, Male:138, Female:128), 572 MCI's (CDR=0.5, Male:227, Female:245), and 188 AD dementia patients (CDR=0.5/1, Male:102, Female:86). Subjects with AD dementia were probable AD dementia according to the NIA-AA diagnostic criteria for AD. Genotype dosage data for AD-associated single nucleotide polymorphisms (SNPs) were extracted from the imputed ADNI genetics archive using sample-major additive coding. Such 29 SNPs were selected, representing a subset of independent SNPs reported to be highly associated with AD in a recent AD meta GWAS study by Jansen and colleagues. Using multinominal linear modeling of diagnosis, we studied the associations between the three individual cohorts (CN, MCI and AD dementia). The differences of the 200 NIMs and 29 SNPs between CN, MCI, and AD dementia cohorts. The results of a 3-way ANOVA (ROI, Dx, SNP) may be less interpretable compared to a multinomial linear modeling (Outcome = Dx). We computed the ORs and relative risks (RRs) for AD and MCI, relative to CN. The MCI and AD effects quantified the metrics «relative to CN». These represent extensions the binary outcome in logistic regression, but reflect 3 categorical outcomes (CN, MCI, AD), which may also be analyzed via more general multi-nominal linear modeling. **Results:** The odds ratios and relative risks for AD and MCI (relative to CN) were predicted using multinomial linear models. In this model, the 29 SNPs did not appear to be significantly asssociated with AD, relative to CN. The RRs for MCI of X7.143108158_T (EPHA1) and X19.1039323_C (ABCA7) were 0.9964 and 0.9973. The observed accuracy of the multinomial model (AD/CN OR; multinomial linear model of diagnosis) was 0.62 (the expectation for a null model would be 0.33) with a 95% CI of (0.6025, 0.6371), corresponding to a p-value $[\text{Acc} > \text{NIR}] < 2.2 \times 10{-}16$ and Kappa = 0.3978. **Conclusions:** We identified the significant correlations between the 29 genomic markers (GMs) and the 200 neuroimaging markers (NIMs). The ORs and RRs for AD and MCI (relative to HC) were predicted using multinomial linear models.

Keywords: ADNI, Alzheimer's disease, mild cognitive impairment, neuroimaging, genetics, prediction.

Disclosure: The authors declared no completing interests.

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Key takeaway message: We tried to predict Alzheimer's disease progression using neuroimaging and genetics biomarkers via multinomial linear modeling.

P252- SEMAGLUTIDE IMPACTS PROTEOMIC SIGNATURES RELATED TO DEMENTIA RISK IN THE SELECT CARDIOVASCULAR OUTCOMES TRIAL.

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Background: Plasma proteomic signatures that precede the onset of dementia can yield insights into disease pathobiology and reveal novel biomarkers and avenues for intervention (1). The Dementia SomaSignal™ Test (dSST) is a blood-based, machine learning–derived 25-protein-only score that predicts 5- and 20-year risk of all-cause dementia (2,3). The model includes proteins related to neuroinflammation and immune dysfunction, synaptic integrity, neurodegeneration, product glycosylation, cell adhesion and metabolic processes, among others. The model's prognostic performance has been shown to be superior to the apolipoprotein E (APOE) genotype and similar to AD-specific plasma biomarkers (Aβ42/40, p-tau181) (2). The model predicts longitudinal declines across multiple cognitive domains, accelerated regional brain atrophy, and elevated measures of neuropathology (2). Glucagon-like peptide-1 receptor agonists (GLP-1RAs) such as semaglutide may have therapeutic potential in Alzheimer's disease (AD), with cumulative evidence indicating a potential reduction in cognitive decline in people with AD (4,5), and real-world evidence demonstrating a decreased dementia risk in people with type 2 diabetes (6,7). Preclinical and biomarker data reveal that GLP-1RAs impact neuroinflammation and other biological processes believed to be involved in AD pathophysiology (8,9). The aim of the present study was to assess the effect of once weekly semaglutide up to 2.4 mg on proteomic signatures of dementia risk in a population aged ≥65 years with obesity or overweight and established cardiovascular disease (CVD) without diabetes, using a subset of serum samples from the SELECT cardiovascular outcomes trial (NCT03574597) (10). **Methods:** The dSST was developed using the SomaScan™ Assay (SomaLogic, Boulder, CO, USA), which uses DNA-based binding reagents (modified aptamers) to assess plasma levels of approximately 5,000 proteins with high specificity and limits of detection largely comparable to antibody-based assays (11,12). It was developed in the Atherosclerosis Risk in Communities cohort (n=11,277) and validated in the Baltimore Longitudinal Study of Aging (n=1,218) and the Japanese National Institute for Longevity Sciences-Longitudinal Study of Aging (n=340) cohorts. It predicts individualized 5-year and 20-year probabilities of dementia diagnosis, which can further stratify individuals into low, medium-low, medium-high, and high-risk of dementia groups, with a 20-year event rate ranging from 3.8% (low) to 35.6% (high) and a 5-year event rate ranging from 1.5% (low) to 20.3% (high) (2,13). The SELECT trial included participants over 45 years of age with obesity or overweight and established CVD, without a history of diabetes, randomised to either once weekly semaglutide up to 2.4 mg or placebo (10). The primary endpoint was a composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke in a time-to-first-event analysis. Serum samples were collected over 5 years. Patients were treated with semaglutide or placebo for 34.2 ± 13.7 months. For the current dSST analysis, non-fasted serum samples of 2,970 participants aged over 65 years enrolled in the SELECT trial collected at baseline, week 20 and week 104 (2 years) were used to assess the 5- and 20-year risk of dementia diagnosis with dSST. The risk was also assessed in a subpopulation of participants ≥65 years of age with reported dementia-related adverse events during the trial, as defined by the narrow scope terms of the standardised MedDRA queries for dementia (SMQ Dementia) (n=18). **Results:** After 2 years of treatment, the 5-year proteomics-based dementia risk prediction had a 2.5 times smaller increase in the semaglutide treatment arm compared with placebo, corresponding to a 26% lower expected 5-year dementia event rate in the active arm (OR=0.74; 95% CI: 0.64–0.85). The 20-year dementia risk prediction in the semaglutide-treatment arm had a 1.67 times smaller increase in the semaglutide-treatment arm compared with placebo, corresponding to an 8.8% (OR=0.91; 95% CI: 0.88–0.94) lower expected 20-year dementia event rate in the active arm. An ordinal regression analysis revealed that semaglutide treatment was associated with a significant decrease in the odds of being in the higher dementia risk groups at the end of the trial compared with placebo (β= -0.44, SE=0.078, p<0.001). This corresponded to a 36% lower odds of being in a higher dementia risk category for treated participants compared with placebo (OR=0.64; 95% CI: 0.55–0.75). This reflects a general downward shift in the distribution of risk levels for treated participants. To further validate the model, we analyzed the dementia risk scores in participants ≥65 years of age with all dementia-related adverse events reported during the SELECT trial (n=18). At baseline, all participants fell into high (n=11, 61%) and medium-high dementia risk (n=7, 39%) categories, further supporting the prognostic value of the score. Importantly, these dementia-related adverse events numbers may represent underreporting, considering only adverse events and serious adverse events leading to discontinuation were reported. **Conclusions:** Proteomic changes in plasma or serum could be useful for dementia risk stratification in individuals with cardiometabolic complications. Semaglutide appears to modify dementia-related proteomic signatures in participants with obesity or overweight and established CVD without diabetes.

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Keywords: Proteomics, semaglutide, dementia risk.

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Key takeaway message: Proteomic changes in plasma or serum could be useful for dementia risk stratification in individuals with cardiometabolic complications. Semaglutide appears to modify dementia-related proteomic signatures in participants with obesity/overweight and established CVD without diabetes.

P253- ROBUSTNESS OF PLASMA Aβ42/Aβ40 AS A PREDICTIVE BIOMARKER FOR BRAIN AMYLOID DEPOSITION: INDEPENDENCE FROM RENAL FUNCTION AND BODY MASS INDEX IN A REAL-WORLD TERTIARY CARE COHORT WITH MILD COGNITIVE IMPAIRMENT.

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Background: Blood-based biomarkers are playing an increasingly pivotal role in the field of Alzheimer's disease, enabling earlier and more accessible detection of pathological changes, facilitating large-scale screening and supporting patient selection and monitoring in both clinical and research settings. For a biomarker to be clinically useful, it must provide reliable information across individuals with varying physiological conditions. Factors such as renal function or body mass index (BMI) may influence biomarker levels and compromise their diagnostic performance (1-4). The aim of this study was twofold: first, to assess the potential influence of glomerular filtration rate (GFR) and BMI on the plasma Aβ42/Aβ40 ratio; and second, to evaluate the robustness of a predictive model—including plasma Aβ42/Aβ40, age, and apolipoprotein E (APOE) genotype—for identifying brain amyloid deposition across different subgroups within a real-world tertiary care cohort of individuals with mild cognitive impairment (MCI). **Methods:** This study included 260 participants with a diagnosis of MCI from the Hospital Universitari Santa Maria (HUSM-Lleida, Spain). Patients were referred to the memory unit from primary care or other specialized departments within the hospital. Amyloid positivity was determined through cerebrospinal fluid (CSF) analysis of either Aβ42/Aβ40 or p-tau181/Aβ42 ratios. Plasma Aβ40 and Aβ42 concentrations were measured using ABtest-MS, an antibody-free liquid chromatography–mass spectrometry (LC-MS) method developed by Araclon Biotech (Zaragoza, Spain). Associations between the plasma Aβ42/Aβ40 ratio and GFR or BMI were assessed using multiple linear regression adjusting for sex, age, and APOE status. BMI was treated as a continuous variable, while GFR was categorized into three groups based on standard clinical thresholds: impaired (<60), low to normal (60–89) and normal (≥90 mL/min/1.73 m^2). Logistic regression and receiver operating characteristic (ROC) curve analyses were performed to evaluate the predictive performance of the model in the overall population and within subgroups defined by Mini-Mental State Examination (MMSE; ≤27 vs. >27), sex, age (≤75 vs. >75 years), BMI (normal weight, overweight, obesity) and GFR (<90 vs. ≥90 mL/min/1.73 m^2). **Results:** Individuals with positive CSF-Aβ status were older than their negative CSF-Aβ counterparts (median [interquartile range, IQR]: 74.0 [71.0–77.0] vs. 70.0 [65.0–74.3]; $P < 0.0001$) and showed lower performance on the MMSE (26.0 [24.0–27.8] vs. 27.0 [24.3–28.0]; $P = 0.020$). Gender distribution did not differ significantly between groups ($P = 0.213$), while APOE ε4 allele distribution was significantly different ($P < 0.0001$). In the overall cohort, CSF-Aβ(+) prevalence was 70%. In multiple linear regression analyses adjusted for age, sex, and APOE status, no significant association was found between plasma Aβ42/Aβ40 ratio (measured by ABtest-MS) and BMI ($P = 0.136$). Similarly, no significant association was observed between GFR and plasma Aβ42/Aβ40 levels. After adjustment for covariates, participants with low to normal or impaired GFR showed no meaningful differences in Aβ42/Aβ40 ratios compared to those with normal renal function ($P > 0.05$). The area under the ROC curve (AUC) for identifying CSF-Aβ positivity was 0.88 (95% confidence interval [CI]: 0.84–0.93) in the overall cohort. AUC values ranged from 0.86 to 0.92 in subgroup analyses. **Conclusions:** Plasma Aβ42/Aβ40 levels were not influenced by BMI or renal function, highlighting the biomarker's physiological robustness and supporting its applicability across heterogeneous patient populations. In this real-world tertiary care cohort, the Aβ42/Aβ40 ratio also showed strong predictive accuracy for identifying CSF-confirmed brain amyloid deposition, with an overall AUC of 0.88 and consistent performance across clinically relevant subgroups.

Keywords: Aβ42/Aβ40, ABtest-MS, renal function, body mass index.

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Key takeaway message: Plasma Aβ42/Aβ40 levels are not influenced by BMI or renal function, highlighting the biomarker's physiological robustness.

P254- MODELING AGE-RELATED AMYLOID-β TRAJECTORIES IN COGNITIVELY UNIMPAIRED INDIVIDUALS USING GAMLSS: A ETHNIC COMPARISON BETWEEN KOREAN AND NON-HISPANIC WHITE COHORTS.

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Introduction: Amyloid-β (Aβ) deposition begins decades before the clinical onset of Alzheimer's disease (AD). Although age-related increases in Aβ positivity among cognitively unimpaired (CU) individuals are well-documented, detailed longitudinal characterization of Aβ

trajectories in this population remains limited. Additionally, age-related Aβ trajectories may vary according to APOE genotypes, sex, and ethnicity. In this study, we applied the generalized additive model for location, scale, and shape (GAMLSS) to cross-sectional data to model age-related Aβ trajectories and validated the models using longitudinal data. **Methods:** We analyzed data from 849 CU Korean participants and 521 CU non-Hispanic Whites (NHWs) after propensity score matching for age, sex, and APOE genotype. Age-related Aβ PET trajectories were modeled using the GAMLSS based on cross-sectional data and validated using longitudinal follow-up data. Subgroup analyses were conducted to examine the influence of APOE ε4 and sex on age-related Aβ PET trajectories. **Results:** The age-related centile curves of Aβ PET centiloid values showed stable distributions in the lower percentiles. Aβ values increased with age in the upper percentiles for both Koreans and NHWs. NHWs exhibited steeper trajectories of Aβ accumulation, particularly among APOE ε4 carriers, compared to Koreans. The reliability of this cross-sectional method was confirmed through robust calibration using the study's own longitudinal dataset. **Conclusions:** Our study developed and validated age-related Aβ PET trajectories in CU individuals using a GAMLSS-based cross-sectional modeling approach. NHWs exhibited steeper trajectories of Aβ accumulation than Koreans particularly among APOE ε4 carriers. These findings highlight the importance of accounting for population-specific Aβ patterns in designing targeted prevention strategies.

Key takeaway message: Cross-sectional modeling using GAMLSS, validated with longitudinal data, revealed steeper age-related Aβ accumulation in non-Hispanic Whites than Koreans—especially among APOE ε4 carriers—highlighting the need for population-specific strategies in Alzheimer's disease prevention.

P255- AGE-RELATED BLOOD CD8 T CELLS BINDING A NON-SELF PEPTIDE/HLA EPITOPE TRACK WITH ALZHEIMER'S AND RELATED MCI STATUS IN HLA-A2+ AND HLA-A2- COHORTS: EXPANDING THE REACH OF A T CELL BIOMARKER ASSAY TO ALL PATIENTS.

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Background: We recently developed a CD8 T cell-induced mouse model that recapitulates definitive hallmarks of Alzheimer's disease (AD) and allowed prediction of previously unknown properties of human sporadic AD (DOI: 10.1073/pnas.2401420121). Identification of a peptide antigen to which the inducing T cells respond in this model (a non-Aβ epitope on Amyloid Precursor Protein [APP]) allowed us to quantify analogous T cells in human brain and blood, using an APP471-479/Human Leukocyte Antigen(HLA)-A2 multimer (pHLA) and flow cytometry on blood. Blood levels of these T cells distinguished AD and related MCI from normal aging controls with high accuracy (AUC: 0.883-0.892), but the assay is currently suitable only for HLA-A2-positive (about half of all) patients due to HLA subtype-restricted binding. **Methods:** Lower level CD8 T cell binding to a non-self (ALIAPVHAV/HLA-A0201) multimer correlated with APP multimer binding in HLA-A2-positive patients (0.42-0.58x relative to APP/HLA-A2; $r = 0.81$; $P < 0.001$). Surprisingly, the same non-self multimer bound at similar levels to HLA-A2-negative patients' T cells. We thus quantified levels of age-related, KLRG1+ CD8 T cells binding to this non-self multimer in HLA-A2-positive ($n = 79$) and -negative ($n = 44$) subjects by flow cytometry from Alzheimer's disease (AD), mild cognitively impaired individuals with CSF biomarkers consistent with AD (MCI-AD), and normal aging control cohorts. We then assessed correspondence of multimer binding to disease status. **Results:** As with the APP pHLA multimer in HLA-A2-positive patients, levels of T cells binding to the non-self pHLA multimer were significantly diminished in AD and MCI-AD, but irrespective of HLA subtype ($P < 0.015$ by 2-sided T-Test). In receiver operating characteristic (ROC) analysis of the HLA-negative cohort, area under the curve (AUC) was 0.878 for AD ($P < 0.00001$; 79% sensitivity, 99% specificity), and 0.816 for MCI-AD ($P < 0.00001$; 78% sensitivity, 100% specificity), close to or better than the APP-specific CD8 T cells in HLA-A2-positive individuals (AUC 0.892 for AD; AUC 0.865 for MCI-AD). Moreover, disease correspondence of the non-self pHLA-binding T cells was also improved in the HLA-A2-positive cohort relative to APP/HLA-binding T cells, particularly for MCI-AD (AUC 0.912 for AD; 0.921 for MCI-AD). **Conclusions:** Subtype-independent pHLA binding by CD8 T cells strongly corresponds to AD and pre-AD MCI status in HLA-A2-negative and HLA-positive individuals, providing a working basis for expanding our AD biomarker assay to all patients. Ongoing work will focus on increasing the sensitivity of HLA-independent multimer binding to further increase assay utility.

Keywords: Blood biomarker, CD8 T cell, HLA.

Disclosures: C.J.W. is the author of patents PCT/US2016/049598, WO2017/040594, and PCT/US2019/017879, which are licensed by Cedars-Sinai Medical Center to T-Neuro Pharma, Inc. C.J.W. has received salary and ownership interest in T-Neuro Pharma, Inc.

Key takeaway message: Levels of APP-specific CD8 T cells in blood correspond to AD status with high accuracy, but their measurement is restricted to HLA-A2-positive patients. Quantitating non-self-peptide-specific CD8 T cells removed this restriction, and improved early disease-tracking.

P256- C2N ELIGIBILITY, APOE GENOTYPE IDENTIFICATION, AMYLOID CONFIRMATION. RESULTS FROM THE AHEAD 3-45 PROGRAMME AT NEUROCLIN GLASGOW.

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Background: Alzheimer's disease (AD) research often focuses on reducing or altering beta-amyloid (Aβ), a protein central to AD pathology and influenced by variations in the APOE gene. This gene encodes for proteins involved in Aβ metabolism and certain variants, particularly APOE4, are strongly associated with increased Aβ oligomerisation and plaque formation—hallmarks of AD. A major challenge in AD clinical research is maximising participant recruitment, often hindered by burdensome procedures, while minimising risk to participants. For example, Amyloid PET scans, used to confirm Aβ presence, involves radiation exposure, potentially deterring participation. These procedures are also time consuming and expensive, which if mitigated could lead to smoother screening resulting in greater participation and retention. The AHEAD 3-45 study sponsored by Eisai, used Precivity test (C2N biomarker assay) to enrich the screening population using an algorithm to predict the centiloid (CL) value based on participant's plasma p-tau217, Aβ42/40, age, and genotype. Threshold for eligibility was adjusted during recruitment and increased from 11CL to 40CL. This approach identified individuals likely to be amyloid-eligible before amyloid PET imaging. The target population was preclinical Alzheimer's disease, defined as cognitively normal subjects with 'Elevated amyloid' (>40 CL) for the A45 arm and 'Intermediate amyloid' (20-40 CL) for the A3 arm. **Methods:** Participants passing an initial screening eligibility questionnaire completed Precivity test to assess potential elevated amyloid levels. Eligible candidates underwent further screening procedures, culminating in confirmatory amyloid and tau PET imaging before randomisation. **Results:** A total of 997 were screened, and 901 C2N tests were performed. Due to factors such as expiration of the screening window, changes in medications, planned surgeries, abnormal test results, or other variables, some participants were re-screened. After accounting for duplicates, 878 tests were analysed. Of these, 229 (26.1%) were C2N-eligible, to continue in screening, with 66.3% of positives being APOE4 carriers. In contrast, only 31.1% of the 649 C2N-negatives were APOE4 carriers. Among the 229 C2N-eligible, 109 underwent

amyloid PET scans, as many screen-failed on other inclusion/exclusion criteria prior to imaging such as cognitive tests. Of PET scans conducted, 59.6% were aPET eligible. Among the 81 APOE4 carriers who received PET scans, 64.2% were amyloid-eligible, compared to 46.4% of APOE4 non-carriers. Notably, 75% of APOE4 homozygotes (n=8) who underwent PET scans were amyloid-eligible. **Conclusions:** This study demonstrates that plasma biomarker screening via C2N testing effectively narrowed the pool of potential participants for confirmatory amyloid PET imaging. The data reinforces known associations between APOE4 status and increased amyloid burden, even in cognitively normal individuals. The gradient in PET eligibility across APOE4 non-carriers, carriers, and homozygotes suggests a dose-dependent genetic influence on amyloid accumulation. This approach illustrates the value of incorporating biomarker-based screening in clinical trial pipelines. By enriching for likely amyloid-eligible individuals, this method reduces the number of participants subjected to invasive procedures and unnecessary radiation, thereby minimising participant burden, enhancing safety, and potentially improving recruitment and retention in preclinical Alzheimer's disease trials.

References: Detection and treatment of Alzheimer's disease in its preclinical stage. Michael S Rafii, Paul S Aisen, Nature Aging, 2023 May;3 (5):520-531.

Key takeaway message: Approach of using Plasma biomarkers to enrich the Preclinical population undergoing complex screening tests can reduce the load of unnecessary radiation and intervention in detecting Early AD pathology.

P257- THE ROLE OF LIPIDS ON CHANGES OF PLASMA PTAU181, PTAU217 AND THE 217/181 RATIO IN ALZHEIMER'S DISEASE OVER TIME: A PILOT STUDY IN A MEMORY CLINIC POPULATION.

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Background: The growing number of people with dementia, together with new ways of treating mild cognitive impairment due to Alzheimer's disease (AD), necessitates the development of minimally or non-invasive, cost-effective biomarkers. Blood-based biomarkers of tau (pTau 181 and pTau 217) have been shown to correlate well with amyloid PET and CSF markers and to increase in the course of AD (1). Lipids, such as cerebral cholesterol, which is transported by ApoE particles and taken up via mainly the low density receptor (LDLR), may be associated with tauopathies and β-amyloid accumulation (2,3). However, the influence of blood lipids on plasma tau 218 and 217 levels in the course of AD has not been sufficiently researched. **Methods:** Data of 62 patients with AD-dementia were included. Levels of plasma pTau 181 and plasma pTau 217 were analyzed with the commercial automated Lumipulse G600II (Fujirebio). All patients underwent routine blood sampling (including cholesterol, triglycerides, low-density-lipoprotein (LDL) and high-density-lipoprotein (HDL) cholesterol), ApoE genotyping, clinical examination, and cerebral imaging. Linear logistic regression, the Wilcoxon Test, and Spearman correlation were performed to determine the influence of blood lipids on changes of plasma pTau (181, 217, and the ratio 217/181) over a follow-up period of 6.7 ± 1.9 month. **Results:** Between baseline (pTau 181: 2.05±0.84 pg/ml, pTau 217: 0.47 ±0.34 pg/ml, pTau217/181 ratio: 0.22±0.08) and follow-up (pTau 181: 1.98±0.97 pg/ml, pTau 217: 0.53±0.39 pg/ml, pTau217/181 ratio: 0.35±0.78) solely the pTau 217/181 ratio increased significantly (mean change ratio:0.14, Z= -2.357, p=0.018), which was due to a small decrease in pTau 181 (mean change: -0.07 pg/ml) and increase in pTau 217 (mean change: 0.06 pg/ml). Correlation analysis showed a positive correlation of pTau 217 with the number of ApoE 4 copies (p=0.017) and baseline cholesterol (p=0.047). The pTau217/181 ratio correlated positively with the number of ApoE 4 copies (p=0.021), with baseline cholesterol (p= 0.040), and with LDL-cholesterol (p=0.032). Changes of pTau 217 and the pTau 217/181 ratio correlated positively with baseline cholesterol (pTau 217: p=0.007, ratio: p= 0.003) and LDL cholesterol (pTau 217: p=0.005, ratio: p< 0.001). The linear logistic regression model with the change in the pTau 217/181 ratio being the dependent variable was statistically significant (p =0.004, $R^2 = 0.419$). Baseline LDL-cholesterol and baseline pTau 217 significantly predicted a later increase in the pTau 217/181 ratio (LDL-cholesterol: p<0.001, 95%-CI [0.007 - 0.021], pTau 217: p= 0.026, 95%-CI [-2.048 - -0.142]. Plasma pTau 181 and all other demographic and clinical measures (age, gender, MMSE score, ApoE 4 allele) were not predictive. **Conclusions:** Our results indicate that the levels of plasma pTau 181 and pTau 217 of patients with AD change in different ways over time. The increase in the plasma pTau 217/181 ratio was significantly influenced by LDL cholesterol levels. We assume that combining pTau 181 and pTau 217 in a ratio increases the validity of plasma Tau measures as progression markers. The influence of LDL-cholesterol in particular on the increase of plasma Tau biomarkers in the course of AD should be investigated in larger follow-up studies. References: 1. Therriault J, et al. JAMA Neurol 2023;80(2):188-99. doi:10.1001/jamaneurol.2022.4485. 2. Ali A, et al. Neurochem. 2025 Jan;169(1):e16294. doi: 10.1111/jnc.16294. PMID: 39777699; PMCID: PMC11731895. 3. Rappoport A, et al. Annu Rev Biochem. 2024 Oct 30. doi: 10.1146/annurev-biochem-052024-115455. Epub ahead of print. PMID: 39476407.

Key takeaway message: We assume that combining plasma pTau 181 and pTau 217 in a ratio increases the validity of plasma Tau measures as progression markers of Alzheimer's disease. The influence of LDL-cholesterol in particular on changes of plasma Tau biomarkers in the course of AD should be investigated in larger follow-up studies.

P258- DEVELOPMENT AND EVALUATION OF AN MTBR TAU FRAGMENT IMMUNOASSAY FOR THE ASSESSMENT OF ALZHEIMER'S DISEASE TAU PATHOLOGY.

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Background: The emergence of tau biomarker testing in peripheral biofluids has transformed the landscape of Alzheimer's Disease (AD) clinical trials. These markers have enabled blood tests that are highly accurate in detecting amyloid positivity, even in pre-symptomatic populations. However, most of these markers correlate best with earlier disease stages and amyloid positivity. A novel peptide at the N-terminal end of the microtubule binding region (MTBR) of tau, MTBR-243, has recently been shown to better reflect tau pathologic progression into later disease stages and demonstrates a stronger correlation with cognition than phospho-tau markers in both plasma and CSF (1,2). **Methods:** Previous approaches to measure MTBR relied on high sensitivity targeted mass spectrometry approaches. Here we present data on our optimization of an immunoassay approach on the Quanterix HD-X platform to measure a small fragment around the N-terminal portion of the MTBR of tau. We utilized high affinity in-house antibodies that bind to a narrow region of tau targeting the fragment of interest. We tested various biochemical and immunological enrichment strategies to enrich for the specific small MTBR peptide of interest, using recombinant protein, brain homogenate, and CSF samples. We compared this novel MTBR-tau assay to a p217+tau assay. **Results:** We developed a high sensitivity assay utilizing two tau mAbs; one targeting amino acids 210-220 with phosphorylation at amino acid 217 and the other targeting amino acids 249-254 (at the start of the MTBR of tau). Our method provided precise measurements in cerebrospinal fluid (CSF). Initial results demonstrated a correlation with the p217+ assay that relies on an N-terminal detection antibody. We observed a similar pattern of response in both the MTBR and p217+ assay from HPLC fractionated CSF. The MTBR immunoassay we developed was able to differentiate of crude CSF AD patients (N=10) from cognitively unimpaired individuals (N=10). Enrichment strategies prior to an MTBR-targeted immunoassay were able to enrich a unique pool of tau peptides to increase the specificity of the assay to small tau fragments. **Conclusions:** Immunoassay

measurements of the N-terminal MTBR region of tau are feasible and enable high throughput measurement of a potentially insightful biomarker. Small peptide enrichment strategies may be able to target immunoassays to the unique tau peptides that best correlate with pathologies of interest.

Keywords: tau, MTBR, immunoassay. Disclosures: All authors are employees of Johnson and Johnson Innovative Medicine.

References: 1. Horie K, Salvadó G, Koppisetti RK, et al. Plasma MTBR-tau243 biomarker identifies tau tangle pathology in Alzheimer's disease. Nat Med. Published online March 31, 2025. doi:10.1038/s41591-025-03617-7. 2. Horie K, Salvadó G, Barthélemy NR, et al. CSF MTBR-tau243 is a specific biomarker of tau tangle pathology in Alzheimer's disease. Nat Med. 2023;29(8):1954-1963. doi:10.1038/s41591-023-02443-z.

Key takeaway message: Immunoassay measurements of the N-terminal MTBR region of tau are feasible and enable high throughput measurement of a potentially insightful biomarker. Small peptide enrichment strategies may be able to target immunoassays to the unique tau peptides that best correlate with pathologies of interest.

P259- TAU-DEPENDENT DIVERGENT ASSOCIATIONS OF SOLUBLE AND PLAQUE AMYLOID WITH GLUCOSE DYSREGULATION.

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Background: Glucose metabolic dysfunction in Alzheimer's disease (AD) may be differentially associated with soluble amyloid-β oligomers (OAβ) and plaque amyloid, yet it remains unclear how tau pathology modulates these effects. **Objectives:** To investigate whether tau pathology modifies the association between Aβ species and systemic glucose metabolism across the AD spectrum. **Design:** Cross-sectional observational study. **Setting:** Memory clinic-based cohort from a single tertiary academic medical center in South Korea. **Participants:** 113 older adults, including cognitively normal individuals, patients with mild cognitive impairment, and Aβ-PET–positive dementia patients. **Measurements:** Plasma oligomeric Aβ (OAβ) levels were quantified using the Multimer Detection System. Aβ plaque deposition and tau pathology were assessed using [18F]-flutemetamol and [18F]-flortaucipir PET, respectively. Glucose metabolism was evaluated using fasting plasma glucose and hemoglobin A1c (HbA1c). Braak stage was determined from tau-PET imaging. Generalized linear models assessed the main and interaction effects of both plasma oligomeric Aβ burden and plaque Aβ measured via PET with tau pathology, adjusting for clinical covariates. **Results:** A significant interaction was found between OAβ burden and Braak stage for HbA1c ($\chi^2 = 22.177$, $p = 0.001$), indicating that elevated OAβ was associated with increased HbA1c only in participants at Braak stage 0. No such associations were observed for fasting glucose or for Aβ-PET measures. These findings suggest a tauopathy-dependent effect of soluble Aβ oligomers on long-term glucose dysregulation. **Conclusions:** Soluble Aβ oligomers, rather than plaque amyloid, are selectively associated with systemic glucose dysregulation in the absence of overt tau pathology. Tau staging may be crucial for identifying AD subgroups vulnerable to metabolic dysfunction driven by early Aβ toxicity.

Key takeaway message: Soluble Aβ oligomers, not plaques, are associated with long-term glucose dysregulation across the Alzheimer's disease spectrum. This effect is restricted to initial Braak stages, highlighting tauopathy-dependent vulnerability to Aβ-driven metabolic dysfunction.

P260- A CORRELATION BETWEEN PLASMA P-TAU181 LEVELS AND CLINICAL DIAGNOSIS OF ALZHEIMER'S DISEASE.

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Background: Traditionally, clinicians have relied on their clinical judgement to diagnose and treat Alzheimer's disease by evaluating medical history, conducting physical examinations, performing basic cognitive tests such as Mini-Mental State Examination (MMSE), ruling out depression, and using laboratory tests and imaging to exclude other common causes of dementia. Over the last 5 years, blood-based markers for Alzheimer's disease (AD) have gained popularity not only in clinical trials but also for outpatient diagnosis of prodromal/ early-stage Alzheimer's Disease (1) with P-Tau181 and P-Tau217 being used extensively to screen patients for AD studies. However, to the best of our knowledge, no studies have evaluated the diagnostic utility of plasma P-Tau181 in Alzheimer's Disease (2). Here we compare the diagnostic accuracy of plasma P-Tau181 to traditional methods of clinical diagnosis for mild to moderate Alzheimer's Disease. **Methods:** Anonymized data were collected from patients who consented to participate in both pharmacological and non-pharmacological therapeutic research for Alzheimer's Disease, both with and without a confirmed diagnosis of Alzheimer's Disease. Each participant was evaluated by at least one board-certified psychiatrist to determine the presence of Alzheimer's Disease. From this cohort, we extracted demographic and clinical variables including age, race, and sex. Baseline values of clinical markers commonly used in the diagnosis of Alzheimer's Disease were collected in a cross-sectional manner, including MMSE scores, Clinical Dementia Rating (CDR) Global scores, ADAS-Cog12 scores, and plasma P-Tau181 levels. Statistical analyses were conducted to assess correlations among these variables. **Results:** There was a total of 138 trial participants with a average age of 73 years old. Of these, 50% were female and 92% identified as white and non-Hispanic. All participants had available MMSE scores and baseline plasma P-Tau181 values. Among them, 130 (94%) participants had corresponding CDR-Global scores, and 67 (49%) had ADAS-Cog scores. Among 31 participants with MMSE scores between 16 and 22, consistent with clinically diagnosed dementia, plasma P-Tau181 levels ranged from 1.09 to 300 pg/mL. Linear regression analysis of plasma P-Tau181 versus MMSE in this group yielded an R2 of 0.0017. For 107 participants with MMSE scores between 23 and 28, indicative of normal cognition to mild cognitive impairment (MCI), plasma P-Tau181 levels ranged from 0.64 to 300 pg/mL with an R2 of 0.0322. Of the 29 subjects who had a CDR – Global score of 1, consistent with clinically diagnosed dementia, plasma P-Tau181 levels ranged from 15.49 to 300 pg/mL. In comparison, among the 101 participants with a CDR – Global score of 0.5, indicative of normal cognition to MCI, plasma P-Tau181 ranged from 6.17 to 300 pg/mL. Among 22 participants with ADAS-Cog12 scores between 20 and 26, consistent with clinically diagnosed dementia, plasma P-Tau181 values ranged from 30.77 to 167.54 pg/mL with an R2 of 0.0574. For the 45 participants with ADAS-Cog12 scores between 0.5 and 20, indicative of normal cognition to MCI, plasma P-Tau181 levels ranged from 30.98 to 300 pg/mL with an R2 of 0.0508. **Conclusions:** In our analysis, 138 clinical trial participants met diagnostic criteria for Alzheimer's disease (AD) based on comprehensive evaluations conducted by board-certified psychiatrists. Clinicians utilized medical records, detailed medical and family histories, cognitive assessments (MMSE, ADAS-Cog, and CDR-GS), and extensive laboratory work to rule out metabolic and deficiency-related dementias. Depression, other significant medical or psychiatric conditions, and alternative causes of dementia were excluded through clinical interviews and MRI imaging. MMSE scores correlated well with the clinical diagnosis of AD and wereused in our analyses. Our findings revealed no clear association between clinically diagnosed AD severity and P-Tau181 levels, which ranged widely from 0.64 to 300 pg/mL. Similarly, no consistent correlation was observed between P-Tau181 levels and scores on ADAS-Cog or CDR-GS. In this limited sample of patients with mild to moderate Alzheimer's disease, P-Tau181 did not

demonstrate meaningful diagnostic value. While previous research has shown plasma biomarkers to correlate with tau-PET imaging and CSF tau markers (3,4), this study appears to be the first to compare P-Tau181 directly with clinical diagnosis, which remains the gold standard. Our findings suggest that P-Tau181 has low sensitivity as a standalone diagnostic tool. If used broadly, it may risk excluding patients who meet clinical criteria but present with "low" biomarker levels. As plasma biomarkers gain popularity in both outpatient settings and as screening tools for AD clinical trials, we face the risk of underdiagnosis or exclusion of eligible participants who may benefit from cognitive interventions. Before these biomarkers are widely implemented, further studies with larger and more diverse populations are needed to validate their utility. In the meantime, comprehensive clinical diagnosis should remain the cornerstone for confirming Alzheimer's disease.

Keywords: Alzheimer's disease, plasma P-Tau181, blood-based biomarkers, diagnostic accuracy.

Disclosures: The authors declare no competing interests.

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Key takeaway message: P-Tau is increasingly becoming a widely used screening marker for Alzheimer's Disease both is clinical and in clinical trial settings. Further studies in larger samples are required to establish the validity of this test.

PROOF OF CONCEPT FOR ALZHEIMER DRUG DEVELOPMENT INTERVENTIONS

P261- CLINICAL AND PET OUTCOMES FOLLOWING Aβ-TARGETING THERAPIES IN SPORADIC EARLY ONSET ALZHEIMER'S DISEASE: TRIAL EMULATION USING THE LEADS COHORT.

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Background: Phase 3 trials of FDA-approved anti-Aβ monoclonal antibodies (aducanumab, lecanemab, donanemab) have demonstrated robust target engagement, with rapid amyloid clearance measured with PET, and slowing of clinical decline. However, real-world evidence on biomarker and clinical outcomes following these therapies remains limited. Observational cohorts offer an opportunity to study treatment-related inflection points in biomarker and clinical trajectories outside the controlled trial setting, notably in subgroups of patients that were under represented in clinical trials, such as patients with early onset Alzheimer's disease. In this project, we aimed to leverage data from the ongoing multisite Longitudinal Early Onset Alzheimer's Study (LEADS, 2018-current), which includes annual follow-ups for all participants, including those who are receiving amyloid targeting therapies as part of their clinical care. More specifically, we compared longitudinal PET and clinical trajectories in treated participants and matched untreated controls to assess whether initiation of Aβ-targeting therapy is associated with measurable inflection in amyloid, tau and clinical change. **Methods:** We identified 63 participants with sporadic EOAD (MCI or mild dementia stage with a positive amyloid PET scan) who had received Aβ-targeting therapies in LEADS. Of those, 31 participants had complete pre-treatment and post-treatment clinical and PET data and comprised the primary analysis sample. In a target emulation design, each treated case (n=31) was matched 1:2 to untreated participants from the same cohort on pre-treatment timepoint, clinical stage, age, sex, APOE genotype, neocortical tau PET burden, amyloid PET burden (Centiloid), CDR global score, and CDR-sum-of-boxes (CDR-SB). For each matched untreated individual, we assigned a pseudo–treatment start equal to the matched treated subject's actual treatment start (i.e. time-zero) for performing comparisons relative to the same index time. We then used piecewise (knot at treatment start) linear mixed-effects models to evaluate change in amyloid burden, tau burden and CDR-SB. Each model included time, a post-treatment slope term, and the interaction between treatment status and the post-treatment slope. Slope estimates are reported with 95% confidence intervals. **Results:** Of 31 treated participants, 27 received lecanemab, 3 received aducanumab and 1 transitioned from aducanumab to lecanemab. Average pre-treatment MoCA was 18 (range: 14–22) and age was 59.7 (55.8–62.7) years; 25/31 (81%) were female and 15/31 (48%) were ApoE4 carriers (6 homozygotes). Mean treatment duration at the time of the last available timepoint was 11 (range: 8–17) months. Prior to treatment, amyloid PET signal was relatively stable (estimate: +0.4 Centiloid/year, 95%CI −2.1 to +2.8). After treatment onset, amyloid decreased by −30.5 Centiloid/year (95%CI −34.7 to −26.2) in treated participants versus +2.9 Centiloid/year (95%CI +0.4 to +5.5) in matched untreated participants (interaction $p < 0.001$). Tau increased pre-treatment by +0.09 SUVR/year (95%CI +0.06 to +0.13); post-treatment slopes were +0.09 SUVR/year (95%CI +0.03 to +0.14) in treated versus +0.07 SUVR/year (95%CI +0.04 to +0.10) in untreated (interaction $p = 0.626$). CDR-SB increased pre-treatment by +0.4 units/year (95%CI +0.2 to +0.7); after treatment the post-treatment slope was +0.9 units/year (95%CI +0.4 to +1.5) in treated versus +1.5 units/year (95%CI +1.2 to +1.8) in untreated (interaction $p = 0.075$). **Conclusions:** Using an emulated trial design with a small sample size and short follow up, we were able to observe rapid amyloid clearance upon the initiation of Aβ-targeting therapy in patients with EOAD. In contrast, tau PET trajectories showed no significant inflection or difference between groups. CDR-SB trajectories showed slower clinical decline in treated versus matched untreated participants, with treatment-effect estimates similar in magnitude to those reported in trials. These findings provide proof-of-concept that real-world observational cohorts with biomarker data can detect biologically meaningful outcomes and offer complementary evidence to randomized trials.

Keywords: Early-Onset Alzheimer's Disease, emulated trial, lecanemab, aducanemab, observational cohort, centiloids.

Disclosures: MCC is a full-time employee of the Alzheimer's Association. BCD receives research support from the NIH and the Alzheimer's Drug Discovery Foundation. He served as a consultant for Acadia, Arkuda, Axovant, Biogen, Cervomed, Eisai, Lantheus, Lilly, Merck, Novo Nordisk, Quanterix, and Wave LifeSciences. He received royalties from Cambridge University Press, Elsevier, Oxford University Press. LGA received grants or contracts from NIH, Alzheimer's Association, AVID Pharmaceuticals, Life Molecular Imaging, Roche Diagnostics, and Eli Lilly. She has served as a paid consultant for Biogen, GE Healthcare, Prothena, Eisai, IQVIA, Roche Diagnostics, Genentech, Alnylam, Siemens, Otsuka, Corium, and Eli Lilly. She received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AAN, Weil Cornell, MIllerMed, MedLearning Group, NACC CME, Prothena, CME Institute, MJH Physician Education Resource, WebMD, PeerView. She received support for attending

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Key takeaway message: These analyses provide proof-of-concept that real-world observational cohorts with biomarker data can detect biologically meaningful outcomes and offer complementary evidence to randomized trials.

P262- ADVANCING AKV9 (NU9) TOWARDS PHASE I CLINICAL EVALUATION: A SMALL-MOLECULE AUTOPHAGY-ENHANCING THERAPEUTIC FOR PROTEINOPATHIES IN ALZHEIMER'S DISEASE AND ALS.

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Background: AKV9 (NU9) is a small molecule drug candidate with a broad-spectrum neuroprotective profile tested against multiple proteinopathies. AKV9 has completed IND-enabling studies for ALS and received FDA clearance for a Phase I trial. Previous studies have demonstrated AKV9's efficacy in ALS models, where it reduced misfolded SOD1 in SOD1G93A ALS models, preserved mitochondrial and ER integrity, improved health of apical dendrites and axons, and improved degenerating upper motor neurons in models of SOD1 toxicity and TDP43 pathology. It also significantly improved the behavior of hSOD1G93A-UeGFP mice on the hanging wire test (1,2). Recent studies demonstrated AKV9 efficacy in Alzheimer's disease models of Ab oligomer pathology, where it shown to reduce AbO build up on dendrites by 80% and retained memory function in a small proof of concept study in 5xFAD mice (3). While AKV9 demonstrates a strong therapeutic profile, its molecular target remains undefined. Our latest data reveal that AKV9 acts as a potent inducer of autophagy, establishing it as a potential first-in-class lead compound that engages neuronal autophagy, with robust preclinical evidence supporting both efficacy and tolerability. Unlike current Alzheimer's disease therapeutics that act on a single disease node with limited efficacy, AKV9 targets an upstream pathway regulating autophagy, thereby modulating multiple downstream proteinopathies and offering greater therapeutic promise in a multifactorial, complex disease such as Alzheimer's disease. **Methods:** Super-resolution microscopy and live-cell imaging with immunofluorescent labeling were employed to assess autophagic activity following AKV9 treatment in mouse and human cell models. Cells modeling both AβOs and mutant SOD pathologies were treated with AKV9 at a range of concentrations, with particular focus on the lowest tested concentration (0.5 μM). Comparisons were made against vehicle-treated controls and Torin1, a selective mTOR inhibitor and known autophagy activator. To monitor autophagic flux, dual reporters were used to differentially label autophagosomes (DAPRed) and autolysosomes (DALGreen). In parallel, immunofluorescence was used to quantify SQSTM1/p62 levels as an additional marker of autophagic degradation. Bafilomycin was employed in select experiments to inhibit lysosomal acidification and assess autophagy dependence in the clearance of aggregated mutant SOD proteins. **Results:** At the lowest concentration tested (0.5 μM), AKV9 treatment produced robust induction of autophagic flux, evidenced by marked increases in DAPRed and DAlGreen vesicles corresponding to autophagosomes and autolysosomes, respectively. This effect was consistent across multiple cellular systems modeling Aβ and mutant SOD pathologies. The magnitude of AKV9's effect was comparable to that of Torin1, confirming its potency as an autophagy inducer. Additionally, AKV9 treatment reduced p62 accumulation, further supporting enhancement of autophagic degradation. Notably, co-treatment with bafilomycin abolished the protective effect of AKV9 against aggregated mutant SOD1, indicating a dependence on intact autophagy pathways for clearance of toxic protein aggregates. Collectively, these findings highlight autophagy activation as a key mechanism of AKV9 action in neurodegenerative models of both ALS and Alzheimer's disease, representing a novel and significant observation (manuscript in preparation). **Conclusions:** The identification of autophagy activation as the underlying mechanism provides critical insight into AKV9's therapeutic potential. This discovery supports and encourages its advancement into Phase 1 clinical trials for ALS, with anticipated Phase 2 studies in both ALS and Alzheimer's disease. Together with preclinical evidence of efficacy, tolerability, and activity across multiple proteinopathies, these findings position AKV9 as a promising first-in-class small-molecule autophagy inducer and a leading candidate for the treatment of Alzheimer's disease and other neurodegenerative disorders.

Keywords: Small molecule, Alzheimer's disease, neurodegeneration, therapeutics.
Clinical Trial Registry: Not applicable.
Data Deposition: Not applicable. Disclosures: RBS is Founder and President of Akava Therapeutics, which has licensed AKV9 (NU-9) from Northwestern University.

References: 1. Genç, B., et al., Improving mitochondria and ER stability helps eliminate upper motor neuron degeneration that occurs due to mSOD1 toxicity and TDP-43 pathology. Clin Transl Med, 2021. 11(2): p. e336. 2. Genç, B., et al., NU-9 improves health of hSOD1(G93A) mouse upper motor neurons in vitro, especially in combination with riluzole or edaravone. Sci Rep, 2022. 12(1): p. 5383. 3. Johnson, E.A., et al., Inhibition of amyloid beta oligomer accumulation by NU-9: A unifying mechanism for the treatment of neurodegenerative diseases. Proc Natl Acad Sci U S A, 2025. 122(10): p. e2402117122.

Key takeaway message: AKV9 (NU9) is a first-in-class small-molecule autophagy inducer, now advancing into clinical trials, with broad preclinical efficacy across ALS and Alzheimer's disease models by targeting an upstream pathway that modulates multiple proteinopathies.

P263- THIETHYLPERAZINE REDUCES PHOSPHORYLATED TAU IN ALZHEIMER'S DISEASE: CONFIRMING IN-BASED RESULTS WITH CLINICAL TRIAL DATA.

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Background: Deficient clearance of soluble amyloid-beta (Aβ) peptides is a recognized driver of sporadic Alzheimer's disease (AD). Thiethylperazine (C-001) is an orally bioavailable small-molecule that was originally developed as an antiemetic, which has been on the market for about 60 years. We and others have found that C-001 allosterically activates ABCC1 (also known as MRP1), an efflux transporter that has been shown in various cell and mouse models to play a critical role in Aβ clearance and modulation of the cGAS-STING pathway, both being of particular importance in Alzheimer's pathology. In line with these findings, C-001 was found to reduce disease pathology in mouse and cellular models of different neurodegenerative diseases. With this in

mind, we wondered if C-001 treatment would have an impact on phosphorylated Tau species. p-Tau181 and p-Tau217 have become established biomarkers for neuronal damage in general as well as for the presence and progression of AD, with elevated levels found in blood and cerebrospinal fluid (CSF). We designed a set of experiments to explore C-001's potential as a first-in-class AD therapy with dual effects on Tau and Aβ. We used human induced neurons (iN) derived by direct neuronal conversion of fibroblast to quantify the effect of C-001 on p-Tau and reanalyzed plasma samples from a clinical proof-of-concept study (DrainAD, NCT03417986) using ultra-sensitive p-Tau assay technologies that were not available at the time of trial conclusion. **Methods:** The in vitro experiments involve reprogramming fibroblasts from 10 donors with AD into human neurons. The effect of C-001 on p-Tau181 levels will be validated using high-content imaging. For clinical confirmation, plasma samples from the DrainAD study were re-analyzed. DrainAD was a proof-of-concept, open-label, exploratory trial that enrolled 15 elderly participants (for re-analysis, samples were available from 5 with early-to-mild AD and 6 cognitively normal controls). Participants received oral thiethylperazine at 26 mg/day for 4 consecutive days. All analyzed blood samples were taken in the morning. The re-analysis quantified p-Tau181 and p-Tau217 levels using ultra-sensitive immunoassays developed by Lilly Research Laboratories on the Meso Scale Discovery platform at pre-dose and post-dose (day 4) timepoints, conducted at Lund University. **Results:** The re-analysis of plasma samples from the DrainAD proof-of-concept study revealed that four out of five Alzheimer's disease (AD) patients (80%) with available paired samples at baseline and after 4 days of treatment demonstrated a clear decrease in both p-Tau181 and p-Tau217 plasma levels, an effect not seen in samples of healthy controls. Importantly, the p-Tau217 status at baseline confirmed the AD/healthy diagnosis for all included samples. This rapid pharmacodynamic impact on Tau pathology observed clinically, despite the small sample size and very short treatment period, showed clear trends for a clinically meaningful effect. The standardized change on p-Tau 217 (Cohen's D of 0.75) was comparable to the mean change seen in the Donanemab phase 2 & 3 trials at 6 months of treatment with this anti-amyloid antibody. Final data from this project's comprehensive iN experiments are currently pending, but preliminary results show the same trend. **Conclusions:** The observed rapid reduction in plasma p-Tau181 and p-Tau217 in AD patients following just 4 days of treatment provides the first clinical evidence of thiethylperazine's Tau-modulating effects. Achieving an effect size comparable to 6 months of anti-amyloid therapy, but in a matter of days and through an oral small molecule, underpins that C-001 represents a fundamentally different multi-modal therapeutic approach. Together with the expected iN data, which will be presented in full at CTAD, these findings support C-001 as a first-in-class dual-action Alzheimer's therapeutic targeting both Aβ and Tau pathology. This human-relevant preclinical validation strategy, combining clinical biomarker data with human neuronal models, is crucial for de-risking and accelerating the development of C-001 as a non-immunogenic, orally accessible, disease-modifying agent for Alzheimer's disease.

Keywords: Thiethylperazine, Alzheimer's disease, phosphorylated tau, iN, ABCC1.

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Key takeaway message: Thiethylperazine rapidly reduced plasma p-Tau181 and p-Tau217 in AD patients within 4 days, with human induced neuron experiments showing concordant effects, supporting its potential as a first-in-class dual-action oral AD therapeutic.

P264- INTRADERMAL BCG IMMUNOTHERAPY INDUCES DURABLE TRAINED IMMUNITY SIGNATURES IN CNS MONOCYTES AND REPROGRAMS NEUROIMMUNE PATHWAYS IN AGING AND ALZHEIMER'S DISEASE.

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Background: Aging changes immune function, leading to chronic low-grade inflammation ("inflammaging") which contributes to Alzheimer's disease (AD) through impaired amyloid-β (Aβ) clearance and persistent neuroinflammation. Trained immunity—epigenetic and metabolic reprogramming of innate immune cells—offers a strategy to restore resilience. The Bacillus Calmette-Guérin (BCG) vaccine is a potent inducer of trained immunity, with epidemiologic studies linking BCG exposure to reduced AD risk and preclinical work showing attenuation of amyloid pathology and neuroinflammation. However, BCG's safety and effects on human central nervous system (CNS) immunity and AD biomarkers remain undefined. **Methods:** We conducted a one-year, open-label study of 23 older adults (≥55 years) with and without AD pathology, classified via CSF ptau181/Aβ42 ratios. All received two intradermal BCG doses (Tokyo 172 strain) one month apart. Peripheral blood and CSF were sampled at baseline, 3 months, and 12 months. Endpoints included safety, peripheral cytokine recall responses, plasma and CSF cytokine dynamics, AD biomarkers, and single-cell RNA sequencing of immune cells from both CSF and blood compartments. **Results:** BCG was safe and well tolerated, with only one mild injection-site reaction. PBMCs demonstrated robust, durable trained immunity responses, including enhanced IFN-γ, IL-1β, IL-6, and TNF-α response recall to hkBCG as well as LPS stimulation through twelve months. Single-cell profiling confirmed distinct blood and CNS (CSF) compartmental compositions and showed durable transcriptional reprogramming in monocytes, with temporally structured gene induction (early metabolic remodeling, sustained inflammatory regulators, late interferon and chemokine programs). Importantly, CSF monocytes exhibited strong LPS responses but not direct BCG recall, suggesting compartment-specific training. Basal transcriptional remodeling also emerged in CSF $CD4^+$ T cells at 12 months. Plasma cytokine trajectories were disease-modulated—AD participants showed phased elevations in IL-2, IL-10, IL-1β, IL-6, and TNF-α—whereas CSF cytokines declined toward a shared immunoregulatory profile across groups. Interstingly, non-AD participants exhibited significant redistribution of Aβ, with decreased CSF Aβ42, increased plasma Aβ42, and a ~38% decline in CSF-to-plasma Aβ42 ratio, suggesting enhanced efflux. These shifts were not observed in AD participants. No significant longitudinal changes were observed for ptau181, NFL, or GFAP. **Conclusions:** Intradermal BCG immunotherapy induced durable, compartment-specific immune remodeling in older adults, including the first evidence of trained immunity in CNS immune cells. By reprogramming monocyte transcriptional responses and modulating cytokine and metabolic pathways, BCG shifted CNS immune tone without provoking central inflammation. In non-AD individuals, BCG altered Aβ dynamics, suggesting enhanced clearance prior to overt pathology. These findings provide proof of concept that BCG vaccination, a widely available intervention, may recalibrate neuroimmune tone, promote resilience in aging, and potentially delay early AD processes. Larger placebo-controlled trials are warranted to validate durability, clarify mechanisms, and assess clinical impact.

Keywords: Inflammaging, trained immunity, BCG vaccine, neuroinflammation, CSF cells, single-cell RNA sequencing, immune remodeling.

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Lilly / Fortrea, Gatehouse Bio, Ionis Pharmaceuticals, Janssen Pharmaceuticals, John Sperling Foundation, NIH, Novartis, Seer Biosciences, Superfluid Dx, and Venture Well. He has received consultancy and/or scientific advisory board payments from Allyx Therapeutics, BioVie, Bob's Last Marathon, Foster & Eldredge, Jocasta Neuroscience, Merck, ProSelect Insurance Co., Sage Therapeutics, Sanofi, and Vandria. MK declares no conflict of interest for the presented work. ZL declares no conflict of interest for the presented work. KM declares no conflict of interest for the presented work. PK declares no conflict of interest for the presented work. AM declares no conflict of interest for the presented work. JG declares no conflict of interest for the presented work. RT declares no conflict of interest for the presented work. SD declares no conflict of interest for the presented work. DF declares research funding for this project is from non-profit support from the public and she receives no industrial grant support. She is a full-time employee of MGH and Harvard Medical School and all technology is fully owned by her employer. She received the BCG drug supply through a licensing agreement with Japan Laboratories. Dr Faustman and her laboratory do not receive grant support from the drug supplier, they do not dictate trial design nor control outcome reporting. Dr Faustman does not receiving consulting income from Japan Laboratories. MW declares no conflict of interest for the presented work. MSW is currently an employee of AbbVie Inc. The research reported here was conducted at Massachusetts General Hospital and Harvard Medical School. AbbVie was not involved in the work.

Key takeaway message: Intradermal BCG vaccination induces transcriptional and metabolic reprogramming of CNS myeloid cells, supporting trained immunity as a strategy to modulate neuroinflammation and AD pathology in aging

P265- PERIVASCULAR MACROPHAGES: A POTENTIAL NOVEL PATHWAY FOR LECANEMAB TO AMELIORATE BLOOD-BRAIN BARRIER INTEGRITY AND COGNITIVE FUNCTION IN THE APP/PS1 MOUSE MODEL OF ALZHEIMER'S DISEASE.

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Background: Perivascular macrophages (PVMs) are increasingly implicated in Aβ clearance and vascular inflammation (1,2). This study aims to explore the role of PVMs in the pathological process of Alzheimer's disease (AD) by characterizing their distribution, impact on blood-brain barrier (BBB) integrity, and response to Lecanemab treatment. **Methods:** PVMs phagocytose tracers and localize to perivascular spaces. Their distribution and renewal in wild-type (WT) and APP/PS1 mice were assessed across different age groups via intracisternal injection of fluorescent tracers into the cerebellomedullary cistern. To investigate their functional contribution, clodronate liposomes were administered to deplete PVMs in the brains. Cognitive performance was assessed using the eight-arm radial maze test (RAM), while BBB permeability was evaluated based on Evans blue extravasation. The expression of tight junction proteins and the extent of Aβ plaque deposition in brain tissues were analyzed through immunofluorescence staining, western blotting, and ELISA. Additionally, to explore the specific mechanism by which PVMs mediate the therapeutic effects of Lecanemab, the antibody was injected via tail vein to APP/PS1 mice, followed by systematic evaluation of blood-brain barrier integrity and cognitive function. Following PVMs depletion, APP/PS1 mice demonstrated significant impairments in short-term memory ($P = 0.02$), long-term memory ($P = 0.004$), as well as a reduction in total arm entries ($P = 0.005$), collectively indicating pronounced cognitive decline. In contrast, the same depletion procedure did not induce significant cognitive deficits in WT group. PVM removal impair blood-brain barrier integrity, as evidenced by increased Evans blue extravasation ($P = 0.03$) and reduced expression of tight junction proteins (ZO-1, Claudin-5, and Occludin; $P = 0.03$ for all). PVM depletion resulted in exacerbated Aβ pathology, characterized by a significant increase in both the average fluorescence intensity of Aβ plaques ($P = 0.02$) and the overall Aβ content ($P = 0.01$). **Results:** Following PVMs depletion, APP/PS1 mice demonstrated significant impairments in short-term memory ($P = 0.02$), long-term memory ($P = 0.004$), as well as a reduction in total arm entries ($P = 0.005$), collectively indicating pronounced cognitive decline. In contrast, the same depletion procedure did not induce significant cognitive deficits in WT group. PVMs removal impair blood-brain barrier integrity, as evidenced by increased Evans blue extravasation ($P = 0.03$) and reduced expression of tight junction proteins (ZO-1, Claudin-5, and Occludin; $P = 0.03$ for all). PVMs depletion resulted in exacerbated Aβ pathology, characterized by a significant increase in both the average fluorescence intensity of Aβ plaques ($P = 0.02$) and the overall Aβ content ($P = 0.01$). Treatment with Lecanemab alleviated cognitive impairment and increased the abundance of PVMs in APP/PS1 mice compared to untreated APP/PS1 controls ($P < 0.05$). **Conclusions:** In AD, PVMs correlates with improved cognitive performance. This correlation may be mediated by the capacity of PVMs to preserve BBB integrity through regulatory effects on tight junction protein expression and amelioration of Aβ pathology. Lecanemab may promote the recruitment and activation of PVMs, which conferring neuroprotective benefits and presenting a potential novel therapeutic avenue for AD.

Keywords: Perivascular macrophages, Alzheimer's disease, blood-brain barrier, lecanemab.

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Key takeaway message: PVMs correlates with improved cognitive performance in AD. Lecanemab may promote the recruitment and activation of PVMs, which conferring neuroprotective benefits and presenting a potential novel therapeutic avenue for AD.

P268- OPTIMIZED DELIVERY OF ANTI-AMYLOID THERAPEUTICS USING BRAIN SHUTTLES AGAINST NOVEL BLOOD-BRAIN-BARRIER RECEPTORS.

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Background: Brain shuttling technologies are poised to transform treatments for neurological disease. However, while current state-of-the-art shuttling strategies improve CNS bioavailability, they also introduce features that have unintended effects that can increase adverse events, reduce tolerability, and limit dosing. For example, while shuttles targeting the transferrin receptor (TfR1) augment anti-amyloid beta (anti-Aβ) antibodies in Alzheimer's disease therapy, the expression of TfR1 on healthy cells can present safety concerns, most significantly hematologic tolerability risks. Furthermore, the broad expression of TfR1 on healthy tissues may undesirably quicken peripheral clearance due to target-mediated drug disposition, leading to suboptimal efficacy. Shuttles directed toward alternative receptors («portals») on the blood-brain-barrier (BBB) offer the opportunity to advance beyond the safety and delivery limitations of first-generation TfR1-targeting shuttles, potentially enabling superior anti-Aβ therapeutics. **Methods:** Here, we present a high-throughput in vivo screening approach utilizing Manifold's mCodeTM technology to discover novel brain shuttles and target portals while assessing the efficacy of these shuttles when paired with a clinically validated anti-Aβ antibody. Through mCodesTM, we assessed the CNS uptake of more than 1000 nanobody shuttle candidates targeting multiple established and emerging BBB portals in pooled reactions of up to 100-plex complexity in murine models and up to 37-plex complexity in non-human primates (NHP). Emerging portals were selected based on criteria including BBB gene expression strength and specificity, with preference given to portals demonstrating enrichment

on brain endothelial cells relative to peripheral tissues. Leading shuttle candidates underwent additional validation examining brain and plasma pharmacokinetics, along with functional assessment when fused to anti-Aβ constructs. **Results:** Our methodology identified novel portals, shuttles, and shuttle-anti-Aβ fusion constructs with varied molecular characteristics. Through high-throughput in vivo screening of dozens of binders per BBB target, we successfully confirmed the shuttling capacity of emerging portals while concurrently identifying promising shuttle candidates against these targets. Quantitative multiplexed screening in NHP enabled accelerated shuttle and portal discovery in a translationally relevant large model organism. Among the portals studied, we highlight results with novel portal PX1, which exhibits highly specific endothelial cell expression, unlike the broad tissue expression profile of TfR1. In mice, PX1-shuttled anti-Aβ antibodies showed significantly improved anti-Aβ antibody delivery to the brain compared to non-shuttled controls, while ameliorating the reticulocyte depletion and acute clinical signs observed with TfR1-shuttled anti-Aβ antibodies. **Conclusions:** Collectively, our findings substantially broaden the repertoire of characterized shuttles and portals for transporting therapeutic cargo across the BBB, establish the potential of these molecules for developing shuttled anti-Aβ treatments, and underscore how multiplexed in vivo screening during early drug discovery phases can yield superior biologic designs. In particular, the discovery of PX1-directed anti-Aβ antibodies decouples the shuttling phenotype from associated tolerability risks preclinically, motivating the further development of a potentially best-in-class next-generation anti-Aβ therapeutic.

Keywords: Shuttle, TfR1, amyloid beta, blood-brain barrier.

Key takeaway message: Manifold's multiplexed in vivo screening approach has identified novel brain shuttles that enhance brain uptake of antibodies while avoiding the safety liabilities of TfR1. This technology enables a potentially best-in-class next-generation shuttled anti-amyloid beta antibody.

P269- TARGETING OF Aβ TOXIC OLIGOMERS VIA A DESIGNED PEPTIDE REDUCES PLAQUE FORMATION IN AN AD MOUSE MODEL.

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Background: Low molecular weight soluble amyloid β peptide (Aβ, 42 amino acids) oligomers have been implicated as the dominant toxic form of Aβ correlating with cognitive decline. Further examination of these toxic oligomers has demonstrated that they adopt a nonstandard secondary structure: α-sheet. We have designed a novel Soluble Oligomer Binding (SOBIN) peptide that selectively targets the α-sheet structure of toxic oligomers. **Methods:** We determined the binding affinity of our SOBIN-01 peptide to different forms of Aβ: monomeric random coil, α-sheet, and β-sheet using biolayer interferometry. We then examined whether SOBIN-01 enhances uptake of fluorescently labeled α-sheet Aβ toxic oligomers in vitro in cultured microglia and macrophage. Finally, we examined in vivo efficacy of SOBIN-01 on short-term memory in the Morris water maze and Aβ plaque accumulation by treating 3-month-old Tg2576 AD mice for 12 months. **Results:** SOBIN-01 was found to bind tightly and preferentially to α-sheet oligomers (KD: 3.4 nM) over both random coil monomers and β-sheet protofibrils (KD: 19200 nM and 92600 nM, respectively). SOBIN-01 enhanced phagocytosis of fluorescently labeled α-sheet Aβ toxic oligomers in a dose-dependent manner in both microglia and macrophages. SOBIN-01 treatment of Tg2576 AD mice improved quadrant discrimination in the Morris water maze assay and reduced plaque levels in the brain. **Conclusions:** Overall, SOBIN-01 specifically targets the α-sheet conformation of Aβ toxic oligomers and leads to neutralization of toxicity and enhanced clearance via microglia and macrophage phagocytosis. The selective targeting and tight binding of SOBIN-01 to the toxic oligomers resulted in improved memory and cognition as well as a inhibition of plaque formation. Altogether, these studies demonstrate that SOBIN-01 targets and stimulates the clearance of Aβ toxic oligomers.

Key takeaway message: SOBIN-01 is a designed, novel therapeutic peptide that selectively binds low-molecular weight toxic Aβ α-sheet oligomers, increasing Aβ oligomer phagocytosis and improving disease outcomes in an AD mouse model.

P270- A TREATMENT MANAGEMENT PLATFORM TO ENABLE SAFE, SCALABLE DEPLOYMENT OF DISEASE-MODIFYING THERAPIES IN ALZHEIMER'S DISEASE.

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Background: The emergence of anti-amyloid disease-modifying therapies (DMTs) has redefined treatment for early Alzheimer's disease (AD), yet access remains limited by system-level constraints (1,2). While considerable attention has focused on diagnostic workflows and infusion capacity, a more fundamental bottleneck may lie in physician capacity and insufficient infrastructure at treatment centers (3). Only a limited number of specialists are currently trained to evaluate, initiate, and monitor patients on DMTs, and the clinical complexity of these therapies, particularly related to ARIA (amyloid-related imaging abnormalities) surveillance, makes scaling difficult, preventing DMT access (1,2). Physicians must interpret serial MRIs, assess evolving risk profiles, and coordinate multidisciplinary decisions, limiting the number of patients they can potentially safely manage. Real-world experience from specialized centers suggests that physician capacity begins to plateau at about 16 patients per physician (234 patients/14 physicians) (4). In settings where DMTs have recently been initiated, or solo practices, this number may be even lower (e.g. <10 patients per physician). These constraints imply that even with robust infrastructure, the ceiling of DMT delivery may be dictated by clinician bandwidth rather than physical resources alone. To address this challenge, we propose to evaluate a recently-introduced treatment management platform

(Foresight™ by Perceiv Research Inc.) designed to streamline safety monitoring and workflow integration for DMTs. The platform incorporates safety monitoring (ARIA and clinical symptoms), protocol initiation and coordination (MRI and infusion), structured data capture, eligibility screening module, clinician-facing decision tools, and real-time alerts. Ultimately, the goal is to support the seamless sharing of information across the circle of care.This abstract outlines a prospective, multi-center, proof-of-concept study to evaluate the platform's real-world implementation and impact on physician treatment capacity. **Methods:** The platform will collect and organize structured data including cognitive and functional assessments, APOE genotype, amyloid/tau biomarker measures, MRI findings and scheduling, infusion records and scheduling, and adverse events (clinical and radiographic). Assembling these data will enable automated real-time monitoring of key safety timelines (e.g., baseline and follow-up MRIs) and trigger escalation alerts if recommended surveillance intervals or decision windows are missed. Physicians will be able to document adverse effects and treatment decisions (e.g. pause, resume, or discontinue therapy). The system will also log the frequency, type, and resolution time of safety-related interruptions such as ARIA or infusion-related reactions. We plan to deploy the platform across 10 memory clinics in North America, Europe, and South America, representing both academic and community-based institutions with varying access to imaging, infusion, and staffing resources. At each site, the platform will be integrated into existing clinical workflows and used to manage patients assessed for or treated with an approved anti-amyloid DMT over a 12-month period. Consecutive patients with early symptomatic AD (mild cognitive impairment [MCI] or mild dementia due to AD) deemed eligible for DMTs according to local or international criteria will be enrolled. The primary endpoint is normalized physician treatment capacity, defined as the number of patients treated with DMTs per full-time equivalent (FTE) physician dedicated to cognitive neurology or memory clinic practice. Secondary and exploratory measures will include workflow interruption frequency, defined as the number of clinically relevant disruptions in the treatment pathway (e.g., missed MRI intervals, delayed infusions, or ARIA-related safety pauses), and protocol deviation resolution rates, measured as the proportion of deviations identified and resolved within appropriate clinical timeframes. These operational metrics will be automatically logged by the platform to assess real-time performance and process safety. Each site will perform a pre-post comparison using historical data preceding platform implementation. A parallel qualitative evaluation will assess user experience, workflow adaptations, and barriers to adoption, with standardized clinician surveys administered at 3, 6, and 12 months. All data will be de-identified and analyzed at both the site and aggregate levels. Success will be defined as a measurable increase in the number of patients managed on DMTs per physician relative to each center's baseline, reflecting improved capacity without compromising safety (5). **Results:** We anticipate that implementation of the platform will increase clinician capacity to manage patients on DMTs, reduce coordination delays, improve adherence to ARIA surveillance protocols, and enable more timely escalation of safety events, ultimately expanding patient access to DMTs. **Conclusions:** This study aims to generate real-world implementation evidence for a treatment management platform to support the safe and scalable use of DMTs in AD. Given that current DMT capacity is typically limited to <10 patients per physician, structured care tools such as the one proposed here may be essential for scaling treatment delivery without compromising safety or clinical oversight. By addressing workflow fragmentation and reducing physician burden, the proposed platform may play a critical role in extending access to DMTs in both specialized and community-based care models and facilitating the entry of newly approved DMTs in the future.

Keywords: Real-world implementation, safety, workflow, treatment management, anti-amyloid therapy, digital platform.

Disclosures: ANC, and CD are affiliated to Perceiv Research Inc. The remaining authors declare no conflicts of interest.

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Key takeaway message: A treatment management platform can address physician capacity constraints and streamline complex workflows, unlocking safe and scalable delivery of Alzheimer's DMTs across diverse care settings while safeguarding clinical oversight and patient safety.

P271- THE BRAIN PERMEABLE IMMUNOPROTEASOME-SELECTIVE INHIBITOR AR-01 IS A PROMISING DRUG CANDIDATE FOR ALZHEIMER'S DISEASE.

