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POSTERS

CLINICAL TRIALS: METHODOLOGY

P001- SCREENING FOR COGNITIVE IMPAIRMENT ACROSS FOUR DIFFERENT EUROPEAN DEMENTIA COHORTS USING AN AUTOMATIC DIGITAL COGNITIVE ASSESSMENT. J. Tröger[1], E. Mallick[1], N. Linz[1], G.S. Benavides[2], I. Ramakers[3], S. Kern[4], I. Skoog[4], S. Köhler[5], S. Teipel[5], A. König[1] *(1. ki elements GmbH - Saarbrücken (Germany), 2. BarcelonaBeta Brain Research Center (BBRC), Hospital del Mar Research Institute - Barcelona (Spain), 3. Maastricht University Medical Center (MUMC+) - Maastricht (Netherlands), 4. Institute of Neuroscience and Physiology at the Sahlgrenska Academy University of Gothenburg - Gothenburg (Sweden), 5. Deutsches Zentrum für Neurodegenerative Erkrankungen e.V. (DZNE) - Rostock (Germany))*

Background: Clinical trials for Alzheimer's disease are large-scale, multinational, and involve numerous sites across different countries. While these trials adhere to overarching inclusion and quality criteria, population characteristics and procedures inevitably vary by location. Therefore, cognitive measures used in these trials must be validated for suitability across diverse study populations and regions. This ensures their effectiveness as reliable endpoints, pre-selection criteria, or screening tools. Hence, we present data from an automatic digital cognitive assessment the ki: digital speech biomarker for cognition (SB-C) from four different clinical cohorts across four different European countries. The aim of this study is to derive and validate one global cut-off for differentiating between cognitively impaired and cognitively healthy subjects and report the respective performance. **Methods:** For this research we used a sample from four different memory clinic populations: the Swedish H70 Birth Cohort study (N=696), the Dutch DeepSpA study (N=134), the German PROSPECT-AD DESCRIBE-AD study (N=96). Additionally, we used a sample of participants with Subjective Cognitive Impairment (SCI): the Spanish PROSPECT-AD Beta-AARC study (N=59). Clinical labels (SCI, MCI, Dementia) of all participants were provided from each cohort site and based on clinical diagnostic routine procedure. We automatically extract the SB-C score and its subscores (executive function, memory, semantic memory, processing speed) from SVF and RAVLT speech recordings using ki:elements' proprietary speech analysis pipeline including automatic speech recognition and feature extraction. We performed (1) inferential statistics comparing cognitively healthy (Healthy Controls or SCI) and cognitively impaired (Mild Cognitive Impairment (MCI) or mild dementia) groups based on the SB-C Cognition Score in each cohort of the sample and (2) determined a global cutoff to differentiate between cognitively healthy and cognitively impaired groups on the whole sample and apply it in the four different cohorts separately. For (1) we performed a non-parametric Kruskal-Wallis test to compare SB-C scores of both cognitively healthy and cognitively impaired groups to check for general feasibility. For (2), we applied an optimal cutoff procedure aimed at maximizing the sum of sensitivity and specificity in discriminating between cognitively healthy and cognitively impaired groups. **Results:** The Kruskal-Wallis test revealed a significant difference of the SB-C score between the diagnosis groups in each cohort (Cognitively Healthy > Cognitively Impaired). The optimal cutoff analysis showed that a cutoff of 0.42 in the SB-C Cognition Score differentiated between diagnosis groups with a balanced accuracy and a ROC AUC score of 0.77. Sensitivity and specificity of the classification were 0.84 and 0.71 respectively. Applied in the four cohorts separately, the cutoff of 0.42 results in balanced accuracies of 0.76 or 0.77, sensitivities greater than 0.61 and specificities greater than 0.68, and most of the patients of PROSPECT-AD Barcelona Beta study are classified as cognitively unimpaired. **Conclusion:** The SB-C reaches classification performance of .75 or higher across all four cohorts for separating cognitively healthy from cognitively impaired subjects. Despite multilingual cohorts (Dutch, Swedish, German & Spanish) in different research contexts i.e. memory clinic based inclusion, longitudinal register cohort or pre-clinical research focused) one global cut-off demonstrated good and more important robust performance. This serves as important evidence to demonstrate the fit-for-purpose of such a digital automatic cognitive speech measure in the area of clinical AD clinical trials. **Keywords:** MCI, Screening, Dementia, Digital Cognitive Assessment, Speech Analysis. **Disclosures:** JT, EM, NL, AK are employed by the digital speech biomarker company ki:elements. JT and NL hold shares in the digital speech biomarker company ki:elements. The other authors have nothing to disclose.

P002- INCREASING STATISTICAL POWER OF EARLY ALZHEIMER'S DISEASE CLINICAL TRIALS WITH THE AD-PXTM PROGNOSTIC MODEL. A. Tam[1], C. Laurent[1], C. Dansereau[1] *(1. Perceiv AI - Montreal (Canada))*

Background: Although cognitive and functional changes are frequent primary outcomes in Alzheimer's disease trials, many participants will remain stable throughout a trial, which reduces a trial's statistical power to detect treatment effects. We explored how to increase statistical power by enriching for likely decliners with a prognostic model. **Methods:** In a sample of 1118 visits from 526 amyloid positive participants with mild cognitive impairment (MCI) and mild Alzheimer's dementia (AD) from ADNI (adni.loni.usc.edu), we calculated the mean and standard deviation of change on CDR-SB over 24 months. With these parameters, we estimated sample size requirements for two-arm placebo-controlled trials to detect 30% slowing on CDR-SB progression over 24 months at 80% and 90% power. These sample size estimates served as benchmarks for a typical clinical trial without enrichment of

decliners. We trained a machine learning model, AD-PxTM, to classify decliners and non-decliners on 9077 visits from 4869 participants with MCI and mild AD from a second dataset (naccdata.org). Decliners were defined as individuals who had higher CDR-SB scores at 24 months of follow-up compared to baseline. Input features included age, sex, APOE4 status, and baseline MMSE and CDR-SB scores. We then used this model to identify an enriched cohort of likely decliners in the first dataset (ADNI) and performed power analyses to quantify the increase in statistical power due to enrichment. The power analyses were performed with bootstrapping (n=1000) to provide 95% confidence intervals (CI). **Results:** The full ADNI cohort had a mean (std) change of +1.72 (2.5) points on the CDR-SB, which required a total of 752 participants to provide 80% power (CI [72, 86]) to a typical trial. The subset of likely decliners had a larger mean (std) change of +2.42 (2.8) points on the CDR-SB, and consequently, enriching a trial with 752 likely decliners yielded 94% power (CI [90, 97]) (14% increase in power). For a typical trial to obtain 94% power without enrichment, 450 additional participants were needed (60% increase in sample size). To obtain 90% power (CI [85, 93]) in a typical trial, 1006 participants were required. An enriched trial of the same size yielded 98% power (CI [97, 99]) (8% increase in power). At this level of power, a typical unenriched trial would need an additional 602 participants (60% increase in sample size). **Conclusion:** AD-PxTM can be used to enrich trials to significantly increase statistical power compared to typical trials at equivalent sample sizes. To power typical trials at such higher levels would require 60% more participants. Using AD-PxTM, trials can gain power without increasing sample sizes, thereby reducing the costs and time associated with larger trials.

P003- CLINICAL TRIALS IN CHRONIC TRAUMATIC ENCEPHALOPATHY: ARE WE THERE YET? C. Bernick[1], G. Shan[2], D. Matthews[3], A. Ritter[4] *(1. Cleveland Clinic - Las Vegas (United States), 2. University of Florida - Gainesville (United States), 3. ADMDx - Chicago (United States), 4. Hoag Medical Center - Newport Beach (United States))*

Background: Traumatic Encephalopathy Syndrome (TES) is considered to reflect the clinical syndrome of Chronic Traumatic Encephalopathy (CTE), a neurodegenerative condition that can develop as a consequence of significant exposure to repetitive head impact and lead to dementia. There have yet to be any clinical trials in TES. This report aims to assess methods of constructing a clinical trial in TES including cohort selection and potential outcome measures. **Methods:** Publications and additional data were reviewed from two longitudinal studies, Diagnose CTE and Professional Athletes Brain Health Study along with data from Multi-modal machine learning detection and tracking of traumatic brain injury neurodegeneration and its differentiation from Alzheimer's disease. In addition, publications relevant to the National Institute of Neurological Disorders and Stroke Consensus Clinical Criteria (NINDS CCC) for TES from 2021-2024 were reviewed. Information was included if the study results had a relationship with post-mortem diagnosis of CTE, predicted clinical decline or was demonstrated to capture clinical change over time in those who fulfilled criteria for TES. **Results:** 14 publications met the search criteria and were reviewed along with unpublished data from the studies mentioned above. The NINDS CCC for TES has been demonstrated to correlate with yearly rate of decline in certain cognitive and MRI based volumetric measures, though information on its' correlation with CTE pathology is limited. Adding baseline MRI regional volume measures can improve correlation with likelihood of cognitive decline. A composite index involving cognitive and behavioral elements has been developed that is based on change in clinical measures in those with TES and may potentially serve as a primary outcome measure. **Conclusion:** Clinical trials in TES are feasible and criteria can be established to identify a cohort that has a likelihood of demonstrating clinical decline; at least one composite index is developed that is sensitive to clinical change over time. However, the correlation of these measures with underlying CTE pathology is still uncertain.

P004- STORYTELLER AS A RECRUITMENT AND PRE-SCREENING TOOL FOR ALZHEIMER'S DISEASE CLINICAL TRIALS. S. Hollingshead[1], J. Norton[1], I. Hernandez[1], J. Weston[2], E. Fristed[2], C. Skirrow[2] *(1. Charter Research - The Villages (United States), 2. Novoic Ltd - London (United Kingdom))*

Background: Patient recruitment for Alzheimer's disease (AD) clinical trials presents marked challenges due to limited patient availability, high screen-failure rates, and extensive screening protocols. Successful clinical trial sites commonly engage in community recruitment efforts combined with detailed pre-screening to identify and qualify patients, but this process can be time consuming and costly. Innovative new approaches to engage, recruit and pre-screen patients are required. Charter Research, a multi-site clinical research center in Florida, is utilising Storyteller, a web-based self-administered cognitive test, for patient recruitment and pre-screening in trials in preclinical, prodromal and dementia stages of AD. This study outlines its deployment and initial findings, including its correlation with the Montreal Cognitive Assessment (MoCA). **Methods:** From April 17th 2024, Charter Research integrated Storyteller into in-clinic prescreening and remote recruitment efforts. Storyteller is a speech-based assessment evaluating memory function via story recall tasks. In clinic, Storyteller has replaced other tests for memory dysfunction (Wechsler Logical Memory test, Rey Auditory Verbal Learning Test), and is used together with the MoCA for cognitive evaluation during pre-screening visits. Remotely, Storyteller serves as a standalone cognitive screening tool. Recruitment includes community outreach and newspaper advertisements, with Storyteller accessed via web link or QR code, and with participants independently initiating and completing assessments. Scores are communicated during subsequent follow-up calls with research staff. **Results:** As of May 28th 2024, 178 individuals completed Storyteller (mean age 72.3 (sd 8.49), 114 female, 64 male), including 148 in-clinic completions (mean Storyteller score 55.19, (sd 15.28)). Correlations between Storyteller scores and MoCA were moderate and highly significant (rho=0.53, $p<0.0001$). Pre-screening from outreach efforts was completed by 30 individuals (mean age 71.4 (sd 11.03), with the majority of responses by women (25/30). Half of participants scored in the low average (8/30, 27%), low and very low normative range (4 (13%) and 3 (10%) individuals, respectively), indicating potential memory decline or impairment. Storyteller scores were similar to those evaluated in-clinic (mean score 58.05, sd 13.98). Site staff report that sharing Storyteller scores aids in initiating conversations with more hesitant participants recruited via outreach efforts. **Conclusion:** Storyteller shows promise for enhancing the efficiency of pre-screening for AD trials, reducing costs at a site level by substituting traditional cognitive evaluations and reducing staff time. At Charter research, Storyteller has replaced more laborious evaluations for amnestic MCI in clinic, while in remote outreach it has

supplanted all other cognitive pre-screening measures. The significant correlation with MoCA scores highlights Storyteller's convergent validity with other common measures used to evaluate cognitive function and suitability for clinical trials. As Charter Research continues to utilise Storyteller and as patients progress through study funnels into clinical trials, more data relating to study inclusion/exclusion will become available, allowing further, more in-depth evaluation of Storyteller as a tool for prequalifying patients for clinical trials. **Keywords:** Cognitive assessment, Alzheimer's disease, pre-screening, digital health tools. **Disclosures:** SH, JN and IH report no conflicts of interest. EF, JW and CS are employed by and/or option- or shareholders of Novoic.

P005- NOVEL PILOT PHASE 1 CLINICAL TRIAL WITH PV-1950R/A VACCINE FOR LEWY BODY DEMENTIA (LBD). J. Galvin[1], M. Agadjanyan[2] *(1. University of Miami Miller School of Medicine - Boca Raton (United States), 2. Institute for Molecular Medicine - San Diego (United States))*

Background: Lewy Body Dementia (LBD) affects an estimated 1.4 million people in the United States and is the second most common form of neurodegenerative dementia. LBD includes individuals who initially present with a cognitive-behavioral disorder (dementia with Lewy bodies) and those who initially present with a movement disorder (Parkinson's disease dementia). LBD often has an earlier age of onset than Alzheimer's disease, progresses faster, and has greater disability and caregiver burden. Currently, there are no medications that the FDA has approved to treat LBD, and only a limited number of medications are being tested in clinical trials, creating a significant gap in available treatments for patients and their families. The key pathology in LBD is the aggregation of the presynaptic protein, alpha-synuclein (AS), in neuronal cell bodies (Lewy bodies), neuronal processes (Lewy neurites), and synapses affecting the neocortex, limbic structures, and peripheral autonomic neurons. Immunotherapy is being explored as a promising treatment option for LBD, as antibodies can prevent the accumulation or possibly inhibit the spreading of pathological aggregated AS that contribute to the disease. Of particular interest to this hypothesis is that a prodromal state of LBD exists in the form of rapid eye movement sleep behavior disorder (RBD), associated with brainstem and peripheral AS aggregates preceding LBD onset by more than two decades, making it an ideal target for our preventive vaccine, PV-1950R/A. **Methods:** We developed a proprietary universal MultiTEP platform technology in the last decade, especially for neurodegenerative disorders, composed of 12 foreign promiscuous T-helper epitopes from various microorganisms. Recently, using this platform, we developed four a-Syn (AS) vaccines targeting different regions of this pathological molecule (amino acids 85-99, 109-126, and 126-140) and tested their immunogenicity and efficacy in an LBD mouse model [1-3]. The most immunogenic and preclinically effective vaccine, PV-1950R/A, targeting three B-cell epitopes of pathological AS simultaneously, was selected to move forward for IND-enabling studies. **Results:** Our published preclinical data shows that this vaccine triggers the production of high-titer antibodies in the LBD mouse model, which can identify all three B-cell epitopes of AS. PV-1950R/A reduced both total and proteinase K-resistant AS, as well as neurodegeneration and brain inflammation. Based on these results, we have progressed PV-1950R/A to preclinical IND-enabling studies and a pilot Phase 1 trial, with support from an NIA grant. **Conclusion:** Our studies will involve the manufacturing of drug products and the completion of the following: a) Safety studies in the LBD mouse model, b) Immunogenicity and overall safety studies in non-human primates. This data will support IND application and FDA clearance for two Phase 1 trials. In the Phase 1a study, we will assess the safety and immunogenicity of increasing doses of PV-1950R/A in healthy volunteers. Following the determination of the maximum tolerated dose (MTD) in Phase 1a, we will proceed with a single-dose Phase 1b study in RBD patients at increased risk of LBD. **Keywords:** Alpha-synuclein, Lewy Body Dementia, REM Sleep Behavior Disorder, Vaccine. **Disclosures:** JEG and MGA are supported by grants from NIH. MGA is Vice President of the Institute for Molecular Medicine. The authors declared no competing interests. **References:** 1. Kim C, Hovakimyan A, Zagorski K, et al NPJ Vaccines. 2022 Jan 10;7(1):1. doi: 10.1038/s41541-021-00424-2. 2. Davtyan H, Zagorski K, Petrushina I, et al. Neurobiol Aging. 2017 Nov;59:156-170. doi: 10.1016/j.neurobiolaging.2017.08.006. 3. Zagorski K, Chailyan G, Hovakimyan A, et al Int J Mol Sci. 2022 May 29;23(11):6080. doi: 10.3390/ijms23116080.

P006- KEY STAKEHOLDER ENGAGEMENT AND PROTOCOL DEVELOPMENT FOR THE IHI-FUNDED PUBLIC-PRIVATE PARTNERSHIP PROJECT PREDICTOM. Z. Khan[1], A.K. Brem[1], A. Mark[1], N. Ashton[1], B. Sigurd[2], A.C. Anne[3], P. Ellie[3], D. Ana[4], F. Holger[5], T.G. Martha[6], M. Gaby[7], M. Matthias[8], S.N. Spiros[9], S. Timo[10], A. Dag[11] *(1. IOPPN, King's College London - London(lon) (United Kingdom), 2. GN Hearing - Copenhagen (Denmark), 3. University of Exeter - London(lon) (United Kingdom), 4. Alzheimer's Europe - Luxembourg (Luxembourg), 5. Fraunhofer Institute for Algorithms and Scientific Computing SCAI - Bonn (Germany), 6. Stavanger Hospital - Stavanger (Norway), 7. Fraunhofer Institute for Algorithms and Scientific Computing SCAI - Erlangen (Germany), 8. Novo Nordisk - Copenhagen (Denmark), 9. CERTH - Thessaloniki (Greece), 10. GE Healthcare - Greater Munich (Germany), 11. IOPPN - London (United Kingdom))*

Background: To address global healthcare challenges, collaborative efforts among universities, companies, patient organizations, and regulators are vital. This abstract presents the journey for protocol development for a multicentral clinical research. PREDICTOM, a project led by Stavanger University Hospital and GE HealthCare, through the European Commission (EU) Innovative Health Initiative. PREDICTOM aims to develop an AI-driven platform for Alzheimer's disease risk screening. **Method:** The protocol development included five key steps, (i) development of research idea based on current gaps, (ii) identification of diverse key stakeholder groups (researchers, clinicians, industrial partners and, importantly, public involvement experts) (iii) consultations with expert panel and key stakeholder, (iv) implementation of feedback from key stakeholder groups and experience from preparing previous clinical studies (RADAR-AD, PROTECT), and (v) input from the operations team (IT developers, programme managers and research coordinators) working on the ground floor to set up study logistics, liaising with industry (testing and selecting biomarkers, identifying technical requirements and planning logistics for data collection and dataflow) and establish the legal framework. The initial research idea was identified and developed (January 2023), this process included two in-person meetings with researchers, clinicians and industrial partners (January and February 2023) and weekly online meetings to develop the application until submission (May 2023). The project received approval in July 2023 from EU with clear work packages to address key aims. The initial draft of the

protocol was written post face-to-face meeting in August 2023, with the first draft being ready by the kick-off meeting in November 2023, followed by the first ethics approval in January 2024. **Conclusion:** Protocol development of large public-private partnership projects is a highly challenging process requiring the collection and integration of information from many key stakeholders.

P007- USING PLASMA PTAU217 RATIO TO FORECAST LONGITUDINAL PROGRESSION SUBSTANTIALLY INCREASES THE EFFICIENCY OF AD CLINICAL TRIALS. V. Devanarayan[1], P. Sachdev[1], A. Charil[1], Y. Ye[1], T. Nelson[1], H. Hampel[1], L. Kramer[1], S. Dhadda[1], M. Irizarry[1] *(1. Eisai Inc. - Nutley (United States))*

Background: Blood-based biomarkers, such as the ratio of phosphorylated to non-phosphorylated plasma Tau217 (pTau217R), have demonstrated significant potential in accurately detecting brain amyloid and tau in Alzheimer's disease (AD). This research aims to determine whether baseline plasma pTau217R can predict the longitudinal clinical decline in patients with early AD (mild cognitive impairment or mild AD). If successful, this biomarker could serve as a valuable tool for clinical trial enrichment, enhancing trial power and reducing the required sample size. **Methods:** Plasma pTau217 and non-phosphorylated tau217 concentrations were quantified via immunoprecipitation-mass spectrometry. The training cohort (TC) comprised 158 amyloid-beta positive (Aβ+) early AD subjects from the placebo arm of a clinical trial. The validation cohort (VC) included 73 Aβ+ placebo arm subjects from another clinical trial, with over 80% diagnosed with MCI. Longitudinal clinical decline was determined by changes from baseline in Clinical Dementia Rating-Sum of Boxes (CDR-SB) at months 3, 6, 9, 12, 15, and 18. Models for predicting the longitudinal clinical trajectory within the TC were constructed using the Stochastic Gradient Boosting algorithm, with separate and combined baseline predictors: (1) plasma pTau217R, (2) cognitive function (clinical) assessments, and (3) structural MRI features. Demographics (age, sex) were considered in all models. Prediction performance was cross-validated within the TC and evaluated in the VC using mean absolute prediction error (MAPE). Due to the limited sample size at later time points, model performance is reported and compared only for month 12. The impact of employing these models to enrich clinical trials with patients predicted to experience clinical progression (CDR-SB change >= 0.5) was assessed through simulations. The goal was to determine the effect on the power and required sample size for detecting a 30% treatment effect at month 18. **Results:** The model predicting longitudinal progression using baseline plasma pTau217R performed comparably to models relying on baseline clinical assessments and structural MRI features in the VC (MAPE of 1.114 versus 1.083 and 1.081, respectively; $p > 0.05$). Adding pTau217R to clinical assessments significantly improved performance (MAPE of 1.02; $p < 0.05$). Including structural MRI features in models with either pTau217R alone or combined with clinical assessments did not significantly enhance performance. Transitioning from pTau217 concentration to pTau217R significantly boosted model prediction performance ($p < 0.05$). Implementing pTau217R-based models for clinical trial enrichment resulted in a 30% reduction in sample size and an increase in power from 80% to 89%. **Conclusion:** Models leveraging baseline plasma pTau217R effectively predict longitudinal clinical progression in early AD, thereby serving as potent tools for clinical trial enrichment and enhancing overall clinical trial efficiency. **Keywords:** blood-based biomarkers, machine learning, enrichment. **Clinical Trial Registry:** NCT03887455; NCT02956486; https://clinicaltrials.gov. **Disclosures:** All authors are employees of Eisai, Inc.

P008- UTILIZING A PATIENT BURDEN SCORING TOOL TO IMPROVE THE PATIENT AND CAREGIVER EXPERIENCE IN CLINICAL RESEARCH IN PATIENTS WITH ALZHEIMER'S DISEASE AND OTHER FORMS OF DEMENTIA. J. Sheldon[1], A. Lysandropoulos[3] *(1. Parexel - Boston (United States))*

Background: Clinical research in Alzheimer's disease and other forms of dementias is an ever-growing field that plays a pivotal role in expanding treatment options for patients. However, enrolling and retaining patients in clinical trials for Alzheimer's disease poses significant challenges (1). These challenges arise due to the complex nature of disease presentation and behaviors, the requirement for significant caregiver involvement, and the logistical difficulties associated with study visits and assessments. Therefore, there is a need to design clinical trials that alleviate the burden on participants and simplify protocol requirements to enhance their experience and facilitate enrollment and retention. **Methods:** To address this issue, we developed a Protocol Burden Scoring Tool. This Excel-based scoring tool calculates how burdensome and how time consuming the Alzheimer's disease study will be on the patient. To develop the scoring, neurologists were surveyed to categorize most frequent procedures, scales and assessments found in Alzheimer's and dementia protocols. These were rated on two scales: time commitment and invasiveness (defined as discomfort or perceived burden to patients) using a scale of 1-5. Collected responses were summarized into ten categories. Formulas were developed incorporating the identified coefficient for invasiveness, time burden, and a combined overall score from tool. The tool auto-creates graphical representations of the burden faced by participants, a "visit-by-visit" assessment, as well a comparison to other scored protocols with similar indication and design. At present, the tool does not account for variables such as different interpretations of protocols by different scorers, but this will be accounted for in future iterations. **Results:** The tool was tested internally on 15 Alzheimer's disease and/or dementia protocols to develop baseline scoring for the indication, and to determine an average range and upper and lower quartile scores. Combined scores ranged from 5.37 to 24.01, with a median of 11.31. Protocols which focused on a behavior of Alzheimer's, such as psychosis or aggression scored in the higher range (>12), as did studies in other types of dementia (i.e., Lewy body).The scores showed that procedures such as lumbar punctures did not make a meaningful difference to the score. Conversely, a shorter treatment period emerged as the primary factor driving higher scores, indicating a more burdensome experience for patients. The median treatment period observed was 22 weeks; those with shorter durations had higher scores due to invasive/painful treatments being performed over a shorter timeframe. **Conclusion:** Scores and the "visit-by-visit" rating could guide sponsors to simplify study design and reduce/combine specific outcomes assessments and scales, and/or to streamline complex imaging procedures for patients. Drug developers could also analyze the interplay of this score with the anticipated study enrollment rate, to determine changes to protocol design to reduce burden, and/or to add tactics to support participation for patients and caregivers where those burdensome procedures are required for

outcomes measurement. **Keywords:** Patient burden, protocol design, patient inclusion, enrollment support. **Disclosures:** authors have nothing to disclose. **References:** (1) Obstacles and opportunities in Alzheimer's clinical trial recruitment. Watson JL, Ryan L, Silverberg N, Cahan V, Bernard MA. Health Aff (Millwood). 2014 Apr;33(4):574-9.

P009- ASSESSING THE FEASIBILITY OF IMPLEMENTING BLOOD-BASED BIOMARKERS AS CONFIRMATORY DIAGNOSTIC TOOLS FOR EARLY ALZHEIMER'S DISEASE IN REAL-WORLD CLINICAL PRACTICE: A PROSPECTIVE, MULTI-CLINIC IMPLEMENTATION SCIENCE AND OBSERVATIONAL STUDY. L. Zullig[1], J. Vandercappellen[2], M.N. Sabbagh[3], S. Mattke[4], H. Hampel[2], R. Batrla[2], D. Jones[2] *(1. Department of Population Health Sciences, Duke University School of Medicine - Durham, (United States), 2. Eisai Inc., Nutley - New Jersey (United States), 3. Department of Neurology, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center - Phoenix (United States), 4. Center for Economic and Social Research, University of Southern California - Los Angeles (United States))*

Background: High-accuracy blood-based biomarkers (BBMs) may allow accessible, scalable confirmation of amyloid pathology in the Alzheimer's disease (AD) care pathway. Some assays have shown test performance on par with cerebrospinal fluid (CSF) testing and positron emission tomography (PET) [1–4]. Thus, these tests may serve as an alternative, more accessible modality to CSF or PET for confirmation of AD pathology. However, establishing acceptable performance does not guarantee uptake in routine clinical practice. This prospective, multi-clinic implementation science and observational real-world evidence study aims to assess the feasibility of implementing BBMs as amyloid pathology confirmatory tools in the diagnosis of early AD, and to assess the time to and resource use for biomarker-confirmed AD diagnosis. **Methods:** This ongoing study is being conducted in three memory clinics in the USA receiving referrals for patients ≥55 years old with suspected cognitive decline. The study assesses implementation science outcomes, including clinician acceptability and appropriateness, and perceived barriers and facilitators for the implementation of confirmatory BBMs, utilizing the Consolidated Framework for Implementation Research (CFIR) model as an analytic framework. The confirmatory BBM studied is the Precivity AD2™, which analyzes the Aβ42/40 ratio and p-Tau217 ratio with a performance meeting the criteria set out by the Global CEO initiative on AD (CEOi) for confirmatory BBMs [5]. Implementation science outcomes will be evaluated using quantitative validated questionnaires (i.e., the Feasibility of Intervention Measure [FIM], Acceptability of Intervention Measure [AIM], and Intervention Appropriateness Measure [IAM]) and qualitative data from semi-structured interviews and focus groups with clinician participants. The observational portion of the study will additionally evaluate the reach (i.e., proportion and representativeness) of patients with a first referral for cognitive decline who receive a biomarker-confirmed diagnosis over a study period of 6 months, compared with the current standard of care, and determine the time to a biomarker-confirmed diagnosis, as well as the number of visits, and cost required. **Results:** The interim analysis will review patient demographics and available diagnostic data and assess available quantitative and qualitative data from the clinician surveys and interviews. It will explore clinician acceptability and appropriateness, and perceived barriers and facilitators for the implementation of confirmatory BBMs. **Conclusion:** The findings from this study will be used to develop a blueprint for implementing confirmatory BBMs into routine care, and to develop educational programs to facilitate the accelerated uptake of confirmatory BBMs, with the aim of simplifying the AD diagnostic pathway. **Keywords:** Implementation science, observational study, blood-based biomarkers, early diagnosis. **Disclosures:** Leah Zullig has received consulting fees from Novartis and Eisai, Inc. Research supported by Eisai, Inc. Marwan Sabbagh has ownership interest (stock or stock options) in NeuroTau, uMethod Health, Athira, Lighthouse Pharmaceuticals, and Alzheon; has consulted for Eisai, Roche-Genentech, Lilly, Synaptogenix, NeuroTherapia, T3D, Signant Health, Novo Nordisk, Corium, Prothena, KeiferRx, Anavex, and Cognito Therapeutics; and is Board of Director for CervoMed; Soeren Mattke serves on the board of directors of Senscio Systems, Inc., and the scientific advisory board of AiCure Technologies, Alzpath, and Boston Millennia Partners; has received consulting fees from Biogen, C2N, Eisai, Genentech, Novartis, Novo Nordisk and Roche/Genentech; and is PI on research contracts between USC and Biogen, Eisai and Roche/Genentech. Jo Vandercappellen, Daryl Jones, Harald Hampel, and Richard Batrla are employees of Eisai Inc., US.; medical writing support provided by Panacea85 Ltd. **References:** 1. Angioni et al. J Prev Alzheimers Dis. 2022;9(4):569–579; 2. Hansson et al. Alzheimers Dement. 2022. 18(12):2669–2686; 3. Teunissen et al. Lancet Neurol. 2022;21(1):66–77; 4. Barthelemy et al. Nat Med. 2024;30:1085–1095; 5. Schindler et al., The Global CEO Initiative on Alzheimer's Disease performance recommendations for blood-based biomarker tests. Nature Reviews Neurology, 2024. [Article in Press].

P010- A NEW PRECISION-PREVENTION APPROACH COMBINING LIFESTYLE CHANGES AND METFORMIN REPURPOSING FOR THE PREVENTION OF COGNITIVE DECLINE: MET-FINGER TRIAL PROTOCOL AND UPDATE. A. Solomon[1,2,3], M. Barbera[1,2], D. Perera[2,4], A. Haqqee[2], J. Lehtisalo[1,5], M. Aspö[3,6], M. Cross[2], C. De Jager[2], E. Falaschetti[2], N. Friel[2], J. Message[2], G. Price[2], C. Thunborg[3,6], F. Mangialasche[3,4], L. Middleton[2,7], T. Ngandu[3,5], M. Kivipelto[2,3,4,6] *(1. University of Eastern Finland - Kuopio (Finland), 2. Imperial College London - London (United Kingdom), 3. Karolinska Institutet - Stockholm (Sweden), 4. FINGERS Brain Health Institute - Stockholm (Sweden), 5. The Finnish Institute for Health and Welfare - Helsinki (Finland), 6. Karolinska University Hospital - Stockholm (Sweden), 7Imperial College Healthcare NHS Trust Hospitals - London (United Kingdom))*

Introduction: Combining multidomain-lifestyle and pharmacological interventions could help address key challenges in dementia prevention. Metformin is a promising candidate for drug-repurposing in this context, given the link between Type-II Diabetes (T2D) and Alzheimer's Disease (AD); emerging scientific evidence also suggests independent neuro-protective effects. In MET-FINGER, we aim to test the FINGER 2.0 multimodal intervention, combining healthy lifestyle changes with metformin, when appropriate (active arm), versus regular health-advice (control/comparator arm), in an APOE ε4-enriched population of older adults at increased risk of dementia. **Methods:** MET-FINGER is a 2-year international randomised, controlled, phase-IIb proof-of-concept clinical trial, where metformin is included through a trial-within-trial design. 600 participants are being recruited at three sites (UK, Finland, Sweden). The lifestyle intervention is an updated

version of the FINGER model, to be consistently delivered in three countries. Participants randomly allocated to the FINGER 2.0 intervention, and at increased-risk of T2D, will be further randomised to additionally receive metformin 2000mg/day, metformin 1000mg/day, or placebo (double-blinded). Metformin is administered as Glucophage®XR/SR 500, (Merck KGaA, 500mg oral tablets). The effect of the FINGER 2.0 intervention on changes in global cognition (primary outcome), as well as memory, executive function, and processing speed; functional ability; and risk factors for AD/dementia (secondary outcomes), will be assessed versus the control/comparator arm. The feasibility, potential interaction (between-groups differences in healthy lifestyle changes), and disease-modifying effects of the lifestyle-metformin combination will be assessed as exploratory outcomes. **Results:** Recruitment started in January 2023. To date, 297 eligible participants have been identified out of 482 screening conducted. 127 participants have been randomised. A progress report from this first FINGER 2.0 model will be presented, with lessons learned for future combination therapies. **Conclusion:** MET-FINGER is the first trial combining a multimodal lifestyle intervention with a putative disease-modifying drug for cognitive decline prevention. Its findings will provide crucial information for innovative precision-prevention strategies aimed to cognitive decline, and evidence to form the basis for a larger phase-III trial design and other future research. **Keywords:** Dementia prevention; Cognitive decline; Lifestyle medication combination; FINGER intervention; Metformin; World-Wide FINGERS; Drug repurposing; APOE. **Clinical Trials Registry:** NCT05109169. **Disclosures:** The authors declared no competing interests.

P011- EVIDENCE-BASED REPORTING OF ETHNICITY IN CLINICAL TRIALS. Z.U.N.E.R. Khan[1], D. Kramarczyk[2], M. Vasconcelos Da Silva[2], K. Mcleish Israel[2], D. Aarsland[2], C. Ballard[3] *(1. Psychological Medicine - London (United Kingdom), 2. Psychological Medicine - 6 De Crespigny Park, London (United Kingdom), 3. University of Exeter - Exeter (United Kingdom))*

Background: Globally, 50 million people have dementia, mostly AD, with prevalence expected to double by 2050. In the USA, approximately 6.7 million Americans aged 65 and older are currently living with Alzheimer's dementia. African Americans are almost twice as likely to develop Alzheimer's disease as compared to white Americans. In the UK, 3% of dementia cases are from Black and Asian Minority Ethnic (BAME) communities, expected to double by 2026, especially among South Asians. Individuals from UK and USA ethnic minorities often face earlier onset and more advanced-stage diagnoses, leading to delayed treatment. Higher cardiovascular conditions in these populations double their dementia risk. Research shows higher vascular dementia rates and earlier onset in Black and Asian populations. With the emerging new treatments, there is increasing importance of evaluating safety and efficacy of emerging treatments across diverse ethnic communities. For example, the new disease-modifying therapies for AD and treatments for agitation have increased the number of new compounds in clinical development. This necessitates a better understanding of benefits and risks across different ethnicities. **Aim:** This review reports the evidence base across clinical trials for different ethnic communities as registered on CT.gov, as a first step to understanding the current evidence base, identifying key current gaps and knowledge and enabling informed recommendations for further developments. **Methods:** A search was conducted on https://clinicaltrials.gov/ (15th September 2023) for studies completed since the year 2000. Inclusion criteria included condition/disease (Alzheimer's Disease), other terms (dementia), study type (intervention), location (UK, USA and Canada), study status (all studies—completed and terminated), phase (2-4), and study results (with results). Reviewers independently screened titles and abstracts. Data on age, gender, and ethnicity were extracted. **Results:** Initial screening identified 1050 studies, for phase 2-4 intervention studies and 308 have currently reported findings. From this group, 163 studies were selected based on their focus within the UK, USA and Canada. Within this subset, 96 studies reported on data on ethnicity. **Demographics:** The majority of studies represented individuals with AD (86.5%), with other conditions including MCI (6.13%), AD with DLB/PD (2.45%), AD with VD (1.85%), and unspecified dementia (3.07%). Mean age of the participants across studies was 70 to 79, with an equal gender mix (52% female). **Ethnicity Breakdown:** Out of the 163 studies, only 96 (58.9%) provided information on ethnicity. Among the studies reporting ethnicity, 15 included almost entirely white participants, while 81 were multicultural, though largely white (80.57%). Black or African American participants comprised 6%, Asians 4%, and Hispanics 2% of the study populations. **Conclusion:** It is serious concern that more than 40 % studies do not report any data on ethnicity and ethnic populations are substantially underrepresented in clinical trials. This analysis underscores the need for more inclusive clinical trials to better understand benefits and risk of emerging treatments across different ethnic communities to enable safe and optimal clinical treatment for all people with dementia. **Keywords:** Dementia , Alzheimer's disease, Ethnicity, Ethnic populations, Clinical Trials.

P012- DIVERSITY IN A REGISTRATIONAL TRIAL FOR ARIBIO'S AR1001 FOR TREATMENT OF EARLY ALZHEIMER'S DISEASE. S. Sha[1], Y. Gonzalez[2], M. Nash[3], J. Rock[4], F. Kim[4], A. Schindler[4], T. Xi[4], J.J. Choung[4] *(1. Neurology & Neurological Sciences, Stanford University - Palo Alto (United States), 2. Verus Clinical Research Corp - Miami (United States), 3. Alcanza Research Site Network-NeuroStudies - Decatur (United States), 4. AriBio Co., Ltd. - San Diego (United States))*

Background: Alzheimer's disease (AD) affects people of all races and ethnicities, yet enrolling a diverse population into AD clinical trials has proven challenging. Recent registrational Phase 3 trials for early AD had populations with less than 3% African-American (AA) and less than 5% Hispanic/Latino (HL) participants. Some of the obstacles to recruiting diverse participants include language and cultural barriers, distrust of the medical establishment, and access to information about trials. Prior to its Phase 3 trial for AR1001, a PDE-5 inhibitor being studied for treatment of early AD, AriBio filed a Diversity Plan with the US Food and Drug Administration that proposed: 1) Selecting diverse investigators and staff to augment trust in participants; 2) Overcoming language and cultural barriers that may exist by placing the trial in research centers with access to a diverse population; 3) Providing advertising and outward facing study materials that are sensitive to a diverse population. The Phase 2 trial of AR1001 for mild-to-moderate AD, conducted in the US, had 20% HL and 13% AA participants. A Phase 3 trial of AR1001 in early AD is currently enrolling and the early demographics are presented. **Methods:** Polaris-AD is a Phase 3, randomized, double-blind study of AR1001 in participants with mild cognitive impairment or mild dementia due to AD. The study will be conducted across 4 regions (North America [US and Canada], United Kingdom/European Union,

South Korea, and China). The trial is using the Diversity Plan in the US to guide the selection of investigators and to recruit participants into the trial. **Results:** As of May 2024, 1105 people were screened across US and South Korea. Other countries will initiate screening in Q2 2024. The screened population averaged 55% female, 73 years of age, and had a racial composition of 83% White (including 33% HL), 10% AA (including 2% HL), 6% Asian, and 1% other. The enrolled population was 81.5% White (including 28% HL), 5.6% AA (including 2% HL), 11.9% Asian, and 0.6% Other. A greater percentage of AA and a smaller percentage of Asians screen failed relative to the overall screening population. The reasons for screen failing was noticeably different in the AA compared to other groups and was mostly due to higher rates of exclusionary depression than other groups as measured by the Geriatric Depress Scale (GDS). In general, sites in South Korea had lower screen fail rates than US sites, resulting in a larger percentage of Asian participants enrolled relative to screened. **Conclusion:** AriBio was able to recruit an ethnically and racially diverse population into its US Phase 2 trial. The Phase 3 Polaris-AD global trial is continuing with these efforts. Initial screening and enrollment data from the US and South Korea indicates higher representation among AA and HL participants than in previous Phase 3 trials for early AD. AriBio will continue to refine its recruitment strategy aimed at a clinical trial population that reflects the diversity of the AD patient community.

P013- ESTIMATING THE BENEFITS OF PRE-SCREENING ALZHEIMER'S TRIALS USING BLOOD-BASED BIOMARKERS AND DIGITAL COGNITIVE ASSESSMENTS. N. Linz[1], R. Ullmann[2], J. Tröger[1], A. König[1], R. Croney[3], T. Bittner[4], T. Perumal[2] *(1. ki:elements GmbH - Saarbrücken (Germany), 2. Roche Pharma Research and Early Development, Roche Innovation Center Basel - Basel (Switzerland), 3. Roche Products Ltd - welwyn Garden City (United Kingdom), 4. F. Hoffmann-La Roche Ltd - Basel (Switzerland))*

Background: Recruitment for Alzheimer's disease (AD) clinical trials has historically been challenging and costly. The average recruitment time for phase II studies is 2.5 years for pre-symptomatic AD and 2.9 years for mild cognitive impairment (MCI), largely due to high screen failure rates exceeding 95% [1]. Additionally, there is generally a lack of diversity among trial participants in AD studies. Advances in blood-based biomarkers (BBBM) and remote digital cognitive assessments (DCA) offer promising strategies to enhance recruitment efficiency. This work models the potential impact on AD trial recruitment costs using different pre-screening strategies with combinations of DCA and BBBM. **Method:** We modeled recruitment costs for AD trials with and without the integration of DCAs and BBBM. A staged funnel approach was employed, incorporating assumed conversion rates and per-participant costs at each stage. The analysis considered two distinct AD study populations and three different recruitment strategies (community-based, primary care, and memory clinic). Prevalence rates for cognitive impairment and PET positivity were derived from existing literature [2]. To estimate pre-screening effectiveness, performance data from current DCAs and BBBM were utilized [3, 4]. **Results:** All pre-screening strategies reduced recruitment costs or were nearly cost-neutral. The combination of DCA and BBBM in a staged approach yielded the greatest cost reduction for the recruitment of participants with MCI (12 to 40%). Using BBBM or DCA alone resulted in varying cost reductions (-3 to 36%), with BBBMs alone being more effective for pre-symptomatic studies, and DCAs for studies focused on MCI. Community recruitment strategies saw the largest cost reductions. Furthermore, although pre-screening strategies necessitated reaching out to more individuals initially to achieve the same recruitment target, they reduced the number of participants needing formal on-site screening by 11 to 68%. This reduction has the potential to decrease timelines and reduce patient burden. In pre-symptomatic studies, the benefit of pre-screening was maintained, with DCAs tending to be cost-neutral overall, resulting in 11 to 33% fewer participants needing on-site screening. **Conclusion:** Pre-screening could be an economically beneficial strategy for AD trials. Since PET scans are typically performed at the end of screening protocols, reducing screen failure rates for PET may have the most significant impact on overall cost reduction. Beyond direct cost savings, pre-screening might expedite overall trial timelines and improve site resource utilization. It may be worthwhile for pre-symptomatic trials and those aiming for diverse participant recruitment from the community to consider implementing these pre-screening methods to potentially enhance efficiency and cost-effectiveness. **Disclosures:** R.U., R.C., T.B., and T. M. P. are employees of and may be shareholders in F. Hoffmann-La Roche Ltd. N. L., J. T., and A. K. are employees of ki elements GmbH. N.L, and J.T. are shareholders of ki elements GmbH. **References:** 1. Malzbender, K., Lavin-Mena, L., Hughes, L., Bose, N., Goldman, D., & Patel, D. (2020). Key Barriers for Clinical Trials for Alzheimer's Disease. White Papers - USC Schaeffer Center. 2. Manly, J. J., Jones, R. N., Langa, K. M., Ryan, L. H., Levine, D. A., McCammon, R., Heeringa, S. G., & Weir, D. (2022). Estimating the Prevalence of Dementia and Mild Cognitive Impairment in the US: The 2016 Health and Retirement Study Harmonized Cognitive Assessment Protocol Project. JAMA Neurology, 79(12), 1242–1249. https://doi.org/10.1001/jamaneurol.2022.3543. 3. Palmqvist, S., Janelidze, S., Quiroz, Y. T., Zetterberg, H., Lopera, F., Stomrud, E., Su, Y., Chen, Y., Serrano, G. E., Leuzy, A., Mattsson-Carlgren, N., Strandberg, O., Smith, R., Villegas, A., Sepulveda-Falla, D., Chai, X., Proctor, N. K., Beach, T. G., Blennow, K., … Hansson, O. (2020). Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. JAMA, 324(8), 772–781. https://doi.org/10.1001/jama.2020.12134. 4. Schäfer, S., Mallick, E., Schwed, L., König, A., Zhao, J., Linz, N., Bodin, T. H., Skoog, J., Possemis, N., ter Huurne, D., Zettergren, A., Kern, S., Sacuiu, S., Ramakers, I., Skoog, I., & Tröger, J. (2023). Screening for Mild Cognitive Impairment Using a Machine Learning Classifier and the Remote Speech Biomarker for Cognition: Evidence from Two Clinically Relevant Cohorts. Journal of Alzheimer's Disease, 91(3), 1165–1171. https://doi.org/10.3233/JAD-220762.

P014- COMPARISON OF THE SCREEN FAILURE RATE IN ALZHEIMER'S CLINICAL TRIALS OF IMMUNOTHERAPIES BETWEEN THE CLINICAL RESEARCH CENTER OF TOULOUSE AND THE OVERALL RATE OVER THE PAST 5 YEARS. D. Pennetier[1], D. Angioni[1], I. Carrie[1], N. Sastre[1], J. Delrieu[1], B. Vellas[1], P.J. Ousset[1] *(1. Centre de Recherche Clinique du Gerontopole, IHU Healthage - Toulouse (France))*

Background: In Alzheimer's clinical trials, high screen failure (SF) rates pose substantial challenges. These failures disappoint patients and result in significant economic costs for industrial sponsors. Reducing the SF rate is thus a critical goal. In Toulouse, we have implemented pre-screening procedures to address this issue and improve our

study outcomes. Our objective is to compare the SF rate at the Toulouse Clinical Research Center with the overall rate in Alzheimer's immunotherapy clinical trials over the past five years. **Methods:** We examined the SF rates in Alzheimer's clinical trials conducted at our research center over the past five years (2019-2024), specifically focusing on immunotherapy trials. These trials share similar inclusion criteria and reasons for SF. We requested the overall SF rates from the sponsors for each selected study and compared our center's rates to the overall rates for these trials. **Results:** The analysis reveals that the SF rate in Toulouse is lower than the global SF rate, with figures standing at 79.25% compared to 56.41%, respectively. **Conclusion:** The implementation of a pre-screening procedure in Toulouse has demonstrated a significant potential for reducing the SF rate in Alzheimer's clinical trials. This procedure involves thorough examination of medical record elements such as age, Mini-Mental State Examination (MMS) score, medical history, treatments, MRI results, and amyloid status prior to proposing therapeutic trials. By targeting eligible patients before screening, this approach helps to minimize screen failures based on verifiable criteria. We suggest that this pre-screening method, not commonly applied on a global scale, could serve as a promising pathway to mitigate the SF rate and alleviate the financial burden on sponsors. **References:** Comparison of the screen failure rate in Alzheimer's clinical trials of immunotherapies between the clinical research center of Toulouse and the overall rate over the past 5 years. D. Pennetier, D. Angioni[1], I. Carrié[1], N. Sastre[1], M. Soto[1], J. Delrieu[1], B. Vellas[1], P.J. Ousset[1] (1. Centre de Recherche Clinique du Gerontopole, IHU Healthage, Toulouse). **Disclosures:** I have no real or potential conflict of interest, whether or not related to the content of this poster.

P015- COMPARING IN-STUDY PERFORMANCE OF EXPERIENCED AND NAÏVE RATERS IN EARLY AD CLINICAL TRIALS. X. Wang[1], A. Kott[2], D. Miller[1] *(1. Signant Health - Blue Bell, PA (United States), 2. Signant Health - Prague (Czech Republic))*

Introduction: Large clinical trials in early Alzheimer's Disease require a rich network of clinical trial sites and many raters skilled in administration and scoring of the various instruments used as efficacy and safety outcomes. The competing landscape and the volume of concurrently ongoing clinical trials may make it difficult for sites to staff studies with raters who have adequate experience. Therefore, clients are seeking novel approaches that allow less experienced (naïve) raters to train and participate in clinical trials. Intensive ("Enriched") training curricula can be implemented during certification process, enabling less experienced raters to quickly gain necessary practical experience with study outcomes. In the current post-hoc analysis, we compare in-study administration and scoring performance of raters who underwent the enriched training with experienced raters in 5 large early AD clinical trials. **Methods:** Raters not meeting sponsor defined experience criteria were required to undertake an enriched training before certification. Once in-study, all CDR assessments were audio recorded and reviewed by blinded, calibrated independent reviewers for the presence of administration and/or scoring errors. GEE (Generalized Estimating Equations) models were used to assess the difference between the experienced raters and the naïve raters. GEE models can accommodate the correlation among the measurement from the same rater. The model used binomial distribution and logit link. Compound symmetry working correlation structure was chosen and the conventional type I error of 0.5 was used as the cut-off for statistical significance. P-values were not adjusted for multiple testing. **Results:** The dataset consisted of a total of 25,068 audio recorded CDR assessments. CDR administration errors were identified in 5,015 (20%) cases while scoring errors were identified in 3,689 (14.7%) cases. As study interaction was not significant, the interaction term was dropped from the model. No significant differences were identified in the presence of administration or scoring errors between experienced and naïve raters. **Discussion:** Our retrospective analysis of rater performance did not identify any meaningful difference in the presence of administration or scoring errors between experienced and naïve raters in 5 large early AD trials. Enriched training curriculum is able to equip inexperienced raters with necessary practical knowledge of the CDR to be able to confidently administer and score the CDR on par with experienced raters. The results of our analyses need to be interpreted with caution. Despite its large size, the analysis is retrospective. As well, the identification of scoring and administration errors relies on the ability of independent reviewers to detect these errors. While all independent reviewers are trained and standardized, individual differences may exist. We plan further analyses with other instruments.

P016- AUTOMATIC SCREENING FOR CDR STAGES IN THE SWEDISH H70 BIRTH COHORT USING A DIGITAL SPEECH BIOMARKER FOR COGNITION SB-C. E. Mallick[1], F. Öhman[2], N. Linz[1], A. König[1], M. Schöll[2], S. Kern[2], J. Tröger[1], I. Skoog[2] *(1. ki elements GmbH - Saarbrücken (Germany), 2. Institute of Neuroscience and Physiology at the Sahlgrenska Academy University of Gothenburg - Gothenburg (Sweden))*

Background: The Clinical Dementia Rating Scale (CDR) is arguably the most widely used instrument to detect and stage dementia, it is one of the most-established clinical trial endpoints in Alzheimer's and is routinely used to characterize trial populations. However, it is not ideal for a clinical trial cost-effective low-burden general population screening funnel. Speech-based digital measures on the other hand can be deployed in a highly automated and scaled fashion. Therefore, we present the results of an CDR stage screening based on a digital Speech Biomarker for Cognition (SB-C) in the Swedish H70 birth cohort study. **Method:** This research is based on a sample from the Swedish H70 Birth Cohort study (N=695; 542 CDR Total score = 0, 153 CDR Total score = 0.5). We automatically extract the SB-C score and its subscores (executive function, memory, semantic memory, processing speed) from SVF and RAVLT speech recordings using ki:elements' proprietary speech analysis pipeline including automatic speech recognition and feature extraction. We weighted the SB-C subscores for CDR sensitivity and performed (1) inferential statistics comparing CDR groups based on the SB-C Weighted Score and (2) determined a cutoff to differentiate between CDR groups (CDR = 0 vs. CDR = 0.5). For (1) we performed a non-parametric Kruskal-Wallis test to compare SB-C Weighted Score of both CDR = 0 and CDR = 0.5 groups to check for general feasibility. For (2), we applied an optimal cut-off procedure aimed at maximizing the sum of sensitivity and specificity in discriminating between CDR groups. **Results:** The Kruskal-Wallis test revealed a significant difference of the SB-C Weighted Score between the CDR groups (CDR = 0 > CDR = 0.5; $\chi 2 = 87.68$ (1), $p < 0.001$). The optimal cutoff analysis showed that a cutoff of -0.53 in the SB-C Weighted Score differentiated between CDR groups with a balanced accuracy and a ROC-AUC score of 0.71. Sensitivity and

specificity of the classification were both 0.71. **Conclusion:** We found that a threshold on the SB-C Weighted Score can separate CDR stages 0 and 0.5 in a representative general population of older people using a speech-based automatic read-out. This method therefore represents a promising alternative for trial population characterization especially in general population screening funnels for preclinical AD trials. **Keywords:** MCI, Screening, Dementia, Digital Cognitive Assessment, Speech Analysis, CDR, General Population. **Disclosures:** EM, NL, AK and JT are employed by the digital speech biomarker company ki:elements. NL and JT hold shares in the digital speech biomarker company ki:elements. The other authors have nothing to disclose.

P017- ENHANCING CLINICAL TRIAL EFFICIENCY IN ALZHEIMER'S DISEASE: AN APPLICATION OF PROGNOSTIC SCORING ADJUSTMENTS TO ADDRESS HETEROGENEITY. H. Parr[1], J. Lin[2], D. Thompson[1], D. Inman[1], A. Perperoglou[1] *(1. GSK - London (United Kingdom), 2. GSK - Philadelphia (United States))*

Background: Alzheimer's Disease (AD) is a complex neurodegenerative disorder characterized by significant heterogeneity in its clinical presentation and progression over many clinical endpoints. Heterogeneity has a sizable impact in the timing of early AD trials and on any inferential analysis that follows. There has been a growing appreciation in recent years for researchers to apply cutting-edge machine learning (ML) techniques that leverage the wealth of existing external data to better understand patient heterogeneity in the pursuit of more efficient AD trials and analyses. Here we demonstrate a novel methodology, illustrate the gains in statistical efficiency and in statistical power, and explore extensions into a repeated-measures framework [1]. **Methods:** Previous work has shown the gains to be made in incorporating prognostic scores (PS) which are additionally robust to violations in key assumptions (e.g. in the presence of treatment heterogeneity) [2]. Here we apply this in a repeated-measures context, the extended framework follows three key stages: (1) an ensemble of ML models are developed and trained on pre-existing data external to the trial; (2) this ML ensemble is applied to give a PS for every patient in the present trial, predicting their likely outcome on a standard-of-care treatment[3]; and (3) the per patient PS is integrated as a 'super-covariate' in the standard Mixed models for repeated measures (MMRM) analysis. We then perform extensive simulations to quantify the power improvement offered by our approach. We additionally stress-test this by considering various scenarios under which required assumptions could be violated, thus highlighting the robustness of the methodology. **Results:** Initial results suggest similar benefits in the repeated-measures context as has previously been demonstrated for cross-sectional analyses for AD trials. The use of PS did not considerably change bias and often improved the precision of our treatment effect estimates. Notably, our approach indicates absolute increases in power of AD trials by an additional >5-10% from the intended 80%, and/or increased to reach an adequately powered threshold. The addition of these PS offers a significant improvement in helping to detect the treatment effect, which can substantially improve the probability of success, or require fewer patients, and hence reduce the duration, cost, and patient burden of these trials. Exhaustive simulations are ongoing, and results will be presented in full. **Conclusion:** The application of machine learning techniques can effectively better capture the relationship between the developed PS and outcome, which may in part address the heterogeneity and temporal dynamics and improve precision in estimating treatment effects within AD trials. This approach boosts trial efficiency, maximizes power, and provides a promising avenue for future AD clinical trials. Given the expected improvement, even under plausible deviations in assumptions and scenarios, these methods should be incorporated into the statistical analysis plan of AD trials where possible. By doing so, we can improve power, reduce sample sizes, and ultimately accelerate the development of effective treatments for AD patients that are so urgently needed. **Keywords:** Prognostic Scores, Mixed models for repeated measures (MMRM), Synthetic Data, Machine Learning. **Clinical Trial Registry:** N/A. **Data Deposition:** N/A. **Disclosures:** All authors are employees of GSK and own shares in the company. References : 1. V. Devanarayan et al., Alzheimers Dement. 20, 1725–1738 (2024). 2. A. Schuler et al., Int. J. Biostat. 18, 329–356 (2022). 3. B. Holzhauer, E. T. Adewuyi, Pharm. Stat. 22, 1062–1075 (2023).

P018- IMPACT OF TRAVEL DISTANCE AND PARTICIPANT AGE ON POTENTIAL ALZHEIMER'S DISEASE TRIAL PARTICIPANT ATTENDANCE AND CLINICAL TRIAL ELIGIBILITY. S. Starling[1], A. Pratt[2], A. Rosen[2], S. Barr[2], B. Billy[2], G. Munoz[2], M. Rapp[2] *(1. Adams Clinical - Watertown (United States), 2. Berman Clinical - New York (United States))*

Background: Identifying factors that can influence potential participants' attendance and eligibility is critical for effective recruitment in Alzheimer's Disease (AD) trials1. Previous studies link further travel distance to higher no-show and drop-out rates in Major Depressive Disorder (MDD) trials2. We explored whether distance from the site and participant age impacted both the likelihood of potential AD participants attending a prescreening visit, and their eligibility to screen into an industry trial. **Methods:** Our sample includes prospective AD trial participants scheduled for pre-screening visits from July 2023 to March 2024. Participants submitted their contact information online in response to ads on Google and Facebook. Recruiters then called these participants to conduct virtual interviews and scheduled potentially eligible participants for an in-person pre-screening visit with a clinician. Advertising was targeted towards individuals located within Manhattan, The Bronx, Queens, and Brooklyn. This analysis examined the impact of age and travel distance from the site on the likelihood of a participant attending a pre-screening visit and eligibility to screen for an industry trial. **Results:** This sample draws from AD participants who scheduled a pre-screening visit (PSCV) with Berman Clinical from JUL2023-APR2024. 1871 participants scheduled a PSCV, of which 1661 reported their address. Further analyses focus on these 1661 participants. Average travel distance to the site was 14.8 miles (SD=17.6). 65% (1081) of participants attended their appointment either on the first scheduling attempt or after rescheduling at least once. Distance from the site influenced PSCV attendance. Participants who lived further from Berman Clinical were less likely to ever attend their PSCV (β=-.016, p<.001) and, if they did eventually attend, were more likely to reschedule at least once (β=.010, p=.015). Age did not impact attendance rate (p=.989). Of those who attended a PSCV, age and travel distance were found to be significant predictors of whether a clinician deemed them eligible to screen for an industry trial, referred to as a PSCV pass. Older participants were more likely to pass the PSCV (β=.048, p<.001). Participants with a further travel distance were also more likely to pass (β=.010, p<.043). **Conclusion:** In

accordance with findings from MDD recruitment data, these results suggest that participants located at a greater distance from our site were less likely to attend their scheduled pre-screening visit. Those that did attend were also found to be more likely to have rescheduled at least once. Critically, however, of the participants that attended, those that lived a greater distance from the site had a higher PSCV pass rate than those with a shorter travel distance. Our results indicate that even if those at a distance from the site had less reliable attendance overall, clinical research sites should continue to recruit these participants as those that make the effort to travel are likely to be deemed eligible to screen for an industry trial. **References:** 1. Puffer, S., & Torgerson, D. (2003). Recruitment difficulties in randomized controlled trials. Controlled Clinical Trials, 24, 214-215; 2. Sauder, C., Sauder D., Engler, J., Evans, M., Vu, A., Domilici, D., Rutrick, D. (2020, September). Assessing the Impact of Travel Time and Distance on Participation in Clinical Research. [Poster presentation]. ISCTM Virtual Conference

P019- IINTEGRATING A SPEECH-BASED PRESCREENING TOOL IN CENTRAL RECRUITMENT STRATEGIES FOR ALZHEIMER'S DISEASE CLINICAL TRIALS: A PILOT STUDY. C. Skirrow[1], A. Block[2], N. Hank[2], J. Weston[1], E. Fristed[1], J. Rock[3] *(1. Novoic Ltd - London (United Kingdom), 2. Perseverance Research Center - Scottsdale, Az (United States), 3. AriBio - San Diego, Ca (United States))*

Background: Identification and recruitment of early-stage Alzheimer's disease (AD) patients for clinical trials poses significant challenges. Centralised recruitment strategies are commonly used to boost patient leads through online advertisement and referrals; however, most centralised recruitment platforms result in high screen failure rates, which not only discourages sites from utilizing such platforms, but demotivates sites from comprehensively recruiting, consequently diminishing uptake of referrals over time. Utilizing disease-sensitive pre-screening measures; however, can potentially enhance referral quality. This pilot study outlines the incorporation of Storyteller, an online, self-administered, speech-based cognitive assessment, into central recruitment efforts for AriBio's Polaris-AD study. The initial aims of the study are to ascertain uptake of the tool and its potential for improving referral quality from central recruitment sources. **Methods:** Polaris-AD is a Phase 3 double-blind randomised placebo-controlled trial evaluating the efficacy and safety of AR1001 in early-stage AD patients. Storyteller has been incorporated into central recruitment efforts for 15 out of 60 Polaris-AD sites in the US since early January 2024. Candidates from online recruitment adverts arrive on the study landing page where they complete an online pre-qualification questionnaire via embedded form (including age, self-reported memory, problem solving or other cognitive impairment, availability of study partner, and demographic information) followed by Storyteller, an online speech-based assessment evaluating memory function via story recall tasks. **Results:** Out of 404 online leads who completed and passed the initial pre-qualification questionnaire, 37.6% (152 individuals) completed Storyteller. Out of the individuals who completed Storyteller, two-thirds scored within the normative ranges indicative of potential memory decline or impairment (low average range N=23 (18%), low range N=20 (13%), very low range N=53 (35%)), indicating their suitability for their further evaluation. **Conclusion:** Central recruitment efforts are costly, can be inefficient and lead to site disengagement. Through integrating cognitive pre-screening tools, the suitability of centrally recruited samples can be enhanced. In the present study, 36.7% of online leads completed an optional cognitive and speech based assessment. A significant number of participants who undertook the Storyteller test demonstrated scores consistent with memory impairment, in keeping with self-reported memory impairment as described during questionnaire pre-qualification. As this pilot study advances, with patients navigating further through the study process, a more detailed assessment of Storyteller's utility as a pre-qualification tool for clinical trials will become attainable. **Keywords:** Alzheimer's disease, early detection, cognitive assessment, Storyteller, clinical trials, pre-screening. **Disclosures:** JW, EF and CS are employed by and/or option- or shareholders of Novoic. AB and NH represent a clinical trial site, JR is employed by and a shareholder of AriBio.

P020- IMPACT OF SCREENING CALL DURATION ON INITIAL EVALUATION ATTENDANCE RATE FOR ALZHEIMER'S DISEASE DRUG TRIALS. Y.J. Huoh[1], B. Martinez[1], S. Hopkins[1], E. Sosa[1], K.J. Sanchez[1], J. Mitolo[1], T. Parnitvithikul[1], E. Lee[1], R. Lee[1] *(1. Irvine Clinical Research - Irvine (United States))*

Background: Alzheimer's Disease (AD) drug trials are slower to enroll and more expensive than trials in most other therapeutic areas. Because the target population for AD drug trials has some form of cognitive impairment, this can lead to low appointment attendance rates; an attendance rate for initial evaluation appointments below 50% is typical across the industry. Given all the time and money spent identifying and scheduling an initial evaluation appointment for a potential participant, even small improvements to attendance rate can lead to big improvements in recruitment efficiency. In this study, we examine the relationship between screening call duration and the attendance rate of downstream initial screening visit appointments that are scheduled as a result of these screening calls. **Methods:** From August 2023 to March 2024, 2,267 potential participants had appointments scheduled for an in-person initial screening at a commercial Alzheimer's Disease site in California. These potential participants were identified primarily through online advertising campaigns. In order to be scheduled for an initial screening appointment, a recruiter reaches out to a potential participant and conducts a phone screening. These screening calls had an average duration of 6 minutes and 35 seconds, with a standard deviation of 4 minutes and 12 seconds. Of these 2,267 potential participants, 1,258 attended their scheduled appointment, 586 modified (canceled or rescheduled) their scheduled appointment, and the remaining 423 did not show up or modify their scheduled appointment. A multinomial logistic regression analysis was conducted to evaluate the impact of the screening call duration on the different outcomes while controlling for how many days out the appointment was scheduled. Previous studies have shown that the number of days between when the appointment is created and the scheduled appointment date (the scheduling lag) to be a significant driver for attendance, modification, and no-show rates for the initial screening visit of Alzheimer's trials. **Results:** A multinomial regression of the appointment outcomes for the initial screening appointment against screening call duration while controlling for appointment scheduling lag showed the impact of screening call duration to be statistically significant. Inclusion of screening call duration into the regression improved the model deviance by 2= 7.136 on two degrees of freedom, yielding a p-value of 0.028. A separate

logistic regression of no show rates (the outcome with the largest screening call duration effect size in the multinomial regression) against screening call duration while controlling for scheduling lag also revealed a clearly significant effect (β = -0.0051, p= 0.026). **Conclusion:** Based on the outcomes of the analysis, it is clear that there is a negative relationship between screening call duration and no-show rates for initial screening appointments for Alzheimer's Disease drug trials; potential participants who spend more time on the phone are less likely to outright not attend a scheduled initial screening appointment. One potential reason for this observed behavior could be that a longer conversation during the phone screening process helps build a better connection between the potential participant and the clinic conducting the trial. This improved rapport leads to higher commitment levels - so even if the person cannot attend their appointment, they will at least call in to cancel their appointment, freeing up the time slot for someone else. Alternatively, a longer conversation on the phone talking about the trial could make it easier for someone with cognitive impairment to remember any subsequent appointments that resulted from that conversation. This could be another potential explanation for the observed relationship between call duration and no show rates. Unfortunately, the analyses conducted in this study are merely correlative and not enough to conclusively infer a causal relationship between phone screen duration and no show rates; additional studies will be necessary in order to determine causality of the relationship.

LP001- FREQUENCY OF SAE AND MORTALITY RATE IN ALZHEIMER'S DISEASE (AD) CLINICAL TRIALS: DATA FROM MEDICAL AND STATISTICAL REPORTS FROM US FDA INCLUDING SEVEN APPROVED MEDICATIONS CONSISTING OF A TOTAL DATABASE OF 19,921 SUBJECTS. A. Arora[1], A. Khan[1] *(1. Northwest Clinical Research Center - Bellevue (United States))*

Background: Although several therapeutic agents have come to market for AD, there is controversy about their safety, specifically related to serious adverse events (SAEs) and mortality risk with these agents compared to placebo and at the severity of the syndrome (Wolk et al, 2023). In order to quantify these risks, we collected data from the clinical trials for four ACh reuptake inhibitors (AChEIs) and the more recently approved three monoclonal antibodies (mAb). **Methods:** We reviewed extensive safety data from the US FDA Medical and Statistical reports from https://www.accessdata.fda.gov/. We focused on the total number of subjects assigned to the drug versus placebo and evaluated the frequency of SAEs and mortality rates. Data was obtained for approved doses of memantine, galantamine, rivastigmine, donepezil, lecanemab, aducanumab, and donanemab. Patient exposure years (PEY), representing the total time participants are exposed to a treatment, were taken from safety data, or calculated by multiplying the exposure duration by the number of patients and summing these products. **Results:** The mortality rate across all AD trials, including 19,921 patients, was 0.8%. This rate was consistent among patients assigned to placebo in trials for AChEIs (78/9,775, 0.8%) and those assigned to the drug (85/11020, 0.8%). In mAb trials, the rate was (29/2858, 1%) in the placebo group and (37/2856, 1.3%) in the drug group. Using the PEY method, the mortality rate of patients in AChEI trials assigned to placebo was 1755/100K/yr, while that of those assigned to the drug was 1719/100K/yr. In mAb trials, the mortality rate for patients assigned to placebo was 585/100K/yr, and for those assigned to the drug, it was 746/100K/yr. A similar pattern is seen among the rate of SAEs. In AChEI trials, the rate of SAEs among patients assigned to placebo was (353/6043 patients, 5.8%), and for those assigned to the drug, it was (504/8164, 6.2%). Among patients assigned to placebo in mAb trials was (376/2858 patients, 13.2%) for those assigned to placebo and (418/2856, 14.6%) for those assigned to the drugs. Using the PEY analysis method, the rate of SAEs for AChEIs was 23,146/100K/yr for placebo and 25,676/100K/yr for the drug. For mAb, the SAE rate was 7,582/100K/yr for placebo and 8,429/100K/yr for the drug. **Conclusion:** The relatively low rate of SAEs and mortality rates were not expected. In other words, even in the relatively longer trials (six to eighteen months) included here, these data are from highly selected outpatients who were not in the terminal stages of the illness and thus do not assess the true morbidity and mortality seen with Alzheimer's disease, between approved medications and placebo. Since some of the AD patients in AChEI trials may have had a more advanced stage of the illness, the morbidity and mortality were somewhat higher among these trials, although still very low. Clinical trials that include subjects with a far more advanced stage of AD or trials that last for much longer periods of participation are needed to truly assess the morbidity and mortality of the newer therapies compared to placebo. **Keywords:** Alzheimer's Disease, Monoclonal Antibodies, Acetylcholine Reuptake Inhibitors, mortality. **Disclosures:** Public domain data used. Authors declared no competing interests. **References:** 1. "DRUGS@FDA: FDA-Approved Drugs." FDA, www.accessdata.fda.gov/scripts/cder/daf/index.cfm. 2. Wolk, D. A., Rabinovici, G. D., & Dickerson, B. C. (2023). A Step Forward in the Fight Against Dementia-Are We There Yet?. JAMA neurology, 80(5), 429–430. https://doi.org/10.1001/jamaneurol.2023.0123.

LP002- THE IMPORTANCE OF RIGOROUS DATA QUALITY ASSURANCE AND MANAGEMENT IN CLINICAL STUDIES OF THE AI ERA: THE INNOVATIVE AI-MIND STUDY. V. Andersson[1], C. Hatlestad-Hall[1], A. Drews[2], H. Renvall[3,4], F. Maestú[5,6], C. Marra[7,8], I.H. Haraldsen[1], P.M. Rossini[9] *(1. Oslo University Hospital - Oslo (Norway), 2. University of Oslo - Oslo (Norway), 3. Helsinki University Hospital - Helsinki (Finland), 4. Aalto University - Helsinki (Finland), 5. Universidad Complutense Madrid - Madrid (Spain), 6. San Carlos University Hospital - Madrid (Spain), 7. Università Cattolica del Sacro Cuore - Rome (Italy), 8. Fondazione Policlinico Universitario Agostino Gemelli IRCCS, - Rome (Italy), 9. IRCCS San Raffaele Pisana - Rome (Italy))*

Background: Dementia, particularly Alzheimer's disease, affects millions of people worldwide, with mild cognitive impairment (MCI) often being a precursor to the disease. Current diagnostic methods are invasive, costly, both in time and financially, and show low sensitivity which limits their effective use in early detection. The AI-Mind project [1] aims to address these challenges. Effective AI-based diagnostic tools require rigorous data quality assurance and automated management systems to ensure the integrity and accuracy of multimodal data, such as EEG recordings, cognitive tests, and biomarkers in case of AI-Mind. Our approach facilitates the development of cost-effective, non-invasive diagnostic tools to identify individuals at dementia risk at a non-symptomatic stage. **Methods:** The AI-Mind project is a five-year initiative with a two-year longitudinal clinical study involving 1,000 MCI participants aged 60-80 years at the time of recruitment from four European countries. Data management is conducted via automated injection procedures to one secure Server for

Sensitive Data (TSD) at the University of Oslo [2]. All metadata, including clinical and socio-demographic data, is collected via the web-based system 'Nettskjema,'3 which directly injects the registered data from all European countries to the TSD server for seamless tabular data collection and storage. M/EEG data and the self-administered computerized cognitive test results are automatedly injected as well daily into the TSD storage area. Blood samples are sent to the one centralised AI-Mind biobank for analyses in collaboration with our partner Roche Diagnostics and PreDiagnostics, resulting in all genetic and protein data information stored on the same TSD server. At the file staging area within TSD, data is verified by the AI-Mind platform quality assurance procedures, curated, and prepared for AI model development, ensuring a secure, smooth and efficient process for all clinical data ingestion and storage. **Results:** By early 2024, 1023 participants have been recruited, with 2-year data already obtained from 163. The AI-Mind database now comprises extensive multimodal data, enabling robust AI model development. The project has established standardised, efficient and user-friendly pipelines for data collection, ingestion, curation, and quality assessment from all sites. All local procedures reaching from how to collect, calibrations of instruments and data transfer are easily accessible by the AI-Mind QR code system. Finally, the platform will now house the two primary AI-based tools: the AI-Mind Connector, which identifies dysfunctional brain networks using EEG data, and the AI-Mind Predictor, which estimates dementia risk on multimodal data. The project aims to achieve specificity and sensitivity levels of 0.90-0.95 for predicting dementia risk. **Conclusion:** The AI-Mind project is poised to revolutionize the early detection of cognitive decline and management of MCI through its innovative use of AI and multimodal data integration in a clinical setting. By providing a non-invasive, cost-effective screening method, AI-Mind addresses the urgent need for improved non specialist diagnostic tools in MCI care. Its success could lead to widespread clinical adoption, improved data quality, better outcomes, and a reduction in the socio-economic burden of the disease. **Keywords:** Mild cognitive impairment, dementia, artificial intelligence, clinical study. **Clinical Trial Registry:** NCT05159661. **Data Deposition:** https://doi.org/10.3389/fnbot.2023.1289406. **Disclosures:** This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 964220. The abstract reflects views of authors and the European Commission is not responsible for any use that may be made of the information it contains. The authors declared no competing interests. **References:** 1. Haraldsen, Ira H., et al. Frontiers in Neurorobotics, vol. 17, 2023, p. 1289406. https://doi.org/10.3389/fnbot.2023.1289406; 2. Program: TSD (Tjeneste for Sensitive Data) facilities, University of Oslo, 2024, Accessible: https://www.uio.no/english/services/it/research/sensitive-data/index.html; 3. Program: Nettskjema, University of Oslo, 2024, Accessible: www.nettskjema.no.

LP003- GAN-SYNTHESIZED RESTING-STATE EEG AND ITS CLINICAL RELEVANCE IN DEMENTIA STUDIES.

V. Andersson[1], C. Hatlestad-Hall[1], H. Renvall[2], F. Maestú[3], C. Marra[4], P. Maria Rossini[5], A. Yazidi[6], I. H. Haraldsen[1], R. Upreti[1] *(1. Oslo University Hospital - Oslo (Norway), 2. Helsinki University Hospital - Helsinki (Finland), 3. Universidad Politécnicade Madrid - Madrid (Spain), 4. Università Cattolica del Sacro Cuore - Milan (Italy), 5. the Scientific Institute for Research, Hospitalization and HealthCare - Rome (Italy), 6. Oslo Metropolitan University - Oslo (Norway))*

Background: To make dementia treatment more accessible, accurate and fast, artificial intelligence (AI)-based screening tools are emerging as potential solutions. However, large-scale high-quality data representing diverse groups (gender, age, geographical location, race, dementia subtypes) are scarce. This limitation hinders the effectiveness of AI screening tools and introduces biases in clinical decision-making. To mitigate this issue, synthetic data, also known as AI-generated data, has emerged as a promising supplemental solution for training AI model in different sectors including healthcare [1] . The AI-Mind project aims to develop and validate AI-based tools to predict the risk of dementia based on longitudinal data of 1023 individuals with mild cognitive impairment from four European countries [2] . The AI-Mind data is collected using well established standard protocols which ensure high data quality. However, AI-based screening tools trained on 1023 samples only may not generalize without risk to unseen new data. Thus, the AI-training data could be further improved by adding artificially generated EEG data. Importantly, the US Food and Drug Administration's (FDA) endorsement of synthetic data for clinical studies in cancer treatment has already demonstrated its potential utility in healthcare applications [3] . Importantly, generative AI models offer the possibility to synthesize data with specific group characteristics (and potentially even personalized data) through simulation techniques. Currently, dementia research has not thoroughly explored the potential of using synthetic data, and existing literature lacks a consensus with regards to accepted methods for assessing the validity of synthetic data from a clinical perspective. **Methods:** Here, we demonstrate an AI-based generative model to synthesize resting-state (eyes closed) EEG data based on the AI-Mind data using generative adversarial networks (GANs) and investigate the quality and usability of synthetic EEG data in improving AI model performance. By scaling the AI-Mind data by multiple factors, especially considering minority groups, may facilitate generalizability of AI models to unseen new data. Our research involves generating high-fidelity synthetic EEG signals that mimic the neurophysiological patterns observed in individuals with dementia-related pathology. To demonstrate the validity of the synthetic data, we have compared the synthetic and real data on well-established neurophysiological markers consistently described in mild cognitive impairment and dementia patient populations. **Results:** Our preliminary results indicate that the synthetic data successfully captures the data distribution and power spectra features of the real data. The power spectra in commonly examined frequency bands over different brain regions are similar between synthetic and real data. With synthetic data, we aim to enhance the accuracy of the AI-Mind Predictor model and to facilitate its generalizability to unseen data by targeting minority and exceptional cases. **Conclusion:** Synthetic data is a promising candidate for enhancing the robustness of AI-based dementia screening tools, including the AI-Mind Predictor, and for paving the

way for more inclusive and widespread diagnostic solutions in clinical settings. **Keywords:** AI-Mind, electroencephalography (EEG), synthetic data, generative adversarial networks (GANs). **Clinical Trial Registry:** Not applicable. **Data Deposition:** Not applicable. **Disclosures:** This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 964220. This presentation/publication reflects the views of the authors, and the European Commission is not responsible for any use that may be made of the information it contains. The authors declare no competing interests. **References:** 1. de Melo, CM, et al. (2022). Trends Cogn Sci, 26(2), 174-187. doi: 10.1016/j.tics.2021.11.008; 2. Haraldsen, IH, et al. (2023). Front Neurorobot, 17, 1289406. doi: 10.3389/fnbot.2023.1289406; 3. Morrison, T. M. Ann Biomed Eng, 51(1), 1-5. doi: 10.1007/s10439-022-03116-7.

LP004- SHIMMER: BASELINE DATA AND EARLY LESSONS FROM THE ONGOING PHASE 2 SIGNAL-FINDING STUDY OF CT1812 IN MILD-TO-MODERATE DEMENTIA WITH LEWY BODIES (DLB). JE Galvin[1], MI Tolea[1], JF Iaci[3], T Devins[3], ME Hamby[3], M Grundman[2], AO Caggiano[3] *(1. Comprehensive Center for Brain Health, Dept of Neurology, University of Miami Miller School of Medicine, Miami, FL (United States), 2. Global R&D Partners, San Diego, CA (United States), 3. Cognition Therapeutics Inc., Purchase, NY (United States))*

Background: CT1812 is an experimental oral, small molecule in clinical development for Alzheimer's disease and dementia with Lewy bodies (DLB). CT1812 is a ligand for the sigma-2 receptor hypothesized to function by preventing binding and displacing toxic amyloid and alpha-synuclein oligomers from receptors on brain cells. The COG1201 "SHIMMER" trial (NCT05225415) is studying the safety, tolerability and exploratory measures of efficacy in people with mild-to-moderate DLB. **Methods:** This multi-center, double-blind, placebo-controlled, parallel-design study is evaluating 300mg or 100mg of CT1812 treatment versus placebo for six months. Randomized participants signed informed consent and met inclusion criteria including age 50-85 years, probable DLB (4th report of the DLB Consortium - McKeith et al. 2017), MMSE 18-27, and without other neurological co-morbidities. Participants were randomized evenly to receive 300mg, 100mg CT1812 or placebo PO daily and assessed throughout the treatment period for safety via reported adverse events, physical exam, vital signs, and laboratory values. Exploratory efficacy measured changes in the Montreal Cognitive Assessment Scale (MoCA), Adapted Clinician Assessment of Fluctuation (CAF), Epworth Sleepiness Scale (ESS), ADCS-CGIC, MDS-UPDRS Part III, ADCS-ADL, and the Mini-Mental State Examination (MMSE). The last participant was randomized in May 2024 and top-line data are expected year end 2024. Demographics and Baseline Characteristics: 293 individuals were screened and 130 randomized. The most common reasons for screen failure were MMSE range, stable con-meds and ability to complete evaluations. At the time of this drafting, 20 participants had discontinued treatment with adverse events as the most common reason. Baseline characteristics include mean age of 72.8 years, 106 males, mostly white and non-Latino. At baseline the mean MoCA score was 18.4, CAF was 5.9, ESS was 8.4, MDS-UPDRS Part III was 27.7, ADCS-ADL was 62.5, MMSE was 24.0. **Outcomes:** Change from baseline for the exploratory efficacy outcomes will be reported with MoCA defined as the first of the exploratory measures. The difference between treatment groups (combined CT1812 vs. placebo) will be assessed using a mixed model for repeated measures with change from baseline values at Months 1, 3, and 6 as the response values, treatment group, time point, and a treatment group by time point interaction as fixed effects, subject as a random effect, and baseline value as a covariate. Alpha-synuclein and amyloid status will be assessed via skin biopsies (CND Life Sciences) and plasma phosph-tau217 with amyloid monomer ratio, respectively. Other plasma biomarkers changes including GFAP and NfL will be evaluated. Initially CSF was collected at baseline and upon completion of the treatment period. CSF collection was made optional with a protocol amendment to enhance recruitment. Other protocol amendments included allowing a drug holiday while participants were treated with nirmatrelvir / ritonavir (Paxlovid) for Covid-19 due to the CYP3A4 inhibition. **Conclusion:** SHIMMER will be the first proof of concept study of CT1812 in DLB with the objectives of identifying a tolerable dose range and trends for slowing cognitive decline. Complete details of study design, baseline characteristics and demographics will be reported.