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Background: We previously reported that inhibition of the immunoproteasome (iP), which is shown to be upregulated in reactive glia surrounding amyloid-β (Aβ) plaques in the brain of patients with Alzheimer's disease (AD), ameliorates cognitive deficit in the AD mouse model (Tg2576) via suppressing microglia-mediated inflammation independently of Aβ buildup. Among the iP inhibitors previously prepared in-house, AR-01, a macrocyclic peptide epoxyketone, displayed significantly improved metabolic stability and permeability compared to its linear counterparts. **Methods:** Here, we evaluated the pharmacokinetic properties and biodistribution of AR-01 in healthy BALB/c mice. The dose-dependent brain permeability of AR-01 was examined using LC/MSMS analysis, proteasome activity assay, and immunoblotting band shift caused by the formation of an irreversible iP-AR-01 complex. Using the AD mouse model (8-month-old 5xFAD mice), we investigated the iP inhibition in the brain after multiple i.p. doses (20 mg/kg/twice a week for 3 weeks) of AR-01. In addition, we assessed the anti-inflammatory effect of AR-01 using ELISA analysis and the behavior change by trace fear conditioning study. **Results:** The brain iP immunoblotting band shift assay showed that AR-01 dose-dependently modifies the iP in the mouse brain following a single intravenous administration (5 mg/kg, 28%; 10 mg/kg, 40%; 20 mg/kg, 69%; 40 mg/kg, 95%; 80 mg/kg, 100% iP band shift). AR-01 also exhibited a dose-dependent inhibition in the iP activity assay (5 mg/kg,13%; 10 mg/kg, 15%; 20 mg/kg, 29%; 40 mg/kg, 45%; 80 mg/kg, 63%, 100 mg/kg, 65%). However, the iP activity inhibition ratio was ~3-fold lower than the corresponding target engagement (iP band shift) ratio, indicating that the fluorogenic iP substrate used in the study may not be specific to the iP in mouse brain tissue lysates. The brain-to-plasma partition coefficient (Kp,brain) value of AR-01 was calculated as 0.017, detecting the area under the concentration-time curve in plasma and brain homogenates. In 5xFAD mice, multiple treatments of AR-01 inhibited the brain iP and decreased inflammatory cytokine production (i.e., interleukin-1α (IL-1α), IL-6, and TNF-α) in the brain as an Aβ independent manner, leading to improved cognitive function. **Conclusions:** The results suggest that AR-01 holds promising potential as an AD drug.

Key takeaway message: AR-01, an irreversible immunoproteasome

inhibitor, is a patient-friendly drug candidate with a distinct mechanism of action from current AD drugs that warrants clinical investigation.

P272- VALILTRAMIPROSATE/ALZ-801 INHIBITS AMYLOID OLIGOMER FORMATION: QUANTITATIVE SYSTEMS PHARMACOLOGY ANALYSIS OF Aβ AGGREGATION DYNAMICS AND IMPACT ON AD PROGRESSION.

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Background: Valiltramiprosate is an oral, small-molecule inhibitor of β-amyloid (Aβ) oligomer formation in development as a disease-modifying AD therapy. This investigation provides a quantitative systems pharmacology (QSP) analysis of the effects of valiltramiprosate on Aβ aggregation dynamics and natural trajectory of AD progression. **Methods:** A mechanistic QSP model of Aβ aggregation in AD (Geerts et al., 2023) was expanded to implement the different APOE4 genotypes. Parameter modifications for Aβ synthesis and microglia-mediated clearance as a function of APOE genotype were calibrated from observational and interventional clinical data including the lecanemab CLARITY and donanemab TRAILBLAZER studies. Valiltramiprosate analysis was based on its primary anti-amyloid aggregation molecular mechanism of action (MOA) and the secondary effect as an APOE4 structural corrector which affects Aβ clearance and synthesis. The projected steady state brain drug exposure following valiltramiprosate 265 mg BID was used. **Results:** In the QSP trajectory model of plasma Aβ42/Aβ40 ratio, there are pronounced APOE genotype dependent differences in disease progression indicative of acceleration, with APOE4/4 >> APOE3/4 > APOE3/3. APOE4/4 genotype exhibits a greater degree of disease acceleration in Aβ pathology compared to the other genotypes, including an earlier onset (~4-year leftward shift), accelerated decline, and an earlier manifestation of pathologies prior to clinical decline. Valiltramiprosate treatment results in an increase in plasma Aβ42/Aβ40 ratio and CSF free Aβ42, a substantial decrease in soluble oligomer and protofibrils which are likely drivers of AD neuropathology progression, with a minimal change in plaques deposition (SUVR). These valiltramiprosate effects are related to exposure, age, APOE genotype and disease stage, and differentiated from the effect of anti-amyloid antibodies lecanemab and donanemab. Over chronic use, valiltramiprosate is predicted to redistribute and maintain the different amyloid species towards the monomer form of Aβ, a hallmark of a healthier brain. **Conclusions:** The QSP results support clinical benefits of valiltramiprosate in modifying the amyloid cascade by substantive reduction of formation of neurotoxic oligomers and protofibrils, thereby reducing the subsequent neurodegeneration and clinical decline, and slowing AD progression. The data also supports the potential greatest clinical benefit of oral valiltramiprosate when used early in the disease pathogenesis, including prevention of disease progression in presymptomatic AD.

Key takeaway message: The QSP results support clinical benefits of valiltramiprosate in modifying the amyloid cascade by substantive reduction of formation of neurotoxic oligomers and protofibrils, thereby reducing the subsequent neurodegeneration and clinical decline, and slowing AD progression.

P273- PROOF-OF-CONCEPT PHASE 2A CLINICAL TRIAL OF A NOVEL SEPTIN MODULATOR REVEALS EARLY EEG PHARMACODYNAMIC EFFECTS IN ALZHEIMER'S DISEASE.

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Background: Alzheimer's disease (AD) is characterized by amyloid-β (Aβ) plaques and neurofibrillary tangles of hyperphosphorylated tau (p-tau). Dysregulated calcium (Ca^{2+}) signaling, driven by tau-mediated disruption of septin-regulated Ca^{2+} channels, impairs synaptic function, accelerates molecular pathology, and drives neuronal dysfunction (1). $Ca^{2}+$ dyshomeostasis also interacts with dopaminergic signaling, where dopamine reductions further exacerbate pathology and contribute to cognitive and non-cognitive deficits, manifested at the network level as altered cortical excitability and neural oscillations (2,3). In AD, reduction in the power of the posterior dominant rhythm is observed, correlating with cognitive impairment, and dopamine depletion further shifts this rhythm to slower frequencies, highlighting the interdependent roles of $Ca^{2}+$ and dopamine dysregulation in AD pathophysiology (4-6). Pharmacological restoration of septin filament integrity has emerged as a promising disease-modifying strategy, with the potential to normalize Ca^{2+} homeostasis, protect synaptic function, reduce molecular pathology, and restore dopaminergic signaling. REM127, a novel septin modulator, has demonstrated preclinical efficacy in restoring Ca^{2+} homeostasis, reducing molecular pathology, and enhancing synaptic function (7). Building on these findings, a phase 2a clinical trial in mild-to-moderate AD evaluated electroencephalography (EEG) spectral features as pharmacodynamic biomarkers of treatment response. **Methods:** In this phase 2a, randomized, double-blind, placebo-controlled trial, participants with mild-to-moderate AD (age 50-85 years, MMSE 12-24, CSF Aβ42 < 1000 pg/mL, CSF p-tau181 > 19 pg/mL) received REM127 at 88 mg/day (n = 5), 350 mg/day (n = 3), or 1400 mg/day (n = 2), or placebo (n = 4), during a 28-day treatment period. The study was terminated early due to off-target, drug-induced liver injury. EEG recordings were obtained using a Sienna Ultimate Amplifier at screening day, on day 1 (baseline), day 15 and day 29 during the treatment phase, including eyes-closed vigilance-controlled (ECV), eyes-closed resting (ECR), and eyes-open resting (EOR) EEG. EEG data were preprocessed to remove line noise using ZapLine (8), band-pass filtered (0.5-40Hz) with a notch filter at 50 Hz, re-referenced to the average, and cleaned of ocular artifacts via independent component analysis. Power spectral density (PSD) was computed for each condition using Welch's method. For occipital electrodes, the PSD was decomposed into aperiodic and periodic components (9). We examined longitudinal changes in periodic features (peak frequency and power at peak frequency characterizing the posterior dominant rhythm) and aperiodic features (offset and exponent reflecting excitability and inhibition balance in the brain), comparing the treatment group and the placebo group. Correlation matrices were generated for peak frequency power, aperiodic features, cognitive scores (MMSE, ADAS-Cog), CSF biomarkers (Aβ, total tau, p-tau181), and neurotransmitters (dopamine and GABA) to evaluate associations between neural activity, biochemical changes, and cognitive performance. **Results:** Subjects receiving REM127 exhibited an increase in power at the peak frequency at ECV on day 15 relative to baseline compared to the placebo group. By day 29, this power declined in the treatment group relative to day 15, whereas the placebo group showed an increase on day 29 relative to baseline, mainly driven by a single subject. Increased peak power on day 15 relative to baseline was mostly observed in the 2 participants who received the 1400 mg dose. This effect was not observed on day 29. The peak frequency at ECV decreased over time in the placebo group, whereas it remained stable in the treatment group on day 15 and showed a reduction only by day 29. The aperiodic exponent decreased in the treatment group on day 15 and on day 29 (ECV and ECR) compared to baseline, while it increased in the placebo group on day 29. For the aperiodic offset (ECR), the treatment group showed a slight decrease on day 15 compared to baseline, returning toward baseline by day 29, whereas the placebo group demonstrated increases on both day 15 and day 29. In AD, a disruption in the excitation-inhibition balance manifests as increased excitation and reduced inhibitory control. Reduction in the aperiodic offset and exponent in the treatment group suggests a restoration of this balance, potentially leading to healthier circuit function, which may impact attention and working memory. No changes were observed in the spectral features during EOR. These results indicate that treatment-specific effects were most evident on day 15 but no

longer clearly visible on day 29, possibly because systemic toxicity emerging after day 15 disrupted cortical dynamics and masked treatment-related oscillatory changes. No significant correlations were observed between the examined EEG features and the other measures (including CSF biomarkers, neurotransmitter levels, or cognitive scores). **Conclusions:** REM127 treatment induced rapid increases in posterior rhythm's power within 15 days, suggesting enhanced cortical excitability and potential symptomatic benefits in AD subjects. Although correlations between EEG features and cognitive or molecular measures were not observed, likely because of the small sample size, EEG spectral features demonstrated sensitivity to early treatment-related effects. Monitoring both periodic and aperiodic features provides complementary insights into cortical excitability and inhibition, and enables evaluation of rhythmic peaks without relying on predefined frequency bands. These findings provide proof-of-concept that EEG spectral features are sensitive, non-invasive biomarkers of early pharmacodynamic activity in AD, supporting the potential of septin-targeted therapies and the use of EEG to monitor treatment response in early-phase clinical trials.

Keywords: Alzheimer's disease, calcium dyshomeostasis, phase 2a clinical trial, EEG, aperiodic and periodic spectral analysis, dopaminergic signaling.

Disclosures: PM is co-founder and shareholder of Clouds of Care NV. VZ, JC, EV, GV, NC are employers of Clouds of Care NV. GG and MN are employers of Remynd NV.

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Key takeaway message: EEG spectral features serve as sensitive and non-invasive biomarkers for detecting early pharmacodynamic effects in Alzheimer's disease, highlighting their value in evaluating septin-targeted therapies and in monitoring treatment response during early-phase clinical trials.

P274- EFFEROCYTOSIS-DRIVEN REDUCTION OF NEUROINFLAMMATION BY NOVEL GAS6 FUSION PROTEIN (GAIA) IN ANTI-Aβ IMMUNOTHERAPIES.

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Background: Anti-amyloid-beta (Aβ) immunotherapy has emerged as a promising approach for treating Alzheimer's disease (AD). Recently, approved anti-Aβ antibodies, such as Lecanemab and Donanemab, have demonstrated substantial reductions in Aβ burden and slowed cognitive decline. However, these therapies are associated with adverse events like amyloid-related imaging abnormalities (ARIA), posing a significant challenge for clinical application. The GAIA platform leverages TAM receptors—Tyro3, Axl and MerTK—to facilitate efferocytosis-mediated Aβ clearance without triggering inflammatory responses, potentially overcoming the limitations of current anti-Aβ immunotherapies. Here, we show that GAIA-Aβ demonstrates a pharmacokinetic (PK) profile and Aβ clearance efficacy comparable to those of conventional anti-Aβ immunotherapies, with enhanced ability to mitigate neuroinflammation and neurotoxicity. **Methods:** We developed GAIA-Aβ chimeric proteins featuring two functional domains: a GAS6 domain for TAM receptor binding and an Aβ-targeting moiety. We confirmed specific binding to oligomeric Aβ (oAβ) and TAM receptors via ELISA. TAM receptor-driven phagocytosis and consequent oAβ clearance were evaluated using HMC3, a human microglial cell line. Additionally, anti-inflammatory responses were assessed in induced pluripotent stem cell (iPSC)-derived monocytes. Pharmacokinetic properties of GAIA-Aβ were analyzed to determine serum exposure and brain-to-serum ratio. To evaluate the in vivo efficacy, GAIA-Aβ was administered once weekly (QW) via intravenous (IV) or intraperitoneal (IP) routes to 4- or 7-month-old 5xFAD mice, respectively, for 8 weeks. Brain tissues were analyzed for Aβ plaque burden, glial phagocytic activity, and inflammatory gene expression. **Results:** GAIA-Aβ exhibited specific binding to oAβ and activated TAM receptors in a dose-dependent manner. Phagocytosis assays demonstrated effective clearance of oAβ while reducing inflammatory cytokines, supporting a non-inflammatory efferocytosis-based mechanism. Pharmacokinetic analysis revealed that GAIA-Aβ possesses properties comparable to those of conventional monoclonal antibodies. In 5xFAD mice, GAIA-Aβ treatment led to significant reductions in Aβ plaques and enhanced glial-mediated Aβ clearance, particularly via astrocyte engagement. Furthermore, GAIA-Aβ increased anti-inflammatory gene expression and reversed synaptic and neuronal damages in the brains of 5xFAD mice. **Conclusions:** GAIA-Aβ demonstrates significant efficacy in reducing Aβ plaque burden while simultaneously minimizing neuroinflammatory responses, presenting a potentially safer alternative to existing anti-Aβ monoclonal antibodies. These findings highlight the potential of GAIA platform as a promising therapeutic approach for AD, addressing key limitations of current anti-Aβ immunotherapies. Beyond Aβ, the GAIA platform exhibits broad applicability for targeting other pathogenic proteins such as tau and α-synuclein. Furthermore, its adaptability allows for potential application in systemic amyloidosis and other inflammatory diseases, leveraging its dual mechanism of antigen clearance and TAM receptor-mediated anti-inflammatory responses.

Keywords: Aβ, anti-inflammatory, efferocytosis, GAS6-mediated anti-inflammatory adaptor.

Disclosures: The authors declared no competing interests.

Key takeaway message: GAIA-Aβ has shown potential as a promising therapeutic candidate for Alzheimer's disease through significant efficacy in reducing Aβ plaque burden while simultaneously minimizing neuroinflammatory responses, presenting a potentially safer alternative to existing anti-Aβ monoclonal antibodies.

TRANSLATIONAL RESEARCH

P275- CLINICAL UTILITY OF PLASMA BIOMARKERS IN ANTI-AMYLOID TREATMENT CLINIC TO EVALUATE TREATMENT RESPONSE AND PREDICT OF SIDE EFFECTS.

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Background: Disease-modifying treatments for Alzheimer's Disease (AD) have been recently introduced in clinical settings, however critical gaps in knowledge limit our ability to predict biological response to treatment and potentially life-threatening side-effects. Current approaches such as MRI and PET are constrained by availability and cost, necessitating alternative strategies such as plasma biomarkers. Plasma

p-tau217 has shown excellent promise in prediction of amyloid positivity via PET and future clinical impairment and was shown to decrease within 12 weeks of donanemab therapy in Phase 3 trial data. However, evaluation of p-tau217 in real-life treatment clinics using lecanemab and donanemab has been limited. Furthermore, there are no clinically available plasma biomarkers that can be used to predict the major side effect of anti-amyloid treatment, amyloid-related imaging abnormalities (ARIA). To address this gap in knowledge in real-world treatment settings, an IRB-approved biobank was established with the founding of the UCSF Alzheimer's Infusion Clinic (AIC) in 2023. All patients approved for anti-amyloid treatment at UCSF are offered the opportunity to participate in this registry. For the first time, we are sharing plasma biomarker data in this cohort from patients receiving lecanemab and donanemab with repeated measurements of p-tau217, neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP). **Methods:** Over 100 patients with a slight female predominance (57%) have agreed to participate and been enrolled in the biobank, all of whom have completed baseline neuropsychological testing. All patients have had plasma biobanking at each infusion for the first three months of treatment (the highest risk period for ARIA), followed by biobanking at subsequent three month intervals, with a subset of patients undergoing biobanking more frequently. Most patients have amyloid PET completed at baseline prior to treatment, with a small subset also having a post-treatment amyloid PET following an 18-month course of lecanemab. P-tau217 values were compiled for individual subjects and analyzed at baseline and 12 week intervals, with ongoing analyses for later timepoints. **Results:** Baseline p-tau217 correlates with degree of amyloid positivity by Centiloid value, with correlation strengthening when excluding patients with decreased renal function ($r = 0.43$). P-tau217 measurements from individual patients demonstrate stability at two and four week intervals throughout treatment with lecanemab and donanemab, respectively. P-tau217 decreases with lecanemab treatment, with changes detectable as soon as 24 weeks (11% decrease) and persisting throughout treatment. Development of ARIA was predicted by ApoE homozygosity. However, there was no significant change in NfL or GFAP at the most proximal timepoint prior to ARIA compared to the preceding measurement or baseline measurement. **Conclusions:** Academic centers can leverage anti-amyloid treatment clinics to establish biobanks to inform collective knowledge of real-world biomarker utility in their patient populations. To our knowledge, these are the first data shared that evaluate repeated measurement of p-tau217 in a real-world treatment clinic with both lecanemab and donanemab, and the first data evaluating longitudinal changes of NfL and GFAP in patients developing ARIA as a side effect of anti-amyloid therapy. These results suggest that p-tau217 may potentially track amyloid clearance in treatment clinics as soon as 24 weeks, although p-tau217 alone may not be sufficient for optimal monitoring of amyloid clearance in real-world populations. Ongoing work is evaluating the performance of different p-tau217 assays with respect to variability in repeated measurements, response to treatment, and amyloid clearance by PET. The lack of change in NfL or GFAP immediately prior to development of ARIA suggests there is no significant neuronal injury or astrocytic activation in ARIA. Identification of novel ARIA biomarkers by proteomic approaches such as nucleic acid linked immune-sandwich assays (NULISA) is ongoing.

Keywords: P-tau217, NfL, GFAP, Alzheimer's Disease, anti-amyloid, lecanemab, donanemab, ARIA, biomarkers.

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Key takeaway message: Academic centers can establish biobanks to study real-world performance of plasma biomarkers. P-tau217 correlates with amyloid PET at baseline and decreases with lecanemab treatment. Neuronal injury and astrocytic activation are unlikely in ARIA.

P276- CROSS-PLATFORM CSF PROTEOMICS REVEALS REPRODUCIBLE BIOMARKERS AND NOVEL MECHANISMS BEYOND AMYLOID AND TAU IN ALZHEIMER'S DISEASE.

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Background: High-throughput proteomics is transforming biomarker discovery in Alzheimer's disease (AD), yet cross-platform comparisons are rare, limiting confidence in reproducibility and biological interpretation. We conducted an evaluation of three proteomic platforms—SomaScan®, Olink®, and data-independent acquisition mass spectrometry (DIA-MS)—in a well-characterized AD clinical trial cohort to identify reproducible CSF protein signatures and uncover novel biology linked to amyloid pathology and disease progression. **Methods:** Baseline CSF samples (n=210; 101 amyloid-positive [A+], 101 amyloid-negative [A−], 8 with missing amyloid status) were obtained from participants with mild cognitive impairment or mild dementia due to AD enrolled in a Phase 3 clinical trial (NCT02956486). Samples were analyzed using three proteomic platforms: SomaScan® 7K Assay (S), Olink Explore HT (O), and DIA-MS with Orbitrap Astral Mass Spectrometer from Thermo Fisher Scientific (D). After platform-specific quality control, 202–205 samples were retained. Proteins with >70% of values below the limit of detection were excluded. Differential expression analyses were performed by amyloid status and disease progression (FDR <0.2, |Cohen's D| >0.8). Amyloid status was determined by PET visual read. Disease progression was defined as an 18-month change in Clinical Dementia Rating–Sum of Boxes (CDR-SB) >1 from baseline, identifying 27 progressors and 21 non-progressors as the subset of the 210 subjects with CSF and longitudinal CDR-SB follow-up data. **Results:** We identified 6,180 (S), 4,106 (D), and 1,081 (O) proteins, with 764 shared across platforms. Among these, 21 were significantly associated with amyloid status (FDR < 0.2, |Cohen's D| > 0.8), and 18 (86%) were reproducibly significant in at least two platforms ($q < 0.2$), highlighting cross-platform consistency. Similarly, 55 shared proteins were associated with disease progression (FDR < 0.2, |Cohen's D| > 0.8); of these, 8 (15%) were reproducibly significant in at least two platforms at $q < 0.2$, and 27 (49%) at $p < 0.05$, indicating moderate consistency. This may reflect the smaller sample size and greater variability in disease

progression analysis. Next, we leveraged the multi-platform approach to broaden biomarker detection for amyloid status and disease progression. Differential analysis across SomaScan, DIA-MS, and Olink revealed 72, 36, and 10 proteins respectively, yielding a total of 107 unique proteins associated with amyloid pathology. These included known markers (e.g., SMOC1, 14-3-3 family) and novel candidates. Notably, 14-3-3 isoforms such as YWHAG, YWHAZ, and YWHAB were detected by SomaScan and DIA-MS but are not included in the Olink Explore HT panel, highlighting platform-specific differences that may influence biomarker detection. For disease progression, 97 (DIA-MS), 52 (Olink), and 12 (SomaScan) proteins were identified, totaling 155 unique markers reflecting biological processes that contribute to neurodegeneration and cognitive decline. Taken together, these findings revealed diverse mechanisms beyond amyloid and tau, including: • Synaptic signaling and scaffolding (e.g., YWHAG, NECAB2), • Tau regulation and phosphorylation (e.g., MAPT, PIN1, PPP3R1), • Immune activation and complement signaling (e.g., HAVCR2, CD163, VSIG4, MIF), • Oxidative stress and lipid metabolism (e.g., PRDX3, FABP3/5, SOD1), • Axon guidance and vascular integrity (e.g., SLIT2, CLEC11A, COMP, ESM1), • Blood-brain barrier and metabolic regulation (e.g., DDAH1, PLPBP, IMPA1).**Conclusions:** This is the first study to integrate SomaScan, Olink, and DIA-MS in an AD clinical trial cohort, profiling ~8,000 unique CSF proteins. We demonstrate cross-platform reproducibility, with significant protein changes confirmed in at least two technologies, and uncover novel biology. Our findings support the development of multiplexed biomarker panels that capture synaptic vulnerability, neuroinflammation, oxidative stress, and vascular dysfunction—mechanisms that may precede amyloid pathology. These insights can inform the design of targeted biomarker panels for stratification, monitoring, and therapeutic response in future AD trials.

Keywords: Cerebrospinal fluid proteomics, amyloid pathology, neuroinflammation, oxidative stress.

Disclosures: All authors are employees of Eisai.

Key takeaway message: This multi-platform CSF proteomics study in an AD clinical trial cohort identified reproducible biomarkers and novel mechanisms beyond amyloid and tau, supporting multiplexed panels for precision diagnostics and monitoring of disease progression and treatment response.

P277- VALILTRAMIPROSATE PREVENTS HIPPOCAMPAL ATROPHY AND CLINICAL DECLINE IN AN EARLY SYMPTOMATIC APOE4/4 AD SUBPOPULATION IN PHASE 3 STUDY VIA POTENTIAL NEUROGENESIS/NEUROPLASTICITY ACTION.

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Background: Progressive brain atrophy, amyloid plaques and neurofibrillary tangles are hallmarks of Alzheimer's disease (AD). The approved anti-amyloid antibodies therapies, while showing cognitive improvement, do not reduce brain atrophy, but may even worsen it. Valiltramiprosate/ALZ-801 is an oral, small molecule inhibitor of amyloid oligomer formation in development as a disease-modifying treatment for AD. While the Phase 3 APOLLOE4 trial did not meet the primary endpoint of cognitive slowing in the overall Early AD population, valiltramiprosate produced a meaningful improvement (ΔADAS-Cog13 = -2.144, p=0.041) and function (ΔCDR-SB = -0.646, p=0.053) in the prespecified Mild Cognitive Impairment (MCI) subjects. Furthermore, valiltramiprosate consistently reduced atrophy in hippocampus (-26%, p=0.0042 in MCI) and other brain regions, indicating substantive neuroprotective benefits. We found that a subpopulation of early symptomatic super responders in the Phase 3 study showed complete prevention of hippocampal atrophy and improved cognition over 78 weeks, suggesting neurogenesis/neuroplasticity effects. **Methods:** The multicenter, randomized, double-blind, placebo-controlled APOLLOE4 Phase 3 trial was conducted in 325 APOE4/4 homozygotes with MCI or Mild AD (MMSE ≥22 and CDR-Global 0.5-1.0). Valiltramiprosate 265 mg or placebo was administered twice daily for 78 weeks. The primary outcome was ADAS-Cog13, and hippocampal volume (HV) by volumetric MRI (vMRI) was the main imaging endpoint. Super responders were defined as an observed increase of HV at 78 weeks over baseline. The analysis was based on subjects with available HV data at 78 weeks, and the boundary shift integral (BSI) vMRI data were used. Longitudinal changes of HV and cognitive/functional measures (ADAS-Cog13, CDR-SB) and clinical characteristics were analyzed in this subgroup. **Results:** Early symptomatic completers with screening MMSE ≥26 included 10/64 and 2/67 super responders in the active and placebo arms, respectively. This represents 16% active and 3% placebo early symptomatic subjects. One additional active super responder had a screening MMSE of 24. Of the 11 active super responders (6 males and 5 females), there was a net increase of 66.0 ± 20.4 mm3 HV at 78 weeks vs. baseline. Also, the active super responders exhibited a younger age, higher screening MMSE, and less baseline hippocampal atrophy as compared to the overall Early AD population. The full prevention of atrophy by valiltramiprosate treatment was accompanied by stabilized ADAS-Cog13 and better than baseline CDR-SB over the 78 weeks. This effect was not related to pharmacokinetic exposures or concomitant use of acetylcholinesterase inhibitors. **Conclusions:** Valiltramiprosate demonstrates potential for preventing hippocampal atrophy and stabilization of cognitive and functional decline in early symptomatic APOE4/4 AD. Valiltrmiprosate selectively targets the most toxic oligomeric amyloid species but without affecting amyloid plaques. In contrast to the brain "pseudo-atrophy" effect of the approved anti-amyloid antibody therapies, valiltramiprosate represents a desirable opportunity for the treatment of early-stage AD that not only slows cognitive decline but also improves brain tissue reserve, a fundamental pathology of AD. Furthermore, we show that in a subpopulation of early symptomatic APOE4/4 AD subjects, valiltramiprosate may have potential to promote neurogenesis/neuroplasticity, thereby restoring HV (i.e., HV increase above baseline at Week 78). We postulate that this effect may be due, in part, to a secondary molecular mechanism of action of valiltramiprosate as an APOE4 structure corrector, which converts the abnormal APOE4 conformation to the more physiological APOE3 like, thus reversing the detrimental effect of APOE4 on neurogenesis. Taken together, these results support the potential disease stabilization benefit of oral valiltramiprosate as a prevention therapy in presymptomatic AD.

Keywords: Valiltramiprosate, ALZ-801, Alzheimer's disease, amyloid oligomers, APOE4, APOE4 structure corrector, hippocampal volume, neurogenesis, volumetric MRI.

Clinical Trial Registry: NCT 06304883 and NCT04693520. https://clinicaltrials.gov.

Disclosures: J Yu, JF Schaefer, S Abushakra, A Power, M Tolar and JA Hey are employees of Alzheon, Inc. and hold stock or stock options of Alzheon, Inc. H Geerts and SM Short are employees of Certara.

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Key takeaway message: Prevention of atrophy by valiltramiprosate in early AD accompanied by stabilized ADAS-Cog13 and CDR-SB over 78 weeks. Results support potential disease stabilization benefit of oral valiltramiprosate as prevention therapy in early and/or presymptomatic AD.

P278- A SIMULATION OF LONG-TERM LECANEMAB TREATMENT EFFECT ON THE ALZHEIMER'S DISEASE PROGRESSION IN APOE4 NON-CARRIERS AND HETEROZYGOUS CARRIERS.

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Background: Alzheimer's disease (AD) is a chronic neurodegenerative condition characterized by a progressive decline in cognitive function and is the most prevalent form of dementia globally. This disease imposes a growing burden on patients, caregivers, and healthcare systems due to its long course and the increasing size of the aging population. Lecanemab received traditional approval from the U.S. Food and Drug Administration (FDA) in July 2023 as the first anti-amyloid antibody for the treatment of Alzheimer's disease. In other countries including the European Union and the United Kingdom, lecanemab is approved for the treatment of adults with mild cognitive impairment and mild dementia due to Alzheimer's disease (early Alzheimer's disease) who have one (heterozygous) or no copy (noncarriers) of apolipoprotein E ε 4 (ApoE4) and have amyloid pathology confirmed. **Methods:** A disease progression model was fit to CDR-SB data from the Alzheimer Disease Neuroimaging Initiative (ADNI) dataset. A cohort within the ADNI dataset was selected to match the patients in the phase III pivotal trial for lecanemab, Clarity AD, by applying the same key inclusion criteria. To develop a natural disease progression curve, a nonlinear mixed effects model using an exponential formula was fit to the data with age, sex, race, and ApoE4 status (noncarrier vs heterozygous) as covariates. To derive progression under the lecanemab treatment, a percentage in time saved from disease progression was calculated from results of Clarity AD and was applied to the natural progression. The time savings relative treatment effect takes a forward projection method which estimates the additional time needed for lecanemab to reach the decline for placebo at 18 months (1,2). For the early AD patient population, an additional 6.7 months was estimated for the lecanemab-treated patients to reach the decline in CDR-SB observed for untreated patients at 18 months, corresponding to a 37% time delay in disease progression. For ApoE4 non-carriers and heterozygous carriers, lecanemab treatment was predicted to save additional 9.1 months (51% time delay) in early stage of the AD spectrum compared to those left untreated. Sensitivity analyses were conducted using data from National Alzheimer's Coordinating Center (NACC). **Results:** For patients initiating lecanemab at CDR-SB 3.2 (in MCI due to AD stage; the average baseline CDR-SB score for the Clarity AD patient population), disease progression to mild AD, moderate AD, and severe AD was delayed on average by 0.5 years, 1.7 years, and 2.5 years, respectively, when compared to natural progression without intervention (the ADNI cohort). For the ApoE4 non-carriers and heterozygous carriers, disease progression to mild AD, moderate AD, and severe AD was delayed on average by 0.7 years, 2.2 years, and 3.3 years, respectively, under lecanemab treatment. **Conclusions:** Lecanemab treatment slows AD progression, maintaining patients in earlier, more manageable stages of disease longer up to approximately 3 years.

Keywords: Alzheimer's disease progression, dementia, lecanemab, time-saved, clinical meaningfulness.

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Key takeaway message: The AD disease progression model fitted using ADNI illustrated the onset of severe AD could be delayed by approximately 3 years when the lecanemab treatment is initiated at CDR-SB=3.2 (late MCI due to AD).

P279- NEURO-DYNAMIC QUANTITATIVE SYSTEMS PHARMACOLOGY (QSP) MODEL PREDICTS INCREASING BENEFITS OF CONTINUED LECANEMAB TREATMENT WITH CLARITY AD 48-MONTH DATA.

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Background: Lecanemab is a humanized IgG1 monoclonal antibody that binds with high affinity to amyloid-beta (Aβ) protofibrils. In the 18-month, phase 3 Clarity AD study, lecanemab demonstrated amyloid reduction and slowing of cognitive and functional decline in participants with early Alzheimer's disease (AD). An ongoing open-label extension (OLE) of Clarity AD evaluating lecanemab's long-term safety and efficacy has shown that the effect on CDR-SB continues to increase with ongoing treatment up to 48 months, compared to ADNI-matched placebo data, supporting a durable disease-modifying effect. The neuro-dynamic quantitative systems pharmacology (QSP) model was updated and used to provide mechanistic insight into the long-term benefit of continued lecanemab treatment, leveraging multivariate clinical data and Clarity AD 48-month results. **Methods:** The QSP model incorporated three interlinked modules describing amyloid pathway, tau pathology and cognitive decline, where amyloid triggers tau pathology and which in turn leads to neuronal damage, degeneration, and eventually to cognitive decline. The model was developed using nonlinear mixed-effect modeling and was successfully fitted and validated with a multivariate dataset (N=4056) comprising cognitive scores (CDR-SB, ADAS-Cog14), imaging data (amyloid PET, tau PET), and fluid biomarkers (plasma Aβ42/40 ratio, p-tau181, and p-tau217) from the lecanemab trials - Study 201 and Clarity AD up to 48 months, as well as amyloid PET, ADAS-Cog13 and CDR-SB data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Simulations were conducted to evaluate long-term benefits of lecanemab on cognitive outcome and biomarkers. **Results:** QSP simulations demonstrated that the treatment difference between lecanemab and placebo—across both clinical and biomarker outcomes—continues to increase over 48 months. Following continued lecanemab treatment, the model predicted a slowing of CDR-SB progression by 0.44 points over 18 months compared to placebo, consistent with observed clinical data. It further projected a treatment difference of 1.25 points at 36 months and 1.82 points at 48 months, representing a 2.8- and 4.1-fold greater cognitive benefit, respectively, than at 18 months. Additionally, the model predicted sustained biomarker improvements with continued lecanemab treatment through 48 months, including ongoing reduction of amyloid plaque and toxic protofibrils, and continued increases in plasma Aβ42/40 ratio and CSF Aβ42. **Conclusions:** Updated neuro-dynamic QSP model predicted the lecanemab treatment benefit continues to increase over 48 months

compared with non-treated. The results are consistent with the durable disease-modifying effect and provide further support for continuing lecanemab treatment after plaque removal.

Keywords: Neuro-dynamic modeling, lecanemab, continued treatment.

Disclosures: All authors are employees of Eisai Inc.

Key takeaway message: QSP simulations demonstrated that the lecanemab treatment benefit continues to increase over 48 months compared with non-treated and are consistent with the durable disease-modifying effect providing further support for continuing lecanemab treatment following plaque removal.

P280- ACE-2223, A NOVEL ORAL SMALL MOLECULE FOR TDP-43 PROTEINOPATHIES, TREATS BOTH GAIN- AND LOSS-OF-FUNCTION TDP-43 PATHOLOGY, EXTENDS SURVIVAL AND DECREASES NFL IN VIVO AND HAS A FAVORABLE PRECLINICAL SAFETY PROFILE.

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Background: RNA binding protein TARDBP (TDP-43) pathology is in approximately 40% of people ages 65 and above and in > 97% of non genetically modified Amyotrophic Lateral Sclerosis (ALS) patients. TDP-43 dysfunction involves both loss of nuclear TDP-43 and gain of TDP-43 cytoplasmic aggregates; targeting this dysfunction may slow the progression of ALS. ACE-2223, a novel orally bioavailable small molecule development candidate, directly engages aggregated TDP-43 and restores the functional form of TDP-43. ACE-2223 not only potently disrupts TDP-43 aggregates in in vitro and in vivo neurodegenerative disease models, but also results in loss of function improvements such as decreased cryptic exons and decreased neurofilament light chain (NfL). In cell lines as well as iPSC-derived motor neuron models of TDP-43 pathology, ACE-2223 rescues both gain- and loss-of-function phenotypes of TDP-43. ACE-2223 reduces insoluble cytoplasmic TDP-43, increases functional nuclear TDP-43 and rescues TDP-43 dependent cryptic exon mis-splicing in proteins such as STMN2, UNC13A and KALRN. ACE-2223 was tested in two independent mouse models of TDP-43 pathology and demonstrated target engagement and functional improvements. In an iTDP43A315T ALS/FTD model, ACE-2223 treatment showed high brain penetrance, reduced TDP-43 pathology and rescued neuroinflammation and behavioral phenotypes. In a ΔNLS-hTDP43 (rNLS8) ALS mouse model, ACE-2223 significantly improved overall animal survival and significantly reduced plasma Nf-L; trends of decreased cryptic exons were also observed. ACE-2223 has completed 28 day in-life GLP toxicity studies and GMP manufacturing for first in human trials. A comparison of the levels of aggregated TDP-43 in ALS human motor cortices and rNLS8 mouse motor cortices confirms that ACE-2223 can be administered at an efficacy dose in humans with desirable safety margins. A Phase Ia in healthy volunteers is planned for early 2026.

Key takeaway message: ACE-2223 is an oral small molecule disruptor of TDP-43 aggregates that has a favorable preclinical safety profile and rigorous preclinical target engagement and functional validation. Dosing of ACE-2223 in healthy volunteers will begin in 2026.

P281- NEONATAL CSF AND PLASMA P-TAU EXCEED ALZHEIMER'S DISEASE LEVELS: INSIGHTS INTO ANTAGONISTIC PLEIOTROPY AND POTENTIAL TAU THERAPIES.

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Background: Antagonistic pleiotropy describes biological mechanisms or genetic variants that confer benefits early in life but contribute to pathology later (1). Classic examples include the APOE ε4 allele, which provides resilience against infections and malnutrition during youth while increasing Alzheimer's disease (AD) risk in later life, and mutant Huntingtin in Huntington's Disease (HD), which enhances neurocognitive and motor development early on but precipitates neurodegeneration in adulthood (2,3). Tau phosphorylation plays a critical physiological role during early brain development supporting neurite outgrowth, axonal transport, and synapse formation (4). Paradoxically, this same process leads to aggregation, tangle formation and neurodegeneration in AD and other tauopathies (5). This paradox raises fundamental, yet unanswered, questions: How does the newborn brain tolerate high levels of p-tau without triggering aggregation or neurotoxicity? What mechanisms govern the transition of tau phosphorylation from a physiological to a pathological process in AD? Comparative insights from HD and APOE ε4 underscore that latent, age-dependent vulnerabilities are often rooted in evolutionarily beneficial processes. Profiling tau biomarkers across the lifespan, from newborns to AD-affected adults, offers the opportunity to identify molecular targets capable of re-engaging early-life protective mechanisms, with potential for disease prevention or therapy. **Methods:** We quantified phosphorylated tau (p-tau) in umbilical cord plasma from newborns and compared these values with those observed in AD patients and healthy controls across the lifespan. Plasma p-tau217 was measured using ultrasensitive Simoa assays, with longitudinal data from preterm infants providing developmental trajectories. Additionally, p-tau181 and p-tau217 were measured in CSF samples from newborns with suspected intraventricular bleeding and compared against CSF from AD and controls using both Simoa and Lumipulse platforms to evaluate consistency across methods and epitopes. **Results:** Our previously published findings demonstrated that plasma p-tau217 is dramatically elevated in newborns, reaching up to 12-fold higher than in healthy controls and 3-fold higher than in AD patients. Longitudinal follow-up of preterm infants revealed a gradual decline in p-tau217 during the first 3–4 months of life, converging toward adult baseline levels. Gestational age and birth weight were inversely correlated with neonatal p-tau217, indicating developmental regulation. In AD patients, plasma p-tau217 was associated with amyloid pathology and cognitive impairment, as expected. Extending these findings, we observed similarly elevated p-tau levels in neonatal CSF, with both p-tau181 and p-tau217 exceeding those of AD patients. Importantly, these results were replicated across two independent assay platforms (Simoa and Lumipulse) and across different p-tau epitopes, reinforcing their robustness. Despite such extreme elevations, no evidence of aggregation-prone tau species or neurotoxicity was detected in newborns. **Conclusions:** Newborns display the highest physiological levels of plasma and CSF p-tau observed across the human lifespan, far surpassing those seen in AD. The consistency of these findings across biological fluids, assay platforms, and epitopes underscores their validity and pathophysiological importance. These results highlight tau phosphorylation as a case of antagonistic pleiotropy, supporting early-life brain development while predisposing to pathology in aging. Understanding the mechanisms that protect the neonatal brain from tau toxicity may reveal novel therapeutic strategies for AD.

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Molecular Neurodegeneration. 2022;17(1):28. doi:10.1186/s13024-022-00533-z.

Key takeaway message: Newborn biofluids exhibit higher levels of p-tau than those of AD. The mechanisms that allow newborns to tolerate p-tau without triggering aggregation or damage remain unclear. Understanding this is essential for developing novel tau-targeting therapies

P282- HIGHER P-TAU217 LEVELS IN TYPE 2 DIABETES MELLITUS: SEX DIFFERENCES IN NEUROPATHOLOGICAL RESILIENCE.

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Background: Type 2 diabetes mellitus (T2DM) is increasingly recognized as a risk factor for Alzheimer's disease (AD). While men have twice the risk for T2DM than women, AD disproportionately affects women. This discrepancy raises critical questions about the underlying mechanisms that contribute to these sex differences. Plasma p-tau217 is one promising biomarker for detecting underlying AD-specific neuropathology before clinical signs emerge. However, the relationship between T2DM with p-tau217 burden is heretofore understudied, and existing research overlooks sex differences in the context of T2DM and AD. Here, we examined the effect of T2DM status on plasma p-tau 217 in a cohort of cognitively unimpaired older African American women and men. **Methods:** Participants were recruited from the Rutgers Aging & Brain Health Alliance (N =134; 78% female). All individuals were categorized based on T2DM status using hemoglobin A1c ($\geq$6.5%, n=28) or non-T2D ($\leq$6.4%, n=106). Blood samples were analyzed for plasma p-tau217. ANCOVAs were used to examine: 1) the main effect of T2DM status on p-tau217 and 2) the interactive effect of T2DM status $\times$ sex on p-tau217 with age, sex, waist-to-hip ratio, and diabetes prescription medication use (0=no, 1=yes) as covariates. **Results:** Participants with T2DM had significantly higher p-tau217 levels ($\eta p2=0.08$, p=.001), independent of covariates.. However, the relationship between T2DM status and p-tau217 varied by sex: women with T2DM showed greater resilience to ptau-217 burden than their male counterparts with T2DM ($\eta p2=0.12$, p<.001). **Conclusions:** In this cohort of cognitively unimpaired older African Americans, T2DM may promote early neuropathological changes that raise AD risk. However, women exhibit greater resilience to AD neuropathology despite higher p-tau217 levels associated with T2DM. These findings warrant further mechanistic explorations (e.g., hormonal influences, genetic predispositions, or lifestyle factors) to better understand sex-differential effects of T2DM on AD risk and highlight the potential for targeted screening and treatment approaches that consider sex differences.

Keywords: Type 2 diabetes, Alzheimer's disease, neuropathology; hemoglobin A1c, blood-based biomarkers.

Disclosures: None.

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Key takeaway message: Sex differences analysis in the association between type 2 diabetes mellitus status and plasma phospho-tau 217 levels reveal greater resilience to Alzheimer's-related neuropathology among women

P283- AN OPTIMIZED POLYGENIC RISK SCORE PREDICTS AMYLOID-β POSITIVITY, LONGITUDINAL COGNITIVE DECLINE, AND BRAIN ORGANOID PATHOLOGY.

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Background: Polygenic risk scores (PRSs) for Alzheimer's disease (AD) have shown promise but are limited by their primary derivation from European ancestry populations and a lack of validation against biological markers and longitudinal cognitive outcomes. This study aimed to develop and validate an optimized PRS (optPRS) for an East Asian population, assess its association with cognitive trajectories stratified by amyloid-β (Aβ) status, and investigate its biological relevance using patient-derived cerebral organoid models. **Methods:** An optPRS comprising 31 SNPs was developed from European-based GWAS summary statistics and validated in multicenter Korean cohorts (discovery n=1,255; replication n=379) and a UK Biobank Chinese cohort (n=1,442). We used logistic regression to test associations with AD dementia and Aβ-PET positivity, and linear mixed-effects models to assess longitudinal cognitive trajectories (n=771). iPSCs from seven donors, stratified by optPRS, were differentiated into cerebral organoids to quantify Aβ insolubility and tau hyperphosphorylation. **Results:** The optPRS robustly predicted AD dementia (OR per SD=2.44, 95% CI 1.65-3.62, P<0.001) and Aβ positivity (OR=2.05, 95% CI 1.37-3.09, P<0.001), with replication in an independent Korean cohort and in Chinese participants from the UK Biobank. In longitudinal analyses, a higher optPRS was associated with significantly accelerated cognitive decline (MMSE, P for trend=0.005; CDR-SOB, P for trend=0.002), most pronounced in Aβ positive individuals. In patient derived cerebral organoids, the high optPRS group showed a higher insoluble to soluble Aβ42 ratio (P=0.030) and increased p Tau181 (P=0.002), indicating greater Aβ aggregation and tau phosphorylation. **Conclusions:** This study establishes an optimized, APOE-independent PRS as a robust predictor of AD risk and cognitive decline in East Asian populations, with its biological relevance confirmed by corresponding pathology in patient-derived organoids. These findings support personalized risk stratification and establish PRS stratified organoids as a platform for drug screening and mechanism informed therapy development.

Key takeaway message: An APOE independent optimized PRS predicts Alzheimer disease, amyloid positivity, and faster cognitive decline in East Asians; high score organoids show greater Aβ insolubility and tau phosphorylation, supporting risk stratification and drug screening.

P284- THE GLOBAL NEURODEGENERATION PROTEOMICS CONSORTIUM (GNPC) V2: EXPANDING REAL-WORLD PROTEOMICS TO INCLUDE LIFESTYLE AND DRUG INTERVENTIONS, ADDITIONAL GEOGRAPHIES, AND MULTIPLE PROTEOMIC PLATFORMS.

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Background: Global Neurodegeneration Proteomics Consortium (GNPC) phase two (V2) builds on the success of its initial harmonized dataset (V1), released on July 1st, 2025, numbering ~250,000,000 protein measurements from 35,000 samples from 23 cohorts. GNPC V2 aims to expand the scale, diversity, and translational relevance of neurodegenerative disease research by integrating new cohorts, analytical platforms, and expanded metadata (49 à 164 features).

Methods: GNPC V2 is designed to intentionally expand on the V1 dataset by incorporating broader demographic representation, deeper phenotyping, and multi-omic profiling. The second version introduces a multi-platform proteomics strategy, leveraging SomaScan 11K, Olink HT, and Alamar Biosciences' NULISA CNS and Inflammation panels. This approach is complemented by efforts to harmonize up to 164 phenotypic clinical variables and to integrate targeted biomarker and imaging data where available. Following the V1 cycle, the GNPC harmonization model includes a 12-month embargo period for contributing partners, followed by open access via the AD Workbench. This structure supports both early discovery and broad dissemination, accelerating the translation of proteomic insights into clinical trial tools. **Results:** Building on the success of GNPC V1, the GNPC V2 expands the scale and scope of the consortium with over 10,000 new samples, 30,000 new analyses, and a growing membership of over 30 global partners. Notably, GNPC V2 includes longitudinal and interventional studies such as WW-FINGERS and the NADALS trial, and emphasizes diversity in disease etiology, geography, and participant demographics, with targeted inclusion of underrepresented populations and non-US/EU sites. These include the KBASE study from South Korea, the Panama cohort from Davos Alzheimer's Coalition, and the Multi-Partner Consortium to Expand Dementia Research in Latin America (ReDLat) via a collaboration with the NIA's Center for Alzheimer's and Related Dementias. These additional cohorts enable a more granular exploration of disease trajectories and biomarker validation across diverse populations, ensuring greater generalizability for biomarker findings applicable to global populations. **Conclusions:** GNPC V2 represents a significant step forward in real-world proteomics, offering a scalable, diverse, and deeply phenotyped resource for the neurodegeneration research community. By embracing the complexity of real-world data, GNPC V2 aims to uncover more personalized and actionable insights into Alzheimer's disease and related disorders.

Key takeaway message: The GNPC V2 builds on the July 2025 V1 release, adding over 10,000 new samples and 30,000 new analyses from a broader coalition of cohorts, multi-platform analytics, and enriched metadata.

P285- TRANSLATIONAL PROGRESS OF NA-831, NA-911, AND NA-931: CLINICAL EVIDENCE SUPPORTING A UNIFIED THEORY FOR ALZHEIMER'S DISEASE, STROKE, AND OBESITY.

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Background: Chronic disorders such as Alzheimer's disease (AD), ischemic stroke, and obesity have traditionally been treated as distinct entities. However, converging evidence from molecular biology, systems medicine, and epidemiology suggests these conditions share overlapping pathophysiological mechanisms. The Unified Theory proposes that disruptions in cellular energy metabolism, chronic inflammation, oxidative stress, impaired IGF-1, insulin signaling and neurogenesis underlie the onset and progression of these diseases. This systemic perspective has guided the development of novel investigational agents—NA-831, NA-911, and NA-931—designed to target shared molecular pathways. These three analogs, although aimed at different indications, demonstrate therapeutic convergence consistent with the Unified Theory. **Methods:** Three Biomed Industries drug candidates—NA-831 for Alzheimer's disease, NA-911 for stroke, and NA-931 for obesity—have undergone clinical or preclinical evaluation to assess safety, efficacy, and translational relevance: NA-831 (Alzheimer's Disease): A randomized, double-blind, placebo-controlled Phase 2 clinical trial (ClinicalTrials.gov ID: NCT03538522) enrolled 112 participants with mild or moderate AD. Inclusion criteria followed NIA-AA diagnostic standards. Participants were stratified by Mini-Mental State Examination (MMSE) score: $\geq$22 for mild cognitive impairment (MCI) and 17–21 for mild-to-moderate AD. Subjects received either placebo or NA-831 at 30 mg/day for 24 weeks. Primary outcomes were change from baseline in ADAS-Cog-13 and Clinical Global Impression of Change using the CIBIC-Plus. NA-911 (Stroke): A preclinical study was conducted using a rat model of middle cerebral artery occlusion (MCAO) to simulate focal ischemic stroke. Adult male Sprague-Dawley rats received a continuous intravenous infusion of NA-911 (3 mg/kg/h) or vehicle. Infarct volume was quantified, and immunohistochemical analysis was performed to assess neural repair mechanisms, including subventricular zone (SVZ) neurogenesis. NA-931 (Obesity): A phase 2, 13-week randomized, double-blind, placebo-controlled, parallel arm study that will evaluate the safety, tolerability, weight loss efficacy of NA-931 in adults who are obese (BMI $\geq$30 kg/m2) or who are overweight (BMI $\geq$27 kg/m2) with at least one weight-related co-morbid condition. (ClinicalTrials.gov ID NCT06564753). **Results:** NA-831 (Alzheimer's Disease): Patients treated with NA-831 demonstrated a statistically significant improvement in cognitive function. The mean ADAS-Cog-13 score improved by 4.1 points compared to placebo at week 24 ($p = 0.001$; ITT population). On the CIBIC-Plus scale, 78% of treated patients were rated as improved ($p = 0.01$). NA-831 was well-tolerated, with no drug-related serious adverse events observed at 30 mg/day. NA-911 (Stroke): In the MCAO model, vehicle-treated animals exhibited a mean infarct volume of 43.4 ± 7.4 mm^2 (n=13). NA-911 treatment reduced infarct volume to 17.3 ± 5.4 mm^2 (n=15; *$p < 0.05$). Behavioral improvements were observed in motor coordination and sensorimotor reflex tests. Immunostaining suggested enhanced SVZ neural progenitor cell activation in the NA-911 group, indicating a role in endogenous neural repair. NA-931 (Obesity): The 13-week MAD study showed NA-931 demonstrated dose-dependent reductions in mean body weight from baseline, up to 14.8 % at 150 mg daily dosage, or 13.2% % relative to placebo. An exploratory assessment of subjects achieving at least 5% weight loss after 13-week demonstrated that up to 72% of NA-931-treated subjects achieved $\geq$12% weight loss, compared with 2% for placebo. No clinically meaningful differences were reported for GI-related adverse events among subjects treated with NA-931 compared with placebo. **Conclusions:** These translational findings support the Unified Theory, which posits shared mechanisms across neurodegenerative, cardiovascular, and metabolic diseases. NA-831, NA-911, and NA-931—while developed for Alzheimer's disease, stroke, and obesity, respectively—exhibit mechanistic convergence through modulation of IGF-1 signaling, inflammation, and neurogenesis. NA-831 demonstrated clinical efficacy in improving cognition in AD patients; NA-911 reduced infarct size and activated neural regeneration in stroke models; and NA-931 produced significant, well-tolerated weight loss in human volunteers. Together, these results highlight the potential of targeting systemic dysfunctions rather than organ-specific symptoms. Further studies are warranted to validate long-term efficacy, elucidate underlying molecular pathways, and explore combination therapies that address the interconnected nature of chronic degenerative diseases.

Key takeaway message: Targeting shared mechanisms such as IGF-signaling, neuroprotection, neurogenesis, and inflammation, NA-831, NA-911, and NA-931 support the Unified Theory and offer a promising strategy to treat interconnected neurodegenerative, cardiovascular, and metabolic diseases systemically.

P286- BIALLELIC HUMAN GENETIC BACKGROUND: FOUNDATION FOR DIVERGENT PATHOMECHANISMS.

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Background: Understanding the fundamental differences between the human and pre-human brain is essential for developing meaningful models and therapies for Alzheimer's disease (AD). One of the key insights that could drive this understanding is the biallelic CHRFAM7A gene, which is human-specific and has a distinct genetic distribution in the human population. Specifically, this gene is present in about 25% of

individuals with one allele, 50% with both alleles, and 25% with neither allele. Both direct and inverted alleles underwent strong selective pressure leading to Hardy-Weinberg equilibrium in Caucasians. We performed molecular genetic and functional characterization of the alleles in an iPSC model and in a pilot human clinical study. **Methods:** Human isogenic iPSC derived MGE progenitors are utilized as experimental system, including null (UB068), isogenic KI (UB068_CHRFAM7A) and isogenic KI inverted (UB068_D2bp). Gene expression of CHRFAM7A, CHRNA7 and ULK4 isoforms are ascertained with qPCR. Patch clamp and Ca2+ imaging are used to characterize α7nAChR and α7/CHRFAM7A nAChR function. Microscopy with live actin and live microtubule imaging is used to visualize cytoskeleton dynamics. Fluorescent ICC and confocal microscopy are used to quantify the Neuronal phenotypes are quantified by Fluorescent ICC and confocal microscopy followed by FUJI Image J analysis. Pilot human cognitive, MRI and functional MRI data is presented from 46 genotyped normal control individuals. **Results:** The translated direct allele humanized the α7nAChR into an α7/CHRFAM7A nAChR heteropentamer. The α7/CHRFAM7A nAChR is hypomorphic for ionotropic and hypermorphic for metabotropic effect switching the Ca2+ pool from the extracellular space to the ER. Intracellular Ca2+ dynamics is modified which activates small GTPase Rac1, a key molecule involved in actin cytoskeleton dynamics. In contrast, the inverted allele is not translated. The inverted allele regulates ULK4 isoform expression through genetic epistasis. Skewing of ULK4 isoform expression leads to microtubule cytoskeleton phenotypes, including migration, neurite tip exploratory movement, debundling and branching of the neuronal processes. The phenotypes are associated with a-tubulin acetylation, the mechanism that has been suggested for ULK4. In the pilot human clinical study genotype specific cognitive, structural and functional MRI readouts are suggested. **Conclusions:** The biallelic CHRFAM7A gene represents a unique and critical element of the human genetic background, and its presence and function may offer insights into why AD and other diseases manifest differently across human populations. From mouse genetics, we have learned that phenotypes and disease mechanisms are profoundly influenced by the genetic background of the organism. This is especially true in the context of neurological diseases like Alzheimer's. While this principle has been applied to animal models, it has not yet been fully explored in humans in terms of personalized medicine, especially not from the standpoint of the specific mechanisms underlying human disease susceptibility. The biallelic CHRFAM7A gene offers a paradigm shift in how we approach diseases like AD. By recognizing that genetic background, defined by CHRFAM7A and its effects on cellular mechanisms, plays a pivotal role in disease susceptibility and drug response, we may be able to bridge the translational gap in AD research and therapy.

Key takeaway message: By understanding the biallelic genetic background defined by CHRFAM7A, we can bridge the gap between preclinical animal models and human patients. This novel approach recognizes the influence of genetic diversity on disease mechanisms and drug responses, paving the way for personalized medicine based on genetic backgrounds rather than just focusing on specific mutations. This could represent a paradigm shift in how we model and treat diseases like Alzheimer's disease, making it possible to design more effective, targeted therapies that are tailored to the individual genetic makeup of each patient.

P288- EXPLORATION OF LONGITUDINAL CHANGES IN GUT MICROBIOME COMPOSITION STRATIFIED BY AMYLOID STATUS.

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Background: Emerging evidence suggests that the gut microbiome, among other factors, may play a role in the development and progression of Alzheimer's disease (AD). While cross-sectional studies indicate that the composition and function of the gut microbiome are altered in AD dementia, less is known about longitudinal changes in AD. Here, we examined longitudinal changes in gut microbiome composition among participants stratified by amyloid status (amyloid status positive: A+; amyloid status negative: A−). **Methods:** Participants (N = 80 per time point (v); v1 = 80 and v2 = 80) from the Wisconsin Microbiome in Alzheimer's Disease Risk Study (MARS) were phenotyped for amyloid status (v1[A+ = 17, A− = 63]; v2[A+ = 18, A− = 62]) and clinical diagnosis (v1[Dementia-AD = 2, MCI-AD = 1, Cognitive Normal = 77]; v2[Dementia-AD = 2, MCI-AD = 4, Cognitive Normal = 74]). Amyloid positivity was based on imaging or fluid biomarker thresholds. The threshold for amyloid PET was defined as a cortical average distribution volume ratio (DVR) $\geq$ 1.19, derived from [^{11}C]PiB PET imaging, and for CSF was Aβ42/Aβ40 $<$ 0.046. In cases where only plasma was used, amyloid positivity required both plasma Aβ42/40 ratio $<$ 0.046 and pTau217/Aβ42 ratio $\geq$ 0.008. Fecal samples were analyzed by shallow shotgun sequencing, and a taxonomic count table was used to analyze differential abundance using the BIRDMAn pipeline. Linear mixed-effects models were used to assess the association between time point and amyloid status on the microbial features, including their interaction (time point × amyloid status). Fixed effects included age, sex, and APOE ε4 carrier status. A random intercept was specified for participants to account for within-subject correlation over time. **Results:** The abundance of Fusobacterium animalis showed a significant interaction between time and amyloid status (β = 1.78, 95% HDI: 0.12 to 3.71), indicating that its temporal trajectory differed based on amyloid status. Increases in the abundance of multiple microbial species, including Klebsiella spp. and Enterobacter spp., from baseline to the second visit were also greater in amyloid-positive participants compared to amyloid-negative participants. **Conclusions:** Our findings suggest that longitudinal shifts in gut microbial composition are associated with amyloid positivity. However, because a small number of individuals with AD dementia and MCI due to AD were included in the amyloid-positive group, we cannot rule out the possibility that these microbial changes are partly driven by clinical disease status rather than amyloid pathology alone. This potential confounding factor limits our ability to attribute the observed microbiome shifts solely to preclinical amyloid changes. Nevertheless, the identified microbes—such as Fusobacterium nucleatum subspecies animalis, known for its links to colorectal cancer, along with other potentially pathogenic taxa—are implicated in inflammation and mucosal barrier disruption (1,2). This inflammatory milieu could plausibly contribute to or exacerbate neurodegenerative processes, underscoring the importance of further mechanistic studies into how these microbial shifts might influence amyloid accumulation and disease progression.

Keywords: Amyloid status, Alzheimer's disease, Gut microbiome.

Disclosures: The authors declare no conflicts of interest.

References: 1. Zepeda-Rivera, Martha et al. "A distinct Fusobacterium nucleatum clade dominates the colorectal cancer niche." Nature vol. 628,8007 (2024): 424-432. doi:10.1038/s41586-024-07182-w. 2. Liu, Le et al. "Extracellular vesicles of Fusobacterium nucleatum compromise intestinal barrier through targeting RIPK1-mediated cell death pathway." Gut microbes vol. 13,1 (2021): 1-20. doi:10.1080/19490976.2021.1902718.

Key takeaway message: Longitudinal gut microbiome changes differ

by amyloid status, with greater increases in taxa that may be inflammatory or opportunistic among amyloid-positive individuals, suggesting a possible link to Alzheimer's disease-related pathology.

P289- ASSOCIATIONS BETWEEN ALZHEIMER'S DISEASE AND STROKE: CLINICAL STUDIES OF NA-831 FOR AD AND NA-911 FOR STROKE.

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Background: Alzheimer's disease (AD) and stroke are among the most prevalent neurological conditions in aging populations, with increasing evidence supporting a bidirectional relationship between them. NA-831 is a novel therapeutic candidate for the treatment of AD. NA-911, an analog of NA-831, functions as a dual IGF-1 and GLP-1 receptor agonist and is being investigated for its potential in treating hypoxic-ischemic injury, hemorrhagic stroke, and chronic neurodegenerative disorders. **Methods:** NA-831 for AD: A randomized, placebo-controlled clinical trial was conducted in 112 participants with mild to moderate AD. Subjects were randomized to receive either NA-831 or placebo. Participants with mild cognitive impairment (MCI) received 10 mg/day orally, while those with mild to moderate AD received 30 mg/day. Eligibility criteria for MCI included meeting NIA-AA core clinical criteria, a Clinical Dementia Rating (CDR) score of 0.5, a Memory Box score of $\geq$0.5 at screening and baseline, and a Mini-Mental State Examination (MMSE) score $\geq$22. Participants with AD met the NIA-AA diagnostic criteria with MMSE scores between 17 and 21. NA-911 for Stroke: Preclinical studies were conducted in adult male Sprague-Dawley rats using the middle cerebral artery occlusion (MCAO) model—a well-established method for replicating the neurological and behavioral deficits associated with human ischemic stroke. Detailed methodology is available upon request. **Results:** NA-831 demonstrated statistically significant cognitive improvements in patients with mild to moderate AD, as measured by a 4.1-point mean improvement in ADAS-Cog-13 scores compared to placebo after 24 weeks of treatment ($p = 0.001$; ITT). Additionally, 78% of patients in the NA-831 group showed clinical improvement on the CIBIC-Plus scale ($p = 0.01$; ITT). NA-831 was well tolerated at a daily dose of 30 mg. In the NA-911 animal study, infarct volume in vehicle-treated rats was 43.4 ± 7.4 mm^2 ($n = 13$). Treatment with NA-911 at 3 mg/kg/h significantly reduced infarct volume to 17.3 ± 5.4 mm^2 ($n = 15$; *$p < 0.05$). Furthermore, NA-911 may activate subventricular zone (SVZ) progenitor cells, suggesting potential for neural regeneration following stroke. **Conclusions:** Clinical and preclinical data support a mechanistic link between AD and stroke, as demonstrated by the therapeutic effects of NA-831 and NA-911. Although a causal relationship has yet to be firmly established, the frequent coexistence of cerebrovascular lesions and AD pathology implies a synergistic interaction, in which stroke may trigger or amplify cognitive decline. Elucidating the shared molecular pathways underlying neurodegeneration and cerebrovascular injury is essential for the development of integrated, dual-targeted therapeutic approaches.

Key takeaway message: An association of Alzheimer's disease and stroke has been suggested with clinical studies of NA-831 and NA-911. Advancing our understanding of their interrelated mechanisms may guide the development of dual-target therapies addressing both neurodegenerative and vascular contributors to cognitive decline.

P290- ASSOCIATIONS BETWEEN ALZHEIMER'S DISEASE AND OBESITY: CLINICAL TRIALS OF NA-831 FOR AD AND NA-931 FOR THE TREATMENT OF OBESITY.

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Background and Aims: This study evaluates the potential association between Alzheimer's disease (AD) and obesity by comparing two orally administered analog drugs: NA-831 and NA-931. NA-831 exhibits neuroprotection, neurogenesis, and memory-enhancing properties for AD treatment, while NA-931, a quadruple receptor agonist of IGF-1, GLP-1, GIP, and glucagon, is designed for obesity treatment. **Method:** NA-831 for AD. A randomized, double-blind, placebo-controlled study to assess the safety, tolerability, and efficacy of NA-831 in Alzheimer patients with mild cognitive impairment. (ClinicalTrials.gov ID NCT03538522). **Key inclusion Criteria:** Is male or female, at 55-85 years of age (inclusive) at screening self-reported memory complaint, corroborated by spouse or companion as appropriate. Wechsler Memory Scale III (WMS-III) age-adjusted Logical Memory II score $\leq$ 5. Mini-Mental State Exam (MMSE) $\geq$23. Center for Epidemiologic Studies-Depression (CES-D) score <27. Key Exclusion Criteria: Subjects who have any significant, untreated psychiatric illness or any CNS condition (such as schizophrenia, Parkinson's disease, stroke, etc.) that could interfere with the study evaluations or procedures or which poses an additional risk. Evidence of a clinically relevant or unstable psychiatric disorder, excluding major depression in remission. History of significant head trauma followed by persistent neurologic defaults or known structural brain abnormalities. NA-931 for Obesity. A phase 2, 13-week randomized, double-blind, placebo-controlled, parallel arm study that will evaluate the safety, tolerability, weight loss efficacy of NA-931 in adults who are obese (BMI $\geq$30 kg/m2) or who are overweight (BMI $\geq$27 kg/m2) with at least one weight-related co-morbid condition. (ClinicalTrials.gov ID NCT06564753). Key Inclusion Criteria: Age $\geq$18 years of age at the time of signing the informed consent. Body mass index (BMI) $\geq$30 kg/m2 or $\geq$27 kg/m2 with at least one weight-related co-morbid condition (treated or untreated), and BMI <50 kg/m2. Key Exclusion Criteria: History of or current clinically significant medical or psychiatric disorder that, in the opinion of the Investigator, does not support study participation. Self-reported body weight change of 5% or more within 3 months of screening. Current or past diagnosis of diabetes mellitus (including type 1, type 2, gestational). **Results:** NA-831 for AD. NA-831 showed a significant improvement for patients with mild and moderate AD with the ADAS-Cog-13 score change of an average of 4.1 as compared to the placebo after 24 weeks of treatment ($p = 0.001$; ITT). CIBIC-Plus showed 78 % patients improved ($p = 0.01$; ITT). It was observed that 66% patients having diabetes on the NA-831 drug treatment reported a loss of up to 13.7% of body weight over 6 months. There were no serious adverse events observed. NA-931 for Obesity. The 13-week MAD study showed NA-931 demonstrated dose-dependent reductions in mean body weight from baseline, up to 14.8 % at 150 mg daily dosage, or 13.2% % relative to placebo.An exploratory assessment of subjects achieving at least 5% weight loss after 13-week demonstrated that up to 72% of NA-931-treated subjects achieved $\geq$12% weight loss, compared with 2% for placebo. No clinically meaningful differences were reported for GI-related adverse events among subjects treated with NA-931 compared with placebo. **Conclusions:** The clinical findings of NA-831 and NA-931 suggest a potential link between Alzheimer's disease, diabetes, and obesity. However, further research is needed to determine whether this association is causal.

Key takeaway message: This study evaluates the potential association between Alzheimer's disease (AD) and obesity by comparing two orally administered analog drugs: NA-831 and NA-931. The findings suggest a potential link between Alzheimer's disease, diabetes, and obesity.

P291- TFR1-BINDING PEPTIDES TO TRANSPORT ANTIBODIES ACROSS BLOOD BRAIN BARRIER IN CYNOMOLGUS MONKEYS.

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Background: Transferrin receptor 1 (TfR1)-binding transporters are widely explored for enhancing brain delivery of therapeutic antibodies. Trontinemab, which utilizes a TfR1-binding Fab, shows promise in early Alzheimer' s disease clinical trials. Here, we report the discovery of TfR1-binding peptides by de novo design and their potential for delivering diverse therapeutic antibodies into the brain of cynomolgus

monkeys. **Methods:** Over 200,000 TfR1-binding peptides were designed de novo and screened for TfR1 affinity. Peptides exhibiting rapid internalization and improved endosomal escape were selected and fused to the C-terminus of one heavy chain of gantenerumab. Brain transport capability was screened in human TfR1 transgenic mice and validated in cynomolgus monkeys, using gantenerumab as a negative control and trontinemab as a positive control. **Results:** Forty peptides demonstrated TfR1 binding affinity in screening, with most showing the desired fast on-and-off kinetics. In hTfR1 transgenic mice, more than ten peptides facilitated optimal brain delivery; two (044 and 071) consistently outperformed trontinemab and were selected for further evaluation. These two peptides demonstrated universal capability, enhancing brain delivery of gantenerumab, lecanemab, donanemab, and ocrelizumab. In cynomolgus monkeys, both peptides showed superior ability to deliver gantenerumab and lecanemab into the brain and cerebrospinal fluid. Apart from a mild decrease in reticulocytes, no significant safety concerns were observed. **Conclusions:** Compared to Fab-based brain transportation strategies, these peptides offer smaller size, sequence diversity, high developability, and significant engineering potential. Validation in cynomolgus monkeys paves the way for first-in-human testing. **Keywords:** De novo design, TfR1, blood brain barrier, cynomolgus monkeys. **Disclosures:** HW, XZ, YQ, FS and YW are employees and receive compensation and stock options from ChainGen Bio. The authors declared no competing interests. **Key takeaway message:** TfR1-binding peptides were discovered by de novo design. Selected TfR1 peptides demonstrated universal capability in enhancing brain delivery of gantenerumab, lecanemab, donanemab, and ocrelizumab in hTfR1 transgenic mice and cynomolgus monkeys.

P292- BINDING PROFILES OF LECANEMAB AND OTHER AMYLOID-BETA ANTIBODIES TO AMYLOID-BETA SPECIES ISOLATED FROM ALZHEIMERS'S DISEASE BRAIN.

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Background: Immunotherapy against amyloid β (Aβ) has emerged as a promising treatment for Alzheimer's disease (AD). In a phase 3 clinical trial in early AD subjects, lecanemab demonstrated disease-modifying effects on clinical endpoints and clearance of amyloid-beta plaques in the brain. Lecanemab is a humanized IgG1 monoclonal antibody that selectively targets amyloid-beta protofibrils. There is strong evidence indicating that soluble Aβ aggregates are more toxic than monomers or insoluble fibrils. Immunotherapy with antibodies targeting Aβ is associated with the risk for amyloid-related imaging abnormalities with edema (ARIA-E). The incidence of ARIA-E might correlate with the antibody's binding to Aβ fibrils in the cerebral vasculature, particularly in cases of cerebral amyloid angiopathy (CAA). **Objectives:** Here, we have examined the binding characteristics of lecanemab and other amyloid-beta antibodies to various Aβ species isolated from post-mortem AD brain tissue. **Methods:** Soluble protofibrils were extracted from human post-mortem cortical tissue, and CAA fibrils were isolated from leptomeningeal tissue of AD patients. The characterization and levels of Aβ in different fractions were measured using Aβ-specific immunoassays. The binding of lecanemab and other amyloid-beta antibodies to the different Aβ species was studied using combinations of immunoassays and immunoprecipitation. **Results:** The majority of Aβ in the temporal cortex was found in the insoluble fraction. Aβ42 was the most abundant form present, particularly in AD subjects, with most soluble Aβ42 existing in soluble aggregated protofibrillar structures. Aβ protofibril levels were much higher in AD subjects compared to controls. Lecanemab showed a strong binding preference for soluble amyloid-beta protofibrils. This specificity was demonstrated through comparative analyses of various amyloid-beta antibodies' binding affinities to species isolated from post-mortem brain tissues. Lecanemab bound to protofibrils, primarily composed of Aβ42, across different severity stages and demonstrated minimal interaction with Aβ40-rich fibrils associated with CAA. **Conclusions:** The unique binding characteristics of lecanemab, which target protofibrils, may influence its effectiveness and safety in treating patients with Alzheimer's disease. Our study suggests that interactions between Aβ antibodies and CAA may contribute to the occurrence of ARIA-E in patients undergoing Aβ immunotherapies. Clinical trials with lecanemab have shown a fairly low frequency of ARIA-E of 12.6% (Clarity AD study), likely due to its reduced binding to CAA fibrils.
Key takeaway message: Lecanemab, a monoclonal antibody targeting amyloid-beta protofibrils, shows promise in Alzheimer's treatment by clearing plaques and minimizing ARIA-E risk due to low binding with cerebral amyloid angiopathy fibrils.

P293- A DIAGNOSTIC AND PROGNOSTIC PLASMA OMICS-BIOMARKERS PANEL FOR ALZHEIMER'S DISEASE BASED ON MICROGLIAL SINGLE-CELL TRANSCRIPTOMICS.

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Background: The recent FDA-approved Alzheimer's disease (AD) blood test, based on pTau217/ß-Amyloid 1-42 Plasma Ratio measures, increases diagnostic accessibility. The test can predict the presence of amyloid plaques; however, the main associated risks are false positive and false negative test results. Furthermore, this blood test is intended for patients who are cognitively impaired. AD initiates decades before clinical symptoms and neuropathological hallmarks appear. Thus, there is an unmet medical need for reliable and accurate biomarkers to identify subjects at high-risk to develop AD years and even decades before we notice symptoms. The role of neuroinflammation and the involvement of microglia in the pathogenesis of AD and related dementias (AD/ADRD) are well-established. Moreover, microglial expressed genes were implicated in AD risk via genome-wide association studies. We and others reported dysregulation of gene expression in microglial cells from postmortem brains of patients compared to age- and sex- matched controls including, (1) transcriptional, i.e., gene expression levels changes, (2) and post-transcriptional, e.g., alternative splicing events. In this study, we aimed to develop a blood-based omics-biomarker panel composed of neuroinflammatory and immune response genes dysregulated at the earliest phases of AD. Thus, the selected genes panel capture molecular changes upstream of the initiation of AD-associated pathophysiological dysfunction of the microglia. **Methods:** The study utilized publicly-available datasets from the ROSMAP study including: (1) single-nucleus (sn)RNA-seq data for microglia (N=465, dorsolateral front cortex, Synapse:syn31512863) and (2) bulk RNA-seq data for monocytes (N=558, peripheral blood mononuclear cells, Synapse:syn22024496). To identify the most informative genes for distinguishing between individuals with and without AD, we applied five different gene selection methods to the microglia cell pseudo-bulk RNA-seq data from brain tissue: ANOVA F-statistics for multi-class comparisons or t-tests for binary comparisons, coefficient of variation (CV), random forest importance, limma-based moderated F-statistics and a weighted composite score based on the other algorithms. The optimal statistical method for gene panel selection is chosen based on F1 statistics. The label transfer process from the brain microglia to the blood monocytes RNA-seq dataset was performed using a Deep Joint Distribution Optimal Transport (DeepJDOT) approach consists of: 1. Encoder network: A neural network with batch normalization and dropout that transforms high-dimensional gene expression data into a lower-dimensional latent space representation. 2. Classifier network: Predicts cognitive diagnosis categories from the latent representation with options for standard classification, binary classification (Normal vs. LOAD), or ordinal regression. Performance of the biomarker panel was measured using receiver operating curves and AUC. **Results:** First, we utilized full-length single-nucleus (sn)RNA-seq data from brain to

identify high-resolution microglia transcriptomic signature for AD. The limma algorithm was found to be statistically optimal for selection of genes from microglia. A 300 genes panel was selected based on the F-statistic using the limma algorithm. A 50 and 30 genes panels were selected using the t-test and composite scores, respectively. We then transferred the AD subtype labels from the microglial transcriptomic signature into blood samples obtained from living subjects using a graph-based mapping approach based on optimal transport statistics. Using the panel of 300 genes, AUC for the label transfer to monocytes was 0.7 with strong accuracy to predict the AD class (75%) however accuracy to predict cognitively normal individuals was 53%. While the 300 genes provided high accuracy, inspection of the distribution of p-values for the gene set showed that the panel could be greatly reduced in size to capture the most significant differences between the diagnostic criteria. The genes in the top 10% of the p-value distribution, would comprise a panel of 30 genes. The accuracy and specificity of the 50 and 30 selected genes were evaluated and demonstrated better balance between prediction of the AD and normal classes with similar AUC to the 300 gene panel. Specifically, the 50 gene panel resulted in, AUC=0.7, AD accuracy 65%, normal class accuracy 71%; and the 30 gene panel demonstrated, AUC=0.7, AD accuracy 64% and normal class accuracy 68%. **Conclusions:** This study is the first development of a plasma omics-biomarkers panel for AD. Here, we developed an omics-biomarkers panel by selecting a microglial AD-transcriptomics signature utilizing single-cell multi-omics technology, and demonstrated the significant accuracy and specificity of its performance by label transferring into monocyte transcriptomic data. Our AD omics-biomarkers panel has a strong translational potential into an indicative diagnostic and prognostic tool with several-folds utilities including, (1) precise early diagnosis, (2) clinical studies design at preclinical stages, and (3) prediction of patients who are responsive vs non-responsive to disease modifying therapies. Moreover, it will enable accurate and sensitive diagnosis of AD at early presymptomatic stages, decades before clinical onset, based on an easy to administer plasma test.

Keywords: Alzheimer's plasma-based omics-biomarker, single-cell transcriptomic, microglia, preclinical Alzheimer's diagnosis.

Disclosures: Duke University is in the process of filing a provisional patent application related to this study. The authors are inventors of the provisional patent application (IP) related to this study.

Key takeaway message: We developed and demonstrated the accuracy and specificity of the first plasma omics-biomarkers for early Alzheimer's (AD) diagnosis, based on a microglial AD-transcriptomics signature from post-mortem brains and label transferred into blood samples from living subjects.

P294- RNA TRANSCRIPTS IN SALIVARY EXTRACELLULAR VESICLE CARGO ISOLATED FROM AGED POPULATIONS.

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Background: Extracellular vesicles (EVs) can be isolated from most biofluids, including blood and saliva, and are increasingly recognized as a promising source of noninvasive biomarkers. Human saliva contains numerous factors, including DNA, RNA, lipids and protein, many of which are packaged within EVs - small, membrane-bound particles released by nearly all cell types, including those of the central nervous system. Because EV contents are believed to mirror the cytoplasm of the cell of origin, they may provide insight into cellular health. Prior studies have demonstrated that salivary EV contents can distinguish individuals with traumatic brain injury from those who have not (1,2), highlighting their potential diagnostic value. Building on this evidence, our research investigates whether salivary EVs contain molecular signatures of Alzheimer's disease and other neurodegenerative disorders, with the goal of improving detection during the prodromal phase, when interventions may be more effective. The primary objectives of this study were to 1) characterize the RNA content of salivary EVs in a cohort of cognitively normal older adults, and 2) compare the findings with the RNA profiles of blood-derived EVs, which have been recently investigated as biomarkers of neurodegenerative disease. **Methods:** We isolated EVs from saliva (salEVs) collected from healthy older adults (65+) with normal cognition and characterized the RNA cargo. We validated the salEV preparations by Western blotting for EV-specific proteins, and by transmission electron microscopy. We performed RNA sequencing on the isolated RNA (RNA-seq) to analyze the mRNA content and other RNA species that are >200 bases in length. We also performed NanoString analysis to investigate the miRNA content. **Results:** We found approximately 48.4% of the RNA-seq reads mapped to the human genome, with the remainder mapping to prokaryotic genomes, likely reflecting the oral microbiome. The transcripts represent protein-coding RNA, long non-coding RNA (lncRNA), and retrotransposons. A significant number of the protein-coding transcripts were associated with pathways involved in neurodegenerative conditions. These included Amyotrophic Lateral Sclerosis, Hungtington disease, Alzheimer's disease, Parkinson's disease, and prion disease KEGG pathways. We also found an enrichment of transcripts containing AP-2ε, HEYL, HES4, and TCFL5 transcription factor binding sites. The lncRNA content was similar between samples, with PCBP1-AS1, TEX41, and PVT1 being the top represented transcripts. There were 286 miRNAs represented in the salEV samples by NanoString analysis. Of the top 20 represented miRNAs, 6 are known to have altered expression levels in neurodegenerative conditions. These include miR-223-3p, miR-155-5p, miR-23a-3p, let-7i-5p, miR16-5p, and miR320e. The KEGG pathways predicted to be affected by the top represented miRNAs include Hippo signaling, TGF-β signaling, Wnt signaling, FoxO signaling, ErbB signaling, axon guidance, and mTOR signaling – all of which are altered in neurodegenerative conditions. We could detect retrotransposon transcripts from LINE, SINE, and LTR elements in salEVs. Retrotransposons are derepressed with age and many are associated with the onset of age-associated conditions including neurodegenerative diseases. When compared to blood-derived EVs, salEVs showed greater representation of transcripts associated with neurodegenerative pathways, with salEVs RNA containing approximately twice the number of neurodegeneration-associated transcripts. **Conclusions:** The non-invasive nature of salEV collection makes saliva a useful tool for screening for neurodegenerative conditions. The greater presence of mRNA transcripts associated with neurodegenerative conditions, and the presence of retrotransposon transcripts and miRNAs in salEVs suggest that saliva may be a better tool to screen for biomarkers of neurodegenerative diseases than EVs isolated from blood.

Keywords: Extracellular vesicle, RNA, biomarker, Alzheimer's disease.

Disclosures: J.M.S. is a cofounder and SAB chair of Transposon Therapeutics. All other authors declare no conflict of interest.

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References: 1. Cheng Y, et al. Journal of cellular physiology 2019;234 (8):14377-88. 2. Cheng Y, et al. Neural Regen Res. 2020;15(4):676-81.

Key takeaway message: Extracellular vesicles (EVs) can be isolated from blood and saliva, and are increasingly recognized as a source of noninvasive biomarkers. Salivary EVs may contain unique molecular signatures of Alzheimer's disease and other neurodegenerative disorders.

P295- AI-DRIVEN PROTEOMICS ANALYSIS REVEALS DISTINCT MOLECULAR SUBTYPES IN NEURODEGENERATION.

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Background: Neurodegenerative diseases present significant heterogeneity in clinical presentation and progression. Understanding the molecular mechanisms underlying this heterogeneity is crucial for developing tailored therapeutic approaches. **Methods:** We analyzed the Global Neurological Proteomics Consortium (GNPC) harmonized dataset, which includes ~33,000 samples from ~17,000 unique patients across multiple neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, frontotemporal dementia, and amyotrophic lateral sclerosis). Proteomic profiling was performed using SomaLogic aptamer-based assays (~7,000 proteins) from cerebrospinal fluid (CSF) samples. Non-parametric statistical analyses were applied to identify proteins associated with each neurodegenerative disease, followed by neural network–based clustering to define molecular subtypes. **Results:** Differential analysis revealed expected disease-related alterations in Alzheimer's disease (AD) and Parkinson's disease (PD) relative to healthy controls. We observed significant elevations of NfL, LRRK2, and YKL-40 in PD (FDR < 0.05), whereas soluble TREM2 and YKL-40 were enriched in AD (FDR < 0.05). Gene set enrichment analysis revealed TNF and metalloproteinase pathways are up-regulated in the CSF of AD subjects. AI-guided clustering revealed distinct AD and PD subgroups, including four AD molecular subtypes, with Type I AD comprising ~72% of cases. Differential analysis indicated that the Type I AD signature is predominantly inflammatory, including strong enrichment of the complement pathway. **Conclusions:** This AI-driven analysis revealed clinically relevant molecular subtypes beyond standard diagnoses, guiding biomarker discovery and precision therapeutic stratification across neurodegenerative diseases, while enabling target discovery and future clinical study design.

Keywords: AI, proteomics, patient stratification, biomarkers.

Disclosures: The authors have no conflicts of interest to declare.

Key takeaway message: AI-guided proteomic profiling reveals distinct molecular subtypes in Alzheimer's and Parkinson's, identifying key CSF biomarkers and pathways to guide future diagnostics and therapeutic development.

P296- QUANTITATIVE SYSTEM PHARMACOLOGY ANALYSIS OF ORAL VALILTRAMIPROSATE NATURAL TRAJECTORY OF ALZHEIMER'S DISEASE PROGRESSION BY APOE4 GENOTYPE: CONTRIBUTION OF ANTI-AMYLOID OLIGOMER AND APOE4 CORRECTOR MODES OF ACTION.

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Background: APOE4 genotype is a major risk factor in late-onset Alzheimer's disease (AD), with APOE4/4 homozygous patients showing the highest risk and most aggressive progression (1). Valiltramiprosate is an inhibitor of β-amyloid oligomer formation in development as a disease-modifying AD treatment. It has been reported that valiltramiprosate, via its active molecules tramiprosate and 3-sulfopropanoic acid (3-SPA), also exhibits APOE4 structure corrector activities, converting the abnormal APOE4 protein to the more physiological APOE3-like conformation and function (2). The present quantitative system pharmacology (QSP) analysis aims to determine the effects of valiltramiprosate on AD progression by integrating its anti-oligomer and APOE4 corrector modes of action. **Methods:** An existing QSP model of β-amyloid aggregation in AD (3) was expanded to include the implementation of different APOE4 genotypes. Subsequently, a novel QSP model for natural AD trajectory of hippocampal volume was developed, integrating factors of age, non-amyloid pathology, amyloid oligomers, protofibrils and plaques, ARIA-E, clearance and microglia activation. Specific parameter modifications for the central nervous system (CNS) synthesis of Amyloid Precursor Protein and microglia-dependent clearance of Aβ species as a function of the APOE genotype were calibrated from longitudinal observational and interventional data from the CLARITY and TRAILBLAZER clinical trials in AD.The valiltramiprosate pharmacology was implemented based on its anti-β-amyloid aggregation and APOE4 corrector mechanisms of action. We projected brain drug exposures based on clinical pharmacokinetic data of valiltramiprosate 265 mg twice daily and the preclinical brain/plasma relationship (4). The effects of valiltramiprosate on β-amyloid forms (monomer, oligomer, protofibril, and plaque) and hippocampal volume over a simulated 2-year treatment in AD were examined. **Results:** The QSP analysis showed that valiltramiprosate treatment reduced Aβ oligomer formation and hippocampal atrophy in all APOE genotypes. The combined anti-oligomer + APOE4 corrector actions produced an additive, positive impact on inhibiting Aβ oligomer aggregation and protofibril formation and reduction of hippocampal atrophy. Sensitivity analyses for the two mechanisms of action indicated that the effect was driven primarily by the anti-Aβ oligomer pharmacology, with a smaller contribution from the APOE4 corrector mechanism operative in APOE4 carrier AD patients. **Conclusions:** The results are consistent with that the primary molecular mechanism of action for valiltramiprosate to reduce AD neurodegenerative pathology is mediated by its anti-aggregation action, which prevents formation of soluble neurotoxic oligomers and protofibrils without directly reducing amyloid plaque load. The APOE4 corrector mechanism of action of valiltramiprosate may contribute to its clinical efficacy in APOE4/4 and APOE4/3 AD patients by structurally switching the phenotype to APOE3/3 like. We presently show the beneficial effects of 2-year treatment with valiltramiprosate. Extended treatment periods beyond 2 years are expected to increase the beneficial impact of the APOE4 corrector effect.

Keywords: Valiltramiprosate, amyloid, oligomers, protofibrils, APOE4, hippocampal volume, quantitative systems pharmacology.

Clinical Trial Registry: NCT06304883 and NCT04693520 https://clinicaltrials.gov.

Disclosures: J.F. Schaefer, J. Yu, S. Abushakra, A. Power, M. Tolar & J. A. Hey are employees of Alzheon, Inc. and hold stock or stock options of Alzheon, Inc.. H. Geerts & S. Short are employees of Certara.

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Key takeaway message: The APOE4 corrector mechanism of action of valiltramiprosate may contribute to its clinical efficacy in APOE4/4 and APOE4/3 AD patients by structurally switching the phenotype to APOE3/3 like.

P297- ANALYTICAL CHARACTERIZATION OF A HIGHLY SENSITIVE AND AUTOMATED IMMUNOASSAY FOR BRAIN-DERIVED PTAU-217 IN HUMAN BIOFLUIDS.

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Background: Blood-based biomarkers can be widely applicable for identification and longitudinal monitoring of Alzheimer's Disease (AD), and pTau-217 has demonstrated high discriminative accuracy for amyloid-PET positivity. However, pTau-217 in blood is derived mainly from peripheral sources and only ~20% of pTau-217 originates from the brain. Thus, there is a need for a highly sensitive assay that can specifically detect brain-derived pTau-217 (BD-pTau-217), a brain-specific isoform, that can more closely reflect the neuropathology of the disease. **Methods:** We have developed the novel proximity ligation-based NULISA technology with built in background suppression steps to achieve attomolar sensitivity and automated detection of proteins across a

range of biofluids (1). We previously developed a multiplex NULISAseq panel incorporating the ability to detect BD-pTau-217 and other BD phosphorylated Taus. Here we sought to develop a highly specific and sensitive NULISA singleplex assay for BD-pTau-217. We characterized and validated the assay for dilution linearity, spike recovery, parallelism, accuracy, precision, reproducibility and specificity. **Results:** Our novel BD-pTau-217 singleplex assay demonstrated robust analytical performance with <20% inter-plate CV across multiple days, operators, and instruments. The BD-pTau-217 singleplex assay has a wide dynamic range from 0.4-14,655 pg/mL and a limit of detection of 0.08 pg/mL. Analysis of normal and AD plasma samples showed >95% detectability. Characterization studies such as dilutional linearity, parallelism and spike recovery in plasma showed good overall assay performance with % recovery within +/- 30%. Additionally, the BD-pTau-217 antibody showed low cross-reactivity with total Tau, pTau-181, pTau-205 and pTau-212 antigens, demonstrating high specificity. **Conclusions:** The NULISA BD-pTau-217 singleplex assay provides a highly sensitive and automated tool for high throughput analysis of BD-pTau-217, enabling more accurate evaluation of neuropathological changes in blood.

References: 1. Feng, W., Beer, J.C., Hao, Q. et al. NULISA: a proteomic liquid biopsy platform with attomolar sensitivity and high multiplexing. Nat Commun 14, 7238 (2023). https://doi.org/10.1038/s41467-023-42834-x.

Key takeaway message: The NULISA BD-pTau-217 singleplex assay can specifically and sensitively detect brain-derived pTau-217 in blood with high accuracy and reproducibility, providing a powerful tool for more precise and automated monitoring of Alzheimer's Disease neuropathology through blood-based biomarkers.

P298- GLP-1 AGONISTS AND COGNITIVE DECLINE IN ALZHEIMER'S DISEASE: REAL-WORLD EVIDENCE FROM THE SITERX ALZHEIMER'S REAL WORLD DATA NETWORK.

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1. SiteRx - New York (United States)

Background: The landscape of Alzheimer's disease (AD) is undergoing a significant stepwise change, marked by both a rapidly evolving understanding of its underlying pathophysiology and the recent emergence of the first disease-modifying therapies. For years, a compelling hypothesis has proposed that AD is a metabolic disease, with some researchers coining the term «Type 3 diabetes» to describe the state of insulin resistance observed in the brain. This growing body of evidence has brought metabolic-targeted therapies, such as GLP-1 agonists, to the forefront as promising candidates for slowing or preventing cognitive decline. However, while the biological rationale is strong, only limited research has been conducted to start to understand the impact GLP-1's may have on Alzheimer's Disease progression. Given the duration and uptake of GLP-1's, real-world evidence tracking patient cognitive scores for those treated and living with disease remain unexplored. **Methods:** SiteRx analyzed de-identified, longitudinal electronic health records (EHR) from its Alzheimer's Real World Database, encompassing both structured and unstructured data across U.S. Neurology practices for patients treated and not treated with GLP-1's. SiteRx conducted a retrospective longitudinal cohort study using dated cognitive assessments/outcomes, age, sex, AD diagnosis, and GLP-1 start date, against a control cohort of similar patients not being treated with a GLP-1. Two cohorts were generated: 1) AD patients with GLP-1 usage 2) AD patients without GLP-1 usage. To identify these cohorts, robust filtering was applied, requiring an AD diagnosis within the last five years, at least 12 months of follow-up from GLP-1 initiation in cohort 1 and from AD diagnosis in cohort 2, absence of other features that could explain cognitive decline (e.g., other neurological disorders and neuropsychiatric conditions), and > 2 documented cognitive testing scores (MMSE recorded or MoCA converted to MMSE (1) within patients' electronic health records. Analyses compared population-level cognitive test score slopes by linear regression on time from index (GLP-1 initiation for users; diagnosis for non-users). **Results:** Preliminary analysis of the two cohorts, which were well-matched on key baseline demographics and cognitive scores, revealed a moderately slower rate of cognitive decline among GLP-1 users compared to non-users over the follow-up period. Although differences did not reach statistical significance in all measures, the annualized slope of decline on cognitive assessments was less steep in the treatment group. Exploratory sub-group analysis suggested that this effect differs when considering the GLP-1 and/or GIP/GLP-1 receptor agonist prescribed, though confirmation in larger samples is required. **Conclusions:** This retrospective real-world evidence study provides an early signal that GLP-1 agonists may be associated with a slower progression of cognitive decline in patients with Alzheimer's disease. Although these preliminary findings are promising, they must be interpreted with caution given the observational design and the potential for unmeasured confounding variables. This analysis underscores the value of using longitudinal real-world data to rapidly investigate novel therapeutic hypotheses. Further research, including larger, more definitive studies, is warranted to confirm this potential neuroprotective effect and its underlying mechanisms.

Keywords: Alzheimer's disease, real-world evidence, GLP-1 agonists, cognitive testing.
Clinical Trial Registry: N/A.
Data Deposition: N/A.
Disclosures: N/A.

References: 1. https://pmc.ncbi.nlm.nih.gov/articles/PMC4371590/.

Key takeaway message: Real-world data from SiteRx provide a preliminary signal that GLP-1 agonists may be associated with slower cognitive decline in AD, underscoring the value of longitudinal EHR-based datasets to rapidly test therapeutic hypotheses and expand the pool of clinically characterized patients for future clinical trials.

P299- UTILIZATION OF ALZHEIMER'S DISEASE DIAGNOSTICS BY PATIENT TYPE: REAL-WORLD EVIDENCE FROM THE SITERX ALZHEIMER'S REAL WORLD DATA NETWORK.

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Background: Alzheimer's disease (AD) diagnostics utilization is experiencing a rapid evolution as new therapies, clinical guidelines, and emerging biomarker modalities / availability reshape clinical practice and identification of disease. Historically, cerebrospinal fluid (CSF) and amyloid positron emission tomography (PET) utilization were concentrated in patients with more pronounced cognitive decline and those most suspected to be living with Alzheimer's Disease. With the emergence of blood-based biomarkers (BBBM) across a variety of settings (patient service centers, lab kits in office, mobile phlebotomy) and the adoption of anti-amyloid therapeutic options (donanemab, lecanemab), diagnostic utilization patterns have been growing and shifting in terms of their use. SiteRx Alzheimer's Real World Database enables an assessment of how diagnostic utilization evolves in the community neurology setting across patient and HCP types, offering real-world insights into how biomarker testing will continue to aid in the identification and care of patients living with Alzheimer's Disease. **Methods:** SiteRx analyzed de-identified, longitudinal electronic health records (EHR) from its Alzheimer's Real World Database, encompassing both structured and unstructured data across U.S. Neurology practices. Patients were identified based on clinical staging through ICD codes and cognitive test results. Utilization patterns of BBBM, CSF, and PET were examined from Q3 2023 to Q3 2025, with analyses stratified by disease severity at the time of testing. Biomarker results were assessed across modalities and biomarker utilization was further examined between prescribers and non-prescribers of anti-amyloid therapies. **Results:** Over time, the proportion of patients with cognitive decline who received diagnostic testing increased across modalities, with signs of expansion into earlier disease stages. BBBM demonstrated the highest relative growth and an increasing amount of multi-biomarker or re-testing is

becoming evident. In aggregate, the proportion of biomarker positive patients rose, reflecting broader use and potentially improved precision in identifying patients with Alzheimer's Disease by clinicians. **Conclusions:** The utilization of AD diagnostics in community neurology is gradually expanding and shifting toward earlier disease stages. This trend aligns with evolving standards of care and enriches SiteRx's EHR-based database with biomarker data and a growing pool of biomarker-confirmed patients, which improve patient identification and access to breakthrough therapies and promising investigational therapies.

Keywords: Alzheimer's disease, real-world evidence, biomarkers, blood-based biomarkers.
Clinical Trial Registry: N/A.
Data Deposition: N/A.
Disclosures: N/A.
References: N/A.

Key takeaway message: Real-world data from SiteRx show AD diagnostics expanding across modalities and into earlier disease stages, enriching the pool of biomarker-confirmed patients to support improved therapy access and precise clinical trial pre-qualification.

P301- ASSESSING THE ROLES OF ESTROGEN, INFLAMMATION AND NUTRITION ON BRAIN AND COGNITIVE DECLINE IN AGING WOMEN: FACTORS REDUCING ALZHEIMER'S DISEASE.

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Background: Someone in the world develops dementia every 3 seconds. There were over 55 million people worldwide living with dementia in 2020, a number projected to increase to 153 million by 2050. The annual global cost of dementia is above 1.3 trillion USD and is expected to rise to 2.8 trillion USD by 2030. The latest Lancet Commission report on dementia provides evidence about dementia prevention, intervention, and care, and several modifiable risk factors have been proposed (such as education, hearing loss, hypertension, smoking, obesity, depression, physical inactivity, diabetes, excessive alcohol consumption, traumatic brain injury, air pollution and social isolation). However, there is a need to address other risk factors for dementia associated in aging women. Often overlooked, estrogen decline and loss influences almost every organ and tissue in the body and leads to inflammation as do nutritional choices, both of which have a profound impact on short- and long-term health and can increase the risk of dementia. **Methods:** In this analysis we focus on associations between hormonal and nutritional factors and their impact on associations with inflammation and potential to prevent and delay AD. The prevention approach addresses the changes in estrogen as women age. The major focus is 17β-estradiol, a molecule that peaks in the mid to late twenties, begins to decline by age 30 with continuing reduction at age 40 during perimenopause with estrogen production that stops at menopause. A scoping review indicates that estrogen has many positive actions including the molecular mechanisms of regulating inflammation. Inflammation, "the fundamental physiological response of the body to injury, infection and homeostatic change", inflammation and its associations with neurodegeneration including AD, have become a forefront of medical research. In addition, nutritional choices significantly impact the risk and progression of AD as demonstrated by biomarkers and diagnostic parameters. Neurodegenerative diseases like AD are multifaceted and require an assessment of estrogen decline, inflammation, and nutrient status. This study is a retrospective analysis of real-world data of patients with AD categorized for analysis focused on estrogen changes, the resultant inflammatory status after estrogen decline and loss, and the assessment of the impact nutrition and nutrient biomarkers on dementia risk and outcome. A total of twenty-three studies were examined, and the results are presented, in brief, into estrogen status and its influence, inflammation, nutrition and lifestyle, factors that were not considered in the latest (2024) Lancet Commission report on dementia. **Results:** Women have a higher risk of AD. Two out of every three AD patients are postmenopausal women contributing to over 60 % of all those affected. AD-related brain changes develop during a 10–20-year phase originating in midlife, thus proximate with estrogen transitions of ageing characteristics of the menopause interval in women. This suggests the possibility that 17β-estradiol exerts a neuroprotective effect shielding women's brains from disease development. Many biological mechanisms support the hypothesis that estrogens protect against AD by influencing neurotransmission, increasing blood flow, modulating growth proteins associated with axonal elongation, and blunting the neurotoxic effects of β-amyloid. The molecular mechanisms of how estrogens decrease or modulate inflammation include several parameters like: inhibition of target genes involved in the inflammatory process through estrogen receptors (ERα, ERβ, and GPR30); regulation of immune cell functions such as macrophage polarization, T-cell differentiation, suppression of pro-inflammatory cytokine production via signaling pathways like NFkB, while at the same time promoting the production of anti-inflammatory cytokines (IL-10 and TGFβ); acting as antioxidant agents to reduce oxidative stress and enhancing the expression of antioxidant enzymes like mitochondrial thioredoxin 2 (TRX2); boosting neural mitochondrial function for energy production via estrogen receptors, and finally, inducing DNA repair mechanisms via growth factors that contribute to cell survival. Several studies suggest that adherence to an anti-inflammatory diet is associated with lower AD risk by evidence of lower C-reactive protein and advanced glycation end-product parameters in clinical investigations. Notably, the Western diet has been linked to enhancing inflammation that could reinforce systemic inflammation involving the gut-brain axis. Further reports postulate that peripheral inflammation may cross the blood-brain barrier where it could promote neurodegenerative changes. Mitigating risk factors have been examined, where an anti-inflammatory diet (Mediterranean diet) has shown promise for neuroprotection. Multiple lifestyle factors such as physical exercise, sleep, stress management, cognitive stimulation, and social engagement may delay the development of neurodegenerative disorders like AD. **Conclusions:** This summary represents the results of a large number of clinical investigations concerning the importance of the most potent steroid hormone in the body, 17β-estradiol, its decline with age but with continued reduction during perimenopause and eventual zero production from the ovaries at menopause, which has broad implications for its protective roles in brain aging and AD. In addition 17β-estradiol has multiple actions to reduce and combat inflammation, but in a women's life, systemic inflammation may represent a phase that enables later neurodegenerative disease like AD. Lifestyle factors such as nutrition, physical activity, sleep, stress management, and social associations appear to have an additional impact in potentially delaying AD. Future efforts should focus on the triad of estrogen, inflammation, and diet to increase awareness and address the progression and amelioration of AD in women.

Keywords: 17β-estradiol, inflammation, nutrition.

Key takeaway message: Future research should focus on the triad of estrogen, inflammation and diet to address the progression and amelioration of Alzheimer's disease in women.

P302- PLASM P-TAU217 PREDICTIVE ABILITY OF COGNITIVE AND FUNCTIONAL DECLINE IN NON-DEMENTED AMYLOID PET POSITIVE OLDER INDIVIDUAL: THREE-YEAR FOLLOW UP DATA FROM JAPANESE TRIAL READY COHORT FOR PRECLINICAL AND PRODROMAL AD.

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Background: A recent study showed that plasma p-tau217 is useful for predicting brain amyloid pathology and the risk of future cognitive decline in older individuals without cognitive impairement. However, it

is unclear whether this ability is the same among older individuals with preclinical or prodromal Alzheimer's disease. In this study, we investigated whether stratified levels of plasma p-tau217 or p-tau217 alone at baseline predict future cognitive and functional decline. **Methods:** We used longitudinal data from 36 participants in the Japanese Trial Ready Cohort for Preclinic and Prodromal Alzheimer's Disease. We used baseline clinical information, APOE genotyping, Preclinical Alzheimer Cognitive Composite (PACC), Cognitive Functional Index (CFI), amyloid PET centiloid scale, and plasma p-tau217 to predict longitudinal functional assessments with the Clinical Dementia Rating (CDR) and cognitive assessments with PACC. **Results:** Higher baseline p-tau217 levels were associated with greater rates of PACC decline. However, no association was found between p-tau217 levels and the likelihood of future functional impairment, defined as a global CDR worsening of 0.5. Logistic regression analysis revealed that self-reported CFI is the only statistically significant explanatory variable. **Conclusions:** In a trial-ready cohort of non-demented older individuals, higher baseline levels of plasma p-tau217 are associated with an increased risk of future cognitive decline. However, baseline CFI should also be considered to predict future functional impairment.

Disclosures: The authors declare no conflict of interest related to this work.

Key takeaway message: In order to consider the future cognitive and functional decline associated with preclinical or prodromal Alzheimer's disease, clinical assessment is essential, as is the use of biomarkers.

P303- AMYLOID AGGREGATION INHIBITION BY PHYSIOLOGICAL LEVELS OF DOPAMINE: TOWARDS LEVODOPA DRUG REFORMULATION FOR CORRECTING MILD DOPAMINE DEFICITS AND DELAYING ALZHEIMER'S DISEASE PROGRESSION.

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Background: While the primary pathological hallmarks of Alzheimer's disease (AD) are amyloid beta (Aβ) plaques and tau neurofibrillary tangles, dopamine deficiency has been linked to AD pathophysiology already in the prodromal stages of the disease (1). On the other hand, AD patients exposed to the dopamine precursor levodopa show lowered CSF levels of Aβ, phosphorylated-tau and total-tau relative to controls and individuals exposed to other anti-parkinsonians (2). Levodopa use is also associated with delayed progression to dementia in individuals with mild cognitive impairment (2). We have now discovered that physiological dopamine levels are sufficient to drastically inhibit Aβ aggregation in vitro. Since this effect is observed at physiologically relevant Aβ concentrations (10 μM), treatment of mild dopamine deficiency in AD emerges as a possible disease-modifying alternative targeting Aβ aggregation. **Methods:** A seeded aggregation assay compatible with high-throughput screening technology was developed to identify inhibitors of Aβ aggregation. Drug-repurposing candidates were screened using compound concentrations of 2 μM and 10 μM depsi-Aβ (1–42) click peptide. Among the identified hit compounds, dopamine hydrochloride was selected for complementary validation studies through Thioflavin-T fluorescence, Transmission Electron Fluorescence (TEM), Dynamic Light Scattering (DLS) and filter retardation analyses. Cell viability in the presence of the Aβ aggregates formed with and without dopamine was measured by the MTT reduction assay using the SH-SY5Y cell line. **Results:** Dopamine hydrochloride is identified as a potent inhibitor of the aggregation of 10 μM Aβ (IC50=0.51 μM). In addition, seven other compounds that are either catecholamines or have a catechol structure similar to that of dopamine were selected as screening hits. These compounds were previously identified as potent inhibitors of ataxin-3 aggregation in the context of spinocerebellar ataxia type 3 (SCA3) drug discovery (3). TEM analysis of the end-products of seeded aggregation of Aβ indicates that physiological levels of dopamine prevent the formation of large bundles of Aβ fibrils. Moreover, the fibrils generated in the presence of dopamine are smaller and less resistant to SDS solubilization than controls. Concerning the effects on SH-SY5Y cell viability, no significant differences are identified between fresh Aβ seeds (70.3% viability relative to control) and the Aβ species produced after seeded aggregation experiments with (71.5%) and without (70.3%) dopamine. To a lesser extent, cell viability is also decreased (to 90.9%) in the presence of the dopamine oxidation products generated upon 48h-incubation of 5 μM dopamine (without Aβ). **Conclusions:** The seeded aggregation of Aβ is inhibited by sub-micromolar concentrations of dopamine. The presence of this catecholamine prevents the formation of large bundles of Aβ fibrils and leads to the formation of smaller and less SDS-resistant aggregates. The effect of these species on cell viability is not stronger than that of the precursor Aβ fibrils used as seeds. Physiological levels of dopamine have also been reported to inhibit the aggregation of ataxin-3, a protein that accumulates as neuronal nuclear inclusions in the SCA3 brain [3]. Since AD and SCA3 are both characterized by mild dopamine deficiency, low-dose levodopa is conceived as a possible anti-amyloid therapeutic alternative for these diseases through correction of the dopaminergic imbalance. Such a strategy will require dopamine-restoring drugs reformulated to decrease the levodopa dosage and keep decarboxylase inhibitors at the dosages required to prevent peripheral levodopa metabolism.

Keywords: Alzheimer's disease, anti-amyloid therapies, dopamine, drug reformulation.

Disclosures: Z.S., S.M.R. and P.M.M. are co-inventors in patent applications for the use of low-dose levodopa formulations for the treatment of neurodegenerative disorders. All other authors report no conflicts of interest.

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Key takeaway message: Dopamine-restoring therapies modified to correct mild dopamine efficiency should contribute to averting the prion-like propagation of amyloid species in neurodegenerative diseases such as AD or SCA3.

P304- FUNCTIONAL DECLINE ASSOCIATED WITH ALL-CAUSE MORTALITY IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DEMENTIA IN REAL-WORLD CLINICAL PRACTICE.

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Background: Alzheimer's disease progression has been reported to increase mortality risk. Crowell et al. found that disease progression was associated with mortality using the mini-mental state examination (MMSE), Neuropsychiatric Inventory Questionnaire (NPI-Q), and Functional Activities Questionnaire (FAQ) to classify Alzheimer's disease severity. However, MMSE is subject to a ceiling effect in the assessment of disease progression which may cause inaccuracy when used to follow patients over time. In a prior study, we demonstrated a linear association between MMSE and instrumental activities of daily living (IADL) scores within the range of early Alzheimer's disease, with the latter instrument having the flexibility to measure a broader range of disease severity. The relationship between declining IADL and mortality has been demonstrated in conditions other than Alzheimer's disease. This study aims to assess disease progression using the Lawton-IADL and its relationship with all-cause mortality in patients with mild cognitive

impairment (MCI) and Alzheimer's dementia (AD). **Methods:** Veterans aged ≥50 years with MCI and AD were identified from the Veteran's Affairs Healthcare System (VAHS; 2016–2024). For this study, approximately 10% of the MCI/AD sample was randomly selected. We used IADL score points, rather than severity categories, to evaluate the functional trajectory over time. A joint model approach was employed to link the longitudinal patterns of functional deterioration from repeated IADL measurements over time with all-cause mortality in the naturalistic clinical practice setting (statistical software: JMbayes2). Specifically, we examined both the level and the speed of IADL score changes and their associations with time to mortality as Alzheimer's disease worsens. Covariates of the joint model included patient demographics, baseline (evaluated during the year prior to the first occurrence of MCI or AD diagnosis coding) medications for Alzheimer's disease (acetylcholinesterase inhibitors and memantine), and the Charlson Comorbidity Index (CCI), which is commonly used in mortality studies across therapeutic areas. **Results:** About 10% of patients (N=9,940; 61.3% MCI; 38.7% AD) were randomly selected from all Veterans with MCI/AD in the VAHS, with the following demographics: mean±SD age of 80.3 ±7.1 years, 2.6% women, 76.9% White, and 17.1% Hispanic. Patients with MCI were about 2.5 years younger than those with AD (79.3±7.1 vs 81.8±6.9). Patient characteristics included CCIs of 2.1±1.9 for MCI and 2.0±1.7 for AD and baseline medication use of 13.9% vs 23.4% in MCI vs AD. Two or more repeated IADL measures were available for about two-thirds of the patients, allowing assessment of longitudinal change in functional status. The average follow-up time from the first IADL assessment was 4.8±2.5 years. The mean (median) IADL scores were 5.8 ±2.7 (8) for MCI and 4.3±3.2 (4) for AD. Over the study period, IADL declined on average from 6.1 to 4.6 (Δ= -1.5±2.8) for MCI and from 4.8 to 3.0 (Δ= -1.8±2.9) for AD. Observed mortality over the 9-year study period was 46.9%, with observed death rates of 392 per 1,000 person-years for MCI and 590 for AD. The IADL score trajectory from the joint model was estimated to decline by 0.31 points per year (β= -0.31; P<0.01). Older age (β= -0.12), AD vs MCI (β= -1.13), female vs male (β= -0.59), Hispanic vs non-Hispanic (β= -0.99), acetylcholinesterase inhibitors and memantine use (β= -0.65), and higher CCI score (β= -0.20) were associated with lower IADL scores (all P<0.01). White vs other race was associated with higher IADL scores (β= 0.27; P<0.01). Estimated mortality from the joint model was associated with lower IADL scores (β= -0.31; P<0.01), but was not associated with the speed of functional decline represented by IADL score changes over time. IADL scores almost completely accounted for the difference in mortality associated with AD relative to MCI (β= -0.01; P=0.72). Female relative to male (β= -0.58; P<0.01) and Hispanic relative to non-Hispanic (β= -0.83; P<0.01) were associated with increased survival, whereas high CCI (β= 0.09; P<0.01) and White relative to other races ((β= 0.29; P<0.01) were associated with mortality risk. Acetylcholinesterase inhibitors and memantine did not have a significant association with mortality (β= -0.08; P=0.06). **Conclusions:** This study applied joint modeling to simultaneously evaluate the trajectory of Alzheimer's disease progression as measured by Lawton-IADL and its association with the all-cause mortality risk. We found that lower IADL scores, reflecting the level of functional worsening, were strongly associated with higher risk of all-cause mortality, whereas the speed of the functional decline was not. Patients with AD had a 20% greater decline in IADL scores over the study period than those with MCI, indicating more rapid functional deterioration in advanced disease. Further, IADL scores, without integrating with a cognitive assessment component, appeared to have almost entirely accounted for the difference in mortality between AD and MCI, suggesting the value of incorporating IADL assessments in patient care practice. **Key takeaway message:** Lower instrumental activities of daily living scores, reflecting the level of functional worsening, were strongly associated with higher risk of all-cause mortality, whereas the speed of the functional decline was not.

P305- INTEGRATING COGNITIVE AND BIOLOGICAL SIGNALS IN EARLY ALZHEIMER'S: PREDICTING P217TAU AND MCI USING THE MULTI-MODAL ALTOIDA NEUROMARKER PLATFORM.

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Background: The diagnostic landscape of Alzheimer's disease (AD) is undergoing a transformation, marked by a shift toward a biomarker-based approach (1). Recent updates to the diagnostic criteria define AD as a biological process that begins with the appearance of AD neuropathologic changes and emphasize physiological conditions like abnormal concentrations of core biomarkers such as amyloid and tau (2). While this represents important progress, these criteria may not fully capture the etiologic complexity and often extended pathological process of AD progression (1), particularly the clinical and cognitive manifestations. To address this gap, we evaluated whether digital cognitive biomarkers derived from a rapid, self-administered multimodal digital cognitive assessment (the Altoida NeuroMarker Platform) could predict both mild cognitive impairment (MCI) diagnosis and p217tau concentration. Our goal was to explore a scalable, objective and less resource-intensive alternative to traditional cognitive measures—particularly for early-stage disease identification. **Methods:** Using data from the Altoida NeuroMarker assessment, we trained two classification models: one to predict cognitive impairment (cognitively normal vs. mild cognitive impairment), and one to predict p217tau concentration (low vs. high p217tau concentration, using a cutoff 0.04 pg/mL on the LucentAD p217tau assay) (3), each using the same version of the Altoida NeuroMarker assessment. Data were collected from participants with and without mild cognitive impairment (MCI) across three multicenter studies in the United States, Spain and Australia (N = 779). The mild cognitive impairment (MCI) model was trained using the subset of participants without p217tau concentration biomarker data (N = 604) and tested using the subset of participants with available p217tau concentration biomarker data (N = 175). The p217tau model was trained on a subset of participants with available p217tau concentration biomarker data (N = 175). **Results:** Applying 5-fold cross-validation, the MCI model demonstrated strong performance (ROC-AUC = 0.88), with sensitivity = 0.76 and specificity = 0.83 at the optimized threshold. When applied to the p217tau subsample (N = 175), the MCI model maintained high predictive accuracy (balanced accuracy = 0.76; sensitivity = 0.65; specificity = 0.87). The p217tau model, also evaluated using the 5-fold cross-validation, achieved ROC-AUC = 0.76, (balanced accuracy of 0.72, with sensitivity = 0.77, and specificity = 0.66) despite a smaller sample size. Predicted MCI classifications were significantly associated with actual p217tau status above and below the 0.04 pg/ml threshold (phi = 0.18, $\chi 2 = 5.76$, p = 0.02), indicating alignment between the cognitive impairment predictions and biomarker-defined pathology. **Conclusions:** The findings demonstrate that Altoida's NeuroMarker platform can accurately predict both clinical impairment (MCI) and tau pathology (p217tau concentration). With continued validation, this approach may offer a scalable, objective diagnostic tool that integrates biologic and cognitive signals indicative of the early stages of AD or other related conditions.

Keywords: p217tau, early detection, digital biomarkers, MCI.

Disclosures: NG, SF, VB-R, MFI, MJ, ES are employees of Altoida, SV, G T-B, AK, ZS, KB, GW are employees of JNJ Innovative Medicine and MK is an employee of Quanterix.

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Key takeaway message: Altoida's NeuroMarker platform can predict clinical impairment and tau pathology. This approach may offer a scalable, diagnostic tool integrating biologic and cognitive signals indicative of early stages of AD or other related conditions.

CLINICAL TRIALS: COGNITIVE AND FUNCTIONAL ENDPOINTS

P306- WORSE COGNITIVE PERFORMANCE AND POORER QUALITY OF LIFE ARE ASSOCIATED WITH LOWER SELF-REPORTED CONFIDENCE IN ACCOMPLISHING PERSONAL PRIORITIES: THE UTILITY OF THE ELECTRONIC PERSON SPECIFIC OUTCOME MEASURE (EPSOM) TOOL.

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Background: It is recognised that what constitutes meaningful treatment benefits is individual and heterogeneous. It is therefore necessary to go beyond a score in given cognitive tasks or standardized questionnaires to quantify the real-world effect of Alzheimer's disease (AD) therapies, instead assessing function on items that are personally meaningful to study participants. The electronic Person Specific Outcome Measure (ePSOM) tool was developed to establish whether new treatments offer clinically meaningful treatment effects in areas that matter the most to an individual. In the ePSOM tool, participants use their own words to define personal priorities and then rate how confident they feel in these areas that matter most. Here, we explore how ePSOM scores relate to objective cognitive status and both self- and partner-reported quality of life and health utility. **Methods:** We evaluated 403 individuals from the representative Scottish IONA cohort study (median age=69 years [SD=8.32], 58.7% female, median education=17 years [SD=3.91]; 7% reported AD). We fitted general linear models (GLM), using ePSOM confidence scores on self-defined brain health priorities as the dependent variable (higher = greater confidence), to evaluate [1] differences based on cognitive status as measured by the Digital Clock and Recall (DCR; Unimpaired, Borderline, Likely Impaired); and [2] associations with self- and partner- reported quality-of-life (QoL) based on the QoL-AD and EQ-5D-5L measures (higher score = greater QoL). Each GLM used Gaussian links for continuous outcomes and Beta for 0-1 bounded continuous outcomes, and they were adjusted for sex, age, and education. **Results:** The Likely Impaired group had significantly lower ePSOM scores than both the Borderline ($\beta = 1.54$, SE $= 0.52$, $p < 0.001$) and Unimpaired ($\beta = 2.05$, SE $= 0.51$, $p < 0.001$). All QoL measures were significantly correlated with ePSOM scores (self-reported QoL-AD: $\beta = 0.21$, SE $= 0.023$, $p < 0.001$; partner-reported QoL-AD: $\beta = 0.16$, SE $= 0.02$; $p < 0.001$; UK EQ-5D-5L: $\beta = 2.53$, SE $= 0.35$, $p < 0.001$). Age was also significantly correlated with confidence across QoL GLMs (all $p < 0.05$). **Conclusions:** In the IONA cohort study in Scotland, we show that individuals' confidence in accomplishing personally meaningful activities has strong convergent validity with self- and proxy-reported quality of life, and is significantly lower for individuals with cognitive impairment. Incorporating tools with robust psychometric properties that capture the patient voice at an individual level in clinical trials targeting early cognitive decline aligns with regulatory guidance to embed the patient voice in outcome assessments. Person-centred tools such as ePSOM could provide further proof of drug effectiveness in addition to objective primary or secondary endpoints, ensuring that treatment benefits reflect what participants consider most meaningful.
Disclosures: SS, CTS, AJ, ST and APL are employees of Linus Health and declare ownership of shares or share options in the company. APL is a co-founder of Linus Health and declares ownership of shares or share options in the company. APL serves as a paid member of the scientific advisory boards for Neuroelectrics, Magstim Inc., BitBrain, AscenZion, and TetraNeuron. CR, SG and MW are employees of Scottish Brain Sciences. CR is founder and CEO of Scottish Brain Sciences.
Key takeaway message: The ePSOM tool captures personally meaningful outcomes in Alzheimer's treatment, demonstrating a strong association with both cognitive status and quality of life, supporting its value in person-centered trial endpoints and regulatory-aligned drug evaluations.

P307- FOUR-YEAR FOLLOW-UP OF A MULTIMODAL INTERVENTION FOR DEMENTIA PREVENTION: EXTENDED RESULTS FROM THE J-MINT PRIME TAMBA RANDOMIZED CONTROLLED TRIAL.

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Background: Dementia is a growing public health concern in aging societies, particularly in Japan, where one in five older adults is expected to develop dementia by 2025. While disease-modifying therapies such as lecanemab have recently become available, there is still no cure, and preventive strategies are urgently needed. The J-MINT PRIME Tamba study previously demonstrated that an 18-month multimodal intervention could significantly improve cognitive function in older adults at risk of dementia. However, it remains unclear whether such cognitive benefits are maintained over the long term. Here, we report the 36- and 48-month follow-up results to evaluate the sustainability of cognitive improvements and domain-specific effects. **Methods:** This ongoing, single-center randomized controlled trial enrolled community-dwelling older adults (age 65–85) in Tamba, Japan, with vascular risk factors (diabetes and/or hypertension) and preserved global cognition (DASC-21: 22–30; MMSE $\geq$24). Participants were randomly assigned (1:1) to a multimodal intervention group or a control group. The intervention included weekly group-based exercise, cognitive training, nutritional counseling, and vascular risk management over 18 months. Cognitive outcomes were evaluated using a composite z-score derived from multiple neuropsychological tests at baseline, 6, 12, 18, 36, and 48 months. Domain-specific composite scores (memory, attention, executive function) were also calculated. Mixed model for repeated measures was applied for longitudinal analyses; paired t-tests compared baseline and 48-month data. **Results:** A total of 203 participants were randomized, with 153 (75.4%) completing the 48-month follow-up. Both groups maintained improved global cognitive composite scores at 36 and 48 months. The intervention group showed greater improvement at 36 months (mean difference vs. control: 0.22, 95% CI 0.06–0.37, $p = .007$) and at 48 months (0.11, 95% CI –0.07–0.28, $p = .234$, not significant). Memory and executive function composite scores showed sustained improvements in the intervention group through 48 months, with significant group differences at 36 months for memory (0.37, 95% CI 0.10–0.64, $p = .008$) and executive function (0.16, 95% CI 0.03–0.30, $p = .018$), as well as at 48 months for executive function (0.15, 95% CI 0.00–0.31, $p = .049$). Paired t-tests confirmed significant within-group improvements in global cognition at 48 months (mean difference: 0.40, 95% CI 0.32–0.48, $p < .001$, Cohen's $d = 0.78$). **Conclusions:** The cognitive benefits of an 18-month multimodal intervention in older adults at risk of dementia were largely maintained up to 48 months, especially in memory and executive domains. Although the between-group differences attenuated at 48 months, both groups exhibited persistent cognitive improvements, suggesting long-term effects of risk management and multidomain approaches. These findings support the

implementation of sustained, community-based multimodal interventions to prevent cognitive decline in aging populations.

Keywords: Dementia prevention, multimodal intervention, randomized controlled trial, long-term follow-up. **Clinical Trial Registry:** UMIN000041938.

Data Deposition: N/A. Disclosures: The authors declare no competing interests.

References: Oki Y, Osaki T, Kumagai R, et al. An 18-month multimodal intervention trial for preventing dementia: J-MINT PRIME Tamba. Alzheimer's Dement. 2024;20:6972–6983. https://doi.org/10.1002/alz.14170.

Key takeaway message: A multimodal intervention in older adults at risk of dementia led to sustained improvements in global cognition, especially memory and executive function, over four years, supporting long-term prevention strategies in aging societies.

P308- COMPARING LONGITUDINAL TRAJECTORIES OF STORYTELLER AND CDR-SB: INITIAL DATA FROM ADNI4.

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Background: Accurate measures of cognitive change are critical for detecting treatment effects in clinical trials for Alzheimer's disease. Storyteller, a self-administered remote story-recall task, enables low-burden repeat assessments in ADNI4. We compared its longitudinal trajectories to the Clinical Dementia Rating sum-of-boxes (CDR-SB) between Mild Cognitive Impairment (MCI) and Cognitively Unimpaired (CU) participants. **Methods:** 289 ADNI4 participants with baseline clinical diagnosis of MCI (n=83) or CU (n=206) who completed both Storyteller and the Clinical Dementia Rating (CDR) at baseline were included. At analysis, 46 (29 CU; 17 MCI) had completed Storyteller and 23 (18 CU; 5 MCI) had completed CDR at one-year follow-up, and 126 (89 CU; 37 MCI) had completed Storyteller at six-month follow-up. Separate mixed models for repeated measures examined fixed effects of time, diagnosis, time*diagnosis interaction, age, sex, and education, with random intercepts by participant. Primary outcome was the time*diagnosis interaction. **Results:** Groups were balanced for age (t=-0.914; p=0.362) and years of education (t=0.0680; p=0.9458), but different in female proportion (CU 65.5%; MCI 45.8%; χ^2=8.80, p=0.003). For Storyteller and CDR-SB, groups differed by baseline score (Storyteller: HC 63.3±12.0, MCI 55.2±12.1, t=5.17, p<0.001; CDR-SB: HC 0.11±0.31, MCI 1.28±1.15, t=-13.4, p<0.001). In the mixed models, Storyteller showed significant time*diagnosis interaction (β=-0.570±0.198, p=0.004), with HC improving (+0.597 points/month) and MCI stable (+0.027 points/month); while CDR-SB showed no significant interaction (β=-0.004±0.022, p=0.854). **Conclusions:** Unlike the CDR-SB, Storyteller showed significant differences in cognitive trajectories between CU and MCI. The findings are limited by the small sample sizes at follow-up. A larger sample is being collected in ADNI4, where the results will be validated.

Keywords: Endpoint, digital cognitive assessment, speech, artificial intelligence.

Clinical Trial Registry: NCT05617014; https://clinicaltrials.gov.

Data Deposition: https://adni.loni.usc.edu/. **Disclosures:** EF and JW are directors and shareholders of and consultants to Novoic Ltd.

Key takeaway message: Storyteller, a remote self-administered story-recall assessment, detected significant longitudinal differences between cognitively unimpaired and MCI participants in an initial sample in ADNI4, while CDR-SB did not.

P309- SPEED-BASED COGNITIVE TRAINING IMPROVES CHOLINERGIC NETWORK HEALTH: IMPLICATIONS FOR COGNITIVE AGING AND DEMENTIA PREVENTION FROM THE INHANCE RANDOMIZED CLINICAL TRIAL.

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Background: A landmark study demonstrated that healthy older adults who engaged in up to 18 hours of speed-based computerized cognitive training exhibited up to a 48% reduction in dementia incidence ten years following the intervention (Edwards 2017). The mechanism underlying this effect is hypothesized to involve the restoration of age-related declines in neuromodulatory function, which in turn facilitates the structural and functional brain adaptations associated with training. This study examined whether speed training modulates the cholinergic system. **Methods:** In a double-blind randomized controlled trial, healthy older adults were randomized to either a speed training intervention or an active control of non-speeded casual video games for 35 hours over 10 weeks. To examine changes in cholinergic neurotransmission, at baseline and immediately post-training, participants completed positron emission tomography using the vesicular acetylcholine transporter ligand [18F]fluoroethoxybenzovesamicol (FEOBV). **Results:** The speed training intervention showed a significant within-group increase in FEOBV binding in the primary region of interest, the anterior cingulate cortex (SUVR change mean: +0.044; 95% CI: 0.006 to 0.082; P = 0.028; medium effect size, $\omega^2 = 0.09$) with the p24c subregion of the anterior cingulate showing a significant between-groups effect that favored speed training (speeded vs non-speeded SUVR change difference: +0.058, 95% CI: 0.007 to 0.110, P = 0.029, small effect size (ω^2) = 0.05). Pre-specified exploratory analyses showed significant within-group effects of increased FEOBV binding for speed training in the hippocampus and parahippocampal gyrus. No effects on FEOBV binding were observed in the non-speeded active control. **Conclusions:** These findings provide the first direct evidence that cognitive training can improve cholinergic network health by reversing age-related reductions in cholinergic terminal density. The results support a biological mechanism through which specific forms of cognitive training confer dementia risk reduction by endogenously augmenting cholinergic signaling – a system known to deteriorate during early stages of dementia – and by promoting synaptic plasticity in brain regions commonly impaired by dementia. The observed 2.3% increase in FEOBV binding over 10 weeks may counter the 2.5% decline typically seen over a decade of natural aging, offering a mechanistic explanation for the long-term protective effects of speed training against dementia.

Keywords: FEOBV-PET, cognitive training, brain training, neuroplasticity, neuromodulatory signaling, acetylcholine, aging.

Disclosures: Mouna Attarha and Thomas Van Vleet are employees of and hold equity in Posit Science, the developer of BrainHQ the intervention used in the study. The study was supported by a grant from the National Institute on Aging (R44AG039965).

Key takeaway message : The first direct evidence that cognitive training can improve cholinergic network health by reversing age-related reductions in cholinergic terminal density, augmenting cholinergic signaling in a system known to deteriorate during early stages of dementia

P310- EVIDENCE SUPPORTING THE USE OF THE CLINICAL DEMENTIA RATING® AS AN OUTCOME MEASURE IN DEMENTIA WITH LEWY BODIES CLINICAL TRIALS.

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Background: Clinical trials for Dementia with Lewy Bodies (DLB) are underway testing novel compounds, however it is unclear which outcome measures are most appropriate for inclusion and monitoring therapeutic responses. We compared the performance of the Clinical Dementia Rating (CDR) and other common outcome measures between

DLB and Alzheimer's disease (AD). **Methods:** 600 patients (359 AD/241 DLB) were evaluated by the same neurologist for diagnosis, staging, and treatment. CDR domains and sum boxes (CDR-SB) were compared between DLB and AD by overall CDR stage: 0.5=very mild, 1=mild, 2=moderate, and 3=severe. Other outcome measures included UDS neuropsychological tests, Montreal Cognitive Assessment, Unified Parkinson's Disease Rating Scale, Lewy Body Composite Risk Score, Functional Activities Questionnaire, Neuropsychiatric Inventory, and Timed-up-and-go. **Results:** Mean age was 77.1+8.3y, 45% Female, 91% non-Hispanic White, with 15.6+3.1y education. DLB was male predominant, while AD was female predominant. DLB progressed faster in timed motor, attention, and executive tasks, while AD progressed faster in episodic memory and language ($p<.001$) with medium-to-large effect sizes. AD had greater change than DLB in MoCA from very mild to mild stage. DLB had more fluctuations, motor, behavioral, and mood symptoms, and functional decline ($p<.001$). When examined by global CDR stage, there was a stage-wide worsening of scores in all outcome measures with greatest differences between DLB and AD at the CDR 0.5 stage. CDR domain scores worsened across CDR stages in both DLB and AD, with early changes in DLB characterized by worse scores in judgement & problem-solving, community affairs, home & hobby domains and CDR-SB. **Conclusions:** This study supports the CDR as a valid outcome measure for DLB clinical trials with early changes in non-memory domains that worsen over time. Other outcome measures used to characterize AD and DLB demonstrate significant change across stages supporting their use in DLB clinical trials for inclusion criteria and outcome measures.

P311- SYNERGISTIC EFFECTS OF POZIBIO AND CERBELLA SUPPLEMENTATION ON BRAIN FUNCTION AND WELLBEING IN OLDER ADULTS.

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Background: Multi-nutrient strategies targeting the gut–brain axis may offer additive benefits for cognitive and emotional health. This study investigated the combined effects of Pozibio and Cerbella supplementation on EEG markers and wellbeing in older adults. **Methods:** This trial was a randomised, placebo-controlled study (March–July 2025) with four arms (N=54): dual active, Pozibio-only, Cerbella-only, and double placebo. EEG and questionnaire data were collected at baseline and Day 60. ERP components and spectral power were analysed during Stroop and NBack tasks. **Results:** A significant condition*day interaction ($p=.048$) was observed for N200 amplitude in the NBack task. Estimated marginal means showed that for Condition 2 (Cerbella active + Pozibio Placebo), N200 amplitude increased from day 0 to day 60. Additionally, enhanced P300 responses to distractors and novel stimuli were observed for Condition 2 versus Condition 4 (diff $\approx +0.8$ μV, $t \approx 3.0$), suggesting improved conflict monitoring and novelty processing following Cerbella intervention. All groups showed increases in delta and theta power ($p<.05$), consistent with practice effects. Questionnaire data revealed improved sleep efficiency, energy, and mental wellbeing in Pozibio-active groups, especially Condition 3 (Pozibio active + Cerbella placebo). **Conclusions:** Cerbella supplementation may enhance attentional and novelty processing, while Pozibio appears to support subjective wellbeing. Combined interventions may offer complementary benefits for cognitive and emotional health in ageing.

Keywords: Multi-nutrient, EEG, wellbeing, ageing.

Clinical Trial Registry: NCT12345678; https://clinicaltrials.gov.

Disclosures: No competing interests declared. Dr. Yadav is a co-owner of Postbiotics Inc., and this study was conducted in another lab (UK Cener), completely independent of.

Key takeaway message: Dual supplementation may yield synergistic benefits for brain function and wellbeing.

P312- TOWARD CLINICAL TRIAL READINESS FOR THE POSTERIOR CORTICAL ATROPHY PHENOTYPE: BASELINE CHARACTERISTICS IN A LONGITUDINAL, PROSPECTIVE COHORT.

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Background: Posterior Cortical Atrophy (PCA) is a rare, atypical presentation of Alzheimer's disease (AD) with prominent, early impairment in visual cortical functions (1). The rarity, visual phenotype, and lack of longitudinal data hinder the inclusion of PCA in AD clinical trials. The sensitivity of AD and PCA-targeted outcomes to measure and detect clinical change in PCA is currently unknown (2). We report baseline characteristics from an NIH-sponsored longitudinal clinical trial readiness study of PCA. **Methods:** Eighteen participants meeting criteria for PCA (1) completed baseline assessments for 1) cognitive outcomes including Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog13), and Addenbrooke's Cognitive Examination (ACE-III); 2) functional/severity outcomes including Clinical Dementia Rating-Sum of Boxes (CDR-SB), Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL), Functional Activities Questionnaire (FAQ); and 3) additional measures including the Neuropsychiatric Inventory (NPI-12) and the Zarit Burden Interview (ZBI). Similarly, participants completed piloted PCA-targeted assessments including the validated Colorado Posterior Cortical Questionnaire (CPC-Q) (3), an English translation of the French-language Self-Assessment Questionnaire of Perceptual Abilities (Q-ACP) (4), a luminance increment detection in noise (LIDN) task (5), and a Graded Incomplete Letters Test (GILT) (6). **Results:** The cohort had a mean age of 67.6 years (SD = 7.1), an average of 16.6 years of education (SD = 2.1), and a mean symptom duration of 76.9 months (SD = 33.9); 83% were female. Average cognitive scores were MMSE 21.2 (SD = 5.4), ACE-III 66.3 (SD = 21.6), and ADAS-Cog13 28.9 (SD = 12.5). Functional/severity scores averaged CDR-SB 4.4 (SD = 2.8), ADCS-ADL 59.1 (SD = 13.9), and FAQ 19.5 (SD = 4.8). PCA-specific assessments averaged CPC-Q 29.9 (SD = 8.1) and Q-ACP 16.7 (SD = 6.4); and analyses are ongoing for the LIDN task and the GILT with no ceiling effects noted for 17/18 and 18/18 participants, respectively. After Bonferroni correction for multiple comparisons, cognitive measures were strongly intercorrelated, with negative associations between ADAS-Cog13 and ACE-III ($r = -0.889$, 95% CI [−0.96, −0.72]) and between ADAS-Cog13 and MMSE ($r = -0.912$, 95% CI [−0.97, −0.78]), and a positive association between ACE-III and MMSE ($r = 0.921$, 95% CI [0.80, 0.97]). Functional/severity measures also correlated, including positive correlations between CDR-SB and FAQ ($r = 0.795$, 95% CI [0.49, 0.93]) and negative correlations between CDR-SB and ADCS-ADL ($r = -0.886$, 95% CI [−0.96, −0.71]) and FAQ and ADCS-ADL ($r = -0.888$, 95% CI [−0.96, −0.70]). Among functional/severity measures, only CDR-SB correlated with cognitive test scores, including ADAS-Cog13 ($r = 0.806$, 95% CI [0.54, 0.93]), the MMSE ($r = -0.799$, 95% CI [−0.92, −0.53]), and ACE-III ($r = -0.819$, 95% CI [−0.93, −0.57]). The ZBI, NPI, Q-ACP, and CPC-Q showed no significant correlations with other assessments. **Conclusions:** Both standard AD and PCA-specific assessments are feasible to administer in individuals with PCA for baseline measurements. Despite a wider range of MMSE scores in this PCA cohort, average scores for the ADAS-Cog13 and CDR-SB scores are similar to those in TRAILBLAZER-ALZ 2. Cognitive measures correlated with each other, as did functional/severity measures, with CDR-SB uniquely bridging the two types of measures. PCA-targeted assessments were successfully performed without ceiling effects, and the

Q-ACP and CPC-Q potentially capture elements not quantified by standard AD assessments. In addition, the lack of significant associations between ZBI and other measures suggests that existing measures may not capture outcomes that contribute to caregiver burden in the PCA syndrome.

Keywords: Posterior Cortical Atrophy Syndrome, Outcome Measures, Trial Readiness.

Disclosures: The authors declare no competing interests.

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Key takeaway message: Standard AD and PCA-specific outcome measures can identify phenotype-relevant deficits, yet the lack of correlation with caregiver burden highlights the need for additional metrics to address outcomes meaningful to patients and caregivers.

P313- MEANINGFUL BENEFITS IN GLOBAL AD TRIALS: FEASIBILITY, APPLICABILITY, AND USER ACCEPTABILITY OF THE EPSOM TOOL IN JAPANESE MEMORY CLINICS.

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Background: Linus Health's electronic Person Specific Outcome Measure (ePSOM) tool captures each participant's unique priority areas of life in their own words and prompts individuals to rate how confident they feel in each area. The tool was designed to assess meaningful treatment effects in areas of life that matter most to individuals, with outputs that can complement objective trial endpoints with the patient voice. Here, we report preliminary findings from a study to assess the feasibility, applicability, and user acceptability of ePSOM among Japanese memory-clinic patients with early symptomatic Alzheimer's disease (AD). **Methods:** Cross-sectional study across two sites (Kobe University and the Tokyo Metropolitan Institute of Gerontology) with n=50 recruitment target of individuals aged ≥60 with MCI or mild dementia due to AD. Each participant completed the ePSOM tool (confidence rating 1-5 in each personal priority, higher score = greater confidence, total score range 5-25) and an 11-item user-acceptability questionnaire with qualitative multiple-choice responses (six items with three response levels; five yes/no), and optional free text comments. We quality controlled the free-text ePSOM responses against predefined criteria. This abstract presents interim feasibility, applicability, and user acceptability results. **Results:** Recruitment began August 2025, interim n=40 (mean age=75 years [SD=6.3], 65% female, most common levels of education high school [40%] and undergraduate degree [33%]; MMSE score mean=23.8[SD=3.5]). All participants were able to complete the ePSOM assessment with 196/200 (98%) free-form responses passed quality control, the median ePSOM score was 19 [IQR=6]. Acceptability was favorable: 45% reported a positive and 40% neutral experience and 85% reported low/moderate effort; 95% had no ethical concerns. Comprehension and clarity rates were high (53% completely understood; 38% somewhat; 65% found all questions clear and easy) and content was viewed as relevant (75% agreed the ePSOM prompts cover important areas). Willingness to repeat was 63% (20% unsure). Notably, many participants had not previously considered discussing "what matters most" with their doctor: 58% were unsure whether clinicians should ask about personally meaningful priorities (38% yes). Similarly, 35% were unsure whether using ePSOM to inform treatment decisions would be helpful (55% yes). Free-text comments indicated perceived value: ePSOM was described as a rare opportunity to reflect on priorities and stimulated clarification of values. **Conclusions:** Interim data support feasibility, high acceptability, and cultural appropriateness of ePSOM in a Japanese clinic context. Critically, the ePSOM tool performed well in Japan without changing its structure as the free-text response format removed the need for cultural adaptation, demonstrating that ePSOM can be deployed in multinational AD trials under a consistent protocol, preserving consistency and comparability while reflecting what matters most to participants. These findings suggest ePSOM is a practical way to incorporate individual participants' voices into study endpoints in different cultural settings. **Key takeaway message:** Interim results from Japanese memory-clinic patients with early Alzheimer's show ePSOM is feasible, acceptable, and culturally appropriate, enabling multinational trials to consistently capture participants' personally meaningful outcomes and complement objective endpoints with the patient voice.

P314- BASELINE STUDY-PARTNER REPORTED ECOG-12 SCORE IS ASSOCIATED WITH SUBSEQUENT PROGRESSION ON CDR-SB OVER 78 WEEKS OF FOLLOW-UP.