LP005- CLINICAL TRIAL ENRICHMENT STRATEGY FOR PARTICIPANT SELECTION IN THE PHASE 3 HOPE STUDY OF ALZHEIMER'S DISEASE: PROGRESS TOWARDS PERSONALIZED MEDICINE. L. Lee[1], C. Houser[1], A. Konisky[1], E. Hempel[1], C. Seshagiri[1], M. Hajos[1], C. Howell[1], R. Kern[1] *(1. Cognito Therapeutics - Cambridge, MA (United States))*

Background: Addressing Alzheimer's disease (AD) biological and clinical heterogeneity is important to appropriately select clinical trial populations [1]. Given the significant familial, societal, and health economic burden of AD, there is an urgency to conduct trials that combine the right participants with appropriate target and predictive biomarkers to increase clinical trial success [2]. Recently, the FDA provided clinical trial enrichment guidance for industry to help advance these objectives [3]. Blood pTau biomarkers have gained important relevance due to their AD biological specificity and as predictive measures of AD amyloid burden, disease severity and progression rate [4]. The ongoing HOPE randomized, controlled, pivotal study (NCT05637801) is evaluating the efficacy and safety of SpectrisTM, a non-invasive, daily, home-use device that evokes brain gamma-band oscillations, for the treatment of mild-moderate AD. We report interim observations of our clinical trial enrichment strategy, focused on confirmation of brain target engagement and measurement of plasma pTau181. **Methods:** Participants are evaluated for the presence of plasma pTau181 (Quanterix, cutoff ≥ 14.2 pg/mL) [5]. Participants then undergo a Tolerance and Gamma Response (T+GR) assessment to confirm target engagement using a participant-specific stimulus range that evokes the target gamma-band EEG activity. **Results:** Interim screening results from the ongoing HOPE study (N=500) demonstrated that 83% of screened participants had a positive pTau181 (mean 32.2 pg/mL; range 14.2 to 212.9 pg/mL). For T+GR evaluation, target engagement was confirmed in 85% of participants screened. The most common reason for T+GR failure was impaired hearing. **Conclusion:** Participant selection through clinical trial enrichment strategy in the HOPE study is being successfully implemented to select a consistent AD patient population who show proof of target engagement. Screening plasma Ptau181 positivity selects participants with a more predictable rate of decline of daily function, cognition and brain atrophy. Proof of target engagement with T+GR confirms that all participants are able to generate an evoked brain gamma response. In the

context of the growing and diverse AD population in clinical trials, this strategy represents progress towards personalized medicine. **Keywords:** Clinical trial enrichment, Alzheimer's Disease, Phase 3. **Disclosures:** Authors are employees of, or own equities in Cognito Therapeutics. **References:** 1. Duara Neurotherapeutics 2022; 2. Cummings Alzheimer's Research and Therapy 2019; 3. Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products | FDA; Gonzalez-Ortiz Molecular Neurodegeneration 2023; 4. Tropea Annals of Clinical and Translational Neurology 2023; 5. Kivisakk Frontiers in Neurology 2023; Alzheimer's Detection Made Simple | Whitepaper (quanterix.com).

LP007- INTERNATIONAL REGISTRY FOR AZHEIMER'S DISEASE AND OTHER DEMENTIAS (INRAD): APPLICATION OF LONGITUDINAL PRACTICE-BASED DATA TO AUGMENT AND CONDUCT CLINICAL TRIALS IN EARLY-STAGE ALZHEIMER'S DISEASE. R. Perneczky[1,2,3], V.B. Johan[4], H. Robert[4], I.G. Ignacio[5], J. Frank[6,7] *(1. Department of Psychiatry, LMU Hospital, LMU Munich - Munich (Germany), 2. German Center for Neurodegenerative Diseases - Munich (Germany), 3. University of Sheffield, Department of Neurosciences - Sheffield (United Kingdom), 4. TW1 Healthcare Consulting Ltd. - London (United Kingdom), 5. Hospital de La Santa Creu i Sant Pau, Department of Neurology, Memory Unit - Barcelona (Spain), 6. Department of Psychiatry, University of Cologne - Cologne (Germany), 7. German Center for Neurodegenerative Diseases - Cologne (Germany))*

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, public awareness and outreach. Registries can be leveraged to accelerate the conduct and execution of clinical trials in Early AD. **Methods:** The International Registry for Azheimer's Disease and Other Dementias (InRAD) is designed as an interactive, dynamic, multinational disease registry aimed at collecting, organizing, and providing feedback based on practice-based data, including patient history, clinical and biomarker outcomes, and safety profiles for AD and dementia care. The harmonised minimum dataset (MDS) and extended dataset (EDS) will form the basis of data captured in InRAD, with longitudinal individual and aggregated data becoming instrumental in identifying disease trajectories, trends, and gaps within specific populations. Registry data as well registry sub-study framework may increase efficiencies in trial design, patient recruitment, trial conduct, extensions of clinical trials at all stages in the development life cycle, addressing impact of post-approval commitments and risk managment. **Results:** The InRAD harmonised MDS and EDS collected longitudinally will enable: The use of disease characteristics and event rates will allow for the optimization of clinical trial designs. This will lead to better-defined target populations and more efficient sample size calculations, contributing to improved outcomes. Pre-screening of InRAD registry data against trials inclusion and exclusion criteria across participating centers will enable efficient identification of potential candidates. This process will focus on patients with objective cognitive impairment, particularly for early-stage AD treatment trials. The InRAD registry can serve as a centralized platform that provides patients, caregivers, and the public with up-to-date information on available clinical trials. The framework and operations of the InRAD registry with systematic historical data collection can provide the basis for continued data collection in clinical trials whether after randomisation to an intervention or procedure or in case-controlled investigations. Additionally, the registry could provide an additional trial arm of patients receiving standard-of-care (contemporaneously propensity-matched). The InRAD registry will document clinical trial participation, providing a framework to ensure for the longterm extended follow-up of patients beyond clinical trial participation. The InRAD platform will enable the systematic collection of key safety and core clinical outcomes, supporting the assessment of post-approval safety, outcome or value-based questions, and the impact of risk minimization efforts. **Conclusion:** A systematic approach to global real-world data both inter- and intra-centre, and internationally, will provide a robust augmentation to the conduct of clincial trials and research in AD. **Keywords:** Alzheimer's disease; dementia; registry; real-world; clinical trial; recruitment; pre-screening. **Disclosures:** 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. 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. IIG received research grants from the Global Brain Health Institute, Alzheimer's Association, the Alzheimers Society and Instituto de Salud Carlos III. He has received honoraria for lectures from Nutricia, Esteve, Almirall, Kern Pharma, and Neuraxpharm and has received consulting fees for his participation in scientific advisory boards from UCB. JVB has no disclosures. RH has no disclosures.

LP008- PARTNERS IN CARE INTERVENTION FOR PERSONS WITH DEMENTIA AND MULTIMORBIDITY. A CLINICAL TRIAL FEASIBILITY STUDY. I. Testad[1,2], L.B. Holteng[1], M.T. Gjestsen[1,3] *(1. Stavanger University Hospital - Stavanger (Norway), 2. University of Exeter Medical School - Exeter (United Kingdom), 3. University of Bergen - Bergen (Norway))*

Background: The global demographic change with an aging population, where the older elderly (80+) are the fastest growing population, is expected to increase from 137 million to 425 million by 2050 (1). Older age, multimorbidity and dementia are all strongly correlated with adverse health outcomes as well as a proxy for loss of independent living (2). The group of carers will grow accordingly (3) and the shortage of healthcare professionals in Norway, will increase with an aging society. Taken together, a need for robust care model involving the families in a structured Care Partner Model is warranted, in order to give high quality and cost effective care to this vulnerable group of people. More specifically we aim to: * Identify the most common care models used in managing persons with multimorbidity with dementia; * Describe the effectiveness of existing care models to develop a Partner in Care Model; * Test the feasibility of a Partner in Care Intervention. **Methods:** Multimethods will be employed in this project, to test the feasibility of the Partner in Care intervention. Three substudies will be performed; 1) Current care models and effectiveness of these 2) Development of a Partner in Care intervention 3) Feasibility of a Partner in Care interventio. **Results:** Addressing fragmented care of persons with multimorbidity and dementia can be expected to increase quality of care and lead to better health outcomes. This project will, through the development of a "Partner in Care intervention" increase the health care professionals' expertise in involving carers in a structured way. This holistic, patient-

centered approach addresses the strong correlation between dementia and multimorbidity, as well as carer stress and burden, complications due to polypharmacy and malnutrition, the lack of psychosocial interventions, and a shortage of health care professionals and can potentially have an impact on adverse health outcomes. User involvement: Patient and public involvement (PPI) is a fundamental part of SESAM's research. To ensure PPI SESAM has established WiseAge; platform for user involvement and community involvement. WiseAge will facilitate the use of older people's expertise and experience in research and knowledge development. **Conclusion:** This project will serve as a feasibility for further research in a large scale RCT if the feasibility- and pilot studies are successful. By mapping the current status concerning the delivery of health care services and identifying gaps in the literature, this project may be a starting point for developing care pathways tailored to or managing persons with multimorbidity and dementia. **Clinical Trial Registry:** The study will seek for approval from the Regional Ethics Committee for Medical and Health Research Ethics (REC). **Data Deposition:** The study will collect sensitive data about the target group. Data will be stored in a non-identifiable form on a research server at Stavanger University Hospital, and the code will be stored separately in a locked cabinet. The participants will be anonymous as they are labels with a code in the data material and this will be stores separately from the participant's name. **Key Words:** Dementia, multimorbidity, care. **Disclosures:** The authors declared no competing interests. **References:** United Nations Department of Economic and Social Affairs. World Population Ageing. Highlights 2017 (ST/ESA/SER.A/397). 2017. Tonelli M, Wiebe N, Straus S, Fortin M, Guthrie B, James M, et al. Multimorbidity, dementia and health care in older people:a population-based cohort study. CMAJ Open. 2017;5(3):E623-E31. Dauphinot V, Delphin-Combe F, Mouchoux C, Dorey A, Bathsavanis A, Makarokk Z, et al. Risk Factors of Caregiver Burden Among Patients with Alzheimer's Disease or Related Disorders: A Cross-Sectional Study. Journal of Alzheimer´s Disease. 2015;44:907-16. Texmon I, Stølen N. Arbeidsmarkedet for helse- og sosialpersonell fram mot år 2030. Dokumentasjon av beregninger med HELSEMOD 2008. Statistics Norway. 2009.

LP009- THE PATIENT VOICE IN DRUG REVIEWS: LEARNINGS FROM OLDER ADULT ENGAGEMENT ON DISEASE-MODIFYING TREATMENTS FOR DEMENTIA IN ONTARIO, CANADA. A. Morrison[1], J. Hogle[1] *(1. Alzheimer Society of Ontario - Toronto (Canada))*

Background: Canada's Drug Agency (CDA) is conducting reimbursement reviews on two disease-modifying treatments (DMTs) for dementia – donanemab and lecanemab. As part of its advocacy efforts for better care and improved quality of life for people living with dementia (PLWD) and their care partners (CPs), the Alzheimer Society of Ontario (ASO) conducted focus groups in Spring/Summer 2024 to seek feedback on DMTs based on lived experience to inform CDA's reviews. **Methods:** ASO worked with clinical trial sites for both drugs to recruit treatment groups (i.e. PLWD in clinical trials and their CPs) and local Alzheimer Societies in Ontario to recruit control groups (i.e. PLWD not in a clinical trial and their CPs) to elicit qualitative feedback on the potential impact of DMTs and system requirements for implementation. Donanemab: treatment group of 2 PLWD and 2 CPs; control group of 3 PLWD and 4 CPs. The 11 participants were 67 to 83 years old (6 men and 5 women). Lecanemab: treatment group of 4 PLWD and 1 CP; control group of 3 PLWD and 4 CPs. The 12 participants were 66 to 89 years old (6 men and 6 women). Each focus group (duration: 2 hours) was asked 8 questions on: experience with Alzheimer's disease; desirable outcomes for future treatments; considerations to support future treatments; and risk tolerance for treatment side effects. Treatment groups were asked 4 additional questions about the impacts of treatment for patients, CPs, and families. Responses were synthesized into patient input submissions for CDA's reviews of donanemab and lecanemab. Participants received a copy of the submission and a small gift of appreciation from ASO. **Results:** Focus groups were unanimous in stating that Alzheimer's disease has upended their day-to-day lives, disrupting life-long plans and redefining their relationships. Several CPs had care experience with different chronic conditions and suggested that care for PLWD is more time-consuming and stressful than any other care they have provided. CPs agreed across all focus groups that there is a lack of caregiving supports available, leaving them to feel inadequate and alone in their role. Most CPs suggested their role consumed the equivalent of a full-time job or more. PLWD in both treatment and control groups expressed enthusiasm to take a drug that might slow the progression of their disease if provided information to make an informed choice, regardless of health risks. Risk tolerance was also high for CPs, who suggested ongoing caregiving support was a higher priority for them. **Conclusion:** Though focus group participants were asked numerous questions about DMTs and their potential impact, most returned to the themes of CP support and quality of life. These themes were perceived as equally important to treatment effectiveness, and more important than potential health risks of treatment by most participants. Results from these focus groups suggest that the wellbeing of CPs is integral to any potential rollout of DMTs for dementia. Further research should examine what is required for a supportive ecosystem for PLWD and their CPs on their dementia journey alongside any treatments under review. **Keywords:** Disease-modifying treatment, dementia, patient engagement. **Disclosures:** The authors are both full-time employees of the Alzheimer Society of Ontario. The authors declare no competing interests.

LP010- AI-GUIDED PATIENT STRATIFICATION IMPROVES EFFICIENCY OF ALZHEIMER'S DISEASE CLINICAL TRIAL. Z. Kourtzi[1], D. Vaghari[1], G. Mohankumar[2], P. Tino[3], C. Shering[4], A. Lowe[2], K. Tan[2] *(1. Univ of Cambridge - Cambridge (United Kingdom), 2. AstraZeneca - Cambridge (United Kingdom), 3. Univ of Birmingham - Birmingham (United Kingdom), 4. AstraZeneca - Boston (United States))*

Background: Clinical trials of potential disease-modifying treatments for Alzheimer's disease (AD) face numerous challenges, contributing to high costs, prolonged timelines and failure. Including patients with symptoms due to comorbidities (e.g. anxiety or mood-related disorders) rather than dementia pathology or patients who have progressed to advanced disease stages may impact trial efficiency, efficacy and costs. Recent positive phase three clinical trial results (i.e. lecanemab, donanemab) highlight the importance of interventions earlier in the progression of disease when treatments may be maximally effective. Yet, we still lack effective tools for precise stratification of patients at risk or early disease stages for inclusion in clinical trials. **Methods:** To address this challenge, we built a robust and interpretable clinical-AI tool based on a predictive prognostic model (PPM) for precise patient stratification at early dementia stages (mild cognitive impairment, MCI). PPM: 1) introduces a transparent trajectory modelling approach to reliably predict

future cognitive health frommultimodal data (β-amyloid, grey matter density, APOE4) 2) delivers an AI-guided multimodal marker that supports more precise prediction of conversion to AD at early stages than standard clinical markers or diagnosis. **Results:** Here, we used PPM to re-stratify the patients in the AMARANTH trial that tested the effect of lanabecestat in reducing β-amyloid and slowing down progression to AD. Despite the fact that the trial was deemed unsuccessful, using the PPM to re-stratify the trial sample to slow vs. rapid progressive based on baseline data before treatment(week 1) showed treatment effects on outcomes (β-amyloid, cognition). In particular, the slow progressive group, comprising patients at earlier stages of neurodegenerative decline, showed not only reduction in β-amyloid but twofold slowing of cognitive decline (i.e. decrease in CDR-SOB, ADAS-Cog13 scores) following treatment (lanabecestat-50 mg, week 104) compared to placebo. In contrast, the rapid progressive group, comprising patients at later stages of neurodegenerative decline, showed higher reduction in β-amyloid but no significant change in cognitive outcomes compared to placebo. Further, we show that using PPM for patient stratification decreases substantially the sample size necessary for identifying significant changes in cognitive outcomes. **Conclusion:** Our results suggest that PPM provides a more sensitive tool for patient stratification than standard approaches used for patient selection in clinical trials (e.g. β-amyloid positivity) with strong potential to enhance clinical trial efficiency (faster and cheaper) and efficacy (better outcomes), as the right patients receive the right treatment at the right time. **Keywords:** patient stratification, predictive modeling, β-amyloid, machine learning. **Conflicts of interest:** none.

LP012- MINIMIZING SCREEN FAILURE RATES AND ACCELERATING CLINICAL TRIAL RECRUITMENT WITH A PROGNOSTIC MODEL. A. Tam[1], C. Laurent[1], A. Noriega[1], C. Dansereau[1] *(1. Perceiv AI - Montreal (Canada))*

Background: Alzheimer's disease (AD) trials have high screen failure rates. Recent trials have enriched for individuals based on tau pathology in addition to amyloid pathology, which can exacerbate screen failures. We explored enrichment for decliners with a model that forecasts clinical progression, AD-PxTM, while minimizing screen failures and avoiding strict biomarker cut-offs. We also compared the cost and duration of screening with AD-PxTM to a typical early AD trial screening process. **Methods:** In amyloid-positive early AD participants from ADNI (adni.loni.usc.edu), we quantified screen failure rates due to enrichment of tau positive individuals with CSF phosphorylated tau 181 (ptau-181) measured by the Roche Elecsys assay at a 26.9 pg/mL cut-off. That cut-off best separated AD and cognitively unimpaired participants. We performed power analyses to estimate sample sizes for detecting 30% treatment effects at 80% power for two-arm trials enrolling participants at this cut-off. We compared the screen failure rates and sample size estimates of the ptau-181 cut-off against enrichment with decliners predicted by AD-PxTM. AD-PxTM is a machine learning model that uses APOE4 status, demographics, clinical assessments, and CSF biomarkers to predict individual risks of decline over 2 years. We replicated these analyses in an independent cohort of amyloid-positive early AD participants from NACC (naccdata.org). Finally, we calculated screening costs of a typical early AD trial, assuming an overall screen failure rate of 73% where 32% is due specifically to biomarkers, and we estimated costs for a hypothetical trial using AD-PxTM. **Results:** In ADNI, the ptau-181 cut-off screen failed 36.2% of participants, and 454 individuals were required to power a trial. AD-PxTM screened out only 16.7% of participants, while maintaining equivalent statistical power with a sample size estimate of 454 participants. AD-PxTM had a 53% smaller screen failure rate than the ptau-181 cut-off ($p < 0.001$). In NACC, the ptau-181 cut-off screen failed 42.1% of participants and 518 individuals were required to power a trial. AD-PxTM screened out only 11.6% patients, while maintaining equivalent statistical power with a sample size estimate of 508 participants. In this replication cohort, AD-PxTM had a 72% smaller screen failure rate compared to ptau-181 ($p < 0.001$). Based on these results, we estimated that a typical trial with an overall screen failure rate of 73% would need to screen 1681 individuals to randomize 454 participants over a period of 24 months and cost $6.4 million. By contrast, a trial using AD-PxTM would have an overall screen failure rate of 56% and would only need to screen 1033 individuals over 14.7 months and cost $3.9 million, representing a 39% reduction in cost and time compared to a typical trial. **Conclusion:** AD-PxTM effectively reduces screen failure rates caused by restrictive biomarker cut-offs, enabling more flexible inclusion criteria while maintaining statistical power. By substantially reducing the number of patients to screen, AD-PxTM can accelerate patient enrollment, lower screening costs, and shorten trial durations by 39% compared to a typical trial without compromising sample quality.

LP013- ENHANCING CLINICAL TRIAL EFFICIENCY: INCREASING SCREENING AND RANDOMIZATION RATES USING RETISPEC'S AI-BASED EYE SCAN FOR PRE-SCREENING IN EYE CARE SETTINGS. J. Lehr[1], S. Grapentine[2], B. Lenox[3], S. Cassidy[3], R. Naureen[2], B. Pendarvis[1], J. Giordano[2], A. Hazan[2], E. Shaked[2], C. Bornbaum[2] *(1. Magruder Eye Institute - Orlando (United States), 2. RetiSpec - Toronto (Canada), 3. K2 Medical Research - Maitland (United States))*

Background: With the ongoing developments in new disease-modifying therapies, early and accurate identification of individuals at risk for Alzheimer's disease (AD) is critical for effective clinical trial enrollment. However, AD trials face screen failure rates as high as 88%, leading to prolonged trial durations and significantly higher per participant costs due to required procedures such as cognitive testing, MRI, PET and CSF testing. Optometry settings present a promising and novel avenue for AD screening as eye-care clinics are widely available, and optometrists routinely identify markers of neurological conditions. Integrating RetiSpec's AI-based retinal imaging technology, which leverages pre-existing fundus cameras, into eye-care settings may provide a non-invasive, accessible alternative for AD screening. This approach holds the potential to enhance patient access to AD screening and facilitate early detection and research participation. **Methods:** This prospective, cross-sectional case study evaluated the impact of integrating RetiSpec's AI-based retinal scan during routine pre-screening activities at an eye-care clinic to enhance AD screening. The study population consisted of individuals aged 50 or older who presented to Magruder Eye Institute for routine clinical visits. The primary objective was to assess whether the use of RetiSpec scans in novel eye-care settings could increase interest and participation in clinical trial screening. Secondary aims related to improving trial screening efficiency and randomization, increasing trial participation among minority and underserved groups, and evaluating agreement between RetiSpec scan results and Ab biomarkers, where applicable. **Results:** In total, 156 participants were

enrolled (59 males [38%]; 95 females [62%]). Over a 3.5-month study period, 154 participants completed the RetiSpec scan, with 40% participants from traditionally underrepresented populations (non-Caucasian [n= 32; 21%], Hispanic/Latino [n=30, 20%]). RetiSpec produced predictions for 146 scans, with a rapid reporting of results within same or next day, showing 86 (59%) participants at increased risk for PET amyloid positivity. Out of the n=156 consented participants, n=64 (41%) completed trial pre-screening at K2 Medical Research. Of those that did not proceed, n=48 (31%) were not interested, n=4 (2%) screen failed, n=1 (1%) did not qualify, and n=39 (25%) were unable to be reached. Of those that completed pre-screening, n=53 consented to the clinical trial (conversion rate=83%), with n=22 (42%) enrolled in a symptomatic study and n=31 (58%) enrolled in an asymptomatic study. At the time of reporting, n=6 participants were successfully randomized into a clinical trial with screening ongoing for others. **Conclusion:** This study demonstrated the successful implementation of the RetiSpec AI-based retinal scan to significantly enhance AD screening conversion rates and randomizations through integration into routine trial pre-screening activities in an eye-care setting. By providing same day results at widely accessible eye-care clinics, this technology enabled timely identification of at-risk individuals eligible for clinical trial screening, especially among non-Caucasian participants. This approach offers significant potential to enhance early detection, accelerate trial pre-screening, reduce screen failure rates, and ultimately facilitate clinical trial enrollment and effectiveness. **Keywords:** Alzheimer's disease, Amyloid burden, Artificial Intelligence, retinal imaging, biomarker, diagnostics, pre-screening, screening. **Disclosures:** Co-authors employed by RetiSpec either hold equity ownership or company options. **Acknowledgements:** We wish to thank the many participants who generously shared their time with us throughout this study.

LP014- DEVELOPMENT OF EDARAVONE TABLETS FOR THE TREATMENT OF ALZHEIMER'S DISEASE---PHASE I TRIALS IN HEALTHY VOLUNTEERS AND PHASE II DESIGN IN EARLY AD. X.F. Zhou[1], J. Wang[2], Y.J. Wang[2] *(1. Suzhou Auzone Biotech - Suzhou (China), 2. Department of Neurology, Daping Hospital, Third Military Medical University - Chongqing (China))*

Background: Alzheimer's disease (AD) is a public health problem worldwide. It is imperative to develop safe, effective and affordable drugs to prevent and halt the progression of early AD. Amyloid beta (Ab) is the main pathogenic factor initiating AD pathogenesis and oxidative stress (OS) plays a critical role in AD progression. We discovered that a small molecule drug edaravone is effective in the treatment of AD in animal models by suppressing oxidative stress and inhibiting Ab deposition (1). For the efficacy trials in AD patients, we have developed oral tablet formula (2,3) which is more compliant for patients with AD or other chronic disease. We have performed phase I clinical trials for its safety and bioavailability in Australia, China and USA. **Method:** A solid dispersion formula of edaravone was developed and its bioavailability and safety were examined in animals and healthy volunteers. Based on the efficacy and safety data of the preclinical and clinical studies, we designed a phase II clinical trial in patients with early symptomatic AD. **Results:** The solid dispersion formula (TTYP-01 tablets) is stable in room temperature for at least 2 years and with NOAEL at 30 mg/kg in dogs for 6 months administration. Single ascending doses of oral intake from 30 mg to 240 mg in a phase 1 trial on adult volunteers in Australia showed an excellent tolerability without significant difference in adverse events between the control and TTYP-01 groups. Compared to intravenous dripping formula of 30 mg edaravone (Radicut), 60 mg TTYP-01 tablets taken orally showed 59% bioavailability. Similar results were obtained from repetitive dosages of TTYP-01 up to 120 mg bid for 7 days in Chinese volunteers with an excellent tolerability. In a cross-over bioequivalence study in 30 healthy volunteers compared with both Radicava and edaravone oral suspension (ORS), 90 mg of TTYP-01 (3 tables) is almost bioequivalent with 60 mg Radicava (iv) and 105 mg ORS without significant difference in adverse events. The positive preclinical and Phase I clinical data allow to move TTYP-01 into Phase II clinical trials in AD. In this study we will recruit 180 early symptomatic AD patients (MCI due to AD and mild AD dementia) at multiple centers from China, USA and Australia. Patients will be randomly treated with placebo, low dosage (TTYP-01 60 mg bid) and high dosage (90 mg bid) groups for 18 months and followed up every three months. The safety and tolerance and CDR-SB will be the primary end points and the changes of brain Ab-PET, Tau-PET and MRI imaging will be the secondary end points at 18 months. We will also examine the correlation between the drug exposure and the efficacy. **Conclusion:** Edaravone solid dispersion formulation (TTYP-01) was efficacious in AD animal models and had an excellent tolerance and safety profile in healthy volunteers. A phase II clinical trial from multiple centers is designed to test its safety and dose-dependent efficacy in 180 early AD patients. **Keywords:** Edaravone, Alzheimer's disease, disease-modifying drug, solid dispersion. **Clinical trial registrations:** CT-2020-CTN-01186-1; CTR20220495; NCT06107205. **Disclosure:** XF Zhou is an employee of Suzhou Auzone Biotech and one of the inventors of Edaravone solid dispersion patents. **References:** Jiao SS et al., PNAS 2015; 112(16):5225-30; Parikh A, Drug Des Devel Ther. 2018;12:2051-2069; Parikh A et al Drug Des Devel Ther. 2018;12:2111-2128.

LP015- CLINICAL TRIALS USING MUSIC INTERVENTIONS FOR ALZHEIMER'S DISEASE AND RELATED DISORDERS IN ETHNICALLY DIVERSE COMMUNITIES. T. Rose[1] *(1. University of Southern California - Los Angeles (United States))*

Background: Over the past two decades, clinical trials of music interventions and therapy programs have demonstrated that music is effective in reducing Alzheimer's disease and related dementia (ADRD) symptoms within the general U.S. population [1, 2]. Given the ethnic and cultural diversity of the U.S., there is a need to enhance the quality and evidence base of music interventions by ensuring greater inclusion of ethnically underrepresented older adults in research studies [3]. This review aimed to examine clinical trials methodology utilizing music interventions for ADRD that incorporate culturally-specific music from African-American, Asian-American, Hispanic/Latino, and Native-American/Alaskan-Native communities, and to compare these with clinical trials that do not focus on a specific cultural group. Clinicaltrials.gov database offers free access to emerging best practices in ADRD clinical interventions along with frequent updates on completed studies and information about ongoing studies [4]. Health care agencies and providers who want to implement their own programs rely upon it as a resource given that fees are often required to access journal articles, and research study results are often published years after data collection is completed. This review analyzed studies from clinicaltrials.gov and aimed to identify the optimal intervention methodologies and factors

affecting treatment effects for these four ethnically diverse communities: African-American, Asian-American, Hispanic/Latino, and Native-American/Alaskan-Native. **Methods:** A search in the clinicaltrials.gov database included keywords related to ADRD and music from database inception through August 2024. The inclusion criteria included music intervention and therapy studies conducted in the U.S. that were active or completed. A subset of these clinical trials also included keywords specific to the four most populous ethnic groups in the U.S. **Results:** Out of a total of 168 studies identified, 61 met inclusion criteria. A total of five studies focused on ethnically identified populations in the US; four of the studies focused on community-dwelling African-Americans using (1) dance, (2) drumming circle, (3) faith-based music, or (4) music exercise programs, and one study focused on three ethnically identified communities with choirs. An additional 11 studies employed participant-selected music accessed using technology. The remaining 44 studies did not focus or refer to any U.S. ethnic or minority populations; these studies integrated active and passive music interventions into arts, exercise, educational or multi-faceted programs, with 38% using music accessed with technology. Comparing studies focusing on ethnic communities to studies on the general U.S. population, the level of participant impairment varied: ADRD (60% vs. 61%), general memory loss (20% vs. 14%), MCI (0% vs. 18%), and normal to at-risk (20% vs. 11%). **Conclusion:** Studies registered in ClinicalTrials.gov suggest that ADRD clinical trials employing music interventions are limited for ethnic communities in the U.S. Given the diversity of the U.S. population and the personalized nature of music therapy, it seems appropriate to broaden the scope of research and increase study participant inclusion. Expanding funding to support add-on components in general population clinical trials could enhance the focus on specific ethnic communities in the U.S. **Keywords:** culturally-specific, ethnically diverse, music interventions. **Disclosures:** The author declares no competing interests. **References**: 1. van der Steen JT, Smaling HJA, van der Wouden JC, Bruinsma MS, Scholten RJPM, Vink AC. Music-based therapeutic interventions for people with dementia. Cochrane Database of Systematic Reviews. 2018; 7. Art. No.: CD003477. DOI: 10.1002/14651858.CD003477.pub4; 2. Lam HL, Li WTV, Laher I, Wong RY. Effects of Music Therapy on Patients with Dementia—A Systematic Review. Geriatrics. 2020; 5(4):62. https://doi.org/10.3390/geriatrics5040062; 3. Rose, T, Music Therapy Clinical Trials in Cross-Cultural Settings. Innovation in Aging. 2020; 5(1):930. https://doi.org/10.1093/geroni/igaa057.3411; 4. Hunter K E, Webster A C, Page M J, Willson M, McDonald S, Berber S et al. Searching clinical trials registers: guide for systematic reviewers. BMJ. 2022; 377 :e068791 doi:10.1136/bmj-2021-068791.

CLINICAL TRIALS: RESULTS

P021- PHASE 1 CLINICAL TRIAL OF LEUCETTINIB-21, A DYRK1A KINASE INHIBITOR AIMING AT THE CORRECTION OF COGNITIVE DISORDERS IN ALZHEIMER'S DISEASE AND DOWN SYNDROME.

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Background: Memory and learning disorders observed in patients with Down syndrome (DS) and Alzheimer's disease (AD) are associated with an excess activity of the DYRK1A protein kinase. Genetic and pharmacological inhibition of DYRK1A corrects these cognitive disorders in DS/AD animal models, encouraging the development of a clinical DYRK1A inhibitor to treat memory/learning difficulties in patients with AD or DS. **Methods:** Inspired by a marine sponge natural product, Leucettamine B, we synthesized, optimized and extensively characterized over 1200 analogues, Leucettines [1-3] and Leucettinibs [4, 5], and selected an orally available drug candidate, Leucettinib-21 [6], which was formulated in immediate-release tablets. **Results:** Regulatory preclinical safety studies, carried out with rats (NOAEL: 20 mg/kg) and mini-pigs (NOAEL: 100 mg/kg), showed that Leucettinib-21 is well tolerated in these animals at doses much higher than active doses (correcting memory disorders) in animal models of DS and AD (0.3-0.5 mg/kg). A double-blind, placebo-controlled clinical phase 1 study ('Leucetta') involving 120 participants, was launched in January 2024 to investigate the safety and pharmacokinetics of Leucettinib-21 [7]. The Leucetta trial comprises Single Ascending Dose, Food Effect and Multiple Ascending Dose studies in 96 healthy volunteers. In addition, 12 adults with DS and 12 AD patients will receive a single Leucettinib-21 dose for pharmacokinetics and biomarkers analysis. Blood plasma samples collected from all participants will be used to analyze plasma proteomic and phosphoproteomic profiles (8,000+ proteins and 6,000+ phosphosites can be identified), as well as AD-specific biomarkers (pThr212-Tau (a phosphorylation site for DYRK1A and recently reported AD biomarker [8]) and p-Thr217-Tau, NfL, amyloids, neuroinflammation markers). The expression level and activity of DYRK1A will be evaluated in plasma and PBMCs. **Conclusion:** The Leucetta study should be completed by the end of Q4-2024 and results of this phase 1 trial will be presented. In addition we will present and discuss the planned phase 2A protocol (not finalized at this stage, but double-blind and placebo-controlled), which will address safety, measure the above-mentioned plasma biomarkers, and make use of various methods to evaluate the ability of Leucettinib-21 to correct cognitive disorders in patients with early AD (such as CDR-SB, ADAS-cog14, ADCOMS; to be defined with our Medical Advisory Board and through discussions at the CTAD conference), and in children with DS, with appropriate cognitive assessment methods (NIHTB-CB, for ex.). **Keywords:** DYRK1A kinase, Leucettinib-21, plasma phosphoproteomics, cognitive functions. **Disclosures:** LM, EC, ED, GH and ML are employees of Perha Pharmaceuticals. LM and ED are coinventors on the Leucettinib-21 patent. LM, ED and ML own stock options of Perha Pharmaceuticals. LM is founder, president and CSO of Perha Pharmaceuticals. **References:** 1. Debdab M, et al. J Med Chem 2011; 54, 4172-4186. http://doi: 10.1021/jm200274d. 2. Tahtouh T, et al. J Med Chem 2012; 55, 9312-9330. http://doi: 10.1021/jm301034u. 3. Tahtouh T, et al. J Med Chem 2022; 65, 1396-1417. http://doi: 10.1021/acs.jmedchem.1c01141. 4. Lindberg MF, et al. J Med Chem 2023; 66, 4106-4130. http://doi: 10.1021/acs.jmedchem.2c02068. 5. Deau E, et al. J Med Chem 2023; 66, 10694-10714. http://doi: 10.1021/acs.jmedchem.3c00884. 6. Lindberg MF, et al. J Med Chem 2023; 66, 15648-15670. http://doi: 10.1021/acs.jmedchem.3c01888. 7. Clinical Trial Registry: NCT06206824; https://clinicaltrials.gov. 8. Kac PR, et al. Nat Commun. 2024; 15, 2615. doi: 10.1038/s41467-024-46876-7.

P022- PHASE 1A SINGLE ASCENDING DOSE STUDY OF PMN310, A MONOCLONAL ANTIBODY DIRECTED AGAINST TOXIC AB OLIGOMERS. L. Altstiel[1], J. Kaplan[1], E. Gibbs[1], M. Lamendola[1], W. Luca[1], G. Malenfant[1], M. Maginn[1], Y. Han[2], N. Cashman[1] *(1. ProMIS Neurosciences - Cambridge, MA (United States))*

Background: Toxic oligomers of misfolded Aβ peptide (AβO) are implicated in the progression of Alzheimer's disease (AD) [1]. PMN310 is a humanized IgG1 monoclonal antibody that binds to a computationally derived three-dimensional epitope (HHQK) specific to misfolded Aβ in AβO. The epitope is absent in native Aβ and inaccessible to antibody in Aβ plaque [2]. PMN310 does not bind to Aβ plaque, binding to AβO is not significantly inhibited by Aβ monomer, and PMN310 preserves memory in mouse models of AD [3]. Because PMN310 can potentially inhibit the toxicity of AβO and does not bind to plaque, thereby possibly limiting the risk of ARIA, it is being developed as a therapy for early AD. **Methods:** This first-in-human study was designed to assess the safety, tolerability, and pharmacokinetics of a single dose infusion of PMN310 in healthy volunteers and guide dose selection for a multiple dose study of PMN310 in early AD patients. The study was a double-blind single ascending dose study in 40 healthy volunteers. Men and women, age 18-65, who had no medical conditions that precluded safe participation in the study were eligible. After providing informed consent and ascertainment of eligibility, patients were randomized to either active PMN310 or placebo in dosing cohorts containing 6 subjects receiving a single intravenous infusion of PMN310 and 2 subjects receiving saline placebo infusion. There were five dosing cohorts: 175 mg, 350 mg, 700 mg, 1400 mg, 2800 mg. The decision to escalate dosing was made by a data safety monitoring board based on safety. Serum PMN310 concentrations were collected before, and at the end of the infusion and at 0.5, 1, 2, 4, 8, 12, 24, 36, 72 ,192 hours and approximately biweekly after infusion. CSF collection was done at day 3 and day 29 after dosing to determine CSF concentration of PMN310. Routine laboratory, and safety assessments were done at screening, before infusion, and periodically post infusion. Anti-drug antibody samples were collected at baseline and on days 29, 57, and 85. **Results:** There were no adverse events that precluded dose escalation. Across the entire dosing range, plasma concentrations of PMN310 were linearly dose proportional as were total exposure (AUC 0-∞) and maximum concentration (Cmax). CSF concentrations of PMN310 were linearly dose-dependent and 100-600 times the estimated CSF AβO molar concentration. The plasma half-life (t ½) was approximately 17.5 days and the CSF t ½ was approximately 27 days. The estimated binding constant of PMN310-AβO binding is 0.5 nM suggesting that the 350 mg dose can provide greater than 50% antibody saturation. **Conclusion:** PMN310 was well tolerated. Data from this study indicate that monthly dosing will provide levels of PMN310 adequate for target engagement. **Keywords:** Phase 1 study, PMN310, Aβ oligomers. **Clinical Trial Registry:** NCT06105528 https://clinicaltrials.gov. **Disclosures:** 1 Employees, or individuals contracted by Promis Neurosciences, 2 Everest Clinical Research. **References:** Cline, EN et al. J Alzheimers Dis. 2018; 64 (Suppl 1): S567–S610 doi: 10.3233/JAD-179941. Gibbs E. et al. Sci Rep 9, 9870 (2019). https://doi.org/10.1038/s41598-019-46306-5 Kaplan, JM et al. bioRxiv. 2024. https://doi.org/10.1101/2024.04.20.