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Background: Clinical trials in early Alzheimer's disease (eAD) are increasingly interested in enriching study populations for participants more likely to progress over the trial duration to improve ability to detect efficacy signals. Inclusion criteria typically include objective memory tests designed to identify typically progressing participants most suited to observable change during the trial. The Everyday Cognition (ECog) scale measures daily functioning and includes both a patient-report version (PRO) and caregiver/study partner report version (ObsRO). Higher scores indicate more impairment, using a 10-year reference point to compare to prior daily functioning. The ECog-12 is less time intensive for patients compared to the original 39-item version, has been validated in older adults with and without cognitive impairment and shows excellent discrimination between dementia and normal cognition. The ECog has potential to replace high-burden memory tests used as inclusion criteria in eAD trials (e.g. RBANs, FCSRT, WMS) if it is associated with disease progression on common trial endpoints over time. In this work we aimed to examine if change in CDR-SB (a frequent endpoint in AD trials) was associated with baseline performance on either version of the ECog-12 scales. **Methods:** To identify an ADNI population similar to an eAD trial cohort, participants in ADNI with the following characteristics were included: 50-80 years with a diagnosis of mild cognitive impairment (MCI) or dementia, ≥6 years of education history, baseline CDR-Global score of 0.5 or 1.0, baseline MMSE score of ≥20, documented amyloid-positivity at any time in the database, baseline CDR-SB score with at least one follow-up score within 5 years of baseline score, and non-missing values for each of the ECog-12 items on either the PRO or ObsRO version of the test at baseline. The total ECog-12 score at baseline for participants was derived from the appropriate item level questions of the ECog-39 questions in the ADNI datasets. Linear mixed models adjusted for age were used to estimate participants' rate of change in CDR-SB scores from baseline standardized to 78 weeks of follow-up and then categorized by their degree of CDR-SB change. Non-progressors/Improvers were defined as those who had a CDR-SB change score of ≤0 points. Rapid progressors were defined as those who had a change of ≥5 points. Normal progressors were defined as those who had a change of >0 but <5 points. Descriptive statistics for these three CDR-SB progression groups were then explored for both the PRO and ObsRO version of the ECog-12 score at baseline to determine if differences existed by subsequent progression group. Tukey post-hoc tests were used to test for statistical differences in means between groups. **Results:** A total of 306 participants were included in our study population of which 54.2% were male with a mean age of 71.1 (SD=6.0). The study population was primarily white (94.4%), non-

Hispanic (95.8%), and highly educated (mean years of education 16.1). At baseline 74.5% had a diagnosis of MCI with the remainder having a diagnosis of dementia. Mean baseline CDR-SB score was 2.3 (SD=1.6) and mean baseline MMSE score was 26.6 (SD=2.7). The study population included N=234 (76.5%) Normal Progressors on CDR-SB, N=67 (21.9%) Non-Progressors/Improvers, and N=5 (1.6%) Rapid Progressors. At baseline, Normal Progressors were significantly older (71.6 years (SD=6.1) compared to Non-Progressor/Improvers (69.3 years (SD=5.4), p=0.02), had more impairment on baseline CDR-SB (p=0.001) and MMSE scores (p<0.001), and a smaller proportion were classified as MCI as opposed to AD (70.5% MCI in Normal Progressors vs 94.0% MCI in Non-Progressor/Improvers) (p<0.001). Only a small proportion of our study population consisted of Rapid Progressors which limited comparisons between groups, but compared to Normal Progressors, Rapid Progressors tended to have worse MMSE scores (p<0.001) and CDR-SB scores (p=0.001) at baseline. No significant differences by progressor group were found for mean PRO baseline ECog-12 score. The mean baseline PRO score for Non-Progressor/Improvers was 19.48 (SD=4.86), for Normal Progressors was 21.47 (SD=6.73), and for Rapid Progressors was 24.33 (SD=14.01). However, baseline means for the ObsRO version of the ECog-12 were significantly different between progressor groups (p<0.001). Study partners rated daily functioning as more impaired than participants in the Normal Progressor and Rapid Progressor groups. The mean for Non-Progressors/Improvers was 18.21 (SD=5.77), for Normal progressors was 26.57 (SD=9.58), and for Rapid Progressors was 36.60 (SD=4.56). In Tukey post-hoc tests, all group means significantly differed from each other. **Conclusions:** The study partner (ObsRO) ECog-12 score at baseline in ADNI generally captured higher levels of baseline functional impairment as compared to the PRO version and was significantly associated with subsequent CDR-SB progression groups over approximately 78 weeks. The study participant (PRO) generally self reported lower levels of impairment and scores were not significantly associated with subsequent progression. These results suggest that impairment as assessed on the ECog-12 test by the study partner may assist researchers in determining who may progress over the course of approximately 18-months. The PRO version of the ECog-12 scale at baseline did not show significant differences by subsequent progression on CDR-SB indicating that the participant may have less insight into their level of impairment compared to their study partner.

Disclosures: All authors are shareholders and employees of Biogen. This study was funded by Biogen.

Key takeaway message: The Study Partner ECog-12 scale may offer helpful insight to clinicians and researchers on who is likely to progress on the CDR-SB over approximately the next 1.5 years.

P315- IDENTIFYING INDIVIDUALLY-DEFINED TREATMENT PRIORITIES SENSITIVE TO CHANGE IN COGNITION.

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Background: Guidance from regulatory bodies recommends including the patient voice into clinical trial outcomes to establish meaningful treatment benefits. The electronic Person Specific Outcome Measure (ePSOM) addresses this by prompting individuals to define personally meaningful activities in their own words and rate their confidence in performing each. Unlike traditional scales with predefined items, ePSOM is fully individualised for each participant. To identify ePSOM outcomes most sensitive to treatment effects, we examine associations between treatment priorities and [1] cognitive impairment and [2] self-reported confidence. **Methods:** We evaluated 377 participants from the Scottish SBS-IONA study (median age=68 years [SD=8.35], median education=16 years [SD=3.24]). Each participant reported five priority areas in free text and rated their confidence in each using the ePSOM tool (1-5, higher = greater confidence, total score range 5-25) . We used the Digital Clock and Recall (DCR) as a measure of cognition (0-5, higher = better performance). We used a transformer architecture from large language models to link each response to one of 74 previously defined themes distilled from a separate database of 16,000 ePSOM responses. We used mixed-effects general linear models (GLM) with age as a covariate to test associations between confidence, themes (present or not), and cognitive performance (random intercepts per participant). **Results:** The most common themes involved "Being a good parent/grandparent" (N = 149), "Volunteering" (137), "Organising home and finances" (117), and "Physical exercise" (100). Total confidence was high (median = 24, IQR = 4), and correlated with cognitive performance ($T = 3.04$, $p < 0.005$). A log-normal model showed lower confidence for "Keeping composure" ($T = -3.16$, $p < 0.005$) and "Having a good memory" ($T = -2.22$, $p < 0.05$). At the individual response level, a continuous ratio mixed effect model showed significantly higher confidence for themes such as "Being a good parent/grandparent" ($z = 2.08$, $p < 0.05$) and "Organising home and finances" ($z = 2.23$, $p < 0.05$), and lower confidence for "Having a good memory" ($z = -4.01$, $p < 0.001$) and "Keeping composure" ($z = -3.17$, $p < 0.01$). Additional models included an interaction between theme and DCR score, showed consistent main effects of age and DCR score (all $p < 0.05$), and main effects of theme presence for "Having a good memory" ($z = -2.55$, $p < 0.05$), "Keeping composure" ($z = -2.47$, $p < 0.05$), and "Organising home and finances" ($z = 2.33$, $p < 0.05$), with no significant interactions. **Conclusions:** Our analysis of individually defined treatment priorities grouped into themes identified specific areas that may be most sensitive to early cognitive impairment, such as loss of confidence in "Having a good memory" and "Keeping composure". Our findings suggest that loss of confidence in specific personally meaningful areas is indicative of cognitive change, and not due to age. Self-reported confidence tracked with objectively measured cognitive performance, indicating that person-specific outcome measures enhance early detection of subtle cognitive change. A person-specific approach can inform study endpoints that reflect meaningful clinical benefits, including domains not typically measured in traditional patient-reported outcome measures used in clinical trials. **Key takeaway message**: ePSOM analysis showed that lower confidence in personally defined areas (e.g., memory, composure) signals cognitive change independent of age; self-reported confidence tracks cognitive performance, supporting ePSOM for early detection and capturing domains beyond traditional PROMs.

P316- VALIDATION OF THE EARLY MILD ALZHEIMER'S COGNITIVE COMPOSITE (EMACC) THROUGH ASSOCIATIONS WITH BLOOD-BASED BIOMARKERS OF ALZHEIMER'S DISEASE.

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Background: The Early Mild Alzheimer's Cognitive Composite (EMACC) is an empirically derived composite of neuropsychological tests designed to be sensitive to cognitive change in biomarker-positive (Aβ+) Alzheimer's disease (AD) patients (Jaeger et al., 2017). It was recently used as the primary endpoint in a phase 2 clinical trial in AD (MINDFuL). Baseline analyses demonstrated strong psychometric properties and criterion validity with established AD outcomes (Barnum et al., 2025). To further validate EMACC, and consistent with FDA guidance on clinical outcome assessments, we examined correlations between EMACC performance and 2 disease-relevant blood-based biomarkers (pTau217 and GFAP). **Methods:** Baseline data were drawn from MINDFuL (NCT05318976), a phase 2 randomized, double-blind, placebo-controlled trial of XPro1595 in early AD (sponsored by INmune

Bio). Participants were selected based on clinical symptoms consistent with MCI or mild AD (NIA-AA stages 3–4) and the presence of pre-specified inclusion biomarkers of inflammation. For this analysis, we included participants with confirmed amyloid pathology, a baseline EMACC, and pTau217 and GFAP data, regardless of their inflammatory status. **Results:** EMACC performance at baseline showed significant negative correlations with pTau217 ($n = 103$; $r = –0.48$; $p < 0.001$) and GFAP ($n = 106$; $r = –0.42$; $p < 0.001$). Based on Cohen's (1988) conventions for effect sizes, these correlations fall in the moderate-to-large range, indicating clinically meaningful associations. Patients with lower EMACC scores, indicating poorer cognitive skills, demonstrated higher levels of blood-based disease biomarkers, indicating greater biological disease burden. **Conclusions:** Strong correlations between EMACC and the measured blood-based biomarkers support its construct and criterion validity. EMACC demonstrates sensitivity to early AD biology, reinforcing its potential to streamline clinical trials by providing a robust, biologically relevant cognitive endpoint in early AD.

Key takeaway message: Baseline Early Mild Alzheimer's Cognitive Composite (EMACC) performance correlates with pTau217 and GFAP, reinforcing its construct validity and potential as a robust cognitive endpoint aligned with disease biology in early Alzheimer's disease.

P317- BEST-FIT CLINICAL OUTCOMES ASSESSMENT MEASURES TO EVALUATE WHAT MATTERS MOST IN ALZHEIMER'S DISEASE: IDENTIFYING A CORE OUTCOMES SET FROM EXISTING MEASURES.

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Background: The What Matters Most (WMM) in Alzheimer's disease (AD) research program seeks to identify and measure disease- and treatment-related needs, preferences, and priorities of people at risk for or living with Alzheimer's disease (PLWAD) and their care partners. This program includes an ongoing series of studies sponsored by the Alzheimer's Disease Patient and Caregiver Engagement (AD PACE) Initiative of UsAgainstAlzheimer's. Previous WMM research identified concepts encompassing symptoms, functioning, and outcomes that were endorsed as important by individuals at risk for or living with mild cognitive impairment (MCI) or mild AD and care partners of those with moderate or severe AD living in the United States (US). This information was used to develop a conceptual model of disease, comprising 50 concepts across 6 domains: Thought Processing, Daily Activities, Emotions, Communication, Social Life/activities, and General Independence. Subsequently, an observational survey-based study was conducted to assess some psychometric properties of the conceptual model and to quantify the prioritization and impact of WMM concepts on daily life among a diverse population of PLWAD and care partners representative of the full spectrum of AD severity. To advance the measurement of concepts that matter most to individuals at risk for or living with AD, this study compared WMM concepts to existing clinical outcome assessments (COAs) including selected neurocognitive measures commonly used in AD clinical trials with a goal of identifying a core set of "best-fit" COAs. Candidate COAs were considered those that best balanced (1) broad coverage and rigorous measurement of the WMM concepts with (2) use or potential use in clinical trials. Results can guide AD researchers in the selection of patient-centric outcome measures with a demonstrated link to priorities among those living with cognitive impairment and their care partners. Further, the concept mapping presented here also provides insights into the limits of existing measures relative to WMM priority concepts, offering a foundation for future support of regulatory and reimbursement evaluations of new drugs. **Methods:** A targeted literature review was conducted to identify candidate COAs, meaning measures with appropriate development and established measurement properties specific for use across the spectrum of AD severity that may capture the WMM concepts as identified by the AD PACE Initiative. ClinicalTrials.gov was searched to identify COAs, including neurocognitive measures that have been used in registries, interventional studies, and recent drug approvals in the US within the past 5 years (2012-2022 primary completion dates). A subset of candidate measures was selected for concept mapping based on relationship to at least 1 WMM domain, measurement properties, and utility (e.g., number of items, response window) of the measure. Consistent with previous mapping of widely used COA items to WMM concepts, items from both frequently used COAs and newly identified, additional ("supplemental") COAs were reviewed and matched either directly or indirectly to WMM concepts. Evidence for each candidate COA was reviewed to determine how existing measures meet needs for assessing the WMM concepts that are of greatest importance to individuals at risk for or living with AD or their care partners. Measurement gaps, where WMM concepts lack a corresponding measure, were identified. **Results:** Among 20 COAs identified as most frequently used in clinical trials, 8 were selected for mapping: ADCOMS, ADCS-ADL-MCI, CDR (including CDR Sum of Boxes), FAQ, iADRS, NPI/NPI-Q, PACC, and QoL-AD. Searches for additional ("supplemental") measures for the WMM model identified an additional 20 measures, 11 of which were selected for mapping of comprehensive coverage of WMM concepts. These included the A-IADLs, ADRQL, AES, BADLs, CMAI, CFIa, CogState C3, Daily Diary Assessments, eCog, NIH Toolbox, and PROMIS/Neuro-QoL Short Forms. Subject-, care partner-, and clinician-reported versions of tools were included. As expected, no single measure was identified that provided complete, direct coverage of all WMM concepts. The selected best-fit measures offered the broadest direct or indirect alignment with the WMM model. However, important measurement gaps were identified regarding coverage and assessment of specific concepts/domains relevant to the WMM prioritization and impact evaluations. **Conclusions:** This work identifies existing COAs that align with concepts from among those identified as "What Matters Most" to PLWAD and their care partners. This work also provides guidance for selecting appropriate outcome measures for the intended population, targeted concepts, and hypothesized trajectory of change relative to the patient-centric WMM concepts. We propose 2 best practice recommendations for implementing measurement of patient-centric concepts: (1) specifically identify and select a combination of measures that provide robust coverage of the concept(s) of interest, and (2) ensure selected measures provide direct coverage of target WMM concepts from multiple perspectives whenever possible (i.e., PLWAD, care partner, clinician). Critically, this work demonstrates the unmet need and measurement gap for WMM concepts that remain indirectly or incompletely covered by existing COAs.

Key takeaway message: This study provides broad guidance for selecting robust measures in Alzheimer's disease that represent patient-centric outcomes for the intended population, targeted concepts, and the hypothesized trajectory of change by concept.

P318- EARLY INFUSION-RELATED REACTIONS WITH CSF INFLAMMATORY CHANGES IN TWO LECANEMAB-TREATED AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE CASES.

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Background: Drug-induced aseptic meningitis (DIAM) is a rare adverse reaction, most often linked to intravenous immunoglobulins and certain monoclonal antibodies. To our knowledge, DIAM has not previously been described in association with anti-amyloid therapies. Lecanemab, a humanized IgG1 targeting Aβ protofibrils, received full FDA approval in 2023 for the treatment of Alzheimer's disease (AD) and is currently administered in the DIAN-TU NextGen trial in combination with E2814/placebo. Here, we report two cases of aseptic meningitis-like infusion reactions following the first infusion of Lecanemab in participants with dominantly inherited AD (DIAD). **Methods:** Clinical, imaging, and cerebrospinal fluid (CSF) data were collected prospectively within the DIAN-TU NextGen E2814 trial. Both participants underwent standard baseline assessments, including MRI, PET, and lumbar puncture. Lecanemab was administered per trial protocol (10 mg/kg biweekly). Diagnostic evaluation during hospitalization for early symptoms after infusion included CSF analysis, MRI, infectious PCR panels, and cultures. Management decisions were guided by local infectious disease and neurology teams. **Results:** Case 1: A symptomatic PSEN1-M146V mutation carrier (EYO +2) developed an initial headache ~6 hours after a 1540 mg Lecanemab infusion, progressing to fever and meningismus within 30–36 hours. CSF revealed 408 cells (90% polymorphonuclear cells [PMN]), elevated protein (107 mg/dL), and preserved glucose. Safety MRI at admission showed convexal sulcal hyperintensities with no evidence of ARIA compared to baseline. Initial management included broad-spectrum antibiotics and antivirals per local protocol, but rapid resolution occurred within 24 hours, temporally associated with corticosteroid therapy. A follow-up CSF examination was normal. The patient had no symptons in subsequent Lecanemab infusions (n=35) with corticosteroid premedication. A potential confounder was a recent tooth extraction with incomplete antibiotic treatment. Case 2: An asymptomatic PSEN1-M146L mutation carrier (EYO –8) developed chills, fever, and headache four hours after a 700 mg infusion. CSF showed 120 cells (75% PMN), mild protein elevation (50 mg/dL), and normal glucose. MRI demonstrated subtle frontal sulcal hyperintensities with no change from baseline. Infectious studies were negative. Corticosteroid treatment led to full recovery within 48 hours. No follow-up lumbar puncture was performed given the favorable clinical course. The patient resumed study treatment without recurrence. Both cases presented as early infusion-related reactions with meningeal signs prompting CSF studies but without evidence of infection. The temporal association with Lecanemab initiation, stereotyped clinical course, and rapid corticosteroid response are most consistent with DIAM. **Conclusions:** These are among the first documented cases of DIAM following Lecanemab infusion. The findings emphasize the need for awareness of this presentation as a potential early infusion-related reactions in anti-amyloid therapy, consistent with infusion reactions described with other IgG antibodies in other treatment areas. Notably, both patients were relatively young (31–40 years), raising the hypothesis that younger individuals may be more prone to IgG infusion reactions or more pronounced manifestations, though this requires further investigation. Importantly, in both cases rapid recognition and management with standard infusion-related reaction protocols, including corticosteroid treatment led to swift recovery. The rapid recovery and absence of recurrence during continued therapy are reassuring and supports sustained treatment safety. **Key takeaway message:** We describe two cases of aseptic meningitis-like infusion reactions following first Lecanemab infusion in DIAD. Both resolved rapidly with corticosteroids, underscoring the need for awareness, prompt diagnosis, and preventive strategies in AD immunotherapy.

P320- VALIDATION OF A NOVEL COGNITIVE-FUNCTIONAL OUTCOME MEASURE OPTIMIZED FOR EARLY AD: EVIDENCE FROM THE VIVA-MIND TRIAL.

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Background: Hybrid composite cognitive-functional measures are increasingly used as primary efficacy endpoints in clinical trials of treatments targeting early Alzheimer's disease (AD). These composites may have better measurement properties and enable trials with smaller sample size compared to trials using co-primary endpoints. More efficient endpoints allow trials to be performed at decreased cost and with less human subject burden. Importantly, in contemporary clinical trials of amyloid-lowering monoclonal antibody treatment enrolling participants with mild cognitive impairment (MCI) and mild AD dementia, composite cognitive-functional measures have been successfully used to demonstrate treatment efficacy (1,2). In these trials the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) has been a preferred primary efficacy endpoint. However, its sensitivity to change in rate of decline relative to other composite cognitive-functional measures has not been rigorously evaluated in a prospective randomized clinical trial (RCT) setting. **Methods:** To explore the sensitivity of alternative cognitive-functional endpoints, we used data from the VIVA-MIND phase 2A/B RCT investigating the safety and efficacy of the small-molecule treatment varoglutamstat in patients with early AD. Participants (n = 109) met clinical inclusion criteria for MCI or mild probable AD and CSF biomarker criteria consistent with AD pathology (3). In mid-2024, the VIVA-MIND trial was prematurely terminated by the study sponsor. Subsequent analyses indicated that none of the primary or secondary efficacy endpoints in VIVA-MIND were reached with the available study sample (4). For VIVA-MIND phase 2B the CDR-SB was the primary efficacy endpoint while the CFC2, a cognitive-functional composite described by Raghavan and colleagues (5), was included as a key secondary endpoint. The CFC2 is composed of Word Recall, Delayed Word Recall, and Orientation from the Alzheimer's Disease Assessment Scale—Cognitive Subscale (ADAS-Cog); box scores for the cognitive components of the CDR (Memory, Orientation, Judgement & Problem Solving); and the Functional Activities Questionnaire (FAQ). Using data from MCI and AD participants in a retrospective analysis of ADNI data, the CFC2 has previously been shown to be more sensitive than the CDR (5). Retrospective observational cohort data may or may not be representative of participants recruited to an active clinical trial, thus replication of this finding in a clinical trial setting is necessary to further validate use of the CFC2 as an efficacy endpoint. We additionally derived an optimally-weighted version of the CFC2 using component measure weights estimated from a representative sample in ADNI. Optimal weights for constructing a composite endpoint are a function of the expected change and covariance of change of the component tests and are intended to maximize the sensitivity to detect rate of decline. Thus, we used the VIVA-MIND data to validate the use of the CFC2 and optimally-weighted CFC2 through comparison against existing benchmarks. Our analysis is based on standard power calculations using parameters obtained from linear mixed effects models fit to the VIVA-MIND data. The most important indication of performance is the signal-to-noise ratio which is a function of the coefficient of change and the variance parameters. Measures that have a high signal-to-noise ratio are the most sensitive to change in rate of decline and would require a lower number of participants per arm to detect a prespecified treatment effect. We report the relative efficiency comparing the CDR-SB with the CFC2 and other secondary and exploratory outcomes including the ADAS-Cog-13, Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), FAQ, and AD Composite Score (ADCOMS). Bootstrap confidence intervals were used to reflect variability in the estimated parameters obtained from the linear mixed effects model. **Results:** According to these comparisons the novel CFC2 cognitive-functional composite was found to be more sensitive to change in decline than the CDR-SB. Relative to the CDR-SB which would require 314 subjects per arm for 80% power to detect a 25% change in rate of decline in a 72 week trial, the CFC2 would require 268 subjects

per arm, representing a 15% gain in efficiency. The optimally-weighted CFC2 showed even greater sensitivity, yielding a 23% gain in efficiency relative to the CDR-SB and also modestly outperforming the ADCOMS cognitive-functional composite. Collectively, the cognitive-functional composites (CDR-SB, CFC2, optimally-weighted CFC2, and ADCOMS) significantly outperformed standard cognitive endpoints including the ADAS-Cog-13, the MMSE, and the MoCA, and the functional endpoint, FAQ. **Conclusions:** Using the prospective VIVA-MIND RCT data we showed that the CFC2 is more sensitive to decline than the CDR-SB in early AD and thus may provide considerable gains in clinical trial efficiency in this population. The optimally-weighted CFC2 offered even greater improvements in efficiency and outperformed ADCOMS, another cognitive-functional composite measure derived from ADNI data and optimized for use in early AD. The VIVA-MIND trial provides evidence that significant improvements in the efficiency of early AD trials may be realized through selection of a primary endpoint optimized to detect change in rate of decline in the targeted clinical trial population. While further research is needed to fully inform the determination of optimal endpoints for early AD, our findings suggest that the CFC2 and optimally-weighted CFC2 may provide practically significant improvements in the efficiency of clinical trials in this population.

Keywords: Cognitive-functional composites, clinical trial efficacy, optimal-weighting.

Clinical Trial Registry: NCT03919162.

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Key takeaway message: The novel CFC2 measure of cognition and function may offer substantial sample size savings over existing cognitive-functional composite endpoints in early AD.

P321- EVALUATING A PERSONALIZED ENDPOINT IN DOWN SYNDROME–ASSOCIATED ALZHEIMER'S DISEASE: FEASIBILITY AND STAKEHOLDER PERSPECTIVES.

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Background: Evaluating health outcomes in Down syndrome-associated Alzheimer's disease (DS-AD) is challenging due to variability in baseline function and cognition. Traditional standardized outcome measures often fail to capture meaningful change in this population due to the wide variability in baseline functioning, symptom manifestations, and the heterogeneous patterns of decline and progression. Personalized, patient-centric assessments, such as Goal Attainment Scaling (GAS), offer a promising solution by allowing for the measurement of treatment effects tailored to individual patient goals (1). However, the successful implementation of GAS in a clinical trial setting requires rigorous standardization to ensure consistency, transparency, and psychometric robustness. The primary objective of this study was to investigate the feasibility and acceptability of a standardized, inventory-facilitated GAS protocol as a patient-centric tool for evaluating treatment response in individuals with DS-AD. **Methods:** This was a prospective, 16-month, non-interventional study. We developed a defined protocol for goal selection, scaling, and utilized a DS-AD goal inventory (2) to guide the clinician-facilitated goal setting with caregivers of individuals with Down syndrome. A total of 46 participants with DS and their caregivers enrolled in the study and completed an initial goal-setting visit at baseline. The caregiver served as the primary interviewee, and the participant was encouraged to be involved in the process whenever possible. Each dyad was required to set a minimum of three personalized goals. GAS interviewers used the provided inventory to facilitate goal selection, but caregivers were not restricted to the inventory and could establish novel «other» goals. DS-AD goal inventory included goals in Behaviour, Cognition, Daily Function, Executive Function, or Physical Manifestations domains. Goal attainment was assessed during two subsequent follow-up interviews at Month 3 and Month 16. Feasibility indicators included the number of goals set, data completeness, and the time required to complete the GAS interviews. To evaluate acceptability, separate end-of-study surveys were administered to both caregivers and GAS interviewers to capture their experiences with participating in and administering the GAS protocol, respectively. These surveys included a combination of multiple-choice and open-ended questions. **Results:** The Goal Attainment Scaling protocol demonstrated strong feasibility and acceptability. Of the 46 enrolled participants, all caregivers (100%) successfully set a minimum of 3 goals, each with a 5-level scale. Goal attainment assessments were completed by 45 participants at the 3-month follow-up and 43 participants at the 16-month follow-up, representing attrition rates of 2.2% and 6.5%, respectively, and indicating high participant retention. The mean time for the initial goal-setting interview was 38.6 ($\pm$10.4) minutes. Subsequent follow-up interviews required significantly less time, with mean times of 17.9 ($\pm$9.5) minutes at Month 3 and 14.5 ($\pm$4.7) minutes at Month 16. Survey results from 33 caregivers indicated a high degree of acceptability. A majority of caregivers reported positive experiences with the GAS process (n=31), found the goals they selected to be highly meaningful (n=31), and valued the improved communication with clinicians that the process facilitated (n=30). A significant number also reported gaining new perspectives and knowledge regarding their loved one's condition and care needs (n=10). **Conclusions:** This study demonstrates that a standardized, inventory-facilitated Goal Attainment Scaling protocol is both feasible and acceptable for assessing patient-centric outcomes in the DS-AD population. The high rates of data completeness and strong positive feedback from caregivers suggest that this methodology can provide a robust and meaningful approach for measuring individualized treatment effects. These findings support the use of GAS as a valuable outcome measure in future clinical trials aimed at evaluating the efficacy of new therapies for Down syndrome-associated Alzheimer's disease. **Keywords:** Down syndrome-associated Alzheimer's disease, outcome assessment, personalized outcomes, goal attainment scaling, feasibility.

Clinical Trial Registry: NCT04149197; https://clinicaltrials.gov.

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Key takeaway message: Goal Attainment Scaling (GAS) is a patient-centric tool that can be used to evaluate health outcomes in Down syndrome-associated Alzheimer's disease; personalized outcome assessment using a standardized, inventory-facilitated GAS protocol is feasible and acceptable.

P322- DEVELOPMENT OF PROGNOSTIC MODELS FOR FIVE-YEAR RISK OF CLINICAL PROGRESSION FROM PRECLINICAL ALZHEIMER'S DISEASE (STAGE 1 AND 2) TO COGNITIVE IMPAIRMENT: FINDINGS FROM THE A4 STUDY.

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Background: Individuals with preclinical Alzheimer's disease (AD) have presence of amyloid pathology but are cognitively unimpaired. This early stage of disease (Stage 1 and 2) represents a critical juncture in the disease continuum; however, the ability to predict who will progress to cognitive impairment in the near-term remains limited. While biomarkers and cognitive measures have been individually linked to risk of progression among individuals with symptomatic AD, few studies have developed integrated prognostic models to estimate the likelihood of clinical progression in cognitively unimpaired populations. Improved tools to identify individuals at highest risk of near-term progression from the preclinical stage (Stage 1 and 2) could inform clinical trial design, enhance participant selection, and support early intervention strategies aimed at slowing progression to early symptomatic AD. **Objectives:** To identify baseline demographic, clinical, genetic, and biomarker factors most strongly associated with rapid clinical progression, develop a five-year prognostic model for estimating risk of near-term progression, and evaluate model predictive performance using internal validation among individuals with preclinical AD. **Methods:** The prognostic modeling study was based on secondary analysis of data from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) study, which enrolled cognitively unimpaired adults aged 65-85 with elevated amyloid on positron emission tomography (PET), consistent with preclinical AD. Participants were included in the analysis if they had Mini-Mental State Examination score of 27–30, Clinical Dementia Rating Global score (CDR-GS) of 0, and $\geq$1 follow-up visit with an available CDR score. Index date was defined as the first visit when these criteria were met. Candidate predictors included demographic, clinical (i.e., cognitive scores, subjective cognitive-functional measures), genetic, and biomarker (i.e., amyloid PET, plasma P-tau217) measures. The outcome for clinical progression was time from index date to first occurrence of CDR-GS $>$0. Predictor variable selection was guided by statistical significance, clinical relevance, and feasibility for use in real-world settings. Random survival forests (RSF) with cross-validated hyperparameter tuning were first applied to rank all potential predictors on permutation-based variable importance. Second, variables with high importance were further refined based on clinical input and availability in real-world settings. Continuous predictor variables were subsequently categorized using clinically relevant thresholds, when available, or data-driven optimal cut-points. Third, Cox proportional hazards models were used to evaluate predictive performance and further select the most informative predictors in a nested k-fold cross-validation procedure. Discrimination was assessed with Harrell's C-Index and time-dependent area under the receiver operating characteristic curve (AUC); calibration was evaluated with the Integrated Brier Score (IBS). Based on the best-performing parsimonious Cox model estimates, continuous risk scores were rescaled to 0–100 range by multiplying model coefficients by a scaling constant. Out-of-fold participants were grouped into risk groups based on quantiles of the risk score, and Kaplan-Meier survival analyses were used to assess the ability of each model to stratify individuals according to 5-year risk of clinical progression. **Results:** Of 1,169 individuals enrolled in A4, 1,034 participants (88.5%) met the inclusion criteria for the analytic sample. Mean (standard deviation [SD]) age at index was 71.8 years (4.7), and 59.6% of participants were female. Median follow-up time was 5.5 years (minimum 1.6 years, maximum 5.5 years). During follow-up, 442 participants (42.7%) experienced AD clinical progression. RSF identified baseline cognitive and subjective cognitive-functional measures (Cognitive Function Index [CFI] combined participant and study partner total score and subcomponents, CDR-Sum of Boxes [CDR-SB] score, Preclinical Alzheimer Cognitive Composite [PACC] score and components), plasma P-tau217, age, and sex as having the highest permutation importance. Three multivariable Cox models were selected, all including age, sex, and education as predictors, and in addition: Model A: CFI combined participant and study partner total score and plasma P-tau217 (C-Index=0.647; AUC=0.706; IBS=0.129) Model B: participant CFI Item 15–Seen a doctor about memory concerns and plasma P-tau217 (C-Index=0.617; AUC=0.680; IBS=0.136). Model C: five CFI participant item scores: 01–Memory declined substantially; 03–Misplacing things more often; 04–Relying more on written reminders; 12–Activities substantially more difficult; and 15–Seen a doctor about memory concerns (C-index=0.632; AUC=0.693; IBS=0.133). Model A had the best performance, showing moderate discrimination and acceptable calibration over 5 years. Models B and C showed somewhat lower performance, offering options where plasma biomarkers or full CFI assessment are not feasible. Kaplan–Meier curves of out-of-fold risk tertile groups demonstrated clear separation for all three models (log-rank P$<$0.0001). Across risk groups, the 5-year cumulative incidence of clinical progression for the low-, intermediate-, and high-risk groups, respectively was 22%, 38%, and 61% (Model A); 22%, 40%, and 57% (Model B); and 24%, 37%, and 61% (Model C). **Conclusions:** Prognostic models using demographic, subjective cognitive-functional, and plasma P-tau217 measures can stratify individuals with preclinical (Stage 1 and 2) AD into distinct risk groups for 5-year clinical progression. The best-performing model combined CFI total score with plasma P-tau217, while simpler models relying on limited items assessing subjective changes in cognition or function or excluding plasma P-tau217 yielded lower but acceptable performance. These findings support the use of demographic characteristics, brief questions on cognitive functioning, and plasma P-tau217 data, to predict near-term progression risk, enhance preclinical AD trial enrollment, and inform early intervention strategies.

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Key takeaway message: Prognostic models combining demographics, cognitive-functional measures, and plasma P-tau217 levels can stratify

individuals with preclinical AD into distinct risk groups for 5-year clinical progression, supporting more targeted trial enrollment and earlier intervention strategies.

P323- REGIONAL DIFFERENCES IN THE PRESENCE OF DATA QUALITY CONCERNS IN DEMENTIA CLINICAL TRIALS.

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Background: Data quality issues are common in Alzheimer's disease clinical trial datasets, often affecting a significant portion of collected data. Many of these issues are concentrated at certain sites and can compromise the validity and interpretability of study outcomes. In this post-hoc analysis of a large database of Alzheimer's disease clinical trials, we aimed to determine whether there are identifiable regional differences in the likelihood that a site will be flagged as problematic. **Methods:** We analyzed data quality metrics from 11 Alzheimer's disease clinical trials, focusing on individual trial sites. For each site, we recorded the number of trials participated in and the number of times the site was identified as problematic—defined as being a significant outlier for at least one data quality concern (e.g., scale administration or scoring errors, discordance within or between scales, extreme variance, inclusionary issues, or suspicious data suggestive of tampering). Using a binomial regression model, we estimated the odds ratios for a site in each country being identified as problematic, using the US as the reference country. **Results:** Among the 1,134 sites analyzed, 744 (66%) participated in only one trial, and 831 (73%) were never identified as problematic. Sites involved in multiple trials had a higher probability of being flagged at least once (42%) compared to those in only one trial (19%) ($p < 0.001$). Of the 390 sites that participated in two or more trials, only 39 (10%) were identified as problematic on more than one occasion. Notably, among countries with at least 10 sites participating in multiple trials, 29% of Spanish sites were repeatedly flagged. The binomial regression revealed significant country-level differences in the odds of a site being problematic when compared to the US. The 3 countries demonstrating the largest increased odds were Brazil ($OR = 7.9$, $p < 0.001$), Serbia ($OR = 7.6$, $p < 0.001$), and Italy ($OR = 3.1$, $p < 0.001$). Conversely, Japan had significantly lower odds ($OR = 0.3$, $p = 0.004$). **Conclusions:** This post-hoc analysis of a large dataset of dementia clinical trial sites found that over 70% of sites provided data of acceptable quality. When data quality concerns did arise, they were typically isolated incidents. However, the likelihood of problematic data varied by region, with certain countries exhibiting significantly higher odds. Additionally, a small subset of sites was repeatedly identified as problematic, representing a potential risk for future studies. Sponsors should carefully evaluate these sites before including them in future trials.

Key takeaway message: The need for sponsors to strongly consider not only a site's historical performance as it pertains to ratings quality, but to also appreciate regional differences as they plan future studies.

P324- COMPARATIVE SENSITIVITY OF MMSE, RESTING-STATE EEG, AND EVENT-RELATED POTENTIALS IN LONGITUDINAL COGNITIVE DECLINE DETECTION.

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Background: Electroencephalography (EEG), a non-invasive method with high temporal resolution, is increasingly used to detect early markers of cognitive decline through measurements of resting-state activity and event-related potentials (ERPs), which reflect spontaneous and stimulus-locked evoked neural processes, respectively. In contrast, the Mini-Mental State Examination (MMSE), though widely used as a clinical screening tool, lacks the sensitivity to detect subtle changes over short intervals. This study investigates whether a pre-defined set of 22 EEG/ERP-based metrics is more sensitive than MMSE in detecting cognitive decline over a one-year period in both healthy older adults and individuals with memory impairment. **Methods:** Participants included volunteer healthy controls with no history of central nervous system disorders (n=30, ages 40–90) and a patient group (n=30, ages 40–90) diagnosed with unspecified dementia, Mild Cognitive Impairment (MCI), or Alzheimer's Disease (AD). All participants completed MMSE and a standardized cognitive task battery, which included eyes-open and eyes-closed resting-state recordings and three ERP-eliciting tasks: an active auditory oddball discrimination task (AAO), an image memory recognition task (SIR), and a three-choice vigilance task (3-CVT). Resting-state features examined included peak alpha frequency, posterior dominance of alpha (PDA), and individualized theta/alpha ratio (ITAR). ERP features included N1 peak latency, P300 latency and amplitude, mismatch negativity, reaction time, and accuracy from the AAO task; P2 peak latency, late positive potential (LPP) mean amplitude, reaction time, and accuracy from the SIR task; and P1 peak latency, LPP mean amplitude, reaction time, and accuracy from the 3-CVT task. Assessments were conducted at baseline and repeated after one year. Paired t-tests were used to evaluate within-subject changes in MMSE scores, resting-state EEG metrics, and ERP features. Effect sizes for significant results were calculated using Cohen's d. The primary objective was to determine whether resting-state and ERP-based EEG measures are more sensitive than MMSE in detecting cognitive decline over a one-year period. **Results:** Both healthy controls and the patient group showed no significant changes in MMSE scores between year one and year two. In the healthy control group, both resting state and ERP measures did not change across all tasks over the one-year period. In contrast, the patient population demonstrated increased N1 peak latency and decreased accuracy in the AAO task ($p=0.02$, Cohen's $d=0.37$; $p=0.04$, Cohen's $d=0.54$, respectively). Patients exhibited significantly slower response times in the SIR task ($p=0.03$, Cohen's $d=0.79$) and reduced accuracy in the 3-CVT task ($p=0.02$, Cohen's $d=0.34$), suggesting emerging impairments in attention, memory, and cognitive processing not captured by MMSE. **Conclusions:** Despite stable MMSE scores over a one-year period, the clinical patient group exhibited significant changes in several EEG measures, including increased N1 peak latency and decreased task accuracy in AAO, prolonged response times in SIR, and reduced accuracy in 3-CVT. These findings suggest that EEG components and behavioral responses acquired during ERP tasks may be more sensitive than MMSE in detecting subtle cognitive decline and may serve as effective biomarkers for monitoring neurodegenerative changes over short intervals. **Keywords:** EEG, resting state, event-related potentials, MMSE, cognitive decline.
Disclosures: This research was supported by the National Institute on Aging, National Institutes of Health, under grant number R44AG050326.

Key takeaway message: EEG and ERP metrics revealed cognitive changes in memory-impaired individuals over one year that were not captured by MMSE, underscoring their potential as more sensitive tools for early detection of neurodegenerative decline.

P325- MEMORY SUPPORT TRAINING AND LIFESTYLE MODIFICATIONS TO PROMOTE HEALTHY AGING IN PERSONS AT RISK FOR ALZHEIMER'S DISEASE: BRAIN BOOSTERS RANDOMIZED CONTROLLED TRIAL INITIAL RESULTS.

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Background: Prior research suggests that modifying certain lifestyle and behavioral factors before symptom onset may prevent up to half of

the dementia cases (1). These effects may be particularly relevant for older adults with subjective cognitive decline (SCD) but normal performance on formal cognitive testing as they are at high risk for developing dementia (2). Additionally, providing memory support through compensatory aids, such as calendars and 'to do' lists, can maintain functional independence (3) and utilization of digital applications can support behavior change (4), thereby reducing dementia risk. Here we report some initial results of a randomized controlled trial designed to test a multidomain 6-month intervention combining training in rehabilitation-based memory strategies and lifestyle modifications (physical exercise, cognitive/social engagement, and well-being exercises) supported by a digital application. The target intervention group is compared to an education only group (matched for social aspects of the intervention). Study aims include: 1) evaluate intervention efficacy on primary (global cognition and self-report daily function) and secondary (proximal measures of behavior change such as engagement in physical and cognitive activity, use of compensation strategies, etc.) outcomes immediately following the six-month intervention and 2) evaluate whether self-determination theory (SDT) (5) and demographic characteristics impact intervention response to better understand who the intervention benefits. Outcomes are measured 6 (immediately following the intervention), 12, and 18 months after baseline; results reported here are the 6-month findings. **Methods:** Enrollment included 270 community-dwelling English-speaking participants age 65+ with SCD. Participants were randomly assigned to either the target intervention or education only group in a 2:1 ratio. Primary outcomes included global cognitive function measured by the modified Neuropsychological Test Battery (6) and self-report daily function measured by the Everyday Cognition questionnaire (7). Secondary outcomes included measures of self-efficacy (8), mood and stress management (9-14), physical performance (15), quality of life (16), informant report of daily functioning (17), compensation strategies (18,19), and health behaviors targeted directly by the intervention (physical exercise, cognitively stimulating activities, social engagement, gratitude, positive and negative affect, and mindfulness) (20-23). Predictors of intervention response included SDT measures around health self-management and perceived competence (24,25), social support (26), and autonomous motivation (27) in addition to dementia risk measured with the CAIDE (28). Using an intent-to-treat framework, multiple linear regression models were built for each primary and secondary outcome to evaluate intervention effectiveness. To better understand for whom the intervention worked, these models were extended to evaluate a pre-specified set of potential treatment modifiers (demographic and SDT measures). **Results:** Immediately following the intervention (6-months from baseline), no significant intervention effects were detected for the primary outcomes of global cognitive or self-report daily function. For the more proximal secondary outcomes, individuals in the target intervention group demonstrated significantly greater improvements in their frequency/week of cognitive activities ($p = 0.01$) and in gratitude ($p = 0.03$) compared to the education only group. When examining predictors of change in treatment response, individuals with higher perceived competence at baseline demonstrated more positive effects from participation in the intervention compared to education only on frequency/week of social activities ($p = 0.04$). Greater baseline autonomous motivation was associated with more positive intervention effects on physical performance ($p = 0.04$) and hours/week of moderate-to-vigorous physical activity ($p = 0.04$). Lastly, higher baseline dementia risk was associated with greater benefit from the intervention on quality of life ($p = 0.04$) and lesser benefit on hours/week of moderate-to-vigorous physical activity ($p = 0.02$). **Conclusions:** Although no significant intervention effects were observed for the primary outcomes immediately following the intervention, the target intervention group showed meaningful improvements in secondary outcomes related to behavior change, including increased cognitive activities and gratitude, compared to the education only group. These more proximal behavior change measures may serve as early indicators of future improvements in daily functioning and cognition, particularly given the established link between lifestyle behaviors and dementia risk reduction (2). Therefore, it will be important to evaluate outcomes at the 12 and 18-month timepoints to determine whether these early behavioral changes for the intervention group result in sustained group differences in daily function and cognition. When examining treatment response, the target intervention provided some benefits for individuals with higher levels of perceived competence and autonomous motivation, which suggests that these SDT characteristics may be important in motivating behavior change during this intervention. Additionally, the target intervention may be particularly efficacious in improving quality of life in individuals with higher dementia risk.

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construct validity and associations with diagnosis and longitudinal change in cognition and everyday function. J Int Soc Neuropsychol 2020; 26 (3): 303-313. http://doi.org/10.1017/S135561771900119X. 20. Stewart AL, et al. CHAMPS physical activity questionnaire for older adults: outcomes for interventions. Med Sci Sports Exerc 2001; 33 (7): 1126–1141. 21. Diener E, et al. New measures of well-being: Flourishing and positive and negative feelings. Soc Indic Res 2010; 39: 247–266. http://doi.org/10.1007/s11205-009-9493-y. 22. McCullough ME, et al. The Grateful Disposition: A conceptual and Empirical Topography. J Pers Soc Psychol 2002; 82 (1): 112–127. http://doi.org/10.1037/0022-3514.82.1.112. 23. Walach H, et al. Measuring mindfulness–The Freiburg Mindfulness Inventory (FMI). Personality Individ Difer 2006; 40 (8): 1543–1555. http://doi.org/10.1016/j.paid.2005.11.025. 24. Anderson-Buther D, et al. Initial reliability and validity of the perceived social competence scale. Res Soc Work Pract 2008; 18 (1): 47-54. http://doi.org/10.1177/1049731507304364. 25. Hibbarb JH, et al. Development and testing of a short form of the patient activation measure. Health Serv Res 2005; 40 (6): 1918-1930. http://doi.org/10.1111/j.1475-6773.2005.00438.x. 26. Sallis JF, et al. The development of scales to measure social support for diet and exercise behaviors. Prev Med 1987; 16 (6): 825–836. http://doi.org/10.1016/00917435(87)90022 3. PMID: 3432232. 27. Ryan RM, et al. Perceived locus of causality and internalization: Examining reasons for acting in two domains. J of Personality and Social Psych 1989; 57 (5): 749-761. 28. Kivipelto M, et al. Risk score for the prediction of dementia risk in 20 years among middle aged people: A longitudinal, population-based study. Lancet 2006; 5 (9): 735-741. **Key takeaway message:** An intervention to prevent or delay dementia in older adults with subjective cognitive decline that combines training in rehabilitation-based memory strategies and lifestyle modifications supported by a digital application resulted in meaningful improvements in secondary outcomes related to behavior change immediately post-intervention and was most efficacious for individuals with high levels of self-determination theroy traits and higher dementia risk.

P326- MEDITERRANEAN DIET IN SUBJECTIVE COGNITIVE DECLINE: COGNITIVE, MOBILITY, AND NEUROIMAGING OUTCOMES FROM A RANDOMIZED CROSS-OVER TRIAL.

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Background: Subjective cognitive decline (SCD) is recognized as a preclinical stage of Alzheimer's disease (AD) and a critical target for prevention. Beyond cognitive complaints, early mobility changes such as gait slowing may also independently signal heightened dementia risk. Adherence to the Mediterranean diet (MeDi) has been associated with reduced cognitive decline and AD risk, but its efficacy in SCD—particularly for cognitive, mobility, and neurobiological outcomes—remains unclear. This study investigated the effects of MeDi on both cognitive and mobility functional outcomes and neuroimaging biomarkers in individuals with SCD, to evaluate its potential role in early dementia prevention. **Methods:** We conducted a randomized crossover trial in which participants were allocated in a 1:1 ratio to either the MV group (Mediterranean diet followed by voluntary diet) or the VM group (voluntary diet followed by Mediterranean diet), with each dietary phase lasting 12 weeks. A washout period was implemented between phases for participants in the MV group. Demographic, clinical, and anthropometric data, ApoE genotype, Alzheimer's disease (AD) plasma biomarkers, and comprehensive blood biochemistry profiles were assessed at baseline and after each dietary phase. Primary outcomes included dual functional metrics encompassing both comprehensive neuropsychological assessments and physical performance measures—specifically gait speed, handgrip strength, and the five-times sit-to-stand test—as well as structural neuroimaging parameters, including total and regional grey matter volumes and white matter hyperintensity (WMH) volume. The secondary outcome was the change in plasma AD-related biomarkers, including Aβ40, Aβ42, and phosphorylated tau-217 (p-tau217). To ensure intervention fidelity—unlike prior studies that relied on self-managed dietary adherence—all Mediterranean diet meals were directly provided to participants. Meal plans were professionally designed by certified nutritionists to align with Mediterranean dietary principles while accommodating individual preferences and minimizing diet fatigue. Participants who consumed all meals as instructed would achieve a minimum Mediterranean Diet Serving Score (MDSS) of 6. All participants received at least two sessions of dietary education prior to the intervention, with the goal of achieving an MDSS $\geq$10 during the Mediterranean diet phase. Adherence was monitored biweekly via telephone or social media using a validated MDSS questionnaire. Baseline group differences were analyzed using non-parametric Mann–Whitney U tests. The effects of dietary intervention were assessed using linear mixed-effects models, adjusting for diet order. **Results:** A total of 93 participants were initially screened. Of these, 31 were excluded: age under 60 (n = 5), contraindications to brain imaging (n = 6), significant cognitive impairment (n = 3), presence of major comorbidities (n = 2), adherence to a vegetarian diet (n = 4), personal reasons (n = 2), identified MRI contraindications (n = 1) or inability to comply with the dietary intervention (n = 8). The remaining 62 participants were randomly assigned to either the MV group (n = 32) or the VM group (n = 30). Subsequently, three participants in the MV group withdrew due to difficulty adhering to the dietary protocol. The MV and VM groups were comparable in demographic characteristics, including age (MV: 68.9 ± 4.9 years; VM: 68.5 ± 4.8 years; p = 0.873), sex distribution (male: MV: 8; VM: 8; p = 1.000), and years of education (MV: 14.3 ± 3.5; VM: 15.4 ± 2.0; p = 0.371). The MV group exhibited significantly higher GDS-15 scores than the VM group (p = 0.022), although mean scores in both groups remained below the clinical threshold for depression (MV: 1.5 ± 1.7; VM: 0.8 ± 1.6). No other significant differences were found in clinical or anthropometric variables, ApoE genotype, AD plasma biomarkers, blood parameters, or brain volumetric measures. Each participant met the dietary adherence criteria during the corresponding dietary phase. Specifically, MDSS scores indicated high adherence to the Mediterranean diet (mean $\geq$ 10) during the MeDi phase, and lower adherence (mean $<$ 10) during the voluntary phase. However, linear mixed-effects models revealed no significant effects of the three-month Mediterranean diet intervention on global or domain-specific cognitive performance. Similarly, no significant changes were observed in physical function measures, including gait speed, handgrip strength, and sit-to-stand time, or in brain volumetric parameters. Regarding secondary outcomes, there were no significant changes in Alzheimer's disease–related serum biomarkers, including the Aβ42/40 ratio and p-tau217. This randomized controlled trial is pioneering in targeting individuals with SCD, and uniquely evaluates the comprehensive effects of a provided Mediterranean diet on cognition, physical performance, plasma AD biomarkers, and brain structure. Adherence to the protocol was high, dropout rates were low, and participant satisfaction was good, indicating successful implementation of the dietary intervention. The absence of significant findings may be due to: (1) Crossover trial design: Participants with preserved cognitive function may have demonstrated learning effects across repeated cognitive assessments. (2) Impact of later intervention: Participants who received the VM diet order had already undergone nutritional counseling and had begun adopting healthier eating habits before the formal intervention started. (3) Higher educated participants: This cohort was generally well-educated and maintained relatively

healthy lifestyles, making it difficult to detect measurable changes over a three-month intervention period. Future studies with a longer intervention duration or alternative target populations with lower educational or socioeconomic status may be needed.

Keywords: Cognitive function, physical ability, subjective cognitive decline, Mediterranean diet.

Clinical Trial Registry: NCT06287489; https://clinicaltrials.gov/study/NCT06287489. **Disclosures:** The authors declared no competing interests.

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P327- THE EFFICACY AND SAFETY OF MOBILE-APP-BASED META-MEMORY COGNITIVE TRAINING FOR MILD COGNITIVE IMPAIRMENT: A MULTICENTER, RANDOMIZED CLINICAL TRIAL.

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Background: Metamemory training (MMT) offers a potential non-pharmacological approach to enhance cognitive function in individuals with mild cognitive impairment (MCI). While digital cognitive training improves accessibility, the effectiveness of mobile-app-based MMT has not been evaluated in a randomized clinical trial. **Objective:** We aimed to evaluate the efficacy and safety of a mobile-app-based MMT program, ET-101, compared to a sham-device control group in individuals with MCI. **Methods:** This multicenter, randomized controlled trial enrolled MCI participants, recruited from seven medical centers, and randomly assigned them to the ET-101 or control group (1:1 ratio). The intervention lasted 12 weeks, with a 12-week follow-up. The ET-101 group received metamemory-based multi-memory strategy training and real-time feedback. Assessments of cognition, the daily activities of living, and quality of life were conducted at baseline, week 12, and week 24. The primary outcome was the proportion of participants who showed cognitive improvement as assessed by the Alzheimer's Disease Assessment Scale-cognitive subscale 14 (ADAS-Cog-14) at weeks 12 and 24. Secondary outcomes included changes in the scores of scales assessing cognition, daily activities, and quality of life. Safety analysis assessed adverse events and their relation to digital therapeutics. **Results:** In the full analysis set, 49 participants were included in the ET-101 group and 50 in the control group. At week 24, the proportion of responders who maintained or improved their ADAS-Cog-14 scores was significantly higher in the ET-101 group than in the control group ($P = .002$). Additionally, the ET-101 group showed a significant improvement in ADAS-Cog-14 scores at week 24 compared to baseline levels (estimates: -2.53, $t265 = -3.05$, Bonferroni-adjusted $P = .003$). A subdomain analysis revealed significant improvements in the memory (estimates: -2.50, $t264 = -4.03$, Bonferroni-adjusted $P < .001$) and language (estimates: -0.807, $t290 = -3.68$, Bonferroni-adjusted $P < .001$) domains at week 24 in the ET-101 group compared to control group. In the safety analysis, six adverse events occurred in the ET-101 group and four in the control group, but none were related to the interventions. The attrition rate in the ET-101 group was 22.4% (11/49). **Conclusions:** ET-101 significantly improved cognitive function compared to the sham device, with effects observed not only in the memory domain but also in the language domain, indicating a transfer effect. Therefore, ET-101 has the potential to provide effective MMT to a broader MCI population by overcoming location and personnel limitations through a mobile-app-based platform.

Key takeaway message: ET-101 has the potential to provide effective MMT to a broader MCI population by overcoming location and personnel limitations through a mobile-app-based platform.

COGNITIVE ASSESSMENT AND CLINICAL TRIALS

P328- SGMA: COMPUTATIONAL PHENOTYPING FOR THE RAPID, REPEATABLE, AND RELIABLE LONGITUDINAL ASSESSMENTS OF LONG-TERM MEMORY FUNCTION IN CLINICAL TRIALS.

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Background: With the recent development of novel disease-modifying treatments, early detection of Alzheimer's disease and related dementias (ADRD) has become increasingly important for primary and specialty care clinicians. However, typical cognitive assessment instruments lack the sensitivity to detect subtle impairments (1), while more sensitive screening tools (such as the MOCA) are associated with sizable practice effects that hinder reliable assessment of progression over time (2). These problems affect both clinical practice and research, as it leads to underdiagnosis in the population (3-5) and reduced sensitivity in cognitive endpoints. The Seattle-Groningen Memory Assessment (SGMA) is a convenient and sensitive 8-minute smartphone-based test that overcomes these difficulties by measuring a patient's episodic memory function through computational phenotyping (6,7). The test is an adaptive variation of the retrieval practice paradigm, in

which patients are required to memorize a series of paired associates and are quizzed at different intervals. As the test is performed, an underlying computational model of memory is adjusted in real-time based on the patient's responses and corresponding reaction times, creating a "cognitive twin" whose parameters reflect different components of performance. The extracted SMGA index reflects the estimated speed at which the episodic trace disappears, normalized and scaled so that the mean value across the population is 100. The test is well-received, brief (8-min), and repeatable without practice effects, and its results are interpretable, making it ideal for tracking long-term memory function over time. **Method:** To test the applicability of SGMA, patients with mild cognitive impairment (MCI; N=24; mean age = 72.7 ± 4.9; Mean MOCA score = 23.6 ± 3.0; 8 Female) and healthy controls (N=27; mean age = 69.2 ± 7.2; Mean MOCA score = 28.3 ± 2.0; 19 Female) were recruited from the University of Washington Alzheimer's Disease Research Center (ADRC). For one year, all participants performed weekly SGMA assessments remotely (either on PC or smartphone). Every week, they were presented with new sets of paired associates, whose content was deliberately tailored to the participants' demographics to maintain engagement (e.g., pictures and names of birds, pasta shapes, vocabulary, etc). **Results:** A total of 1,968 weekly tests were collected, with an average of 38.6 weekly assessments per individual (range 11–46). All data were analyzed with a linear mixed effect model, which included the main effects of the group (MCI vs controls), the temporal order of each lesson within a participant's schedule (weeks since enrollment), and their interaction. Sex and age were included as covariates, along with a group-by-age interaction. To account for within-subject and within-lesson variability, the model included random intercepts and random slopes for week for each participant, as well as random intercepts for each lesson. The model showed a significant difference between groups, with MCIs' SGMA score being 12.36 points (14.7%) lower than controls. Despite the massive amount of practice, practice effects were extremely modest to non-existent (0.17 points/week). SGMA scores were stable across all sets of materials and showed robust test-retest reliability (spearman r = 0.71). The test was also found to be highly diagnostic: lower SGMA scores were reliably associated with greater probability of an MCI diagnosis ($p < 0.001$), and a binary classifier trained on individual SGMA tests could correctly identify MCI patients with 84% accuracy on held-out, out-of-sample data. The diagnostic out-of-sample accuracy of the test was comparable to that of the MOCA (86%), despite the latter being longer, testing a wider range of function, and requiring in-person administration. **Conclusions:** SGMA is the first convenient, accurate, and reliable assessment entirely based on computational phenotyping. It is well-received by patients due to its adaptive nature (which ensures that its difficulty is titrated to patient ability), its convenience, and its brevity. Our pilot study shows the test reliably distinguishes between MCI and health control. These characteristics make SGMA an reliable tool for end-point cognitive assessments and an ideal instrument for longitudinal assessments of memory functions. Its repeatability makes SGMA particularly useful to track the time course and washout periods of active treatments in clinical trials. Further investigations in larger cohorts are in progress with the SGMA as a potential early cognitive assessment tool that can be utilized by individuals concerned about their cognitive health, also when access to memory specialists is limited or symptoms still seem to be mild.

Keywords: Alzheimer's disease, dementia, mild cognitive impairment, long-term memory, memory assessment; computational phenotyping.

Disclosures: Andrea Stocco and Hedderik van Rijn are the scientific co-directors of MemoryLab Health, a University of Washington-supported spin-off to which the Seattle-Groningen Memory Assessment is licensed to. Holly Hake, Anais Capik, Maarten van der Velder, and Thomas Wilschut were employed by MemoryLab Health while this study was carried out. Michael Rosenbloom has received honoraria from Eisai, Eli-Lilly, Johnson & Johnson, Medscape, and CME Outfitters. No commercial or financial interests have influenced the setup, analysis, or reporting of this study.

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Key takeaway message: Computational phenotyping provides a viable alternative to traditional cognitive assessment, allowing repeated, reliable, and precise monitoring of memory in clinical trials.

P329- REFER-MCI: ENRICHING REFERRALS OF PATIENTS TO MEMORY CLINICS FOR MILD COGNITIVE IMPAIRMENT (MCI).

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Background: Timely diagnosis of mild cognitive impairment (MCI) in Alzheimer's disease (AD) is crucial for early interventions, but its broad implementation in healthcare is often challenging due to the complexity and time burden of required cognitive assessments. To address these challenges, the usability of new unsupervised digital remote assessment tools needs to be validated in a routine care context. **Methods:** The Refer-MCI study compares the referral decisions made by office-based specialists based on a remote digital self-assessment (the neotivCare app) with the referral decisions made using the usual care approach. The reference test is the diagnosis of MCI due to AD at memory clinics according to national guidelines, including blood-based biomarkers for AD (pTau-217). In addition, all patients will undergo an office-based MoCA assessment. The primary endpoint compares the proportion of correct MCI due to AD referrals between remote testing and usual care. **Results:** N=500 office-based care (N=27 offices) patients, aged 60-80 years who seek advice for self-reported or care partner-reported cognitive complaints are being screened for participation, 75% (N=400) are expected to consent. The office-based outpatient specialists document their diagnosis and referral decision prior to and following the use of neotivCare, before referring all patients to one of 10 participating memory clinics for guideline-based diagnosis with additional blood biomarker testing. First patient in was in September 2025 and last patient out is expected in March 2026. **Conclusions:** The goal of Refer-MCI is to investigate the potential of digital remote self-assessment for improving correct referral of patients with suspected MCI due to AD, from specialized care to memory clinics. Refer-MCI will identify barriers and facilitators for efficient and timely referral of these patients to improve

case finding in routine care.
Key takeaway message: The Refer-MCI study evaluates the potential of digital remote self-assessment tools for improving accurate MCI due to AD referrals, identifying barriers and facilitators to enhance case finding in routine healthcare.

P330- AN INTEGRATED MODEL OF DIAGNOSIS, TREATMENT, PREVENTION AND RESEARCH: PATIENT JOURNEYS AT THE GENEVA MEMORY CENTER.

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Memory clinics are increasingly called upon to address the full spectrum of cognitive health, from dementia prevention to symptomatic and potentially disease-modifying treatment. Yet few centers have implemented structured patient pathways integrating prevention, diagnosis, treatment, and research. The Geneva Memory Center (GMC) has developed a comprehensive framework to guide individuals across this spectrum according to their cognitive status, biomarker profiles, and risk factors. We mapped all patient journeys at the GMC, from first visit to follow-up, highlighting three main pathways: (1) Clinical Workup, for individuals with objective cognitive impairment; (2) Brain Health Service for dementia prevention (dBHS), targeting cognitively unimpaired individuals at risk of cognitive decline; and (3) Research Workups, accessible from both dBHS and clinical care. Core assessments include demographic, medical, neurological, and cognitive evaluations, complemented as needed by advanced neuroimaging (3T MRI, PET), cerebrospinal fluid analysis, or other procedures (EEG, DaTscan). Genetic, biological, psychological, and lifestyle risk factor assessments support personalized risk communication and reduction strategies, tailored to neurodegenerative or vascular profiles. Participants may be referred to non-pharmacological clinical programs or research projects testing multidomain neurodegenerative interventions (e.g. brain stimulation and supplements). Follow-up visits are scheduled across pathways to monitor progression and adapt interventions. This framework enables tailored management: cognitively unimpaired individuals undergo risk profiling, communication, and personalized risk reduction; individuals with cognitive impairment receive a full diagnostic workup and, when appropriate, symptomatic treatment or access to clinical trials. Research workups integrate seamlessly within both streams, fostering recruitment and translational research. Clear diagnostic disclosure and structured follow-up anchor all pathways, ensuring continuity of care.
Key takeaway message: By embedding prevention, care, and research within interconnected patient journeys, the GMC model supports precision medicine approaches to cognitive disorders and accelerates dementia prevention efforts.

P331- PREVENTING COGNITIVE DECLINE IN AGING: A NETWORK META-ANALYSIS OF NUTRITIONAL SUPPLEMENT TRIALS IN COGNITIVELY UNIMPAIRED OLDER ADULTS.

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Background: The global prevalence of dementia is projected to increase substantially in the coming decades, posing major public health and socioeconomic challenges (1). Because neuropathological changes often precede symptoms by 10-20 years, prevention strategies targeting cognitively unimpaired (CU) older adults are critical. Nutritional supplements have been proposed as low-cost, accessible interventions to delay cognitive decline (2). However, evidence remains fragmented and comparative effectiveness is unclear (3). To address this gap, we conducted a systematic review and network meta-analysis of randomized controlled trials (RCTs) evaluating nutritional supplements for global cognition in CU older adults. **Methods:** We systematically searched PubMed and Embase from inception to May 7, 2024, following a preregistered protocol (PROSPERO CRD42024601975). We included RCTs enrolling CU adults aged $\geq$50 years, comparing any nutritional supplement with placebo, active controls, or other supplements, and reporting outcomes on global cognition (e.g., MMSE, MoCA, or validated composite scores). Observational studies, participants with mild cognitive impairment or dementia were excluded. We performed random-effects network meta-analysis using standardized mean differences (SMDs) and 95% confidence intervals (CIs) to compare each supplement with placebo. Heterogeneity was quantified with τ^2 and I^2, and network consistency was examined using Q statistics. **Results:** From 10,200 citations and 1,183 full texts screened, 57 RCTs were included, encompassing 20,426 CU participants and 12 intervention categories: amino acids/peptides/proteins, blends of multiple nutrients, botanicals/botanical compounds, botanicals combined with lipids, lipids alone, lipids with vitamins/minerals, probiotics/prebiotics, vitamins/minerals alone, whole foods, no intervention arms, active control comparators (i.e., low dose), and placebo. Compared with placebo, botanicals/botanical compounds showed a statistically significant improvement in global cognition (SMD 0.35; 95% CI 0.21 to 0.49; $p < 0.0001$). Other supplement categories, including vitamins/minerals (SMD 0.07; 95% CI –0.03 to 0.17), probiotics/prebiotics (SMD 0.07; 95% CI –0.14 to 0.28), amino acids/peptides/proteins (SMD 0.12; 95% CI –0.15 to 0.38), and blends (SMD 0.14; 95% CI –0.17 to 0.45), did not demonstrate significant benefit over placebo. Network heterogeneity was moderate ($\tau^2 = 0.0174$; $I^2 = 57.4\%$ [41.5–69.0%]). Tests of inconsistency revealed some disagreement between direct and indirect comparisons (Q_between = 15.06, df = 6, p = 0.0198), indicating that some network estimates should be interpreted with caution. **Conclusions:** In this large-scale synthesis of 57 RCTs, botanical supplements were associated with small but statistically significant improvements in global cognition among CU older adults, while other nutritional supplement classes showed no clear cognitive benefit compared with placebo. However, it is important to note that heterogeneity and some inconsistency were present underscoring the need for more rigorously designed, longer-duration RCTs with standardized cognitive outcomes. Some nutritional supplements, such as botanical compounds, may represent a potential tool for dementia prevention programs because of their scalability, while acknowledging that current evidence remains modest and further replication is needed.
Key takeaway message: Botanical supplements modestly improved global cognition in cognitively unimpaired older adults, whereas other nutritional supplements showed no clear benefit, highlighting the need for rigorous, long-term RCTs to inform dementia prevention strategies.

P332- SPEECH MEASURES ENHANCE THE PREDICTION OF ALZHEIMER'S DISEASE BIOMARKERS.

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Background: Speech and language characteristics change in mild cognitive impairment (MCI) and Alzheimer's disease (AD). Digital voice-based assessments offer scalable, low burden ways to measure these changes which could enhance sensitivity to disease-related changes. One potential application of this technology is as a screening tool for MCI/AD, for the purposes of early identification and clinical trial recruitment. We examined whether voice-based measures enhanced the prediction of

AD biomarkers, including Aβ42/40 ratio, CSF total tau, and cortical thickness, in a mild-to-moderate AD sample. **Methods:** Participants included 429 English-speaking participants with mild-to-moderate AD in a Phase 2/3 clinical trial (M/F = 243/186; mean age = 69.5 (SD = 6.77); mean MMSE = 18.1 (SD = 3.07). At baseline, participants completed a voice-based assessment including picture description, letter fluency and category fluency assessments in-clinic via the Winterlight Speech Assessment. Aβ42/40 ratio and levels of t-tau were assessed via CSF assay, and cortical thickness in AD-specific regions of interest (ROI) including entorhinal, inferior temporal, middle temporal, and fusiform cortex was assessed via MRI. We assessed the relationships between speech measures and AD biomarkers using Pearson partial correlations, controlling for age and sex. We then used LASSO regression and linear models to predict AD biomarkers based on age, sex, MMSE score and selected speech measures. **Results:** Significant correlations between single speech measures and AD biomarkers ranged from r = 0.1-0.43 ($p < 0.05$, uncorrected). There were more significant relationships between speech measures and cortical thickness in the AD-specific ROI, compared with the CSF biomarkers, Aβ42/40 ratio and tau levels. The strongest relationships were with speech measures relating to vocabulary, word types, information content and scores on the fluency tests. In all cases, the addition of selected speech measures to the base regression models which included age, sex and MMSE score resulted in significantly better prediction of AD biomarkers ($p < 0.05$). The prediction model for cortical thickness achieved the highest proportion of variance explained (speech model R2 = 0.35) and the largest increase compared to the base model (predictors = MMSE, age and sex; R2 = 0.21). The base model for Aβ42/40 ratio had R2 = 0.12 compared to the speech model which achieved R2 = 0.25, and for tau the base model only reached R2 = 0.04, while the speech model increased to R2 = 0.11. **Conclusions:** The results of this study demonstrate the potential utility for voice-based assessments in screening and early identification of MCI/AD. A speech assessment including three tasks, typically taking around 5 minutes to complete, resulted in significantly improved accuracy in predicting the presence of AD biomarkers compared to demographics and paper-and-pencil cognitive assessments. The highest accuracy was for prediction of cortical thickness in AD-specific brain regions, suggesting that speech and language measures may be more indicative of current neurodegeneration rather than levels of AD pathophysiology based on CSF. Nonetheless, in all cases, the addition of speech improved the prediction of CSF and brain-based AD biomarkers. Future work can build on this to determine if the addition of digital cognitive assessments enhances prediction further, and how these results generalize to novel blood-based biomarkers for AD.

Keywords: Speech, language, voice, screening, biomarkers.

Disclosures: All authors are current full-time employees of Cambridge Cognition.

Key takeaway message: Speech biomarkers enhance predictive models of AD biomarkers including amyloid beta, tau and cortical thickness, indicating the potential utility of speech as a screening tool in MCI and AD.

P333- ERP BIOMARKERS OF COGNITIVE DYSFUNCTION IN ALZHEIMER'S DISEASE: REAL-WORLD EVIDENCE FOR TRANSLATION INTO CLINICAL TRIAL ENDPOINTS.

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Background: Recent clinical trials of anti-amyloid therapies for Alzheimer's disease (AD) have demonstrated modest cognitive benefit despite successful clearance of molecular pathology (1). This underscores the need for neurophysiological biomarkers that can link molecular pathology to the higher-order cognitive function. Electroencephalography (EEG), particularly event related potential (ERP) paradigms, have shown promise as a reliable and scalable biomarker, especially in early-stage Mild Cognitive Impairment (MCI) (2). **Methods:** We used a standardized EEG/ERP-based assessment platform (BEAMTM) in a real-world memory clinic setting (Hawaii Pacific Neuroscience) to collect data from patients diagnosed with MCI (n=168, ages 41-89) and AD (n=14, ages 57-85). The protocol included an auditory oddball ERP task to evaluate neural processing of auditory discrimination and executive function (3). Each patient group was compared to age-matched healthy controls. Group level ERP differences were analyzed using Hedges' g effect sizes (ES). **Results:** Compared to controls, N100 latency was significantly delayed in both MCI (Δ=10.4 ms, ES=0.97, $p<0.001$, df=220) and AD (Δ=18.1 ms, E.S=2.42, $p<0.001$, df=26). P300 latency at Fz was also delayed in MCI (Δ=13.9 ms, ES = 0.33, p=0.04, df=221) and AD (Δ=28 ms, ES = 0.63, p=0.1, df=26). Amplitude of P300 was reduced in MCI (Δ=3.23 μV, ES=0.6, $p<0.001$, df=221) and AD (Δ=2.75 μV, ES=0.5, p=0.18, df=26). **Conclusions:** ERP paradigms can be deployed in real-world, point-of-care settings. Patients with MCI and AD exhibited measurable delays and amplitude reductions in ERP components, with more pronounced deficits in AD. These findings support the use of ERP biomarkers as potential endpoints for monitoring cognitive decline and treatment response in Alzheimer's disease.