P024- COMPREHENSIVE ANALYSIS OF PHASE 2 TRIAL RESULTS AND POST-HOC FINDINGS OF ABVAC40, AN ANTI-AB40 VACCINE. M. Pascual-Lucas[1], A.M. Lacosta[1], M. Montañés[1], J. Canudas[1], J. Loscos[1], J.A. Allué[1], L. Sarasa[1], N. Fandos[1], J. Romero[1], M. Sarasa[1], G. Piñol-Ripoll[2], J. Terencio[1,3], M. Boada[4,5] *(1. Araclon Biotech-Grifols - Zaragoza (Spain), 2. Cognitive Disorders Unit, Cognition and Behaviour Study Group. Hospital Universitari Santa Maria - Lleida (Spain), 3. Grifols - Barcelona (Spain), 4. Ace Alzheimer Center Barcelona – Universitat Internacional de Catalunya - Barcelona (Spain), 5. Networking Research Center on Neurodegenerative Diseases (CIBERNED), Instituto de Salud Carlos III - Madrid (Spain))*

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. Initial results from the phase 2 clinical trial of ABvac40 showed positive results with a favourable safety profile, robust immunogenicity, and promising trends in cognition and brain atrophy. Here we present a comprehensive compilation of all available results from the study, alongside new insights from additional post-hoc analyses, to further elucidate the therapeutic potential of ABvac40. **Methods:** AB1601 was a multicenter, randomized, double-blind, placebo-controlled phase 2 study (NCT03461276) involving 124 patients with amnestic mild cognitive impairment (a-MCI) or very mild AD (vm-AD). Of these, 92 (74.2%) were amyloid-PET positive. Participants received five monthly subcutaneous injections plus a 6-month delayed booster of ABvac40 or placebo. Primary endpoints were safety, tolerability, and immunogenicity. Secondary endpoints included neuropsychological tests, cortical fibrillary amyloid deposition and brain volumetric analysis. Post-hoc analyses comprised analysis of the subgroup of amyloid-PET positive patients. **Results:** The primary results demonstrated that ABvac40 was safe and well-tolerated, with no cases of ARIA-E or aseptic meningo-encephalo-myelitis and a similar incidence of ARIA-H between treated (12.5%) and placebo (15%) groups. ABvac40 induced a strong, specific, and sustained immune response in plasma, with CSF antibody penetration correlating with plasma levels. Positive trends favouring ABvac40 in cognitive tests and brain atrophy were observed in the overall population. Specifically, the MMSE scores showed an LS-mean difference of up to 1.44 (95% CI: 0.18, 2.69; P=0.0252), TMT-A up to an LS-mean difference of –13.65 s (95% CI: –25.81, –1.48; P=0.0283), and brain atrophy up to an LS-mean difference of –1.48% (95% CI: –2.79, –0.16; P=0.0282). Importantly, the post-hoc analysis of the a-PET positive subgroup revealed more pronounced numerical differences. In this subgroup, the MMSE scores showed an LS-mean difference of up to 1.77 (95% CI: 0.37, 3.17; P=0.0141), TMT-A up to an LS-mean difference of –19.07 s (95% CI: –32.62, –5.52; P=0.0066), and brain atrophy up to an LS-mean difference of –1.86% (95% CI: –2.84, –0.88; P=0.0005). **Conclusion:** The comprehensive analysis of the Phase 2 clinical trial data for ABvac40 underscores its potential as a therapeutic candidate for AD. The overall population showed favourable trends, while the amyloid-PET positive subgroup demonstrated more pronounced benefits. These findings suggest that patients with confirmed amyloid pathology may respond better to ABvac40. Future studies are needed to further investigate these findings and to explore the mechanisms underlying the observed effects. **Keywords:** ABvac40, vaccine, Aβ40, clinical trial, Phase 2, immunotherapy, CAA. **Disclosures:** MPL, AML, MM, JC, JL, JAA, LS, NF and JR are full-time employees of Araclon Biotech-Grifols. GPR has consulted for Araclon, Grifols,

Esteve, Zambon. He received fees from lectures from Araclon, Grifols, Nutricia, Esteve, Zambon, Ferrer, Alter. JT is a full-time employee of Grifols. MB has consulted for Araclon, Avid, Grifols, Lilly, Nutricia, Roche, Eisai and Servier. She received fees from lectures and funds for research from Araclon, Biogen, Grifols, Nutricia, Roche and Servier. She reports grants/ research funding from Abbvie, Araclon, Biogen Research Limited, Bioiberica, Grifols, Lilly, S.A, Merck Sharp & Dohme, Kyowa Hakko Kirin, Laboratorios Servier, Nutricia SRL, Oryzon Genomics, Piramal Imaging Limited, Roche Pharma SA, and Schwabe Farma Iberica SLU, all outside the submitted work. She has not received personal compensations from these organizations. **Clinical Trial Registry:** NCT03461276.

P025- SPECTRISTM TREATMENT REDUCED ALZHEIMER'S DISEASE DEPENDENCE SCORE IN OVERTURE I/II PHASE 2 STUDY. R. Kern[1], M. Sabbagh[2], M. Hajos[1], B. Vaughan[1], C. Howell[1], C. Houser[1], M. Hull[1], L. Lee[1] *(1. Cognito Therapeutics - Cambridge (United States), 2. Barrow Neurological Institute - Phoenix (United States))*

Background: The OVERTURE I (NCT03556280) randomized controlled trial (RCT) evaluated SpectrisTM in mild-moderate Alzheimer's disease (AD) [1]. Participants who completed the RCT enrolled in a separate 12-month open label extension (OVERTURE II) study. AD Dependence Score (DS) is derived from ADCS-ADL data, evaluates the required amount of assistance from others that a patient with AD needs because of disease progression and correlates with MMSE cognitive decline and healthcare costs [2, 3]. We report estimated 18-month DS derived from ADCS-ADL data. **Methods:** Participants who completed the 6-month OVERTURE I (active: sham, 2:1 randomization) were eligible to enroll in the separate OVERTURE II study, and to receive 1-hour daily active treatment for 12 additional months. 44 of 53 (83%) RCT completers entered the OLE, 39 participants (25 active: 14 sham) were evaluated at month 9, and 22 at month 18 (15 active: 7 sham). ADCS-ADL data was obtained either at clinic visits or by telephone interviews. DS was evaluated using specific ADCS-ADL items as described [2]. Regression modeling was performed to confirm DS outcomes in the active and sham groups. MMSE and age were included as baseline covariates in the analysis using a random slope model. **Results:** 135 participants were screened, 74 were treated and 53 completed the RCT (20 sham, 33 active). Tolerability and adherence were confirmed, and no serious treatment-related adverse events or ARIA was observed. Baseline ADCS-ADL total scores (mean, SD) were not significantly different in treatment groups [active (66.9, 8.54) vs sham (63.3, 10.65), p=0.16]. Baseline DS scores (mean, SD) were not significantly different in treatment groups [active (1.6, 1.12) vs sham (1.9, 1.25), p=0.34]. At 18 months, a significant difference in DS change from baseline (mean, 95% CI) was observed in favor of the active treatment versus sham treatment group (+0.96, 0.47-1.44 vs. +2.20, 1.17-3.24, difference -1.24, p=0.04). **Conclusion:** SpectrisTM treatment significantly reduced estimated Alzheimer's Disease dependence score (DS) over 18 months in the OVERTURE I/II study. Dependence is an important consequence of AD progression; a 1-point reduction corresponds to a 5.70% reduction in medical costs, a 10.50% reduction in non-medical costs, and a 4.10% reduction in caregiver time4. These meaningful outcomes will be further evaluated in the ongoing HOPE pivotal trial of SpectrisTM in mild-moderate AD (NCT05637801). **Keywords:** Gamma Oscillations, Alzheimer's Disease, Dependence Score. **Clinical Trial Registry:** OVERTURE: NCT03556280. **Disclosures:** RK, MH, BV, CH, CH, MH, LL are employees of, or own equities in Cognito Therapeutics. **References:** 1. Hajos et al. Front Neurol 2024. 2. Zhu et al. Alzheimer's Research & Therapy 2018. 3. Brickman et. al., Arch Neurol 2002. 4. Frank et al., American Journal of Alzheimer's Disease & Other Dementias 2010.

P026- SPECTRISTM OVERTURE I RESPONDER ANALYSIS DEMONSTRATES CONSISTENT PRESERVATION OF FUNCTION AND BRAIN STRUCTURE. R. Kern[1], M. Hajos[1], B. Vaughan[1], C. Houser[1], A. Konisky[1], L. Lee[1], J. Christensen[2], B. Haaland[2], S. Hendrix[2] *(1. Cognito Therapeutics - Cambridge (United States), 2. Cognito Therapeutics - Salt Lake City (United States))*

Background: The OVERTURE I (NCT03556280) randomized controlled trial (RCT) evaluated SpectrisTM in mild-moderate Alzheimer's disease [1]. Consistency between treatment effects on clinical and MRI brain atrophy outcomes in Alzheimer clinical trials are an important therapeutic objective [2]. **Methods:** In a post-hoc analysis of OVERTURE I RCT data, responders were identified as participants with ≥0 ADCS-ADL total score change from baseline at 6 months and compared whole brain volume (WBV) change from baseline in responders and non-responders. A one-way ANOVA and pairwise Welch's t-tests were conducted to compare WBV change at 6 months between responders, non-responders, and sham patients. **Results:** 135 participants were screened, 74 were treated and 53 completed the RCT (20 sham, 33 active). Of the 53 completers, 45 had visits windowed to 6 months of which one was excluded as an outlier. Tolerability and adherence were confirmed, and no serious treatment-related adverse events or ARIA were observed. Baseline ADCS-ADL total scores (mean, SD) were not significantly different in treatment groups [active (66.9, 8.54) vs sham (63.3, 10.65), p=0.16]. Active vs. sham treatment resulted in a 77% reduction in decline of ADCS-ADL total score over 6 months (p=0.0004). 52% of active treated participants (n=16/31) showed ADCS-ADL total score ≥0 change from baseline at 6 months compared to 0% of sham treated participants (0/13), resulting in a number needed to treat (NNT) of 1.9. WBV change from baseline (cm3) showed different trends in active responders compared to active non-responders and sham participants (-4.6 vs. -10.0 vs. -16.6, p=0.0547, ANOVA). The active responder group differed significantly from the sham group (p=0.0291, t-test). **Conclusion:** Approximately half of the active treated participants showed no decline or improvement in function, in contrast to no patients in the sham treatment. Active treatment responders showed a significantly greater slowing of WBV loss at 6 months compared to the sham group. This analysis confirms the consistency of treatment effects on daily function and MRI brain atrophy outcomes in the OVERTURE I Phase 2 clinical trial. These important outcomes will be further evaluated in the ongoing HOPE pivotal trial of SpectrisTM in mild-moderate AD (NCT05637801). **Keywords:** Gamma Oscillations, Alzheimer's Disease, Activities of Daily Living, Brain Atrophy. **Clinical Trial Registry:** OVERTURE I: NCT03556280. **Disclosures:** Authors are employees of, or own equities in Cognito Therapeutics or Pentara Corporation. **References:** 1. Hajos et al. Front Neurol 2024. 2. Ten Kate. JPAD 2023.

P027- A PHASE II CLINICAL TRIAL OF INTERLEUKIN-2 (IL-2) IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE. A. Faridar[1], N. Gamez[1], A. Thome[1], W.H.Z.H.A. Zhao[1], D. Beers[1], J. Thonhoff[1], M. Nakawah[1], G.C.R.O.M. Roman[1], J. Toledo[1], C. Davis[2], M. Pascual[1], M. Grundman[3], J. Masdeu[1], S.A.P.P.E. Appe[1] *(1. Houston Methodist Hosital - Houston (United States), 2. CSD Biostatistics - Csd Bioscience (United States), 3. Global R&D Partners - Global R&d Partners (United States))*

Background: Inflammation is a significant component of Alzheimer disease (AD). We have recently demonstrated that regulatory T cells (Tregs) have a compromised phenotype and reduced suppressive function in AD patients, skewing the immune system toward a proinflammatory status and potentially contributing to disease progression1. Low dose interleukin-2 (IL-2) is now viewed as a promising immunoregulatory drug with the capacity to selectively expand and restore functional Tregs. In a recent open-label Phase 1 study, we administered low dose IL-2 to 8 AD patients2. IL-2 immunotherapy restored Tregs and ameliorated systemic pro-inflammatory mediators in these individuals. To confirm and expand on our findings, in the present study, we conducted a phase 2a double-blinded, randomized, placebo-controlled clinical trial to assess low-dose IL-2 immunotherapy in subjects with mild to moderate AD. **Methods:** This study is a phase II, randomized, double-blinded, placebo-controlled study to assess low dose IL-2 therapy in AD patients. 38 AD patients in the mild- to moderate clinical dementia stages (MMSE scores: 12-26) were enrolled. The first 22 participants were randomized to five-day courses of subcutaneous IL-2 (1MUI/day) or placebo administered every 4 weeks for a total of 21 weeks. In the next step, 16 additional participants were randomized (2:1) to five-day-courses of subcutaneous IL-2 (1MUI/day) or placebo administered every 2 weeks for a total of 21 weeks. Patients were followed for 9 weeks after the last five-day course of treatment for a total of 30 weeks. Measurements at each time point were summarized descriptively. Mean change from baseline for biomarker and clinical endpoints that involve multiple collection timepoints were evaluated using a mixed-model repeated measures (MMRM) analysis with treatment as the main effect; visit, baseline value of the variable being evaluated, APOE ε4 (+ or -) status at baseline as covariates, and treatment by visit as an interaction term. **Results:** The primary objective of this study was to assess the safety and the tolerability of low dose IL-2 administration in AD patients. There were no serious adverse events reported following IL-2 administration. The most common adverse event was injection site irritation/redness. The secondary endpoint of this study includes the pharmacodynamic effect of two different doses of Low dose IL-2 immunotherapy, their immunomodulatory effect on blood and cerebrospinal fluid (CSF) inflammatory markers, AD-related CSF biomarkers and cognitive and functional assessments. The study is already completed and is in database lock process. The outcome measures, including changes in Treg numbers and immunosuppressive functions, blood and CSF inflammatory markers, AD-related CSF biomarkers, and cognitive and functional changes, will be analyzed and presented at the CTAD 2024 conference. **Conclusion:** In this phase II, randomized, double-blinded, placebo-controlled study, low dose IL-2 immunotherapeutic strategy was safe and well-tolerated. The study is completed and is in database lock process. The impact of two different doses of low dose IL-2 immunotherapy on blood and CSF immune biomarkers, established AD-related CSF biomarkers, and cognitive and functional endpoints will be assessed and presented in CTAD2024.

P028- LONG-TERM EFFECTS OF FORTASYN CONNECT (SOUVENAID) ON BRAIN ATROPHY MEASURES IN MCIAD: RESULTS FROM THE DOUBLE-BLIND RANDOMISED LIPIDIDIET TRIAL. T. Hartmann[1,2], J. Tohka[3], Y. Liu[3], P.J. Visser[4,5], K. Blennow[6,7], H. Soininen[8,9], M. Kivipelto[8,10,11,12], A. Solomon[8,10,11,12] *(1. Deutsches Institut für Demenz Prävention (DIDP), Medical Faculty, Saarland University - Homburg (Germany), 2. Department of Experimental Neurology, Saarland University - Homburg (Germany), 3. A.I. Virtanen Institute for Molecular Sciences, University of Eastern Finland - Kuopio (Finland), 4. Department of Psychiatry and Neuropsychology, Alzheimer Center Limburg, University of Maastricht - Maastricht (Netherlands), 5. Department of Neurology, Alzheimer Center, VU University Medical Center - Amsterdam (Netherlands), 6. Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at University of Gothenburg - Mölndal (Sweden), 7. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital - Mölndal (Sweden), 8. Department of Neurology, Institute of Clinical Medicine, University of Eastern Finland - Kuopio (Finland), 9. Neurocenter, Department of Neurology, Kuopio University Hospital - Kuopio (Finland), 10. Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institute - Huddinge (Sweden), 11. Clinical Trials Unit, Theme Aging, Karolinska University Hospital - Huddinge (Sweden), 12. Ageing and Epidemiology Research Unit, School of Public Health, Imperial College - London (United Kingdom))*

Background: Lifestyle factors such as nutrition are increasingly recognized as modifiable risk factors for the progression of mild cognitive impairment (MCI) to dementia due to Alzheimer's disease (AD). Synaptic and neuronal loss contribute to brain atrophy on structural Magnetic Resonance Imaging (MRI) and all correlate with cognitive impairment observed already in the early AD stages. The multi-nutrient combination 'Fortasyn Connect' was developed to address nutritional needs in individuals in the early AD stages and shown to have neuroprotective properties. The LipiDiDiet [1, 2] clinical trial was conducted to investigate the effects of Fortasyn Connect in individuals with prodromal AD/MCIAD. Significant group differences included reduced cognitive-functional decline over time for CDR-SB (-45%, p=0.014), NTB-5 (-60%, p=0.014) and NTB-memory (-76%, p=0.008). It also effectively reduced brain atrophy (hippocampal atrophy -33%, p=0.002; whole brain atrophy -22%, p=0.021; ventricular enlargement -20%, p=0.042) over 3 years of intervention [3, 4]. Cumulatively, these intervention effects translated in an overall slowing of disease progression by 38% (p=0.007) over the first 2 years (equivalent to 9 months saved) [5] and by 58% (p<0.001) over the first 3 years of intervention (equivalent to 21 months saved out of 36 months intervention period). Here, we present the MRI results for the first 4 years of intervention. **Methods:** LipiDiDiet was a double-blind, parallel-group, multi-center randomized controlled clinical trial conducted across Finland, Germany, the Netherlands, and Sweden. A total of 311 participants with prodromal AD, defined according to the IWG-1 criteria, were enrolled and randomized (1:1) to the active product (125ml once-a-day drink; Fortasyn Connect) or a calorie and taste-matched placebo control. Following the first 2 years of intervention, participants could opt in for annual extensions up to a maximum of 6-year double-blind intervention. When participants started the trial, they were not

taking any AD drugs. Once individual participants progressed to mild dementia during the double-blind intervention period, they were provided with AD drugs and/or open-label Fortasyn (together referred to as open-label medication) and could continue in the trial. Main outcomes included NTB composites on overall cognition and memory, the CDR-SB, and MRI markers of neurodegeneration (i.e. hippocampal, whole-brain and ventricular volumes from 3D T1-weighted anatomical scans assessed annually and analysed centrally using MAPS-HBSI for hippocampal volume (HCV), BSI for whole-brain volume (WBV) and longitudinal Freesurfer for ventricular volume (VV) and/or Longitudial Freesurfer 7.4.1 for WBV and VV and SynthSeg 2.0 for HCV. Modified intention-to-treat analyses (all randomized participants with MRI data, excluding visit data after the start of open-label medication) were performed over 4 years of intervention using a joint model combining longitudinal and survival data. **Results:** An overview of the intervention effects on longitudinal MRI markers of neurodegeneration (hippocampal, whole-brain and ventricular volumes) will be presented. In addition to the already demonstrated sustainable cognitive/functional benefits of Fortasyn Connect in individuals with prodromal AD/MCIAD, combined with feasibility of its long-term use without indications for health concerns we report first intervention results on long-term brain atrophy. **Conclusion:** Over the years, LipiDiDiet results include significantly less total hippocampal atrophy and significant effects on changes in other measures in the active compared to the control group. **References:** 1Dutch Trial Register: NL1620 (NTR1705). 2. Funding by EU-FP7 211696, EU JPND EURO-FINGERS. 3. Soininen H, et al. Lancet Neurol. 2017;16:965-975. 4. Soininen H, et al. Alz Dementia. 2021;17:29-40. 5. Dickson S, et al. J Prev Alz Dis. 2024.55. **Disclosures:** The main funding for the LipiDiDiet consortium was provided by the European Union. Additional funding was received from Danone Research & Innovation for the intervention period from 24 to 96 months and the Consortium distributed the funding to their members to conduct the trial and analysis. TH, MK, and HS received additional funding from EU Joint Program - Neurodegenerative Disease Research (MIND-AD, EU-FINGERS, Multi-MeMo) for this study. PJV reports grants from Innovative Medicine Initiative and ZonMw, during the conduct of the study, and non-financial support from GE Healthcare and grants from Biogen, outside the submitted work. AS reports grants from Academy of Finland and European Research Council, during the conduct of the study. KB has served as a consultant and at advisory boards for Abbvie, AC Immune, ALZPath, AriBio, BioArctic, Biogen, Eisai, Lilly, Moleac Pte. Ltd, Neurimmune, Novartis, Ono Pharma, Prothena, Roche Diagnostics, and Siemens Healthineers; has served at data monitoring committees for Julius Clinical and Novartis; has given lectures, produced educational materials and participated in educational programs for AC Immune, Biogen, Celdara Medical, Eisai and Roche Diagnostics; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, outside the work presented in this paper.

P029- ORALLY AVAILABLE PRI-002 FOR THE TREATMENT OF ALZHEIMER´S DISEASE: PHASE 1A DATA AND DESIGN OF THE PHASE 2A STUDY. O. Peters[1], J. Kutzsche[2], N.C. Cosma[1], G. Kauselmann[3], G. Tischler[4], D. Jürgens[3], D. Willbold[5] *(1. Charité - Berlin (Germany), 2. FZ Jülich - Jülich (Germany), 3. Priavoid - Düsseldorf (Germany), 4. Prinnovation - Leipzig (Germany), 5. Priavoid - Jülich (Germany))*

Amyloid beta (Aβ) oligomers are synaptotoxic and responsible for reduced synaptic plasticity, impaired neuronal function and thus for development and progression of Alzheimer's disease (AD). PRI-002 was developed to disassemble toxic Aβ oligomers and to restore synaptic plasticity in early AD stages. By this PRI-002 has the potential to be disease modifying but may also have a short-term effect improving cognition. Target engagement has been demonstrated in vitro an in vivo. PRI-002 has previously been shown to reverse cognition deficits in four different animal models in four different laboratories. PRI-002 has also demonstrated to be safe and well tolerable in healthy volunteers. Here we want to demonstrate safety in MCI and mild AD patients and to explore efficacy. We carried out a randomized, placebo-controlled, double-blind, Phase 1b study to evaluate safety, tolerability and pharmacodynamics of PRI-002 in early AD. Eligible patients were randomly assigned (1:1) to receive 300 mg PRI-002 per day or placebo for 28 days. Follow-up assessment took place on day 56. The trial is registered in EudraCT 2020-003416-27. 19 patients were randomly assigned to PRI-002 (n=9) or placebo (n=10) and completed the study per protocol. PRI-002 was overall well tolerated. No SAEs were reported. No significant changes in clinical chemistry, hematology or hematoserology were detected. ECG, EEG and MRI revealed no changes. No ARIA-E were observed. No biomarker changes were detected in in CSF (p-tau, t-tau, Aβ 1-40, Aβ 1-42 and Aβ oligomers). In contrast to patients in the placebo group, each of the patients in the verum group had increased short-term-memory abilities as demonstrated in the CERAD word list at day 56 vs. baseline ($p<0.01$). A phase 2a study (NCT06182085) has been started to assess the potential therapeutic benefit of PRI-002 in 270 patients with mild neurocognitive impairment and mild dementia due to AD. In this ongoing randomized placebo-controlled trial patients are treated for with PRI-002 300mg or 600mg or placebo (1:1:1) for at least one year.

P030- EFFECT OF BASELINE AMYLOID LEVEL ON COGNITIVE DECLINE IN ADULTS WITH PRECLINICAL ALZHEIMER'S DISEASE ENROLLED IN THE A4 CLINICAL TRIAL, MEASURED WITH COMPOSITE SCORES FROM THE COGSTATE BRIEF BATTERY. P. Maruff[1], D. Rentz[2], K. Papp[2], M. Donahue[3], A. Lui[3], P. Aisen[3], R. Sperling[2], A. A4 Study Team[4] *(1. Cogstate Ltd - Melbourne (Australia), 2. Department of Neurology, Massachusetts General Hospital and Harvard Medical School. Department of Neurology, Brigham and Women's Hospital and Harvard Medical School - Boston (United States), 3. Alzheimer Therapeutic Research Institute, Keck School of Medicine, University of Southern California, San Diego, CA, USA - San Diego (United States), 4. A4STUDY.ORG, San Diego (United States))*

Background: The Anti-Amyloid Treatment in Asymptomatic Alzheimer's disease (A4) Study (4) was a Phase 3 clinical trial evaluating the effect of solanezumab on cognitive decline in preclinical AD. While solanezumab had no effect on cognitive decline, measured using composite scores derived from

standardized (PACC) or computerized cognitive (C3) tests, A4 trial data is an important resource for understanding and improving trial design in preclinical AD. Post-hoc challenges used to understand the behavior of the different clinical trial endpoints in A4 have compared rates of decline between A4 subgroups with <46.1 centiloid CL, 46.1-to-77.2CL or >77.2CL amyloid levels at baseline. The Cogstate Brief Battery (CBB) was included in A4 as part of the computerized cognitive test battery. While natural history studies show cognitive decline in preclinical AD is characterised on the CBB by a decline in the learning working memory (L/WM) composite with relative stability in the psychomotor attention (PSY/ATT) composite scores, the CBB composites have not been evaluated in A4 clinical trial data. **Methods:** The A4 study took place at 67 sites in Australia, Canada, Japan and the United States Data for the CBB L/WM and PSY/ATT composite scores was derived from cognitively unimpaired older adults (n=1117, Mean Age=71.9, 60.7% female) with elevated brain amyloid levels on 18F-florbetapir positron-emission tomography A4 participants who were assigned randomly to solanezumab doses up to 1600 mg intravenously every 4 weeks (n=549) versus placebo (n=568). The CBB was completed as part of the cognitive battery at 6-month retest intervals. **Results:** Separate natural cubic spline models were used to compare differences between baseline amyloid subgroups in change from baseline to 240 weeks and assumed a heterogeneous Toeplitz variance-covariance indicated there were there no differences between the baseline amyloid subgroups for both CBB composites. Comparison of change from baseline between amyloid subgroups at the week-240 visit indicated that for the L/WM composite, performance improved from baseline in the <46.1CL subgroup, and in the 46.1-to-77.2CL subgroup but to a significantly reduced extent. The LWM composite score declined significantly from baseline in the >77.2CL subgroup. A qualitatively similar pattern of change was observed for the PSY/ATT composite. Performance in the <46.1CL subgroup had not changed from baseline at week-240, Compared to this, performance in 46.1-to-77.2CL subgroup had declined significantly and performance in the >77.2CL subgroup declined further. **Conclusion:** The effect of baseline amyloid level in the A4 study on the CBB L/WM and PSY/ATT composites was qualitatively similar. There was some improvement from baseline evident for the subgroup with low levels of baseline amyloid. However, subgroups with medium or high baseline levels of amyloid showed decline on both CBB composites. Together these data provide a form foundation for understanding performance on the CBB in clinical trials of preclinical AD.

P032- A PHASE 1 RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF SINGLE ASCENDING DOSES OF CS6253 IN HEALTHY VOLUNTEERS. J.O. Johansson[1], B. Winblad[2], D.M. Michaelson[3], H. Zetterberg[4], H. Zetterberg[5], J.L. Cumming[6], H.N. Yassine[7] *(1. Artery Therapeutics, Inc. - San Ramon (United States), 2. Department of Neurobiology, Care Sciences and Society, Center for Alzheimer Research, Division of Neurogeriatrics, Karolinska Institutet - Solna (Sweden), 3. Tel Aviv University - Tel Aviv (Israel), 4. Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg - Mölndal (Sweden), 5. Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, Dementia Research Institute - London (United Kingdom), 6. Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Nevada Las Vegas - Las Vegas (United States), 7. University of Southern California - Los Angeles (United States))*

Background: The increased AD-risk in APOE4 carriers is associated with impaired cholesterol transport. The ABCA1 agonist small molecule peptide CS6253 augments cholesterol transport within glial cells and between brain cells and also peripherally. CS6253 20 mg/kg IP QOD for 6 weeks has shown therapeutic benefit in APOE4 targeted replacement (TR) mice. In APOE4 TR mice and in Non-Human-Primates CS6253 facilitates Ab42 removal from brain with increased plasma Ab42/40-ratio and apoE concentrations. A Phase 1 SAD-MAD study was performed. We hereby report the Phase 1 SAD study results. **Methods:** In Phase 1 SAD cohorts 1-4 CS6253 1, 2.4, 6, and 10 mg/kg, respectively, was administered to young HV as IV bolus injection. In cohort 5, 10 mg/kg was administered to elderly men and women. All cohorts comprised 6 active and 2 placebo subjects. Subjects were assessed for adverse effects, PK, clinical chemistry, and biomarker effects. **Results:** No treatment-related adverse effects or out-of-range clinical chemistry were observed by CS6253 compared to placebo. Plasma PK was dose-proportional, with a terminal half-life of approximately 24 hours. Plasma and CSF biomarker results will be presented, relationships between CS6253 induced cholesterol-transport/lipoprotein effects and AD- biomarkers assessed. **Conclusion:** The CS6253 data from Phase 1 SAD dosing up to 10 mg/kg shows safety, tolerability and favorable PK. The development of a safe and efficient ABCA1 agonist addresses several indications with unmet medical need, notably for Alzheimer's disease. **Keywords:** ABCA1, ApoE4, Cholesterol Transport. **Clinical Trial Registry:** NCT05965414. **Disclosures:** All authors have stocks / options in Artery Therapeutics, Inc. **References:** Noveir SD, Kerman BE, Xian H, Meuret C, Smadi S, Martinez AE, Johansson J, Zetterberg H, Parks BA, Kuklenyik Z, Mack WJ, Johansson JO, Yassine HN. Effect of the ABCA1 agonist CS-6253 on amyloid-β and lipoprotein metabolism in cynomolgus monkeys. Alzheimers Res Ther. 2022 Jun 24;14(1):87. doi: 10.1186/s13195-022-01028-1. Hafiane, A., Bielicki, J. K., Johansson, J. O. & Genest, J. Novel Apo E-Derived ABCA1 Agonist Peptide (CS-6253) Promotes Reverse Cholesterol Transport and Induces Formation of preβ-1 HDL In Vitro. PloS one 10, e0131997, doi:10.1371/journal.pone.0131997 (2015). Boehm-Cagan A, Bar R, Liraz O, Bielicki JK, Johansson JO, Michaelson DM. ABCA1 Agonist Reverses the ApoE4-Driven Cognitive and Brain Pathologies. J Alzheimers Dis. 2016 Oct 4;54(3):1219-1233, DOI: 10.3233/JAD-160467.

P033- HARNESSING PERIPHERAL IMMUNITY IN EARLY ALZHEIMER'S DISEASE: SAFETY AND TOLERABILITY OF IBC-AB002 IN A PHASE 1B CLINICAL TRIAL. T. Croese[1], K. Baruch[1], E. Yoles[1], A. Kertser[1], E. Schochat[2], M. Schwartz[3], K. Sanjay[1] *(1. ImmunoBrain Checkpoint Inc. - New York (United States), 2. Schochat Pharma Services - Basel, 3. Weizmann Institute of Science - Rehovot (Israel))*

Background: The increasing understanding of the role of immune cells in Alzheimer's disease (AD) pathology has paved the way for novel therapeutic approaches. Pre-clinical data suggest that discontinued rather than continuous activation of the immune system, as achieved with a short half-life and intermittent dosing regimen, was able to reduce amyloid and tau burden, reduce neuroinflammation, and improve memory performance in different animal models of AD. IBC-01-01 is a Phase 1b clinical study that investigates the safety, tolerability, and preliminary efficacy of IBC-Ab002, a novel immunomodulatory agent designed to harness peripheral immunity by targeting the immune checkpoint axis PD-1/PD-L1. **Methods:** This randomized, placebo-controlled, dose-escalation study aims to enroll 40 patients aged 50-80 with early AD, regardless of ApoE gene status. Participants in each cohort receive four doses of IBC-Ab002 administered intravenously every 12 weeks, with escalating doses across 5 cohorts. The primary and secondary endpoints are safety, tolerability and pharmacokinetic of IBC-Ab002. Exploratory endpoints include changes in biomarkers of neuroinflammation and neurodegeneration in cerebrospinal fluid (CSF) and blood as well as changes in cognitive function assessed by the Cognitive Functional Composite (CFC). **Results:** As of May 2024, IBC-Ab002 was well-tolerated with no severe adverse events reported in the study and no evidence of Amyloid-Related Imaging Abnormalities (ARIA). Preliminary pharmacokinetic (PK) and receptor occupancy (RO) data indicate that the drug reached the expected Cmax and short half-life, as projected in preclinical models. Notably, the systemic exposure to IBC-Ab002 is considerably less than that of commercially available anti-PD-L1 antibodies. **Conclusions:** IBC-01-01 adopts an innovative approach in AD treatment, targeting for the first time a peripheral immune checkpoint for the treatment of dementia. Preliminary findings from initial cohorts demonstrate that IBC-Ab002 has a favorable safety and tolerability profile in patients with MCI and early AD, with evidence of intended peripheral target engagement and immune activation. The short half-life and Q12W dosing regimen support an advantageous safety profile by ensuring rapid clearance of the antibody from circulation, while maintaining ongoing therapeutic effects on brain pathology. **Keywords:** Phase 1b, immunotherapy, PD-L1, immune system. **Clinical Trial Registry:** NCT05551741; https://clinicaltrials.gov. **Disclosures:** TC, KB, EY, MS, SK are employees of Immunobrain Checkpoint, Inc (IBC). ES received compensation from IBC. The authors declared no competing interests.

P034- HYPERBARIC OXYGEN THERAPY FOR COGNITION IN OLDER ADULTS WITH TYPE 2 DIABETES. M. Schnaider Beeri[1], O. Benari[2,3], S. Efrati[2], M. Sano[4], B.B. Bendlin[5], A. Livny[2], M. Harel[3], G. Almog[3], Y. Ouyang[4], Y. Mardor[3], A. Hadanny[6], R. Ravona-Springer[2,3] *(1. Herbert and Jacqueline Krieger Klein Alzheimer's Research Center, Robert Wood Johnson Medical School, Rutgers University - New Brunswick (United States), 2. Faculty of Medicine, Tel Aviv University - Tel Aviv (Israel), 3. Sheba Medical Center - Ramat Gan (Israel), 4. Department of Psychiatry, Icahn School of Medicine at Mount Sinai - New York (United States), 5. Wisconsin Alzheimer's Disease Research Center, University of Wisconsin-Madison School of Medicine and Public Health, Madison - Wisconsin (United States), 6.Shamir Medical Center - Rishon Lezion (Israel))*

Background: Hyperbaric oxygen therapy (HBOT) involves administering oxygen-enriched air (up to 100%) to patients in a pressurized chamber at pressures above one atmosphere absolute. HBOT is clinically accepted for treating peripheral vascular diseases like non-healing ischemic foot ulcers, improving ischemic damage by stimulating regenerative processes and angiogenesis. Type 2 diabetes (T2D), a cardiovascular disease with vascular damage peripherally and in the brain, increases the risk for mild cognitive impairment (MCI) and dementia. However, no specific interventions exist for T2D-related cognitive decline. We present initial results of a double-blind placebo-controlled clinical trial examining HBOT effects on cognition in older adults with T2D and MCI. **Methods:** The study included HBOT and sham treatment arms. Assessments were conducted at baseline, 3 months, post-treatment, and 6 and 12 months to examine long-term HBOT effects. The primary outcome was global cognitive change assessed by a composite z-score from a cognitive battery. Secondary outcomes included Clinical Dementia Rating (CDR) sum of boxes, Activities of Daily Living (ADL), Instrumental ADL (IADL), and Beck's Depression Inventory (BDI). While data collection ended, brain imaging data post-processing and unblinding are still pending. Therefore, we present 12-month trends for primary and secondary outcomes irrespective of treatment groups using within subject UNIANOVA analysis. **Results:** One hundred and fifty-five participants met eligibility (mean age 71.0 [SD=3.9], 31% female, education 14.2 [SD=3.1] years). Significant improvements over time were found for the global cognition composite z-score ($F=9.28$; $p<0.001$) which was driven by the specific cognitive domains of semantic memory ($F=5.65$; $p<0.001$), episodic memory ($F=10.01$; $p<0.001$) and executive functions ($F=4.85$; $p=0.002$) but not by the language domain ($F=1.76$; $p=0.13$). Significant improvements over time were also found for the CDR sum of boxes ($F=22.79$; $p<0.001$), ADL ($F=3.25$; $p=0.007$), IADL ($F=7.99$; $p<0.001$), but not for depression symptoms ($F=0.49$; $p=0.85$). Tuckey posthoc analyses for the outcomes with significant changes over time revealed that the scores at 3, 6, and 12-months follow-ups were better than the baseline scores, but did not differ significantly among themselves. **Conclusion:** Our study is the first to investigate HBOT effects on cognitive function in older T2D adults at high dementia risk due to MCI. If positive, results could provide compelling evidence for HBOT benefits on brain function and cognition in this growing yet understudied population. The blind of the trial will be broken on June 15th allowing for group comparisons by the CTAD conference in October 2024.

P035- HEALTH ECONOMIC IMPACT OF DISEASE MODIFYING THERAPIES SUCH AS MONOCLONAL ANTIBODIES. S. Dickson[1], C. Mallinckrodt[1], S. Hendrix[1] *(1. Pentara Corporation - Salt Lake City (United States))*

Background: Alzheimer's disease (AD) and other dementias likely exceed $27,000/yr over costs for cognitively normal individuals. Cost differences associated with mild cognitive impairment (MCI) over cognitively normal individuals may be minimal, but those with early dementia incur costs over 50% relative to prevalent dementia. With disease-modifying monoclonal antibodies now available, estimating cost savings associated with slowing of disease progression will be important. We demonstrate potential cost savings for different effect sizes and use a meta-analytic time component test (TCT) to estimate time savings for disease-modifying treatments. **Methods:** Estimated costs of care across stages of dementia were aggregated from various sources to estimate expected cost of care for individuals through their disease course. Cost savings of treatments are estimated through each year of the disease based on when treatment is started. Using the TCT, we estimate expected time savings for recent monoclonal antibodies in the treatment of AD using ADAS-Cog, ADCS-ADL, and CDR-SB when available and show potential cost savings associated with each treatment based on early intervention. **Results:** Potential cost savings associated with 25%, 50%, and 75% slowing of disease progression when intervention is begun at MCI, early dementia, and prevalent dementia stages are shown in the table below (Dickson, AD/PD 2023). Based on recent clinical trial results, potential cost savings associated with time savings with current treatments may be as high as $138,000 across the disease course. Current treatments may achieve these levels of savings. **Conclusion:** Treatment effect size affects cost savings, which should factor into decisions related to initiating treatment, pricing and reimbursement or coverage for treatment.

P036- EFFECT OF THE TIMING OF ACETYLCHOLINESTERASE INHIBITOR INGESTION ON SLEEP. S.Y. Park[1], W.M. Bahk[2], B.H. Yoon[3], K. Lee[4], S.Y. Lee[5], H.M. Sung[6], M.K. Song[7] *(1. Keyo Hospital - Uiwang (Korea, Republic of), 2. Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul - Seoul (Korea, Republic of), 3. Naju National Hospital - Naju-Si (Korea, Republic of), 4. College of Medicine, Dongguk University - Gyeongju (Korea, Republic of), 5. Wonkwang University Hospital, Wonkwang University School of Medicine - Iksan (Korea, Republic of), 6. Soonchunhyang University Gumi Hospital, College of Medicine, Soonchunhyang University - Gumi (Korea, Republic of), 7. St. Mary's Gong-Gam Mental Health Clinic - Siheung (Korea, Republic of))*

Objective: Many patients with Alzheimer's disease experience sleep disturbances, and donepezil is usually prescribed for night-time administration. However, increased acetylcholine is associated with cortical arousal. We evaluated whether subjective sleep quality differed according to the timing of medication administration. **Methods:** Ninety-two patients with mild to moderate Alzheimer's disease who had taken donepezil at night (n =54) or galantamine in the morning (n=38) were recruited for this study. Scores on the sleep visual analogue scale (VAS) for sleep quality and daytime drowsiness were obtained. **Results:** The mean sleep-quality and daytime-drowsiness VAS scores of the donepezil and galantamine groups differed significantly at baseline (44.0±26.4 vs. 55.2±27.3, respectively; $P < 0.001$ and 48.8±28.8 vs. 38.8±25.3, respectively; $P < 0.001$). The patients taking donepezil were then randomly assigned to take donepezil in the morning (n= 24) or at night (n= 30). Eight weeks later, VAS scores also differed among the three groups ($P < 0.001$ for both sleep quality and daytime drowsiness). The VAS scores of patients taking galantamine and donepezil in the morning were different from those taking donepezil at night at week 8. Significant changes in VAS scores emerged only in the group taking donepezil in the morning (4.6±26.5, $P = 0.046$ for sleep quality; – 7.1±26.1, $P < 0.001$ for daytime drowsiness). **Conclusion:** These results suggest that taking acetylcholinesterase inhibitors in the morning can improve the sleep states of patients with Alzheimer's disease. **Keywords:** Alzheimer's disease, donepezil, galantamine, sleep. **Conflicts of interest:** There are no conflicts of interest. **References:** 1. Ancoli-Israel S, Amatniek J, Ascher S, Sadik K, Ramaswamy K (2005). Effects of galantamine versus donepezil on sleep in patients with mild to moderate Alzheimer disease and their caregivers: a double-blind, head-to-head, randomized pilot study. Alzheimer Dis Assoc Disord 19:240–245. 2. Cooke JR, Loredo JS, Liu L, Marler M, Corey-Bloom J, Fiorentino L, et al. (2006). Acetylcholinesterase inhibitors and sleep architecture in patients with Alzheimer's disease. Drugs Aging 23:503–511. 3. Dooley M, Lamb HM (2000). Donepezil: a review of its use in Alzheimer's disease. Drugs Aging 16:199–226. 4. Hornung OP, Regen F, Danker-Hopfe H, Schredl M, Heuser I (2007). The relationship between REM sleep and memory consolidation in old age and effects of cholinergic medication. Biol Psychiatry 61:750–757. 5. Lilienfeld S (2002). Galantamine – a novel cholinergic drug with a unique dual mode of action for the treatment of patients with Alzheimer's disease. CNS Drug Rev 8:159–176. 6. Mizuno S, Kameda A, Inagaki T, Horiguchi J (2004). Effects of donepezil on Alzheimer's disease: the relationship between cognitive function and rapid eye movement sleep. Psychiatry Clin Neurosci 58:660–665. 7. MoraesWS, Poyares DR, Guilleminault C, Ramos LR, Bertolucci PHF, Tufik S (2006). The effect of donepezil on sleep and REM sleep EEG in patients with Alzheimer disease: a double-blind placebo-controlled study. Sleep 29:199–205. 8. Singer M, Romero B, Koenig E, Fo¨ rstl H, Brunner H (2005). Nightmares in patients with Alzheimer's disease caused by donepezil. Therapeutic effect depends on the time of intake. Nervenarzt 76:1127–1128, 1129. 9. Stahl SM, Markowitz JS, Gutterman EM, Papadopoulos G (2003). Co-use of donepezil and hypnotics among Alzheimer's disease patients living in the community. J Clin Psychiatry 64:466–472. 10. Sukys-Claudino L, Moraes W, Guilleminault C, Tufik S, Poyares D (2012). Beneficial effect of donepezil on obstructive sleep apnea: a double-blind, placebo-controlled clinical trial. Sleep Med 13:290–296. 11. Vazquez J, Baghdoyan HA (2001). Basal forebrain acetylcholine release during REM sleep is significantly greater than during waking. Am J Physiol Regul Integr Comp Physiol 280:598–601. 12. Vitiello MV, Borson S (2001). Sleep disturbances in patients with Alzheimer's disease: epidemiology, pathophysiology and treatment. CNS Drugs 15:777–796.

P037- ANALYSIS OF THE CARDIOVASCULAR SAFETY OF CHOLINE ALPHOSCERATE TREATMENT IN THE ASCOMALVA TRIAL. E. Traini[1], A. Carotenuto[1], A. Fasanaro[2], F. Amenta[1] *(1. University of Camerino - Camerino (Italy), 2. Neurology and Stroke Unit-Neurology, A. Cardarelli Hospital - Napoli (Italy))*

Background: L-α-glyceryl-phosphorylcholine (α-GPC, choline alphoscerate), is a choline-containing phospholipid which increases the bioavailability of choline and acetylcholine and which is used as a prescription or nonprescription

medication to help manage or prevent the progression of adult-onset dementia disorders. Some studies have suggested that high levels of plasma choline, as in α-GPC supplementation, may be associated with a high risk of cardiovascular disease and stroke. This assumption is not consistent with a recent review accompanied by meta-analysis demonstrating the effectiveness of α-GPC in improving neurological function, functional recovery, and positive outcomes in terms of activities of daily living in patients after an acute thrombotic or hemorrhagic stroke. **Methods:** In view of these discrepancies, we did a post-hoc analysis of the cardiovascular safety in patients participating to the ASCOMALVA (Association Between the Cholinesterase Inhibitor Donepezil and the Cholinergic Precursor Choline Alphoscerate in Alzheimer's Disease with Cerebrovascular Injury) trial. ASCOMALVA is a double-blind multicentre trial that has evaluated in 4 years 210 patient that were randomly allotted to an active treatment group (donepezil+ α-GPC) or to a reference treatment group (donepezil+placebo). The length of the trial makes it one of the longest studies on Alzheimer's disease. **Results:** During treatment, patients were also monitored for blood chemistry parameters, particularly those relating to iron metabolism, the dysregulation of which has been observed in many types of cardiovascular diseases. These evaluations were further analyzed to assess the safety and possible occurrence of cardiovascular problems in patients belonging to the donepezil+ α-GPC arm. **Conclusion:** The analysis of adverse events, withdrawals and blood chemistry parameters demonstrated that treatment with α-GPC is safe, especially for cardiovascular risk. **Keywords:** Safety; Choline alphoscerate; Iron metabolism; Cardiovascular diseases. **Clinical Trial Registry:** 2008-004667-19. **Disclosures:** The authors declared no competing interests.

P038- EXPLORING THE EFFECT OF BASELINE CHARACTERISTICS ON THE EFFICACY OF MULTIDOMAIN DEMENTIA PREVENTION IN LATE-LIFE: A POOLED ANALYSIS OF INDIVIDUAL PARTICIPANT DATA FROM THE MAPT AND PREDIVA TRIALS. N. Coley[1,2,3], M.P. Hoevenaar-Blom[4,5], J. Shourick[1,2,3], E.P. Moll Van Charante[4,5], J.W. Van Dalen[6,7], W.A. Van Gool[5], E. Richard[5,6], S. Andrieu[1,2,3] *(1. Aging Research Team, Centre for Epidemiology and Research in Population health (CERPOP), INSERM-University of Toulouse UPS - Toulouse (France), 2. Department of Epidemiology and Public Health, Toulouse University Hospital - Toulouse (France), 3. IHU HealthAge - Toulouse (France), 4. Department of General Practice, Amsterdam UMC, University of Amsterdam - Amsterdam (Netherlands), 5. Department of Public and Occupational Health, Amsterdam UMC, University of Amsterdam - Amsterdam (Netherlands), 6. Department of Neurology, Donders Institute for Brain, Cognition, and Behaviour, Radboud University Medical Center - Nijmegen (Netherlands), 7. Department of Neurology, Amsterdam University Medical Center, Location AMC - Amsterdam (Netherlands))*

Background: Multidomain interventions have been advocated for healthy brain ageing, but randomised controlled trials (RCTs) have provided limited evidence of their efficacy, particularly in terms of preventing incident dementia. One reason for this may be that such interventions are only effective in certain subgroups of individuals. Some evidence suggests greater efficacy in those with increased dementia risk, but mostly from underpowered subgroup analyses, which predominantly focused on cognitive function outcomes rather than incident dementia. We studied whether multidomain interventions may reduce incident dementia in certain subgroups of older adults, defined by dementia risk factors, using pooled data from two large dementia prevention RCTs with long-term follow-up. **Methods:** We pooled data from the MAPT and preDIVA RCTs, which evaluated the efficacy of multidomain interventions, targeting lifestyle and cardiovascular risk factors, for the prevention of cognitive decline or dementia in individuals aged 70+ at baseline. The MAPT trial had a 3-year intervention period, followed by 2 years of observational follow-up. The preDVIA trial had a 6-8 year intervention period, with observational follow-up for up to 10-12 years post-baseline. Our primary outcome was incident all-cause dementia, with AD dementia and cognitive (MMSE) change as secondary outcomes. Subgroups were pre-specified using the following baseline characteristics which were expected to be associated with dementia risk: age (<75/≥75), sex (male/female), level of education (low/medium/high), APOE genotype (ε4 non-carrier/carrier), cognitive status (MMSE≥26/<26), BMI (≤30/>30), total cholesterol (≤6.5 mmol/l/ >6.5 mmol/l), physical activity (≥150 min. per week/ <150 min. per week), systolic blood pressure (SBP; ≤140mmHg/>140mmHg), untreated hypertension (no/yes), CAIDE dementia risk score (<6/≥6). Analyses were performed using shared frailty Cox models and longitudinal mixed effects models. Additionally, we performed an exploratory, data-driven analysis using a recursive partitioning algorithm aiming to identify subgroups, defined by single or combinations of risk factors, with differential intervention effects on incident dementia. **Results:** The pooled dataset included 5205 participants, of whom 486 developed dementia (MAPT: 77/1679 (4.6%); preDIVA: 409/3491 (11.7%)) during 37,782 person-years of follow-up. Dementia incidence was higher in older participants, APOE ε4 carriers, and those who were physically inactive, had an MMSE<26 or had higher SBP, but was not associated with education, sex, BMI, cholesterol, untreated hypertension, or CAIDE dementia risk score. In the pooled dataset, there was no effect of multidomain intervention on the risk of all-cause dementia (HR=0.98, 95%CI=0.80-1.21), and the intervention effect did not differ between trials (p-interaction=0.928). There was also no difference in the effect of the intervention on incident all-cause or AD dementia in any of the pre-specified subgroups. The recursive partitioning algorithm also did not detect any subgroups showing a differential intervention effect. **Conclusion:** We did not detect any significant multidomain intervention effects on incident dementia in either the total population or in any subgroups. Based on our results and those of other RCTs, the potential impact of multidomain interventions for dementia prevention at the individual level appears modest at best, even amongst those at greatest risk of dementia. Population-level approaches may be a complementary approach. **Keywords:** Multidomain interventions; prevention; randomised controlled trials. **Disclosures:** none.

P039- ONLINE ADVERTISING RESULTED IN MORE EDUCATED PARTICIPANTS AND NON INFERIOR SCREEN FAIL RATES WHEN COMPARED TO OFFLINE METHODS IN AN ALZHEIMER'S DISEASE CLINICAL TRIAL. Y.J. Huoh[1], R. Lee[1], C. Sholes[1], B. Martinez[1], S. Hopkins[1], J. Mitolo[1], T. Parnitvithikul[1], E. Zamrini[1], E. Lee[1] *(1. Irvine Clinical Research - Irvine (United States))*

Background: Alzheimer's Disease (AD) drug trials are slower to enroll and more expensive than trials in most other therapeutic areas. Historically, participants have been identified through offline methods including database searches,

community outreach events, and word of mouth referrals. Sites have increasingly turned to online advertising to speed up recruitment and reach potential participants outside of traditional offline methods. In this study, we investigate if online recruitment methods, compared to offline recruitment methods, have an effect on the education levels of recruited participants, as well as the screen failure rate of study participants in industry-sponsored AD drug trials. **Methods:** In 2023, 208 participants screened at a commercial site in California for a clinical trial of an investigational anti-amyloid monoclonal antibody in participants with early symptomatic Alzheimer's disease. Of the 208 participants, 75.5% (157) of the participants were recruited through online advertising and the remaining 24.5% (51) through offline means - such as a database search, in-person outreach event within the community, or a referral via friend or family member. The screening process for a trial involves a number of examinations and assessments in order to (i) ensure the person can safely participate within the study (ii) has the appropriate indication for the treatment being evaluated and (iii) take the relevant baseline measurements in order to evaluate the effectiveness of the drug. Of the 208 screened participants, of which 48 made it through the screening process successfully and enrolled into the study. During the screening process, a number of demographic characteristics about the participant is also collected and recorded - including gender, ethnicity, and the years of formal education received by the participant. Collection of these characteristics is optional - a participant could decline to answer any of the questions. Of the 208 participants, 17 declined to answer the question about their education. For the 191 participants that answered, the mean years of education was 15.28 years, with a standard deviation of 2.99 years. The median years of education was 16, so the data is very slightly skewed upwards by a handful of participants with very advanced degrees. **Results:** Across all 258 participants in screening in both studies, the average years of education for someone recruited through online advertising was 15.57 years. For a person recruited through offline channels, the average years of education was 14.35 years. Assuming unequal variances across the two populations, this difference of 1.22 years was statistically significant ($p = 0.015$). The screening failure rate of persons recruited through online advertising was 76.4% (120 of 157). The screening failure rate of persons recruited through offline methods was 78.4% (40 of 51). Using a 2-sample t-test for proportions, this difference of 2.0% was not statistically significant ($t = -0.29$, $p = 0.77$). **Conclusion:** From the analyses of the screening failure rates, it is unlikely that the recruitment method has any impact on a participant's ability to pass screening and successfully enroll into a study for an AD treatment. This finding is unsurprising given that the criteria for screen failures are typically clinical (no biomarkers present, not enough cognitive impairment), which should be uncorrelated with how this person was identified for the study. However, finding a significant effect between years of education and recruitment method is unusual, but not too surprising. It is quite reasonable to expect the wider audiences that online advertising gives research sites access to result in different demographics for those recruited. Unfortunately, there is no obvious explanation for the observed directionality - why does online advertising result in a more educated participant or conversely why do offline recruitment channels yield a less educated participant? A more thorough investigation into the specific offline recruitment methods and the nuances between them would be necessary to identify the driving factors behind this effect.

P040- POTENTIAL EFFICACY OF ORAL NICOTINAMIDE RIBOSIDE (NR) SUPPLEMENTATION IN OLDER ADULTS WITH SUBJECTIVE COGNITIVE DECLINE AND MILD COGNITIVE IMPAIRMENT. C.Y. Wu[1], A. Kupferschmid[1], A. Mcmanus[1], P. Kivisakk[1], J. Galler[1], N. Schwab[1], L. Desruisseaux[1], V. Williams[1], J. Gerber[1], M. Riley[1], C. Young[1], H. Dodge[1], R. Tanzi[1], C. Singer[2], S. Arnold[1] *(1. Massachusetts General Hospital/ Harvard Medical School - Boston (United States), 2. Northern Light Health - Bangor (United States))*

Background: Age-associated depletion in nicotinamide adenine dinucleotide concentrations (NAD+) have been implicated in metabolic, cardiovascular, and neurodegenerative disorders. Supplementation with NAD+ precursors, such as nicotinamide riboside (NR), offers a potential therapeutic avenue against neurodegenerative pathologies in aging, Alzheimer's disease and related dementias (ADRD). A crossover, double-blind, randomized placebo (PBO) controlled trial was conducted to test the safety and efficacy of eight weeks' active treatment with NR on cognition and plasma AD biomarkers in older adults with subjective cognitive decline (SCD) and mild cognitive impairment (MCI). **Methods:** Participants were recruited from two sites: MGH (Boston, MA) and Northern Light Health (Bangor, ME). The trial consisted of a four-week lead-in period followed by two consecutive eight-week treatment periods (Block 1 and Block 2). After the PBO lead-in period, participants were provided either NR (250 mg, 2 pills twice per day) or PBO (two pills twice per day) based on their sequence assignment. NR or PBO was switched at the end of Block 1 (crossover) without washout. The primary efficacy outcome was the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Secondary outcomes included plasma phosphorylated tau 217 (pTau217), glial fibrillary acidic protein (GFAP), and neurofilament light chain (NfL). To characterize meaningful biomarker changes, reference change values (RCVs) were used to represent the percentage shifts needed between two consecutive measures to distinguish real changes from analytical and biological variations. Daily Lumosity game play was used as an additional exploratory outcome for cognition. Convergent validity and test-retest reliability of RBANS, plasma biomarkers, and Lumosity were assessed. **Results:** Forty-six participants aged over 55 were randomized to NR-PBO or PBO-NR groups; 41 completed baseline visits [67±7.4 years old; 22 females (54%)]. There were no differences in the pill taking compliance between two groups and across time. NR supplementation was safe and well tolerated with no differences in adverse events reported between NR and PBO treatment periods. There was a significant between-group difference in the fold change of pTau217 at crossover (Cohen's d=0.8, p=0.02), but no differences were found for RBANS, other plasma biomarkers, or Lumosity games. Across all participants, the fold changes in pTau217 and GFAP were lower when taking NR supplementation compared to when taking the PBO (p=0.006; p=0.03); 23% of participants showed a reduction in pTau217 levels that exceeded the RCVs, compared to only 6% who experienced such reductions after taking PBO (p=0.04). Small-to-moderate associations were found between pTau217, GFAP, and immediate and delayed memory of RBANS (ρ=-0.29 to -0.37). Lumosity performance exhibited a moderate correlation with RBANS total scores (ρ=0.55±0.09). ICCs were high for repeated RBANS total scores (ICC=0.80), pTau217 (ICC=0.91), and Lumosity total scores (ICC=0.63). **Conclusion:** Eight weeks NR supplementation is safe and lowered pTau217 levels but did not alter cognition as measured by conventional or novel digital assessments.

The integration of game-based assessments presents a promising adjunctive approach for tracking cognitive changes throughout ADRD trials. Further research is warranted to validate NR's efficacy in altering pathological brain aging processes. **Keywords:** phosphorylated tau pathologies; treatment heterogeneity; reference change values; nicotinamide adenine dinucleotide. **Clinical Trial Registry:** NCT04078178. **Disclosures:** C.Y.W., A.K., A.J.M., P.K., J.A.G., N.S., L.A.D., V.J.W., J.G., M.R., C.Y., H.H.D., C.M.S. have no declarations of interest directly related to the contents of the work presented herein. S.E.A. has no declarations of conflict of interest directly related to the work presented here, but has consulted and/or served on advisory boards for Allyx Therapeutics, BioVie, Bob's Last Marathon, Daewoong Pharmaceuticals, Foster & Eldridge, LLP, Quince Therapeutics, Sage Therapeutics, and Vandria; received sponsored research grant support via his institution from the following commercial entities: AbbVie, Amylyx, Athira Pharma, Cyclerion Therapeutics, EIP Pharma, Ionis Pharmaceuticals, Janssen Pharmaceuticals, Inc., Novartis AG, Seer Biosciences, Inc. and vTv Therapeutics, Inc; and has received sponsored research grant support via his institution from the following non-commercial entities: Alzheimer's Association, Alzheimer's Drug Discovery Foundation, Challenger Foundation, Cure Alzheimer's Fund, John Sperling Foundation, the National Institutes of Health and the Prion Alliance. R.E.T. is a paid consultant for, and holds equity in Chromadex and was not involved with the execution of the trial. The study was funded by the Challenger Foundation and the McCance Center for Brain Health. NR and matching PBO were provided by Chromadex, Inc.

LP016- EFFECTS OF SENSORY-EVOKED GAMMA OSCILLATION ON NEUROPHYSIOLOGICAL SIGNALS OF VISUAL AND COGNITIVE PROCESSING IN ALZHEIMER'S DISEASE. R. Fernández Romero[1], D. Grant[1], B. Jackson[2], C. Seshagiri[2], M. Hajós[2] *(1. The University of Tennessee Medical Center - Knoxville (United States), 2. Cognito Therapeutics - Cambridge (United States))*

Background: Sensory evoked steady-state gamma oscillation has been recognized as a potential therapeutic intervention in Alzheimer's disease (AD). Recent clinical trial demonstrated that evoked gamma oscillation improved brain functional connectivity, reduced cerebrospinal cytokines and neuroinflammatory markers in mild cognitive impairment participants [1], and improved visual pathway connectivity in participants with AD [2]. Furthermore, a six-month, daily, 1-hour treatment reduced decline in cognitive and functional abilities and reduced brain atrophy in participants with mild to moderate AD [3]. Visual and cognitive event related potentials reflect higher order cortical processing and can differentiate early-stage AD from normal cognitive aging. In previous research, we have explored the utility of these signals as functional biomarkers of AD [4-6]. The present study uses ERPs to evaluate the effects of sensory evoked gamma oscillation on visual and cognitive processing after 8-weeks of treatment with SpectrisTM (Cognito Therapeutics, Cambridge, MA, USA) medical device in participants with AD (NCT05206305). **Methods:** Twenty participants aged 60 and older with mild- to moderate, biomarker confirmed AD are recruited for this pilot study. Adequate visual and auditory evoked steady-state gamma oscillation confirmed using a 128-channel EEG system (EGI) is one of the inclusion criteria for the trial. Additional EEG recordings are obtained while subjects are engaged in an optic flow (OF) perception and discrimination task and a word delayed match to sample task (DMTS). EEG recordings are obtained prior to first exposure to treatment and repeated after 8 weeks, 1-hour daily treatment. EEG is processed to extract the corresponding OF and DMTS waveforms. Participants who completed the first phase of the study could enroll in an additional nine-months open label extension. **Results:** This study is designed to evaluate potential effects of steady-state gamma oscillations evoked by SpectrisTM on visual and cognitive processing using neurophysiological measurements. Preliminary findings support the tolerability of the intervention and replicability of ERP signals over an 8-week period. The changes observed in ERP responses could provide insight into mechanisms of evoked gamma oscillation on clinical benefits of this treatment in AD and the observed increments in P3b amplitude may provide an objective measure of improved cortical processing and working memory. **Keywords:** Steady-State Gamma Oscillation, Alzheimer's Disease, Visual Processing, Neurophysiology of Delayed Match to Sample. **Clinical Trial Registry:** NCT05206305. **Disclosures:** BLJ, CVS, MH are/were employees and own stock options in Cognito Therapeutics, Inc. **References:** 1. He at al., Alzheimers Dement (N Y). 2021, 7(1):e12178. doi: 10.1002/trc2.12178. 2. Chan et al., PLoS One. 2022;17(12):e0278412. doi: 10.1371/journal.pone.0278412. 3. Hajós et al., Front Neurol. 2024;15:1343588. doi: 10.3389/fneur.2024.1343588. 4. Fernandez R, Monacelli A, Duffy CJ. Visual motion event related potentials distinguish aging and Alzheimer's disease. J Alzheimers Dis. 2013;36(1):177-83. doi: 10.3233/JAD-122053. PMID: 23594601; PMCID: PMC3732796. 5. Fernandez R, Duffy CJ. Early Alzheimer's disease blocks responses to accelerating self-movement. Neurobiol Aging. 2012 Nov;33(11):2551-60. doi: 10.1016/j.neurobiolaging.2011.12.031. Epub 2012 Feb 17. PMID: 22341609; PMCID: PMC3689010. 6. Fernandez R, Dean, K (2023). «Multidomain Event Related Potentials as Functional Biomarkers of Early-Stage Alzheimer's Disease.» Society for Neuroscience, Nov. 2023, Washington, DC.

LP017- TRANSITIONING FROM CLINICAL TRIAL TO CLINICAL PRACTICE FOR LONG-TERM LECANEMAB TREATMENT IN EARLY ALZHEIMER'S DISEASE: PERSPECTIVES FROM AN ALZHEIMER'S DISEASE TREATMENT CENTER. D. Watson[1], M. Neam[1], M. Stafford[1], C. Bouchard[1], V. Ranney[1], S. Werner[1] *(1. Alzheimer's Research and Treatment Center - Wellington (United States))*

Background: Lecanemab is an anti-amyloid monoclonal antibody that binds with highest affinity to soluble Abprotofibrils, which are more toxic than monomers or insoluble fibrils/plaque. In the phase 3 Clarity AD trial, lecanemab reduced markers of amyloid in early symptomatic Alzheimer's disease and slow decline on clinical endpoints of cognition and function at 18 months. In addition, benefits of lecanemab treatment can be maintained longer-term as demonstrated the ongoing open-label extension (OLE) study. In Clarity AD, lecanemab was associated with a relative preservation of health-related quality of life and less increase in caregiver burden. The objective of this abstract is to provide perspective from 136 individuals with early Alzheimer's disease who were treated at our center as part of lecanemab clinical trials. A total of 66 individuals (44 from Clarity AD; 22 from the phase 2 lecanemab Study 201) that completed the double-blind Core phase of the lecanemab clinical trials and transitioned to the OLE portions respectively, with 13 completing 5 years of treatment in the OLE in addition to the 18 months in the double-blind Core phases of the trials. **Methods:** We conducted a single-center, retrospective case

series investigation in people with confirmed early Alzheimer's disease treated with lecanemab at the Alzheimer's Research and Treatment Center in Wellington Florida. Patients had been initiated on lecanemab therapy as part of lecanemab Study 201 or the phase 3 Clarity AD trial, and then continued lecanemab for long-term treatment in our center. Data collection included demographic characteristics, clinical history, lecanemab treatment exposure, and safety. Clinician and patient perspectives from our real-world experience with lecanemab will also be provided. **Results:** At our center, 136 people were randomized to receive either lecanemab or placebo in either lecanemab Study 201 (lecanemab:53; placebo:16) or Clarity AD (lecanemab:37; placebo:30). Overall, 40 patients with >3 years on lecanemab, including 24 with >4 years exposure and 13 with >5 years exposure. Baseline characteristics were similar at our center and the lecanemab clinical trials. The patients at our center had a mean age of 74.7 years, 48.5% female, mostly had Alzheimer's disease with mild cognitive impairment (67.6%), a majority were ApoE4 carriers (56.6%), and had a mean CDR-SB score at baseline of 2.64. No new long-term safety signals were observed for individuals at our center, with no treatment discontinuations due to adverse events. Adverse events, including ARIA, were consistent with the published lecanemab safety profile. **Conclusion:** In our center, real-world experience with long-term lecanemab treatment was similar that observed in clinical trials. Continued long-term treatment with lecanemab beyond the double-blind trials supports efficacy that is cognitively and functionally meaningful for patients as well as safety. Most patients in the clinical trials elected to stay on long-term lecanemab therapy and believe the therapy is extending/improving their lives. With the largest number of subjects in a lecanemab study site throughout the world, our patients' feedback as well as our observations and experiences using lecanemab have been validated by the positive trial results. **Keywords:** lecanemab, real-world experience, long-term treatment. **Disclosures:** DW was a clinical trial investigator for AbbVie, Alector, Alzheon, Anavir, Cassava, Cerevel, Cortexyme, Eisai, Eli Lilly, Hoffman-LaRoche, Genentech, Janssen Biotech, Synaptogenix, and TauRX. MN, MS, CB, VR, and SW have nothing to disclose.

LP018- ADDITIONAL ANALYSIS OF A 52-WEEK PHASE II TRIAL OF NEUROMODULATION OF THE DEFAULT MODE NETWORK TO OPTIMIZE DESIGN OF A PHASE 3 TRIAL TO DEMONSTRATE CLINICAL MEANINGFULNESS. S. Hendrix[1], L. Fosdick[2], G. Duncan[1], S. Dickson[1], G. Koch[2,3] *(1. Pentara Corporation - Salt Lake City (United States), 2. Sinaptica Therapeutics - Cambridge (United States), 3. University of Rome Tor Vergata - Rome (Italy))*

Background: Repetitive transcranial magnetic stimulation (rTMS) is emerging as a non-invasive therapeutic approach in Alzheimer's disease (AD). AD patients primarily show alterations of the default mode network (DMN) for which the precuneus is a key node. Personalized neuromodulation of the DMN (nDMN) was assessed in a randomized, double-blind, sham controlled, 52-week trial in 48 mild to moderate AD patients. Topline pre-specified results from this clinical trial are being presented at this meeting and show that this therapy may slow down cognitive and functional decline as evaluated using differences between treatment and sham in mean change from baseline on validated clinical outcome assessments (COA). Recently there has been increased interest in considering time-savings estimates or meaningful within person change (MWPC) as endpoints in clinical trials of neurodegenerative diseases as this concept may be easier to understand clinically meaningful benefit to patients. In preparation for an upcoming Phase 3 trial of nDMN, various possible endpoints and analytic methods were explored using this dataset. **Methods:** Data from this RCT was used to calculate two additional outcome measures from the COAs collected during the trial both of which combine inputs from multiple sources including patient, care partner and clinician and represent the domains of global performance, cognition and function. The iADRS measures the impact of cognitive loss on the ability to conduct everyday activities and is a combination of the ADAS-Cog and ADCS-iADL. A Global Statistical Test (GST) calculation assesses combined global, functional, and cognitive outcomes in one overall statistical test combining CDR-SB, ADAS-Cog, and ADCS-ADL. Time-saved was calculated using the least square means from the primary analyses of the COAs and linear interpolation to assess the horizontal distance between the rTMS and sham groups. The changes in individual CDR-SB scores were used to identify individuals that demonstrated no progression of disease defined as a CDR-SB score change from baseline of less than or equal to 0 perform a progressor analysis. **Results:** The iADRS and GST endpoints demonstrated significant differences between treatment groups at 52-weeks. The estimated mean change in iADRS after 52 weeks was -6.8 for rTMS and -20 for sham approximately 66% slowing. The estimated mean change in GST after 52 weeks was -5.4 for rTMS and -11 for sham approximately 51% slowing. At fifty-two weeks disease progression was delayed by 4.1, 5.5, 10.4, 8, and 5.4 months by CDR-SB, ADAS-Cog, ADCS-ADL, iADRS and GST respectively. Thirty-seven percent of rTMS patients vs 8.3% of sham patients demonstrated no progression of disease defined as a CDR-SB score change from baseline of less than or equal to 0. **Conclusion:** Fifty-two weeks of non-invasive personalized neuromodulation of the DMN slowed down cognitive and functional decline in this AD patient population as analyzed by a wide variety of endpoints and analytic methods. It is important to note that the analyses described here are post-hoc and are being used exploratively to collaboratively optimize the final design of an upcoming Phase 3 trial that will be conducted to support a De Novo classification request to the FDA. **Keywords:** Neuromodulation, P2 clinical trial, clinical meaningfulness, time-saved. **Clinical Trial Registry:** NCT05454540; https://clinicaltrials.gov/. **Disclosures:** SH is owner and employee of Pentara, a company that provides consulting services for dozens of companies in the Alzheimer's disease space, and is a paid consultant for Sinaptica Therapeutics. LF is a paid consultant for Sinaptica Therapeutics. GD is an employee of Pentara. SD is an employee of Pentara. GK is scientific co-founder and holds stocks of Sinaptica Therapeutics. GK has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from: Epitech, Roche, Novo Nordisk. GK has a patent on the use of rotigotine in combination with cholinesterase inhibitors in patients with Alzheimer's disease and another on systems and methods for providing personalized targeted non-invasive stimulation to a brain network.

LP019- INTRACEREBROVENTRICULAR INJECTION OF AUTOLOGOUS ADIPOSE-DERIVED STEM CELLS FOR THE TREATMENT OF ALZHEIMER'S DISEASE: EXPERIENCE WITH THE FIRST OF THREE 3-PATIENT COHORTS IN A "FIRST IN HUMAN" PHASE 1 FDA TRIAL.

C. Duma[1], G. Alva[2], H. Keirstead[1], G. Nistor[1], R. Lynn[1], J. Buxton[1], S. Farmer[1], K. Chung[1], A. Harris[1], Z. Hareng[1] *(1. Regeneration Biomedical, Inc., Newport Beach, CA - Newport Beach (United States), 2. Hoag Memorial Hospital, Newport Beach, CA - Newport Beach (United States))*

Background: It has been more than 20 years for a new treatment for Alzheimer's Disease (AD) to emerge. These treatments have recently been in the form of monoclonal antibodies targeting the accumulated end-products of neuron self-maintenance. We are testing the safety of a novel approach using activated stem cells injected directly into the ventricles of the brain. **Methods:** After animal testing, we received FDA clearance for a 3 + 3, Phase 1 trial in 9 patients using escalating doses of the test product. Patients were screened for age less than 80 years, FAST stage 4 or 5, having a Mini Mental Status Exam (MMSE) between 11 and 20 inclusive, as well as exhibiting brain amyloid PET and CSF AD markers. This 3-patient cohort was the first of 3 cohorts of escalating stem cell dosages (2 million, 5 million and 10 million cells.) The patients underwent a 3-step process: 1) liposuction, 2) Ommaya reservoir implantation, and 3) injection following cell selection and expansion based on Wnt expression in the lab (the test product). The patients were admitted to the hospital and injected a median of 53 days (range: 43-62) after initial lipoaspirate, and observed overnight. Three ml. of the test product containing 2 million cells was injected per protocol. Vital signs (VS) and clinical examinations were performed per protocol. MRI, cognitive testing and Amyloid PET imaging were and will be performed at specific intervals per protocol. **Results:** There were minor adverse events reported during the first 2 steps in the patient's procedures, which included minor bruising and discomfort post-liposuction and mild incision pain after Ommaya reservoir implantation. The 3rd step, injection process, required 3 minutes to perform, without anesthetic. This was well-tolerated with no reported adverse events in all 3 patients, including immediate or remote headache, nausea, vomiting or change in VS for at least 7 weeks (range: 7-25 weeks) post-injection as of this publication. CSF analysis in all three patients showed a decrease in p-Tau from a median of 60.2 pg/ml (range: 59.2-76.1) to a median of 38.6 (range 27.3-46.2, normal) after 4 weeks. For the 2 patients at 12 weeks, median p-Tau was reduced to 33.9 (range 22.4-45.3, normal). Amyloid Pet scans returned to "no longer consistent with AD" in 2 of 2 patients tested at 12 weeks. **Conclusion:** This "first in human" trial of intracerebroventricular injection of Wnt-expressing, adipose-derived stem cells proved well-tolerated and safe for our first cohort of 3 injected patients with a minimum of 7 weeks follow-up. Phase 2 trials will be submitted to the FDA using this Phase 1 data, for treatment of patients with AD, MS-P, Parkinson's Disease, CTE, and ALS. **Keywords:** Alzheimer's Disease, intracerebroventricular, stem cells, Wnt, intraventricular, clinical trial, Phase 1. **Disclosures:** Dr. Duma receives compensation from Regeneration Biomedical, Inc. **References:** Duma C, et al. Mol Biol Rep. 2019 Oct;46(5):5257-5272. doi: 10.1007/s11033-019-04983-5. Epub 2019 Jul 20.

LP020- TREATMENT OF MODERATE ALZHEIMER'S DISEASE SUBJECTS WITH EXPANDED NON-GENETICALLY MODIFIED NATURAL KILLER CELLS (TROCULEUCEL; SNK01) WITH ENHANCED ACTIVITY —REPORT OF THE PHASE I RESULTS OF THE PHASE I/IIA STUDY.

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Background: Natural Killer (NK) cells play a profound role in the innate immune system and their importance in neurodegenerative disease has largely been overlooked despite preclinical studies demonstrating their ability to reduce neuroinflammation, which may be related to their ability to identify and kill activated T cells, their capability of balancing the ratio of protective to proinflammatory microglia, their secretion of anti-inflammatory cytokines, and their ability to discard neurotoxic aggregates. SNK01 is an autologous non-genetically modified cryopreserved NK cell product with highly enhanced cytotoxicity and receptor expression. We have previously shown in a Phase I trial that 4 treatments with suboptimal doses of SNK01 in Alzheimer's Disease (AD) subjects was well tolerated and showed preliminary ability to impact cognition and improve protein aggregates and neuroinflammation biomarkers. We hypothesize that SNK01 at a higher dose can be safely infused in the Phase I part of this study and strive to confirm the positive impact on cognition and biomarkers in the double-blind randomized Phase IIa part of the study. **Methods:** In the Phase I part of the study, SNK01 was IV administered to 3 subjects with moderate AD (median age 80 years, median CDR-SB of 11) at a dose of 6 x 109 cells. For this first part, the primary endpoint was safety, monitored for 21 days after the first dose for each subject. These 3 subjects will continue to be treated every 3 weeks for 17 doses. In the Phase IIa part of the study (n=30), SNK01 or placebo (2:1) will be administered every 3 weeks for 17 doses, to subjects with moderate AD. The primary endpoints will be safety and preliminary efficacy, with cognitive changes measured using CDR-SB, MMSE, NPI, ADCS-ADL-Severe and ADAS-Cog scales. The secondary endpoints will include changes in protein aggregate and neuroinflammation biomarker levels. **Results:** Three (3) subjects were enrolled in the Phase I cohort. Early review of the data shows that after 3 months' treatment with a dose of 6 x 109 cells every 3 weeks, the 3 subjects had no treatment-related adverse reactions, and exploratory efficacy analyses showed that 2 of the 3 subjects went from a moderate to a mild AD rating on the CDR-SB scale while all 3 subjects had either a stable or improved ADCOMS score. These findings are similar to the SNK01-MX04 Phase I AD study (NCT04678453), where the product was well tolerated, and the one moderate AD subject who received the highest dose (a dose of 4B) also went from a moderate to a mild rating on the CDR-SB. **Conclusion:** SNK01 at the highest dose given to moderate AD subjects was well tolerated in this Phase I part of the study, and in 2/3 subjects appeared to result in a clinical improvement from moderate AD to mild AD after only 3 months on therapy. This study aims to confirm previous preliminary efficacy seen on both cognitive and biomarker changes in AD subjects. SNK01 will be evaluated for safety and efficacy in the randomized, placebo-controlled Phase IIa part of the study. **Keywords:** natural killer cells, neuroinflammation. **Clinical Trial Registry:** NCT06189963. **Disclosures:** Authors Song, Betito, Mata, Lee and Hui, are all employees and shareholders of NKGen Biotech who is the sponsor of this trial.

LP021- POST-MARKETING STUDY OF SODIUM OLIGOMANNATE: LONG-TERM SAFETY AND EFFECTIVENESS OF AN AGENT TARGETING THE GUT MICROBIOME FOR THE TREATMENT OF ALZHEIMER'S DISEASE. X.X. Xin[1], J.H. Li[1], X. Li[2], M.Y. Geng[3], Q.H. Guo[4] *(1. Green Valley (Shanghai) Pharmaceuticals Co., Ltd. - Shanghai (China), 2. Department of Geriatric Psychiatry, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine - Shanghai (China), 3. State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences - Shanghai (China), 4. Department of Gerontology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine - Shanghai (China))*

Background: Sodium Oligomannate (GV-971) is a marine-derived oligosaccharide compound. GV-971 was approved in China on November 2, 2019, for the treatment of mild to moderate Alzheimer's disease (AD) to improve cognitive function [1, 2]. Following its market release, study of the drug's long-term efficacy and safety has continued, aiming to provide better guidance for its clinical use. **Methods:** The post-marketing study (PMS) of Sodium oligomannate (GV-971), PMS-B, is a multicenter, single-arm, open-label study conducted across 42 study sites in China. The study enrolled 800 patients aged 50-85 years, who met the clinical diagnostic criteria for probable Alzheimer's disease-related dementia as defined by the National Institute on Aging and Alzheimer's Association (NIA-AA). Participants evidenced mild to moderate AD, with a Mini-Mental State Examination (MMSE) total score ranging from 11 to 26 (inclusive). Efficacy and safety data were collected at baseline and after 24, 48, 72, and 96 weeks of treatment with GV-971. The primary efficacy endpoint was the change from baseline in cognitive function as measured by ADAS-Cog/11. Secondary efficacy endpoints included the change from baseline in MMSE and ADCS-ADL. Concurrently, changes in blood biomarkers and gut microbiota after treatment were observed to explore and validate the mechanism of action of GV-971. **Results:** This report presents the interim analysis results of GV-971 treatment over 48 weeks. 790 subjects among the 800 subjects enrolled received GV-971 treatment, and 657 subjects completed the 48 week's visit, 133 subjects (16.6%) withdraw within 48 weeks. The average age was 71.0±7.8, 60.0% were female patients, and baseline MMSE was 18.9±4.28 with 48.4% of them were mild subjects (20≤MMSE≤26). After 48 weeks' treatment with GV-971, the change from baseline of ADAS-Cog/11 was 1.18±6.756, MMSE -1.1±3.84, ADCS-ADL -3.4±11.40, respectively. As shown in the subgroup analysis, treatment naïve patients had continuous and stable improvements above baseline in both cognitive function and daily living abilities compared to baseline (ADAS-Cog/11 improved 0.83±5.528, MMSE improved 0.7±3.97, ADCS-ADL improved 2.0±9.78 respectively after 48 week's treatment). Patients on conventional treatment (previously used or are currently using cholinesterase inhibitors and/or memantine) exhibited a trend toward deterioration in cognitive function and daily living abilities compared to baseline. The safety data indicated that mild to moderate AD patients treated with GV-971 for 48 weeks had good safety and tolerability profiles. The analysis on mechanism of action showed that the differential efficacy trends observed between treatment naïve and non-naïve patients were associated with differences in baseline gut microbiota and the reconditioning of different gut microbiota post-treatment. **Conclusion:** GV-971 targets the gut microbiota to improve or delay the deterioration of cognitive function and daily living abilities in patients with mild to moderate AD. Among these patients, those who are treatment-naïve experienced continuous and stable improvements in cognitive function and daily living abilities, benefiting the most from the treatment. **Keywords:** Sodium Oligomannate, Alzheimer's Disease, Post-marketing Study, Gut-Brain Axis. **Clinical Trial Registry:** NCT05181475; https://clinicaltrials.gov. **Disclosures:** The authors declared no competing interests.**References**: 1. Wang T, et al. Alzheimers Res Ther. 2020;12(1):110. DOI: 10.1186/s13195-020-00678-3; 2. Xiao SF, et al. Alzheimers Res Ther. 2021;13(1):62. DOI: 10.1186/s13195-021-00795-7.