Key takeaway message: ERP biomarkers measured via auditory oddball tasks can detect cognitive dysfunction in Alzheimer's and MCI. Findings support their feasibility as real-world, point-of-care tools and their potential as clinical trial endpoints.

P334- INTEGRATING PLASMA PTAU-217 AND DIGITAL COGNITIVE ASSESSMENTS FOR EARLY DETECTION IN ALZHEIMER'S DISEASE.

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Plasma pTau-217 has emerged as a sensitive and specific biomarker for early detection of Alzheimer's disease, yet the timeline linking pathology to meaningful cognitive decline remains poorly defined. In parallel, digital cognitive assessments offer a scalable approach for capturing subtle changes in cognition, but their standalone predictive utility is still being established. In this study, we examined whether combining these two low-burden, non-invasive tools improves the early identification of cognitively unimpaired individuals at elevated risk for future cognitive decline. We analyzed data from 954 amyloid-positive, cognitively unimpaired individuals who completed a brief digital memory assessment and provided plasma samples for pTau-217 quantification. We assessed their ability to predict decline on the Preclinical Alzheimer's Cognitive Composite and Mini-Mental State Exam over a five-year period. Models that combined low memory performance with elevated pTau-217 outperformed models using either measure alone, even after adjusting for age, sex, education, and baseline cognitive performance. Importantly, while predictive performance was consistent across sexes, the combined model was significantly more accurate in APOE4 non-carriers than carriers, suggesting that digital memory assessments may capture vulnerability to decline more effectively in the absence of this risk factor. Together, these findings support the integration of digital cognitive assessments and plasma biomarkers as a practical, scalable, and highly sensitive approach for identifying individuals in the earliest stages of Alzheimer's disease. This combined framework has immediate translational potential, not only to improve early diagnosis in clinical settings, but also to optimize participant selection, stratification, and enrichment strategies in Alzheimer's disease clinical trials, where targeting the right individuals at the right time is critical for therapeutic

success.

Key takeaway message: Combining digital memory assessments with plasma pTau-217 improves early detection of Alzheimer's risk offering a scalable, sensitive approach for clinical and trial applications.

P335- COMBINING PLASMA PTAU217 AND A REMOTE DIGITAL COGNITIVE ASSESSMENT TO PREDICT COGNITIVE DECLINE IN COGNITIVELY UNIMPAIRED OLDER ADULTS.

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Introduction: Accurately identifying cognitively unimpaired (CU) individuals at highest risk of imminent cognitive decline is critical for Alzheimer's disease (AD) prevention, especially given recent advances in anti-amyloid therapies that modestly slow progression during the symptomatic stage. Plasma phosphorylated tau 217 (pTau217) is a promising blood-based biomarker, showing strong correlations with amyloid PET imaging and offering comparable accuracy to cerebrospinal fluid measures. However, even among those with elevated pTau217, it remains difficult to predict who is most likely to decline, highlighting the need for complementary behavioral markers. Although traditional cognitive assessments can detect changes associated with elevated amyloid in cognitively unimpaired individuals, these changes typically become more prominent over several years. In contrast, the multi-day Boston Remote Assessment for Neurocognitive Health (BRANCH)—a self-administered digital assessment of memory and processing speed—has been shown to detect diminished cognitive performance associated with elevated amyloid, by measuring learning dynamics over the course of a week. In this study, we examined whether combining BRANCH performance with plasma pTau217 improves prediction of future cognitive decline and enables more accurate risk stratification among CU individuals with elevated pTau217. We also compared BRANCH with the baseline Preclinical Alzheimer's Cognitive Composite (PACC5), to assess its relative predictive value. We hypothesized that individuals with elevated pTau217 and lower BRANCH performance would exhibit steeper cognitive decline, while those with better BRANCH scores would remain stable despite biomarker positivity. **Methods:** CU older adults (N=145, age=72.4±7.6 years, 71% female, education=16.6±2.4 years) completed baseline and annual follow-up PACC5 assessments over a mean follow-up period of 2.7±0.8 years after the first BRANCH administration. Participants underwent plasma pTau217 measurements quantified using the Meso Scale Discovery immunoassay within a maximum interval of 1000 days from their baseline. BRANCH, a web-based, self-administered cognitive assessment completed remotely over seven days, was administered within one year of the baseline PACC5 assessment. BRANCH includes two associative memory tests and a processing speed test, with identical stimuli repeated across seven days to estimate individual learning curves. Multiday learning curve (MDLC) scores were calculated using area-under-the-curve methods, capturing both initial performance and learning over time. To evaluate the prognostic value of these measures, we fitted a series of linear mixed-effects models. We first tested whether plasma pTau217 predicted longitudinal PACC5 trajectories and then assessed the incremental prognostic value of adding MDLC scores using likelihood ratio (χ^2) tests. Finally, a three-way interaction term (pTau217×MDLC×time) was included to determine whether BRANCH performance further stratified cognitive trajectories among those with elevated pTau217. Marginal slope estimates were calculated at the 25th, 50th, and 75th percentiles of pTau217 and MDLC scores to identify groups exhibiting the steepest annual cognitive decline. All models were adjusted for age, sex, education, and baseline PACC5 scores. We applied linear regression models to assess the extent to which baseline plasma pTau217, BRANCH, and PACC5 scores explained individual trajectories of cognitive change (PACC5 slope). Predictor contributions were estimated via variance decomposition (1,000 bootstrap). To address potential bias due to timing differences between BRANCH and plasma collection, sensitivity analyses were conducted in a subset (N=47) with plasma collected within 180 days of both baseline PACC5 and BRANCH. **Results:** Higher baseline plasma pTau217 significantly predicted greater PACC5 decline (β=-0.04, p=0.002). Models including the BRANCH MDLC scores also showed a significant MDLC interaction with time (β=0.09, p<0.001), demonstrating incremental prognostic value beyond plasma pTau217 alone. Adding BRANCH significantly improved model fit (χ^2=63.18, p<0.001), increasing marginal R^2 from 0.73 to 0.77 (+3.7%). Finally, the three-way interaction of pTau217 and MDLC scores over time was significant (β=0.06, p<0.001), indicating that BRANCH performance moderated the relationship between plasma pTau217 and PACC5 trajectories. Marginal slope analyses, aimed at refining risk stratification among individuals with elevated pTau217, estimated that individuals with elevated pTau217 (75th percentile) and low MDLC score (25th percentile) exhibited the steepest PACC5 decline (estimated annual slope=-0.10, p<0.001). In contrast, those with similarly elevated pTau217 (75th percentile) but higher MDLC score (75th percentile) were estimated to show a slight increase in scores over time (estimated annual slope=0.07, p<0.001). In the regression model explaining PACC5 slope (R^2=0.251), both MDLC score (β=0.04 p<0.001) and pTau217 (β=-0.02, p=0.002) were significant predictors, while baseline PACC5 (β=-0.01, p=0.188) was not. MDLC score explained the largest share of variance at 71% [CI: 41–88], followed by plasma pTau217 at 22% [CI: 3–51], and baseline PACC5 at 7% [CI: 4–25]. Sensitivity analyses confirmed consistent and significant results across models, where BRANCH accounted for the largest proportion of explained variance (84%) in the variance decomposition. **Conclusions:** Integrating plasma pTau217 with daily BRANCH performance significantly demonstrated added prognostic utility for steeper cognitive decline in CU older adults beyond plasma biomarkers alone. BRANCH stratified risk within biomarker-positive individuals, distinguishing those most likely to decline from those who remained stable. Interestingly, among those with elevated pTau217, individuals with higher BRANCH scores showed slight improvement, possibly reflecting retest-related practice effects. BRANCH demonstrated greater predictive utility for PACC5 decline than baseline PACC5 performance, highlighting its added value in forecasting future decline. These results underscore the utility of combining biological and sensitive cognitive measures to better identify individuals at greatest risk for future cognitive decline. Its remote, self-administered design supports scalable screening in clinical trial settings.

Key takeaway message: Combining BRANCH with plasma pTau217 improves prediction of future cognitive decline compared to plasma alone, enabling more accurate risk stratification in cognitively unimpaired older adults.

P336- SPEECH-BASED DIGITAL COGNITIVE ASSESSMENTS FOR SCALABLE AND COST-EFFECTIVE PRE-SCREENING OF PRECLINICAL ALZHEIMER'S DISEASE: INSIGHTS FROM THE RETAIN STUDY.

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Background: RETAIN is a phase 2b study evaluating the efficacy, safety, and immunogenicity of phosphorylated tau-targeted active immunotherapy in individuals with preclinical Alzheimer's disease (AD). To

identify individuals with preclinical AD, the study incorporates an innovative prescreening strategy that includes a speech-based digital cognitive assessment developed by ki:elements GmbH along with a blood-based p217+tau assay developed by Johnson & Johnson and available on the Quanterix platform (LucentAD) (1). The speech based digital cognitive assessment was included to collect data to inform whether it could serve as a low-burden and efficient tool for identifying individuals who are likely in the preclinical stage of disease and support blood-based biomarker testing. Patient identification through this dual approach is aimed at reducing screen failure rates, minimizing trial costs, and improving recruitment efficiency. **Methods:** During the prescreening phase, individuals completed the cognitive assessment via an automated phone call using ki:elements' Mili platform. The assessment consisted of two gold-standard cognitive tests: four repetitions of the Rey auditory verbal learning test (i.e., learning and recalling of a word list) followed by a semantic verbal fluency test. Three speech-based cognitive (SB-C) scores representing an individual's learning and memory, executive function, and processing speed as well as one composite cognition score were automatically generated using audio recordings of these tests (2). At the end of the assessment, prescreened individuals were asked to rate their experience with the assessment using an optional Likert scale ranging from 1 ("very unpleasant") to 5 ("very pleasant"). SB-C scores are currently being analyzed for correlations with p217+ tau read-outs obtained via the LucentAD assay. Additionally, SB-C's discriminative performance to classify individuals as cognitively normal (CN; CDR-GS = 0 and MMSE $\geq$ 27 with education adjustment) or cognitively impaired (CI) is being evaluated using the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating Global Score (CDR-GS) data. **Results:** A total of 16,842 participants underwent the speech-based digital cognitive assessment between April 9, 2024, and May 7, 2025, with the majority from the U.S. (79.7%), followed by Japan (12.5%), the U.K. (6.2%), and others (1.6%). Assessments were conducted in eight languages, primarily U.S. English (73.9%) and Japanese (12.5%). Of the total, 98% (16,496) completed the assessments using the primary automated modality, while 2% (346) completed it via a fallback method. The median completion time was 9 minutes and 4 seconds (Q1-Q3: 8 minutes 6 seconds - 9 minutes 7 seconds), indicating a low time burden. 10,757 (63.9%) participants rated their experience with the assessment; the rating question was optional. Overall, 8,851 (82.2%) participants rated their experience as either 4 («pleasant») or 5 («very pleasant»), with a median score of 5.0 (Q1-Q3: 4.0-5.0), reflecting a high level of satisfaction and user acceptability. Among the remaining 18%, the majority (15.1%) provided neutral ratings (score of 3), while only 2.7% rated their experience as unpleasant, 0.7% gave a score of 1 and 2% gave a score of 2, indicating a notably low rate of dissatisfaction compared to typical digital health benchmarks. The high level of satisfaction and acceptability was also observed across different demographic subgroups. Ratings were consistent across gender (85.2% of females, 77.3% of males rated $\geq$ 4), age (median: 66 years), and education level (median: 14 years), with weak inverse correlations observed (age: Spearman rho = -0.12; education: rho = -0.17; both p's $<$ 0.001). Similar findings were observed in each country and language group when analyzed separately. Time of the day did not influence ratings, indicating that any fatigue accumulated throughout the day does not affect participant satisfaction. **Conclusions:** The speech-based digital cognitive assessment developed by ki:elements and used in RETAIN is feasible, scalable, and well accepted across diverse populations. Implemented in over 16,000 participants, it demonstrated high satisfaction, brief administration time, and minimal burden, ideal for large-scale cognitive screening. The assessment achieved a 99.3% compliance rate with staff assistance provided as needed, demonstrating strong usability in clinic-based administration and supporting further exploration of its use in unsupervised or at-home settings. As demonstrated previously2, SB-C shows promise in distinguishing cognitively unimpaired from impaired AD individuals. Data on the speech-based cognitive assessment's ability to distinguish cognitively unimpaired from impaired individuals will be presented at the conference, supporting its potential use as a prescreening tool for Alzheimer's disease trials. By identifying preclinical AD cases and excluding cognitively impaired individuals, this tool may enhance recruitment, reduce costs, and improve the efficiency of biomarker-driven clinical trial designs.

Keywords: Alzheimer's disease, preclinical AD, digital biomarkers, digital cognitive assessment, artificial intelligence, clinical trial recruitment, patient identification, p217 tau.

Clinical Trial Registry: NCT06544616; https://clinicaltrials.gov.

Disclosures: NL, JT and JH are shareholders and employees of ki elements GmbH.

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Key takeaway message: The speech-based digital cognitive assessment used in over 16,000 participants showed high feasibility, scalability, and acceptance, supporting its potential as an efficient, low-burden prescreening tool to improve recruitment in Alzheimer's disease clinical trials.

P337- ELECTRIC FIELD OF THE DEFAULT MODE NETWORK IS CORRELATED WITH EFFECTS OF TRANSCRANIAL ALTERNATING CURRENT STIMULATION IN MILD ALZHEIMER'S DISEASE.

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Background: Transcranial alternating current stimulation (tACS) is a non-invasive brain stimulation technique that modulates brain activity by generating electric fields in targeted brain regions. Recent studies have shown that neuroanatomical individual differences and the resulting variations in internal brain electric fields may influence the efficacy of tACS. However, predicting clinical outcomes based on induced electric field calculations remains a significant challenge. Therefore, this study aims to investigate the relationship between the electric fields of default mode network by tACS and the therapeutic effects on mild Alzheimer's disease. **Methods:** We conducted tACS on 46 participants with mild Alzheimer's disease, with the electrodes placed over the prefrontal cortex (F1, F2, Fpz). These participants underwent a randomized, double-blind design and received 40Hz, 15mA tACS treatment for consecutive 15 days, totaling 30 sessions (twice daily, 1 hour per session). To assess the relationship between electric fields in the default mode network and intervention efficacy, we performed electric field modeling on the pre-treatment MRI data of 23 true-stimulation participants, creating individualized models of tACS-induced electric fields within the brain. **Results:** The electric field distribution results indicated that 15mA tACS significantly impacted the default mode network, including the bilateral hippocampus and parahippocampal gyrus. Correlation analysis between the induced electric field and cognitive changes revealed that the electric field in the default mode network correlated with cognitive changes before and after the intervention (MoCA: r = 0.537, P = 0.032; MMSE: r = 0.534, P = 0.033; Digital Span Test-backward: r = 0.665, P = 0.005), after adjusting for age, sex, and education. Further analysis of the primary brain regions and cognitive changes showed that the hippocampus and parahippocampal gyrus were associated with MMSE (Left Hippocampus: r = 0.592, P = 0.016; Right Hippocampus: r = 0.685, P = 0.003; Left

ParaHippocampal: r = 0.581, P = 0.018; Right ParaHippocampal: r = 0.589, P = 0.016) and the Digital Span Test-backward (Left Hippocampus: r = 0.561, P = 0.024; Left ParaHippocampal: r = 0.637, P = 0.008; Right ParaHippocampal: r = 0.534, P = 0.033). Notably, the electric field value in the default mode network effectively predicted intervention efficacy (AUC = 0.88, P < 0.05). **Conclusions:** These findings suggest that the electric field in the default mode network obtained through electromagnetic field finite element simulation is a reliable, non-invasive biomarker for predicting the efficacy of 15mA tACS intervention in mild Alzheimer's disease. Therefore, pre-intervention evaluation of the electric field can optimize personalized treatment efficacy and improve the cost-effectiveness distribution of medical resources.

Key takeaway message: Keywords: Alzheimer's disease, Transcranial Alternating Current Stimulation, Default Mode Network, Electric Field.

P338- THE VALIDATION OF THE NEW CHINESE SHORT COGNITIVE PERFORMANCE TEST (SKT).

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Background: The new Chinese version of the SKT Short Cognitive Performance Test (Guo et al., 2022) is designed to detect early cognitive impairment. Based on several particular features, it can be suggested that the SKT is a valuable addition to the existing battery of neuropsychological tests in China. This study has three aims: 1. to determine whether the SKT can be compared in terms of its diagnostic accuracy with established tests of cognitive impairment (e.g., Addenbrooke's cognitive examination-III (ACE-III); Hsieh et al., 2013) and Montreal Cognitive Assessment-Basic (MoCA-B); Chen et al., 2016); 2. to investigate whether the three psychometric tests demonstrate intra-individual differences according to different types of mild cognitive impairment (MCI; e.g., amnestic or multiple domains MCI); 3. to investigate whether the cognitive assessment tests can detect differences between individuals with no cognitive impairment and those with subjective cognitive decline (SCD). **Methods:** The study design was as follows: The validation sample consisted of 1038 older adults (mean age = 70.04, SD = 6.05) who were part of the Chinese Preclinical Alzheimer's Disease Study (C-PAS; Cui et al., 2023). Participants were required to complete tests of cognitive impairment. They were also classified by consensus diagnosis as having normal cognition, MCI, or dementia. Sensitivity and specificity for all tests were calculated, as well as ANOVAs for differences in detection of the different MCI types and t-tests to investigate the difference between no cognitive impairment and SCD. **Results:** The SKT discriminated best between normal cognition and cognitive impairment (MCI or dementia), with a sensitivity of 85.4% and a specificity of 69.8%. All three tests showed significant differences in test scores between different types of MCI. The t-tests for all assessment tools for detecting a difference between patients without cognitive impairment and patients with SCD were significant (p < 0.01). **Conclusions:** The new Chinese version of the SKT represents a valuable contribution to the field of cognitive impairment testing. Furthermore, the results of all cognitive impairment tests even suggest the potential for early detection of cognitive impairment in individuals with SCD.

Keywords: Chinese version of SKT, short cognitive performance test, sensitivity, specificity.

Disclosures: Studies related to the SKT were financially supported by Dr. Willmar Schwabe Gmbh & Co KG, Karlsruhe, Germany.

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P339- SUBJECTIVE COGNITIVE COMPLAINTS AND STAGES OF OBJECTIVE MEMORY IMPAIRMENT (SOMI) PREDICT CLINICAL PROGRESSION.

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Introduction: Only 20-30% of amyloid positive cognitively normal individuals develop mild cognitive impairment (MCI) or clinical AD over 5 years (1). We sought to identify at-risk individuals by combining objective and subjective measures of cognitive functioning. The Stages of Objective Memory Impairment (SOMI) system defined by Free and Cued Selective Reminding Test (FCSRT) scores classifies increasing storage and retrieval deficits into 5 stages (2). Compared to participants with no memory impairment, the higher the SOMI stage the higher the risk of progression (3). The Cognitive Function Inventory (4) assesses self-perceived decline in cognition by comparing current level of cognitive functioning to functioning 1-year earlier. CFI predicts clinical progression and tracks with the trajectory of cognitive decline (5). In this study, we assessed the incremental predictive validity combining SOMI and CFI in contrast with models that include just one of these predictors using data from the Anti-Amyloid in Asymptomatic Alzheimer's Disease (A4) study (6). **Methods:** A total of 1,107 cognitively normal, amyloid-positive participants (baseline CDR = 0) were included, each with longitudinal FCSRT, CFI, and CDR data. Clinical progression was defined as the occurrence of two consecutive CDR scores greater than 0, over up to 4.5 years of follow-up. The CFI was dichotomized according to an optimal cut score determined through logistic regression with receiver operating characteristic (ROC) analysis, using 10-fold cross-validation, and validated in an external dataset. The 5 stages of the SOMI system were also dichotomized into participants whose memory was unimpaired (SOMI-0) versus those with increasing memory impairment (SOMI 1-4). Cox proportional hazards models, adjusted for age, sex, and APOE, were applied to examine the predictive value of CFI, SOMI, and their combination for incident clinical progression. A partial likelihood ratio test between models assessed model improvement when the predictors were combined. **Results:** Participants had a mean age of 71.9 years (SD = 4.8). The majority were female (58.7%), and 59.3% were APOE4 carriers. At baseline, 38.61% were classified as SOMI 0, while 61.40% were in SOMI stages 1–4. Overall, 32.3% of participants progressed during follow-up. Within the SOMI 0 group, 67.68% had low CFI and 32.31% had high CFI; in contrast, among participants in SOMI 1–4 group, 63.91% had low CFI and 36.08% had high CFI. The optimal CFI cut score of 2.58 achieved 67% accuracy in distinguishing progressors from non-progressors. In Cox proportional hazards models, using SOMI 0 as the reference, participants in SOMI 1–4 had a significantly higher risk of progression (HR = 1.63, 95% CI = 1.30–2.04, p < 0.001). High CFI scores (>= 2.58) were also associated with increased risk (HR = 1.84, 95% CI = 1.51–2.24, p < 0.001), adjusting for age, sex, and APOE genotype. The model including CFI, SOMI, and amyloid burden—adjusted for age, sex, and

APOE—outperformed all other models, achieving the highest C-index and the lowest AIC. Importantly, SOMI and CFI remained significant predictors when modelled together and their effects persisted after further adjustment for amyloid level as determined by PET scan. Cognitive impairment–free survival declined in a stepwise manner with increasing SOMI stage and higher CFI categories (log-rank $p < 0.0001$). **Conclusions:** Both CFI and SOMI independently predict progression and, together, offer a simple tool to identify amyloid positive cognitively normal older adults at risk for developing mild cognitive impairment.

Keywords: Clinical trial phase, subjective cognitive decline, preclinical AD, cognitive functional index, stages of objective memory impairment, free and cued selective reminding test.

Clinical Trial Registry: NA.

Data Deposition: a4studydata.org.

Disclosures: Ellen Grober, PhD. receives a small royalty for commercial use of the FCSRT.

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Key takeaway message: CFI and SOMI separately and jointly predict clinical progression in cognitively normal amyloid-positive older adults. When combined, they provide a simple tool to select individuals at elevated risk for progression to enrich secondary prevention trials.

P340- THE DIGITAL CLOCK AND RECALL IDENTIFIES ELIGIBLE CANDIDATES FOR ALZHEIMER'S DISEASE-MODIFYING TREATMENT.

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Background: Developing and prescribing disease-modifying treatments (DMT) for Alzheimer's disease (AD) suffers from two key challenges. First, during drug development, it is critical to identify individuals who are likely to randomize into modern trial designs to minimize the already inflated cost of clinical trials and reduce the high screen failure rate. Emerging solutions to this problem include prescreening individuals with brief digital cognitive assessments (DCA) that can identify two critical aspects: cognitive impairment status and brain amyloid-beta (Aβ) status. Second, during post-market prescription, DMT eligibility must be rapidly and accurately assessed to avoid placing undue burden on an already overtaxed health system. Again, emerging solutions include the use of DCAs that are capable of simultaneously assessing cognitive impairment and Aβ status. Previous work has detailed the ability of the Digital Clock and Recall (DCR), a 3-minute DCA, to accurately characterize an individual's cognitive and amyloid-positivity status using separate machine learning (ML) models. The goal of the current research was to evaluate the ability of the DCR to help identify AD patients suitable for DMT by combining insights from these models to identify cognitive impairment likely due to Alzheimer's disease. **Methods:** 859 participants from the Bio-Hermes (BH) study (ClinicalTrials.gov NCT04733989) underwent the DCR, MMSE, RAVLT, FAQ, and an Aβ-PET scan. Participants were classified by the BH study team into CU (n=378), MCI (n=269), or mild dementia (n=212) cohorts based on traditional assessment results, clinical interview, and medical records. We defined the DMT-eligible group as individuals within the MCI and mild dementia cohorts who were Aβ+ on PET. We leveraged two separate pretrained ML models to estimate the cognitive impairment probability (CIP) and amyloid risk score (ARS) based on algorithmically selected subsets of 2000+ process-based features of the DCR, including temporal/kinematic/stylus telemetry and DCTclock subscores, acoustic/linguistic features from Immediate/Delayed Recall, traditional measures of accuracy, and age. The derived metrics represent the process each participant used to complete their assessment rather than merely the final product. Models were trained using nested leave-one-out cross-validation, and the binary results (1 if impaired/positive and 0 if otherwise) of CIP and ARS models were combined in a logistic-regression model to identify individuals who were potentially eligible for DMT. Evaluable subjects were split 70/30 into separate training and testing sets. We assessed performance using standard metrics of sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV). **Results:** In the BH sample, 18% were found to be CI+ and Aβ+ and thus DMT-eligible. The higher-level model combining CIP and ARS model outputs achieved an overall accuracy of 84.7% with AUC=0.84, sensitivity=0.83, specificity=0.85, NPV=0.93, and PPV=0.68 in identifying the likely DMT-eligible participants in the testing set. **Conclusions:** The 3 minute DCR demonstrated strong performance in identifying individuals with cognitive impairment and amyloid-PET positivity who are at an early, DMT-eligible stage of Alzheimer's disease. By leveraging combinations of probabilistic models that integrate both cognitive and amyloid risk, the DCR offers a feasible, rapid, and scalable solution for both clinical trial recruitment and real-world prescribing decisions. Importantly, its high negative predictive value suggests that it could substantially reduce costly screen failures in research settings and prevent unnecessary follow-up testing in routine care. Given its efficiency and existing deployment in primary care, the DCR holds promise as a frontline digital assessment that not only broadens access to DMTs by streamlining eligibility determination but also alleviates burden on specialized memory clinics. Future work should evaluate its implementation in longitudinal clinical workflows and its impact on accelerating trial enrollment, lowering system costs, and improving timely access to emerging therapies for Alzheimer's disease.

Key takeaway message: The 3 minute Digital Clock and Recall reliably identifies Alzheimer's patients eligible for disease-modifying treatments, offering a rapid, scalable tool to streamline trial recruitment, reduce screen failures, and support real-world prescribing decisions in primary care.

P342- CLINICAL OUTCOMES AND PATIENT EXPERIENCE OF SUBCUTANEOUS LECANEMAB ADMINISTRATION FROM AN ALZHEIMER'S DISEASE TREATMENT CENTER.

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Background: Lecanemab is an anti-amyloid monoclonal antibody that targets plaques and neurotoxic amyloid-β (Aβ) protofibrils, which are more toxic than monomers or insoluble fibrils/plaque (1-4). In the phase 3 Clarity AD trial, lecanemab significantly reduced markers of amyloid and slowed decline on clinical endpoints of cognition and function over 18 months in individuals with early Alzheimer's disease (AD; mild

cognitive impairment [MCI] and mild AD) (5). Beyond 18 months, benefits of lecanemab can be maintained with long-term treatment, as demonstrated in the ongoing open-label extension (OLE) study through 48 months, including a subcutaneous arm (6,7). We analyzed OLE clinical efficacy data through 24 months at the largest enrolling US site, and assessed experiences of patients and care partners from this site who transitioned to subcutaneous (SC) lecanemab. **Methods:** This retrospective cohort study analyzed Clinical Dementia Rating–Sum of Boxes (CDR-SB) data for 28 trial patients who transitioned to SC lecanemab after 18-month IV lecanemab treatment. Patients and/or their care partners were asked to complete a survey at the Alzheimer's Research and Treatment Center in Wellington, Florida. A matched Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort (N=352) served as a historical control for comparison beyond 18 months. The patient/care partner satisfaction survey evaluated the experience of individuals with early Alzheimer's disease or their care partners with the subcutaneous formulation of lecanemab. The survey included 10 single-choice questions using a Likert scale and one open-ended question to capture experiences with SC administration. Survey questions were adapted from the Therapy Administration Satisfaction Questionnaire (TASQ-SC) © and the Patient Preference Questionnaire (PPQ)©. Surveys were completed by either patients (n=25) or care partners (n=9). **Results:** Mean age of the SC lecanemab patients was 72.4 years (standard deviation, SD=7.8), 75% had MCI, 25% mild AD, and mean baseline CDR-SB score of 2.39 (SD = 1.23). Mean age of the matched ADNI cohort was 73.4 years (SD=7.4), 76% had MCI, 24% mild AD, and mean baseline CDR-SB score of 2.29 (SD = 1.43). At 24 months, CDR-SB scores for the 28 lecanemab-treated patients demonstrated a continued slowing of cognitive decline, compared to the matched ADNI cohort. The patient/care partner satisfaction survey was completed by a total of 34 participants, and the questions were based on the patient's most recent SC treatment experience. Survey responses demonstrated high satisfaction with the SC lecanemab administration. Nearly all respondents reported very favorable or favorable experiences with treatment satisfaction (97%) and convenience (97%). All patients preferred SC over IV dosing, citing quickness, ease, and comfort as the main reasons. Most respondents expressed comfort with self-injection (91%) and confidence in remembering doses (94%), while 85% reported that treatment will help them return to normal life. All participants indicated they would recommend SC treatment to others (94% definitely, 6% probably). No patients reported feeling restricted by treatment or burdened by the time required. **Conclusions:** Patients treated with lecanemab had slower decline on CDR-SB relative to a natural history cohort at 18 months, which continued through 24 months of treatment, supporting the benefit of sustained treatment. The SC lecanemab formulation was highly preferred by patients and care partners, with feedback highlighting reduced treatment burden and strong acceptability.

Keywords: Lecanemab, subcutaneous, long-term treatment, patient-reported outcomes.

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Key takeaway message: Subcutaneous lecanemab was associated with continued slowing of cognitive decline through 24 months and was highly preferred by patients and care partners due to its convenience, ease of use, and reduced treatment burden.

P343- PREDICTION OF PLASMA P-TAU217 STATUS AND ALZHEIMER'S RISK WITH THE REMOTE-READY DIGITAL ASSESSMENT OF COGNITION.

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Background: Screening for clinical trials of Alzheimer's disease (AD) and related dementia is an extremely expensive and time-consuming endeavor. Given the limitations of current screening methods, which often rely on outdated and lengthy pencil-and-paper cognitive assessments, it remains challenging to identify suitable participants, and screening failure rates remain high. In response, the focus has shifted to prescreening patients using emerging protocols administered in healthcare settings or community screening events that incorporate brief digital cognitive assessments and blood biomarkers. The Digital Assessment of Cognition (DAC) is a brief (7-minute), remote-enabled digital cognitive assessment that identifies cognitively unimpaired, mild cognitive impairment, and dementia with very high performance (AUCs>0.97). DAC includes two trials of immediate recall, one trial of delayed recall, and delayed recognition components of a 6-word verbal list learning test of memory (Philadelphia Verbal Learning Test [PVLT]), a 1-minute verbal fluency test of semantic memory and lexical access (Semantic 'Animal' Fluency), and 3-trials of a working memory test to evaluate attention and executive function (Backward Digit Span Test). The goal of the current work was to investigate whether the DAC could also estimate the likelihood of testing positive on a blood test for p-tau217 and provide guidance for which participants are likely to test positive for amyloid-beta on a brain positron emission tomography (PET) scan. In this way, the DAC could provide insights into the presence or absence of both symptoms and pathology of AD. **Methods:** 358 participants in the Apheleia-001 study (ClinicalTrials.gov NCT05364307) underwent a blood draw and p-tau217 blood assay and completed an in-clinic DAC. Automated speech recognition, signal processing, and process-based analytics were used to produce measures of traditional accuracy (e.g., total unique animals spoken), process metrics (e.g., speaking rate), and acoustic features (e.g., shimmer). A machine-learning model was trained on the measures extracted from DAC to estimate the likelihood of plasma p-tau217 positivity. The pretrained model was then externally validated using data from three community-screening events held in the upper-midwest (N=312). Participants at these events were administered the DAC to assess their cognitive impairment status and received a blood test for p-tau217. We modeled performance using standard metrics of sensitivity, specificity, negative predictive value (NPV, and positive predictive value (PPV). Finally, we used patterns of performance on DAC subtests to investigate cognitive phenotypes by dividing MCI groups into primarily dysexecutive or primarily amnestic profiles, and investigated whether p-tau217 levels varied by phenotype. **Results:** The DAC-based classifier achieved AUC=0.83 for identifying p-tau217-positive participants in Apheleia, with sensitivity=0.78, specificity=0.75, NPV=0.86, and PPV=0.64. The same model achieved AUC=0.77, sensitivity=0.74, specificity=0.70, NPV=0.94, and PPV=0.30 on unseen real-world data acquired at community screening events, and maintained high NPV and specificity for the cognitively unimpaired cohort (N=84, sensitivity=0.17, specificity=0.97, NPV=0.94, PPV=0.33). Additionally, applying DAC-derived cognitive phenotyping rules to Apheleia participants revealed biologically coherent gradients: cognitively unimpaired and dysexecutive profiles exhibited significantly lower p-tau217 levels and p-tau217/np-tau217 ratios than amnestic and mild-dementia profiles (p's<0.0001), linking DAC performance to both underlying AD pathology and cognitive phenotype. **Conclusions:** The DAC provides scalable, remote-ready estimation of p-tau217 status and biologically anchored cognitive phenotyping for trial prescreening and community screening. Its strong AUC and high NPV support use as a front-end screener to prioritize confirmatory testing and enrichment for biomarker-positive individuals, while minimizing unnecessary blood draws among low-likelihood candidates. These findings highlight the potential of multimodal, process-based digital assessments such as DAC to accelerate AD trial recruitment and broaden access to brain-health screening.

Key takeaway message: The Linus Health Digital Assessment of Cognition (DAC) effectively predicts p-tau217 blood biomarker status, enabling scalable remote screening for Alzheimer's disease clinical trials and community brain-health assessments.

P344- ADVANCING PRECISION IN COGNITIVE IMPAIRMENT RESEARCH: THE ROLE OF THE INSTITUTE FOR COGNITIVE INTERVENTION.

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The Institute for Cognitive Intervention (ICI), a research affiliate of International St. Mary's Hospital Incheon, South Korea, serves as a leading academic center dedicated to advancing translational research in dementia and age-related cognitive disorders. Our integrated pipeline spans clinical phenotyping, cognitive profiling, neuroimaging, neuroinformatics and cognitive inyervention. **Company Therapeutic Area:** Neurocognitive disorders, such as Alzheimer's disease and related dementias, vascular cognitive impairment, and age-related cognitive decline with a focus on early detection, stratification, and cognitive intervention using AI-based tools. **Company & Pipeline Description:** ICI is an academic research institute dedicated to advancing diagnostics and therapeutic strategies for Alzheimer's disease and cognitive impairment. Our research portfolio includes national dementia registry contributions, precision cognitive classification using the Seoul Neuropsychological Screening Battery-II (SNSB-II), vascular burden analysis through white matter hyperintensity quantification, and multimodal neuroimaging data integration. SMART BRAIN® will be an AI-powered multidomain cognitive training tool designed to deliver personalized, adaptive interventions across memory, attention, executive function, visuospatial and language domains. SMART BRAIN® dynamically adjusts difficulty and training targets based on real-time user performance. ICI is committed to translational dementia research and welcomes strategic collaborations for clinical validation, implementation trials, and digital therapeutics development. **Innovation/Product/Device to be Presented (To Be):** SMART BRAIN® – an AI-based, multidomain cognitive intervention platform offering personalized training across cognitive domains for individuals with mild cognitive impairment and early-stage dementia. Designed for clinical scalability and remote application. **Academic Collaboration & Training:** ICI actively promotes early-career engagement in dementia research through its Student Research Assistant Program, inviting undergraduate and graduate students to participate in the aforementioned projects. Although positions are unpaid, selected students gain: Access to dedicated research space, Flexible working arrangements, Opportunities for co-authorship on peer-reviewed manuscripts and international conference presentations. **Key takeaway message:** We welcome academic, clinical, and industry partnerships to expand our translational capabilities in dementia research.

P345- INTERVIEW QUALITY MATTERS: A CROSS-TRIAL ANALYSIS OF CDR ADMINISTRATION ERRORS IN ALZHEIMER'S DISEASE CLINICAL RESEARCH.

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Background: The Clinical Dementia Rating (CDR) scale is a widely used tool for staging Alzheimer's disease (AD) severity and determining trial eligibility. Its semi-structured format assesses six cognitive and functional domains, relying heavily on clinical dementia experience, scale knowledge and interview skill acumen. While current training programs indeed focus on standardized scale administration along with scoring conventions, they may not always provided necessary emphasis on the nuanced clinical interviewing skills required to conduct accurate assessments—particularly in the context of global, multicenter trials involving culturally diverse populations. **Methods:** A cross-study evaluation was conducted across three multinational AD clinical trials to assess clinician performance during CDR administration at screening visits. Scale data and accompanying audio recorded study partner and subject interviews were reviewed by trained central reviewers to identify and classify administration and scoring errors. Flagged issues were categorized by domain and error type which consisted of administration, scoring, and/or other errors (i.e., missing audio). **Results:** Analysis identified widespread and recurrent errors, often associated with suboptimal clinical interviewing techniques. These included the use of leading, paraphrased, or closed-ended questions, insufficient probing of deficits, failure to obtain concrete examples of changes endorsed, inadequate explanation and clarification of questions, rater provided hints and non-neutral feedback, irrelevant conversations, and skipped questions within the scale interviews. Despite meeting standard qualification criteria, clinicians demonstrated inconsistencies in CDR execution. Quantitative review revealed the most prevalent administration errors occurred in the following domain areas: Memory (Study Partner): Administration errors in 15.24% of assessments (1,890 of 12,403). (i.e., Lack of details gathered in one – week/one -month events to adequately assess subject's recall; lack of examples gathered, or probes utilized to capture supporting evidence of memory changes from pre-morbid functioning).Judgment and Problem Solving (Subject): Administration errors were present in 9.36% of assessments (1,117 of 11,937). (i.e., Rater failed to adequately present similarities/differences examples instructions or probe for additional responses when subject responses failed to merit an initial score of "0". Rater often provided subject hints during calculations, reminding subjects of last number response and/or number being subtracted. Home and Hobbies (Study Partner): Administration errors in 6.28% (779 of 12,403). (i.e., lack of probes to determine changes in abilities; skipped questions.). Memory (Subject): Administration errors in 6.19% (739 of 11,937). (i.e., rater did not appropriately provide prompt support when subject was unable to recall one week or one month event; rater provided hints to subject during registration task.). Orientation (Subject): Administration errors in 5.16% (616 of 11,937). (i.e., rater accepted full date response for initial questions, skipping questions, and instead inserting responses for other orientation questions based on the initial response.). Community Affairs (Study Partner): Administration errors in 4.95% (614 of 12,403). (i.e., rater failed to provide descriptors and anchor responses to allow study partner to fully understand levels of loss; rater did not properly define the meaning of "casual observer" to the study partner.). Orientation (Study Partner): Administration errors in 4.80% (595 of 12,403). (i.e., rater did not provide anchor responses; rater did not adequately explain how study partner should gauge "time relationships"). Personal Care (Study Partner): Administration errors in 4.64% (575 of 12,403). (i.e., rater did not present instructions correctly or sufficiently probe for deficits; rater did not incorporate accurate examples to support study partner understanding of questions). **Conclusions:** Overall, errors were observed across nearly all CDR domains, affecting both subject and study partner interviews. These findings highlight a critical gap in real-world interviewing proficiency, with potential implications for participant eligibility, data integrity, and trial outcomes. While training and scoring standardization remain absolutely essential, they may not be fully sufficient to ensure accurate CDR administration in global trials. Enhancing clinician interviewer training with a focus on practical communication, probing, and cultural sensitivity may reduce administration and scoring errors. Interview Skills training allows for a thorough evaluation of each rater's abilities prior to study start by assessing rater scale knowledge, rater areas requiring targeted focus, presentation of realistic and hypothetical subject scenarios, rater scoring consistency,

exploration of rater confidence and decision making, along with dedicated feedback in order to equip raters with best practice standards as well. A more comprehensive qualification process—incorporating interview skills observed in assessments may support consistent, high-quality CDR data collection from the outset of AD trials.

Keywords: Alzheimer's disease, clinical dementia rating, clinical interview skills, rater training.

Disclosures: The authors have no conflicts of interest.

References: Morris JC. The Clinical Dementia Rating (CDR): Current version and scoring rules. Neurology. 1993;43(11):2412–2414.

Key takeaway message: Widespread CDR administration interview errors highlight the need for enhanced training focused on communication, probing, and cultural sensitivity to ensure accurate scoring, improve data quality, and support consistent outcomes in global Alzheimer's disease trials.

P346- LINKING THE MINI-MENTAL STATE EXAMINATION AND THE 13-ITEM VERSION OF ALZHEIMER'S DISEASE ASSESSMENT SCALE-COGNITIVE SUBSCALE.

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Background: Clinical trials in early Alzheimer's disease (AD) frequently employ multiple cognitive assessment scales—such as the Mini-Mental State Examination (MMSE), Clinical Dementia Rating Scale Sum of Boxes (CDR-SoB), and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog)—to evaluate disease severity and longitudinal change. While this multi-instrument approach enhances data richness, it introduces the risk of discordant measurements that may compromise the validity of trial outcomes. Understanding inter-scale relationships and addressing clinically inconsistent discrepancies is therefore essential to ensure trial integrity. This study applies equipercentile linking to systematically compare the MMSE and ADAS-cog, aiming to establish a framework for reconciling disparities between these widely used cognitive scales. **Methods:** We conducted post-hoc analysis of pooled clinical trial data containing repeated measures of the MMSE and ADAS-Cog, 13-item version. To address within-subject correlations, we implemented a bootstrap resampling procedure with 1,000 iterations, randomly selecting one observation per participant per iteration. MMSE scores were inverted (30 − raw score) to align directionality with ADAS-Cog, where higher values indicate greater impairment. For each bootstrap sample we calculated percentile ranks and merged MMSE/ADAS-Cog distributions by matched percentiles. Score equivalents were derived as the minimum and maximum ADAS-Cog values associated with each MMSE total, aggregated across iterations using median estimates. We validated the results using correlation analysis of the inverted MMSE scores and «linked» ADAS-cog scores. **Results:** Analysis of 47,718 MMSE-ADAS-Cog paired assessments from 11,871 subjects revealed some variability in score equivalences. Equipercentile linking demonstrated that single MMSE scores corresponded to up to 4-point ADAS-Cog ranges across most impairment levels (MMSE 0-28). Higher MMSE scores showed wider variability: MMSE=30 mapped to ADAS-Cog 0-10, while MMSE=29 corresponded to 11-15. At the common trial eligibility threshold (MMSE=22), equivalent ADAS-Cog scores spanned 30-32 points. The Spearman correlations increased from 0.75 in the original dataset to 0.99 in the linked data, in both instances the results being significant ($p<0.001$). **Conclusions:** This study extends cognitive measure linkage research by equating the MMSE with the 13-item ADAS-Cog version, contrasting prior work using the 11-item variant (Levine et al., Balsis et al.). While earlier equipercentile analyses (Levine et al.) found 2 ADAS-Cog points per MMSE point, our larger dataset (12 early AD trials, N=11,871) revealed broader intervals (up to 4 ADAS-Cog points for most MMSE points), reflecting enhanced sensitivity from the expanded ADAS-Cog scale. The use of resampling addressed trial heterogeneity and restricted score ranges at entry visits, stabilizing crosswalk precision. Despite protocol differences across source trials, the approach yielded robust mappings. These findings underscore version-specific linking needs and the value of large samples for establishing cognitive outcome equivalences.

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Key takeaway message: To understand equipercentile linking and gain a better appreciation of the impact a scale version has on mapping intervals.

P347- DEVELOPMENT AND PRELIMINARY FINDINGS OF THE MOCA-COGNITIVE HEALTH QUESTIONNAIRE.

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Background: Research has consistently shown that the risk of dementia later in life can be predicted by several lifestyle and medical factors. Based on previous research, the 2024 report of the Lancet standing Commission describes 14 modifiable risk factors for dementia and provides the population attributable fractions for each of the risk factors based on their prevalence and relation with dementia (1). **Methods:** Drawing on this study, we developed the MoCA-Cognitive Health Questionnaire (MoCA-CHQ) translating the 14 identified risk factors into a questionnaire and adding a number of other factors that can indirectly affect dementia risk, such as diet and sleep. The different risk factors have been grouped into five categories: physical health, emotional well-being, diet, exercise, and cognitive and social engagement. Based on the population attributable fractions for each of the risk factors, we developed an algorithm to provide both a total brain health score and a score for each of the five categories. After completing the MoCA-CHQ, individuals receive a total score, category scores as well as personalized recommendations about how they can improve their lifestyle to reduce their individual risk of dementia. **Results:** The MoCA-CHQ has been available online since February 2025 and has been completed by more than 5000 individuals. Preliminary analyses of this real-world data (N=3862) show that a highly educated and predominantly female sample reported a wide range of lifestyle and health-related risk factors for cognitive decline. Despite a high mean CHQ score, high prevalences were found for history of depression (32.4%), obesity (43.3%), head injury (22.1%), and physical inactivity (19.1%). A relation was found between education level and CHQ score with individuals with a higher education level having higher CHQ scores. Additionally, health issues such as hearing and vision difficulties, smoking, head injury and hypertension were more prevalent in individuals with lower education levels. Notably, many respondents expressed concern about their brain health with the mean CHQ score being significantly lower in individuals reporting that they are very worried about their brain health than in individuals reporting that they are not worried ($F(2, 3859)=105.62$, $p<.001$). **Conclusions:** The MoCA-CHQ expands the scope of cognitive assessments with self-reported indicators of lifestyle and health thereby addressing the need for a multidimensional approach to cognitive health. In addition, the large number of individuals who have filled in the MoCA-CHQ since its publication shows that the instrument also addresses a public need for an assessment of dementia risk and evidence-based guidance on modifiable lifestyle factors to support cognitive health. Future directions include combining the MoCA-CHQ with the MoCA in populations with known MCI and early-stage dementia as well as using the MoCA-CHQ in longitudinal studies to validate its predictive performance.

Reference: 1. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission, Livingston, Gill et al. The Lancet, Volume 404, Issue 10452, 572 - 628.
Key takeaway message: The MoCA-Cognitive Health Questionnaire (MoCA-CHQ) assesses dementia risk using 14 modifiable factors. Completed by over 5,000 users, early results show lifestyle-related risk disparities linked to education, highlighting its public relevance and clinical potential.

P348- COGNITIVE TRAJECTORIES IN ALZHEIMER'S DISEASE: FINDINGS FROM THE MULTINATIONAL CICERO-AD CHART REVIEW STUDY.

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Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by cognitive, functional, and behavioural decline. While the overall trajectory is one of gradual deterioration, substantial heterogeneity exists in the pace and pattern of progression. Understanding this variability is critical for accurate diagnosis, prognosis, personalized care, and caregiver support and for design of clinical trials. However, real-world longitudinal data on disease progression, especially across countries, remain limited. This study aimed to characterize cognitive trajectories in AD and explore cross-national differences. **Methods:** This retrospective, observational study analysed longitudinal data from medical chart reviews conducted at 26 sites across France, Germany, Italy, Spain and the UK. Eligible patients were over 55 years at diagnosis, had a clinical diagnosis of probable AD, and had a Mini-Mental State Examination (MMSE) score between 20 and 28 at diagnosis, consistent with mild cognitive impairment and mild dementia. Patients were required to have received routine clinical care and to have had at least one documented visit to a participating centre from 15 to 4 years before the date of data collection. Patients were excluded if they had a history of stroke or transient ischemic attack, Parkinson's disease prior to or at AD onset, frontotemporal dementia, or probable Lewy body disease. Data extracted included demographics, comorbidities, clinical characteristics, AD diagnostic and treatment pathways, and longitudinal outcomes across cognitive (MMSE, BNT, CDT, ADAS-Cog), functional (IADL, ADL, Barthel), and behavioural (NPI-derived) domains. Additional variables included caregiver characteristics (e.g., relationship, living arrangement), and AD–related hospitalizations. Change-point analysis was applied to identify statistically significant shifts in cognitive trajectories. Latent class growth modelling (LCGM) with finite mixture models was employed to classify patients into distinct cognitive decline trajectories based on MMSE scores. The model was iteratively refined using covariate selection and flexible functional forms (e.g., splines), guided by change-point analysis. Final model selection was based on Bayesian Information Criterion (BIC) to ensure optimal fit and parsimony. Country-specific analyses explored heterogeneity in patient profiles and disease progression. Kaplan-Meier and Cox proportional hazards models were used to assess time to institutionalization or death. **Results:** The analysis included 800 patients: Germany (n=197), Spain (n=288), Italy (n=143), France (n=120), and the UK (n=52) with a median follow-up of 4.42 years from diagnosis and diagnosis dates spanning between 2008 and 2019. The average age at baseline was 75.7 years (SD: 7.50; range: 56–96), 60.8% were female, and the mean MMSE at AD diagnosis was 23.5 (SD: 2.37). Comorbidities were common although burden varied, with 23.3% having cardiovascular condition(s) and 27% presenting with psychiatric or neurologic disorders. Caregiver support was reported in 85% of cases, primarily from spouses (60.2%) and adult children (34.5%). Professional caregivers were involved in 15.8% of cases. The mean number of AD-related hospitalizations was 0.9 (SD: 1.18), with a rate of 0.21 (95% CI: 0.18–0.25). Patients with caregivers had significantly more hospitalizations (mean 1.2 vs. 0.5, $p<0.05$). Overall, 25.8% of patients experienced institutionalization or death: 18.3% were institutionalized, and 7.5% died. Substantial cross-country differences were observed. Although MMSE was consistently used (per inclusion criterion), functional and behavioural assessments varied widely, with over 32 instruments (cognitive n=18, functional n=9, behavioural n=5) employed across sites. Diagnostic practices also differed; for example, amyloid testing was most frequent in Germany (84.3%), and absent in the UK. Age at diagnosis ranged from 73.2 (SD=6.68) years in Germany to 81.4 (SD=6.30) years in the UK. Longitudinal MMSE data revealed a consistent decline from five years pre-diagnosis (n=12, mean: 28.1, SD: 1.98) through two years pre-diagnosis (n=57, mean: 26.1, SD: 2.32), two years post-diagnosis (n=354, mean: 19.9, SD: 4.91), five years post-diagnosis (n=106, mean: 18.2, SD: 5.33) to eight years post-diagnosis (n=14, mean: 15.6, SD: 3.67). Change-point analysis identified two inflection points: approximately one year before diagnosis showing acceleration and approximately 2.5 years after, indicating shifts in the rate of decline. LCGM identified three distinct cognitive decline trajectories—slow, moderate, and rapid decline— with a classification accuracy of 95.4%, underscoring the robustness of the model. **Conclusions:** This large, multinational chart review highlights the heterogeneity in long term cognitive trajectories, patient characteristics among individuals with AD, as well as diagnostic procedures and assessment instruments used in routine clinical practice to reach a diagnosis and inform relevant clinical trial design. These findings also underscore the need for harmonised, comprehensive and longitudinal assessments to better capture disease progression and support individualized care across diverse healthcare settings.
Keywords: Alzheimer's disease, cognitive trajectory, chart review, Europe.
Disclosures: Diego Novick is a full-time employee of Eli Lilly and Company and minor shareholder in the company. Giuseppe Bruno serves as a Principal Investigator for Eli Lilly and Company studies. Grazia dell'Agnello and Anthony Zagar are full-time Eli Lilly and Company employees. Agota Szende and Victor Kiri are full-time employees of Fortrea. Mercè Boada has participated in Eli Lilly and Company Data Safety Monitoring Boards or Advisory Boards and has received consulting fees from Eli Lilly and Company. The authors declared no competing interests.
Key takeaway message: This study highlights the heterogeneity in cognitive trajectories, patient characteristics, diagnostic procedures and assessment instruments in routine clinical practice, which are important to patient care and clinical trial design.

P349- AUTOMATED LINGUISTIC AND ACOUSTIC METRICS OF A SMARTPHONE-CAPTURED CUED NARRATION AND RECALL ASSESSMENT FOR DETECTING EARLY MEMORY AND BIOMARKER CHANGES IN EARLY ALZHEIMER'S DISEASE.

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Background: The early identification of Alzheimer's disease (AD) is paramount for timely implementation of emerging disease-modifying therapies. Self-assessments of cognition using Digital Health Technologies (DHTs), such as smartphone apps, enable scalable, remote, and frequent measurements with the potential to detect early signs of the disease, even before symptoms appear, helping identify individuals at

risk of cognitive decline due to AD. The earliest signs of AD include subtle episodic and semantic memory impairments, which may be quantifiable with remotely administered and automatically scored speech-based DHT assessments. **Objectives:** This work evaluated the reliability and clinical validity of automated linguistic and acoustic metrics derived from Story Time (ST), a smartphone-based cued story narration and recall task, in individuals across the preclinical to early symptomatic AD spectrum. **Methods:** A total of 123 individuals (aged 65–89 years) with two different native languages (English and Spanish) participated [ISRCTN17035495]. These included 30 amyloid positive participants with early symptomatic AD (esAD, Clinical Dementia Rating (CDR)=0.5), 30 amyloid positive individuals with subjective cognitive decline (SCDp, Cognitive Change Index (CCI)≥16, CDR=0), 31 amyloid negative individuals with subjective cognitive decline (SCDn, CCI≥16, CDR=0), and 32 healthy volunteers (HC, CCI<16, CDR=0). Participants completed a baseline neuropsychological assessment and 28 days of unsupervised at-home cognitive testing on a study smartphone with a maximum of nine administrations of the Story Time task (ST). ST involved narration of a comic strip panel by panel (Narration), followed by immediate free (Immediate Recall) and more than 24-hour delayed free (Long Recall) recalls. Participants' speech was recorded with the smartphone, transcribed by trained transcriptionists, and processed with an automatic natural language processing (NLP) and acoustic analysis pipeline to generate three key outcome metrics: (1) content coverage of the stories (mean similarity (1-cosine distance) between story entities and transcript contents, after projection to a semantic space), (2) pause duration (cumulative pause duration at Narration; relative pause duration at Recall compared to Narration), and (3) word diversity (word entropy normalized by the logarithm of the number of unique words). Test-retest reliability was assessed with intraclass correlation (ICC) [McGraw and Wong, 1996], and convergent validity with regularized ridge regression [Friedman et al., 2010], where metrics were used to predict Boston Naming Test (BNT) or Free and Cued Selective Reminding Test (FCSRT immediate/delayed free recall). Known-groups validity (i.e., group differences) was evaluated with proportional odds logistic regression models (POLR) [Harrell, 2015]. All models were adjusted for age, sex, education, and study site (inherently tied to language) as covariates. Nominal significance threshold was set at alpha=0.05 and resulting adjusted R2 values, interpreted as square of partial correlation coefficients, are presented as effect sizes. **Results:** Metrics indicated moderate-to-good reliabilities at Narration (ICCs 0.74-0.85) and moderate at both Recalls (ICCs 0.50-0.72), except relative pause duration at Long Recall (ICC=0.17). For convergent validity, none of the metrics from Narration predicted BNT scores (R2≤0.05, insufficient variance in BNT scores preventing the model from converging), potentially due to strong ceiling effects in participants' BNT scores. Content coverage at each delay predicted the respective FCSRT (i.e. immediate/delayed) recall (R2≥0.14, p≤0.007), as did relative pause duration at Immediate Recall (R2=0.18, p=0.03). For known-groups validity, Narration yielded comparable content coverage across all groups (absolute log odds ratio — |LOR|≤0.71, p≥0.18), despite the greater esAD word count [Kurniawan et al., CTAD 2023], indicating less efficient speech in esAD. However, higher cumulative pause duration was observed in both amyloid positive groups (i.e., SCDp and esAD) compared to both amyloid negative groups (i.e., HC and SCDn) (LOR≥1.48, p≤0.006). Word diversity at Narration exhibited a decreasing gradient along the preclinical to esAD continuum, differentiating esAD from both HC and SCDn (LOR≤-1.26, p≤0.02), and SCDp from HC (LOR=-1.16, p=0.03). Both Recalls showed reduced content coverage in esAD compared to SCDn and SCDp (LOR≤-1.19, p≤0.03). Relative pause duration was lower in esAD compared to other groups during Immediate Recall (LOR≤-1.59, p≤0.005), and remained lower compared to HC and SCDn at Long Recall (LOR≤-1.46, p≤0.01). No consistent trends emerged for word diversity at both Recalls, which may be limited by the overall low word count at Recalls. **Conclusions:** These results indicate that scalable, automated analyses of remote, smartphone-based speech assessments may yield reliable and clinically valid metrics of language and memory deficits in individuals across the preclinical to early symptomatic AD spectrum.

Keywords: Digital biomarkers, speech biomarkers, early Alzheimer's disease, cognitive endpoints.

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Clinical Trial Registry: ISRCTN Registry identifier: ISRCTN17035495. Accessed online at https://www.isrctn.com/ISRCTN17035495 on October 7, 2022.

Key takeaway message: Scalable, automated analyses of remote, smartphone-based speech assessments may yield reliable and clinically valid metrics of language and memory deficits in individuals across the preclinical to early symptomatic AD spectrum.

BEHAVIORAL DISORDERS AND CLINICAL TRIALS

P350- PAIN SEVERITY MODERATES EFFICACY OF NABILONE FOR AGITATION IN ALZHEIMER'S DISEASE.

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Background: Agitation in Alzheimer's disease (AD) is a common and challenging symptom that can be exacerbated by underlying pain, which is often underrecognized in AD. Agitation affects up to 70% of individuals with AD, leading to increased caregiver burden, earlier institutionalization, and higher morbidity. The pathophysiology of agitation has been documented to show imbalances between cortical and subcortical structures. The prefrontal cortex, anterior cingulate cortex, insula and the amygdala have shown imbalanced activity in agitation compared to normal function, favouring hyperexcitability of the subcortical regions (1). The perception of and response to pain is also controlled by these same structures in persons experiencing chronic pain (2). Behavioural responses in persons with chronic pain are commonly expressed through anger, frustration and fear, showing similarities to persons with agitation in AD (2). It is possible that a subtype of agitation may be a consequence of unrecognized or unexpressed pain. We hypothesize that, due to the analgesic properties of nabilone, baseline pain severity moderates the treatment response observed in a clinical trial testing nabilone for agitation in AD (3). **Methods:** We analyzed data from 39 patients with probable AD, or mixed AD with vascular dementia, who participated in a phase II crossover trial evaluating the safety and efficacy of nabilone for agitation in AD. The trial participants were 77% male, with a mean age [SD] of 87 [10.2], and had mean standardized Mini-Mental State Exam (sMMSE) scores of 6.5 [6.8], indicating severe impairment. There were no detectable order ($t(31) = 0.2$, $p = 0.85$) or carryover ($t(32 = 1.6$, $p = 0.11$) effects between phases

and the intraclass correlation coefficient of the model was 0.014, suggesting negligible within-subject correlation. Thus, we treated phase-specific baselines as independent datapoints, yielding 71 observable cases. We categorized responders as those with a reduction of 8 points or more on the Cohen-Mansfield Agitation Inventory (CMAI) from baseline during each phase (4). We used logistic regression to define this response score based on the most recent minimal clinically important difference thresholds (5). A generalized linear model was used to test whether the interaction between treatment group and baseline pain severity (measured by the Pain Assessment in Advanced Dementia scale) (6), predicted responder status. Baseline CMAI scores and concomitant analgesic use were included as covariates. **Results:** Treatment phases showed no difference in baseline CMAI and pain scores ($t(69) = 0.43$, $p = 0.66$; $W = 651$, $p = 0.81$). Logistic regression was conducted in 64 cases after exclusion of cases with missing data. The interaction between pain and treatment was significant ($OR = 3.28$, $p = 0.04$), indicating that each unit increase in baseline pain was associated with a more than threefold increase in the odds of response to nabilone. Higher baseline pain severity showed a trend of lower placebo response ($OR = 0.41$, $p = 0.06$). In addition, a higher baseline CMAI score predicted greater odds of response ($OR = 1.06$, $p < 0.01$). Concomitant analgesic use (39% of participants) did not affect treatment response rates ($OR = 0.58$, $p = 0.40$). **Conclusions:** The data presented in this study suggest that baseline pain severity moderates the efficacy of nabilone in treating agitation, and highlights the importance of including pain evaluations in persons with AD to optimize agitation management. In addition, this analysis agrees with previous literature identifying pain as a modifiable trigger for agitation (7). Further investigation may identify a pain-agitation phenotype that may benefit from psychotropic interventions with analgesic properties.

Keywords: Precision medicine, cannabis-based medicine, neuropsychiatric syndromes, agitation, nabilone.

Clinical Trial Registry: NCT02351882; https://clinicaltrials.gov.

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Key takeaway message: Higher baseline pain severity in Alzheimer's disease predicts greater response to nabilone for agitation, supporting pain assessment as a key factor in optimizing agitation management in dementia.

P351- PHARMACOLOGICAL CLASS AND DOSE EFFECTS ON NEUROPSYCHIATRIC SYMPTOMS AND DISEASE SEVERITY IN DEMENTIA: A DEFINED DAILY DOSE-BASED COHORT STUDY.

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Background: Neuropsychiatric symptoms (NPS) are common in dementia and significantly impact patient outcomes and caregiver burden. While pharmacological treatments are frequently used, their efficacy remains unclear, particularly in real-world settings where polypharmacy is common. This study evaluates the impact of different medication classes and cumulative dosages—standardized by Defined Daily Dose (DDD)—on NPS and dementia severity. **Methods:** In this retrospective cohort study, 133 patients with dementia were assessed at baseline and after one year. Medication use across 46 drugs was categorized into four classes and quantified using DDD. Cox regression analyses examined the relationship between drug exposure and time to improvement in NPS severity, caregiver distress, and global Clinical Dementia Rating (CDR), adjusting for demographic and baseline variables. **Results:** Antidepressant use was associated with faster improvement in NPS severity ($OR = 3.05$) and caregiver distress ($OR = 5.16$), though higher cumulative doses did not accelerate improvement. Dementia severity improvement was significantly predicted by male sex and younger age, rather than pharmacological factors. **Conclusions:** Antidepressants may be effective in alleviating NPS and reducing caregiver burden in dementia, but increasing doses does not enhance the speed of improvement. Demographic factors play a more prominent role in dementia severity outcomes than medication exposure.

Keywords: Dementia, neuropsychiatric symptoms, antidepressants, polypharmacy, defined daily dose.

Disclosures: Yu-Ruei Lin and Jong-Ling Fuh have nothing to disclose.

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P352- EVALUATION OF THE BENEFITS OF BENZGALANTAMINE (ZUNVEYL®) THERAPY ON SLEEP QUALITY AND BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA IN ALZHEIMER'S DISEASE PATIENTS, AND ON REDUCTION OF CARE-PARTNER BURDEN: A PROPOSED STUDY DESIGN.

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Background: Compromised sleep quality is highly prevalent among patients with Alzheimer's Disease (AD). Sleep disturbances are implicated not only in cognitive impairment but also in the progression of AD pathology. Given the long prodromal phase of AD, sleep disruption is considered as both an early clinical marker and a potential contributor to disease progression. This may occur through impaired glymphatic function (1) resulting from reductions in slow wave sleep [NREM3] during which glymphatic function is most active (2,3). Acetylcholine plays a key role in sleep regulation, and some acetylcholinesterase inhibitors (AChEIs) are associated with sleep disturbances in patients with AD. Donepezil use is associated with insomnia and vivid dreams, potentially attributable to its long half life of ~ 70 hours (4). Rivastigmine has shown mixed effects, with reports of both sleep disruptions and modest improvement (transdermal formulation), which was observed to reduce sleep apnea in a small cohort of probable AD patients (5). In contrast, galantamine demonstrated either a neutral impact (6,7) or modest improvement to sleep quality (8,9). Behavioral and psychological symptoms of dementia [BPSD] occur in up to 80% of AD patients (10). Galantamine has demonstrated significant benefits in reducing BPSD, measured by the Neuropsychiatric Inventory (NPI) (11). A meta-analysis of pooled NPI data from three galantamine trials, nine donepezil trials and one rivastigmine trial, found that galantamine use significantly reduced NPI scores compared to placebo, whereas no significant effects were observed for donepezil or rivastigmine (12). The use of AChEIs in AD provides modest benefits in reducing care-partner burden. In two studies of five and six months duration, galantamine demonstrated significant improvements in behavioral symptoms and global functioning, accompanied by reductions in caregiver distress as measured by the Neuropsychiatric Inventory Caregiver Distress Scale (NPI-D) (13,14). A secondary analysis showed that galantamine reduced both the emergence and severity of behavioral disturbances and resulted in a 29–48% improvement in patients' behavioral symptoms from baseline, which was associated with significantly reduced caregiver distress (NPI-D, $P<0.05$) (15). Benzgalantamine is an essentially pharmacologically inert prodrug of galantamine, formulated as a delayed release oral medication. It is absorbed in the proximal small intestine and is anticipated to cause fewer gastrointestinal side effects with resultant improved tolerability. In 2024 benzgalantamine (ZUNVEYL®, Alpha Cognition Inc., Grapevine, TX) was approved by the FDA for treatment of dementia associated with mild to moderate AD. Approval via the 505(b)(2) pathway was based on the determination of bioequivalence in three clinical studies in healthy adults under fed and fasted conditions (16), steady state conditions (17), as well as a fourth study confirming dose proportionality across the 5, 10 and 15 mg marketed dosages (18). **Methods:** We propose to (i) assess sleep quality and BPSD outcomes in individuals diagnosed with mild to moderate AD over a 12-week treatment period using the NPI, as well as documenting sleep quality by EEG using a validated, wearable device and (ii) assess the consequence of improved patient outcomes on care partner burden/distress using the (NPI-D) (19). Newly diagnosed AD patients and their care-partners will be randomized to one of two active treatment arms, benzgalantamine or donepezil. Donepezil was selected as the active comparator rather than an untreated placebo control, to allow direct comparison between the two AChEIs, and to ensure that newly diagnosed patients are not deprived of therapy for the duration of the study. The study will be powered for superiority in specific subdomains of the NPI, comparing outcomes following 12 weeks of treatment to baseline scores. We propose to assess patient outcomes using two complimentary approaches. Firstly, NPI/NPI-D: Patient BPSD will be measured with the 12-subdomain version of the NPI (including night-time behavioral disturbances), while care-partners will self evaluate their level of distress using the NPI-D. Secondly, EEG: Patient sleep architecture will be assessed using a wearable EEG monitor as described by Kent et al. (2), with particular attention to deep sleep stage (slow wave sleep) which is compromised in AD. Patients will undergo EEG monitoring for five consecutive nights prior to therapy initiation, and again for five nights at week 12. Both patients and their care-partners will be assessed using the NPI and the NPI-D respectively, both at baseline and at week 12. Anticipated Outcomes: We hypothesize that treatment with benzgalantamine will improve sleep quality and reduce BPSD in patients with AD, leading to a corresponding reduction in care-partner burden.

Keywords: BPSD, sleep, care-partner burden.

Disclosures: All authors are employees and shareholders of, or hold stock options in Alpha Cognition Inc.

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Key takeaway message: We hypothesize that treatment with benzgalantamine will improve sleep quality and reduce BPSD in patients with AD, leading to a corresponding reduction in care-partner burden.

HEALTH ECONOMICS AND CLINICAL TRIALS

P355- COST SAVING BY PLASMA P-TAU217 VERSUS P-TAU217/Aβ42 RATIO USING TWO-STEP APPROACH IN THE JAPANESE HEALTH CARE SYSTEM.

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Background: Anti-amyloid β (Aβ) therapies, lecanemab and donanemab, are already available in Japan and the cost of amyloid PET or cerebrospinal fluid (CSF) Aβ42/40 measurement is covered by the national health care system to determine drug eligibility. Blood-based biomarkers (BBMs) including plasma p-tau217 have recently shown excellent diagnostic accuracy especially using the two-step approach. Plasma p-tau217/Aβ42 ratio has even more advantage of reducing the individuals in the intermediate zone that needs confirmatory tests (1), and has been approved by the FDA. The introduction of BBM not only reduce the burden of the patients and health care professionals but may also have the advantage of cost saving (1). However, each country has different system and, thus the potential cost saving effect of BBMs in the Japanese healthcare system remained undetermined. **Methods:** We used the recently released app (https://bbrc-lab.shinyapps.io/Cost-effectiveness_analysis_plasma_p-Tau217/) (1) to estimate the cost saving effect of plasma p-tau217 or p-tau217/Aβ42 using the two-step approach in Japan. The estimated costs mainly used in this study for amyloid PET was 1550 USD and that for CSF Aβ42/40 was 880 USD including one-night stay for lumbar puncture. The costs of BBMs were simulated from 100 to 800 USD. Sensitivity analyses were conducted using different estimated costs for PET and CSF. **Results:** The cost saving was 34–79% against PET and -5.6%–74% against CSF, when default setting of 14.7% was applied for the intermediate zone. When 7% was applied for the intermediate zone based on recent report using p-tau217/Aβ42 in secondary clinics (1), the cost saving was higher at 41–87% against PET and 2.1–82% against CSF. In sensitivity analyses, cost-saving effect remained positive until 700 USD against PET, until 300 USD against in-patient CSF, and until 90–100 USD against out-patient CSF. Based on the assumption that the cost of measuring two analytes (p-tau217/Aβ42) is required to reduce the intermediate zone from 14.7% to 7% despite doubling the price, the cost saving effect was compared between one versus two analytes. The cost saving effects were comparable at 70–80% at 100 USD per analyte, 48–72% at 200 USD per analyte, and gradually differed (one better than two analytes) when costs per analyte was increased. **Conclusions:** We demonstrated that both plasma p-tau217 and p-tau217/Aβ42 ratio using two-step approach have large cost-saving effect also in the Japanese health care system. The cost saving was comparably high at lower cost per analyte (100-200 USD), even after considering that measuring two analytes may double the cost to reduce intermediate zone. Given that reducing intermediate zone have the benefit of timely diagnosis and less burden for both patients and health care professionals, these estimates may be useful to determine the use of p-tau217 versus p-tau217/Aβ42 in each country.

Keywords: Blood-based biomarkers, plasma p-tau217, two-step approach, cost saving, clinical implementation. **Disclosures:** MK has received lecture fees from Eisai, Eli Lilly, and John Wiley & Sons; patent assignment fee from FUJIREBIO; and research support from Nihon Medi-Physics. RI has received advisory fees from Eli Lilly; and lecture fees from Eisai and Eli Lilly. KS's affiliation "Dementia Inclusion and Therapeutics" is an endorsed course funded by Effissimo Capital Management Pte Ltd. AI has received advisory fee from Eisai and Eli Lilly; stock ownership/capital gain from Eisai; lecture fees from Eisai, Eli Lilly, John Wiley & Sons, FUJIREBIO, HU Frontier, and Sysmex; and grants for commissioned/joint research from Eisai, Eli Lilly, FUJIREBIO, and Sysmex.