LP022- REGIONAL VARIATION OF AMYLIN, B AMYLOID AND AMYLIN-B AMYLOID IN SPORADIC, LATE-ONSET AD BRAINS. D. Kotiya[1], P.T. Nelson[1], G.A. Jicha[1], L.B. Goldstein[1], F. Despa[1] *(1. University of Kentucky - Lexington (United States))*

Background: Amylin, an amyloidogenic hormone secreted from the pancreas, forms cerebral plaques and synergistically co-aggregates with vascular and parenchymal β-amyloid (Aβ) in the human brain. Amylin amyloid and amylin-Aβ pathologies may differentially affect brain regions, brain function and progression of Alzheimer's disease (AD). We analyzed the relationships among amylin, Aβ and amylin-Aβ hetero-oligomer levels in the frontal and occipital lobes and the cerebellum. **Methods:** The University of Kentucky AD Research Center (UK-ADRC) provided frozen tissue samples from the frontal and occipital lobes and cerebellums from 23 brains (69 samples). Observer-masked amylin and total Aβ concentrations were measured using commercially available ELISAs. Amylin-Aβ hetero-oligomer levels were measured using a custom sandwich amylin-Aβ ELISA that relies on a monoclonal anti-Aβ middomain antibody (detection) and a polyclonal anti-amylin antibody (capture). The anti-amylin capture antibody was designed to recognize an epitope that is distinct from the high affinity amylin-Aβ binding sites. Samples were un-masked after measures were competed. **Results:** Samples from the frontal and occipital lobes and cerebellum had different mean levels of total Aβ (0.2489 ± 0.02871 ng/mg vs. 0.1878 ± 0.01027 ng/mg vs. 0.1297 ± 0.00865 ng/mg; one-way ANOVA, P = 0.0001), amylin (9.113 ± 1.716 ng/mg vs. 15.50 ± 1.761 ng/mg vs. 8.083 ± 1.805 ng/mg; one-way ANOVA, P = 0.008) and amylin-Aβ hetero-oligomers (0.1545 ± 0.01617 ng/mg vs. 0.1113 ± 0.00595 ng/mg vs. 0.0791 ± 0.00413 ng/mg; one-way ANOVA, P < 0.0001). The mean Aβ level was higher in the frontal vs. the occipital lobe (by 0.0611 ng/mg, P = 0.0547) and cerebellum (by 0.1192 ng/mg, P < 0.0001). Mean amylin levels were higher in occipital vs. frontal lobes (by 6.383 ng/mg, P = 0.0334) and cerebellum (by 7.413 ng/mg, P = 0.0112). The mean amylin-Aβ hetero-oligomer level was higher in the frontal vs. the occipital lobe (by 0.0432 ng/mg, P = 0.0110) and cerebellum (by 0.0754 ng/mg, P < 0.0001) with a similar trend of regional distribution as for the mean total Aβ level. **Conclusion:** We found that amylin, Aβ and amylin-Aβ hetero-oligomer levels have spatially distinct patterns in human frontal, occipital, and cerebellar brain regions. Future studies are needed in a larger sample to more accurately evaluate spatial patterns of amylin amyloid and amylin-Aβ pathologies in the brains of humans with AD and to determine their potential distinct impact on brain function and AD progression. The author declare that no conflict of interest exists.

LP023- APOE4 AND BUNTANETAP IN PHASE II/III ALZHEIMER'S PATIENTS. C. Fang[1], M. Maccecchini[1] *(1. Annovis Bio - Malvern (United States))*

Background: Overexpression of neurotoxic proteins drives downstream events that dysregulate axonal transport, lead to inflammation, nerve cell death, and loss of function [1-4]. By inhibiting the translation of neurotoxic aggregating proteins - amyloid precursor protein, tau, alpha-synuclein, TDP43 etc., buntanetap restores axonal transport, lowers inflammation, and protects nerve cells from dying [5]. In the early to moderate Phase II/III Alzheimer's (AD) study we evaluated the efficacy and safety of buntanetap in APOE4 homozygote, heterozygote, and non-carriers in Alzheimer's patients on drug or placebo. **Method:** Randomized, double-blind, placebo-controlled, dose-ranging, multicenter study in 340 mild to moderate AD patients. Subgroup analyses: pTau217/tTau>4.2%; APOE 4 homozygous/heterozygous/non-carriers; efficacy/safety. **Results:** The data from this Phase2/3 study showed that buntanetap has a dose-dependent effect on improving mild AD patients (pTau217/tTau>4.2%, MMSE21-24) ADAS-Cog11. 15mg and 30mg both significantly improved ADAS-Cog11 in mild AD comparing to placebo and baseline. APOE4 carriers were enriched in the pTau217/tTau>4.2% to 78% versus 22% in the pTau217/tTau<4.2% population. While; the efficacy of buntanetap in APOE4 carriers was comparable to the efficacy in non-carriers, due to the smaller number of patients, the improvement compared to placebo was a trend; Instead the15mg and 30mg buntanetap treatment groups showed a statistically significant improvement compared to baseline. **Conclusion:** Buntanetap is both safe and efficacious in ApoE4 carriers and non-carriers. We will conduct an additional phase III study in biomarker-positive mild AD patients for 6-month to confirm the safety, efficacy, and symptomatic efficacy of buntanetap and an 18-month study to show potential disease-modification. We further want to evaluate the relation of buntanetap with APOE4 carriers and non-carriers. **Disclosures:** Cheng Fang, and Maria Maccecchini are employees of Annovis Bio. The authors declared no competing interests. **Keywords:** Alzheimer's, ApoE, phosphorylated Tau, ADAS-Cog11. **References:** 1. Petersen, R. C. (2018). How early can we diagnose Alzheimer disease (and is it sufficient)? Neurology, 91, 395-402. 2. Tzioras, M., McGeachan, R.I., Durrant, C.S. et al. (2023). Synaptic degeneration in Alzheimer disease. Nat Rev Neurol 19, 19-38. 3. Mangalmurti, A., & Lukens, J.R. (2022). How neurons die in Alzheimer's disease: Implications for neuroinflammation, Current Opinion in Neurobiology. 4. Millecamps, S., & Julien, J. P. (2013). Axonal transport deficits and neurodegenerative diseases. Nat Rev Neurosci, 14, 161-176. 5. Chen XQ, Barrero CA, Vasquez-Del Carpio R, Reddy EP, Fecchio C, Merali S, Deglincerti A, Fang C, Rogers J, Maccecchini ML. Posiphen Reduces the Levels of Huntingtin Protein through Translation Suppression. Pharmaceutics. 2021 Dec 7;13(12):2109. doi: 10.3390/pharmaceutics13122109. PMID: 34959389; PMCID: PMC8708689.

LP024- A PHASE 3 STUDY OF SUBLINGUAL DEXMEDETOMIDINE FOR EPISODIC TREATMENT OF AGITATION ASSOCIATED WITH ALZHEIMER'S DEMENTIA. R. Risinger[1], L. Rajachandran[1], H. Robinson[1], J. Cummings[2], G. Grossberg[3] *(1. BioXcel Therapeutics - New Haven (United States), 2. University of Nevada - Las Vegas (United States), 3. St Louis University - St Louis (United States))*

Background: Agitation is a severe, disruptive, and morbid complication of dementia. Currently, commonly used agents for the treatment of this condition are antipsychotics and benzodiazepines. Though efficacy has been demonstrated for these agents, side effects remain a concern, particularly for elderly patients with greater medication and disease burden. BXCL501, a sublingual film formulation of dexmedetomidine, a highly selective α2 adrenoceptor agonist, is currently approved in adults for the acute treatment of agitation associated with schizophrenia or bipolar disorder (120 μg and 180 μg doses). BioXcel Therapeutics, Inc. is currently developing BXCL501 for the acute treatment of agitation in patients with Alzheimer's dementia. **Methods:** TRANQUILITY II was a Phase 3 multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study of as-needed (PRN) dosing of BXCL501 over a 12-week period in subjects with agitation associated with probable Alzheimer's. Subjects were randomized were randomized 1:1:1 to receive BXCL501 40 μg, BXCL501 60 μg, or matching placebo film. Each subject was intended to receive at least one and no more than 28 doses over the 12-week study period. The primary endpoint was a change from pre-dose in Positive and Negative Syndrome Scale – Excited Component (PEC) total score at 2 hours post-dose for the first treated episode of agitation. **Results:** One hundred fifty-one subjects were randomized and analyzed (50 subjects in the BXCL501 60 μg treatment group, 48 subjects in the BXCL501 40 μg treatment group, and 53 subjects in the Placebo treatment group). The study met the primary endpoint of statistically significant improvement in the PEC total scores at 2 hours post-dose for the first episode of agitation treated with 60 μg BXCL501 compared with placebo (least square of the mean [LSM] difference in change from baseline [standard error {SE}]: -2.1 [0.8]; 97.5% confidence interval [CI]: -4.0, -0.3; $p = 0.0112$). There was no statistically significant difference in the change from baseline in PEC scores compared with placebo for the first episode of agitation treated with 40 μg BXCL501. A total of 443 episodes were dosed over the 12-week trial period. There was a statistically significant improvement in PEC scores (reduction in agitation) at 2 hours from pre-dose compared with placebo over all episodes of agitation treated with 60 μg BXCL501. All treatment-emergent adverse events (TEAEs) within 24 hours of the first dose and any dose were mild or moderate. The most commonly reported moderate TEAE of special interest was hypotension followed by orthostatic hypotension, bradycardia, and somnolence. **Conclusion:** The study findings suggest that BXCL501, at doses of 60 μg and 40 μg, was generally well-tolerated in subjects diagnosed with probable Alzheimer's disease who had agitation. At the 60 μg, the treatment showed efficacy in reducing symptoms of agitation. A second Phase 3 study of BXCL501 in this indication is currently being planned. **Keywords:** Phase 3 clinical trial, agitation, dexmedetomidine, BXCL501. **Clinical Trial Registry:** NCT05271552; https://clinicaltrials.gov. **Disclosures:** RR, LR, and HR are employees of Bioxcel Therapeutics, the sponsor of the trial. JLC received compensation for consultation to Acadia, Acumen, ALZpath, Annovis, Aprinoia, Artery, Biogen, Biohaven, BioXcel, Bristol-Myers Squib, Eisai, Fosun, GAP Foundation, Green Valley,

Janssen, Karuna, Kinoxis, Lighthouse, Lilly, Lundbeck, LSP/eqt, Merck, MoCA Cognition, New Amsterdam, Novo Nordisk, Optoceutics, Otsuka, Oxford Brain Diagnostics, Praxis, Prothena, ReMYND, Roche, Scottish Brain Sciences, Signant Health, Simcere, sinaptica, TrueBinding, and Vaxxinity pharmaceutical, assessment, and investment companies. GG received compensation for consultation to Acadia, Biogen, BioXcel, Genentech, Karuna, Lundbeck, Otsuka and for for serving on a Speakers Bureau for Acadia and for Biogen.

NEW THERAPIES AND CLINICAL TRIALS

P042- SPECIALIZED INFRASTRUCTURE IN A TERTIARY HOSPITAL TO ADMINISTER DISEASE MODIFYING TREATMENTS IN ALZHEIMER'S DISEASE. T. Nathan[1], E. Ash[1,2,3], S. Dror[1], N. Trabulus[1], A. Bar-David[1], M. Hay Levy[1], G. Wolpe[1], T. Shiner[1,2,3], N. Bregman[1,2,3] *(1. Cognitive Neurology Unit, Tel Aviv Sourasky Medical Center - Tel Aviv (Israel), 2. Department of Neurology and Neurosurgery, Sackler School of Medicine, Tel Aviv University - Tel Aviv (Israel), 3. Sagol School of Neuroscience, Tel Aviv University - Tel Aviv (Israel))*

Background: Lecanemab (LEQEMBI®), a humanized monoclonal antibody targeting Amyloid-beta (Aβ) protofibrils, received full FDA approval in July 2023 for treating early-stage Alzheimer's disease (AD). This abstract highlights Tel Aviv Medical Center's (TLVMC) specialized infrastructure for early AD diagnosis and treatment and includes presenting baseline characteristics of initial patients opting for LEQEMBI®. **Methods:** Outlining our clinics' operational experience in establishing the Center for advanced treatments for AD, treatment protocol, and a descriptive analysis of baseline assessment data including demographics, baseline Magnetic-Resonance-Imaging (MRI), Cerebrospinal-fluid (CSF)/PET biomarkers, pre-treatment cognitive evaluations (Mini-Mental-State-Examination (MMSE)/Montreal-Cognitive-Assessment (MoCA)), and Apolipoprotein-E (APOE) status. **Results:** Rigorous screening and specialist approval were prerequisites for candidate selection, adhering with published appropriate use recommendations. All patients, diagnosed with Mild-Cognitive-Impairment (MCI)/mild dementia due to AD confirmed by biomarkers, underwent APOE testing. Lecanemab Administration commenced in Israel in November 2023, with 31 patients (F=15, mean age=72) initiating treatment by year-end. 22 underwent neurological evaluation within a year of symptom onset. Mean MMSE=24 (n=27, SD=3) mean MoCA=23 (n=4, SD=2). CSF testing (27 patients), showed mean levels (pg/ml) of total-Tau=585 (SD=251), phosphorylated-Tau=121 (SD=38) and Aβ=261 (SD=172). APOE ε4 polymorphism was present in 55%, with 18% showing 1-2 micro-hemorrhages on baseline MRI, compared to 8% of non-carriers. **Conclusion:** The evolving landscape of AD treatments necessitates complex screening and comprehensive clinical-radiological follow-up. Establishing specialized medical infrastructures is crucial to enable the wide and safe administration of new treatments, reflecting the ongoing paradigm shift in AD management. **Keywords:** Alzheimer's disease. **Disclosures:** Dr. Bregman and Dr. Shiner have been on the advisory board for Eisai Co. Ltd.

P043- COGNITIVE VERGENCE PREDICTS AD, CORRELATES WITH CSF BIOMARKERS AND IMPROVES AFTER DIGITAL TREATMENT. H. Supèr[1] *(1. University of Barcelona - Barcelona (Spain))*

Background: Vergence eye responses, which have a role in cognitive processing, can be used to classify Alzheimer´s Disease (AD) with high accuracy (Hashemi et al, 2023), and predict the severity of AD (Jiménez et al., 2021,) and the risk of progressing from MCI towards AD (Hashemi et al., 2023). Here we test whether vergence correlates with CSF core biomarkers of early AD. AD pathology manifests in the Locus Coeruleus (LC). Eye movements induce LC activity. LC drives pupillary response via the Edinger Westphal Nucleus, which integrates attention and vergence commands. To test whether training the attention-oculomotor system improves AD symptoms, we trained patients in an interactive eye-tracking game and compared their behavioural, vergence and pupil responses to those of a group of AD patients playing the same game with a mouse. **Methods:** A total of 44 MCI/AD patients (biomarker study) were recruited from the Hospital Mar and Hospital Clinic de Barcelona, and 37 MCI patients (treatment study) were recruited from day care centres. Cognitive performance was assessed using the Montreal Cognitive Assessment (MoCA) and the Cambridge Neuropsychological Test Automated Battery (CANTAB®; Cambridge Cognition Ltd., UK). To assess pupil and vergence responses, patients performed a visual oddball task (Braingaze, Spain). Eye data were recorded with an X2-30 remote eye tracker (Tobii Technology AB, Sweden). CSF (Ab40, Ab42, ptau and ttau) concentrations were measured through the single-molecule array technology in a Simoa HD-X Analyzer® (Quanterix) and Lumipulse. The video game consisted of a stationary or moving target and a distractor. Patients had to look at the target and avoid looking at the distractor to score points. Recorded eye position was fed back to the presentation software to control the game. In the control group, patients used the mouse cursor as a controller instead of eye gaze. Participants played 3 sessions per week for 15 min each for 1 month. **Results:** Cognitive vergence responses negatively correlate (Pearson rho, P<0.01) with Ab42 (rho: -0,46), Ab40(rho: -0,38), Ratio Ab42/40 (rho: -0,40), and Ratio Ab42/ptau (rho: -0,38) CSF concentrations. The MoCA score improved from 14.64 ± 4.28 (mean ± SD) at baseline to 15.52 ± 4.76 after gaming ($p < 0.03$; Hedges' g factor: 0.20), especially in the visuospatial domain (($p < 0.002$; Hedges' g factor: 0.52). Kruskal–Wallis ANOVA demonstrated a significant effect of gaming ($F(3,82) = 26,51, p = 7 \times 10-6$). Also, cognitive performance significantly improved in the CANTAB RVPA task ($p < 0.001$; Hedges' g-factor: 0.67). After gaming, there was an improvement in pupil responses (mean ± SD: pre: −0.012 ± 0.24; post: 0.032 ± 0.17; $t = -2.41$, $p = 0.016$). Vergene responses showed near significant improvements (mean ± SD: pre: −0.034 ± 2.77; post: 0.15 ± 2.35; $t = -1.9$, $p = 0.057$). No significant improvements on any of these tests nor vergence/pupil responses were found in the control group. **Conclusion:** Cognitive vergence correlates with cognitive brain processes and standard CSF biomarkers for AD. Gaze-controlled gaming improves cognitive vergence and cognitive brain processes. The next study will test whether these improvements translate to CSF biomarkers.

P044- INCREASING REPRESENTATION AND DIVERSITY IN CLINICAL TRIALS OF ALZHEIMER'S DISEASE: RECRUITMENT OF ETHNICALLY DIVERSE PARTICIPANTS WITH ALZHEIMER'S DISEASE IN THE PHASE 1 ASCENT CLINICAL TRIALS OF PRX012. C. Swanson[1], F. Martényi[1], R.E. Tooker[1], D. Masterman[1], C. Fitzgerald[1], A. Johnson[1], L. Li[1], M.E. Quiceno[1], G.G. Kinney[1], H. Garren[1] *(1. Prothena Biosciences Inc - Brisbane (United States))*

Background: An estimated 6.9 million adults aged 65 years and older are living with Alzheimer's disease (AD) in the United States (US), with two-thirds being women [1]. Black and Hispanic older adults appear more likely to have AD or other dementias than White older adults, and some data indicate age-matched Hispanic older adults in the US are approximately 1.5 times more likely to have AD or other dementias than non-Hispanic older adults [1]. Historically, populations participating in AD clinical trials have been predominantly White older adults. Lack of ethnic and racial diversity in clinical trials may limit confidence that study findings apply to all at-risk populations [2]. **Methods:** PRX012 – an investigational humanized monoclonal antibody that targets the N-terminus of amyloid beta and clears its known pathogenic aggregated forms – is being developed for monthly subcutaneous (SC) use for the treatment of AD. The ASCENT clinical trial program includes two currently ongoing Phase 1 clinical studies, a single-dose study and a multiple-dose study, using a staggered but complementary approach where a dose level is first explored in the single-dose study followed by the multiple-dose study. ASCENT-1 is a randomized, double-blind, placebo-controlled, single-ascending dose clinical trial evaluating the safety, tolerability, immunogenicity, and pharmacokinetics of PRX012 in healthy volunteers and participants with biologically confirmed AD (via amyloid PET imaging). Participants receive PRX012 or placebo via SC administration. ASCENT-1 is being conducted across multiple trial sites in the US. ASCENT-2 is a randomized, double-blind, placebo-controlled, multiple-dose clinical trial evaluating the safety, tolerability, immunogenicity, pharmacokinetics, and pharmacodynamics of PRX012 in participants with biologically confirmed AD. Participants receive once-monthly SC injections of PRX012 or placebo over six months. Most ASCENT-2 clinical trial sites are in the US, with additional sites in Europe. Recruitment efforts, including translation of key screening and participant-facing materials, travel support, and site selection, were proactively implemented to help increase ethnic diversity and representation in the ASCENT studies. Both trials are ongoing; analyses include data available as of May 1, 2024. **Results:** In ASCENT-1, 54% of randomized participants with AD are female and 15% are Hispanic or Latino. Participation of racially diverse populations with AD (including African American, Asian, Pacific Islander, and other) is 12%. In ASCENT-2, 67% of randomized participants with AD are female and 29% are Hispanic or Latino. Participation of racially diverse populations is 3%. Across the ASCENT program, 65% of participants with AD are female, 27% are Hispanic or Latino, and 4% are racially diverse. **Conclusion:** The ASCENT clinical trial program is investigating PRX012, a humanized anti-amyloid antibody being developed for monthly SC administration in AD. Targeted recruitment efforts to increase ethnic diversity in the current trials resulted in good representation of Hispanic or Latino older adults with AD (27%). Continued efforts to increase ethnically and racially diverse participation in clinical trials of AD may result in improved representation of at-risk populations and potentially expand applicability of study results. **Keywords:** diversity, recruitment, AD clinical trial. **Disclosures:** All authors are employees of Prothena Biosciences Inc and shareholders of Prothena Corporation plc. GGK is an employee of Prothena Biosciences Inc, a stockholder in Prothena Corporation plc, is an inventor on Prothena patents and patent applications, and has received personal compensation for serving as an officer or member of the Board of Directors for Prothena and for Libra Therapeutics. This study is sponsored by Othair Prothena Limited, a member of the Prothena Corporation plc group. **References:** 1. Alzheimer's Association. 2024 Alzheimer's Disease Facts and Figures. Alzheimers Dement 2024;20(5). https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf; 2. Schwartz AL, et al. N Engl J Med 2023;388(14):1252–1254. http://doi.org/10.1056/NEJMp2215609.

P045- ADVANCES IN CLINICAL TRIALS FOR ALZHEIMER'S DISEASE IN DOWN SYNDROME. M. Rafii[1], J. Fortea[2], B. Ances[3] *(1. University of Southern California - San Diego (United States), 2. Hospital de la Santa Creu i Sant Pau - Barcelona (Spain), 3. Washington University - Saint Louis (United States))*

Background: People with Down Syndrome (DS) have a genetic form of Alzheimer's disease (AD) with near full penetrance [1]. DSAD is now the leading cause of death of adults in this population [2]. **Methods:** Recent data from the Alzheimer's Biomarker Consortium – Down syndrome (ABC-DS) and the Down Alzheimer Barcelona Neuroimaging Initiative (DABNI) have enabled the design of clinical trials targeting across the AD continuum in people with Down syndrome. Thresholds have been proposed for the biomarker evidence of AD pathology marking various stages of DSAD in the context of clinical thresholds marking clinical symptoms [3-5]. **Results:** The NIH-funded Alzheimer's Clinical Trial Consortium for Down Syndrome (ACTC-DS) launched the Trial Ready-Cohort for Down syndrome (TRC-DS). TRC-DS has enrolled 250 participants with DS ages 25-55 into a longitudinal run-in study in advance of upcoming randomized, placebo-controlled clinical trials. The planned ION269 HERO trial will enroll participants for testing an antisense oligonucleotide (ASO) that selectively targets the amyloid precursor protein (APP) RNA. Binding of ION269 to the APP RNA promotes degradation of the APP RNA, thus selectively preventing production of the APP protein and all its proteolytic products, including amyloid beta. Since increased APP gene dosage is linked to early-onset AD in DS [6,7], reducing APP expression is hypothesized to be a disease modifying therapy against DSAD. The HERO trial is a Phase 1b, multicenter, open-label, single dose study in adult participants (35-55 years) with DS. Participants will receive a single dose of ION269 administered intrathecally. The primary objective is to evaluate the safety and tolerability of ION269 in cognitively stable participants with DS who have evidence of brain amyloid positivity. Secondary objectives include the evaluation of the pharmacokinetic (PK) profile of ION269 in CSF and plasma and an evaluation of the effects of ION269 on the levels of CSF soluble amyloid precursor protein alpha and CSF soluble amyloid precursor protein beta. **Conclusion:** ACTC-DS serves as a platform to bring the latest advances in AD therapeutics to the DS population. Several clinical trials including the ABATE and HERO trials are underway or being planned. **Keywords:** Down syndrome, Alzheimer disease, biomarkers, plasma, csf, PET, amyloid, tau. **Disclosures:** MSR- AC Immune, Alzheon, Aptah Bio, Biohaven, Ionis, Keystone Bio; BA- Nothing to

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P046- CLINICAL EXPERIENCE WITH AMYLOID-LOWERING TREATMENTS IN AN ACADEMIC DEMENTIA SPECIALTY PRACTICE. M. Paczynski[1], S. Schindler[1,2], E. Musiek[1,2], D. Holtzman[1,2], T. Benzinger[1,2], A. Dow[3], S. Namazie-Kummer[3], Z. Posey[1,2], D. Ellington[1,2], J. Morris[1,2], B. Snider[1,2] *(1. Washington University School of Medicine - Saint Louis (United States), 2. Knight Alzheimer Disease Research Center - Saint Louis (United States), 3. Barnes Jewish Corporation - Saint Louis (United States))*

Implementation of amyloid-lowering treatments in clinical care for early symptomatic Alzheimer disease (AD) raises many challenges. Although one million or more people in the US may be eligible for treatment, less than 3,000 patients had been treated 6 months after approval of lecanemab. The Memory Diagnostic Center (MDC), the dementia specialty practice associated with Barnes-Jewish Hospital/Washington University School of Medicine (BJH/WUSM), has 17 clinicians (12 physicians and 5 advanced practice providers) who see over 2,000 patients with memory disorders per year. BJH is the academic flagship of BJC HealthCare (BJC), an integrated health system in St. Louis, Missouri. Leadership of BJC/WUSM and MDC staff met regularly for two years in anticipation of amyloid-lowering treatments becoming available. BJC/WUSM decided not to offer aducanumab (Aduhelm®) but did approve use of lecanemab (Leqembi®) after it received FDA approval in July 2023. Providing amyloid-lowering treatments required coordination with BJC administration, neuroradiology, infusion centers and the clinical practice. Patients meeting appropriate use criteria were identified prior to approval of lecanemab. The utilization of different AD biomarkers has evolved over time, changing from cerebrospinal fluid biomarkers to blood tests to amyloid PET imaging after Medicare reimbursement for amyloid PET became more routine. The first MDC patient received lecanemab within 6 weeks of FDA approval. Barriers to treatment included limited availability of appropriate MRI imaging, lack of reimbursement for AD blood tests and potentially high out of pocket costs for amyloid PET, limited capacity of infusion centers, and issues with private insurers. The MDC developed an on-call system for response to infusion reactions and other adverse events and a tracking system for infusions and monitoring MRIs. Mechanisms were developed in the electronic medical record to alert Emergency Department providers that patients on lecanemab being evaluated for stroke could be at increased risk of bleeding from thrombolytic therapies. Increasing capacity for patient assessments, biomarker testing, infusions, and follow-up appointments has required adding advanced practice providers and office staff and presents challenges for reimbursement. As of May 2024, 180 MDC patients had received at least one lecanemab infusion and 82 had received 10 or more infusions. 66 patients reported infusion reactions. 26 patients had one or more amyloid related imaging abnormality (ARIA): 16 had ARIA with edema (ARIA-E); 17 had ARIA with microhemorrhage (ARIA-H); 4 had superficial siderosis. Most patients with ARIA were asymptomatic and infusions were continued. Lecanemab was discontinued due to ARIA in five patients and two required hospital admission for monitoring and treatment. Ongoing challenges include extending amyloid immunotherapy beyond the academic medical center, which will require training neurologists throughout the BJC system and developing sustainable staffing and billing models for management of amyloid-lowering treatments.

P047- A RANDOMIZED, DOUBLE-BLIND TRIAL OF THE EFFECTS OF A LIVE BIOTHERAPEUTIC PRODUCT IN PRECLINICAL ALZHEIMER'S DISEASE. K.H. Lee[1], K.Y. Choi[2], S. Kang[1], J.H. Lee[3], W.S. Choi[3], J.H. Lee[2] *(1. Gwangju Alzheimer's & Related Dementia Cohort Research Center, Chosun University - Gwangju (Korea, Republic of), 2. Kolab Inc. - Gwangju (Korea, Republic of), 3. Chonnam National University - Gwangju (Korea, Republic of))*

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder, characterized by memory loss, amyloid accumulation, and neuroinflammation. Recent studies suggest that the microbiota plays a crucial role in modulating neuro-inflammation which in turn influences Aβ deposition and Alzheimer's disease. In addition, there is some evidence to suggest that probiotics may have a positive effect on cognitive function. In this study, we explored the impact of our probiotics (KL-P301) on anti-inflammation and cognitive enhancement using mouse models. Additionally, we are currently conducting a randomized, double-blinded, placebo-controlled clinical trial to assess the effects of these probiotics on cognitive function. To investigate the effect of probiotics on anti-inflammation and cognitive function, inflammation-induced mice were orally administrated with probiotics and examined for the Morris water maze test, nitric oxide (NO) assay, and interleukin (IL)-1β Elisa assay. For the clinical trial, the participants aged over 60 years were supplemented with probiotics or a placebo for 24 weeks to assess the effects on cognitive function, metabolic status, and anti-inflammation. The participants were randomly divided into two groups treated with either control supplements or a mixture of probiotics. In mice that received probiotics, the blood levels of NO and IL-1β were significantly decreased, and cognitive evaluation using the Morris water maze test showed significantly improved values

in the latency and target quadrant percentages compared to control mice. In the clinical trial, participants visited twice to undergo assessments including the MMSE, CERAD and blood tests, etc. The changes in each test score after 24 weeks were then evaluated. These probiotics have been shown to improve cognitive function and memory through anti-inflammatory mechanisms in an in vivo study using inflammation-induced mice. Furthermore, our ongoing clinical study is awaiting the positive effect of probiotics on cognitive function and blood biomarkers, suggesting a potential therapeutic use of our probiotics for cognitive impairment and Alzheimer's disease. **Keywords:** Probiotics, Cognitive impairment, Alzheimer's disease, Anti-inflammation, Gut-brain axis, Clinical trial. **Disclosures:** Kyu Yeong Choi and Jung Hee Lee are affiliated with Kolab, Inc. The remaining authors declare no conflicts of interest. **References:** Heneka MT, Carson MJ, El Khoury J, et al. Neuroinflammation in Alzheimer's disease. Lancet Neurol. 2015;14(4):388-405. Dominy SS, Lynch C, Ermini F, et al. Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. Sci Adv. 2019;5(1):eaau3333. Brown, G.C., Heneka, M.T. The endotoxin hypothesis of Alzheimer's disease. Mol Neurodegeneration 19, 30 (2024). Lee S, Eom S, Lee J, et al. Probiotics that Ameliorate Cognitive Impairment through Anti-Inflammation and Anti-Oxidation in Mice. Food Sci Anim Resour. 2023;43(4):612-624. Kim YJ, Mun BR, Choi KY, Choi WS. Oral Administration of Probiotic Bacteria Alleviates Tau Phosphorylation, Aβ Accumulation, Microglia Activation, and Memory Loss in 5xFAD Mice. Brain Sci. 2024;14(3):208.

P049- SELF-REPORTED SLEEP QUALITY AND AMYLOID BURDEN IN COGNITIVELY UNIMPAIRED ADULTS FROM THE AMYPAD STUDY. N. Tort-Colet[1,2], L. Stankeviciute[1], C. Ritchie[3], M. Boada[4,5], W. Van Der Flier[6], B.J. Hanseeuw[7], P. Martinez-Lage[8], P.J. Visser[9], M. Schöll[10], G.B. Frisoni[11], C. Buckley[12], F. Jessen[13], L.E. Collij[9,14], F. Barkhof[9,14,15], O. Grau-Rivera[1,2,16,17] *(1. Barcelonaβeta Brain Research Center (BBRC), Pasqual Maragall Foundation - Barcelona (Spain), 2. Hospital del Mar Research Institute - Barcelona (Spain), 3. Centre for Clinical Brain Sciences, University of Edinburgh - Edinburgh (United Kingdom), 4. Ace Alzheimer Center Barcelona - Barcelona (Spain), 5. Networking Research Center on Neurodegenerative Diseases (CIBERNED), Instituto de Salud Carlos III - Madrid (Spain), 6. Amsterdam UMC Location VUmc - Amsterdam (Netherlands), 7. Institute of Neuroscience (IONS), Université Catholique de Louvain - Burssels (Belgium), 8. Fundacion CITA Alzheimer - San Sebastian (Spain), 9. Department of Radiology and Nuclear Medicine, Amsterdam University Medical Center, location VUmc - Amsterdam (Netherlands), 10. Department of Psychiatry and Neurochemistry, University of Gothenburg - Gothenburg (Sweden), 11. Laboratory of Neuroimaging of Aging (LANVIE), Université de Genève - Geneva (Switzerland), 12. GE Healthcare - Amersham (United Kingdom), 13. Department of Psychiatry, University Hospital of Cologne - Cologne (Germany), 14. Amsterdam Neuroscience, Brain Imaging - Amsterdam (Netherlands), 15. Centre for Medical Image Computing, and Queen Square Institute of Neurology, UCL - London (United Kingdom), 16. Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable, Instituto de Salud Carlos III - Madrid (Spain), 17. Servei de Neurologia, Hospital del Mar - Barcelona (Spain))*

Background: Sleep disturbances are frequent among patients with mild cognitive impairment and Alzheimer's disease (AD) dementia [1, 2], and poor sleep quality (SQ) is increasingly recognized as a risk factor for AD [3, 4]. This study investigated cross-sectional and longitudinal associations of self-reported SQ with amyloid PET burden in cognitively unimpaired participants from the Amyloid Imaging to Prevent Alzheimer's Disease (AMYPAD) project [5,6]. **Methods:** We included N=527 cognitively unimpaired (CDR=0) adults from the AMYPAD study. Self-reported SQ was measured with the Pittsburg Sleep Quality Index (PSQI) total score (range 0-21, with higher scores indicating poorer SQ). Amyloid burden was measured with amyloid-PET centiloids (CL), categorizing baseline amyloid levels as negative, grey-zone, or positive using thresholds of 12 and 50 CL, respectively. CL rate of change (ROC) was measured among 421 participants with an available follow-up amyloid-PET scan performed 3.26 ± 1.26 years after on average. We used linear regression models to analyze (1) associations between baseline SQ and CL, and (2) associations between baseline SQ and amyloid ROC. These models were adjusted by age, sex, presence of anxiety and depression, and time between sleep assessment and first PET scan (70 ± 83 days on average). We also investigated whether baseline amyloid categories (negative, grey-zone, or positive) modified the association between SQ and amyloid ROC, to account for potential nonlinear longitudinal trajectories of amyloid accumulation. **Results:** On average, participants were 63.9 (± 6.67) years old, 62% females, 42% APOE ε4 carriers, 75% free from anxiety or depression, and had a PSQI total score of 5.79 (± 3.53). We neither found significant associations between PSQI and amyloid burden cross-sectionally (β=-0.001, CI = [-0.007,0.005], p=0.726) nor longitudinally (β=0.002, CI = [-0.001,0.006], p=0.186). We did find a significant interaction between baseline amyloid levels and SQ on amyloid ROC ($p<0.05$). After stratifying by baseline amyloid levels, worse SQ was significantly associated with higher amyloid ROC only in the grey-zone group (β=0.011, CI = [0.004,0.019], p=0.003), N=88), but not in the negative (β=0.001, CI = [-0.003,0.005], p=0.555, N=310) or positive (β=0.009, CI = [-0.021,0.003], p=0.118, N=23) groups. **Conclusion:** Our results indicate that worse sleep quality predicts an increased rate of amyloid accumulation among individuals with intermediate amyloid levels. The lack of association in the amyloid-positive group may be due to amyloid accumulation reaching a plateau among individuals with high amyloid burden, potentially attenuating the relationship between sleep and amyloid accumulation. These findings underscore poor sleep quality relevance as a potential AD risk factor, suggesting that cognitively unimpaired individuals with intermediate amyloid levels are ideal targets for AD prevention interventions focused on sleep. **Keywords:** self-reported sleep quality, PSQI, amyloid, PET. **Disclosures:** nothing to disclose. **References:** 1. Brzecka A , Leszek J , Ashraf GM et al. Sleep disorders associated with Alzheimer's disease: a perspective. Front Neurosci 2018;12: 330. 2. Ju, Y. E. S., Lucey, B. P., & Holtzman, D. M. (2014). Sleep and Alzheimer disease pathology—a bidirectional relationship. Nature Reviews Neurology, 10(2), 115-119. https://doi.org/10.1038/nrneurol.2013.269. 3. Yaffe, K., Falvey, C. M., & Hoang, T. (2014). Connections between sleep and cognition in older adults. The Lancet Neurology, 13(10), 1017-1028. https://doi.org/10.1016/S1474-4422(14)70172-3. 4. Lucey, B. P., Hicks, T. J., McLeland, J. S., Toedebusch, C. D., Boyd, J., Elbert, D. L., ... & Bateman, R. J. (2018). Effect of sleep on overnight cerebrospinal fluid amyloid β kinetics. Annals of neurology, 83(1), 197-204. 5. Frisoni, G. B., Barkhof, F., Altomare, D., Berkhof, J., Boccardi, M., Canzoneri, E., ... & Raffa, N. (2019). AMYPAD diagnostic and patient management study: rationale and design. Alzheimer's & Dementia, 15(3), 388-399. 6. Collij, L. E., Farrar, G., Valléz García, D., Bader, I., Shekari, M.,

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P050- PHASE 1, FIRST-IN-HUMAN, SINGLE AND MULTIPLE ASCENDING DOSE STUDY OF A NOVEL ORALLY ADMINISTERED TREM2 AGONIST (VG-3927) IN HEALTHY VOLUNTEERS: INTERIM RESULTS.
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Background: VG-3927 is a highly potent, selective, brain penetrant, oral, small molecule TREM2 agonist that is currently under development for the treatment of Alzheimer's disease. TREM2, a receptor expressed on microglia in the brain is critical to microglial function. Among microglia-associated AD risk genes, partial loss-of-function variants of TREM2 confer 2-3 fold increase in risk for developing AD, motivating efforts to identify pharmacological agonists targeting TREM2. VG-3927 is designed to act as a molecular glue that potentiates the TREM2 signaling response to natural damage ligands and is hypothesized to promote microglial function and health, and tissue repair mechanisms regulated by microglia thereby aiming to slow disease progression in AD. **Methods:** The Phase 1 randomized, double-blind, placebo-controlled study will evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics after single- (SAD) and multiple-ascending dose (MAD) of orally administered VG-3927 in healthy volunteers as well as an open-label single dose in participants with AD. The study will enroll healthy adults aged 18 to 55 years and include SAD and MAD cohorts that are planned to be tested sequentially in a dose-escalating manner. Eight participants will be randomized in a 6:2 allocation ratio to VG-3927 or placebo into each of the planned cohorts. The single dose open-label AD cohort will comprise of approximately 10 participants with MCI or Mild AD with biomarker evidence of amyloid pathology. The treatment period for the SAD and the MAD portions will be 1 day and 14 days respectively with safety follow-up through at least 28 days after the last dose for both portions. Study assessments to investigate safety and tolerability will include physical exams, neurological exams, vitals, ECG, clinical laboratory, C-SSRS and AE reporting in all cohorts. Blood samples will be collected in all cohorts to characterize the pharmacokinetics and CSF samples will be collected in selected cohorts to investigate biomarkers of target engagement and pharmacodynamic activity. **Results:** The study dosed its first participant in October 2023 and is currently ongoing. The interim results from the healthy volunteer SAD and MAD cohorts will be presented at the time of the meeting. **Conclusion:** The ongoing Phase 1 study will assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of VG-3927 in healthy volunteers and individuals with AD. The findings are expected to inform subsequent development in AD.
Keywords: VG-3927, TREM2, Microglia, Neuroinflammation.

P051- INTERIM SAFETY AND BIOMARKER DATA FROM UPLIFT-D, A PHASE 1B TRIAL OF PBFT02 IN FRONTOTEMPORAL DEMENTIA AND MUTATIONS IN THE GRANULIN GENE (FTD-GRN).
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Background: Frontotemporal dementia (FTD) is a neurodegenerative clinical syndrome characterized by various combinations of disturbances in behavior and deficits in executive function and language. Approximately 25-30% of FTD is caused by autosomal dominant mutations, usually in one of three genes, C9orf72, GRN, or MAPT. GRN mutations result in a progranulin (PGRN) haploinsufficiency leading to neurodegeneration, likely related to lysosomal dysfunction and inflammation. There are currently no disease-modifying treatments approved for FTD, including FTD due to GRN mutations, or FTD-GRN. **Methods:** PBFT02 is an adeno-associated virus serotype 1 (AAV1) vector that delivers a functional copy of the human GRN gene to neurons and glia with the goal of correcting the PGRN haploinsufficiency characteristic of FTD-GRN. Since PGRN is a secreted protein, PBFT02 expression impacts both directly transduced cells and surrounding tissues. PBFT02 is administered directly to the cerebrospinal fluid (CSF) via a single CT-guided intra-cisterna magna (ICM) administration. The ICM approach allows for broad CNS biodistribution with lower doses compared to IV systemic delivery and limits the impact of circulating neutralizing antibodies to AAV1. PBFT02 is currently being studied in a first-in-human, dose escalation clinical trial, upliFT-D (NCT04747431 [ClinicalTrials.gov]), which will enroll two sequential FTD-GRN cohorts, with an optional third cohort. Subjects ≥35 and ≤75 years of age with symptomatic FTD-GRN are being enrolled. The primary objective is safety and tolerability; secondary objectives include biomarkers of target engagement (e.g., PGRN), biological activity, and disease progression. The 2-year trial will be followed by a 3-year extension to assess safety and durability of effect. **Results:** As of June 2024, dosing of Cohort 1 is complete; 5 subjects have received PBFT02 at a dose of 4.5 x 1013 genome copies. PBFT02 was generally well-tolerated with a steroid regimen of 1 g IV methylprednisolone on study days 1 to 3, followed by 60 mg oral prednisone on days 4 to 60. Notably, there has been no evidence of dorsal root ganglion toxicity, as measured by nerve conduction studies, and no complications related to the ICM procedure. As expected, baseline levels of CSF and plasma PGRN were below levels of healthy adult controls. Following PBFT02 administration in the initial 3 participants, CSF PGRN levels at day 30 post treatment increased to

2.2 to 3.6x higher than the mean of healthy adult controls and were above the upper limit of the range of the control population in all participants. In the initial 2 participants followed out to 6 months post-dose, CSF PGRN levels were maintained with concentrations 4.6 to 5.7x above the mean of healthy adult controls. Updated data will be included at the time of the presentation including CSF PGRN data from the full cohort. **Conclusion:** Interim safety and biomarker data from the upliFT-D trial provides initial evidence that PBFT02 has potential as a one-time therapy for FTD-GRN, thus supporting further clinical development. **Keywords:** Frontotemporal dementia, FTD, Progranulin, Gene Therapy. **Clinical Trial Registry:** NCT04747431; https://clinicaltrials.gov. **Disclosures:** JC, PT, YGN, SEB, SR, and MSF are full-time employees of Passage Bio. SD, DJI, IS, PES, LTT, MCT, and LCS serve as principal investigators in clinical trial agreements with Passage Bio. SD serves as principal investigator in clinical trial agreements with NovoNordisk, Janssen, Biogen, Alnylam, and Innodem Neurosciences, has consultancy agreements with Eisai, Eli-Lilly, NKGen, and QurAlis, and serves on the DSMB for AviadoBio and IntelGenX. DJI serves as principal investigator in clinical trial agreements with Prevail, Transposon, Alector, and Denali. IS serves as principal investigator in clinical trial agreements with Alector. PES is an investigator in clinical trial agreements with Lilly, Alzheon, Acadia, Alnylam, Nova Nordisk, Janssen, UCB Pharma, Alzheimer's Association, Weston Brain Institute and the Neurodegeneration Consortium. PES also receives grant support from the NIH. MCT serves as an investigator in clinical trial agreements with Biogen, Avanex, Green Valley, Roche/Genentech, BMS, Eli Lilly/Avid Radiopharmaceuticals, Janssen, UCB, and Novonordisk, and serves as a consultant for Eisai and Lilly. MCT also receives grant support from the NIA, Weston Brain Foundation, and the Tanenbaum Institute for Science in Sport. LTT serves as principal investigator in clinical trial agreements with Denali. TV and KJQ, declared no competing interests.

P052- ALZHEIMER'S DISEASE AND MICROBIOTA: THE MICMALZ STUDY. G. Busto[1], L. Kundura[2], S. Artero[2], Y. Dauvilliers[3], K. Bennys[4], S. Claeysen[2], A. Gabelle[1] *(1. Center for Memory Resources and Research (CMRR), Department of Neurology, Montpellier University Hospital, Montpellier, INM, Univ Montpellier, Montpellier, France - Montpellier (France), 2. IGF, Univ Montpellier, CNRS, INSERM, Montpellier, France. - Montpellier (France), 3. Sleep and Wake Disorders Centre, Department of Neurology, Gui de Chauliac Hospital and INM, Univ Montpellier, Montpellier, France. - Montpellier (France), 4. Center for Memory Resources and Research (CMRR), Department of Neurology, Montpellier University Hospital, Montpellier, France. - Montpellier (France))*

Background: The gut microbiota plays essential role in human health and influences brain functioning. Age, nutrition and sleep modify the composition of the microbiota and are also risk factors for Alzheimer's disease (AD). AD patients exhibit dysbiosis characterized by changes in the relative proportions of specific bacterial phyla [1]. Fecal microbiota transplants (FMT) show promising results on cognition and amyloid-β biomarkers in preclinical studies and rare human case reports [2, 3]. Our aims are to describe the metagenomic and metabolomic signature of the microbiota in AD patients compared to controls, to decipher the role of cofounding factors i.e. diet and sleep, and to test the impact of a well characterized FMT on genetic AD mouse models. **Methods:** AD patients with confirmed AD biomarkers and age- and sex-matched controls were recruited. Metagenomic and metabolomic analyses were performed in stool, and blood. We compared the two groups, taking into account sociodemographic and cognitive profile, CSF biomarkers (Aβ42, Aβ40, p-tau181, and t-tau), sleep parameters and dietary habits using validated questionnaires. The impact of FMT on microbiota composition, cognition, molecular and cellular biomarkers of AD pathophysiology were established using pooled stool samples from humans AD and controls transferred to 5XFAD mice or their control littermates (n=10-12/group, 4 experimental sessions). **Results:** 48 AD patients [age 74 (SD 6.3), 48% women, Mini-Mental State Examination (MMSE) 22 (interquartile range, IQR, 17-26)] and 46 controls [age 71 (SD 9.3), 54% women, MMSE 29 (IQR 27-30)] were compared. BMI, MNA, and educational level were similar in both groups. As expected, AD patients showed increased CDR scores, more frequently in APOE4 carriers, a reduced CSF Aβ42/Aβ40 ratio, elevated p-tau181 and t-tau levels, and hippocampal atrophy on MRI. Preliminary results indicate a dysbiosis in AD patients compared to controls. The metagenomic profile in blood and stools will be described. The FMT experiments showed engraftment of specific bacterial genera into 5XFAD and controls mice, resulting in impaired memory performance associated with higher levels of Aβ42 in the brains of recipient mice. **Conclusion:** Our results suggest that gut microbiota dysbiosis is associated with AD status and highlight specific bacterial genera. Moreover, FMT from AD patients in an AD mouse model recapitulates important features of the disease, including memory impairment and Aβ42 accumulation. **References:** 1. N. M. Vogt et al., "Gut microbiome alterations in Alzheimer's disease," Sci Rep, vol. 7, no. 1, p. 13537, Oct. 2017; 2. J. Sun et al., "Fecal microbiota transplantation alleviated Alzheimer's disease-like pathogenesis in APP/PS1 transgenic mice," Transl Psychiatry, vol. 9, no. 1, p. 189, Aug. 2019; 3. S. Hazan et al., « Rapid improvement in Alzheimer's disease symptoms following fecal microbiota transplantation: a case report» J Int Med Res. 2020 Jun;48(6). §The MICMALZ group: IGF: Clayesen S, Kundura L, Artero S, SMekki LN, Curel T., Deri G., Ismeurt C., Gaven F., Giannoni P., La Thuy, Maillou J.: CMRR: Gabelle A, Bennys K, Busto G, Ban D., Bruchet L.-M., Cambiaire E., Dornadic M., Flores M., Gouirand J., Grasselli-Monboisse C., Huby S., Léger C., Manzano-Gonzalez G., Nguyen C., Turpinat C. Sleep: Dauvilliers Y, Pesenti C., Thobois O. CREFRE: Bernal T., Collet X., Waget A. Vaiomer: Fourtanier J., Lelouvier B., Servant F.

P053- TREM2 AGONISM STIMULATES HUMAN MICROGLIA RESPONSES IN THE PRESENCE OF AMYLOID PATHOLOGY. M. Polydoro[1], I. Geric[2], J. Zheng[3], T. Sommer Bisgaard[3], L. Wolfs[2], A. Misbaer[2], A. Nair[2], L. Sans[3], M. Dalby[3], J. Vilstrup[3], P. Flagstad[3], R. Balice-Gordon[4], B. De Strooper[5,6], N. Plath[3] *(1. Muna Therapeutics, Copenhagen, Denmark - Boston (United States), 2. Muna Therapeutics, Copenhagen, Denmark - Leuven (Belgium), 3. Muna Therapeutics, Copenhagen, Denmark - Copenhagen (Denmark), 4. Muna Therapeutics, Copenhagen, Denmark - Philadelphia (United States), 5. UK Dementia Research Institute - London (United Kingdom), 6. KU Leuven - Leuven (Belgium))*

Background: Microglia function as brain-resident innate immune cells that maintain brain health and play a critical role in resolving Alzheimer´s and other pathology. TREM2 is a key signaling receptor expressed in microglia that modulates microglia migration, proliferation, phagocytosis and cytokine release. Pharmacological activation of TREM2 represents a novel therapeutic approach to slow Alzheimer´s disease

progression, strongly supported by human genetics linking TREM2 to early- and late-onset AD. Lack of TREM2 locks microglia in a homeostatic state in animal models, preventing a phagocytotic response to amyloid pathology and leading to exaggerated neurodegeneration. Here, we study the impact of TREM2 agonism on the receptor signaling complex and downstream signaling cascades leading to microglia activation. **Methods:** TREM2 agonist induced receptor complex dynamics were assessed in vitro in CHO, HEK, THP-1 and hIPSC derived microglia cells by nanoBiT, western blot and alphaLISA assays. Functional effects were studied in vitro though phagocytosis and migration assays. To monitor TREM2 agonism induced effects on human microglia in the presence of amyloid pathology in vivo, xenografted mice and hTREM2 knock-in were treated systemically and chronically with increasing doses of selective, potent and brain penetrant TREM2 agonists. Subsequently, human microglia were isolated and analyzed by qPCR and single-cell RNA sequencing. **Results:** Small molecule mediated TREM2 activation leads to TREM2/DAP12 receptor complex formation required for downstream signaling and microglia activation. In vivo, human TREM2 is expressed by pathology associated microglia and induced by amyloid plaques. Systemic treatment with TREM2 agonists leads to differential gene expression patterns in xenografted human microglia only in the presence of amyloid pathology. Specifically, TREM2 agonism up-regulates interferon-related genes and down-regulates disease associated microglial genes. Effects were observed at compound exposure levels in the brain consistent with in vitro agonist potency. **Conclusion:** Muna Therapeutics advances a potent, brain exposed and selective small molecule agonist into clinical studies. We show here how TREM2 activation by small molecule agonists leads to the rapid formation of a receptor complex required for downstream signaling and microglia activation to resolve neuropathology and support neuronal function. In vivo, TREM2 agonism modulates gene networks in human microglia selectively in the presence of amyloid pathology. The present studies collectively underline the therapeutic potential of TREM2 agonism for the treatment of early Alzheimer´s disease.

P054- TARGETING A-SYNUCLEIN FIBRIL'S DISORDERED REGION WITH SMALL MOLECULE INHIBITORS: A THERAPEUTIC STRATEGY FOR PARKINSON'S DISEASE.
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Background: Parkinson's Disease (PD) is the second-most common neurodegenerative disorder, primarily impacting dopaminergic neurons in the substantia nigra and leading to motor symptoms like bradykinesia, rigidity, and tremor. A crucial aspect of PD pathology involves the aggregation of α-synuclein (α-syn) fibrils, which form the core of Lewy bodies and neurites, disrupting neuron function and protein homeostasis. These fibrils, particularly through their C-terminal intrinsically disordered region, play a key role in neuron-to-neuron transmission and neuroinflammation by interacting with specific membrane receptors on neurons and microglia [1-5]. Targeting these interactions presents a promising avenue for therapeutic development to mitigate α-syn related pathologies. **Methods and Results:** In this study, through high-throughput screening, we discovered Givinostat (GS) as a potent inhibitor that impedes α-syn fibrils' interaction with LAG3 and RAGE receptors. Following this discovery, we embarked on a structure-activity relationship (SAR) exploration, creating and assessing approximately 100 GS derivatives (GSDs) to identify several optimally performing compounds, such as GSD-16-24. Using solution-state and solid-state NMR alongside Cryo-EM techniques, we established that GS and GSD-16-24 bind directly to the C-terminal IDR of α-syn, overlapping with the binding sites for binding receptors. The GSD-16-24 impedes the association of α-syn fibrils with membrane receptors, significantly reducing both neuronal propagation and inflammatory responses attributed to α-syn fibrils. **Conclusion:** Our findings underline the potential of GS, and its derivatives, as promising candidates for preventing the pathological progression of PD by specifically targeting and modulating the interactions of α-syn fibrils with crucial neuronal and microglial receptors. This approach represents a significant advancement in the development of targeted therapies for PD, offering hope for more effective treatments that address the underlying mechanisms of the disease. **Keywords:** α-Synuclein, intrinsically disordered region, Parkinson's disease, inhibitors. **References:** 1. N. Uemura, M. T. Uemura, K. C. Luk, V. M. Lee, J. Q. Trojanowski, Cell-to-Cell Transmission of Tau and α-Synuclein. Trends Mol Med 26, 936-952 (2020). 2. X. Mao et al., Pathological α-synuclein transmission initiated by binding lymphocyte-activation gene 3. Science 353 (2016). 3. S. Zhang et al., Mechanistic basis for receptor-mediated pathological α-synuclein fibril cell-to-cell transmission in Parkinson's disease. Proc Natl Acad Sci U S A 118 (2021). 4. H. Long et al., Interaction of RAGE with α-synuclein fibrils mediates inflammatory response of microglia. Cell Rep 40, 111401 (2022). 5. S. Zhang et al., Conformational Dynamics of an α-Synuclein Fibril upon Receptor Binding Revealed by Insensitive Nuclei Enhanced by Polarization Transfer-Based Solid-State Nuclear Magnetic Resonance and Cryo-Electron Microscopy. J Am Chem Soc 145, 4473-4484 (2023).

P055- DIFFERENT CHARGED BIOPOLYMERS INDUCE A-SYNUCLEIN TO FORM FIBRILS WITH DISTINCT STRUCTURES.
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Background: The deposition of α-Synuclein (α-syn) fibrils has long been considered as a key pathological hallmark of Parkinson's disease (PD) and other synucleinopathies, such as multiple system atrophy and dementia with Lewy bodies. Varied clinical and pathological manifestations seen in these disorders are believed to arise from the diverse structural polymorphs of α-syn fibrils [1, 2]. Numerous factors, including lipids, chaperones, and metabolites, have been identified to contribute to pathological α-syn aggregation [3]. The unique structure of α-syn, with a lysine-rich N-terminal and a negatively charged C-terminal, facilitates interactions with a range of polycations and polyanions, affecting fibrillation kinetics. In this work, we evaluate the specific effects of these charged biopolymers on the α-syn fibrillation process and resultant fibril structures. **Methods:** We conducted a comprehensive investigation into the kinetic and structural

impacts of various biopolymers on α-syn fibril formation using the Thioflavin-T (ThT) fluorescence assay for kinetics monitoring. Negative-staining transmission electron microscopy (TEM) confirmed and characterized the quantity and morphology of α-syn fibrils. High-resolution structural details were elucidated using cryo-electron microscopy (cryo-EM) to analyze structural alterations induced by these biopolymers. **Results:** Our findings reveal that both cationic and anionic biopolymers, such as polyphosphate (polyP), polyuridine (polyU), and polyamines (including putrescine, spermidine, and spermine), accelerate α-syn aggregation. Detailed analysis showed that these biopolymers distinctly influence the structural polymorphs of α-syn fibrils. For instance, polyamines modify fibrillation kinetics without altering the overall fibril structure, whereas polyU and polyP affect both kinetics and final morphology, resulting in a range of morphologies for polyU-induced fibrils and untwisted fibrils from polyP. These findings indicate that the nature of the biopolymer plays a crucial role in dictating the structural outcome of α-syn fibrillation. **Conclusion:** This study highlights the crucial role of biopolymers in the aggregation process and structural outcomes of α-syn fibrils, enhancing our understanding of the structural variations in α-syn fibrils across different pathological conditions and their potential therapeutic implications. **References:** 1. Li, D. and C. Liu, 2022. Conformational strains of pathogenic amyloid proteins in neurodegenerative diseases. Nat Rev Neurosci 23(9), 523-534. 2. Peelaerts, W., et al., 2015. alpha-Synuclein strains cause distinct synucleinopathies after local and systemic administration. Nature 522(7556), 340-4. 3. Li, D. and C. Liu, 2021. Hierarchical chemical determination of amyloid polymorphs in neurodegenerative disease. Nat Chem Biol, 17(3), 237-245.

P056- DEVELOPMENT AND EFFICACY ASSESSMENT OF A VIDEO-BASED REMINISCENCE THERAPY USING MEDIAL ARCHIVES FOR EARLY-STAGE DEMENTIA: A PILOT STUDY.

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Introduction: Reminiscence therapy, a non-drug intervention for dementia patients, aims to evoke past emotions and memories. Widely used in dementia management, it has shown positive effects, helping individuals reflect and gain insights. Traditionally, reminiscence therapy has often been conducted in group settings using photographs or thematic word cards. However, there is growing interest in using Information and Communication Technologies like computers and TVs for digital reminiscence programs. In this study, in collaboration with Dingding University company of Munhwa Broadcasting Corporation (MBC), we developed a video-based reminiscence therapy program consisting of 12 sessions using materials from dramas, news, documentaries, and other broadcasts aired on MBC. To determine We conducted a preliminary efficacy assessment of the program at the Yangcheon Center for dementia to determine its effectiveness. **Methods:** Twenty-three dementia patients participated in a 12-session reminiscence therapy program at the Yangcheon Center for Dementia. The program conducted twice a week for 50 minutes per session. During the program, participants watched themed video clips and answered questions. Each group had six participants and one occupational therapist. Primary outcomes were changes in cognitive impairment screening test (CIST) and Korean Mini-Mental State Examination 2 (K-MMSE-2) scores. Secondary outcomes included changes in geriatric depression scale and subjective memory questionnaire scores, along with program satisfaction. **Results:** The study included participants with an average age of 73.9 years. The gender distribution was 10 males to 13 females, with an average educational level of 8.6 years. Baseline cognitive assessments revealed a mean Korean Mini-Mental State Examination (K-MMSE-3) score of 21.3 ± 4.4 and a Global Deterioration Scale score of 4.2 ± 0.4. The mean attendance rate for the program was 74%. Despite high levels of participant satisfaction, there were no significant changes in cognitive function, depression, or subjective memory scores following the program. For the sensitivity analysis, participants were divided into two groups based on attendance: those who attended 80% or more of the program (n=10) and those who attended less than 80% (n=13). While there was a trend towards improved MMSE/CIST scores in the higher attendance group, the differences were not statistically significant. Both groups also exhibited non-significant trends towards improved depression and memory levels. **Conclusion:** Although program satisfaction was high, the video-based 12-session reminiscence therapy did not produce significant improvements in cognitive function or reductions in depression/subjective memory decline among early-stage dementia patients. Given the gradual cognitive decline characteristic of dementia, determining the program's effectiveness based solely on the current single-group design without a control group is challenging. Future evaluations through longer-term studies with larger participant cohorts and control groups are necessary to comprehensively assess the program's efficacy.

P057- PREDXCLEARANCE, EXPLORING NEW BIOMARKERS TO PREDICT ARIA/CAA AND PERSONALIZE THERAPY IN AD.

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Background: Alzheimer's disease (AD) is a progressive brain disorder causing irreversible neurodegeneration, impacting millions worldwide. Emerging AD immunotherapies using Aβ-specific antibodies offer hope by potentially halting AD progression. However, up to 40% of patients undergoing immunotherapy experience adverse effects linked to Cerebral Amyloid Angiopathy (CAA), known as Amyloid-Related Imaging Abnormalities (ARIA) [1]. ARIA presents as brain swelling, sometimes progressing to bleeding, causing lasting damage and, in severe cases, becoming life-threatening. Successful clinical implementation of these drugs requires early AD detection and complementary diagnostics for assessing ARIA/CAA risk. Current monitoring for ARIA involves frequent MRI scans, increasing the strain on patients, healthcare system, and treatment costs. Hence, urgent development of lower-cost, personalized tools for ARIA risk identification is necessary. It is hypothesized that during immunotherapy, Aβ removal may instigate a detrimental feedback loop by worsening the Aβ clearance system. Consequently, a compromised Aβ clearance system could serve as a predictor for adverse effects associated with immunotherapy.

Additionally, monocyte/macrophage clearance capacity has an important role in AD and the depletion of perivascular monocytes/macrophages causes an increased risk of ARIA/CAA and Aβ accumulation [2]. **Methods:** Based on the information presented above, we are developing an in-vitro tool capable of measuring monocytic Aβ clearance capacity from a whole-blood 6ml-EDTA tube from samples of the AI-Mind Biobank. Aβ1-40 is added into our monocytic culture system and incubated for 3h. After, monocytes are isolated and lysed. Intracellular Aβ1-40 and Aβx-34 (Immunoassay with proprietary antibodies) will be measured at different time points to evaluate the Aβ proteolytic capacity of the monocytes. In addition, ptau217 was measure in plasma by the MSD S-PLEX Human Tau(pT217) Kit. **Results:** Our results showed that a higher pTau217 concentration is linked to APOE4+ genotypes in an MCI cohort. However, pTau217 alone is not sufficient to distinguish different subsets of AD/MCI patients that could indicate a higher risk of ARIA. By measuring monocytic clearance capacity with our cell culture system, AD patients with higher pTau217 concentration and APOE4+ genotypes can be further subgrouped into those with high and low Aβ clearance capacity, with the latter being more likely to develop ARIA. **Conclusion:** In this study, we provide the first evidence of the potential for this novel tool to predict the risk of ARIA with an in-vitro and non-invasive test. This will lead to more effective, accessible, and safer treatments for AD patients. **Keywords:** Alzheimer's Disease, immunotherapy, ARIA, CAA, monocytes, Aβ clearance, AI-Mind biobank. **Disclosures:** This study is partially funded by the Research Council of Norway. The cohort used in the study consists of a subgroup selected from the AI-Mind project 2023 Norwegian samples. This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 964220. This publication reflects the views of the author and the European Commission is not responsible for any use that may be made of the information it contains. **References:** 1. John R Sims et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAM doi: 10.1001/jama.2023.13239(2023). 2. Lapenna, A., De Palma, M. & Lewis, C.E. Perivascular macrophages in health and disease. Nature reviews immunology doi: 10.1038/s41577-018-0056-9 (2018).

P058- EVALUATION OF SQUARE-STEPPING EXERCISE ON PLASMA AMYLOID-BETA LEVELS AND COGNITIVE FUNCTION IN OLDER ADULTS: A RANDOMIZED CONTROLLED TRIAL.

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Background: Japan is a rapidly aging society, and extension of healthy life expectancy is considered an important societal issue. Among the methods that have been proposed to extend healthy life expectancy, the square-stepping exercise (SSE) has been attracting increasing attention. This exercise program involves stepping on a mat divided into 25-cm squares, which has beneficial effects on physical and cognitive function. We investigated the potential of SSE as a preventive measure against Alzheimer's disease, by examining changes in blood amyloid (Aβ) levels in older adults after an 18-month SSE intervention. **Methods:** A total of 65 participants (aged 65–85 years, mean age=73.6) were assigned to an SSE group (SSEG), a basic walking group (WALKINGG), and a control group (CG) for this randomized, parallel-group study. The inclusion criteria were as follows: (1) aged 65–85 years, (2) not requiring long-term care, (3) no dementia, and (4) no prior experience with SSE.Plasma levels of Aβ1-42 and Aβ1-40 were measured using a previously described method based on matrix-assisted laser desorption-ionization time-of-flight mass spectrometry [1]. Cognitive function was measured via five cognitive function tests [2]. All analyses were performed using repeated-measures ANCOVA with age and educational level as covariates. Effect sizes (Cohen's d) of the pre- and post-test data were determined using the average change, excluding the pre-test standard deviation. **Results:** No significant differences in clinical characteristics were observed among the three groups at baseline (p=0.575–0.822). A significant time-by-group interaction was found in terms of Aβ1-40, and Aβ1-42 (p=0.048 and 0.032, respectively). A simple main-effects analysis showed that the SSEG and CG groups had higher levels of contribution than the WALKINGG in the post-test Aβ1-40 data ($p \leq 0.001$). In addition, the SSEG had a higher contribution than either the WALKINGG and CG in the post-test for Aβ1-42 (p=0.001). No significant time-by-group interaction were found for Aβ42/40 and cognitive function domain (p=0.123–0.998). The effect size of SSEG was –0.96 to 1.19, that of WALKINGG was –0.75 to 0.51, and that of CG was –0.91 to 1.14. **Conclusion:** A significant interaction was found for Aβ1-40 and Aβ1-42. In particular, the 18-month intervention suggested that the concentration of Aβ1-42 in the SSEG was significantly higher than that of WALKINGG and CG. This result is consistent with those of previous studies examined by a recent cross-sectional study [3]. Patients with Alzheimer's disease often have decreased Aβ1-42 levels [4], so maintaining or increasing blood Aβ1-42 levels through SSE may contribute to preventing the onset of this condition. However, no significant interaction for Aβ42/40 in blood and cognitive function were found from this intervention study.One limitation of this study is that the intervention was implemented between 2020–2022, when group activity was restricted because of the COVID-19 pandemic. Therefore, the frequency of SSE (a group exercise) was reduced by ~30%, and the participants' daily activities were unpredictable. **Keywords:** Square-stepping exercise, Amyloid beta, Cognitive function. **Clinical Trial Registry:** UMIN000050240; https://www.umin.ac.jp/. **Disclosures:** This study was supported by JSPS KAKENHI Grant Number 20H04063 and JST Grant Number JPMJPF2017. The authors declared no competing interests. **References:** 1. Nakamura A, et al. Nature 2018; 554(7691): 249-254. http://doi.org/10.1038/nature25456; 2. Yatomi N, et al. Psychogeriatrics 2006; 6: A58; 3. Yoon J, et.al. Journal of Alzheimer's Disease 2023; 96: 1801-1812. http://doi.org/10.3233/JAD-230675; 4. Blennow K, et al. Nature Reviews Neurology 2010; 6(3): 131-144. http://doi.org/10.1038/nrneurol.2010.4.

P059- EVALUATION OF AN UPPER ALPHA NEUROFEEDBACK INTERVENTION ON MILD AMNESTIC COGNITIVE IMPAIRMENT: A RANDOMIZED, DOUBLE-BLIND, SHAM-CONTROLLED RESEARCH PROJECT (ESPERANZA STUDY). E. Jubera Garcia[1,2], C. Escolano[1], E. López-Larraz[1], J.G. Klinzing[1], J. Ventura[1], B. Hornillos[1], L. Pampliega[1], N. Molina-Torres[3,4], J.M. Pérez-Trullén[3,5], E. Muñoz Farjas[6], E. Lobo[3,7], A. Lobo[3,8], T. Beckinschtein[2], P.J. Modrego[3,9], J. Minguez[1] *(1. Bitbrain - Zaragoza (Spain), 2. Department of Psychology, University of Cambridge - Cambridge (United Kingdom), 3. Instituto de Investigación Sanitaria de Aragón - Zaragoza (Spain), 4. Servicio de geriatría, Hospital Nuestra Señora de Gracia - Zaragoza (Spain), 5. Servicio de neurología, Hospital Nuestra Señora de Gracia - Zaragoza (Spain), 6. Servicio de neurología, Hospital Clínico Universitario Lozano Blesa - Zaragoza (Spain), 7. Department of Preventive Medicine and Public Health, Universidad de Zaragoza - Zaragoza (Spain), 8. Department of Medicine and Psychiatry, Universidad de Zaragoza - Zaragoza (Spain), 9. Servicio de neurología, Hospital Universitario Miguel Servet - Zaragoza (Spain))*

Background: Patients diagnosed with Alzheimer's Disease exhibit a reduction in the power and relative frequency of alpha oscillations [1] associated with poorer cognitive performance [2]. In Mild Cognitive Impairment (MCI) stage, which precedes dementia, these alterations in alpha oscillations have been linked to deficits in cognitive functioning [3]. EEG-based neurofeedback is an intervention based on monitoring EEG brain activity and provides real-time feedback based on specific biomarkers, which creates a closed-loop neuromodulation system that allows users to adjust their brain activity towards desired levels. Recent scientific works have shown the effectiveness of NF to enhance cognitive performance for the general population [4, 5] and for MCI (see [6] for a review and recent randomized controlled trials [7, 8]). Our NF intervention aims at increasing the subject-specific upper-alpha activity in aMCI to achieve cognitive improvement. The contribution is to apply this intervention in a more homogeneous population (aMCI), and the focus of the intervention in the frontal cortex. **Methods:** The ESPERANZA study, a pre-registered, double-blind, placebo-controlled clinical trial will investigate the effects of neurofeedback (NFB) intervention in 64 patients diagnosed with aMCI. The NF intervention will consist of eight sessions over a two-week period. The primary outcome measure will assess the pre-post intervention effectiveness at the electrophysiological level, specifically focusing on an increase in upper-alpha activity. Secondary outcomes will evaluate the intervention's effectiveness on cognitive function, particularly improvements in cognitive variables related to episodic and working memory. We hypothesize an increase in upper-alpha activity in the stimulation condition related to a higher post-intervention memory performance. **Results:** We have performed a series of pilot studies on 34 healthy older adults and 20 aMCI patients with a total of 272 and 418 sessions respectively (minor variations on the protocol to test a different number of sessions and their cadence). The data collection is still ongoing. The preliminary results have confirmed the feasibility of the approach: patients are able to follow the intervention and no side effects have been reported so far. Up to now, we can report preliminary results that show a significant increase in upper-alpha activity in the stimulation condition compared to the sham condition, both in healthy and aMCI populations. The final clinical trial is planned to begin during the second half of 2024. **Conclusion:** This trial investigates upper alpha neurofeedback's potential as the first effective, non-drug symptomatic treatment for aMCI patients. Success could pave the way for future studies in dementia. **Keywords:** MCI, neurofeedback, neurotherapeutics. **Clinical Trial Registry:** C.I. PI 23/186; Comité de Ética de la Investigación de la Comunidad Autónoma de Aragón. Registration in clinicaltrials.gov in progress. **Data Deposition:** In progress. **Disclosures:** Authors affiliated to Bitbrain are employed by the company. **References:** 1. Wright, P., Sigmundsson, T., & Lucey, J. V. (2012). 35—Electroencephalography and neuroimaging. In P. Wright, J. Stern, & M. Phelan (Eds.), Core Psychiatry (Third Edition) (pp. 521–533). W.B. Saunders. https://doi.org/10.1016/B978-0-7020-3397-1.00035-5; 2. Baars, B. J., & Gage, N. M. (Eds.). (2013). Chapter 8—The brain is conscious. 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P060- PATIENT CONSIDERATIONS IN THE DEVELOPMENT AND DELIVERY OF NOVEL TREATMENTS FOR ALZHEIMER'S DISEASE. A. Silber[1], A. Athavale[1], M. O'hara[1], D. Masterman[2], P.S. Bajaj[1] *(1. Trinity Life Sciences - Waltham, MA (United States), 2. Prothena Biosciences, Inc - Brisbane, CA (United States))*

Background: Anti-amyloid β treatments are the first disease-modifying therapies for Alzheimer's disease (AD) that achieve slowing of cognitive decline. These therapies have the potential to transform care for individuals with AD and have many implications for patients, care partners, the healthcare system, and future drug development/innovation in this space. However, early use of the first commercially available treatments, intravenous (IV) infusions administered at two- or four-week intervals, has been limited. Potential factors cited for slow uptake include functional barriers that impede patient access to infusions (e.g., distance to infusion centers and time required). This study sought to characterize the current and/or potential burden of IV infusion treatments for AD patients, focusing on the barriers to treatment of current anti-amyloid

therapies. **Methods:** A quantitative survey was fielded in the US between November 2023 and January 2024 among individuals with mild cognitive impairment (MCI) due to AD, individuals with mild AD dementia, and care partners of individuals with MCI due to AD or mild AD dementia. Recruited patients (and patients for whom care partners were responding) had not previously received anti-amyloid IV therapy and were diagnosed ≥1 year before participation. Data captured from care partners were evaluated as proxy responses for the patients and were reported accordingly. **Results:** The study sample included N=404 respondents (N=153 patients and N=251 care partners), with an average patient age of 65.7 years and a mean time since diagnosis of 4.2 years. 61% (N=246) had been diagnosed with mild AD dementia, and 39% (N=158) had been diagnosed with MCI due to AD; respondents were diagnosed with a mean of 3.6 health conditions. Most patients (92%, N=371) had a care partner. Respondents were recruited from diverse US geographies: Northeast (26%), Midwest (19%), West (14%), and South (42%), and community types: urban (30%), suburban (36%), and rural (34%). Nearly half (45%, N=182/404) of patients do not plan to seek treatment or are unsure about seeking treatment with an anti-amyloid IV therapy, and more than three quarters (78%, N=315) would need support traveling to a treatment center. The most commonly-cited barriers resulting in patients not planning to receive anti-amyloid IV therapies include concerns about side effects (48%, N=195), cost of treatment (47%, N=189), fear/lack of comfort with receiving infusions (35%, N=146), fear/lack of comfort receiving a new treatment (28%, N=113), distance to an infusion center (27%, N=110), and cost of traveling to an infusion center (26%, N=106); overall, 72% (N=290) cited infusion-related concerns as barriers to receiving anti-amyloid IV therapy. Most patients (85%, N=342) indicated that a subcutaneous option would increase the likelihood that they would seek AD treatment. **Conclusion:** This research demonstrates substantial barriers to treatment with IV anti-amyloid β therapies. Route of administration is cited as one of the largest barriers by patients/care partners, but is addressable. Clinical research should focus on interventions that can be administered with lower care barriers, reduced frequency, and more accessible routes of administration and sites of care. These are critical considerations for ensuring new therapies are tailored to and accessible for this highly burdened population. **Keywords:** limitations of therapies, anti-amyloid limitations, patient concerns. **Disclosures:** This study is funded by Prothena Biosciences, Inc. Silber A, Athavale A, and O'Hara M are employees of Trinity Life Sciences, and Masterman D and Bajaj PS are employees of Prothena Biosciences, Inc.

P061- THE NANA STUDY: AUDITORY SIMULATION DURING SLEEP AS A SYMPTOMATIC TREATMENT FOR MILD COGNITIVE IMPAIRMENT. E. Jubera-García[1], S. Clemente Jiménez[1], G. Fierro[1], E. López-Larraz[1], D. Oriol[1], A. Robledo-Menéndez[1], J.M. Pérez-Trullén[2,3], E. Muñoz Farjas[4], P.J. Modrego[2,5], A. Lobo[2,6], J. De Francisco Moure[2,7], C. Almárcegui[2,7], J. Minguez[1], J.G. Klinzing[1] *(1. Bitbrain - Zaragoza (Spain), 2. Instituto de Investigación Sanitaria de Aragón - Zaragoza (Spain), 3. Servicio de neurología, Hospital Nuestra Señora de Gracia - Zaragoza (Spain), 4. Servicio de neurología, Hospital Clínico Universitario Lozano Blesa - Zaragoza (Spain), 5. Servicio de neurología, Hospital Universitario Miguel Servet - Zaragoza (Spain), 6. Department of Medicine and Psychiatry, Universidad de Zaragoza - Zaragoza (Spain), 7. Servicio de neurofisiología Clínica, Hospital Universitario Miguel Servet - Zaragoza (Spain))*

Background: Cognitive decline in mild cognitive impairment (MCI) and Alzheimer's Disease (AD) is linked to impairments of sleep [1]. On a neural level, two sleep-specific oscillations have been shown to be deteriorated: slow oscillations and sleep spindles [2]. These two brain rhythms are involved in sleep-associated memory consolidation [3] and their disruption is linked to memory decline and even structural changes in ageing and dementia. Interestingly, a technique called 'auditory stimulation during sleep' can be used to elicit slow oscillations and spindles. The procedure, in which short tones are played at specific time points during Non-Rapid Eye Movement (NonREM) sleep has been shown to improve declarative memory performance in healthy adults. The technique is non-invasive, does not disturb the participants, and tends to deepen sleep. Demonstrating positive effects on declarative memory consolidation in patients with mild cognitive impairment (MCI) would constitute a first step towards a potential non-pharmacological symptomatic treatment. Results might subsequently be extendable to patients who have progressed to dementia, such as Alzheimer's disease. **Methods:** In a pre-registered, double-blind placebo-controlled clinical trial, 34 patients with amnestic MCI (aMCI) will receive auditory stimulation during NonREM sleep in a controlled sleep laboratory environment. The intervention will be performed using a comfortable EEG headband developed for self-applied long-term use at home. A calibration night will be performed, in which the stimulation is personalized to each patient, based on the individual hearing threshold, spontaneous sleep rhythms, as well as neural responses to tones presented during sleep. In a balanced cross-over design, all patients will subsequently participate in one night under real and one night under sham stimulation. Memory tests before sleep, after sleep, and one week after the intervention will be performed to compare declarative memory consolidation during sleep between the stimulation conditions. We hypothesize an increase in sleep-associated memory consolidation in the stimulation condition as evidenced by higher post-sleep memory performance. **Results:** We have performed several pilot studies on healthy older adults and aMCI patients that have confirmed the feasibility of the approach. In these pilots, a total of 68 stimulation nights have been performed on 29 participants (14 of which were > 60 years old; 2 were diagnosed aMCI patients). The procedure robustly induced slow oscillations and spindles in all patients tested so far. The final clinical trial is planned to begin during the second half of 2024. **Conclusion:** This will be the first larger-scale investigation of potential memory benefits of auditory stimulation during sleep in patients with aMCI. If successful, our trials will be an important step in the development of the first effective non-pharmacological therapy

option for mild cognitive impairment. Moreover, it would kickstart follow-up long-term trials and studies on patients that have already progressed to dementia. **Keywords:** Mild cognitive decline, brain stimulation, sleep, declarative memory, memory consolidation. **Clinical Trial Registry:** In progress. **Data Deposition:** Will be performed at publication of the results. **Disclosures:** EJB, SCJ, GF, ELL, ARM, JM, and JGK are employed by the company Bitbrain. **References:** 1. Naismith, S. L., & Mowszowski, L. (2018). Sleep disturbance in mild cognitive impairment: A systematic review of recent findings. Current Opinion in Psychiatry, 31(2), 153–159. https://doi.org/10.1097/YCO.0000000000000397; 2. Mander, B. A., Winer, J. R., & Walker, M. P. (2017). Sleep and Human Aging. Neuron, 94(1), 19–36. https://doi.org/10.1016/j.neuron.2017.02.004; 3. Klinzing, J. G., Niethard, N., & Born, J. (2019). Mechanisms of systems memory consolidation during sleep. Nature Neuroscience, 22(10), 1598–1610. https://doi.org/10.1038/s41593-019-0467-3.

P062- PROSPECTS FOR THE TREATMENT OF ALZHEIMER'S DISEASE. A. Scarso[1], G. Santos[1], G. Almeida[1] *(1. Faculdade Sao Leopoldo Mandic de Araras, Medical School - Araras (Brazil))*

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder with no cure, marked by deterioration of memory and cognitive functions, as well as behavioral and neuropsychiatric changes (1). Its importance is based on the fact that it is the most common cause of dementia, accounting for 50 to 60% of cases (2). Worldwide, it is believed that there are more than 55 million people with dementia, which could rise to 139 million by 2050 (2). Its growing incidence represents a major public health problem (3, 4). As it is still a disease without a cure, the therapies currently available are aimed at relieving symptoms, with limited benefits in terms of cognitive function, without preventing the progression of the disease (1,5). The objective of this study, therefore, is to identify new therapeutic strategies for the treatment of Alzheimer's disease, highlighting the main advantages, mechanisms of action and probable risks of these developing technologies. **Methods:** A literature review on new drug therapeutic possibilities for the treatment of AD, carried out between April 2023 and June 2024, with a survey of scientific articles found in the PubMed database. Publications published less than 10 years ago were preferred. A total of 57 scientific articles were selected for analysis of 11 drugs: aducanumab, solanezumab, crenezumab, gantenerumab, donanemab, LMTM, neflamapimod, AADVAc1, CAD106, BACE inhibitors and cannabinoids. **Results:** Of the 11 drugs analyzed, 6 are monoclonal antibodies - of which 2 failed and 4 passed phase III clinical trials - and the rest are tau aggregation inhibitors (LMTM, phase III), selective p38α kinase inhibitors (neflamapimod, phase II), anti-Tau vaccines (AADVAc1, phase II), immunotherapy with active Aβ (CAD106, phase II), BACE1 inhibitors and cannabinoids. Monoclonal antibodies have generally shown good results in reducing cerebral amyloid load, but a variable incidence of cerebral edema and/or hemorrhage has been reported as relevant adverse events (6-35). LMTM showed a potential reduction in the rate of cognitive decline and brain atrophy in monotherapy (36-39). Neflamapimod can improve episodic memory in patients with mild AD and reduce pathological biomarkers in cerebrospinal fluid, despite the limitations of the studies (40-43). CAD106 and AADVAc1 showed a good immunogenicity and tolerability profile (44 - 52). Cannabinoids have a possible neuroprotective effect and BACE inhibitors have not had satisfactory results, with the presence of relevant adverse effects, such as elevated liver enzymes (53-63). **Conclusion:** Although the results of the clinical trials of most of the new drugs are encouraging, more studies are needed to prove the efficacy and safety of their use in patients with AD, as there is still no proven disease-modifying agent. **Keywords:** Alzheimer's disease, Beta amyloid peptides, Tau protein, Alzheimer's vaccines, Anticholinesterase drugs. **Disclosures:** There are no conflicts of interest on the part of the authors and co-authors.