Reference: 1. Palmqvist S, et al. Nat 2025; 31(6): 2036-2043. doi: 10.1038/s41591-025-03622-w.

Key takeaway message: Both plasma p-tau217 and p-tau217/Aβ42 ratio had cost-saving effect also in the Japanese health care system. The cost of measuring two analytes seemed to be feasible to reduce intermediate zone at lower price per analyte.

P356- A LOW-COST, SCALABLE BLOOD BIOMARKER ASSAY FOR ALZHEIMER'S DISEASE TESTING IN RESOURCE- LIMITED SETTINGS.

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Background: As therapeutic options become available, diagnosing Alzheimer's disease has taken on additional importance. Because diagnosis remains highly challenging in primary care, tests such as amyloid PET scans and CSF tests are relied upon for accurate diagnosis. However, costs – both in terms of infrastructure as well as per test – for the gold standard methods remain high and limit their ability to be made available across a wide array of healthcare settings. Beyond lacking access to these critical diagnostics, populations in resource-limited settings are also excluded from clinical trials due to the same reason. Yet enabling their participation in trials is essential to ensure that novel therapeutics deliver equitable health benefits across diverse patient populations. Blood-based biomarkers (BBM) offer the opportunity to provide patients with a less invasive sample draw method and a less daunting testing method. Recent FDA approval of a blood-based diagnostic test further underscores the fact that BBM can provide meaningful impact for Alzheimer's disease diagnosis. However, even with recent advancements, the capital investment required for BBM testing platforms is still in the range of hundreds of thousands of dollars USD. Similarly, the per test costs are several hundred dollars per test. Although more affordable than traditional gold-standard tests, this still presents significant barriers to a substantial portion of the world. Here we present an ultrasensitive, fully manual assay that can quantify ninety-six samples in under four hours with an ELISA-like workflow while requiring no capital investment and utilizes instruments that already exist in a diagnostic laboratory. Taudia's unique Dual-Conjugation Proximity Ligation Assay (dcPLA) platform can be performed entirely manually and quantifies protein targets on a standard qPCR instrument. This eliminates the need to ship bulky equipment to a lab and the need to ship samples to a central lab – empowering onsite testing. We believe this assay platform can provide a truly scalable solution to bring BBM testing for Alzheimer's disease to healthcare settings that are not accessible with other technologies. **Methods:** To demonstrate the ability to perform sensitive, multiplexed biomarker measurement using a manual assay, we created a duplex pTau-217/Aβ42 assay and characterize the assay's performance in the following areas – linearity, spike and recovery, ability to differentiate between AD- and AD+ plasma samples and concordance with a leading on-market platform. Briefly, the assay begins with an incubation step of the antibody pair and the sample to allow the formation of the immunocomplex. The complex is then captured with a magnetic bead and washed. Importantly, only a single wash step is needed for the Taudia assay. After washing, master mix is mixed with the beads, and qPCR is performed on a conventional instrument to amplify the signal. The entire workflow involves less than 30 min of hands-on time and can be completed in under 4 hours. Linearity was tested by examining the standard curve from 1000 pg/mL to less than 0.01 pg/mL created using commercially available peptide. Spike-and-recovery was tested by spiking in identical quantities of the peptide into 2X diluted plasma and buffer and comparing the quantified concentration. For differentiating AD-/AD+ patient plasma samples, 20 samples (10 AD+ and 10 AD-) were tested using the manual assay. The same 20 samples were quantified using a commercially available platform and assay. **Results:** All dcPLA assays were performed in Taudia's lab with full manual workflow

including bead washing and pipetting. The assay was able to demonstrate linearity over 4-logs, from 1000 pg/mL to lower than 1 pg/mL, with a R2-value greater than 0.99 for both targets. Spike-and-recovery testing revealed recovery rates close to 100% of the spiked-in reference materials (with all samples between 80% to 120%) in 2X diluted plasma. The pTau-217/Aβ42 duplex assay showed comparable performance against single-plex assays for the two targets. Linear range for the standard curves and quantitative measurements of real patient samples using the two formats show no statistically significant difference. All 20 clinical samples were quantified and correspond to the clinical evaluation with a single threshold separating AD+ and AD- plasma samples. When compared to values measured using the commercially available platform, the dcPLA values correlated extremely well, with a R2-value greater than 0.95 for both targets. Overall, dcPLA showed more consistent results with lower CVs – out of the 20 samples the commercial platform testing resulted in three samples with CV greater than 10% and two out of the three having CVs greater than 20%. **Conclusions:** In this study, we demonstrated a low-cost, scalable, and ultra-sensitive blood biomarker assay that can be performed using a fully manual workflow, eliminating the need for significant capital investment. By utilizing existing qPCR instrumentation commonly found in diagnostic laboratories, this assay platform has the potential to make blood-based Alzheimer's disease diagnostics accessible in healthcare settings where current technologies are impractical or unreachable. We believe Taudia's assay platform represents a transformative step forward in Alzheimer's diagnostics, with the potential to democratize access to blood biomarker testing on a global scale.

Key takeaway message: A fully manual, ultra-sensitive blood assay using standard qPCR enables scalable Alzheimer's diagnostics without capital investment—supporting global access, equitable trial inclusion, and high-performance biomarker quantification comparable to commercial platforms.

P357- ECONOMIC VALUE OF A BLOOD TEST FOR ALZHEIMER'S DISEASE PATHOLOGY IN PRIMARY AND SPECIALTY CARE IN THE U.S.

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Background: Blood tests for the pathology of Alzheimer's disease (AD) are emerging as an alternative to amyloid PET scans and cerebrospinal fluid (CSF) analysis as a rule out or even as confirmatory test. However, their economic value, which depends not only on the accuracy of a test but also its effect on clinical decision-making or clinical utility, remains unclear. **Methods:** We use a Markov model to estimate the value-based price of a blood test with published sensitivity of 88% and specificity of 89%1 with four contexts of use: triage and confirmation of the AD pathology and both in primary and in specialty care. We modeled the 10-year timeframe from 2025 to 2034 and used the U.S. population aged 65 and older as the intended use population. The value-based price was defined as the price of the test, at which overall diagnostic cost per true positive case of early-stage AD would equate that under standard of care. Robustness of the estimates was tested by varying specificity between 85% and 93% and sensitivity between 82% and 92%. The standard of care pathway was identification in primary care and referral to specialty care based on the results of a brief cognitive test, confirmation of early-stage cognitive impairment, biomarker testing with PET or CSF, adjudication and treatment decision. Assumptions for the effect of test use on clinical decisions came from a structured expert consultation process involving five physicians with experience in evaluating AD patients (one geriatric psychiatrist, two neurologists, and two geriatricians): In the absence of a blood test, 60% of patients with an abnormal brief cognitive test in primary care would be referred to specialty care. If a blood test were subsequently administered prior to the referral decision, 80% of those with a positive test and 40% with a negative result would be referred. Specialists would conduct CSF or PET testing in 40% of patients with confirmed early-stage cognitive impairment, if no blood test results were available, and in 80% and 10% of those with a positive and negative test, respectively, if the blood test were labeled as triage test. If the test were labeled as confirmatory, 30% and 10% of cases would undergo additional testing with PET or CSF. In other words, specialists would consider a positive blood test result as sufficient to establish the AD pathology in 20% of cases, if the test were labeled as triage test, and 70%, if it were labeled as confirmatory test. The final estimate was that 75% of confirmatory tests would be based on amyloid PET scans and 25% on CSF analysis. Utilization of medical services during this hypothetical journey was tracked and converted to cost based on 2024 Medicare billing rates with a 3% annual inflation of cost for subsequent years. Those services are primary care office visit ($61.82), specialist consultation ($182.56), lumbar puncture ($159.65), CSF assay for AD pathology ($312.31), brain PET scan ($1,480.34) and amyloid PET tracer ($3,257.44). **Results:** If used in primary care, the value-based price would be $290 ($220-$360) for a triage and $1,150 ($925-$1,200) for a confirmatory test, respectively, as use of PET or CSF testing would decline by 47% and 86%, respectively. If used in specialty care, i.e., after confirmation of early-stage cognitive impairment by the specialist, the overall number of blood tests would decline with the same effect on utilization of PET and CSF testing. Consequently, the value-based price would increase to $450 ($325-$600) for a triage test and $1,950 ($1,500-$2,250) for a confirmatory test. **Conclusions:** The results project substantial economic value of using a blood test for AD pathology within the diagnostic pathway based on modeling results. Future research should confirm the findings with actual data and analyze the ability of a blood biomarker to address bottlenecks in the diagnostic pathway during evaluation of cognitive impairment. **Key takeaway message:** The value-based price for an AD blood test with sensitivity of 88% and specificity of 89% would be $290 for a triage and $1,150 ($925-$1,200) for a confirmatory test, if used in primary care, and $450 and $1,950, respectively, if used in speciality care.

P358- COST-EFFECTIVENESS ANALYSIS OF INITIATING NOVEL MONOCLONAL ANTIBODIES AT EARLY ALZHEIMER'S DISEASE STAGES.

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Background: Patient and caregiver burden of Alzheimer's Disease (AD) increases with the disease severity (1,2). Introduction of disease-modifying therapies to facilitate early treatment of AD has been recognized as a major milestone to reduce the disease-related clinical and economic burden (3). Among the three novel monoclonal antibodies (mAbs) that received regulatory approval as AD treatments, two (Lecanemab and Donanemab) remain available for early AD patients with the lowest severity, Mild Cognitive Impairment (MCI), and the next severity, Mild AD. However, the cost-effectiveness of these agents remains in question. This research aims to compare the clinical and economic outcomes of early initiation of the treatments at MCI versus late initiation of the treatments at Mild AD. **Methods:** A Markov cohort simulation model was developed representing a delay in AD progression to compare treatment initiation at different stages of early AD. The model incorporated progression profiles, safety profiles, and cohort characteristics that mirrored Phase 3 clinical trials of Lecanemab and Donanemab (4,5). Progression trajectories and other model inputs were obtained from published literature. Wholesale acquisition costs were

sourced from Micromedex® RED BOOK®. The model used a 1-week cycle length and estimated the cost and health outcomes over a 10-year time horizon. Incremental cost-effectiveness ratios (ICER) per quality-adjusted life years (QALY) were reported as compared to the standard of care (SoC). Results were presented from a societal perspective, which included patients' and care partners' healthcare costs, non-healthcare costs, out-of-pocket costs, and productivity consistent with treatments, disease states, and treatment-related adverse events. 3% discount rate was applied for cost and outcomes. **Results:** Early initiation of mAbs at MCI demonstrated minimal gain in life years (LY) of 0.08 and 0.04 for Lecanemab and Donanemab, respectively, compared with late initiation at Mild AD. Although minimal, early initiation demonstrated a loss in QALY of 0.002 in Lecanemab and a loss of 0.02 for Donanemab. Despite the minimal impact on health outcomes, early initiation incurred additional $25,900 for Lecanemab and $14,400 for Donanemab, which were largely driven by treatment costs. Early initiation of the mAbs demonstrated ICERs of $194,800 and $202,000 for Lecanemab and Donanemab, respectively, per QALY, which did not meet the health-benefit price benchmark (HBPB) of $150,000/QALY. In comparison, late initiation resulted in cost-effectiveness of $118,400 and $154,100 for Lecanemab and Donanemab, respectively. Late initiation of Lecanemab was the only strategy that demonstrated cost-effectiveness from the societal perspective, with $39,149 added cost and 0.33 QALY gained compared to SoC. **Conclusions:** Early initiation of mAbs was estimated to add substantial cost compared to late initiation, with minimal benefit in health outcomes. These findings highlight the pressing need for treatment options with meaningful progression delay and more affordable price.

Keywords: Cost impact, QALY, cost-effectiveness, disease-modifying therapy, monoclonal antibody, early AD, mild cognitive impairment, mild AD.

Disclosures: The authors declared no competing interests.

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Key takeaway message: Current disease-modifying treatments for early AD demonstrate limited cost-effectiveness, regardless of the stage at which the treatment was initiated. This analysis highlights the urgent need for more affordable therapies.

P359- NEUROLOGISTS' PERCEPTIONS AND EXPERIENCES WITH AMYLOID-TARGETING THERAPIES IN ALZHEIMER'S DISEASE IN THE UNITED STATES: BASELINE DATA.

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Background: Alzheimer's disease (AD) is a leading cause of dementia and the seventh most common cause of death in the United States (US) (1). Amyloid-targeting therapies (ATTs) aim to reduce Aβ plaques in the brain, showing significant cognitive and functional benefits in early-stage AD patients (2). This presentation examines baseline survey data from US prescribers and non-prescribers of ATTs to understand their perceptions of ATT use and efficacy. A follow-up survey will be conducted six months after baseline to evaluate changes in perceptions. **Methods:** In September 2025, data were collected via an online survey from US neurologists treating patients with AD in the mild cognitive impairment (MCI) or mild dementia stages. The survey assessed perceptions of ATT use, safety, and efficacy in these patients, as well as factors influencing early diagnosis of AD and ATT utilization. Data were analyzed descriptively. **Results:** Of the 81 neurologists who completed the survey, 56 (69.1%) self-reported prescribing ATTs to patients with AD in the MCI or mild dementia stages ("patients"). Forty-three percent (n=35/81) manage an annual panel of 51-100 patients in these stages. Most practices are in urban areas (n=48/81; 59.3%), and 62 (76.5%) work in hospital-based outpatient clinics. Neurologists primarily self-identified as White (n=35/81; 43.2%) or Asian (n=27/81; 33.3%). Just over half are male (n=47/81; 58.0%), and 33 (40.7%) are female. Most have been practicing for 10 or fewer years since completing their training (n=53/81; 65.4%). Approximately 40% (n=22/56) of ATT prescribers reported having 11 to 20 patients currently on ATTs. A little over 40% reported initiating their first patient on ATTs 1-2 years ago (n=24/56; 42.9%). Lecanemab (52/56; 92.9%) and donanemab (37/56; 66.1%) were most prescribed. Neurologists were surveyed on factors impacting early detection and diagnosis of AD. Among prescribers, 71.4% (n=40/56) agreed or strongly agreed they had access to necessary services and tools for diagnosing patients compared to 92.0% (n=23/25) of non-prescribers. Noteworthy variations were observed in the use of blood biomarkers for diagnosis, with 71.4% (n=40/56) of prescribers and 56.0% (n=14/25) of non-prescribers affirming their use. Additionally, 89.3% (n=50/56) of prescribers and 96.0% (n=24/25) of non-prescribers agreed or strongly agreed that primary care physicians should detect cognitive issues earlier and refer patients to specialists now that preventive treatments are available. Most neurologists agreed or strongly agreed that the clinical evidence supporting the effectiveness of ATTs in slowing cognitive and functional decline in patients with AD in the MCI or mild dementia stages is strong (n=52/81; 64.2%). However, there were noticeable differences between ATT prescribers (n=40/56; 71.4%) and non-prescribers (n=12/25; 48.0%). Similarly, most neurologists believed that ATTs are more impactful in the long-term compared to existing symptomatic therapies (n=58/81; 71.6%), with higher agreement among ATT prescribers (n=46/56; 82.1%) than non-prescribers (n=12/25; 48.0%). Furthermore, most neurologists considered ATTs to represent a significant advancement in the treatment of patients with AD in the MCI or mild dementia stages (n=62/81;76.5%), with ATT prescribers (n=45/56; 80.4%) showing higher agreement than non-prescribers (n=17/25; 68.0%). Nearly 90% (n=72/81) of all neurologists agreed or strongly agreed that trial data show that treating earlier is better since patients with early-stage AD saw better efficacy results. Confidence in using ATTs varied significantly, with 78.6% (n=44/56) of prescribers and 52.0% (n=13/25) of non-prescribers agreeing or strongly agreeing. Additionally, 84.0% (n=68/81) of all neurologists felt confident in evaluating patient eligibility for ATTs. Approximately 40% (n=33/81) of neurologists expressed reluctance to prescribe ATTs due to the risk of ARIA, with prescribers (n=20/56; 35.7%) showing less reluctance than non-prescribers (n=13/25; 52.0%). Disparities were also noted in agreement with ATTs fitting within their current treatment approach, with prescribers (n=45/56; 80.3%) showing higher agreement than non-prescribers (n=14/25; 56.0%). Notably, 80.4% (n=45/56) of prescribers felt they had access to the necessary information to prescribe ATTs, compared to only 52.0% (n=13/25) of non-prescribers. Neurologists were asked about factors impacting utilization of ATTs; 44 of 56 (78.6%) prescribers reported having sufficient knowledge to manage ARIA in patients on ATTs, compared to 14 of 25 (56.0%) non-prescribers. Additionally, 67.9% (n=38/56) of prescribers believed the benefits of ATTs outweighed the risks, compared to 44.0% (n=11/25) of non-prescribers. Positive patient outcomes with ATTs were reported by 69.6% (n=39/56) of prescribers. Logistical challenges such as insufficient staff to handle insurance logistics (e.g., pre-authorization requirements) and lack of time for patient care coordination (e.g., MRIs, prescriptions, infusions) were identified as impediments to ATT use. Financial barriers were overwhelmingly agreed upon as a difficulty for patient access to ATTs, with 82.1% (n=46/56) of prescribers and 96.0% (n=24/25) of non-prescribers agreeing or strongly agreeing. **Conclusions:** Both prescribers and non-

prescribers of ATTs acknowledge that ATTs can slow cognitive decline in patients with AD in the MCI or mild dementia stages compared to existing symptomatic therapies. However, this survey identified several factors contributing to hesitancy in prescribing ATTs among neurologists. The findings underscore the need for enhanced support, including access to resources to overcome logistical challenges, to improve ATT adoption and utilization in the care of patients with AD in the MCI or mild dementia stages. Changes and drivers of perceptions will be reevaluated in six months.

Keywords: Alzheimer's disease, amyloid-targeting therapies, prescriber perceptions, survey study.

Disclosures: OJV, AH, and TS are employees and minor shareholders of Eli Lilly and Company. BG and VN are employed by Thermo Fisher Scientific (TFS). BG and VN are minor shareholders of TFS.

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Key takeaway message: Amyloid-targeting therapies (ATTs) show significant benefits in early-stage Alzheimer's disease, highlighting the importance of early adoption. However, logistical and financial barriers hinder ATT utilization among neurologists, necessitating enhanced support and resources.

P360- ENHANCING ALZHEIMER'S DISEASE DIAGNOSTIC EFFICIENCY AND ACCURACY WITH PLASMA-BASED PTAU217 TESTING: A COMPARATIVE ANALYSIS IN PRIMARY AND SECONDARY CARE.

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Background: Growing availability of Alzheimer's isease (AD) disease-modifying therapies (DMTs) increases the demand for early diagnosis. Current AD diagnosis relies on clinical, cognitive, and imaging tests prior to assessment of amyloid pathology via more invasive amyloid positron emission tomography (PET) or cerebrospinal fluid (CSF) testing. This research examines the impact of adding a plasma-based pTau217 test for amyloid assessment in the US diagnostic pathway versus the Standard of Care (SoC) from a healthcare system perspective. **Methods:** A cohort-based model simulates 1000 patients being assessed for cognitive symptoms in primary and secondary care under two scenarios 1) pTau217 implementation in primary care with 9.95% prevalence of amyloid positivity and 2) pTau217 implementation in secondary care with 37.3% prevalence of amyloid positivity. Both scenarios were compared to SoC which was diagnostic workup in primary and secondary care settings respectively. Data was taken from published literature (1) and internal Roche data on file. A three step diagnostic pathway is modelled with first presentation in primary care, referral to secondary care for 70% of positive tested patients and exclusion for negative tested patients, and lastly amyloid confirmation for70% of positive tested patients and DMT initiation for 50% of positive tested patients and exclusion for negative tested patients. False negative patients are assumed to reenter the diagnostic pathway after a period of time and experience a delayed diagnosis. The waiting time between the steps of the diagnostic pathway ranged from 9 to 18 weeks. The study evaluates the effects of introducing pTau217 compared to SoC on amyloid PET or CSF utilization, false positive DMT initiation, number of diagnostic procedures, healthcare visits, number of true and false negative and true and false positive patients, and the accuracy and timeliness of AD diagnoses. **Results:** The implementation of pTau217 led to a 27.14% decrease in re-assessment for patients that got a delayed diagnosis due to being identified as false negative for amyloid pathology in the primary care setting, compared to current SoC. The resource use per patient was increased by 9.37% and 8.47% in primary and secondary care, respectively. Specialist care visits decreased by 2.50% in primary and 5.00% in secondary care scenarios. However, primary care showed a greater reduction in calendar time to an AD diagnosis (minus 5 days per patient vs. minus 1 day per patient in secondary care). Healthcare visits until diagnosis dropped more substantially in primary care than secondary care (17.65% vs. 3.57%), as well as procedures needed until diagnosis (18.42% vs. 1.43%). Amyloid PET or CSF testing after introducing pTau217 decreased by 77.56% in the primary care scenario and 18.79% in the secondary care scenario. The increase in true positives identified by amyloid PET or CSF was 31.39% in the primary care scenario and 6.03% in the secondary care one. 39.68% more true negative patients were ruled out before confirmatory testing with amyloid PET or CSF compared to SoC in the primary care scenario, and 25.94% in the secondary care scenario. DMT initiations after amyloid confirmation at specialist decreased by 4.69% when implementing pTau217 in the primary care scenario. In secondary care, the implementation of pTau217 led to a 50.00% reduction in AD-negative patients wrongly starting DMTs. Improvements in timely diagnosis and treatment for AD-positive patients ranged from 6.03% to 31.39% in primary and secondary care scenarios, respectively. In summary, implementing pTau217 in primary or secondary care as part of the diagnostic workup showed reductions in calendar time to diagnosis, healthcare visits, and procedures needed, as well as a higher number of AD-positive patients with a timely and correct diagnosis compared to SoC. The primary care scenario with lower prevalence yielded greater improvement in diagnostic pathway outcomes compared to the secondary care scenario with higher prevalence. **Conclusions:** Incorporating plasma pTau217 testing enhances AD diagnostic efficiency. The placement of pTau217 in primary care leads to reduced diagnostic time and visits, while in secondary care it improves accuracy. Both implementation scenarios benefit from better identification and timely treatment compared to SoC. These findings underscore the importance of pTau217 integration for optimal resource allocation and patient outcomes.

Keywords: Alzheimer's disease, blood based biomerakers, health economics.

Disclosures: SR and MG are full-time employees of Roche Diagnostics International Ltd, Switzerland. GO is an employee and stockholder of Quantify Research AB, providing consultancy services to pharmaceutical companies and other private and public organizations and institutions.

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Key takeaway message: Implementing pTau217 testing compared to standard of care enhances Alzheimer's diagnosis, improving efficiency and accuracy in both primary and secondary care settings, leading to better patient outcomes.

P361- SOCIETAL COST AND EFFICIENCY COMPARISON OF SUBCUTANEOUS VS INTRAVENOUS LECANEMAB FOR EARLY ALZHEIMER'S DISEASE IN THE UNITED STATES.

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Background: Intravenous (IV) therapies often impose significant burdens and costs on payers, providers, patients, and caregivers. A fixed-dose subcutaneous (SC) formulation may enhance convenience, improve outcomes, and reduce societal costs compared with weight-based IV dosing. This study estimated the relative societal value and cost implications of IV versus SC lecanemab administration for early Alzheimer's disease (AD) in the United States. **Methods:** A targeted literature review identified outcomes related to IV and SC modes of administration across therapeutic areas to inform and parameterize a

cost-comparison model. The model incorporated direct treatment costs; economic value of administration time for providers, patients, and caregivers; and quality-of-life (QOL) impacts for patients and caregivers. Costs were estimated from a societal perspective over four years, including a per-patient head-to-head savings analysis and a population-level assessment accounting for population size, current treatment rates, and SC uptake. Scenario analyses evaluated the impact of key inputs and assumptions on study findings. **Results:** SC lecanemab was estimated to yield per-patient savings of $72,891–$80,925 over four years compared with IV administration, corresponding to annual savings of $18,223–$20,231 at willingness-to-pay thresholds of $150,000 and $200,000 per quality-adjusted life-year gained, respectively. Savings stemmed from a $40,638 reduction in treatment costs, an $8,151 decrease in administration time costs, and $24,102–$32,136 reduction in QOL-related costs. At the population level, assuming current treatment rates and 49.4% SC uptake, total savings of $3.16–$3.71 billion were projected over four years. Sensitivity analyses indicated per-patient savings varied based on site of care, IV drug wastage, and caregiver disutilities, while population-level savings were most sensitive to treatment rates and SC uptake. **Conclusions:** Subcutaneous lecanemab administration potentially offers substantial societal savings by lowering treatment costs, minimizing time demands, and relieving QOL burdens for patients and caregivers. These findings underscore the potential value of SC formulations in improving treatment delivery and alleviating AD economic impact.

Keywords: Alzheimer's disease, lecanemab, subcutaneous administration, intravenous administration, drug delivery, cost analysis, efficiency, quality of life.

P362- MEDICATION ADHERENCE AND COST OF CARE FOR COMORBID CONDITIONS IN PATIENTS WITH EARLY ALZHEIMER'S DISEASE: A RETROSPECTIVE COHORT STUDY USING THE AXON REGISTRY AND CLAIMS DATA.

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Background: Alzheimer's Disease (AD) is the most common etiology of dementia and represents a growing public health concern. Patients with AD typically have multiple comorbidities treated with multiple medications. The complexity of their medication regimens combined with cognitive impairment places them at elevated risk for poor medication adherence. This lack of adherence could lead to suboptimal care. We sought to better understand medication adherence for commonly used medications, and the associated cost of care, which might provide valuable insights for clinical care and trial design. **Methods:** This retrospective cohort study utilized data extracted from the American Academy of Neurology's Axon Registry that was de-identified, tokenized, and linked to patient-level adjudicated claims data from Komodo Health's Research Dataset. Patients with early AD, classified as either mild cognitive impairment (MCI) due to AD or mild AD dementia based on cognitive test scores (Mini-Mental State Examination and Montreal Cognitive Assessment were used), were included from January 2015 to March 2023. Patient demographics, clinical characteristics, comorbidities, cost of care and medication adherence for 10 classes of medications for chronic conditions were assessed. Medication adherence was evaluated using the mean proportion of days covered (PDC), and adherence rate (AR) defined as the proportion of patients with a PDC of $\geq$80% based on the observation period from the first fill through 365 days following medication index date. Comorbidities were assessed based on ICD-9-CM or ICD-10-CM diagnosis codes in medical record entries logged over the 12-month period following the cognitive test, and healthcare and pharmacy costs were analyzed using summed costs over the same period. **Results:** Our study included 333 patients with early AD (MCI due to AD: 98, mild AD dementia: 235). The mean (standard deviation; SD) age of the patients was 76.8 (7.8) years, 64.0% were female, 52.3% White, 2.1% Black or African American, 0.3% Asian, 1.8% Other, and 43.5% Unknown. Among the participants,14.7% reported ethnicity as Hispanic or Latino. Cardiometabolic and psychiatric comorbidities were common in the study population, including hypertension (56.8%), hyperlipidemia (49.2%), cardiovascular disease (30.0%), Type 2 Diabetes (24.3%), and Major Depressive Disorder (21.6%). Across all 10 classes of medications evaluated, the overall mean (SD) PDC was 74.4% (1.7). Cholinesterase inhibitors were the most commonly taken medication, used by 63.4% of patients (mean [SD] PDC=72.0% [28.4]; AR=50.4%). Statins were taken by 46.8% of the patients (mean [SD] PDC=78.8% [23.8]; AR=60.5%). Serotonin–norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors were taken by 38.4% of the patients (mean [SD] PDC=74.6% [26.9]; AR=54.7%), while angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers were taken by 34.8% of the patients (mean [SD] PDC=75.2% [25.4]; AR=55.3%). Among the 10 medication classes evaluated, the mean number of medications per patient was 3.0 during the study period, with a mean (SD) annual pharmacy cost of $3,452 (13,188) and mean (SD) annual medical cost of $13,709 (23,004). **Conclusions:** In this study, patients with early AD commonly had comorbid conditions and typically take multiple medications. We observed suboptimal medication adherence and a high level of healthcare and pharmacy costs in this population. These factors should be considered in future trial design and during the development of AD treatment infrastructure.

Keywords: Early Alzheimer's disease, comorbidity, medication adherence, cost of care.

Disclaimer: The Axon Registry® is an initiative of the American Academy of Neurology ('AAN'). There are limitations of the Axon Registry data (Baca CM et al. 2019). The views expressed in this manuscript represent those of the authors and do not necessarily represent the official views of the Axon Registry or the AAN.

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Key takeaway message: This study found that early Alzheimer's patients commonly had multiple comorbidities requiring multiple medications. Medication adherence was suboptimal, and healthcare costs high. These factors should inform future Alzheimer's Disease treatment development in clinical trials.

EPIDEMIOLOGY AND CLINICAL TRIALS

P363- HIGHER DNA METHYLATION-BASED INTRINSIC CAPACITY REFLECTS RESILIENCE AGAINST NEURODEGENERATION IN MIDLIFE: INSIGHTS FROM THE INSPIRE-T LIFESPAN COHORT.

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Background: Intrinsic capacity (IC) is a cornerstone of healthy longevity, more recently identified as a potential target for dementia prevention. Declines across functional domains are interconnected with neurocognitive disorders including Alzheimer's disease (AD) and share aging biology pathways including epigenetic alterations. However, limited research has examined how a global metrics of IC relates to

neurodegeneration. We newly developed a DNA methylation (DNAm) IC predictor (DNAm IC) which captures multisystem functional aging and reflects upstream molecular changes preceding overt decline. In parallel, plasma p-tau217 and neurofilament light chain (NFL) provide minimally invasive early indicators of AD pathology, neurodegeneration, and future cognitive decline. Whether DNAm IC is associated with AD blood biomarkers is currently unknown. Addressing this gap could provide insights on the early biological mechanisms connecting functional aging and brain health, and extend the value of both biomarkers for multidomain risk stratification and prevention. **Methods:** We included 933 individuals (aged 20-103 years old, 62% female) from the INSPIRE-T human lifespan translational cohort. Using baseline DNAm and Elastic Net Regression, we previously built a DNAm IC predictor trained on the clinical evaluation of cognition, mobility, mental health, vitality, vision and hearing. Plasma p-tau217 and NFL were assessed at baseline. We used linear regression models to investigate the association of DNAm IC (higher is better) with AD blood biomarkers (lower is better). Results are presented per 10-unit increase in DNAm IC. P-tau217 and NFL showed skewed distributions and were thus log transformed to improve normality and meet linear regression assumptions. **Results:** In unadjusted models, higher DNAm IC was associated with lower p-tau217 levels (log(p-tau217): ß = -0.46, 95% CI [-0.54; -0.39], p<0.0001). No interaction was observed with age and the association did not remain significant after adjustment for age, sex, education and ApoE4. In unadjusted models, higher DNAm IC was significantly associated with lower NFL (log(NFL): ß = -0.95, 95% CI [-1.01; -0.89], p<0.0001). A significant interaction (p<0.001) showed that the association between DNAm IC and NFL significantly varied by age. After adjustment for sex, education, and ApoE4, higher DNAm was significantly associated with lower NFL in individuals aged [20-50[(log(NFL): ß = -0.65, 95% CI [-0.85; -0.45], p<0.0001) and [50-70[(log(NFL): ß = -0.42, p<0.0001). However, the association was no longer significant in individuals aged [70-80[(ß = -0.19; p=0.09) or 80+ years old (ß = -0.06; p=0.60). **Conclusions:** Higher DNAm IC, an epigenetic predictor of multisystem functional aging, showed a strong and robust association with lower NFL levels in younger and midlife individuals, indicating that it captures resilience molecular processes linked to preserved neuroaxonal integrity and reduced risk of early neurodegeneration. In older individuals, the cumulative burden of aging and heterogeneity of late-life biological processes may overshadow this specific molecular signal. Clinically, this implies that enhancing IC as early as possible may help preserve neuroaxonal integrity and reduce neurodegeneration risk, highlighting midlife as a critical window for preventive interventions. **Key takeaway message:** Higher DNAm IC, an epigenetic predictor of functional aging, is associated with lower NFL levels in younger individuals, reflecting preserved neuroaxonal integrity. This highlights midlife as a decisive window for enhancing IC to strengthen resilience against neurodegeneration and dementia prevention.

P364- POPULATION-BASED REFERENCE VALUES FOR ALZHEIMER BLOOD BIOMARKERS IN FRANCE.

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Background: Blood biomarkers for Alzheimer's disease (AD), such as plasma phosphorylated tau (p-tau181) and Aβ42/40, are promising tools for diagnosis and population screening. However, their clinical use is limited by the absence of reference values, as concentrations vary with demographic and physiological factors. **Methods:** We analyzed plasma samples from 5,123 participants in two French population cohorts (CONSTANCES and 3C). Reference equations were modeled using generalized additive models for location, scale, and shape (GAMLSS), adjusting for age, sex, body mass index, and renal function. Normalized Z- and T-scores anchored at age 40 were derived. Validation was performed in the ALZAN memory cohort (n=369) using CSF Aβ42/40-defined amyloid status. We also assessed associations with APOE ε4 carriership and estimated amyloidosis prevalence across age groups. **Results:** Reference curves highlighted strong age- and kidney-related effects on biomarker levels. In the ALZAN cohort, the p-tau181/Aβ42 T-score achieved the highest diagnostic accuracy (AUC 91.4, 95% CI 88.3–94.5) for amyloidosis and 91.1 (95% CI 88.0–94.2) for AD diagnosis. T-scores significantly outperformed raw values for p-tau181, while Z-scores were superior for identifying APOE ε4 carriers. Applying a p-tau181 T-score threshold of 1.88, estimated amyloidosis prevalence ranged from 2.6% (ages 23–45) to 56% (≥85 years). **Conclusions:** We provide the first population-based reference framework for plasma AD biomarkers. T-scores offer an age-independent measure of absolute pathological burden, supporting diagnosis and prevalence estimates, while Z-scores capture early risk-related deviations. These complementary tools may enhance clinical decision-making, stratify trial participants, and improve large-scale detection of Alzheimer's disease.

Keywords: Alzheimer's disease, blood biomarkers, prevalence, reference values.

Disclosures: The authors declare no competing financial interests.

Key takeaway message: Population-based reference equations and normalized Z-/T-scores for plasma Alzheimer's biomarkers enable age-independent interpretation, improving diagnostic accuracy, prevalence estimates, and clinical trial stratification, thereby supporting implementation of blood biomarkers in research and clinical practice.

P365- MCI DETECTION IN PRIMARY CARE IN THE U.S.: WHO IS FINDING THE CASES?

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Background: Mild cognitive impairment (MCI) is vastly underdiagnosed in the U.S., with detection rates of 7-11% as published in the literature. These low detection rates contribute to the slow uptake of the recently approved treatments for Alzheimer's Disease in the U.S. and the difficulties to enroll clinical trials in spite of a large and almost completely treatment-naïve population. As the first point of contact when a patient seeks care, primary care clinicians play an important role in detection of MCI. Competing priorities, lack of dedicated reimbursement for brief cognitive tests, gaps in training and confidence, and conflicting guideline statements about whether to screen all have been named as obstacles to increase detection rates in primary care. Understanding better what types of clinicians detect MCI at a reasonable rate despite of these obstacles might inform targeted efforts to increase detection rates. Here, we used Medicare data to analyze the relationship of clinician characteristics and MCI detection rates. **Methods:** Following established methods (1), we used the 100% Medicare fee-for-service and Advantage Plan data from 2017 to 2019 to identify primary care clinicians who had been diagnosing MCI among beneficiaries of age 65 or older. Patients were attributed to clinicians based on plurality of office visits. For the attributed patient panel, we computed each clinician's observed rate of patients with a diagnosis of MCI and estimated the expected rate of cases based on a predictive model using patient characteristics (age, sex, race/ethnicity, and dually eligibility for Medicare and Medicaid). The detection rate was then quantified as the ratio between the observed or diagnosed rate and the expected or predicted rate. Based on the distributions of the clinician-level detection rates, we considered a clinician diagnosing MCI at a meaningful rate if either condition was satisfied: (a) a detection rate of 0.2 or higher, suggesting that the clinician detected at least 20% of expected cases, around the 90th percentile of all detection rates; or (b) an observed rate of 0.1 or higher, implying at least 10% of the clinician's attributed patients had been diagnosed with MCI, given the 99th percentile of 7.8% among all observed rates. We then used logistic regression to predict a clinician's likelihood of having diagnosed MCI at a meaningful rate, compared to

those diagnosing at lower rates. Predictors included: the clinician's specialty (internal medicine, family medicine, geriatric medicine, obstetrics/gynecology, and nurse practitioner/physician assistant), sex, and whether the practice was located in a metropolitan area. The model further adjusted for state fixed effects, the percent of clinician's attributed panel being non-Hispanic white patients, and the percent being dually eligible for Medicare and Medicaid. **Results:** Out of 223,199 primary care clinicians who had at least 25 attributed Medicare beneficiaries, 20,556 (9.2%) had diagnosed MCI at a meaningful rate, whereas the remaining clinicians included 73,062 (32.7%) who did not have a single patient diagnosed with MCI. About a quarter (25.3%) of clinicians practiced internal medicine, 35.3% specialized in family practice, 36.5% served as nurse practitioners or physician assistants, 2.5% practiced in obstetrics/gynecology, and 0.4% specialized in geriatric medicine. Most of the clinicians (84.5%) had practices located in a metropolitan area, and slightly more than half (55.0%) were female. Additionally, the attributed panels consisted of an average of 77.6% (SD=24.7%) non-Hispanic white patients and 13.5% (SD=15.8%) dually eligible for Medicare and Medicaid. Logistic regression revealed that after accounting for the patient characteristics and state fixed effects, clinicians specialized in geriatric medicine – despite being a small group – were more likely to have a meaningful detection rate, compared to those practicing internal medicine (adjusted odds ratio [AOR]=5.32, 95% CI=4.61, 6.14). In contrast, those practicing family medicine (AOR=0.65, 95% CI=0.63, 0.68) or served as nurse practitioner or physician assistant (AOR=0.76, 95% CI=0.73, 0.79) were less likely, while no difference for those specialized in obstetrics/gynecology (AOR=1.07, 95% CI=0.98, 1.16). Irrespective of specialty, female clinicians and clinicians practicing in metropolitan areas were more likely to diagnose MCI than male clinicians (AOR=1.39, 95% CI=1.35, 1.44) and those practicing in less population dense regions (AOR=1.70, 95% CI=1.62, 1.79), respectively. After the covariate adjustment, 38.0% of clinicians practicing geriatric medicine had diagnosed MCI at a meaningful rate, followed by 11.9% for obstetrics/gynecology, 11.2% for internal medicine, 8.9% for nurse practitioner/physician assistant, and 7.7% for family practice. Additionally, 10.4% of female clinicians had diagnosed MCI, about 34 percent higher than 7.7% of male clinicians. Finally, in contrast to 6.1% of clinicians practicing in non-metropolitan areas, 9.8% of those having office in metropolitan area had diagnosed MCI at a meaningful rate, about 61 percent higher. **Conclusions:** To our knowledge, this work is the first to systematically examine the association between clinician characteristics and MCI detection at the national level. The findings suggest difference in MCI detection by clinician's specialty, sex, and office location, pointing to future directions to further understand in what ways such characteristics may drive clinician's practice style in detecting early-stage cognitive impairment.

Keywords: Mild cognitive impairment, Alzheimer's disease, primary care, early detection.

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References: 1. Liu Y, Jun H, Becker A, Wallick C, Mattke S. Detection Rates of Mild Cognitive Impairment in Primary Care for the United States Medicare Population. J Prev Alzheimers Dis. 2024;11(1):7-12. doi:10.14283/jpad.2023.131.

Key takeaway message: The study found differential detection of mild cognitive impairment in the U.S. by clinician's specialty, sex, and urbanicity of office location, suggesting clinician's practice style may potentially influence the early detection of cognitive impairment.

P366- ODOR IDENTIFICATION AND TAU BURDEN IN PERSONS WITHOUT DEMENTIA: INSIGHTS FROM THE MAYO CLINIC STUDY OF AGING.

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Background: Impaired olfaction affects more than half of those 65 years and older. Most patients with Alzheimer's Disease (AD) have olfactory dysfunction, commonly presenting before clinical symptomatology. The study aimed to examine the association between odor identification (OI) [as assessed by the Brief Smell Identification Test (BSIT)] and tau burden [as assessed by 18F-flortaucipir (FTP) PET] in community-dwelling participants of the Mayo Clinic Study of Aging (MCSA). **Methods:** The study sample comprises 795 MCSA participants, aged 50 years and older, without a previous dementia diagnosis, who underwent FTP-PET within 6 months of a 12-item BSIT assessment (BSIT score possible range 0-12). All participants also underwent amyloid PET (11C-Pittsburgh Compound B; PiB). We examined the cross-sectional association between tau burden and OI (outcome) using generalized linear models, adjusting for age, sex, and education. For tau burden, we used the entorhinal cortex (ERC) and inferior temporal (IT) tau standardized uptake value ratio (SUVR), as well as the mesial temporal lobe (MTL) and the temporoparietal region (neocortical; NEO) CenTauRz. We examined interactions by age, sex, and amyloid (A) status by PiB-PET (i.e., A+/A-). **Results:** The mean (SD) age of the study population was 69 (10) years, the mean (SD) years of education were 15 (2.4), and 51.4% were male. Nine percent of participants (n=71) had mild cognitive impairment. The mean (SD) BSIT total score was 9.4 (2.3). There was an inverse association between BSIT score and ERC SUVR (estimate -0.007 (95% Confidence Interval (CI) -0.012, -0.003; p-value 0.001) as well as BSIT score and MTL CenTauRz (estimate -0.062 (95% CI -0.107, -0.017; p-value 0.007). There were no statistically significant interactions with age or sex; there was a statistically significant interaction with amyloid PET (A+/A-) status. The associations were stronger in participants with positive amyloid PET (A+) for both the BSIT score and ERC SUVR estimated association (estimate -0.014 (95% Confidence Interval (CI) -0.025, -0.003; p-value 0.011), and the BSIT score and MTL CenTauRz estimated association (estimate -0.115 (95% CI -0.231, 0.001; p-value 0.052). **Conclusions:** The study findings agree with limited prior research supporting that worse olfaction is associated with higher tau burden, especially in the ERC region and in participants with high amyloid burden.

Keywords: Odor identification, smell, BSIT, tau PET, flortaucipir PET.

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Key takeaway message: Worse smell is linked to higher brain tau protein, especially in the entorhinal cortex and in individuals with amyloid plaques, suggesting an early Alzheimer's connection.

P367- CROSS-COHORT VALIDATION OF METABOLOMIC PREDICTORS OF GLOBAL COGNITION USING ELASTIC NET REGRESSION.

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Background: Data on metabolites associated with cognition throughout the life course remain limited. Identifying metabolites predictive of cognition and replication of findings may help elucidate early metabolic alterations linked to age-related cognitive trajectories. This is particularly important especially for people without dementia and of younger ages. **Methods:** The current study included examination of 241 metabolites measured in Hellenic Longitudinal Investigation of Aging and Diet (HELIAD, N=389), Aiginition Longitudinal Biomarker Investigation Of Neurodegeneration (ALBION, N=174), and the Cognitive Reserve and Reference Abilities Neural Network (CR/RANN, N=161) study cohorts. All cohorts included participants without dementia. Participants with cross-sectional metabolite and standardized global cognition measurements from the HELIAD cohort were used as the discovery dataset, which was randomly split with 90% as the training set, and the remaining 10% as the test set. Elastic net regression (20-loops) was used to find the best alpha and lambda based on lowest RMSE for predicting global cognition. Of the 241 metabolites, 36 metabolites had non-zero coefficients in at least 60% of iterations and their coefficients were included in the final model. The metabolic pathways in which the metabolites were involved were identified using MetaboAnalyst. Model performance was evaluated in the participants in the ALBION cohort with available metabolic and cognitive data, as well as a subsample of propensity matched ALBION participants to account for age, sex, and education imbalances between HELIAD and ALBION cohorts. **Results:** HELIAD participants had a mean age of 74.8 years, a mean education of 5.6 years, and 58% were female. ALBION participants had a mean age of 64.1 years, a mean of 13.4 years of education, and 67% were female. CR/RANN participants had a mean age of 57.1 years, a mean of 15.9 years of education, and 52% were female. Elastic net regression conducted in the HELIAD training set resulted in the selection of 36 metabolites for the final model. Significant metabolic pathways were related to linoleic acid metabolism (p=0.001), biosynthesis of unsaturated fatty acids (p=0.003), pentose and glucuronate interconversions (p=0.011), propanoate metabolism (p=0.015), and glycerophospholipid metabolism (p=0.038). Evaluation of the final model in the HELIAD test set demonstrated moderate performance (RMSE: 0.85, R2: 0.08, Pearson: 0.29). The performance was reduced when evaluated in the full ALBION cohort (RMSE: 1.00, R2: 0.03, Pearson: 0.17). After propensity matching ALBION participants to HELIAD participants, the ALBION subsample (N=53) became more similar on age (72 years), education (9.4 years) and proportion of females (58%) to the HELIAD participants. The final model with the 36 metabolites demonstrated improved prediction of global cognition in this propensity matched ALBION subsample (RMSE: 1.24, R2: 0.09, Pearson: 0.30). Replication in a third American cohort (CR/RANN) will be conducted and presented. **Conclusions:** Our findings suggest a combination of 36 metabolites are consistently associated with global cognition scores across cohorts of healthy adults. Understanding the impact of these metabolites on cognition may better inform individualized – precision medicine aspects of cognitive aging and neurodegeneration.

Keywords: Metabolomics, global cognition, elastic net, preclinical study.

Disclosures: The authors declared no competing interests.

Key takeaway message: Our findings suggest a combination of 36 metabolites are predictive of global cognition across cohorts of healthy adults. Understanding the impact of these metabolites on cognition may inform precision medicine in cognitive aging and neurodegeneration.

P368- SEX/GENDER DIFFERENCES IN THE ASSOCIATIONS BETWEEN PARENTAL EDUCATION AND HIPPOCAMPAL VOLUME IN THE OLDEST-OLD: THE LIFE AFTER 90 STUDY.

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Background: Higher education has been shown to have protective effects in aging by buffering against lowered hippocampal volume and by slowing cognitive decline. However, there is limited to no work examining relationships between parental education, participant education, and hippocampal volume in the oldest-old, and whether these relationships differ by sex/gender. Here, we assessed whether parental education and participant education would be differentially related to hippocampal volume by sex/gender, and whether parental education would moderate the associations between participant education and hippocampal volume. **Methods:** We included participants from LifeAfter90, a multiethnic cohort of individuals aged 90 years and older. T1-weighted images from 3T MRI were acquired to measure total hippocampal volume, and adjusted for intracranial volume (ICV). Participant and parental (maternal and paternal) years of education were self-reported by the participant. We tested the main effects and sex/gender-stratified associations of parental education and participant education on hippocampal volume using linear regressions. We then tested whether parental education moderates the association between participant education and hippocampal volume in sex/gender-stratified models. All linear regression models were adjusted for age at MRI acquisition. **Results:** Participants (N=277) had a mean age of 93.1 + 2.22 (range: 90.4-103.42), 57.6% were women, and self-identified race/ethnicity were 24.5% Asian, 23.1% Black, 19.9% Latinx, and 26% White. Participants had a mean years of education of 14.6 + 3.2 years, paternal education of 10.6 + 5.1 years, and maternal education of 10 + 4.5 years. Overall, neither participant, paternal nor maternal education was associated with hippocampal volume (all p>0.05). When stratified by sex/gender, maternal education was associated with higher hippocampal volume in men, yet was associated with lower hippocampal volume in women (men: b=0.026, 95% CI [0.0002, 0.051], p=0.048; women: b=-0.041, 95% CI [-0.066, -0.017], p=0.001). Maternal education moderated the association between participant education and hippocampal volume only in men, such that the association of higher participant education with higher hippocampal volume was stronger in men with higher parental education (interaction term: b=0.007, 95% CI [0.001, 0.013], p=0.024). Paternal education did not moderate the association between participant education and hippocampal volume in either sex/gender (interaction term in men: b=0.003, 95% CI [-0.003, -0.008], p=0.385; interaction term in women: b=0.009, 95% CI [-0.004, 0.022], p=0.16). **Conclusions:** Higher maternal education was associated with higher hippocampal volume only in men and moderated the association between participant education and hippocampal volume in men. These findings highlight the importance of parental education on late-life imaging outcomes in offspring and the potential roles of sex/

gender. A future direction would be to examine the effects of sex/gender, participant education, and parental education on other markers of medial temporal lobe integrity and memory function in the oldest-old.
Keywords: Education, sex/gender, parental education, hippocampus, aging, oldest-old.
Disclosures: None.
Key takeaway message: We found that higher maternal education is associated with higher hippocampal volume only in men, and higher maternal education also moderated the association between participant education and hippocampal volume in men.

P369- ASSOCIATIONS BETWEEN EPIGENETIC AND INFLAMMATORY AGING, COGNITIVE FUNCTION,AND BLOOD-BASED BIOMARKERS OF ALZHEIMER'S DISEASE: CROSS-SECTIONAL AND LONGITUDINAL FINDINGS FROM THE INSPIRE-T COHORT.

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Background: DNA methylation and systemic age-related inflammation patterns have been employed to develop epigenetic and inflammatory aging clocks as a measure of biological aging. The extent to which it impacts cognition remains unclear, and the link with blood-based biomarkers of Alzheimer's disease (AD) has yet to be investigated. **Methods:** We included 586 participants (median age 51 [37-61] years, women 66%) from the INSPIRE-T cohort. At baseline, 5 measures of epigenetic age accelerations were considered from Horvath pan tissue, Horvath skin and blood, Hannum, PhenoAge and GrimAge epigenetic aging clocks. Inflammatory age acceleration was estimated from iAge clock. Biological age accelerations were calculated as the residuals from a linear regression of biological age on chronological age. Cognition was assessed at baseline and annually over 3 years. Global cognition was calculated as a composite measure using the average of Z scores for the MMSE orientation items (orientation), FCSRT (episodic memory), DSST (processing speed) and CNT (verbal fluency) tests. Each domain was also assessed separately. Blood NFL and p-tau217 were measured at baseline. **Results:** In cross-sectional analyses and after adjustment for chronological age and sex, only GrimAge accelerated epigenetic aging was associated with lower global cognition (β = -0.18, 95% CI [-0.33; -0.03], p=0.02). Further adjustment for education and ApoE4 genotype did not modify the results. Accelerated inflammatory aging was not associated with global cognition (p=0.55). Longitudinal analyses did not reveal any significant interaction effect between GrimAge epigenetic aging and advancing chronological age. Skin and blood Horvath's accelerated epigenetic aging was associated with lower processing speed (β = - 1.49, 95% CI [-2.70; -0.27], p=0.02) with advancing age. In fully adjusted models, neither epigenetic nor inflammatory accelerated aging were significantly associated with p-tau217 levels (p>0.05 for all clocks). However, accelerated inflammatory aging was associated with higher NFL levels (β = 0.76, 95% CI [0.23; 1.30], p<0.01). **Conclusions:** Our findings showed that accelerated GrimAge epigenetic aging was associated with lower cognition. Accelerated inflammatory aging was linked to higher blood NFL levels. Our research could pave the way for an early molecular identification of at-risk individuals, enabling personalized medicine interventions to promote brain health.
Key takeaway message: Our findings suggest that biogical age acceleration could help identify individuals at greater risk for cognitive decline and neurodegenerative disease supporting early personalized interventions to preserve brain health.

P370- CARDIORESPIRATORY FITNESS AND BRAIN ATROPHY: SEX DIFFERENCES AND POTENTIAL VASCULAR MECHANISMS.

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Background: Neurodegeneration and brain atrophy are key downstream features of AD pathological processes. Literature supports a protective role for cardiorespiratory fitness (CRF) against age- and disease-related atrophy. Present study examined 1) the relationships between CRF and the rates of age-related brain atrophy, 2) potential sex differences, and 3) whether there is a moderation of relationships when including vascular mechanisms [cerebral blood flow (CBF) and arterial stiffness], in a cohort cognitively unimpaired and enriched for AD risk based on parental history at enrollment. **Methods:** Sample consisted of 1086 participants, prospectively followed through the Wisconsin Alzheimer's Disease Research Center and the Wisconsin Registry for Alzheimer's Prevention studies, with available MRI-derived volumes [intracranial volume (ICV), cerebrospinal fluid (CSF), grey matter (GM), white matter (WM), hippocampus, and Global Atrophy (GA)=CSF/(GM+WM)]. Estimated cardiorespiratory fitness (eCRF) was derived for the entire sample using a validated equation. A subset of 136 participants underwent a maximal exercise treadmill test (ETT; VO2predicted=predicted peak maximal oxygen consumption derived from oxygen uptake efficiency slope) and vascular MRI to measure CBF and arterial stiffness [aortic pulse wave velocity (aoPWV)]. Differences in atrophy rates by CRF were calculated via covariate-adjusted linear mixed effects models and repeated after stratifying by sex. Analyses including an interaction term between VO2predicted and CBF or aoPWV examined potential moderation of aforementioned relationships. **Results:** Both the entire sample and ETT subsample were on average college educated and 65 years of age at baseline, ~70% female and ~90% white. Higher CRF was associated with slower GA in both the entire sample (p=0.03) and ETT subsample (p=0.007); in stratified analyses the relationship was only significant for females (ps≤0.001). Additionally, in females, both higher eCRF and VO2predicted were associated with slower GM and hippocampal atrophy (ps≤0.01) , and eCRF alone was associated with slower WM atrophy (p=0.003). In males, higher eCRF was associated with slower hippocampal atrophy (p=0.002). Higher VO2predicted attenuated the adverse relationship between arterial stiffness and hippocampal atrophy in females only (p=0.04). **Conclusions:** CRF was protective against age-related global atrophy. Sex-stratified analysis suggests that this finding was driven by females. CBF or arterial stiffness did not significantly moderate the observed relationships between CRF and brain structure. CRF, however, conferred resilience against hippocampal atrophy in females with higher arterial stiffness. Overall, our results highlight the need to uncover pathways underlying the protection offered by CRF and the importance of considering sex differences.
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related to this study. S.C.J. has served on advisory boards for ALZPath and Enigma Biosciences. All other authors have no disclosures to report. We would like to acknowledge and thank the staff and study participants of the Wisconsin Registry for Alzheimer's Prevention and the Wisconsin Alzheimer's Disease Research Center.

Key takeaway message: Cardiorespiratory fitness is associated with decreased brain atrophy independent of two vascular mechanisms. This relationship, largely apparent among females, highlights the need for future research to uncover pathways underlying CRF protection while considering sex differences.

P371- ABIDEING WITH AUTOMATED CEREBROSPINAL FLUID ASSAYS; UPDATE OF AN MCI TO DEMENTIA PREDICTION MODEL.

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Background: Automated cerebrospinal fluid (CSF) biomarker assays have largely replaced manual immunoassays for measuring amyloid pathology. Their relevance is increasing as amyloid-targeting therapies (ATTs) are becoming available for amyloid-positive mild cognitively impaired (MCI) individuals. Therefore, we refitted and validated the ABIDE model, predicting progression from MCI to dementia, with CSF measurements from the automated Elecsys® platform. Additionally, we evaluated the performance in an amyloid-positive subpopulation, potentially eligible for ATTs. **Methods:** We combined data from MCI participants of seven single-centre and multicentre observational cohorts: Amsterdam Dementia Cohort (n=688), Alzheimer's Disease Neuroimaging Initiative (n=544), BioFINDER (n=212), European Medical Information Framework for Alzheimer's Disease (n=809), Lleida (n=88), National Alzheimer's Coordinating Centre (n=63), and Wisconsin Alzheimer's Disease Cohort (n=9). Participants were included with MCI at baseline, a baseline Mini-Mental State Examination, either a magnetic resonance imaging hippocampal volume or CSF Aβ1-42 and pTau181 measurements, and at least six months of follow-up. Elecsys was used in 737 (47%) participants, and CSF INNOTEST® (796; 51%) and Luminex® (41; 3%) measurements were bridged to Elecsys. A Cox model was used to predict time to dementia using the variables in the previous ABIDE model (Maurik et al. 2019). Model discrimination and calibration were evaluated with leave-one-cohort-out cross-validation. Calibration was visually assessed in the total population and amyloid-positive (A+) subgroup by comparing the observed and predicted progression risk, stratified by predicted risk: Low (<P16), Low-Medium (P16-P50), Medium-High (P50-P84), and High (>P84). **Results:** Of 2412 MCI participants (70±8yrs, 57%F; 40% amyloid-positive) with a median follow-up of 2.1yrs, 1034 (42%; 576 [58%] amyloid-positive) developed dementia (IQR:1.3-3.2yrs). The refitted coefficients resemble the prior model, except for a larger effect of the Aβ1-42*pTau interaction. Discrimination was similar to the prior ABIDE model, with Harrell's C of 0.70 (95%CI: 0.69 to 0.70), and calibration was good in the total population cohort, the amyloid-positive subgroup, and across CSF assays. In the amyloid-positive subgroup, all four risk groups had a substantial progression risk with a median predicted progression time of 7.4 years (95%CI: 6.4 to 8.1) in A+-Low, 4.0 years (95% CI: 3.6 to 4.1) in A+-Low-Medium, 2.8 years (95%CI: 2.5 to 3.0) in A+-Medium-High, and 2.0 years (95%CI: 2.0 to 2.1) in A+-High.

Discussion: We updated the ABIDE model for predicting MCI to dementia progression with automated CSF measurements. The model was well calibrated in amyloid-positive patients and may support clinical discussions regarding the initiation of ATTs.

Keywords: Mild cognitive impairment, prediction, biomarkers, Alzheimer's disease.

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Key takeaway message: The ABIDE MCI to dementia prediction model was refitted with additional Elecsys CSF measurements and was well calibrated for all CSF assays and in amyloid-positive participants. The model may support clinical discussions regarding ATT initiation.

P372- REAL-WORLD ELIGIBILITY FOR LECANEMAB AND DONANEMAB BASED ON APPROPRIATE USE RECOMMENDATIONS IN KOREA.

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Background: The Appropriate Use Recommendations (AURs) for newly approved anti-amyloid therapies, such as lecanemab and donanemab, have been developed based primarily on evidence from Western populations. However, it remains unclear whether the current AUR eligibility criteria are applicable to clinical populations in Asian countries, including South Korea, which may differ in demographic and clinical characteristics. **Objective:** To estimate the proportion of patients eligible for lecanemab and donanemab under the current AURs and to evaluate the applicability of these guidelines in patients who visited a memory clinic at a tertiary university hospital in South Korea, particularly focusing on cognitive test thresholds. **Design:** Cross-sectional study. **Setting:** Memory Clinic at Seoul National University Hospital (SNUH), South Korea. **Participants:** Among a total of 2,726 patients who visited the memory clinic and underwent comprehensive clinical and neuropsychological assessments, brain magnetic resonance imaging (MRI), and amyloid positron emission tomography (PET) between 2016 and 2024, 1,005 patients who were amyloid PET–positive, had completed brain MRI, and had available global Clinical Dementia Rating (CDR) data were included in the primary analysis. **Measurements:** Eligibility for lecanemab and donanemab was assessed using AUR criteria. Cognitive status was determined using both fixed MMSE cutoffs and age-, sex-, and education-adjusted z-scores. For the cognitive criterion, we applied not only the fixed MMSE raw score thresholds (≥22 for lecanemab; ≥20 for donanemab) but also an alternative criterion defined as meeting either the raw score threshold or an MMSE z-score ≥ –2.0. **Results:** Among the 1,005 amyloid-positive participants diagnosed with MCI or mild dementia, 247 (24.6%) and 281 (28.0%) met AUR-based eligibility criteria for lecanemab and donanemab, respectively. Z-score–adjusted MMSE thresholds increased eligibility to 38.4% and 33.7%, respectively. Over one-third of otherwise eligible patients were excluded due to MRI findings associated with ARIA risk.

Demographic subgroup analysis revealed that z-score–based criteria identified older and less-educated individuals who would have been excluded using fixed cutoffs alone. **Conclusions:** Our study indicates that approximately one-fourth of memory clinic patients with both pathological amyloid deposition and a diagnosis of MCI or mild dementia are eligible for lecanemab and donanemab under the current AUR criteria. Additionally, our findings emphasize the importance of adopting culturally and demographically appropriate cognitive criteria when selecting patients for anti-amyloid treatments.

Key takeaway message: Only a small proportion of Korean patients are eligible for anti-amyloid therapy; applying MMSE z-scores improves estimates, while MRI findings often exclude otherwise eligible cases—underscoring the need for culturally and clinically appropriate criteria.

P373- THE ALZHEIMER'S DISEASE SEQUNECING PROJECT PHENOTYPE HARMONIZATION CONSORTIUM.

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Background: The Alzheimer's Disease Sequencing Project Phenotype Harmonization Consortium (ADSP) was established in 2021 to provide deep, harmonized endophenotype data to facilitate to genomic analysis. We have established a group of experts in neuropathology, fluid biomarker, neuroimaging, vascular risk factors, and cognitive data harmonization to provide gold-standard harmonization across more than 30 cohorts and 100k participants. **Methods:** Cognitive data were harmonized leveraging item response theory methods to provide composite measures of executive function, language, memory, and visuospatial skills. Magnetic Resonance Imaging data were harmonized with established deep learning based pipelines for diffusion tensor imaging (DT1), structural T1, and FLAIR imaging to capture changes in both grey and white matter structures. Positron Emission Tomography images for both tau and amyloid ligands were harmonized leveraging both linear (e.g., Centiloid) and non-lines (e.g., NoDIM) based approaches. Fluid biomarkers were harmonized using a custom non-linear mapping pipeline. Neuropathology data were harmonized to align with the National Alzheimer's Coordinating Center common data elements. Vascular risk factors were harmonized using novel data driven and established composite approaches. **Results:** In our last data release, we included harmonized data from 413,5000 visits including imaging data from more than 20k participants, cognitive data from 95k participants, and paired endophenotype and whole genome sequencing data from 37k participants. For our release in December of 2025, we expanding by 7k participants, 2 new phenotypes including blood-based biomarkers, and 20k new imaging visits. All data are available via dss.niagads.org. Additional information about the data harmonization can be found at www.vmacdata.org/adsp-phc. **Conclusions:** The ADSP-PHC has provided an unprecendented dataset to facilitate novel genomic discovery, and to analyzy harmonized imaging, cognitive, biomarker, and neuropathology data from both clinical trial datasets and longitudinal cohorts studies of aging and Alzheimer's Disease.

Key takeaway message: The ADSP-PHC has provided an unprecendented dataset to facilitate novel genomic discovery, and to analyzy harmonized imaging, cognitive, biomarker, and neuropathology data from both clinical trial datasets and longitudinal cohorts studies of aging and Alzheimer's Disease, available at dss.niagads.org

P374- EQUOL-PRODUCING STATUS IS ASSOCIATED WITH GREATER FRONTAL CORTEX VOLUME IN COMMUNITY-DWELLING OLDER ADULTS: BASELINE FINDINGS FROM THE ACE TRIAL.

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Background: Effective prevention strategies are urgently needed to prevent Alzheimer's disease and related dementia (ADRD) (1). Soy isoflavones, phytoestrogens with potential cognitive benefits, have shown inconsistent results in clinical trials. Equol, a gut microbiome-derived metabolite of a soy isoflavone, is more bioavailable than other soy isoflavones and may influence brain health (2). The ability to produce equol varies across populations, which could potentially explain the inconsistent benefits observed with soy isoflavone supplementation. While equol-producing status has been associated with cognitive status and brain health (3,4), its relationship with brain morphological measurements remains unclear. This cross-sectional analysis aims to examine associations between equol-producing status and brain morphological measurements. We hypothesize that equol producers will have greater cortical brain volume compared with non-producers. **Methods:** We analyzed 344 participants (mean age 71.7 $\pm$ 4.7 years; 51% female; 20% African American) without dementia from the Arterial Stiffness, Cognition, and Equol (ACE) trial (R01AG074971, NCT: 05741060) with baseline 3T magnetic resonance imaging (MRI) data (5). Equol-producing status was defined as the urinary equol-to-daidzein ratio (log10 $\geq$ -1.75) after a three-day soy challenge. Total intracranial volume (ICV), cortical volume, and regional brain volumes were estimated using FastSurfer (version 2.5.0). Associations between equol-producing status and brain morphology were assessed using two-sample t-tests and multivariable linear regression, adjusting for demographics, APOE-ε4 status, and cardiovascular risk factors. **Results:** Of 344 participants, 103 (30%) were equol producers. Compared with non-producers, equol producers had larger total cortex volume (β= 6.3 cm^3, 95% CI: [-0.07, 13], P=0.05). Regional analysis revealed significantly greater frontal lobe volume in equol producers after adjusting for age, sex, body mass index (BMI), education, and ICV (β=2.9 cm^3, 95% CI: [0.24, 5.5], P=0.03), a result that remained significant after further adjusting for APOE-ε4 and cardiovascular risk factors (β=2.8 cm^3, 95% CI: [0.20, 5.5], P=0.04). No significant associations were observed in other lobes or hippocampal volume. **Conclusions:** Equol-producing status was associated with greater frontal lobe cortex volume in older, non-demented adults. These findings suggest that the gut microbiome's capacity to metabolize soy isoflavone may influence brain structure relevant to cognitive aging. Longitudinal analyses of equol, microbiome composition, and brain changes are warranted to clarify causal pathways and prevention potential.

Keywords: Equol, soy isoflavones, gut microbiome, MRI, cortex volume, Alzheimer's disease prevention.

Disclosures: The authors declared no competing interests.

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Key takeaway message: Among older adults, equol producers showed significantly greater frontal cortex volume compared with non-producers. This suggests the gut microbiome's capacity to metabolize soy isoflavone may influence brain structure relevant to cognitive aging.

P375- A MACHINE LEARNING APPROACH TO PREDICT COGNITIVE DECLINE USING PHYSICAL, BEHAVIORAL, AND BLOOD MARKERS: INTERPRETING XGBOOST WITH SHAP.

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Background: There is currently no cure for dementia. However, subtle pathophysiological and cognitive changes, which are precursors of dementia, can be observed for up to two decades before clinical diagnosis. Thus, early identification of cognitive decline is crucial for effective dementia prevention. To facilitate the early identification of cognitive decline and guide targeted risk reduction strategies, it is essential to identify contributing lifestyle factors and their associated risks. A cross-sectional study was conducted to investigate the contributions of lifestyle and physical function to cognitive decline in Japan. **Methods:** Between 2023 and 2024, 260 people (mean age 71.9±7.2 years) participated in the Tsukuba Happiness Life Study in Japan. The primary outcome was the Mini-Mental State Examination, with scores ≤26 indicating cognitive decline. XGBoost, a machine learning model, was used to predict cognitive decline using blood tests, physical and cognitive performance measures, behavioral variables assessed with ActiGraph (wGT3X-BT), and other health-related factors. The Shapley Additive Explanation (SHAP) method was used to interpret the XGBoost model results and determine the direction and magnitude of each variable. **Results:** The XGBoost model demonstrated a strong discriminative ability (AUC = 0.857) and high sensitivity (0.857). Among all variables, the Digital Trail Making Peg test (DTMP) had the most considerable mean SHAP value (2.206), followed by wake after sleep onset (WASO; 0.887), sleep onset time (SOT; 0.656), body mass index (BMI; 0.650), and high-density lipoprotein- cholesterol (HDL-C; 0.450). Other features in the top list included lower limb strength, creatinine, sleep duration, and dietary factors (sequential SHAP values of approximately 0.400–0.290). **Conclusions:** A longer time to complete DTMT, longer WASO, earlier SOT, higher BMI, and lower HDL-C levels were associated with a greater predicted risk. Overall, the results suggest that DTMT is a reliable indicator of cognitive decline. The substantial contribution of modifiable lifestyle factors, such as sleep duration, obesity, and diet, supports the feasibility of simple assessment tools and effective interventions for cognitive decline.

Keywords: dementia predictor, mild cognitive impairment, eXtreme gradient boosting, SHapley Additive exPlanations.

Clinical Trial Registry: UMIN000051941 (https://www.umin.ac.jp/). Disclosures: This study was supported by the Japan Science and Technology Agency (grant number JPMJPF2017) and Japan Society for the Promotion Science KAKENHI (grant number 25K03004). The authors declare no competing interests.

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P376- THERAPEUTIC TIME WINDOW OF DISEASE-MODIFYING THERAPY FOR EARLY ALZHEIMER'S DISEASE IN JAPAN.

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Background: The indication of lecanemab and donanemab as disease-modifying therapies (DMTs) for early Alzheimer's disease (AD) requires amyloid positivity, a Clinical Dementia Rating-Global Score (CDR-GS) of 0.5 or 1, and Mini-Mental State Examination (MMSE) scores of 22–30 (lecanemab) or 20–30 (donanemab). Prior analyses using the National Alzheimer's Coordinating Center (NACC) and Alzheimer's Disease Neuroimaging Initiative (ADNI) datasets suggested that baseline CDR-GS and MMSE predict a limited "therapeutic time window," but generalizability to Asian cohorts is uncertain (1). **Methods:** We analyzed data from the Japanese ADNI (J-ADNI). Amyloid-positive participants were divided into two sets, aligned with label criteria: MMSE 22–30 (lecanemab group, n = 129) and MMSE 20–30 (donanemab group, n = 156). Loss of eligibility was determined by CDR-GS >1 or MMSE below the set threshold upon the first visit. We estimated Kaplan–Meier (KM) curves over 24 months and fitted Cox proportional-hazards models adjusted for age, sex, baseline MMSE, and CDR-GS; education years, apolipoprotein-E ε4 (APOE-ε4) status, and CDR-Sum of Boxes (CDR-SOB) were tested individually, reporting hazard ratios (HRs) with 95% confidence intervals (CIs). **Results:** In J-ADNI, higher baseline CDR-GS (1 vs 0.5) predicted a shorter eligibility period. For the lecanemab group, CDR-GS was not significantly associated with survival (p=0.65; 12-month KM 70.4% vs 64.3%, 24-month KM 57.6% vs 51.4%). For the donanemab group, higher CDR-GS strongly predicted shorter survival (p<0.0001; 12-month KM 86.5% vs 48.5%, 24-month KM 74.0% vs 34.6%). Education, APOE-ε4, and CDR-SOB were not consistently associated after adjustment. This pattern was closely comparable with those in NACC/ADNI, where higher CDR-GS and lower MMSE predict a shorter window, whereas APOE-ε4 is not a consistent predictor after adjustment. **Conclusions:** Baseline CDR-GS emerges as a strong predictor of the therapeutic time window for early AD DMTs also in the Asian population, supporting cross-population generalizability, providing important information on patient prioritization and scheduling for AD DMTs under resource constraints.

Keywords: Japanese Alzheimer's disease neuroimaging initiative, disease-modifying therapies, clinical dementia rating-global score.

Disclosures: The authors declared no competing interests.

References: 1. Nakashima S, et al. Alzheimers Dement (NY). 11:e70102, 2025. doi: 10.1002/trc2.70102.

Key takeaway message: Baseline CDR-GS and MMSE predict the therapeutic time window for lecanemab and donanemab. Findings in J-ADNI mirror Western cohorts, supporting cross-population generalizability and helping clinicians prioritize patients and schedule treatments under limited resources.

P377- CAREGIVING AND ECONOMIC BURDEN OF ALZHEIMER'S DISEASE IN JAPAN.

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Background: Japan is among the top 10 countries with the highest prevalence of Alzheimer's disease, with 2,637 patients per 100,000 people (2021). As the patient number rises, society continues to incur socioeconomic consequences and deficits in individual quality of life (QoL) for patients and caregivers. Availability of anti-amyloid therapy in Japan marks an important advance in Alzheimer's disease management. This study aimed to characterize caregiver burden in Japan defined by caregiver plus patient QoL and economic impact, especially intangible

cost, and cost to business. **Methods:** A third-party agency was recruited to conduct the survey with a double-blinded approach: survey participants had no awareness of the study sponsor, likewise the study sponsor was blinded to both the third-party agency and survey participants. Caregivers for patients with mild cognitive impairment (MCI), and mild, moderate, or severe Alzheimer's dementia (AD) were identified from a pre-existing physician panel of Alzheimer's specialists from Japan. The caregiver sample was administered either an online or paper questionnaire to accommodate online access issues. The survey included the CarerQoL, DEMQOL-Proxy, Dependence scale, Work Productivity and Activity Impairment (WPAI) questionnaire, and a comorbidity check list. Intangible costs for caregivers and patients were derived from the CarerQoL and DEMQOL-Proxy, respectively. Cost conversion from utility was based on $100,000/QALY. The cost to business included 3 components: absenteeism, presenteeism, and worker replacement cost. Patient QoL assessed by the caregiver reported DEMQOL-Proxy was included to enable calculation of total indirect cost (intangible costs to patients and caregivers + unpaid caregiving costs + costs to business). **Results:** Caregiver respondents (N=54) were providing care for 12 patients with MCI, 12 with mild AD, 17 with moderate AD, and 13 with severe AD. Most (93%) caregivers were aged >45 years and 60% were women. About two-thirds of caregivers were married or in a civil partnership, over half were college graduates. Nearly two-thirds of caregivers were employed at least part-time and 65% reported low rate of employment turnover. All caregivers were family members. The mean duration of caregiving was 1.5±0.9 years for MCI and 3.3±3.1 years for AD. Additional paid caregiving was more common for AD (40.5%) than MCI (16.7%). Patient QoL measured by DEMQOL-Proxy showed little variation across disease severity. Patient dependence steadily increased with disease severity, from 4.7 for MCI to 11.8 for severe AD. Caregiver QoL measured by CarerQoL-7D utility declined slightly from mild to severe AD. There was a monotonic increase in indirect costs with disease severity, except for moderate AD. Combined intangible costs per patient per month to patients and caregivers were ¥266,104 for MCI and ¥293,573 for AD. Unpaid caregiving cost per patient per month was ¥86,865 for MCI and ¥117,698 for AD. Cost to business per patient per month was ¥52,399 for MCI and ¥35,667 for AD. The total indirect cost per patient per month was ¥405,367 for MCI and ¥446,938 for AD. **Conclusions:** The societal burden of Alzheimer's disease in Japan is substantial even in early stages, with economic and QoL impacts increasing alongside disease severity. The annualized indirect costs per patient reached ¥4.9 million and ¥5.4 million for MCI and AD, respectively. Caregiver QoL declined despite patient QoL appearing stable, suggesting proxy limitations in assessing patient well-being. Growing dependence, longer caregiving duration, and increased reliance on paid support underscore the progressive nature of caregiver burden. Early intervention with anti-amyloid therapies may reduce long-term societal costs and alleviate pressure on families and the healthcare system.

Keywords: Alzheimer's dementia, anti-amyloid therapy, caregiver burden, intangible costs, mild cognitive impairment.

Disclosures: Ran Gao, Babak Haji, Raymond Zhang, Quanwu Zhang, and Amir Abbas Tahami Monfared are employees of Eisai Inc. Noemi Hummel, Dave Morton, Marta Martinez, and Stephanie Read are employees of Certara, which is a paid consultant to Eisai Inc.

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Key takeaway message: The societal burden of Alzheimer's disease in Japan is substantial even in early stages, with economic and QoL impacts increasing alongside disease severity. Early intervention with anti-amyloid therapies may reduce long-term societal costs and alleviate pressure on families and the healthcare system.

P378- HIGH ELIGIBILITY OF FRAIL OLDER ADULTS WITH EARLY AD FOR LECANEMAB TREATMENT IN REAL-WORLD PRACTICE: IS THERE A NEED FOR NEW CLINICAL TRIALS?

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Background: Lecanemab has received marketing authorization from the European Medicines Agency (EMA) and is expected to become available across Europe (1). In real-life settings, older adults with early AD meeting frailty criteria could be considered as potential candidates for this treatment. The aim of the study was to estimate the proportion of individuals potentially eligible for lecanemab treatment by applying the CLARITY-AD trial eligibility criteria, as well as French and American appropriate use recommendations, to a real-world population of prefrail and frail older adults. **Methods:** We included all participants from the CogFrail cohort (2) with confirmed amyloid positivity (n = 120). Amyloid status was assessed via amyloid Positron Emission Tomography (visual reading) or cerebrospinal fluid analysis (Aβ42 levels or Aβ42/Aβ40 ratio). Frailty was defined according to the Fried phenotype: individuals meeting ≥3 out of 5 criteria were classified as frail (3). **Results:** The median age of the sample was 82.0 years (IQR: 79–85), and 65% (n = 78) were women. Overall, 20.0% (n = 24) met the Clarity-AD eligibility criteria, while 50.8% (n = 61) and 48.3% (n= 58) were potentially eligible according to the American and French AURs, respectively. 9.1% (n = 4) of frail individuals met the Clarity-AD criteria, 50.0% (n = 22) and 47.7% (n = 21) of frail individuals were potentially eligible according to the American and French AURs, respectively. **Conclusions:** Although fewer than one in ten participants would have been eligible for the CLARITY-AD trial, a significantly higher proportion - approximately half of the cohort - would potentially be eligible for lecanemab treatment under American and French recommendations. New clinical trials and/or real-world data are needed to better understand the safety and efficacy of lecanemab administration in this specific population.

Keywords: Lecanemab, frailty, clinical trials.

Disclosures: The authors declared no competing interests.

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Key takeaway message: While frail patients may have access to Lecanemab treatment in real-life, the low-proportion of frail individuals eligible for Clarity-AD suggests that frailty may have been underrepresented, raising concerns about the generalizability of the findings.

P379- PHYSICIAN PERCEPTION OF TREATMENT LANDSCAPE AND READINESS IN CARE DELIVERY WITH ANTI-AMYLOID THERAPY FOR ALZHEIMER'S DISEASE IN CHINA.

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Background: China bears the highest dementia burden among the G20 nations, and its patient population with Alzheimer's disease continues to rise. We conducted a physician survey study in China to characterize patterns of care delivery, clinical assessment approaches, anti-amyloid therapy (AAT) readiness, and barriers to AAT implementation. **Methods:** In 2024, Alzheimer's care specialists (N=20) in China filled in an online questionnaire. Survey respondents were selected from a pre-existing national physician panel of providers treating patients with confirmed diagnoses of mild cognitive impairment (MCI), and mild, moderate, or severe Alzheimer's dementia (AD). The survey covered six domains: diagnostic practices, disease severity assessment, referral pathways, treatment modalities, AAT access, and perceived barriers to AAT adoption. **Results:** Survey respondents specialized in neurology (n=14), geriatrics (n=4), and psychiatry (n=2). Most (n=15) reported ≥10 years of practice in their specialty. The majority (80%) reported spending over half of their working hours (≥60%) treating patients and all practiced in hospital settings. Less than 20% of patients were referred from other practices. Patterns of care delivery revealed high rates of resource utilization: 208.5±359.6 patients with MCI and 182.2±438.3 patients with AD were treated in the past year, with 60% of respondents seeing their patients for Alzheimer's disease ≥6 times; 85% of respondents reported using magnetic resonance imaging (MRI) to confirm MCI/AD diagnosis, followed by cerebrospinal fluid (CSF) tests (60%), blood biomarker testing (60%), position emission tomography (PET)/single photon emission computed tomography (SPECT) scans (45%), and computed tomography (CT) scan (20%). 95% of respondents used donepezil for both MCI and AD; 95% used memantine for MCI, despite its indication for moderate-to-severe AD, and 80% used it for AD. The most commonly used instruments/tools for clinical assessments included the Mini-Mental State Examination (MMSE) (95%), Montreal Cognitive Assessment (MoCA) (90%), Activities of daily living (ADL) assessments (n=16), Alzheimer's Disease Assessment Scale (ADAS) (80%), and Clinical Dementia Rating (CDR) (60%). Multidimensional approaches were applied to assess disease severity: functional (100%), cognitive (95%), behavioral (70%), and psychiatric (55%) evaluations. AAT readiness can be highlighted by the willingness of nearly half of respondents to treat >20% of their eligible patients with AAT within 12 months of approval. Patient factors impacting AAT readiness include rural vs urban residence, insurance coverage, social-economic conditions, age, employment, and caregiver availability. Barriers to AAT that were reported most often included the "burden of therapy and monitoring on patients", followed by "patient refusal to initiate AAT", "challenges related to identification of patients most likely to benefit from AAT", "delays in diagnosis leading to many patients progressing past point of eligibility for AAT", "frequency of required MRIs", and "access to amyloid PET scans to confirm patient eligibility for AAT". **Conclusions:** This Alzheimer's specialist survey has highlighted standard care practice and clinical readiness for AAT in China. Survey respondents reported a high patient volume, low rates of interdepartmental referral, common use of a multidimensional assessment approach, and high willingness to treat patients with AAT. Nearly half of respondents expected to treat ≥20% patients with AAT, reflecting a considerable potential patient volume to receive AAT infusion. The top 3 barriers to AAT were "burden of therapy and monitoring" (which may also include infusion schedule, costs, etc.) on patients, "patient refusal to initiate AAT", and "challenges related to identification of patients most likely to benefit from AAT". The findings from this survey highlight opportunities to support health system readiness for AD treatments, including physician education, investment in diagnostic infrastructure, and streamlining of patient pathways, especially with the potentially sizable number of patients to be treated in China.

Keywords: Alzheimer's dementia, anti-amyloid therapy, mild cognitive impairment.

Disclosures: Ran Gao, Raymond Zhang, Babak Haji, Quanwu Zhang, and Amir Abbas Tahami Monfared are employees of Eisai Inc. Noemi Hummel, Dave Morton, Marta Martinez, and Stephanie Read are employees of Certara, which is a paid consultant to Eisai Inc.

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Key takeaway message: The findings from this survey highlight opportunities to support health system readiness for AD treatments, including physician education, investment in diagnostic infrastructure, and streamlining of patient pathways, especially with the potentially sizable number of patients to be treated in China.

ANIMAL MODEL AND PRECLINICAL TRIALS IN AD

P380- TRIM21 MEDIATED CLEARANCE OF INTRACELLULAR PROTEIN PATHOLOGIES.

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Many studies have demonstrated antibodies ability to remove extracellular protein large aggregates and neutralize seeds implicated in the prion like spreading of tau and synuclein pathology. Recently, the focus shifted to studying the clearance on intracellular toxic aggregates, tripartite motif-containing protein 21 (TRIM21) mediated clearance has emerged as the leading mechanism through proteasomal degradation of antibody-bound aggregates. The removal on intracellular tau associated with restoring neuronal function and improving cognitive performance. This highlights the need for innovative strategies capable of addressing intracellular aggregates. Advances in antibody engineering and delivery systems now offer the potential to overcome these limitations. Specifically, conformation-specific antibodies targeting intracellular aggregates of and tau, coupled with innovative delivery methods, present a promising therapeutic approach. Furthermore, our recent study demonstrate antibodies loaded in micelles and administered through the intranasal route, efficiently entered the brain effectively cleared pathological tau, elevated synaptic proteins levels, and improved cognitive functions in aged tauopathy mice. Mechanistic studies confirm that TRIM21 facilitate proteasomal degradation of cytosolic antibody-bound proteins and suggest the need for designing effective immunotherapies using TRIM21 mediating the clearance of intracellular protein aggregates such as Tau, α-Synuclein and TDP-43.

Conflict of interests: Rakez Kayed is the inventor on patents involving the compositions and methods related to tau oligomers and antib.

Key takeaway message: Discussing the emerging role of TRIM21 in mediating the clearance of intracellular protein aggregates. Evaluating the efficacy of antibodies in micelles against intracellular tau and α-syn toxic aggregates.

P381- FUSING TRANSFERRIN RECEPTOR BINDERS TO THE AβO-TARGETING ANTIBODY SABIRNETUG ACHIEVES INCREASED BRAIN PENETRATION IN MICE WHILE PRESERVING TARGET BINDING.

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Background: It is well established that IgG antibodies delivered intravenously (IV) have poor brain penetration, generally around 0.1% of antibody administered. Receptor mediated transcytosis (RMT) has been used to mitigate this issue and increase brain penetration of antibodies. Here, we have applied the J-Brain Cargo® technology targeting the transferrin receptor (TfR) to the candidate Alzheimer's disease (AD) therapeutic sabirnetug, which is a humanized monoclonal IgG2 antibody targeting amyloid β oligomers (AβOs) in the brain. The goal of this approach is to exploit RMT via the TfR to increase sabirnetug brain penetration. **Methods:** Three different fusion proteins comprising sabirnetug fused to antibody fragments ("binders") targeting the murine transferrin receptor (mTfR) with either high or low affinity were prepared. The binding affinities of each fusion protein to mTfR were measured by bio-layer interferometry. The binding affinities of each fusion protein to AβOs and Aβ monomer were measured by surface plasmon resonance. Plasma and brain pharmacokinetics (PK) were measured in wild-type (WT) mice following a single 2 mg/kg IV injection using immunoassays. Subsequently, target engagement, measured as the drug-AβO complex, was assessed in the ARTE10 AD mouse model following a single 2 mg/kg IV injection using an immunoassay on MSD's S-PLEX® ultrasensitive assay platform. **Results:** All fusion proteins had comparable or improved AβO affinity and selectivity for AβOs over Aβ monomers when compared with sabirnetug. One fusion protein had high affinity for mTfR and the other two had relatively lower affinities. When injected into WT mice, all three mTfR-targeting fusion proteins showed an increased brain exposure when compared with sabirnetug. Greater affinity to mTfR corresponded with a more rapid brain accumulation, higher maximum brain exposure (35-fold over sabirnetug), and more rapid clearance from the brain and from plasma. Comparatively, the fusion proteins with 10-15-fold lower affinities to mTfR showed a more gradual brain accumulation, modest maximum brain exposure (17-fold over sabirnetug), and more gradual clearance from the brain and plasma. Brain exposure of the three fusion proteins was similar at 24 hr after dosing and then diverged again, with the higher affinity fusion protein clearing more quickly. When injected into ARTE10 AD mice, all three fusion proteins crossed the blood-brain-barrier and engaged their intended AβO targets in the brain to a similar extent 24 hr after dosing. This observation correlated with the brain PK profiles in WT mice, which showed similar brain exposure of the three fusion proteins 24 hr after dosing. **Conclusions:** Our results indicate that utilizing J-Brain Cargo® technology targeting the TfR is a promising approach to increase the brain penetration of IV administered candidate AD immunotherapeutic sabirnetug. Fusion of sabirnetug with the mTfR-targeting binders did not disrupt the in vitro or in vivo target binding capabilities of either sabirnetug or the mTfR-targeting binder. Importantly, the J-Brain Cargo® technology increased the brain penetration of sabirnetug 17-35-fold. In addition, accessing the brain through the TfR is predicted to result in low ARIA rates due to the high expression of TfR on capillaries and low expression on arteries, where vascular amyloid is located primarily. Ultimately, the enhanced safety profile of this brain delivery strategy for sabirnetug is expected to enable dose selection to be focused on maximizing efficacy. Efforts are ongoing to create and test fusion proteins of sabirnetug with antibody fragments targeting the human TfR.

Keywords: J-Brain Cargo® technology, transferrin receptor, amyloid β oligomers, sabirnetug.

Clinical Trial Registry: not applicable.

Data disposition: not applicable.

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Key takeaway message: Utilizing J-Brain Cargo® technology targeting the transferrin receptor increased the brain penetration of candidate Alzheimer's disease immunotherapeutic sabirnetug in transgenic mice. This approach has the potential to maximize efficacy while minimizing side effects.

P382- APOE-TARGETED MICROGLIA-SPECIFIC EPIGENOME THERAPY FOR ALZHEIMER'S DISEASE.

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Background: The key role of microglia in the etiology of Alzheimer's disease (AD) has been well established. Apolipoprotein E gene (APOE), the strongest and most reproducible genetic risk factor for late-onset AD (LOAD), is abundantly expressed in microglia and accumulating evidence suggested the pathogenic effect of the e4 risk-allele in the microglia. Numerous studies provided strong support to the concept that reducing the levels of ApoE, and specifically ApoEe4, potentially have beneficial therapeutic effects. Moreover, using single-nucleus (sn) transcriptomic (snRNA-seq) data we and others showed a significant increase in APOE expression levels in microglia from LOAD brain tissues compared to age- and sex- matched healthy controls. Correspondingly, our single-nucleus chromatin accessibility data (snATAC-seq) also demonstrated that APOE overexpression was correlated with more open chromatin sites in microglia from LOAD brains. Our overarching goal is to shift the paradigm of LOAD drug discovery towards the development of cell type- and gene- specific therapeutics targets. In this study, we translated discoveries from an integrative bioinformatics analysis of microglia multi-omics dataset into the development of an epigenome therapy platform to precisely and specifically repress APOEe4 expression in the microglia. **Methods:** In this study, we utilized (sn)multi-omics data to develop an all-in-one AAV vector for APOE-targeted epigenome-editing based on CRISPR/Cas technology, and validated the efficacy and specificity of our epigenome therapy platform in vitro and in vivo. In vitro studies were carried out using human induced pluripotent stem cell (hiPSC)-derived microglia like cells model from a LOAD patient homozygote for the APOEe4 allele. In vivo studies utilized mouse models including: (1) wild-type (WT) mouse, (2) human APOEe4 knock-in mouse (B6.129P2-Apoetm3(APOE*4)Mae N8, hereafter E4KI), and (3) our newly developed humanized mouse model generated by targeted replacement of the entire mouse region with the human (h)APOE and the adjacent hTOMM40 loci including their upstream and downstream flanking regulatory sequences (hereafter, TR hAPOE-TOMM40). **Results:** Our epigenome therapy platform is based on all-in-one AAV vector comprises of CRISPR/deactivated(d)SaCas9, fused with a synthetic repressor molecule and driven by an engineered microglia-specific promoter. The therapeutics, AAV/gRNAAPOE-dSaCas9-repressor vector, downregulates APOE transcription by targeted modification of the epigenome landscape across APOE regulatory region. First, we screened several AAV serotypes and found that AAV2.6 resulted in the most efficient transduction into microglia cell-type detected by GFP expression. Next, using the LOAD microglia (sn)multi-omics data datasets, we engineered regulatory sequences based on promoters of

human microglia genes for specific and efficient expression of the therapeutic platform in microglia cells. Transduction of the lead therapeutic AAV vector driven by an engineered human microglia regulatory sequence demonstrated a significant microglia-specific reduction in APOE-mRNA levels, amounting to ~30% lower levels compared to the control vector. The repression of APOEe4 expression in the hiPSC-derived microglia resulted in a significant increase in Aß clearance such that the increased Aß uptake was similar to that of APOEe3 microglia. In addition, evaluation of inflammatory response and activated microglia markers validated that the reduction in APOEe4 expression rescued inflammation, characteristic of APOEe4 microglia cells. Next, we moved onto animal studies and administrated the therapeutics AAV/gRNAAPOE-dSaCas9-repressor vector by stereotactic injection into the mice hippocampus. Overall, the results demonstrated a strong and efficient repression in vivo. In the WT mouse we observed a significant decrease in mouse endogenous Apoe expression, amounting to ~70%. Similar significant and robust effects were observed in both APOE-humanized mouse models, the E4KI and the TR hAPOE-TOMM40 mice. Interestingly, the reduction effect in the hippocampus of the TR hAPOE-TOMM40 model was sex-dependent, amounting to ~70% in males vs 30% in females. In addition, no changes in weights or welfare criterions were observed, and the mice displayed normal grooming and eating/drinking behaviors indicating no safety issues. **Conclusions:** Collectively, our results provided in vitro and in vivo proof-of-concept for the utility, efficacy, and specificity of the APOE-targeted microglia-specific epigenome therapy. Furthermore, our therapeutics platform offers the opportunity to fine-tune APOEe4 expression, and to refine for achieving gene- allele- and cell-type- specific therapies. Thus, enabling the advancement towards precision medicine in LOAD. In conclusion, our epigenome therapy strategy is translational into a novel therapeutic approach to prevent, delay onset and/or halt the progression of LOAD. **Keywords:** APOE, gene therapy, hiPSC- derived microglia (iMGL), APOE-humanized mouse model. **Disclosures:** Drs. Kantor and Chiba-Falek are Co-Founders at CLAIRIgene. CLAIRIgene has an exclusive, worldwide option agreement from Duke for the related patent portfolio for all fields of use. This work was funded in part by the National Institutes of Health/National Institute on Aging (NIH/NIA) [R41 AG077992 to CLAIRIgene, LLC]. Other authors declared no competing interests.

Key takeaway message: APOE-targeted epigenome-editing therapy precisely and specifically reduces the expression of APOEe4 in the microglia and by that ameliorates Alzheimer's related neuropathologies. Thus, has a strong translational potential for therapeutics development towards precision medicine in Alzheimer's.

P383- PASSIVE IMMUNOTHERAPY TARGETING TAU OLIGOMERIC STRAINS REVERSES TAUOPATHY PHENOTYPES IN AGED IN A MOUSE MODEL SEPECIFIC MANNER.

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Tau oligomers are one of the most toxic species, displaying prion-like strains which have different conformations resulting in different tauopathies. Passive immunotherapy targeting different tau species is a promising therapeutic approach. Age is one of the greatest risk factors; however, most immunotherapy studies are done in young to middle-aged mice tauopathy models, which is not representative of the many clinical trials done with older humans with established tauopathies. Our objective was to utilize two different clones of tau oligomer monoclonal antibodies (TOMAs) in aged Htau and JNPL3 mouse models to investigate the potential of passive immunotherapy. We used aged mice which recieved a single intravenous injection of 120 µg/animal of either TOMA1, TOMA3 clones or a non-specific IgG. Their cognitive functions were assessed one-week post-injection using Y-maze and novel object recognition tests. Brain tissues were analyzed using biochemical and immunological assays. TOMA 1 and 3 rescues cognitive phenotypes in aged animals in a mouse model-specific manner, indicative by a reduction in tau oligomers levels. The TOMAs were shown to have strong reactivity with different tau oligomeric species in the different mouse models in vitro and ex vivo. This study is first of its kind to test tau passive immunotherapy in aged animals and supports previously done studies, suggests that multiple tau oligomeric strains exist in aged animals; therefore, it is of great importance to further characterize these strains. **Key takeaway message**: Immunotherapy, Passive immunotherapy, tau/

P385- LECANEMAB AMELIORATES ALZHEIMER'S DISEASE-RELATED SLEEP DISORDERS VIA MODULATING THE OREXINERGIC SYSTEM AND MICROGLIAL FUNCTION: EVIDENCE FROM TRANSLATIONAL MODELS.

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Background: Alzheimer's disease (AD) accounts for 60-80% of all-caused dementia cases, exerting a heavy substantial public health and socioeconomic burden. Sleep disorders affect approximately 40% of AD patients, which not only deteriorates patient quality of life but also significantly elevates long-term care costs. Importantly, sleep disorders are now recognized as a modifiable risk factor for AD, with accumulating evidence indicating that chronic sleep disruption accelerates cerebral amyloid-β (Aβ) aggregation and deposition. However, the underlying molecular and cellular mechanisms remain incompletely elucidated. The orexinergic system, primarily localized to the lateral hypothalamus, serves as a core regulatory hub for sleep-wake cycle homeostasis, while microglial dysfunction is a well-characterized mediator of both AD pathogenesis and sleep dysregulation. Notably, lecanemab, an Aβ-targeted monoclonal antibody, has demonstrated efficacy in reducing Aβ deposition and slowing cognitive decline in AD patients (1). Yet, whether Aβ pathology impacts the orexinergic system, and if lecanemab improves AD-related sleep disorders via modulating orexinergic system and microglial function, remains uninvestigated. This study aims to unravel the mechanism by which Aβ pathology contributes to sleep disturbances via regulating the orexinergic system and to clarify lecanemab's interventional effect on the orexinergic system and AD-related sleep disorders, verifying whether lecanemab ameliorates sleep disturbances by restoring impaired orexinergic system function while reducing Aβ burden. **Methods:** To delineate the impact of Aβ pathology on the orexinergic system, two AD models were employed, including transgenic APP/PS1 mice and wild-type C57BL/6 mice subjected to intracerebral injection of exogenous Aβ in three forms (monomer, oligomer, and long peptide). Cognitive function was evaluated using the Morris water maze and the passive avoidance test, while sleep architecture was characterized via 72-h continuous EEG/EMG recordings. Specifically, wake, non-rapid eye movement (NREM) sleep, and rapid eye movement (REM) sleep were classified based on fast Fourier transform (FFT)-derived δ/θ wave power ratios and EMG amplitude (2). Spatial and subcellular co-localization of Aβ and orexinergic components (Orexin A, OX1R, OX2R) was examined via immunofluorescence (IF) staining. Orexin metabolism was quantified via multiple targeted assays. The production, precursor cleavage and degradation were measured by ELISA, qPCR and Western blot, while membrane transport was analyzed by flow cytometry and IF. Orexinergic neural projections were analyzed using a combination of techniques. IF was utilized for counting orexin-positive neurons and assessing morphology in the hypothalamus, co-localization of orexin and c-Fos, immunohistochemistry for measuring orexin-positive fiber density in target regions, and whole-cell patch-clamp for recording to evaluate firing frequency and resting potential of hypothalamic orexin neurons. Besides, exogenous orexin or orexin receptor antagonists were administered to confirm whether Aβ-induced sleep effects depend on the

orexinergic system. APP/PS1 mice were treated with lecanemab (Leqembi®, Eisai Co., Ltd. and Biogen Inc.) at different doses to investigate lecanemab's interventional effects, followed by repetition of the aforementioned cognitive, sleep, and orexin-related assays. Additionally, hypothalamic transcriptome sequencing was performed to explore differentially expressed genes, and orexin regulators were used to verify the dependence of applying lecanemab on the orexinergic system. To elucidate the role of microglia in these processes, in vitro and in vivo experiments were conducted. In vitro, primary microglia were treated with exogenous orexin or orexin receptor antagonists, and the microglial activation, proliferation, migration, phagocytosis and inflammatory responses were detected by flow cytometry, MTT, transwell assay and ELISA, respectively. In vivo, mice fed with the CSF1R inhibitor PLX5622 to deplete microglia, or Cx3cr1creERT2 transgenic mice which subjected to orexin receptor knockout in microglia were employed, with subsequent evaluation of the efficacy of lecanemab. For population-level validation, over 3,000 samples from our AD cohort were analyzed via ELISA to measure orexin levels in cerebrospinal and peripheral blood, with correlations assessed between CSF AD biomarkers (Aβ1-42, Aβ1-40, p-tau, t-tau), soluble TREM2 (sTREM2), sleep scale scores, and cognitive scores. Then, the clinical trial including lecanemab-treated AD patients, untreated AD patients and healthy controls were compared to analyze differences in sleep and orexin levels. **Results:** Preliminary data collection is ongoing, with preliminary findings indicating that Aβ pathology disrupts orexinergic signaling and microglial function, thereby contributing to sleep disturbances. Lecanemab is expected to attenuate Aβ-induced orexinergic system dysfunction, normalize sleep architecture, and improve cognitive performance. The current study further hypothesizes that microglial depletion or orexin receptor knockout will attenuate the beneficial effects of lecanemab on sleep, thereby supporting an interactive role between microglia and the orexinergic system. Clinically, AD patients treated with lecanemab are expected to exhibit improved sleep metrics and stabilized orexin levels compared to untreated patients. **Conclusions:** This study systematically investigates the mechanism by which Aβ pathology promotes AD-related sleep disorders via the orexinergic system and microglia, and verifies the potential effect of lecanemab to improve sleep disorders. If confirmed, it will clarify the bidirectional AD-sleep interaction pathway, fill gaps in current understanding, provide new therapeutic targets for AD-related sleep disorders, and support lecanemab's multidimensional value in enhancing the living quality of AD patients and reducing care costs.

Keywords: Lecanemab, Alzheimer's disease, sleep disorders, orexinergic system, microglia.

Disclosures: The authors report no potential conflicts of interest relevant to the manuscript.

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Key takeaway message: Lecanemab can ameliorate AD-related sleep disorders by regulating orexinergic system and microglial function.

P386- ADMINISTRATION OF BENZGALANTAMINE, A GALANTAMINE PRODRUG, REDUCES MULTIPLE FORMS OF HYPERPHOSPHORYLATED TAU AND MITIGATES NEUROPATHOLOGY IN TWO ANIMAL MODELS OF TRAUMATIC BRAIN INJURY: POTENTIAL IMPLICATION FOR REDUCED DEMENTIA RISK.

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Background: A history of traumatic brain injury (TBI) has been associated with up to a two-fold increase in the risk of Alzheimer's Disease and related dementias (doi:10.1001/jamaneurol.2018.0815). The development of Tau pathology is the earliest neuropathological change observable in the pathogenesis of Alzheimer's disease (AD). Here we report the benefits of benzgalantamine treatment following mild to moderate TBI, assessing neuropathological indices of brain trauma mitigation and post-traumatic Tau pathology. Benzgalantamine is a prodrug of galantamine. Benzgalantamine' s active metabolite is both an acetylcholinesterase inhibitor, and a nicotinic receptor agonist. It was FDA approved in 2024 for treatment of mild to moderate Alzheimer's disease [ZUNVEYL®, Alpha Cognition Inc., Grapevine, Tx]. Methods: Study 1: Benzgalantamine administration in a rat preclinical model of moderate traumatic brain injury. Adult male Wistar rats (2-3 months) received a controlled cortical impact injury (CCI) consisting of a single impact at 4.0 m/sec, with a deformation depth of 2.5 mm to the left parietal cortex. Following injury, animals were then administered benzgalantamine at 4.5 mg/kg or vehicle (purified water as treatment control) intranasally (IN), with treatment initiated 2 hr after injury and continued twice (6 h interval) daily for 35 days. A third cohort underwent surgical preparation for TBI without injury (sham controls). Neuropathology was assessed histologically and by immunohistochemistry (IHC). All rats were sacrificed at 35 days following TBI, and brain tissue was subjected to the following analyses, determination of: lesion volume (H&E), neuronal cell loss in injured cortex and hippocampus (NeuN IHC), total Tau and pTau (AT8) burden (Tau/p-Tau IHC), neuroblast number (doublecortin IHC) and, newborn neurons (NeuN/BrdU double label IHC). To label proliferating cells bromodeoxyuridine (BrdU), was administered to all animals for seven days starting at one day post CCI. Study 2: Benzgalantamine administration in a mouse preclinical model of repetitive mild traumatic brain injury (mTBI). Neuropathological correlates of repeated blast-induced mTBI were assessed in a well-established shock-tube mouse model. Briefly, isoflurane-anesthetized male and female mice (3 months) were exposed to 3x blast mTBI (1/day for 3 consecutive days; each ~20 psi, ~5.6 ms positive phase duration) or a sham condition without blast exposure, before recovering in their home cage for 1, 3 or 6 months before sacrifice. Mice were treated for 30 days following the last blast/sham procedure with either intranasal vehicle or benzgalantamine. ngfr, ccr2, chat mRNA-cDNA levels were measured by TaqMan real-time PCR in forebrain sections from 30-day timepoint male mice receiving doses of 0.3, 1.5, or 3.0 mg/kg benzgalantamine. In both male and female mice, immunohistochemical signal intensities for markers of tauopathy and gliopathy were measured independently in separate tissue sections using a comprehensive unbiased machine learning-augmented digital pathology platform. More than 850 near midline, sagittal brain sections were analyzed. **Results:** Study 1: In comparison to the vehicle control (purified water), benzgalantamine treatment initiated 2 hours post-injury and continued twice daily for 35 days, demonstrated clear evidence of neuroprotection, resulting in; 1) significantly reduced lesion size (28% decrease), 2) significantly reduced neuronal cell loss in the cortex and hippocampus of the injured side, 3) significantly enhanced neurogenesis including augmentation of doublecortin positive neuroblasts as well as BrdU/NeuN positive new neurons in the dentate gyrus of the hippocampus, 4) significant reduction of p-Tau (AT8) burden in the cortex and hippocampus without changes in total-Tau expression. Note that functional recovery following benzgalantamine treatment was significantly enhanced and will be reported elsewhere. Study 2: The level of ngfr mRNA was increased in a benzgalantamine dose dependent manner, whereas chat and ccr2 remained unchanged. Benzgalantamine (3 mg/kg, BID) reduced the brain wide frequencies of AT8+, Tau p217+, GFAP+ cells at 3 and 6 months post repetitive blast-mTBI. Additionally, Tau p231 levels were decreased in tissue lysates measured by validated electro-chemiluminescent assay at 6 months following blast injury. These results were specific to male mice and not seen in female mice under similar injury and treatment conditions. In summary, benzgalantamine administration following both repetitive mild and moderate TBI, mitigated important indices of neuropathology. With specific reference to Tau pathology, benzgalantamine reduced AT8

positive Tau deposition in both studies 1 and 2. Using super high-resolution electron microscopic techniques Colom-Cadena et al. (doi: 10.1016/j.neuron.2023.04.020) examined postmortem temporal and occipital cortical tissue from patients with Alzheimer's disease. Their analysis demonstrated post-synaptic oligomeric tau frequently co-localized with AT8-positive tau, even in regions lacking overt neurofibrillary tangles, suggesting this is an early event in AD pathogenesis. In Study 2, benzgalantamine treatment also reduced of both Tau p217 and p231. Both forms of hyperphosphorylated Tau are recognized as being very early biomarkers of AD. **Conclusions:** Tau pathology can develop following TBI. Preclinical findings suggest that this pathology can be suppressed by treatment with benzgalantamine. In humans, the spread of pathological Tau is known to occur over a long prodromal period. In Alzheimer's disease, Tau pathology is histologically detectable roughly a decade before the appearance of amyloid plaques and shows a stronger correlation with grey matter loss (doi: 10.1002/alz.12192). These observations suggest that benzgalantamine may not only offer acute therapeutic benefits following TBI but may also have potential for long-term neuroprotective effects by modulating Tau-related pathology.

Keywords: pTau, proteopathy, gliopathy, TBI.

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Key takeaway message: Benzgalantamine administration acutely reduces Tau and other indicies of neuropathology following TBI, suggesting it may not only offer acute therapeutic benefit following TBI, but may also have potential for long-term neuroprotective effects.

P387- THE APOE4 KNOCK-IN APPSWE/PSEN1DE9/TAU-P301S TRIPLE TRANSGENIC (E4-3TG) MOUSE MODEL EXHIBITED TAK1–NF-κB-MEDIATED ASTROCYTIC C3 OVERPRODUCTION, NEURODEGENERATION AND A SEVERELY REDUCED LIFESPAN.

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Background: Recent studies have shown that increased neuroinflammatory responses in the central nervous system (CNS) are closely linked to the progression of Alzheimer's Disease (AD), which contributes to neuronal dysfunction. The astrocyte is the most abundant glial cell in the brain and plays an important role in supporting neurons through astrocyte–neuron communication, however, in AD, astrocytes become over-activated, acquiring a neurotoxic phenotype known as A1 astrocytes. A1 astrocyte activation is accompanied by the over-production of complement C3 (C3) via the NF-κB pathway, which contributes to tau pathology-associated neurodegeneration through C3–C3aR signaling. Until now, effective strategies specifically targeting astrocytic NF-κB pathway and C3 production in AD remain limited. Furthermore, the impact of Abeta accumulation on tau (P301S)-mediated neurodegeneration and mortality remains unclear. **Methods:** In this study, we created a unique triple transgenic (E4-3Tg) mouse model with a human APOE4 knock-in and APPswe/PSEN1dE9/Tau-P301S, in order to compare the phenotype with that of a genuine APOE4 knock-in Tau-P301S transgenic (TE4) mouse (1,2). Changes in astrocytes were examined in terms of the phosphorylation of TAK, an upstream signal of NF-κB, and the expression of complement C3 (3). Meanwhile, neurodegeneration was assessed in terms of the survival of hippocampal neurons. Cognitive function was assessed using the Y-maze and fear conditioning, and lifespan was assessed using a survival curve according to a standardized method. Anserine, an anti-inflammatory agent used in a previous study (4), was employed to reduce changes in both mice. To investigate the effect of anserine has on TAK phosphorylation, an astrocyte cell culture system was employed. It has been found that anserine reduces cognitive decline and the progression of dementia in individuals with ApoE4-positive mild cognitive impairment (MCI) (5,6). **Results:** The lifespan of the TE4-3Tg mice was considerably reduced, with fatalities emerging in some subjects as early as five months old. The time at which these dead mice appear is significantly earlier than in TE4 mice, and this is the key difference between the two types of mice. This indicates that Abeta accumulation affected the progression of tau-associated pathologies and the lifespan of individual mice. We also observed astrocytic C3 over-production at earlier stage in E4-3Tg mice. Anserine had a beneficial effect on astrocyte over-activation, neuronal degeneration, cognitive decline, and reduced lifespan in both E4-3Tg and TE4 mice. We further demonstrated that anserine can effectively suppress the production of C3 by astrocytes by inhibiting the activation of NF-κB via the TAK1 pathway in cultured astrocytes stimulated by either TNF-α or IL-1β. Using kinase assays, we discovered that anserine inhibits the enzymatic activities of TAK1 and IRAK1, which are related to TNF-α and IL-1β- mediated NF-κB activation and C3 over-production. **Conclusions:** We insist that E4-3Tg mouse model become a useful AD model not only focused on neurodegeneration, but also offered severely reduced lifespan. The findings of this study demonstrate that anserine can suppress the overproduction of astrocytic C3 by inhibiting Tak1-mediated NF-κB activation, thereby blocking neurodegeneration, cognitive deficits, and reduced lifespan. In other words, by alleviating tau-associated neuronal degeneration, the natural anti-inflammatory peptide anserine can prevent the progression of Alzheimer's disease.

Data Deposition: None.

Disclosures: None.

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Key takeaway message: The APOE4 knock-in APPswe/PSEN1dE9/Tau-P301S triple transgenic (E4-3Tg) mouse model is a useful AD model not only focusing on neurodegeneration but also offering severely reduced lifespan, both are ameliorated by a natural anti-inflammatory peptide anserine.

P388- A CONDITIONALLY ACTIVATED SIRNA (CASI) TARGETING APOE FOR THE TREATMENT OF ALZHEIMER'S DISEASE.

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1. Switch Therapeutics - San Francisco (United States)

Background: The greatest genetic risk factor for Alzheimer's disease (AD) is Apolipoprotein E (APOE), with two copies of ε4 allele leading to a significant increase in chance of developing biological and clinical AD with an earlier disease onset. ε4 homozygous AD patients are either currently contraindicated in EU or face strict ARIA monitoring guidelines in the US/UK from the amyloid targeting passive immunotherapies. Since ε4/ε4 patients have the greatest risk and the highest unmet need in AD, we sought to address this patient subpopulation with a APOE targeting siRNA. We describe a CASi targeting APOE, as a clinical candidate that is being developed to reduce APOE level in the CNS of ε4/ε4 carriers. **Methods:** A library of siRNAs targeting APOE were designed, synthesized, annealed into Switch's proprietary CASi format, and transfected into iPSC astrocytes to determine IC50 values for the initial screening. APOE CASi molecules were next screened in human APOE4 (hE4) transgenic mice dosed i.c.v with 10 nmole. 30 days post-dose, brain and liver tissues and serum were collected and analyzed to

ensure CNS-specific activity. The PK/PD relationship in brain tissue was established after a dose-response study of 1, 3, and 10 nmole of the lead molecule. Brain tissues from one hemibrain were analyzed for APOE transcript levels and the other for the quantification of siRNA guide strand. The durability of the lead molecule in hE4 mouse brain tissue was determined up to 6-months post-administration of 15 nmole dose. This molecule was further evaluated in nonhuman primate (NHP) studies, administered via the cisterna magna (i.c.m) at two dose levels. Knockdown of APOE and siRNA exposure were assessed in brain tissues after 1 month to establish a PK/PD relationship. For clinically relevant siRNA delivery, additional NHPs were dosed intrathecally with the higher dose of the CASi. Knockdown of CSF APOE protein was assessed at multiple time points. Durability of activity was measured in brain and liver tissues at 1 and 3 months. **Results:** The lead molecule was identified from iPSC astrocyte screening with an IC50 value of <20pM. A 10 nmole dose in hE4 mice yielded 85% reduction of APOE mRNA in hippocampal tissue after 1 month. The molecule was well-tolerated in mice and distributed throughout the brain with APOE mRNA knockdown of 75-85% in cortex, striatum, midbrain, cerebellum, and brainstem. A dose-response study demonstrated a significant ($P<0.0001$) PK/PD correlation of drug level to activity in the hippocampus and most brain regions. Despite comparable accumulation of siRNA, there was no change in APOE mRNA levels in the liver or increases of total cholesterol in the serum. A durability study in hE4 mice showed deep (>80%) reduction of APOE mRNA in the hippocampus up to six months post-administration of 15 nmole dose. There was again no change in the liver tissue APOE levels. Testing in NHP demonstrated 50-75% APOE mRNA knockdown 1-month post i.c.m. administration in cortical brain regions and the hippocampus. A PK/PD analysis revealed a significant ($P<0.0001$) correlation of drug level to activity across multiple brain regions. Furthermore, the duration was assessed over time in NHPs after intrathecal delivery for up to three months. APOE protein knockdown of 50-70% was sustained in the CSF for three months. Plasma APOE levels and total plasma cholesterol remained unchanged. APOE mRNA knockdown in cortical brain regions and the hippocampus was ~50% at 1- and 3-month timepoints, demonstrating both the biodistribution and durability of the lead molecule. **Conclusions:** We identified a CASi against CNS-derived APOE. In addition, a unique and clinically attractive property is the lack of unwanted effects on liver APOE levels or peripheral cholesterol despite drug accumulation. This effect was demonstrated in hE4 mice and NHPs over multiple months. This molecule holds promise as a future therapeutic for ε4 carriers suffering from MCI/AD, many who are contraindicated for the currently approved immunotherapies.

Keywords: APOE, siRNA, ε4/ε4.

Disclosures: Each author is either a current or former employee of Switch Therapeutics.

Key takeaway message: APOE targeted siRNA for Alzheimer's Disease.

P389- A CONDITIONALLY-ACTIVATED SIRNA TARGETING MAPT FOR THE TREATMENT OF TAUOPATHIES.

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1. Switch Therapeutics - San Francisco (United States)

Background: Tau pathology is associated with various neurodegenerative diseases through production of abnormal tau, aggregation of tau, and poor clearance of abnormal tau (MAPT gene product). Abnormally phosphorylated tau protein plays a significant role in Alzheimer's disease (AD), a secondary tauopathy, contributing to the formation of neurofibrillary tangles and disease progression. Contrary to AD, primary tauopathies such as Progressive supranuclear palsy (PSP), is driven exclusively through aberrant tau. As such, the goal of the program was to discover siRNA sequences that target transcripts of MAPT for therapeutic benefit in AD and PSP. **Methods:** In-vitro testing was conducted in HEK293 cells and iPSC neurons under transfection conditions. For in-vivo testing, humanized MAPT (hTau) mice (https://www.jax.org/strain/005491) were used where 10 nmoles of conditionally activated siRNA (CASi) were dosed i.c.v. followed by endpoint transcript measurement on day 14. Duration of action studies were conducted for a length of 1, 3 and 6 months in mice. In NHP, i.t. dosing was administered, and brain tissue regions were harvested at 1, 3 and 6 month time points for assessing MAPT and tau levels. **Results:** siRNA constructs targeting the human MAPT coding sequence were designed, synthesized and annealed in the Switch proprietary format called CASi. CASi molecules were then screened for MAPT knockdown in HEK293 cells, followed by assessing MAPT knockdown in iPSC neurons. Based on potency (IC50 < 1 nM), a subset of CASi molecules were screened for in-vivo activity at 10 nmoles in humanized MAPT transgenic mice; MAPT targeted CASi molecules that reached 75% knockdown (KD) in hippocampus and >50% in midbrain and striatum were assessed for off-target activity. Two lead CASi molecules (SWT-A and B) were then scaled up for duration of action studies in hTau mice (i.c.v dose). Greater than 75% MAPT KD was observed and maintained for 6 months after a single i.c.v dose of 10 nmoles. During the in-life portion of in-vivo experimentation, one CASi produced some untoward effects leading to the selection of the other molecule (SWT-B) as a potential lead molecule for testing in NHPs. After a single intrathecal dose, we observed > 75% MAPT KD in NHP brain regions of interest, both at the transcript and protein level at 3-month time point (6-month data pending). **Conclusions:** SWT-B is a potent and durable CASi molecule to KD MAPT transcript and tau protein and is being scaled up for IND-enabling toxicology studies.

Keywords: MAPT, PSP, tauopathy.

Disclosures: Each author is either a current or former employee of Switch Therapeutics.

Key takeaway message: Discovery of a potent MAPT siRNA with a durable knockdown of tau protein in NHPs

P390- ANTIBODY EFFECTOR FUNCTION OF THE MURINE ANALOGUE OF ETALANETUG DRIVES EFFICACY IN AN ANIMAL MODEL OF PATHOLOGICAL TAU SEEDING AND SPREADING.

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Background: Tau deposition in the brain is a pathological hallmark of Alzheimer's disease (AD). As disease progresses, pathological tau spreads through the brain via synaptically connected pathways. Tau proteins (full length or fragments) containing the microtubule binding region (MTBR) are essential to form extracellular 'seeds' that initiate and propagate tau pathology. Etalanetug (E2814) is a humanised IgG1 antibody that binds to the tau-MTBR. To gain further insight into how mechanistically E2814 may exert a therapeutic effect, the role of antibody effector function was evaluated in an in vivo seed-injection model. **Methods:** Human-derived AD seed or PBS was injected into the left hippocampus of 6- to 7-month-old hTau mice that overexpress all six isoforms of human tau. Mice were treated systemically once a week at 40 mg/kg for a period of 12 weeks with either the murine analogue of E2814 (7G6-IgG2a), an effectorless equivalent (LALA-PG) or an isotype control antibody. Brains were extracted for biochemical analysis ($n = 15$ per treatment group) to measure sarkosyl-insoluble tau or fixed in paraformaldehyde for immunohistochemical staining ($n = 9$-10 per treatment group) with the AT8 antibody which recognises pathological phospho-tau epitopes. Statistical analyses were performed for cortex and hippocampus using ANCOVA followed by LSD post-hoc tests. **Results:** In areas of cortex, brain regions distal but synaptically connected to the injection site, sarkosyl-insoluble tau levels were significantly reduced ($p<0.05$) following administration of 7G6-IgG2a antibody compared to the IgG control. Also in cortex, significantly less AT8-positive cells were observed in the 7G6-IgG2a treatment group compared to the control group. No statistically significant reduction in either sarkosyl-insoluble

tau levels or numbers of AT8-positive cells were observed for the LALA-PG effectorless antibody. **Conclusions:** This data demonstrates that presence of the full effector function of 7G6-IgG2a is a driver of pathological tau reduction in an animal model of tau seeding and spreading. It also provides supporting evidence that the IgG1 full effector function of Etalanetug would provide greater benefit compared to other antibodies on a different backbone e.g. IgG4 isotypes that have reduced effector functionality.
Key takeaway message: The full IgG1 effector function of Etalanetug can drive the reduction of pathological tau spread in the brain, leading to greater benefit compared to other antibodies of different isotypes.

P391- SUVN-I6107, A TRUE POSITIVE ALLOSTERIC MODULATOR AT MUSCARINIC M1 RECEPTOR FOR TREATMENT OF COGNITIVE DISORDERS, UPDATE ON THE DEVELOPMENT.

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Background: SUVN-I6107 is a novel and selective positive allosteric modulator (PAM) of the M1 subtype of the muscarinic acetylcholine receptors (mAChRs) being developed for the treatment of cognitive disorders. In the current research, the pharmacological properties of SUVN-I6107 were investigated in animal models. **Methods:** SUVN-I6107 was characterized using a calcium mobilization assay and the binding affinity towards the orthosteric M1 - M5 site was investigated to assess the selectivity. The effect of SUVN-I6107 on neuronal spike rate in coronal hippocampal slice electrophysiology was studied in agonist and PAM modes of testing. The pharmacokinetic properties of SUVN-I6107 were studied both in rodent and non-rodent species. The effect of SUVN-I6107 was assessed on delay, MK-801 and scopolamine induced memory deficits in rats using object recognition task (ORT), delay-induced social memory deficits in rats using social recognition task (SRT) and scopolamine induced memory deficits in rats using contextual fear conditioning task. Furthermore, effects of SUVN-I6107 on neuronal markers like soluble amyloid precursor protein (sAPPα) and inositol 1 phosphate (IP-1) levels were studied in rats. **Results:** SUVN-I6107 showed allosteric potency at M1 receptor with very good selectivity against orthosteric site of M1-M5 receptors. It also improved the hippocampal neuronal firing, when tested in combination with EC20 of carbachol. SUVN-I6107 showed good oral bioavailability in rats, dogs, and monkeys. SUVN-I6107 was found to have good brain penetration properties with high free fraction. In a rat model, SUVN-I6107 reversed the delay, scopolamine and MK-801 induced amnesias in ORT. SUVN-I6107 also significantly improved the memory in contextual fear conditioning task and SRT. Treatment with SUVN-I6107 produced significant increase in the levels of cortical sAPPα and striatal IP-1 in rats. **Conclusions:** Results from the non-clinical studies suggest SUVN-I6107 may have utility in the treatment of various cognitive disorders. SUVN-I6107 is currently being studied in a Phase-1 study (NCT06705088) to evaluate its safety, tolerability, pharmacokinetics, and pharmacodynamic effects after single and repeated administrations in healthy human subjects.
Key takeaway message: SUVN-I6107 is a pure and potent, positive allosteric modulator at muscarinic M1 receptor and may have an utility in the treatment of various cognitive disorders.

DIGITAL HEALTH/E-TRIALS

P392- DEMENTIA TRIALS ACCELERATOR: UK SERVICES FOR CLINICAL TRIALS IN DEMENTIA AND RELATED DISORDERS.

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Background: Trials in disease modifying therapies for Alzheimer's disease and other dementias have recruited slowly in the UK. Challenges include high screen failure rates, difficulty measuring disease biomarkers, and underrepresentation of people by ethnicity, region, and deprivation. To address these problems, the Dementia Trials Accelerator (DTA) will use UK research and NHS datasets to develop a pre-screened trial ready cohort with measurement of trial inclusion criteria, cognition, and blood biomarkers for RCTs of dementia prevention and treatment. **Methods:** The DTA provides two main services, both informed by feedback from trialists and from public contributors. The first service is a tool to discover potential participants in existing cohorts and data resources. The tool enables trialists to assess the feasibility of RCTs by identifying the number of potential participants in cohorts meeting inclusion criteria, without accessing individual-level data. Participating cohorts map pseudonymised records to the Observational Medical Outcomes Partnership Common Data Model (OMOP), allowing secure execution of queries within custodians' environments. Users select RCT inclusion criteria, with results returned as aggregated counts subject to suppression of small numbers. Access is governed through the Five Safes framework, ensuring secure, ethical, and auditable use. The second service is a mechanism for determining trial eligibility using digital cognitive testing, questionnaires and a centralised plasma and DNA bank with secure database for re-contact. Participant recruitment will begin in early 2026. Participants will be recruited from cohorts and registries, initially targeting 10,000 65–75-year-old UK residents who have consented to re-contact. Recruitment will be by email through the parent cohort. Consent is staged: e-consent at collection of information (trial inclusion questionnaires and electronic cognitive test); confirmation of consent at in-person visits; and study-specific consent for subsequent trials. At a clinic visit, staff will verify identity, record weight and blood pressure, administer MMSE, and collect blood. Samples are processed within 2 hours, and plasma will be aliquoted, frozen, shipped cold-chain, stored at −80°C; and DNA extracted from whole blood at a central repository. Plasma p-tau217 and other biomarkers will be assayed centrally, including at the UK Dementia Research Institute (UK DRI) Biomarker Factory. Identifiers will be kept in a trusted research environment. Participants will receive feedback and continuing engagement from the DTA, and support from the Alzheimer's Society during the process. Access to the resource will be controlled by an access committee with patient/citizen involvement. The clinical trial, AD SMART, a multi-arm multistage platform trial in symptomatic dementia, will be a test of these services. The ultimate success of the DTA will depend on improving the speed of recruitment to UK clinical trials, as part of the wider RCT ecosystem. **Conclusions:** The DTA is a scalable participant-centred prescreening service designed to improve the speed and inclusiveness of recruitment to studies of dementia prevention and treatment, aiming to start in early 2026. The programme aims to reduce screen failure rates and costs for RCTs, broaden participation, and accelerate the evaluation and delivery of effective therapies. **Keywords:** Trial ready recruitment, cognitive screening, plasma biomarkers, dementia prevention.
Disclosures: SC is the Director of the UK DRI. AM is the Director of Health Data Research UK (HDR UK). IK has received honoraria for advisory or non-promotional medical educational roles to Novo Nordisk, Johnson and Johnson, Argenx, Biogen, Zylorion. He is a medical advisor to Oxford Brain Diagnostics (fees paid to Imperial College London), dementia health tech companies Prima Mente Five Lives, Paloma Health (remunerated with personal fees and stock options for all). HDR UK and UK DRI are working in partnership to deliver the DTA. Funded by the Medical Research Council (MRC), the DTA is supporting the Dame Barbara Windsor Dementia Goals programme.
Key takeaway message: The DTA will harness large UK health and

research datasets to identify large biomarker-eligible cohorts for trials in dementia treatment and prevention. We warmly welcome applications by industry and academic trialists to use this service.

P393- QSP MODEL FOR NEXT-GENERATION BRAINSHUTTLE ANTIBODIES.

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Background: Recently approved anti-amyloid monoclonal antibody (mAb) treatments for Alzheimer's disease (AD) have shown moderate slowing of disease progression; however, they also carry a risk of ARIA that has led to concerns about the risk-benefit trade-offs of treatment in some populations. These limitations have motivated research into improving the speed and degree of amyloid clearance to boost clinical benefit and reduce ARIA incidence. A new generation of drugs that leverage receptor-mediated transcytosis (RMT) to increase mAb transport across the blood brain barrier appear to be advantageous on both counts. The most advanced example of this class of drugs, trontinemab, showed extremely rapid amyloid clearance and very few cases of ARIA in phase Ib/IIa clinical trials. Following the recent announcement of the phase III trontinemab trial design, we aimed to develop a QSP model for brainshuttle antibodies that we use to simulate trontinemab treatment. **Methods:** Following our recent systematic review, we developed a QSP model for simulating anti-amyloid mAb treatments for AD with a focus on reproducibility and the provision of user-friendly code, having identified these as key limitations of existing models. We found that our original model, using a structure similar to other previously developed models, could capture treatment with previous generation mAbs, such as aducanumab, lecanemab, and gantenerumab, but was not well-suited to also modelling the new iterations leveraging RMT, namely trontinemab. We therefore adjusted our model to include a more realistic representation of plaque and plaque clearance to obtain a model capable of accurately representing the impact of both classes of drugs on amyloid plaque clearance. **Results:** We found that the way the structure and organisation of brain amyloid is represented in the model influences its ability to capture the effects of both classes of antibodies. Unlike previous models, we considered plaque as roughly spherical structures, such that only amyloid on the surface of plaque can be bound by antibodies, with those amyloid-antibody complexes then triggering clearance of both bound and unbound amyloid in plaque. Using our model, we simulated treatment with trontinemab at the phase Ib/IIa dose, predicting the large and rapid reduction in amyloid PET observed in the clinical trial. Based on these simulations, we predict the plasma to brain transport rate of trontinemab is approximately 50-fold faster than that of non-'brainshuttle' antibodies. This results in a brain:plasma ratio of ~10% for trontinemab in a simulated healthy individual compared to the ~0.1% brain:plasma ratio generally reached with mAbs that rely only on passive diffusion to enter the brain. **Conclusions:** By more accurately modelling the concentration of brain amyloid that is available for mAb binding, we were able to develop a model that captures the effects of treatment with first-generation antibodies, such as aducanumab and lecanemab, as well as the next-generation drugs with boosted shuttling across the brain, such as trontinemab. Using the model, we predict trontinemab brain exposures approximately 45x higher than those achieved with the same dose of lecanemab, a non-RMT mAb. Our simulations support the hypothesis that trontinemab's higher brain exposure drives its much greater efficacy with respect to amyloid clearance. Considering the specific organisation of amyloid in the brain will be important when developing QSP models for AD drugs with alternative mechanisms of action, such as donanemab's specificity for pyroglutamate-modified amyloid-beta.

Keywords: Quantitative systems pharmacology; receptor-mediated transcytosis; anti-amyloid monoclonal antibodies.

Disclosures: N.F., O.S., G.S., A.P., and J.W., are employees of AC Immune SA. N.S. was previously an employee of AC Immune SA. L.H. has recieved funding from AC Immune SA.

Key takeaway message: Using a QSP model with a more realistic representation of amyloid plaque, we captured differences between lecanemab and trontinemab treatment, estimating a brain exposure of trontinemab that is approximately 45-fold higher than that of lecanemab.

P394- VALIDATING A MULTI-DOMAIN DIGITAL ENDPOINT PLATFORM (NEULOGIQ) FOR DECENTRALIZED ALZHEIMER'S TRIALS: RESULTS FROM THE CNS-101 STUDY.

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Background: Current endpoints contribute to the high costs, long timelines and low success rates in trials of Alzheimer's Disease therapies. Common clinical outcomes, such as ADAS-Cog, lack granularity, are prone to variability in administration, and cannot be administered frequently or remotely. The NeuLogiq platform was developed with a consortium of ten large pharma companies to provide unified, multimodal quantitative assessments to accelerate therapy development in Alzheimer's disease and other neurodegenerative conditions. Individual assessments were selected to enable valid and repeated sampling and administration in clinic, or self-administered by patients at home, across 5 domains: cognition, neurophysiology, language, mood and sleep. The consortium co-designed the CNS-101 study to validate the platform with dementia patients on these criteria: 1. Technical robustness and remote deployment. 2. Patient usability. 3. Sensitivity to disease at baseline. 4. Sensitivity to disease progression. **Methods:** Fifty-nine mild dementia patients (mean age 73.8 yrs, ACE-III score 77.6) and sixty matched controls (mean age 71.1 yrs, ACE-III score 94.8) were recruited at 7 UK sites. After training in-clinic, participants were asked to use the system autonomously (assisted by a study partner if required) at-home repeatedly over the course of 1 year (46 behavioural/EEG sessions of ~25 minutes requested, alongside 23 sleep EEG sessions). ADAS-Cog-13, VPA, DSST and other benchmarks were administered in-clinic at months 0, 6, and 12. Plasma was collected to assess biomarker status. A Statistical Analysis Plan pre-identified 42 endpoints across the five domains as candidate markers of disease at baseline, and of longitudinal change. Change scores on conventional cognitive tests and digital endpoints were analyzed using linear mixed-effects models to estimate group-by-time interactions. Comparative sensitivity was visualized using volcano plots of effect size vs. statistical significance. In post-hoc analyses we examined endpoints for sensitivity to plasma markers, and evaluated the potential of NeuLogiq digital markers to streamline trial designs. Study scaling factors were applied to estimate what shorter duration of study, or smaller number of participants, was possible without compromising study power. Cost-saving projections were then grounded in typical CNS clinical trial costs, derived from DiMasi (2), with application to an illustrative phase 2 design in AD. **Results:** Ninety-seven participants completed the year-long study (patient withdrawals 27%, controls 10%). Patient adherence was 79% for wake EEG/behavioural sessions (>4700 sessions total), and 70% for sleep EEG (total >1500 sessions). Using the lower threshold (1) for ALZPATH ptau-217 (0.42pg/ml), 72% of patients and 45% of controls had positive AD pathology. In a cross-sectional analysis at baseline, using data from the first 5 at-home sessions, multiple endpoints reached significance, including symbol coding, associative visual memory, and resting theta-band EEG. In the longitudinal analysis two endpoints were significantly sensitive to progression: - Associative visual memory correctness (standardised β =-0.45, $p<0.001$), - Psychomotor speed reaction time (standardised β =

0.29, p<0.001) Three further endpoints were comparable to the ADAS-Cog-13 composite benchmark (standardised β = 0.197, p=0.02): - Picture description task information units. - Resting state EEG alpha band coherence.
- Resting state EEG beta band coherence. The associative memory task and the symbol coding executive function task were both sensitive to patients' p-tau217 pathology status. For the associate memory endpoint a 9 months study duration provided equal sensitivity to longitudinal change observed using ADAS-Cog over 12 months (a 25% reduction in patient burden). Correspondingly, 10.5 months duration (12.5% reduction) was required for the psychomotor speed endpoint. In terms of cohort size, a permutation analysis estimated that the associative memory and psychomotor speed tasks enabled designs with 50% or 40% reductions in patient numbers, respectively. Trial designs exploiting these efficiencies were drafted to illustrate the benefits of earlier statistical signal detection. Using costs levels from (2), a putative phase 2 study on AD with 270 patients participating for 18 months each, and lasting 3 years would cost $142.6m. Assuming early termination on futility, direct cost savings were projected between $67.9m and $85.7m (depending on balance between fixed and time-variable patient costs). **Conclusions:** The CNS-101 study demonstrates that the NeuLogiq platform is technically robust and can be deployed effectively across multiple sites and at home, with high levels of patient adherence on complex behavioural and neurophysiological protocols. Multiple domain-specific endpoints show sensitivity to clinical state at baseline, and to underlying Alzheimer's pathology. Multiple endpoints show similar or superior sensitivity to disease progression, relative to a registered endpoint. While digital measures of neurocognitive function are not yet FDA-approved as primary trial outcomes for efficacy, our results support their utility as early indicators of efficacy or futility in AD trials, offering significant efficiency gains in phase 2 trials. Composite endpoints including digital measures from multiple domains may provide further increases in sensitivity to disease severity and progression.
Keywords: Dementia, Alzheimer's disease, decentralised trials, tracking progression, at-home sampling.
Disclosures: BM, AB, LRD, SD, are all employees of Cumulus Neuroscience, and with addition of RMcK hold shares in the company.
References: 1. Ashton, Nicholas J., et al. «Diagnostic accuracy of a plasma phosphorylated tau 217 immunoassay for Alzheimer disease pathology.» JAMA neurology 81.3 (2024): 255-263. 2. DiMasi, Joseph A., et al. «Assessing the net financial benefits of employing digital endpoints in clinical trials.» Clinical and Translational Science 17.8 (2024): e13902.
Key takeaway message: The NeuLogiq platform enables remote, high-frequency digital assessments across five domains, demonstrating sensitivity to Alzheimer's progression and pathology, and offering substantial trial efficiency gains in duration, sample size, and cost for phase 2 studies.

P395- DOUBLE XPRESSO: REPEATED ONLINE PRESCREENING OF COGNITIVE IMPAIRMENT.

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Background: XpressO is self-administered cognitive prescreener developed by MoCA Cognition [1]. It was made available online in 2024. From the first 50,000 self-enrolled users 12,482 spontaneously completed two sessions or more. However, the online results suggested a self-selection bias: users with a lower initial XpressO test score were more likely to complete two sessions or more. To help interpret the online findings, we gathered test-retest data in a clinical and community setting. **Methods:** We recruited 88 patients and caregivers from the MoCA Clinic and a retirement home near Montreal. Each participant completed a paper MoCA test and two XpressO sessions on the same day. Participants were categorized as cognitively normal (CN) or having mild cognitive impairment (MCI) based on a MoCA total score with 25 and above being CN [2]. Results are characterized by the mean, standard deviation (SD), Spearman correlation coefficient (ρ) and the intraclass correlation coefficient (ICC). **Results:** Mean age was 71.8 (SD = 11.0), 54 female / 33 male, and 14.2 years of education (SD = 4.3), 41 CN / 47 MCI. The mean XpressO score in session 1 was 45.3 (SD = 34.4) and 57.0 (SD = 34.3) in session 2. We observed an association between the MoCA score and the first XpressO score ($\rho = 0.629$, $p < 0.001$) and second XpressO score ($\rho = 0.702$, $p < 0.001$). The correlation between the XpressO score in session 1 and 2 was ($\rho = 0.832$, $p < 0.001$) and the ICC was 0.753. We observed a practice effect, as participants showed an average 11.7 points (SD = 22.0) improvement between XpressO sessions. This practice effect was more pronounced in CN participants with a lower initial score (<50): an average increase of 28.6 points (SD = 24.1) as compared to MCI participants having an average increase of 13.9 (SD = 21.7). In participants with a higher initial score (>=50), we found a smaller practice effect: CN increased on average 5.91 points (SD = 13.5), while MCI participants showed an average decrease of -5.70 points (SD = 30.1). **Conclusions:** XpressO showed good test-retest reliability, despite a practice effect. Using parallel task versions, with different memory items and logical sequences, may further improve the test-retest reliability. Future studies will examine if the practice effect has clinical utility for the prognosis of cognitive decline and for screening preclinical stages of Alzheimer's disease.
Disclosures: The study was funded by MoCA Cognition. Authors WH, KP, JK, JG, MG and ZN are employees or consultants of MoCA Cognition. HAW contributed to this study in a personal capacity.
Key takeaway message: XpressO demonstrated good test-retest reliability, though a practice effect was observed—especially in cognitively normal individuals—highlighting its potential for prescreening early cognitive decline.

P396- ADHERENCE TO A MULTI-DOMAIN, PERSON-CENTERED, DEMENTIA RISK FACTOR MANAGEMENT INTERVENTION TO PREVENT COGNITIVE DECLINE (THE BETTERBRAINS TRIAL).

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Background: Modifying health behaviours to reduce dementia risk remains a significant public health challenge. Even in well-resourced multi-domain intervention trials, adherence to prescriptive lifestyle-based interventions remains very low (e.g., 19% in FINGER, 50% in MAPT, 34% in Maintain Your Brain) (1,2), threatening the validity, generalisability and translation potential of trial findings. Taking a personalised approach to risk factor management that considers an individual's specific risks, interests, and capabilities may help increase adherence, especially as dementia risk factors differ between individuals. This study reports the adherence to, and satisfaction with, an online person-centered dementia risk factor management program (BetterBrains) designed to prevent cognitive decline in community-dwelling, middle-aged adults with a family history of dementia. **Methods:** Between August 2021 and July 2023, 1,830 participants enrolled in BetterBrains and 1,053 were randomised (57%). Randomised participants were aged 59.7 (±6.8) years, 83% women, 90% had ≥12 years of education, 93% were White, and 86% reported a first-degree family history of dementia. The intervention arm (N=526) received online, telehealth-based, person-centered goal setting, motivational interviewing, and follow-up support, health care provider communication and community linkage to additional healthcare supports for management of known modifiable dementia risk factors over 12-months (3). Intervention adherence was assessed according to: (1) BetterBrains pre-specified adherence, defined as completion of $^{3}6$ telehealth coaching sessions, and (2) a commonly used criterion in

behavioural interventions of completion of ³66% of intervention activities, defined here as attending ≥4 of 6 telehealth coaching sessions. Participant satisfaction with the intervention, disengagement, and discontinuation rates are also described. **Results:** At final visit, 83% of participants adhered to the intervention according to the BetterBrains pre-specified adherence criterion, while 89% of participants met the more commonly used behavioural adherence criterion over the 12-months. On average, participants completed 7.0 (±2.6) telehealth coaching sessions (range=0-15), set 4.8 (±3.0) personalised goals to modify dementia risk (range=0-16), and achieved 3.3 (±2.4) goals (range=0-13). Almost all participants (95%) attended ≥1 telehealth coaching session and set ≥1 goal (96%) over 12-months. Disengagements were infrequent, with 86% of participants never rated as disengaged by their coach during the 12-month intervention phase. Few individuals (2.9%) discontinued participation. Results of the participant experience survey suggest that 97% reported satisfaction with their coach and 96% considered intervention information and resources as clear and accessible. Additional quantitative and qualitative results regarding intervention adherence, goal setting and achievement, and participant satisfaction will be presented in exclusivity at CTAD. **Conclusions:** High intervention adherence (~85%) and participant satisfaction suggests that the BetterBrains methodology is highly acceptable and tolerable. This methodology, including remote administration of the intervention and incorporating key techniques to elicit health behaviour change (e.g., motivational interviewing), represents a scalable and individualised approach to identifying and modifying dementia risk factors.

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Key takeaway message: The BetterBrains trial shows that a personalised, telehealth-delivered intervention can achieve high adherence in at-risk adults—supporting the feasibility of scalable, person-centred dementia prevention strategies.

P397- A HOLISTIC APPROACH FOR UNDERSTANDING ALZHEIMER'S DISEASE VIA WEARABLES, SPEECH, AND ECOA.

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and functional impairment. There are estimates that inform that the people impacted globally by the disease is around 416 million. While cognitive decline can be effectively measured and detected using traditional clinical outcome assessments such as the ADAS-Cog, as well as through digital cognitive assessments, the functional aspect of AD often necessitates assessment through objective measures derived from medical wearable sensors. Traditional assessment methods often rely on infrequent clinical visits and subjective evaluations, which may not capture the subtle, continuous changes associated with early AD progression. Digital cognitive assessments and cognitive screening tools that assess multiple cognitive domains are an important aspect to understand Alzheimer's disease. However, we also recognize that changes in mobility, sleep patterns, and overall real-world behavior are crucial for understanding how individuals «EXPERIENCE» Alzheimer's disease and its impact on their daily lives. The analysis from these multiple sources of information (cognitive, behavioral, and physiological) can significantly contribute to early detection and continuous monitoring, which are crucial for timely intervention, disease management, and enhancing clinical trial efficacy. Here, we present a novel, integrated digital platform that enables objective, remote, and scalable data capture of sensor-derived mobility algorithms, quality of life(QoL) data, and speech algorithms that complement the subjective data captured through eCOA technology, deriving a more comprehensive understanding of an individual's health status in their AD progression.

Key takeaway message: Continuous Real-World Monitoring: Collecting data outside clinics gives a more realistic view about how patients experience Alzheimer's and the impact of treatment. Synergistic Data Integration: Combining multiple sources of medical information offers richer understanding of Alzheimer's, discovering novel biomarkers and accurately tracking progression and treatment. AI-Powered Predictive Insights: AI analyzes complex data for subtle patterns, enabling early Alzheimer's risk identification, improved trial recruitment, and proactive interventions.

P398- IMPACT OF TELEMEDICINE ON TIME AND PROCESS MEASURES ASSOCIATED WITH DETECTION AND DIAGNOSIS OF ALZHEIMER'S DISEASE.

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Background: Alzheimer's disease (AD) is the leading cause of dementia and is the 7th leading cause of death in the US (1). It is estimated that approximately 7 million people in the US have AD dementia, and an additional 5 to 7 million people have mild cognitive impairment (MCI) due to AD (2). By 2050, the incidence of AD in the US is projected to double (3). In parallel to this increasing demand, there remain numerous challenges in identifying these patients and making a diagnosis of AD early in the course of the disease so that patients can more quickly take action or intervene in the disease progression. Clinicians and people living with AD have expressed the need to increase our capacity to diagnose and manage this population (1). Many patients, especially those living in remote and underserved areas, face prolonged wait times to be evaluated by a specialist (4,5). Additionally, nearly 1 in 5 Medicare beneficiaries drive more than 50 miles each way to see a neurologist (6). As a result, it can take more than 2 years after the onset of symptoms for a patient to be appropriately diagnosed with AD (7). Early detection is critical to help patients and families manage the complications of this disease and allows for better planning and resource management and improves the prognosis of patients. Once individuals progress to moderate or severe dementia, treatment options are more limited, and patients experience greater dependence on others (1,8). These factors point to the need for novel programs, including care delivery models that support earlier detection and diagnosis of AD, which in turn can support effective and efficient AD management (1). Telemedicine is a promising option for patients to initiate a conversation about cognitive changes or concerns and to seek appropriate evaluation and care for their memory and thinking issues. Telemedicine has demonstrated safety, efficacy, and cost-effectiveness, along with patient and provider satisfaction in numerous therapeutic areas including stroke, Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and cognitive dysfunction [9,10]. While evidence supports the need, feasibility, and acceptability among patients, care partners, and healthcare professionals, (HCP), the full potential of telemedicine in cognitive disorders remains underutilized. LillyDirect® is a freely accessible digital healthcare experience for patients in the US who have certain chronic conditions. In March 2025, Eli Lilly and Company expanded LillyDirect® to offer connection an independent telehealth provider specializing in neurodegenerative care (11). Its offerings include live video visits, 24-hour access when needed, ongoing medication and care management, and behavioral health and lifestyle support. Their virtual care model

helps patients and families access independent specialty care for neurodegenerative conditions including but not limited to AD. The goal of this virtual care model in AD is to more quickly connect patients to expert neurologists to conduct cognitive and neurologic assessments and subsequently support a timely and accurate diagnosis as well as facilitate longitudinal care plans for the patient. **Methods:** A literature search was conducted to assess factors that should be considered in evaluation of a telemedicine program. The MeSH terms Health Impact Assessment/Patient Outcome Assessment/Treatment Outcome/Outcome Assessment (Health Care) were combined with telemedicine and with the following disease states independently: PD, stroke, ALS, dementia, and cognitive dysfunction. The studies were filtered to include case reports, clinical studies, clinical trials, comparative studies, controlled clinical trials, equivalence trials, evaluation studies, multicenter studies, observational studies, and randomized controlled trials, all published in English between 2010 and 2025. The LillyDirect® expansion to include Alzheimer's disease support was announced on March 27th, 2025 (11). We aim to report on the descriptive performance metrics from the first 5 months of implementation (April – September 2025) that will provide insight to the impact and potential hypothesis generation regarding the utility of telehealth on patient engagement, evaluation, and diagnosis of cognitive disorders and will compare these performance metrics with benchmarks from the literature. **Results:** This PubMed search strategy returned 291 studies, among which 16 were related to PD, 190 to stroke, four to ALS, 58 to dementia, and 23 to cognitive dysfunction. Performance metrics we intend to report on and consistent with the literature in this space include descriptive patient demographics, as well as patient/caregiver initiation, engagement, and retention as indicated by the number of patients who complete sign-up/register, complete intake discussions, complete a synchronous video call with a HCP, and the number of patients who follow up with testing and with a second video call. We will also report on time-based conversion metrics to include time to visits, time to evaluations, and time to actions (e.g. testing) taken. Diagnostics and diagnosis data reported will include clinical testing data, neuroimaging data, laboratory tests, and genetic testing, the numbers of patients receiving a diagnosis of AD, and time and number of visits to arrive at a diagnosis. **Conclusions:** Conclusions are pending completion of data collection and the planned analyses.

Keywords: Alzheimer's disease, telemedicine, telehealth, dementia.

Disclosures: EGK, CP, JG, A, BV, and JB are employees of Eli Lilly and Company, and may own Lilly stock. ERA is an employee of Synapticure.

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Key takeaway message: Key takeaway message will be provided once data collection and planned analyses are completed.

P399- A DIGITAL OLFACTORY BIOMARKER PLATFORM FOR PROGNOSTIC ENRICHMENT OF NEURODEGENERATION.

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Background: Blood-based biomarkers for Alzheimer's disease, such as pTau217, are being approved for clinical use and are gaining wider adoption. These biomarkers can detect preclinical (asymptomatic) AD, a stage where therapeutic intervention may have the highest likelihood of disease modification. However, their cost, infrastructure requirements, and limited laboratory capacity pose significant barriers to implementation in low- and middle-income countries (LMICs). To ensure equitable and cost-effective deployment of blood-based diagnostics, a scalable triaging strategy is essential to prioritize individuals most likely to benefit from confirmatory biomarker testing. Olfactory dysfunction is one of the earliest and most consistent prodromal features of neurodegenerative diseases, including Alzheimer's and Parkinson's disease. Despite its diagnostic value, traditional olfactory tests such as UPSIT and Sniffin' Sticks require manual administration, are resource-intensive, and have limited cultural adaptability. To address this, the Davos Alzheimer's Collaborative (DAC) Global Cohorts Program is piloting digital olfactory assessment in Egypt and Kenya. These studies aim to validate a low-cost, scalable, and culturally adaptable digital olfaction tool for use in resource-constrained environments. **Methods:** The Davos Alzheimer's Collaborative (DAC) Global Cohorts Program (GCP) is a global initiative aimed at diversifying Alzheimer's disease (AD) research and enhancing early detection, prevention, and treatment strategies. The ScentAware Digital Olfactory test is being piloted in three DAC GCPs: Egypt, Kenya and India. In Egypt, as part of the North African Dementia Registry (NADR), adults aged 55–85 were assessed with the ScentAware digital olfactory test and Egyptian HCAP memory domain. AD-DETECT-Kenya study aims to discover, optimize, standardize, and validate measures and biomarkers specifically for dementia research in Kenya. ScentAware olfactory test consists of 16 culturally familiar odors delivered via inhaler tubes labeled with QR codes and self-administered using a mobile interface. **Results:** Healthy controls' scores were normally distributed (mean=8.95, SD=2.95), with highest accuracy for coffee (86%) and garlic (80%), and lowest for smoke (30%) and orange (36%). Internal consistency was acceptable (α=0.71). Scores positively correlated with education level (rho=0.58; $p<0.001$) and negatively with age (r=-0.53; $p<0.05$). The intra-rater reliability showed 75% agreement on peppermint identification (Cohen's $\kappa = 0.44$). The test duration averaged 7 minutes. Clinically diagnosed AD participants scored lower (0–8, mean=5.2, SD=2.8). ROC analysis determined that an optimal cut-off score of 8 with sensitivity of 94% and specificity of 67%. Both participants and providers rated the tool highly for scalability, adaptability, and ease of use. Among cognitively normal individuals 40% had olfactory impairment, 28% had memory impairment, and 20% showed deficits in both. At-risk individuals show worse olfactory function than their low-risk peers with a gradient in memory deficits, highlighting early sensory deficits before detectable cognitive decline. These findings indicate a partial but clinically meaningful overlap between olfactory and cognitive impairment in a cognitively normal population. **Conclusions:** Preliminary findings indicate that the digital olfactory test has acceptable psychometric properties in healthy controls, while AD patients score significantly lower. Use of olfactory function testing through digital technology is practical, scalable, and biologically grounded triage framework for early AD risk stratification

and offers a promising pathway for triaging for confirmatory diagnostics.

Keywords: Olfaction, digital health, triage, prognostic enrichment.

Disclosures: SM and FW are founders of Sensify Inc which developed the ScentAware digital olfactory test. Other authors have no conflicts of interest to declare.

Key takeaway message: Digital olfactory testing in at-risk individuals shows promise as a scalable, low-cost screening tool for early Alzheimer's detection in resource-limited settings, potentially triaging patients for expensive blood biomarker confirmation.

P400- TECHNOLOGY AND HUMAN SUPPORT: A COMBINED APPROACH TO IMPROVING QUALITY OF LIFE IN OLDER ADULTS LIVING AT HOME WITH COGNITIVE IMPAIRMENTS.

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Background: Cognitive impairments affect approximately 23.7% of older adults and represent a major public health challenge in aging populations (1). Although disease-modifying treatments for dementia are emerging, no pharmacological therapy currently addresses cognitive frailty. Preventive strategies have been implemented worldwide, relying on either technology-based interventions or human support. However, the impact of a combined approach, integrating both technology and human support, on cognitive impairments remains unexplored. Furthermore, 77% of older adults wish to remain at home for as long as possible while maintaining good quality of life (2). **Methods:** This ongoing longitudinal cohort study is conducted among community-dwelling older adults (aged >60 years) in three departments in France. Two departments implemented a combined intervention consisting of technology and human support, while the third offered either a single intervention (technology or human support) or none. The technological interventions were grouped into three packs: (1) fall prevention (lighted pathways, teleassistance), (2) cognitive stimulation (tablet-based interactive memory games), and (3) social engagement (video calls via tablet and social visits). These interventions were delivered by trained caregivers with expertise in gerontology, gerontechnology, and aging, who installed equipment, trained participants, and provided ongoing support as needed (3). Cognitive impairments were screened using Step 1 of the ICOPE (Integrated Care for Older People) program, cognitive domain (4). Data were collected via telephone interviews by a study coordinator within the VIVADOM project, with assessments performed every six months. **Results:** A total of 202 older adults were included (mean age 85.0 ± 4.5 years; 79.2% women). Cognitive impairment was identified in 69 participants (34.2%), of whom 72.5% were women. At baseline, 24 participants (34.8%) received the combined intervention, while 45 (65.2%) did not. The groups were comparable in terms of age, Activities of Daily Living (ADL), and overall perceived health, but differed significantly in Instrumental Activities of Daily Living (IADL), favoring the intervention group ($p = 0.006$). After six months, 11 participants (47.8%) remained in the combined intervention group and 20 (51%) in the control group. No significant differences were observed in ADL or IADL outcomes. However, perceived health was significantly higher in the intervention group (mean 69.54 ± 11.93) compared with the control group (mean 54.74 ± 11.93; $p = 0.004$). **Conclusions:** Screening using the ICOPE program indicates that approximately half of the patients with an initial alert at baseline remain impaired at six months. The combination of technological tools and human support appears to improve perceived health among older adults with cognitive impairments. Ongoing follow-up at 12 and 18 months will determine whether these benefits are sustained over time and whether they also translate into improvements in (IADL).

Keywords: Cognitive impairments, technology-based interventions, human support, quality of life, aging.

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Conflict of interest: The authors declare no conflicts of interest.

Study registration: VIVADOM study registered on the French Health Data Hub (N° F20220214102025).

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Key takeaway message: Combined intervention consisting of technology and human support is associated with significantly better perceived health among cognitively impaired older adults living at home, compared to single or no interventions ($p = 0.004$).

P401- ASSESSING THE VALIDITY OF THE MIND GAMEPACK: A NOVEL DIGITAL HEALTH TECHNOLOGY (DHT) FOR THE COLLECTION OF SUPPLEMENTARY COGNITIVE DATA USING GAMES.

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Background: Many efforts have been made to adapt neuropsychological assessments to digital platforms for easier and more frequent measurement of cognitive functioning. However, these still require a participant's concerted effort and can be tiresome for those with cognitive impairment. Moreover, compliance in home settings is often poor and reliability of measurements is uncertain. To address these limitations, we took a converse approach by "cognifying" familiar and enjoyable games for tablet play to capture semi-passive neurocognitive data. The MIND GamePack© is an iPadOS application suite of four familiar games developed in house. Participants are instructed to play these games on a study issued device, where a cloud-based architecture supports off-prem data collection. Previous research on the MIND GamePack© has demonstrated both feasibility and proof of concept in a cohort of older adults without cognitive impairment (1). The current study provides a comprehensive evaluation of the MIND GamePack©'s adherence, validity, reliability, and effectiveness in differentiating cognitive status through both three and six months of gameplay. **Methods:** The MIND GamePack© includes four iPadOS games: Memory Match (pair matching), Word Scramble (Boggle), FreeCell (Solitaire), and Block Drop (Tetris). Sixty participants participated in the study: 37 cognitively normal (CN) with either no cognitive complaints (NCC, n=26), or with subjective cognitive complaints (SCD, n=11), and 23 cognitively impaired (CI) with either mild cognitive impairment (MCI, n=15) or mild dementia (MD, n=8). NCC participants engaged with the MIND GamePack© over the course of 3 months, while SCD, MCI, and MD participants engaged with the MIND GamePack© over the course of 6 months. In all cohorts, participants were instructed to play each game for a minimum of five minutes/day, five days/week. Compliance was assessed using each participant's median weekly gameplay time. Game features were generated to assess game specific performance, such as within-session match accuracy in Memory Match (Normalized Accuracy), total score in Word Scramble (Total Score), total lines 'Hard Drop' moves in Block Drop (Hard Drop Count), and valid moves for sorting cards in FreeCell (Normalized Valid Move Rate). Ten game features selected across four games were chosen to serve as target digital biomarkers for validation against neuropsychological tests. Spearman's correlation was used to validate digital biomarkers against the Montreal

Cognitive Assessment (MoCA), specific indices of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and the Trail Making Test (TMT). Ten gameplay features summarized from two weeks of gameplay were analyzed across cohorts using Wilcoxon rank sum test to examine group differences across game features. Intra-class coefficients (ICCs) were utilized to assess test-retest reliability. The predictive capabilities of the MIND GamePack© were assessed using mixed models for repeated measures (MMRMs) to compare changes in game features from baseline to three (NCC) and six (SCD, MCI, MD) months. **Results:** NCC participants achieved a median compliance of 165 minutes per week [Q1, Q3 = 140, 252], while SCD, MCI, and MD achieved median compliance of 210 minutes per week [Q1, Q3 = 171, 387]. Normalized Accuracy (Memory Match) displays high correlation with RBANs Immediate & Delayed Memory Indices [r = 0.60 to 0.75] and MoCA [r = 0.69]. Hard Drop Count (Block Drop) displays similarly high associations with TMT A & B [r = -0.61 to -0.71] and Total Score (Word Scramble) yielded moderate association with RBANs Language Index [r = 0.5]. Normalized Valid Move Rate (FreeCell) displayed moderate correlation with RBANS Delayed Memory Index [r = 0.54]. All game features yielded good to excellent reliability (ICCs = 0.85-0.95) when analyzed across the first two weeks of data. Nine of ten features differentiated normal cognition [NCC/SCD] from impairment [MCI/MD], with CI participants displaying worse median game performance on Normalized Accuracy (Memory Match) [CI = -1.25 (-1.83, -0.48), CN = -0.17 (-0.52, 0.16); p <.001], Normalized Valid Move Rate (FreeCell) [CI = -1.06 (-1.42, -0.57), CN = -0.01 (-0.64, 0.45); p <.001], and Hard Drop Count (Block Drop) [CI = 27 (10.25, 37), CN = 37 (-29, 46); p = .012] compared to participants with NCC and SCD. **Conclusions:** Participant compliance measured greater than 150% in all cohorts, suggesting the MIND GamePack© may serve as an engaging user-driven platform. Game features associated with Memory Match yielded high construct validity with memory and learning domains of the RBANs. The MIND GamePack© requires two weeks of gameplay to achieve good to excellent test-retest reliability for most game features but may require as little as one day for specific game features to achieve excellent reliability, such as Hard Drop Count (Block Drop) (ICC = 0.87). Game features effectively differentiate CN from CI individuals over two weeks of data with digital biomarkers highlighting differences in memory, language, and executive function. Gamified assessments can be incorporated into clinical trials to facilitate screening, track performance over time and may be sensitive measures of cognitive stability, decline or treatment response.

Reference: 1. Schwab N, Wu CY, Galler J, et al. Feasibility of common, enjoyable game play for assessing daily cognitive functioning in older adults. Front Neurol. 2023;14:1258216. doi:10.3389/fneur.2023.1258216.

Key takeaway message: The MIND GamePack© is a unique digital health technology (DHT) that uses games to assess cognitive function and may provide reliable, engaging, and validated supplementary cognitive data.

P402- ASSOCIATION OF LINGUISTIC AND ACOUSTIC DIGITAL LANGUAGE MARKERS WITH CSF BIOMARKERS OF ALZHEIMER'S DISEASE.

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Background: The number of individuals with Alzheimer's Disease (AD) and related dementia is increasing. This highlights the necessity of developing deep-learning-based diagnostic tools that are accessible, scalable, and more efficient for deployment in clinical settings (1). Spontaneous speech analysis is a prime example of such accessible and scalable tools. While prior studies have shown that changes in speech patterns can differentiate between cognitively impaired and healthy control participants, there remains a critical need to validate these digital markers against the biological changes of AD and dementia. In this study, we examined how specific linguistic and acoustic markers of spontaneous speech relate to CSF phosphorylated tau (p-tau), total tau (t-tau), and Amyloid beta (Aβ42). Understanding how specific speech features and established cerebrospinal fluid (CSF) biomarkers of AD pathology (p-tau, t-tau, and Aβ42) are associated is essential for developing more reliable and generalized diagnostic technologies using digital markers that have more predictive power (2,3). **Methods:** To conduct this study, speech recordings from semi-structured interviews were obtained from 85 participants enrolled in the Alzheimer's Disease Research Center (ADRC) at the University of California, Irvine. The cohort included cognitively unimpaired individuals (n=68), those with a clinical diagnosis of Alzheimer's type dementia (n=10), and those who were diagnosed with mild cognitive impairment (MCI) (n=7). Audio samples were semi-automatically processed using Audacity software to isolate the participant's speech from the interviewer's sound and to remove background noise by using the participant's voice profile over the whole data sequence in each sample. The processed audio samples were then subjected to a feature extraction process. For the linguistic analysis (4), audio was transcribed manually, and the transcriptions were validated for accuracy. Linguistic features, including Vocabulary Richness, Language Errors, Sentiment Score, Speech Rate, Average Word Length, Average Sentence Length, Syntactic Complexity, and Semantic Coherence, were extracted using SpaCy and VADER natural language processing models that would analyze the language Grammar and Sentiment. For the acoustic analysis[5], Root Mean Square Energy (RMSE), Harmonics-to-Noise Ratio (HNR), Formants, Mel-Frequency Cepstral Coefficients (MFCCs), Mel Spectrogram, Spectral Centroid, and Speech Rate were extracted using the Librosa library to capture characteristics of loudness, voice quality, and intonation. All extracted features were normalized, and a series of linear regression models was used to study the association between each of the linguistic and acoustic markers and the three primary CSF biomarker outcomes: p-tau, t-tau, and the p-tau/Aβ42 ratio. **Results:** The study included 85 participants (68 Normal, 7 MCI, 10 AD) with a mean age of 76.1 ± 7.8 years, mostly female (57/28), and an average education of 16.7 ± 2.0 years. Our analysis [SS1] [PM2] revealed significant associations between both acoustic and linguistic features and the CSF biomarkers of AD pathology in both male and female cohorts. For the acoustic markers, several features demonstrated associations with the mentioned biomarkers. Formants (a measure of vowel measurement) and Mel Spectrogram (a representation of spectral power) were significantly associated with all three CSF measures: p-tau (p=0.001 and p=0.022, respectively), t-tau (p=0.001 and p=0.016, respectively), and the p-tau/Aβ42 ratio (p=0.001 and p=0.010, respectively). RMSE (energy) showed significant associations with p-tau (p=0.016), t-tau (p=0.013), and the p-tau/Aβ42 ratio (p=0.005). Other features, including Speech Rate, Spectral Centroid, and MFCCs, also showed significant associations with at least one of the CSF biomarkers. For the linguistic markers, Average Word Length showed significant association with p-tau (p<0.0001), t-tau (p<0.0001), and the p-tau/Aβ42 ratio (p<0.0001). This indicates that by the progression of AD, individuals would use shorter, less complex words in their speech. Furthermore, Sentiment Score (p=0.039) was also significantly associated with the p-tau/Aβ42 ratio, suggesting that changes in emotional tone are linked to the biomarkers of AD. **Conclusions:** This study demonstrates that both acoustic features (e.g., RMSE, Formants, and Mel Spectrogram) and linguistic digital markers (e.g., Average Word Length) from spontaneous speech had significant associations with all three CSF biomarkers of AD. These results provide a strong foundation for the development of multi-modal deep learning-based models that can integrate these features to create a two-sided

model using combined acoustic and linguistic digital markers for the early detection of Alzheimer's Disease. **Keywords:** Artificial Intelligence, digital markers, CSF biomarkers, association analysis.
Date Deposition: Data is in possession of Alzheimer's Disease Research Center (ADRC) at UCI MIND.
Disclosures: This Study was supported by UCI Institute for Memory Impairments and Neurological Disorders Grant (IRPA-01-2024), NIH National Institute of Aging (NIA) TITAN T32 Grant (AG073088), and UCI ADRC Grant (P30 AG066519).
Declaration of generative AI and AI-assisted technologies in the writing process: During the preparation of this work, the author(s) used ChatGPT (GPT 5) to improve the text readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.
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Key takeaway message: The acoustic and linguistic digital markers showed associations with CSF biomarkers, which assist in the development of Alzheimer's Disease detection using deep learning models.

P403- FEDERATED DATA PILOTS FOR INTERNATIONAL COLLABORATION IN ALZHEIMER'S DISEASE AND DEMENTIA RESEARCH.

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Background: Access to comprehensive health imaging and linked electronic health record datasets is essential for advancing dementia research; however, cross-border collaboration is constrained by legal, ethical, and technical barriers. The Alzheimer's Disease (AD) Data Initiative Data Pilots enabled secure federated access to UK brain and retinal datasets, supporting international research to improve early diagnosis, risk prediction, and treatment strategies in Alzheimer's disease and dementia. **Methods:** Over two years, the programme piloted the AD Workbench, a global Trusted Research Environment (TRE), and the Federated Data Sharing Appliance to allow authorised UK and international researchers to perform federated analyses on pseudonymised datasets. Participating datasets included the Brain Health Data Pilot at Public Health Scotland and the Dementia Dataset, featuring AlzEye, at Moorfields Eye Hospital. Researchers accessed dedicated workspaces, executed remote federated queries via the Federated Query Builder Tool, and submitted outputs for comprehensive verification under the Five Safes Framework (Safe People, Safe Data, Safe Projects, Safe Settings, and Safe Outputs). **Results:** The pilots facilitated secure cross-border access to brain and retinal data, enabling foundation model development and analyses of brain age from CT and MRI scans, as well as AI-derived retinal biomarkers and evaluation of interocular asymmetry in dementia subtypes. A pilot study site involved collaboration with researchers at Stanford University to access Moorfields Dementia Dataset, featuring AlzEye, to examine the association between herpes zoster vaccination and dementia risk using retinal biomarkers. Federated queries preserved data privacy while supporting collaborative discovery. The studies demonstrated improved research readiness, enhanced accessibility of high-quality datasets, and identification of potential early predictors of dementia onset. **Conclusions:** The AD Data Initiative Data Pilots provide a scalable, secure model for international collaboration in dementia research. Federated TRE based approaches accelerated data driven insights while maintaining legal and ethical compliance. Integration of TREs, federated tools, and multi stakeholder governance proved essential for advancing global brain health research.
Disclosures: This work is funded by the Alzheimer's Disease Data Initiative and convened by Health Data Research UK. The referenced projects use data provided by patients and collected as part of their care and support by Public Health Scotland and Moorfields Eye Hospital NHS Foundation Trust. The authors wish to recognise these patients for their contribution of the data that made these research projects possible. The authors declared no competing interests.
Keywords: Alzheimer's disease, federated data sharing, trusted research environment, early diagnosis.
Key takeaway message: The AD Data Initiative Data Pilots demonstrate secure, federated access to UK brain and retinal datasets, enabling international collaboration, AI discovery, and early dementia predictor research while preserving privacy, compliance, and research readiness across borders.

P404- PROTOCOL FOR SUPERBRAIN-BOOM TRIAL: A MULTICENTER, RANDOMIZED CONTROLLED FEASIBILITY STUDY ON SOUTH KOREAN STUDY TO PREVENT COGNITIVE IMPAIRMENT AND PROTECT BRAIN HEATH VIA BEHAVIORAL, OPTIMIZED, ORGANIZED MOVEMENT THERAPY IN MILD COGNITIVE IMPAIRMENT.

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Background and Objectives: The South Korean Study to PrEvent Cognitive ImpaiRment and Protect Brain Health through Lifestyle Intervention (SUPERBRAIN) demonstrated the feasibility of a multidomain lifestyle intervention, which targeted vascular risk, cognitive training, physical activity, nutrition, and motivation. However, the original intervention faced challenges in scalability due to its high resource demands and insufficient personalization. To address these challenges, SUPERBRAIN-BOOM, a mobile application that expands the SUPERBRAIN research, was created. The «BOOM» acronym represents Behavioral, Optimized, and Organized Movement therapy, a treatment consisting of choreographed dance and nutritional education with mindfulness meditation. We designed a multicenter, randomized controlled feasibility trial to assess the acceptability, adherence, and initial effectiveness of SUPERBRAIN-BOOM in older adults diagnosed with mild cognitive impairment (MCI). **Methods:** The 12-week pilot trial aims to recruit 45 participants between 50 and 85 years of age who have been diagnosed with MCI and meet one or more modifiable risk factors for dementia. Participants will be allocated randomly in a 1:1:1 ratio to either a control group, a tablet-based intervention group, or a smartphone-based intervention group. The intervention is structured into four 3-week cycles, each comprising 30-minute daily sessions. These sessions include 20 minutes of choreographed dance and 10 minutes dedicated to combined nutritional education and mindfulness meditation, with personalization achieved through a stratification algorithm founded on baseline physical fitness, vascular risk factors, and cognitive status. Key primary outcomes for this study are participant retention, adherence to the intervention (defined as $\geq$70% completion), and changes in cognitive function. Secondary outcomes will encompass

changes in physical fitness, nutritional status, vascular risk factors, mood, quality of life, and motivational levels. **Results:** Recruitment and data collection are currently underway, with interim results analysis expected to be completed by November of this year. We expect to observe high compliance rates with favorable trends in both cognitive and physical outcomes. **Conclusions:** This study is expected to provide valuable insights into creating a scalable digital dementia prevention program targeting at-risk older adults.

Keywords: Mild cognitive impairment, dementia prevention, digital therapeutics, feasibility trial, mobile dance intervention.

Disclosures: This work was supported by the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare and the Ministry of Science and ICT, Republic of Korea [grant number RS-2024-00337993]. The authors have no potential conflicts of interest to disclose.

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Key takeaway message: SUPERBRAIN-BOOM is a mobile-based, personalized intervention consisting of choreographed dance, and nutritional education combined with mindfulness meditation for MCI elderly, aiming for proven efficacy via RCTs as a digital therapeutic for dementia prevention.

P405- IN-AIR-TIME DURING DRAWING TESTS AS A POTENTIAL PREDICTOR OF AMYLOID POSITIVITY IN MILD COGNITIVE IMPAIRMENT PATIENTS.

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Introduction: Mild Cognitive Impairment (MCI) patients transit to dementia state at an accelerated annual rate of 10-15%, significantly higher than the general population whose annual dementia incidence is 1-2%. However, not all MCI patients would progress to dementia, and the risk of progression varies depending on the underlying causes. Therefore, early identification of MCI patients with a high probability of progression is essential. Amyloid positron emission tomography (PET) positivity shows definitely increased risk of transit to Alzheimer's dementia, because of its high cost and accessibility, it is not available to all MCI patient. Previous studies showed that digital assessments using digital pen demonstrated more sensitive and low cost in detecting Mild Cognitive Impairment (MCI) because of their ability to capture nuances related to the drawing process that may remain latent in the test outcomes. In this study, we aimed to compare subtle differences related to the drawing process between amyloid-negative and amyloid-positive MCI. **Methods:** MCI patients who met the criteria proposed by Peterson and colleagues were selected from those who visited the Memory Disorder Clinic at Jeonbuk National University Hospital in Jeonju, Korea, between July 1, 2021, and December 30, 2023. All Participants performed the simplified RCFT using digital pen on a tablet in portrait orientation as reported in our previous research. We measured the following variables during the test: total time taken for the test (total time), number of digital pen strokes (number of strokes), the sum of time intervals during which the digital pen was in contact with the tablet surface while drawing (on-surface-time), and the sum of time intervals during which the digital pen was in the air between strokes (in-air-time). We selected the first in-air-time from the rest, labeling it as «initial-in-air-time,» while the others were referred to as «in-air-time» because the first time-gap represents the time spent conceptualizing before actually beginning the drawing, making it distinct from the remaining time gaps. We also computed the «on-surface-time (%)» and «in-air-time(%)» using the following formulas: {On-surface-time/Total time} *100(%); {In-air-time/Total time} *100(%). **Results:** In the simplified RCFT, the median number of strokes in aMCI(-) and aMCI(+) were 23 and 24, respectively. Number of strokes did not show a significant difference between aMCI(-) and aMCI(+) patients. In terms of duration, aMCI(+) patients showed significantly greater in-air-time (sec) ($U=443$, $p = 0.008$) and in-air-time (%) ($U=411$, $p = 0.044$) compared to aMCI(-) patients. However, initial in-air-time was not significantly different aMCI(-) and aMCI(+) patients. On-surface-time (sec) and on-surface-time (%) were not significantly different between aMCI(-) and aMCI(+) patients. **Discussion:** Our results suggested that the in-air-time during the performance of simplified RCFT may have the potential to predict amyloid positivity in MCI patients.

Key takeaway message: In-air-time during simplified figure drawing may serve as a potential digital biomarker to distinguish amyloid-positive from amyloid-negative MCI patients, aiding early detection of high-risk dementia progression.

P406- REAL-WORLD CARE OF ALZHEIMER'S DISEASE PATIENTS (N=2,358) IN GERMANY: INSIGHTS FROM REGISTRY OF THE NEUROLOGISTS NETWORK NEUROTRANSDATA (NTD) USING THE PHYSICIAN/PATIENT PLATFORM (DESTINY).

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Background: Dementia affects approximately 1.7 million people in Germany, rising to an estimated 3.3 million by 2060 (1). Alzheimer's disease (AD) is the most common subtype, characterized by progressive cognitive decline across memory, orientation, language, and function (DZNE, 2024). In the EU (including Germany), only Lecanemab (Leqembi) is approved for amyloid-lowering Alzheimer's treatment. Aducanumab (Aduhelm) and donanemab (Kisunla) are not authorized in the EU. In other regions—such as the United States—both aducanumab and donanemab have approvals in addition to Lecanemab (2). In routine German practice, evaluations for mild cognitive impairment (MCI) and early AD combine standardized cognitive tests (e.g., MMST, MoCA), structural imaging (MRI or CT), and, selectively, cerebrospinal fluid (CSF) biomarkers via lumbar puncture (LP), as well as ApoE genotyping. However, real-world data detailing these diagnostic processes and treatment patterns across cognitive stages remain sparse. This study uses the NeuroTransData (NTD) registry to characterize early AD patient demographics, diagnostic pathways, CSF biomarker utilization, and medication patterns in a multicenter German cohort (3,4). **Methods:** We retrospectively analyzed anonymized data from patients with MCI due to AD or mild AD dementia (ICD-10 F00/G30) across 42 practices (September 1998–April 2025). It's worth mentioning that of approximately 16,162 ICD F00/G 30 patients with dementia, 2,358 patients are evaluated from our registry. Patients were grouped by first MMST score: < 16 ($n = 325$), 16–25 ($n = 1,065$), and ≥ 26 ($n = 396$). Extracted data included age, gender, cognitive tests (MMST, MoCA, DemTect, CERAD), imaging modality (MRI/CT), LP usage with CSF biomarkers (p-tau, total tau, Aβ42), and antidementia medications (Donepezil, Rivastigmine, Galantamine, Memantine, Ginkgo). All diagnoses relied on imaging and/or testing; purely clinical diagnoses did not occur. Data were sourced from DESTINY, supplemented by Practice Management System (PMS). Descriptive analyses included age by MMST, gender, and medication use. **Results:** Sample Size and Distribution: Of 2,358 patients, 396 (16.8 %) had MMST ≥ 26 (MCI), 1,065 (45.2 %) had $16 \leq$ MMST < 26 (mild/moderate dementia), and 325 (13.8 %) had MMST < 16

(severe dementia). MMST scores were missing for 572 (24.3 %) of registry entries.Age Distribution: Overall mean age was 82.5 years (range 44–100). Group means: MMST < 16, 79.7 years (58–95); 16 ≤ MMST < 26, 78.3 years (52–100); MMST ≥ 26, 75.2 years (44–94). Among males (n = 1,016), mean age was 81.1 years (44–97); among females (n = 1,342), 83.6 years (48–100). Gender Distribution: Female patients comprised 56.9 % (n = 1,342); male patients comprised 43.1 % (n = 1,016). Diagnostic Practices: All 2,358 diagnoses used imaging (MRI/CT) plus neuropsychological testing; none relied solely on clinical evaluation. Documented MRI sequences included T1, T2, rarely FLAIR, and DWI. LP data were scarce in DESTINY (15 p-tau, 15 total tau, 17 Aβ42), as most CSF results resided in PMS. ApoE ε4 genotyping occurred mainly in privately insured patients, with exact counts unspecified. Medication Patterns: Of 2,358 patients, 1,715 (72.7 %) received at least one antidementia medication. Overall prescription counts: donepezil 819 (47.8 %), Memantine 619 (36.1 %), Rivastigmine 139 (8.1 %), Galantamine 123 (7.2 %), Ginkgo 15 (0.9 %). The remaining 643 had no recorded antidementia therapy or missing data. By MMST category: MMST < 16 (n = 325): 289 (88.9 %) treated—Memantine 152 (52.6 %), Donepezil 106 (36.7 %), Rivastigmine = 21 (7.3 %), Galantamine = 9 (3.1 %), Ginkgo = 1 (0.3 %). 16 ≤ MMST < 26 (n = 1,065): 1,065 (100 %) treated—Donepezil = 515 (48.4 %), Memantine = 382 (35.9 %), Rivastigmine = 82 (7.7 %), Galantamine = 77 (7.2 %), Ginkgo = 9 (0.8 %). MMST ≥ 26 (n = 396): 267 (67.4 %) treated Donepezil = 150 (56.2 %), Memantine = 55 (20.6 %), Galantamine = 31 (11.6 %), Rivastigmine = 25 (9.4 %), Ginkgo = 6 (2.2 %). Precise dosage and treatment duration data were largely absent in DESTINY. LP Contraindications & PET Imaging: Contraindications to LP (e.g., lumbar spine degeneration, anticoagulant use) were noted but not quantified; and are empirically rare. Amyloid-PET was performed only in privately insured patients, because there is no reimbursement for public health patients in Germany. Data Completeness and Missing Data: MMST was missing for 24.3 % of patients. Although PMS and DESTINY aren't fully integrated at this time, aligning them more closely will enable comprehensive analyses of MRI timing, complete CSF biomarker panels, ApoE status, and detailed medication records. **Conclusions:** In this cohort (n = 2,358), early AD/MCI diagnostics paired cognitive testing with structural imaging and CSF biomarkers were routinely accomplished. Treatment followed stage-based guidelines—cholinesterase inhibitors predominated in MCI/mild dementia, while Memantine was common in severe dementia. Significant missing data in CSF results, MRI timestamps, and detailed medication regimens limit comprehensive analysis of diagnostic intervals and treatment trajectories. To address this, integrating DESTINY with PMS for complete imaging, laboratory, and medication data is crucial. These problems will be solved by doing projects prospectively in the future.

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Key takeaway message: Using the DESTINY registry, early AD/MCI diagnoses in 2,358 German patients combined cognitive testing and imaging, guided by evidence-based treatments; this registry approach underscores the value of integrated data for enhancing care and future research.

P407- LEVERAGING THE FTD DISORDERS REGISTRY TO ENHANCE CLINICAL TRIAL RECRUITMENT IN FRONTOTEMPORAL DEGENERATION.

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Background: Frontotemporal degeneration (FTD) is an umbrella term for a group of rare disorders characterized by neurodegeneration in the frontal and temporal lobes, leading to progressive impairments in behavior, motor function, language, and cognition. The rarity and clinical variability of FTD disorders present significant challenges to timely diagnosis and, consequently, to the recruitment of research-ready participants for clinical trials. There are currently no approved disease-modifying or symptomatic therapies for FTD disorders which underscores the substantial unmet medical need in this population. The FTD Disorders Registry, a direct-to-participant registry launched in 2017, was designed to address these challenges by connecting individuals diagnosed with an FTD disorder, biological family members, and care partners with research opportunities. By enabling rapid outreach to an engaged, self-identified population, the Registry offers a unique resource to accelerate recruitment, diversify study cohorts, and facilitate patient-centered trial design. **Methods:** The FTD Disorders Registry collects data through two primary mechanisms: a Contact Registry, which gathers basic demographic and disease interests, and the Registry Research Study, which collects longitudinal data on diagnosis, symptoms, caregiving, and research participation barriers. Adults living the United States and Canada, including those diagnosed with an FTD disorder, biological family members, and current or former care partners, are eligible to enroll in the Registry Research Study online. Anyone who joins the Registry can be notified about research opportunities. To support clinical trial recruitment, the Registry engages in the following activities: • Collaborating with study sponsors to design and disseminate IRB-approved, tailored email outreach campaigns to eligible participants based on self-reported characteristics and interests. • Conducting participant prescreening and matching to appropriate study sites based on eligibility criteria and geographic location. • Providing aggregate, de-identified feasibility data to sponsors and investigators to assess recruitment potential. • Offering the option of an integrated e-consent service, enabling researchers to efficiently obtain and manage informed consent from participants for their studies. **Results:** As of May 2025, the FTD Disorders Registry includes 5,740 contactable participants with 1,072 active Registry Research Study participants. The Registry Research Study includes representation across the spectrum of those impacted by FTD disorders including 27% individuals diagnosed with an FTD disorder, 27% biological family members, 24% current or former caregivers, 16% legally authorized representatives, and 6% reporters. Among active participants with diagnosed or suspected FTD, 88% report a diagnosis of FTD and/or a specific subtype of FTD. Of those who reported a specific subtype, 18% reported behavioral variant FTD (bvFTD), 21% primary progressive aphasia (PPA), 5% corticobasal degeneration (CBD), 4% progressive supranuclear palsy (PSP), and 3% frontotemporal dementia and amyotrophic lateral sclerosis (FTD-ALS). From July 2024 – April 2025, the Registry facilitated recruitment for 22 studies. Targeted campaigns resulted in accelerated enrollment for many of these studies. For example, a study evaluating a mental health program for individuals recently diagnosed with an FTD disorder recruited 66% of its participants through the Registry. **Conclusions:** The FTD Disorders Registry demonstrates a scalable, patient-centered approach to overcoming the recruitment challenges inherent in frontotemporal degeneration research. By directly engaging individuals and

families impacted by FTD disorders and facilitating targeted outreach, the Registry has been able to rapidly connect eligible individuals with research opportunities and supported enrollment across a range of studies, from observational studies to interventional trials. As the landscape of FTD therapeutics evolves, the Registry is well-positioned to serve as a critical infrastructure for accelerating trial readiness, improving cohort diversity, and amplifying the voice of the FTD community in research.

Keywords: Frontotemporal degeneration (FTD), digital health tools, clinical trial recruitment, patient registry, research enrollment, patient-centered research.

Disclosures: The authors declared no competing interests.

Key takeaway message: The FTD Disorders Registry accelerates clinical trial recruitment by connecting research-ready individuals impacted by FTD disorders with research opportunities, supporting faster enrollment, broader representation, and more patient-centered study design in a rare disease landscape.

P408- EXPLORING PERSONA-BASED LARGE LANGUAGE MODEL SIMULATION FOR SOCIAL SURVEYS ON DEMENTIA TREATMENT.

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Background: The potential of persona-based Large Language Model (LLM) simulation, wherein LLMs are provided with attribute information to generate social survey responses and decision-making aligned with their persona, has attracted increasing attention. In this exploratory study, we investigated the potential and biases of persona-based LLM simulation using data from a survey on attitudes towards Alzheimer's disease (AD) disease-modifying drugs conducted in Japan in 2023, just prior to the clinical implementation of lecanemab. **Methods:** We utilized response data from a web questionnaire administered to approximately 2,000 participants of the J-TRC Webstudy via Google Form between November and December 2023. The survey questions assessed participants' degree of concern regarding Amyloid-Related Imaging Abnormalities (ARIA) and their acceptance of prioritizing patients for treatment under hypothetical resource-scarce conditions. For each human respondent, attributes such as age group, gender, years of education, living arrangement (alone or not), family history of dementia, and co-payment ratio for medical expenses were input via API into ChatGPT and Gemini. The LLMs were prompted to independently infer the individual's values and personality traits based on these attributes and subsequently answer the survey questions accordingly. We evaluated both individual-level and group-level agreement between human and LLM responses, as well as differences in response patterns based on attributes. This study received ethical approval. The web questionnaire was conducted anonymously, and only de-identified data was collected and used. Furthermore, we opted out of LLM data storage. **Results:** Individual-level agreement between human and LLM responses was negligible (Kappa < 0.1). At the group level, the response distributions showed some similarity. While no gender-based differences in response patterns between humans and LLMs were observed, distinct differences were observed, particularly for younger (50s) or older (80s) participants. **Conclusions:** The findings suggest that LLM-based simulations could serve as an auxiliary tool in the preliminary design phases of dementia-related research, such as for feasibility assessments or pilot surveys.

Disclosures: The authors declare no conflict of interest related to this work.

Key takeaway message: Persona-based LLM simulation showed poor individual-level agreement but reproduced group-level trends, highlighting its promise under careful use as a supplementary tool for feasibility assessments and pilot planning in social dementia research.

P409- PRELIMINARY EFFICACY OF THE HEALTHY ACTIONS AND LIFESTYLES TO AVOID DEMENTIA (HALT-AD) PROGRAM FOR ENHANCING DEMENTIA-RISK KNOWLEDGE, SELF-EFFICACY, AND DIET QUALITY IN PRIMARY-CARE PATIENTS.

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Background: More than 40 % of dementia risk is attributable to modifiable risk factors (MRFs) such as physical inactivity, poor diet and limited social engagement. Primary-care visits seldom allow sufficient time for personalized risk-reduction counseling and support (1). Healthy Actions and Lifestyles to Avoid Dementia (HALT-AD) - a bilingual, web-based program combining 11 self-directed educational modules, goal-setting tools, and weekly support group sessions - may serve as an adjunct to support dementia preventive care within primary care (2). While HALT-AD's usability is documented, data on its efficacy to improve knowledge, self-efficacy, and MRF-related behaviors is limited. **Methods:** In a single-arm implementation study at two UC San Diego Health primary-care clinics, N=130 patients (50-85 y; no neurodegenerative diagnosis) were referred electronically, consented online, and enrolled in HALT-AD for 18 weeks. Pre–post surveys were administered to assess changes in dementia-risk knowledge, self-efficacy, and MRF-associated behaviors. Within-subject change was analyzed with paired t-tests ($\alpha = 0.05$). n=33 participants have completed the study to date. **Results:** Baseline knowledge score was 81.6 ± 13.2 %, increasing to 91.1 ± 11.4 % post-program ($\Delta \approx +9.5$ % on a 100-point scale; $p <$ .001). Self-efficacy improved from 30.4 ± 5.4 to 33.0 ± 4.3 ($\Delta \approx +2.6$ points on a 40-point scale; $p = 0.009$). Diet scores increased from 26.0 ± 4.0 to 27.6 ± 5.0 ($\Delta \approx +1.6$ points on a 40-point scale; $p = =.032$). No significant changes in sleep, social connectedness, medication use or other MRFs were found. **Conclusions:** These preliminary findings over 18 weeks suggest HALT-AD may be efficacious in improving knowledge and MRF-associated behaviors. Subsequent analyses with the full sample (N=130) will determine whether other MRFs have also improved significantly and will underscore whether there is value in embedding HALT-AD as a scalable adjunct program within primary-care settings to mitigate dementia risk. A longer intervention will be necessary to determine whether HALT-AD's beneficial effects on lifestyle are sustained over time.

Keywords: Dementia prevention, lifestyle modification, digital health, primary care, HALT-AD.

Disclosures: The authors declare no competing interests.

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Key takeaway message: Completers of the HALT-AD program demonstrated improvements in their dementia-risk knowledge, self-efficacy, and dietary composition over 18 weeks.

CLINICAL TRIALS EARLY CAREER INVESTIGATOR SHOWCASE

PEC001- PLASMA P-TAU181 LEVELS ARE ASSOCIATED WITH COGNITIVE AND PHYSICAL DECLINE IN A POPULATION OF OLDER ADULTS MEETING FRAILTY CRITERIA: LONGITUDINAL DATA FROM THE COGFRAIL STUDY.

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Background: High plasma p-tau181 levels may indicate decline across multiple domains. As a marker of cognitive decline, most evidence comes from studies in younger, selected populations and may not be directly generalizable to older adults meeting frailty criteria in clinical

settings. The association between plasma p-tau181 levels and physical parameters has been only sparsely investigated. **Aim:** To assess the association between plasma p-tau181 levels and the trajectories of cognitive and physical decline in pre-frail and frail older adults. **Methods:** We performed a 2-year longitudinal analysis using data from the CogFrail study. High p-tau181 levels were defined as values in the highest tertile of the distribution. Longitudinal changes from baseline in cognitive/functional outcomes (MMSE, comprehensive neuropsychological battery, CDR-SoB, ADL) and physical outcomes (gait speed, handgrip strength, SPPB, chair rise time) were compared between participants with high versus low/intermediate plasma p-tau181 levels using linear mixed-effects models. **Results:** A total of 227 patients were included in this analysis (mean age 82 ± 5.1 years, 65% women), of whom 77 (38.5%) were classified as having high plasma p-tau181 levels. Significant differences in changes from baseline to 2 years were observed between individuals with high versus low/intermediate p-tau181 values for CDR-SoB (+0.43 [95% CI 0.24–0.63; p<0.0001]), MMSE (−2.09 [−3.17 to −1.02; p=0.0002]) and ADL (−0.31 [−0.54 to −0.08; p=0.008]), as well as for grip strength (−2.66 [−4.10 to −1.23; p=0.0003]), with a trend toward significance for gait speed (−0.06 [−0.12 to 0.00; p=0.0646]). **Conclusions:** Older pre-frail and frail patients with objective cognitive impairment and elevated plasma p-tau181 levels experienced greater cognitive and physical decline over a 2-year period. These findings should be confirmed in larger population samples.

Key takeaway message: Age-related loss of proteostasis, leading to amyloidopathy and associated tauopathy, may contribute not only to cognitive but also to physical decline, representing a potential target for preventive and therapeutic interventions.

PEC002- EFFECTS OF ESCITALOPRAM ON NEURO-PSYCHIATRIC SYMPTOMS IN ALZHEIMER'S DISEASE: A SECONDARY ANALYSIS FROM THE S-CITAD STUDY.

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Background: In the Escitalopram for agitation in Alzheimer's disease (S-CitAD) study, escitalopram was not found to be superior to placebo in reducing symptoms of agitation in Alzheimer's disease (AD) (1). Using Neuropsychiatric Inventory (NPI) data from the S-CitAD study, the authors explored the potential impact of escitalopram on other neuropsychiatric symptom domains and caregiver distress scores. **Methods:** A secondary analysis was conducted on data from the S-CitAD study to determine the effect of escitalopram on NPI domain scores outside of agitation. Caregiver-rated scores were compared from baseline to week 12 in 173 participants receiving escitalopram (5-15mg/day) or placebo regarding the presence or absence of individual neuropsychiatric symptoms, emergence of new symptoms, and median score severity by domain. Caregiver distress scores were additionally examined by NPI domain at baseline and at week 12 for between-group changes. **Results:** Statistical significance was seen in the depression/dysphoria domain median scores favoring the escitalopram group at week 12 (median=1 [interquartile range (IQR)=2, 6] compared with median=5 [IQR=2, 6]; p=0.04). Median and IQR refer to frequency by severity score among participants reporting the symptom. Higher scores indicate more frequent and/or more severe symptoms. No other NPI domains displayed significant differences between groups at week 12. While median NPI domain scores weren't statistically different, caregiver distress scores in the domains of apathy/indifference (median=1.5 [IQR=1, 2.75] compared with median=2.5 [IQR=1, 2.75]; p= 0.016) and irritability/lability (median=2 [IQR=1, 3] compared with median=3 [IQR=1, 3]; p=0.029) were significantly lower in the escitalopram group versus placebo. Caregiver distress scores in the domain of depression/dysphoria were numerically lower in the escitalopram group but did not reach statistical significance (median=1.5 [IQR=0, 3] compared with median=2 [IQR=0, 3]; p=0.06). The total number of caregivers reporting distress in any NPI domain was numerically lower in the escitalopram group after 12 weeks (N=61, 77%) compared to placebo (N=66, 84%) but not statistically significant (95% CI 0.77- 1.14, p=0.518). In evaluating the emergence of new symptoms over the 12-week period, no participants (0%) in the escitalopram group reported new hallucinations versus 5 participants (7%) in the placebo group. **Conclusions:** In this secondary analysis of NPI data from the S-CitAD study, escitalopram was found to be efficacious in reducing symptoms of depression/dysphoria at 12 weeks. This is encouraging as prior data on the efficacy of SSRIs in treating symptoms of depression in Alzheimer's disease have been mixed (2-4). Findings of reduced caregiver distress in the domains of apathy/indifference and irritability/lability may signal early benefit with escitalopram; however, further research beyond 12 weeks is needed as there was no statistically significant difference in the median NPI scores in these domains versus placebo at 12 weeks. While this secondary analysis did not show a statistical difference in severity of hallucination domain scores between groups after treatment (median=4 [IQR= 3, 6] compared to median=6 [IQR=3, 6]; p=0.59), no new symptoms of hallucinations emerged in the escitalopram group throughout the 12-week trial. An interesting comparison to the secondary analysis of NPI scores from the CitAD study, where authors noted a statistically significant reduction in severity of hallucination domain scores in the citalopram group versus placebo after 9 weeks of treatment but data on new hallucinations were not published (5). The comparison is limited, and neither the CitAD study nor the S-CitAD study was powered to detect differences in individual NPI domains. However, these findings may suggest a potential direction for future research into SSRIs and the delay of psychotic symptom onset in Alzheimer's disease.

Keywords: Escitalopram, agitation, neuropsychiatric symptoms, Alzheimer's disease.

Disclosures: The S-CitAD study received grant funding from the National Institutes of Health/National Institute on Aging (R01AG052510). Dr. Emily D. Clark has no personal financial conflicts to disclose.

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Porsteinsson, A. P. (2016). Effects of citalopram on neuropsychiatric symptoms in Alzheimer's dementia: Evidence from the CITAD study. American Journal of Psychiatry, 173(5), 473–480. https://doi.org/10.1176/appi.ajp.2016.15020248.

Key takeaway message: In this secondary analysis of NPI data from the S-CitAD study, escitalopram reduced symptoms of depression/dysphoria in participants and reduced caregiver distress scores in the domains of apathy/indifference and irritability/lability after 12 weeks.

PEC003- PLASMA AND CSF PROTEOMIC SIGNATURES OF LIFE-STYLE ACTIVITIES: A SEARCH FOR BIOMARKERS OF COGNITIVE RESERVE IN THE STANFORD AGING AND MEMORY STUDY (SAMS).

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Background: The mechanisms underlying the effects of healthy lifestyle on cognition remain inadequately explored (1). Physical, social, and cognitive activities have the potential to modulate circulating proteins, and this study aimed to systematically identify cerebrospinal fluid (CSF) and plasma proteins associated with these activities. Ultimately, these lifestyle-protein associations have the potential to reveal biological outcomes in future non-pharmacological clinical trials and hold promise as future therapeutic targets. **Methods:** 173 cognitively unimpaired older adults (69.0 $\pm$ 6.4 years) completed a CHAMPS questionnaire regarding frequency and hours per week of 29 physical, 7 social, and 5 cognitively engaging activities. Of 173 individuals, 142 provided plasma samples, and 123 underwent lumbar punctures. Plasma and CSF samples were quantified for >7000 plasma proteins and >5000 CSF proteins using the SomaScan assay. Linear regression covariates included age, sex, education, and APOE genotype. Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), and Reactome (REAC) databases were used for pathway enrichment analysis. Benjamini-Hochberg (BH) procedure was used to account for multiple hypotheses. **Results:** After correction for multiple hypotheses, 15 plasma proteomic markers were significantly associated with physical activity, 609 with cognitive activity, and none with social activity (BH corrected $p < 0.05$). One plasma protein, Fibronectin Leucine Rich Transmembrane Protein 3 (FLRT3), was negatively associated with both physical activity and cognitive activity (physical: ß = -1.35x10-5, corrected BH $p = 0.034$, cognitive: ß = -0.0047, corrected BH $p = 0.043$). Additionally, after correction for multiple hypotheses, 7 CSF proteins were significantly associated with cognitive activity (BH corrected $p < 0.05$). None were associated with physical or social activity. Only one protein, fibroblast growth factor 22 (FGF22), was significantly associated with cognitive activity (frequency/week) in both plasma and CSF after correction (plasma: ß = 0.0063, BH corrected $p < 0.001$; CSF: ß = 0.0026, BH $p = 0.021$). A pathway analysis revealed that the most enriched pathways for plasma were related to regulation of protein metabolism, cell organization, catabolic processes, protein localization, cell macromolecule localization, cell localization, and vesicle-mediated transport. Amongst CSF proteins, the most enriched pathway was related to fibroblast growth factor receptor 1b (FGFR1b) ligand binding and activation, which includes binding of FGF22 to FGFR1b. **Conclusions:** We performed large-scale proteomic analyses in a deeply characterized cohort and identified several proteins (e.g., FLRT3, FGF22) that may be associated with lifestyle activities. FLRT3 is essential for hippocampal axon guidance, cell migration, and excitatory synapse formation (2,3). FGF22 signaling is also essential for excitatory synapse formation in hippocampi and may serve as a future therapeutic target (4,5). Plasma and CSF proteomic analyses allow discovery of changes at the molecular level associated with lifestyle-mediated cognitive reserve. Additionally, they can guide the discovery of biomarkers for non-pharmacological trials as well as therapies for pharmacological clinical trials.

Keywords: Proteome, lifestyle, cognitive reserve, CSF, plasma.

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PEC004- TESTING AND TAILORING GROUP COGNITIVE BEHAVIORAL THERAPY FOR INSOMNIA (CBTI) WITH PERSONS WITH EARLY-STAGE ALZHEIMER'S DISEASE AND THEIR CARE PARTNERS.

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Background: Progressive neurodegeneration is associated with Alzheimer's disease and Related Dementias (ADRD) and can lead to alterations in the 24-hour sleep-wake cycle. Consequently, up to 50% of individuals with ADRD experience sleep disturbances such as delayed sleep onset, frequent awakenings, poor sleep efficiency, and excessive daytime-napping. Neuropsychiatric symptoms (NPS), such as nighttime wandering and sundowning regularly accompany these sleep-wake changes, negatively impacting the sleep of care partners, a factor cited as one of the primary reasons for seeking institutional care. These sleep disturbances may manifest during the mild cognitive impairment (MCI) stage, when early treatment strategies provide the most benefit and participants can actively participate in treatment. Cognitive Behavioral Therapy for insomnia (CBTi) is the recommended first-line treatment for sleep disturbances in older adults, despite limited access to behavioral sleep medicine providers and lack of tailoring for the unique changes that occur as we age and with memory impairment. Limited published research exists on CBTi in MCI and dyadic populations, with most studies utilizing web-based CBTi, with recruitment currently underway. As neurodegeneration progresses, persons living with ADRD become more dependent on their care partners, altering their original interpersonal relationship. Care partners may experience changes in how they provide cognitive, mental, social, functional, and physical support. This can negatively impact the care partners' physical and mental wellbeing, quality of life, and financial situations. Importantly, dementia care partners are significantly more likely to develop and experience frailty, a syndrome that increases an individual's vulnerability to adverse health outcomes. Persons living with dementia may also develope and experience frailty. Care partners often need more emotional and social support. Social networks, such as in group-based support, are vital to dementia care and create a supportive environment that counteracts the isolating effects of caregiving. Group CBTi has demonstrated feasibility and acceptability in older adults without cognitive impairment, and preliminary results showed improved subjective and objective measures of sleep as well as significantly lower levels of fatigue which could have important implications for addressing frailty. **Methods:** This trial will employ in-person group CBTi for dementia-dyads, with adaptations

informed by the Unmet Needs Model and the Transdiagnostic Framework for Early Dyadic Interventions for Neurodegenerative Diseases. Specifically, disease- and dyad-specific content and coping strategies will be adapted to mitigate the unmet need of adequate sleep. The group setting may help normalize unique difficulties the individual members of the dyad face. This trial will explore the feasibility and acceptability of group CBTi, amongst persons with MCI and their care partners. Furthermore, we will explore sleep quality and actigraphic measured sleep and rest-activity parameters in the intervention group compared to a sleep hygiene education (SHE) control group. The following aims will be tested: **Aim 1:** Determine the feasibility of group CBTi among persons with MCI and their care partners using the NIH Behavior Change consortium guidelines and the Acceptability/Appropriateness of Intervention Measure. Hypothesis. Group CBTi will be feasible and acceptable in the dementia-dyad population. **Aim 2:** Explore preliminary effects of group CBTi on 1) subjective sleep quality and 2) actigraph-derived sleep and rest-activity parameters compared to SHE. Hypothesis. Persons with MCI and their care partners will demonstrate greater improvements in sleep quality (Insomnia Severity Index; ISI) and in actigraph-derived sleep and rest-activity rhythm parameters, compared to SHE. Exploratory aim: Explore preliminary effects of group CBTi on 1) neuropsychiatric symptoms and 2) frailty in persons living with MCI and their care partners. Hypothesis. Persons with MCI and their care partners will demonstrate greater improvements in neuropsychiatric and frailty symptoms compared to SHE. **Results:** Results from this trial will provide preliminary data to apply for an R01 and other competitive grant funding mechanisms to implement group CBTi in decentralized, multisite, randomized effectiveness trials with the eventual goal of creating clinical guidelines aimed at prevention of disease development and treatment of symptoms through CBTi over the course of the disease. **Conclusions:** As our population ages, ADRD will affect more families and sleep is an important, undertreated aspect of the disease that affects both members of the dementia-dyad. There is a shortage or CBTi trained clinicians, therefore group CBTi will allow early stage (MCI) dementia-dyads quicker access to this effective gold standard treatment.

Keywords: Alzheimer's disease, memory, caregiver, dyad, sleep, CBTi.

Disclosures: The authors declare no competing interests.

Key takeaway message: Cognitive Behavioral Therapy for Insomnia (CBTi) is an effective treatment for sleep disturbances, which affects both members of the dementia-dyad. Research is limited on the acceptability, feasibility, and tailoring of this treatment for dementia-dyads.

PEC005- MRI UTILIZATION FOR ARIA RESPONSE IN PATIENTS RECEIVING LECANEMAB.

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Background: Amyloid-related imaging abnormalities (ARIA-E and ARIA-H) are frequent and sometimes serious adverse events among individuals receiving treatment with monoclonal antibodies (mAb) that target amyloid-β, particularly in APOEε4 carriers. The U.S. Food and Drug Administration (FDA) labeling indicates drug-specific frequencies for monitoring the development of ARIA. Appropriate use recommendations include directions to obtain sequential brain MRIs to monitor the progression or resolution of ARIA events. However, the number and frequency of additional MRIs are not discussed in the published Phase III clinical trials results (1,2). Additional brain MRIs add to the potential overall direct cost and patient burden associated with mAb treatment. We assessed MRI utilization among ARIA-positive and ARIA-negative patients receiving mAb treatment. **Methods:** We conducted a retrospective chart review of patients with early Alzheimer's disease with at least 2 doses of lecanemab at the UAB Brain Aging and Memory Clinic from June 2023 to December 2024. Data included patient demographic and clinical characteristics, ARIA event occurrence, routine scheduled, and ARIA event-monitoring brain MRIs. The number of patients receiving donanemab over this interval was too small to conduct meaningful analysis. The UAB Institutional Review Board considered this study-exempt research. **Results:** Of 147 patients on lecanemab, 60 % were women, 90 % were White, 59.86 % were ApoE ε4 heterozygotes, and mean age was 72.4 years (±7). Overall, 25.17% (n=37) experienced either ARIA- E or ARIA-H. APOE distribution of ARIA+ and ARIA- patients did differ (p= 0.0010). ARIA+ patients were more likely to be ApoE ε4 homozygotes (n = 8; 21.62%). Regarding additional brain MRIs for monitoring ARIA events, patients were monitored every four weeks until the ARIA was either resolved or stabilized. ARIA+ patients underwent between 1 and 8 brain MRIs (Mean 1.66, SD 1.60) in addition to the routine scheduled scans. A higher frequency of MRIs was associated with ARIA-type, radiographic severity, and symptoms. Asymptomatic ARIAs were more likely to be detected in the scheduled safety MRIs. 17.95 % (n=7) of the ARIA + patients did not have additional MRIs. **Conclusions:** Based on Medicare reimbursement rates, each additional MRI adds approximately $58 to the direct patient costs of healthcare related to mAb therapy. In addition to the individual risks to patient safety, ARIA contributes to the financial impact, patient and caregiver burden, and resource utilization associated with mAB treatments. Research should continue to ascertain the factors that may influence the economic impact of mAB treatments on families, the healthcare system, and society as well as inform utilization outcomes in clinical trials design and implementation.

Keywords: Alzheimer's Disease, ARIA H, ARIA E, amyloid targeting therapies,health economics.

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Key takeaway message: Research should continue to ascertain the factors that may influence the economic impact of mAB treatments on families, the healthcare system, and society as well as inform utilization outcomes in clinical trials design and implementation.

PEC006- FEASIBILITY AND ACCURACY OF THE LILA APP: PILOT STUDY OF A FULLY REMOTE, SELF-ADMINISTERED, VERBAL LIST LEARNING TASK FOR COMMUNITY COGNITIVE SCREENING.

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Background: As effective pharmaceutical therapies for Alzheimer's Disease (AD) continue to emerge, screening strategies that are cost efficient and scalable are critically needed to identify individuals who could most benefit from these therapies. Digital cognitive assessments that are sensitive to changes in learning and episodic memory offer the opportunity for community screening of cognitive function. Such tools

could be used to identify individuals who may be in the early stages of AD and could be good candidates for intervention. LILA is a self-administered assessment completed via smartphone app, which leverages the well validated International Shopping List Test (ISLT) to assess learning and episodic memory (1,2). The aims of this study were to assess the feasibility of using LILA as a cognitive screening tool in the general population within the United States, as well as the accuracy of LILA in extracting spoken words from speech and scoring test responses. **Methods:** Social media advertisements were used to recruit a general population sample to participate in the study. Advertisements were shared with English-speaking individuals aged 50-70 years located in the United States, with a target of recruiting 20 participants. The pilot study included n = 22 participants (mean (SD) age = 58 (5.4) years), who installed the LILA app and completed the assessment via their personal smartphone device. The LILA assessment is based on the ISLT, which is a verbal list learning task consisting of 3-learning rounds and 1-delayed recall round. Each round is scored according to the total number of words correctly recalled by the participant. Within the app, the 12-item shopping word list is played aloud for the participant and verbal responses are recorded. Responses are then analyzed and scored using Natural Language Processing (NLP). The feasibility of the LILA app as a community screening tool was determined according to the number of clicks on the social media advertisements, subsequent registrations of interest in participating in the LILA feasibility study, as well as completion rates for each stage of the LILA assessment. Audio recordings for each LILA assessment were manually reviewed by study staff and scored according to the number of individual words correctly recorded and number of rounds correctly scored by the NLP. **Results:** Recruitment of the pilot sample was completed within 72 hours. There were n = 993 clicks on the social media advertisements and n = 142 individuals completing an enrollment form to register their interest in the study within the 72-hour period before recruitment was closed. Of the 22 participants who completed LILA, 100% (n = 22) completed the first three rounds and 82% (n = 18) completed the delayed recall round for at least one LILA assessment session. A total of 37 sessions were initiated, as participants were able to complete multiple assessment sessions. Across all sessions there were 1105 words, and 136 rounds captured. The review of the audio recordings identified 31 errors for individual words detected by the NLP. The most common word detection errors were related to misidentification of compound words (e.g. hotdog) and homophones (e.g, steak/stake). Overall, the accuracy of the NLP for detection of individual words was 97.2%. **Conclusions:** We observed a high level of interest among middle age and older adults in completing a self-administered app-based memory assessment. All participants recruited to the study were able to successfully install the app and complete the initial rounds of the assessment, demonstrating that older adults in the general population can successfully engage with digital cognitive assessments with minimal supervision or support. Accuracy of the NLP was high for word recognition. Based on learnings in this pilot sample, the words included in LILA assessments were updated to exclude compound words and homophones to improve future accuracy of results scored by the NLP. Taken together, the results of this study support the feasibility and accuracy of LILA as a fully remote and self-administered community cognitive screening tool.

Keywords: community screening; digital cognitive assessment; natural language processing; learning and memory.

Disclosures: KD Harrington, J Segura, S Archer, L Miller, R Ray, N Farouk, KM Sink and P Ventola are full-time employees of Cogstate Ltd. S Lerdahl and A Nordblom are full-time employees of Asteroidea Ventures LLC, DBA Formative.

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Key takeaway message: The results of this study support the feasibility and accuracy of LILA as a fully remote and self-administered community cognitive screening tool.

PEC007- A PRELIMINARY STUDY ON THE EFFECTIVENESS OF THERAPEUTIC AGRICULTURAL PROGRAMS FOR HEALTHY INDIVIDUALS AND PATIENTS WITH DEMENTIA.

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Background & Objective: Therapeutic agriculture represents an innovative non-pharmacological intervention for enhancing cognitive and emotional well-being in older adults, particularly those with cognitive impairments. This preliminary study investigated the possible effects of a structured agricultural program on normal aging and dementia patients using pre and post-intervention assessments. **Methods:** The 6-week agricultural intervention involved weekly 120-minute gardening sessions focusing on sensory engagement, plant cultivation, and social interaction. Evaluation instruments included: Cognitive Impairment Screening Test (CIST), Geriatric Depression Scale (GDS) and Subjective Memory Complain Questionnaire (SMCQ). Measurements were conducted at baseline and post-intervention. **Results:** Participants included 15 individuals: 7 cognitively normal older adults (mean age 74.1 ± 2.6 years, education year 5.7±3.4 years) and 8 patients with mild to moderate dementia (mean age 77.8 ± 2.3 years, education year 5.3±3.0 years). The results demonstrated significant improvements were observed in both groups in GDS score ($p<0.05$). Normal aging participants showed statistically significant improvement frontal executive function score in CIST ($p<0.05$). Dementia patients exhibited improved GDS score ($p<0.05$). **Conclusions:** Depressive symptoms are most effective in therapeutic agriculture program. In normal individuals showed improved executive function through therapeutic agriculture program. CIST scores indicated cognitive maintenance in dementia group and partial cognitive enhancement in normal aging group. These findings suggest therapeutic agriculture as a promising non-pharmacological intervention for cognitive and emotional well-being in older populations, warranting further comprehensive and large-scale longitudinal research to validate long-term benefits.

Key takeaway message: Therapeutic agriculture represents an innovative non-pharmacological intervention for enhancing cognitive and emotional well-being in older adults, particularly those with cognitive impairments

PEC008- BROAD REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) OF THE PRECUNEUS IN ALZHEIMER'S DISEASE: A RATIONALE, STUDY DESIGN, AND PRELIMINARY OPEN-LABEL DATA.

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Background: Brain network dysfunction, particularly within the default mode network (DMN), is an increasingly apparent manifestation of Alzheimer's Disease (AD) progression. Repetitive transcranial magnetic stimulation (rTMS) can target key DMN hubs, maintain signaling function, and delay or improve clinical outcomes in AD. We present here the rationale and design of a study using off-the-shelf equipment and the latest clinical evidence to expand on prior rTMS work and reduce

participant burden in the process. **Methods:** We are conducting a two-stage trial of large-coil rTMS targeting the precuneus (a key hub in the DMN affected by AD) in 54 participants with mild to moderate Alzheimer's Clinical Syndrome focused primarily on determining tolerability and feasibility and secondarily studying short-term efficacy for episodic memory. The currently active first stage involves 5-10 participants receiving open-label treatment for protocol refinement. The subsequent stage will consist of a 1:1 randomized, double-blind, sham controlled clinical trial to study feasibility and tolerability while exploring target engagement and short-term efficacy for memory. Participants will undergo 16 total rTMS brain stimulation sessions over the course of 5 weeks. A full open-label extension treatment course will be offered to the sham group after unblinding. Outcomes focus on completion rates and adverse events to demonstrate feasibility and tolerability. Further exploratory outcomes will include neuropsychological assessments, electroencephalography (EEG), neuroimaging, and blood biomarkers to demonstrate feasibility of collection and explore preliminary changes in these measures. **Results:** We anticipate this treatment is feasible and tolerable and may show evidence of target engagement and clinical improvement. We plan to present current preliminary open-label data as analyzed at CTAD. **Conclusions:** Should we achieve expected positive outcomes in feasibility and tolerability, this will justify future work focusing on clear demonstrations of clinical efficacy and biomarker engagement, as well as enhancement of generalizability and scalability.

Trial Registration: Clinicaltrials.gov NCT06597942.

Key takeaway message: This ongoing study examines repetitive transcranial magnetic stimulation as a treatment for Alzheimer's Disease and the physiologic changes it induces in brain networks. It focuses on feasibility while exploring biomarkers and clinical change.