LP025- PRECLINICAL EVIDENCE FOR ANTI-INFLAMMATORY AND IMMUNOMODULATORY EFFECTS OF NEURORESTORE ACD856, A TRK-PAM IN CLINICAL DEVELOPMENT FOR THE TREATMENT OF ALZHEIMER'S DISEASE. C. Parrado-Fernández[1,2], R. Gera[3], V. Lidell[1], A. Rasti[1], S. Mitra[3], M. Backlund[1], G. Nordvall[1,3], M. Jönsson[1,3], J. Sandin[1,4], M. Eriksdotter[3,5], P. Forsell[1,4] *(1. AlzeCure Pharma AB, Hälsovägen 7 - Huddinge (Sweden), 2. Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet - Stockholm (Sweden), 3. Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet - Stockholm (Sweden), 4. Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet - Stockholm (Sweden) - Stockholm (Sweden), 5. Theme Inflammation and Aging, Karolinska University Hospital - Stockholm (Sweden))*

Background: Neurotrophins like BDNF, NGF, NT-3, and NT-4/5 are essential for neuron development and survival, acting through Trk receptors (TrkA, TrkB, TrkC). They play key roles in neurodegenerative diseases, including Alzheimers Disease (AD), by supporting neuronal survival, plasticity, and cognition. NeuroRestore ACD856, developed by AlzeCure, is a positive allosteric modulator of Trk receptors, enhancing neurotrophin signaling. It has successfully completed phase I clinical trials, demonstrating very good safety and pharmacokinetics, and good CNS activity of ACD856. In in vivo models, ACD856 has demonstrated pro-cognitive effects, increased BDNF levels and long-lasting antidepressant-like effects. In vitro, ACD856 displayed enhanced neurite outgrowth and neuroprotective effects i.e. against Aβ toxicity, indicating both cognitive enhancing/symptomatic and disease-modifying properties. Given that NGF, BDNF, and their Trk receptors are not only expressed by neurons, but also immune cells, microglia, and astrocytes, and are involved in modulating immune function, i.e. enhancing B- and T-cell survival and regulating cytokine and antibody production, we aimed to explore ACD856's potential immunomodulatory and anti-inflammatory effects in AD and other age-related disorders. **Methods:** ACD856 was tested for effects on inflammatory processes in normal aged as well as APP mice. Aged male C57BL/6J mice (21-months-old) received daily subcutaneous ACD856 (5 mg/kg,n=12) or vehicle (n=11) for 28 days, with vehicle-treated 4-months-old mice as young controls. In the AD model, 24 female APP-knock in mice (APPNL-G-F mice) and 12 female wild-type C57BL/6JRJ 10-11 months old were given ACD856 (3 mg/kg,p.o.) or vehicle twice daily for 30 days. The health status and body weight were recorded every other workday. Both the plasma and brain were subsequently used for analysis of IgG, IgM and inflammatory markers determined by ELISA or western blot. **Results:** Treatment with ACD856 for 4 weeks significantly reduced the levels of the pro-inflammatory mediators IL-6 and IL-1β in brains of aged mice, which were significantly increased as compared to young animals. Both IgG

and IgM were also increased in the brain of old mice. Notably, ACD856 lowered light and heavy chain IgG protein levels in aged mouse brains. Likewise, total IgG showed a considerable rise in brain and plasma of aged mice that was substantially reduced by ACD856, while IgM remained unchanged. In APPNL-G-F mice, ACD856 also normalized increased brain IL-6 and plasma IgG levels to wild-type levels after 30 days of administration of the molecule, with no effect on IgM. This indicates that ACD856 may serve as an anti-inflammatory and immunomodulatory agent for AD and age-related diseases. **Conclusion:** The findings revealed a significant age and genotype effect on the immune response with old C57BL/6J mice and APPNL-G-F mice exhibiting higher levels of pro-inflammatory IL-6 and IL-1β cytokines and IgG and IgM when compared to respective control animals. Using NeuroRestore ACD856 to positively modulate Trk signalling we demonstrate a novel neuroprotective strategy by preventing altered secretion of inflammation-associated mediators. These findings suggest that ACD856 could play a novel anti-inflammatory and immunoregulatory role, alongside its cognitive-enhancing and disease-modifying effects, offering a promising strategy to slow neurodegeneration in AD and other diseases characterized by a neuroinflammatory component. **Keywords:** Neurotrophin, Trk-receptor, Inflammation, Immunoregulation. **Disclosures:** Authors CPF, VL, AR, MB, GN, MJ, JS and PF, are employees at AlzeCure Pharma.

LP026- BHV-8000, A SELECTIVE BRAIN-PENETRANT TYK2/JAK1 INHIBITOR IN DEVELOPMENT FOR NEUROINFLAMMATORY AND NEURODEGENERATIVE DISEASES, DEMONSTRATES FAVORABLE PK/PD AND SAFETY PROFILE IN PHASE 1 STUDIES. P. Ackerman[1], N. Kozauer[1], R. Bhardwaj[2], B. Shankar[1], B. Asware[1], R. Killingsworth[1], E. Ashbrenner[1], J.A. Malatesta[2], E. Thompson[1], D. Walters[1], A. Cheng[1], L. Lair[1], R. Bertz[1], B. Car[1], I. Qureshi[1], V. Coric[1] *(1. Biohaven Pharmaceuticals - New Haven (United States), 2. Certara - Radnor (United States))*

Background: Central and peripheral inflammation both play important roles in the onset and progression of neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's disease (PD) [1, 2, 3]. One potential explanation as to why previous therapeutic approaches targeting pathological immune responses in these disorders have failed is the inability of anti-inflammatory drugs to readily cross the blood-brain barrier and produce concentrations that achieve target engagement in the brain [4]. BHV-8000 is a novel, brain-penetrant, investigational oral small molecule highly selective against the TYK2 and JAK1 enzymes within the JAK-STAT pathway; avoiding the safety liabilities of JAK2 and JAK3. Notably, signaling through TYK2 and JAK1 is essential to the mixed inflammatory response that underlies the pathophysiology of AD and leads to the development of amyloid-related imaging abnormalities (ARIA)[5,6,7]. **Methods:** BHV8000-101 and -102 are Phase 1 double-blind, placebo-controlled studies conducted in healthy adults. The -101 study included 3 cohorts within both the single- and multiple-ascending dose (SAD: 10, 20, and 30 mg; MAD: 6, 10, and 20 mg) phases. The -102 study included one multiple-dose cohort (20 mg). Across all dose groups, 8 participants were randomized 3:1 to receive blinded BHV-8000 (extended-release formulation) or matching placebo. Multiple-dose cohorts received study drug once-daily for 14 and 7 days in the -101 and -102 studies, respectively. The primary objectives for each study were safety, tolerability, and pharmacokinetics (PK). Inflammatory biomarkers were measured in the -101 MAD phase and cerebrospinal fluid (CSF)-to-plasma concentration ratio was estimated in the -102 study. **Results:** The median Tmax ranged from 4-6 hours. The geometric mean t1/2 for BHV-8000 ranged from 11-14 hours. The accumulation ratio at steady state for AUC and Cmax was ~1.7-fold. The mean (CV%) CSF-to-plasma ratio at 6- and 24-hours post-dose was 0.43 (10.1) and 0.50 (13.3), respectively. Across the two Phase 1 studies, there were comparable rates of adverse events (AEs) between participants receiving BHV-8000 (~25%) and PBO (~33%). All AEs were mild in intensity except one (moderate headache in -102 participant receiving BHV-8000 20 mg). There were no serious AEs. In the -101 MAD phase, there was dose-associated lowering of the platelet count, consistent with known JAK1 class effects. All platelet decreases were limited to CTCAE Grade 1. There were no adverse trends across other laboratory parameters including hemoglobin, creatine kinase, or hepatic aminotransferases observed in either study. In the -101 MAD phase, reductions from baseline in inflammatory biomarkers (IP-10, hsCRP, and IFN-ß) were numerically greater for BHV-8000 treated participants compared to placebo. **Conclusion:** In these two Phase 1 studies, BHV-8000 was generally safe and well-tolerated, while demonstrating anti-inflammatory effects on biomarkers and a favorable PK profile in both the periphery and the CNS. These results support continued development of BHV-8000 for the treatment and prevention of a broad range of neuroinflammatory and neurodegenerative conditions, including specifically AD and ARIA. **Keywords:** Brain-penetrant small molecule, JAK-STAT inhibitor, AD disease modifying therapy and ARIA prevention, Phase 1 clinical trial. **Disclosures:** 1Employee and shareholder of Biohaven Pharmaceuticals **References:** Allen Reish, Standaert. J Parkinsons Dis. 2015;5(1):1-19. Pascoal et al. Nat Med. 2021;27(9):1592-1599. Chen et al. Nature. 2023;615(7953):668-677. Pardridge. Pharmaceuticals. 2020;13(11):394. Hampel et al. Brain. 2023;146(11);4414-24. Rodriguez et al. Nat Commun. 2021;12(1):1033. Nevado-Holgado et al. Cells. 2019;8(5):425.

LP027- BLOCKING THE FAM19A5-LRRC4B COMPLEX WITH AN ANTI-FAM19A5 ANTIBODY RESTORES LOST SYNAPSES AND REVERSES COGNITIVE DECLINE IN MOUSE MODELS OF ALZHEIMER'S DISEASE BLOCKING THE FAM19A5-LRRC4B COMPLEX WITH AN ANTI-FAM19A5 ANTIBODY RESTORES LOST SYNAPSES AND REVERSES COGNITIVE DECLINE IN MOUSE MODELS OF ALZHEIMER'S DISEASE. H.B. Kim[1], S. Yoo[1], H. Kwak[1], S.X. Ma[1], R. Kim[1], M. Lee[1], N. Ha[1], S. Pyo[1], S.G. Kwon[1], E.H. Cho[1], S.M. Lee[1], J. Jang[1], W. Kim[1], Y. Park[1], J.Y. Seong[1,2] *(1. Neuracle Science Co., Ltd. - Seoul (Korea, Republic of), 2. Department of Biomedical Sciences, Graduate School of Medicine, Korea University - Seoul (Korea, Republic of))*

Background: FAM19A5 is a secretory protein primarily expressed in neurons of the central and peripheral nervous systems [1, 2]. Although its role in synaptic function has been suggested [3], the precise molecular mechanisms underlying FAM19A5's effects at the synapse remain unclear. Given that synaptic loss is a critical hallmark of Alzheimer's disease (AD) and significantly contributes to cognitive deficits [4], elucidating the mechanisms involving FAM19A5 could provide valuable insights into reversing synaptic loss in AD. This study demonstrated that inhibiting FAM19A5 function with an anti-FAM19A5 antibody restores synaptic integrity and enhances cognitive function in AD, suggesting a novel

therapeutic strategy for AD. **Methods:** The binding partner of FAM19A5 was identified through Co-immunoprecipitation experiments of mouse brain tissue and immunocytochemistry performed on mouse hippocampal neurons. The role of FAM19A5 in reducing spine density in hippocampal neurons was evaluated by overexpressing FAM19A5, treating neurons with recombinant FAM19A5 protein, and/or using an anti-FAM19A5 antibody NS101. To confirm target engagement of NS101, we measured FAM19A5 levels in mouse CSF and serum, as well as human serum, at specific time points post-antibody injection using ELISA. Changes in spine density and dynamics in AD mouse models were assessed via Golgi staining and two-photon microscopy after systemic administration of NS101. The synaptic strengthening of hippocampal neurons in AD mice after NS101 treatment was assessed by measuring miniature excitatory postsynaptic currents (mEPSCs) and field excitatory postsynaptic potentials (fEPSPs). Cognitive performance in AD mice after NS101 treatment was measured using the Y-maze, passive avoidance, and Morris water maze tests. **Results:** FAM19A5 binds to LRRC4B, a postsynaptic adhesion molecule, leading to reductions in spine density in mouse hippocampal neurons. Inhibiting FAM19A5 function with NS101 increased spine density. Intravenous administration of NS101 increased spine density in the prefrontal cortex of P301S tauopathy mice, which initially showed reduced spine density compared to wild-type (WT) mice. NS101 normalized the spine elimination rate in P301S mice, restoring the net spine count to levels comparable to WT mice. Furthermore, NS101 treatment enhanced the frequency and amplitude of mEPSCs and fEPSPs in the hippocampal synapses of APP/PS1 amyloidopathy mice, leading to improved cognitive function. The observed increases in CSF and serum FAM19A5 levels upon systemic NS101 administration suggest that the antibody effectively engages its target and facilitates the transport of FAM19A5 from the brain. Clinical safety was confirmed with no serious adverse events and minimal anti-drug antibody activity. **Conclusion:** Targeting FAM19A5 may hold clinical promise for treating AD by restoring lost synapses. **Keywords:** FAM19A5, NS101, Synapse restoration, 1b/2a clinical trial. **Clinical Trial Registry:** NCT05143463; https://clinicaltrials.gov/study/NCT05143463. **Deta Deposition:** https://www.biorxiv.org/content/10.1101/2023.11.22.568357v2. **Disclosures:** HB.K, SJ.Y, HY.K, SX.M, RH.K, MH.L, N.H, EH.C, SM.L, JW.J, WK.K, YS.P, SI.P, SG.K and JY.S are employed by Neuracle Science, Co., Ltd. MH.L, SM.L, WK.K and JY.S are shareholders of Neuracle Science, Co., Ltd. The remaining authors have no conflicts of interest to declare. **References:** 1. Tom Tang Y et al. Genomics. 2004; 83:727–34. doi:10.1016/j.ygeno.2003.10.006; 2. Kwak H et al. 2020; 2020.02.19.955351. doi:10.1101/2020.02.19.955351; 3. Shahapal A et al. 2024; 2024.04.29.591582. doi:10.1101/2024.04.29.591582; 4. Tzioras M et al. Nat Rev Neurol. 2023; 19:19–38. doi:10.1038/s41582-022-00749-z.

LP028- COMPARISON OF VISUALLY EVOKED STEADY-STATE OSCILLATIONS BETWEEN TWO SPECTRIS™ EYESETS. J. Leach[1], B. Jackson[1], M. Hernandez[1], O. Rowe[1], K. Kolin[1], D. Grant[2], R. Fernandez-Romero[2], M. Hajós[1,3], C. Seshagiri[1] *(1. Cognito Therapeutics - Cambridge (United States), 2. University of Tennessee Medical Center - Knoxville (United States), 3. Yale University School of Medicine - New Haven (United States))*

Background: Sensory-evoked steady-state gamma oscillation has been recognized as a potential treatment for Alzheimer's disease (AD). A recent clinical trial (Overture, NCT03556280) evaluating the Spectris™ medical device (Cognito Therapeutics, Inc., Cambridge, MA, US), which elicits steady-state gamma oscillations via visual and auditory stimulation as confirmed by EEG, demonstrated reduced decline in cognitive and functional abilities as well as reduced brain atrophy in participants with mild-to-moderate AD. Here, the power of visually evoked gamma oscillations between Spectris™ eyesets with different levels of visibility were compared in a study of cognitively healthy older adults along with an interim comparison in an ongoing AD study (NCT05206305). **Methods:** Sensory-evoked steady-state gamma response was measured via EEG in 31 cognitively healthy older adults (mean age 59.7 ± 8.3 years, 52% female) and 14 participants with mild-to-moderate AD (mean age 70.9 ± 6.9 years, 50% female). Visual 40Hz stimulation was delivered continuously for 3 minutes using two different Spectris™ eyesets: one with low visibility that limits the participants' ability to see through the lenses, similar to the configuration used in the Overture trial, and one with high visibility that allows participants to view their environment; visual stimuli for both eyesets were presented at the same illuminance. EEG data was acquired with a 32-channel cap (ANT-Neuro) in the cognitively healthy cohort and a 128-channel cap (EGI) in the AD cohort. To compare the evoked gamma response between cohorts, the 128-channel data was reduced to match the 32-channel montage. The relative power at 40Hz was computed for each channel; as in the Overture trial, the evoked gamma response was sufficient if two or more channels per hemisphere exceeded threshold. The global gamma response was computed by averaging the relative power at 40Hz across all channels. In the cognitively healthy study, the global power was compared between the two eyesets using a paired t-test; global power was not compared in the AD cohort as the study is still ongoing. **Results:** In the cognitively healthy cohort, the evoked gamma response elicited by both eyesets (high-visibility: 6.27 ± 0.55 dB vs. low-visibility: 5.67 ± 0.57 dB [mean global power ± SE]) was similar ($p=0.185$) and exceeded the minimum required power. The AD cohort also demonstrated sufficient evoked gamma responses with both eyesets (high-visibility: 4.50 ± 0.52 dB vs. low-visibility: 5.53 ± 0.85 dB [mean global power ± SE]). In both cohorts, the mean global power evoked by either eyeset is higher than the average power of the AD cohort in the Overture trial (3.86 ± 0.25 dB [mean global power ± SE]). **Conclusion:** Here we demonstrate that both high- and low-visibility Spectris™ eyesets produce evoked gamma responses in both AD and control groups that meet previously applied criteria for target engagement. As the evoked gamma response provides the primary mechanism underlying the therapeutic effects of Spectris™, these results suggest interchangeability of Spectris™ eyesets with similar downstream clinical outcomes.

LP029- LOMECEL-B INHIBITION OF MMP14 ACTIVITY PREDICTS LOMECEL-B BIOACTIVITY IN THE TREATMENT OF MILD ALZHEIMER'S DISEASE. B. Rash[1], J. Botbyl[1], S. Kopcho[1], Z. Zainul[1], N. Agafonova[1], L. Mcclain-Moss[1], K. Ramdas[1], E. Naioti[1], B. Varnado[1], K. Peterson[1], M. Brown[1], T. Leal[1], R. Carballosa[2], P. Patel[3], M. Brody[3], B. Herskowitz[3], A. Fuquay[3], S. Rodriguez[3], J. Hare[1] *(1. Longeveron Inc - Miami (United States), 2. First Excellent Research - Miami (United States), 3. ERG Clinical - Miami (United States))*

Background: Alzheimer's disease (AD) is associated with amyloid and Tau pathology, progressive neuroinflammation, and brain atrophy. Lomecel-B is a novel cell-based therapy with

potential for clinical benefit in AD though immunomodulatory and pro-vascular effects, but precise molecular mechanisms of action remain controversial1-3. Matrix metalloprotease (MMP) activity is reportedly upregulated in AD4-7. We hypothesize that excess MMP14 activity may contribute to AD pathogenesis, at least in part, by cleaving TIE2 (Tyrosine kinase with Immunoglobulin and Epidermal growth factor homology domains), a cell-surface tyrosine kinase receptor for the angiopoietins, which activates downstream signaling pathways that regulate endothelial cell health and inflammatory responses8-10. We tested the hypothesis that Lomecel-B's capacity to inhibit MMP14, potentially through tissue inhibitor of metalloprotease (TIMP) secretion11, correlates with improved clinical and biomarker outcomes in mild AD. **Methods:** We measured MMP14 inhibitory (MMP14i) activity using an enzymatic assay, as well as TIMP2 and vascular endothelial growth factor A (VEGF-A) levels in supernatant from the Lomecel-B lots (N=8) used in the CLEAR-MIND trial (N=49) of Lomecel-B in patients with mild AD. Data from Lomecel-B supernatant were normalized according to cell density. **Results:** Supernatant from Lomecel-B clinical lots contained MMP14i activity (median 1.90 x 10-7 %/cell/L), high levels of TIMP2 (median 2.43 x 10-7 ng/cell/L) and VEGF-A protein (mean 3.87 x 10-5 ng/cell/L). Patients receiving Lomecel-B lots with above-median MMP14i activity demonstrated enhanced responses vs. placebo on the composite Alzheimer's disease score (CADS, the study secondary endpoint) than those who received below-median potency lots (high: N=13; p=0.031; low: N=19; p=0.360). Similar associations were evident with responses in the MoCA, ADCS-ADL, and left hippocampal volume. High MMP14i lots were also more effective in suppressing elevations in soluble TIE2 in study patients, suggesting a potential downstream effect of MMP14i in AD. MMP14i correlated with TIMP2 (R2=0.82; N=8; p=0.001) and VEGF-A (R2=0.69; N=8; p=0.011) in Lomecel-B supernatant. **Conclusion:** Together these findings suggest that ability to exert MMP14 inhibition through TIMP2 secretion may protect TIE2 receptor integrity and underlie, at least in part, the immunomodulatory and pro-vascular effects of Lomecel-B in mild AD. The findings offer potential mechanistic and clinical insights in the development of cellular-based therapy for AD. **Keywords:** Mesenchymal stem cell, mesenchymal stromal cell, medicinal signaling cell, Lomecel-B. **Clinical trial registry:** ClinicalTrials.gov NCT05233774. **Disclosures:** Joshua Hare, MD, is a co-founder and equity owner in Longeveron Inc (LGVN). Dr. Hare is an inventor of technologies licensed from the University of Miami to Longeveron Inc. **References:** 1. Brody M, Agronin M, Herskowitz BJ, et al. Alzheimers Dement 2023;19(1):261-273. DOI: 10.1002/alz.12651. 2. Oliva AA, McClain-Moss L, Pena A, Drouillard A, Hare JM. Aging Med (Milton) 2019;2(3):142-146. DOI: 10.1002/agm2.12079. 3. Pittenger MF, Discher DE, Peault BM, Phinney DG, Hare JM, Caplan AI. NPJ Regen Med 2019;4:22. DOI: 10.1038/s41536-019-0083-6. 4. Martins D, Moreira J, Goncalves NP, Saraiva MJ. Dis Model Mech 2017;10(10):1253-1260. DOI: 10.1242/dmm.028571. 5. Liao MC, Van Nostrand WE. Biochemistry 2010;49(6):1127-36. DOI: 10.1021/bi901994d. 6. Yamada T, Yoshiyama Y, Sato H, Seiki M, Shinagawa A, Takahashi M. Acta Neuropathol 1995;90(5):421-4. DOI: 10.1007/BF00294800. 7. Llorente P, Martins S, Sastre I, et al. Oxid Med Cell Longev 2020;2020:5917187. DOI: 10.1155/2020/5917187. 8. Idowu TO, Etzrodt V, Seeliger B, et al. Elife 2020;9. DOI: 10.7554/eLife.59520. 9. Joussen AM, Ricci F, Paris LP, Korn C, Quezada-Ruiz C, Zarbin M. Eye (Lond) 2021;35(5):1305-1316. DOI: 10.1038/s41433-020-01377-x. 10. Reusch P, Barleon B, Weindel K, et al. Angiogenesis 2001;4(2):123-31. DOI: 10.1023/a:1012226627813. 11. Lozito TP, Tuan RS. J Cell Physiol 2011;226(2):385-96. DOI: 10.1002/jcp.22344.

LP030- EMERGING NON-INVASIVE BRAIN STIMULATION TECHNIQUES FOR ALZHEIMER'S TREATMENT: CURRENT STATE AND FUTURE DIRECTIONS. G. Blivet[1], T. Sacrez[2], G. Temiz[3], M. Weiner[4], M. Sabbagh[5], J. Touchon[2], J. Cummings[6] *(1. REGEnLIFE - Paris (France), 2. University of Montpellier - Montpellier (France), 3. TheraPanacea - Paris (France), 4. University of San Francisco - San Francisco (United States), 5. Barrow Neurological Institute - Phoenix (United States), 6. University of Nevada, Las Vegas - Las Vegas (United States))*

Background: Recent FDA approvals of anti-amyloid antibodies have advanced Alzheimer's disease (AD) treatment. Because AD is a complex, multifaceted disease with multiple pathological processes involved in its development and progression, combination treatments are expected to evolve. In this context, non-pharmacological interventions are gaining prominence as potential key components of a comprehensive combination treatment plan. Among these, non-invasive brain stimulation (NIBS) approaches are subject to growing clinical evaluation. Consequently, a critical review of their current state in AD treatment is both timely and crucial. This systematic analysis aims to elucidate the current state of NIBS targeting AD, providing a critical assessment of their potential integration into AD combination treatment strategies. **Methods:** A systematic literature search, limited to articles published from 2014, was conducted on PubMed using specific keywords related to Alzheimer's disease and NIBS techniques: transcranial magnetic stimulation (rTMS), transcranial electric stimulation (TES), focused ultrasound (FUS), gamma visual and auditory stimulation (GVAS), transcranial photobiomodulation (tPBM), and transcranial electromagnetic treatment (TEMT). Initial screening of 388 articles based on titles and abstracts excluded non-relevant cohorts, pharmacological treatments, and invasive procedures. A secondary screening of the remaining 64 articles applied additional exclusion criteria: unavailable full texts, animal studies, sleep or pain-focused studies, letters, reviews, studies focusing solely on cognitive training, lack of NIBS-related outcomes, irrelevant cohorts, protocols only, and ongoing trials without results. The measures used for assessment in each study were also screened to ensure relevance and comparability. Finally, 27 articles were selected and analysed. **Results:** The review identified six NIBS technologies evaluated for Alzheimer's disease treatment. rTMS was the most frequently studied (40.7%), followed by TES (18.5%), FUS (11.1%), GVAS (7.4%), tPBM (7.4%), and TEMT (3.7%). Studies averaged 39 participants with a mean treatment duration of 12 weeks (median 6 weeks), indicating early-stage efficacy research. Most studies reported promising results and high tolerability, with adherence rates exceeding 80%. **Conclusion:** This systematic review highlights the growing interest in NIBS medical devices as potential therapy for Alzheimer's disease (AD). While current studies are primarily in early efficacy stages, the promising results and high tolerability observed across multiple NIBS modalities warrant further investigation. The high adherence rates suggest that NIBS could be a well-tolerated, non-pharmacological option in AD management. However, future research should prioritize robust methodologies, including standardized protocols and larger, well-characterized cohorts, to enhance the reliability and generalizability of findings. Critical areas of focus should

include assessing long-term outcomes and exploring side effects and efficacy differences between novel anti-amyloid therapies and NIBS. These efforts will help establish the optimal parameters for each NIBS technique and determine their efficacy as an AD treatment and an essential component of the future combination therapy in AD. **Keywords:** Alzheimer's disease, brain stimulation, neurostimulation, neuromodulation, non-pharmacological, non-invasive. **Disclosures:** GB is an employee of REGEnLIFE and owns equity. GT is an employee of TheraPanacea. JT has provided consultation to Medesis Pharma, REGEnLIFE, Ariana Pharmaceuticals. MS has provided consultation to Roche-Genentech, Eisai, Lilly, NeuroTherapia, Signant Health, Novo Nordisk, Prothena, Anavex, Cognito Therapeutics, GSK, Abbvie. MS has stocks/options in OAthira, Lighthouse Pharmaceuticals. MS is a member of EIP Pharma/CervoMed Board of Directors. JC has provided consultation to Acadia, Acumen, ALZpath, Annovis, Aprinoia, Artery, Biogen, Biohaven, BioXcel, Bristol-Myers Squib, Eisai, Fosun, GAP Foundation, Green Valley, Janssen, Karuna, Kinoxis, Lighthouse, Lilly, Lundbeck, LSP/eqt, Merck, MoCA Cognition, New Amsterdam, Novo Nordisk, Optoceutics, Otsuka, Oxford Brain Diagnostics, Praxis, Prothena, ReMYND, Roche, Scottish Brain Sciences, Signant Health, Simcere, Sinaptica, TrueBinding, and Vaxxinity pharmaceutical, assessment, and investment companies. JC owns the copyright of the Neuropsychiatric Inventory. JC has stocks/options in Artery, Vaxxinity, Behrens, Alzheon, MedAvante-Prophase, Acumen. JC is supported by NIGMS grant P20GM109025; NIA grant R35AG71476; NIA R25 AG083721-01; Alzheimer's Disease Drug Discovery Foundation (ADDF); Ted and Maria Quirk Endowment; Joy Chambers-Grundy Endowment.

LP031- PHASE 2A CLINICAL TRIAL SUPPORTS THERAPEUTIC EFFICACY OF SEPTIN MODULATION IN MILD-TO-MODERATE ALZHEIMER'S PATIENTS.

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Background: Calcium dyshomeostasis plays a central role in Alzheimer's disease (AD) pathophysiology [1]. Septin filaments regulate calcium homeostasis in neurons by controlling store-operated calcium (SOC) channels [2]. In AD, pathological tau impairs structure and function of these filaments leading to excessive SOC channel activity and consequently to neurotoxic calcium concentration in the cytosol. REM0046127 is a small molecule drug that acts as a molecular glue restoring the integrity of septin filaments, thereby normalizing calcium homeostasis, without impacting physiological calcium signaling [2]. In AD mouse models, administration of REM0046127 is neuroprotective, restores synaptic function and cognition, and mitigates amyloid-beta protein (Ab) and tau pathology. A phase 2 clinical trial was carried out to assess safety and efficacy in AD patients. **Methods:** A randomized, placebo-controlled, double-blind Phase 2a study was conducted to evaluate the safety, tolerability, pharmacokinetics and PK/PD effects of REM0046127 in participants with mild to moderate AD. The treatment included a 14-day placebo run-in period, followed by a 28-day treatment with placebo (n=4) or REM0046127 administered at the following doses: 1400 (n=2), 350 (n=2) and 88 (n=5) mg/day. Endpoints to quantify PK, safety and efficacy relative to baseline were assessed. **Results:** In a subset of participants, Drug Induced Liver Injury (DILI) was observed after 3-4 weeks which led to premature discontinuation of the study. All available data of the participants who had completed the 28-day treatment were analysed. REM0046127 concentration in CSF was consistent with full target engagement at all doses, allowing combined analysis of all dose groups as one verum group. Analysis of this limited population revealed a significant improvement on memory retrieval, normalization of EEG activity and an increase of neurotransmitter dopamine in the CSF. Comparison with reference data of healthy subjects indicated large effect sizes. In addition, CSF levels of phospho-tau181 and total tau were decreased in the verum group indicating a potential disease-modifying effect. **Conclusion:** Under the conditions of this study, treatment with REM0046127 for 28 days improved activity and function of neuronal pathways underlying memory in AD patients. Markers of AD tau pathology were also mitigated by the compound, indicating that restoration of septin filaments confers, besides fast symptomatic benefit, also potential disease-modifying effects. These findings highlight the therapeutic potential of septin modulators for AD patients. The occurrence of DILI with REM0046127 warrants follow-up studies with an optimized lead compound in patients. **Keywords:** Clinical trial, septin, disease-modification, symptomatic benefit. **Clinical Trial Registry:** NCT0547803, https://clinicaltrials.gov/. **Disclosures:** GG, MF, KP and ED own shares and/or warrants of reMYND. JC has provided consultation to reMYND. **References: 1.** Webber et al. Alzheimer's Dement. 2023; 19: 3701–3717. https://doi.org/10.1002/alz.13065; 2. Princen et al. Science 2024; 384: 6260. 10.1126/science.add6260.

LP034- USE OF RESVERATROL TO PREVENT MILD COGNITIVE DECLINE AND ALZHEIMER'S DEMENTIA.

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Studies point to the importance of new treatments for the prevention of mild cognitive decline, focusing on reducing the activity of phospholipase A2 (PLA2) and the hypotheses of the amyloid and cholinergic cascade. In this context, resveratrol, a polyphenol found in the peels of jabuticaba, a type of berry found only in Brazil, has been studied for its therapeutic properties.Preliminary results indicate that resveratrol exerts significant neuroprotective effects, suppressing the formation of free radicals, modulating the metal ionic balance in the brain and activating SIRT1, in addition to interfering with signaling pathways such as NFκB and STAT, reducing neuronal inflammation. Resveratrol exhibits strong antioxidant properties, as demonstrated by in vitro and in vivo studies. Oxidative stress occurs due to an imbalance between pro-oxidant and antioxidant activities in the body, leading to excessive production of ROS, free radicals and peroxides. Brain tissue is more susceptible to oxidative stress due to its higher rate of oxygen consumption, high content of peroxidizable fatty acids, and low amounts of antioxidants.activation of microglia, astrocytes, lymphocytes and macrophages releases pro- and anti-inflammatory mediators. Amyloid β peptides activate microglia via TLR4. Resveratrol has anti-inflammatory action, preventing the activation of macrophages and microglia induced by LPS and Aβ, interfering with signaling pathways such as NFκB and STAT. Studies show that resveratrol reduces microglial activation, modulates NF-κB, reducing iNOS, PGE2, cathepsin and NO. It also reduces astroglial and microglial activation and regulates iNOS and COX-2. Its neuroprotective

effects include reducing lipid peroxidation, protecting against brain mitochondrial deletion, and improving learning and memory. The studies also point to the need for additional information on the bioavailability, stability and safety of resveratrol. Our study deals with the use of Jabuticaba extract, rich in Resveratrol, in participants with and without mild cognitive decline, in a randomized manner, for subsequent analysis of cognitive profiles that can confirm neuroprotection.

LP035- LECANEMAB EXPERIENCE AND ARIA OBSERVATIONS AT A LARGE COMMUNITY-BASED HEALTH CARE SYSTEM. Shawn Kile[1], Armen Moughamian[2], Jane Kim[2], Chen Zhao[1], Travis Urban[2], Lisamarie La Vallee[3], Govind Mukundan[4], Mary Vaughn[1], Janet Horel[1], Sylvia Sudat[5], *(1. Sutter Neuroscience Institute-Memory Clinic, 2. Ray Dolby Brain Health Center, Sutter Health, 3. Sutter Health Neuroscience Service Line, 4. Sutter Diagnostic Imaging, 5. Sutter Health Center for Health Systems Research))*

Background: Lecanemab received accelerated approval January 2023 and full FDA approval July 2023 [1]. Amyloid monoclonal antibody treatments, like lecanemab, have been associated with side-effects including ARIA (amyloid related imaging abnormalities) and death, requiring careful screening and monitoring, which can be logistically challenging [2, 3]. [2]Sutter Health, a community-based health care system caring for 3.5 million people in California, has two Memory Centers with 5 memory specialists and >100 neurologists throughout the system. Here we summarize our experience with this new medication. **Methods:** This data collection was approved by the Sutter Health institutional review board. All subjects were screened at either a specialized memory clinic or through the Advanced Therapeutics for Alzheimer's Disease (ATAD) Review Board. Eligibility for lecanemab treatment was determined by the FDA labelling without exception and Appropriate Use Recommendations were followed as a guideline with very few exceptions. All subjects had biomarker confirmation of AD with either CSF or amyloid PET. APOE genotyping was completed with all candidates. MRI monitoring for ARIA was scheduled per guidelines; MRI prior to 26th infusion was only completed in select higher-risk patients. **Results:** 234 patients have been infused with lecanemab within Sutter Health; 210 through the one of the two memory clinics and 24 through the ATAD review board. 14 patients were APOE 4 homozygotes and 133 APOE 4 heterozygotes. The mean age was 75 years. 70% had MCI and 30% had mild dementia. 31% experienced infusion related reactions. 10.6% discontinued due to the following reasons: side-effects/tolerability issues; ARIA; progression to moderate stage; other active medical illness unrelated to lecanemab. There were two deaths of lecanemab treated patients, both determined to be unrelated to treatment. There were 27 cases of ARIA; 6 were APOE 4 homozygotes. 15 ARIA-E (6.4%); 23 ARIA-H (9.8%); 11 with both ARIA E + H (4.7%). Seven were considered severe; 3 of these severe cases were symptomatic (confusion and headache in all cases); 3 patients had macrohemorrhages; there were no residual neurological deficits except one patient with quadrantanopia. A majority of ARIA occurred in the posterior cortex, especially the occipital lobes. ARIA-H often occurred in the same region of ARIA-E. Most cases of ARIA were observed on the MRI prior the 5th infusion. ARIA-E usually resolved after 3 months of monitoring. Interestingly the 3 macrohemorrhages occurred after a delay of 4-12 weeks after stopping lecanemab due to ARIA. **Conclusion:** Careful selection using FDA and Appropriate Use Recommendations at two specialized memory clinics as well as the use of a review board model for general neurologists with the health care system was associated with efficient and safe access to lecanemab, including lower ARIA rates than in the phase 3 study and no deaths associated with treatment. Observations of the characteristics of ARIA also help us anticipate and hone our understanding of this salient side-effect. **Disclosures:** Armen Moughamian has consulted for Eisai and is part of the lecanemab speaker bureau. All other authors declared no competing interests. **References:** 1. US Food and Drug Administration. Lecanemab-irmb injection, full prescribing information; 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269s000lbl.pdf. 2. van Dyck, CH, et al. N Engl J Med 2022; https://doi.org/10.1056/NEJMoa2212948. 3. Cummings, J., et al. J Prev Alz Dis 2023; 10(3): 362–377. https://doi.org/10.14283/jpad.2023.30.

BEYOND AMYLOID AND TAU

P063- NOVEL BLOOD-BASED MITOCHONDRIAL BIOMARKERS FOR THE PROGNOSIS OF PROGRESSION FROM MILD COGNITIVE IMPAIRMENT TO ALZHEIMER'S DISEASE DEMENTIA. J.L. Mosquera[1], M. Blanch[1], N. Rojo[2], J. Campdelacreu[2], J. Bello[3], A. Lleo[4], P. Martínez-Lage[5], A. Tort-Merino[6], R. Sanchez-Valle[6], C. Cruchaga[7], C. Fowler[8], S. Laws[9], C. Mehanian[10], J. Gascon-Bayarri[2], M. Barrachina[1] *(1. ADmit Therapeutics - Barcelona (Spain), 2. Bellvitge University Hospital-Bellvitge Biomedical Research Institute-IDIBELL - Barcelona (Spain), 3. Complex Hospitalari Moisès Broggi. L'Hospitalet/Sant Joan Despí - Barcelona (Spain), 4. Institut de Recerca Sant Pau - Hospital de Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain. Centro de Investigación Biomédica en Red en Enfermedades Neurodegenerativas (CIBERNED) - Barcelona (Spain), 5. Center for Research and Memory Clinic. CITA-alzheimer Foundation - San Sebastián (Spain), 6. Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona - Barcelona (Spain), 7. Washington University School of Medicine - Sant Louis (United States), 8. The Florey Institute, The University of Melbourne - Melbourne (Australia), 9. Collaborative Genomics and Translation Group, Centre for Precision Health, School of Medical and Health Sciences, Edith Cowan University - Joondalup (Australia), 10. University of Oregon and Global Health Labs - Eugene (United States))*

Background: Prediction of progression to Alzheimer's Disease Dementia (ADD) from Mild Cognitive Impairment (MCI) is an unmet medical need. Several studies have reported mitochondrial dysfunction in AD at cerebral and systemic levels, reinforcing the idea that it is one of the first events that triggers the AD etiopathogenesis. Mitochondria is a cellular organelle that contains its own DNA, the mitochondrial DNA (mtDNA). Our proof of concept showed an altered mtDNA methylation pattern along AD progression in human post-mortem brains. Similar results have also been described in AD blood and plasma cell-free DNA samples by other authors. ADmit has developed an epigenetic Next-Generation Sequencing approach for identifying differential mtDNA methylation patterns in blood samples from MCI patients. The methylation measures, along with non-invasive clinical features, have been integrated into a classification model that predicts the probability of progression to ADD. **Methods:** A total of 600 subjects were recruited from seven cohorts, Hospital Universitari Bellvitge (n=125), Hospital Clínic Barcelona (n=79), Hospital Santa Creu i Sant Pau (n= 5); Hospital General de L'Hospitalet (n=4); AIBL (n=248), Fundación CITA-Alzhéimer,

(n=75), and Knight Alzheimer Disease Research Center (n=64). Our current classifier model is based on age, CDR-SOB, and APOE genotype as clinical variables, and over 200 methylation features generated using the MiSeq Illumina platform. Each feature represents the methylation cytosine frequency within CpG, CHG, and CHH contexts across D-loop, and ND1 mitochondrial loci. Only blood samples collected at the baseline visit from Cognitively Normal (CN, CDR=0) and MCI patients (CDR=0.5) were analyzed. An MCI patient was considered to progress to ADD when one of the following criteria was met: CDR change from 0.5 to ≥1, or ≥2-point deterioration in CDR-SOB from baseline, or ≥1-point deterioration in at least four instrumental activities of daily living measured by the FAQ adaptation questionnaire. A Random Forest (RF) model was trained using supervised learning. Optimal hyperparameters were determined using a triply repeated 10-fold cross-validation process. The final RF model was trained on the entire training subset using the optimized hyperparameters. **Results:** Three groups of subjects were considered: CN (n=168, CDR=0, MMSE=28.97±1.20, age 66±6, CDR-SOB=0, 22.62% E4-carriers, and clinical follow-up between 5.4-15 years); MCI Non-progressed to ADD (n=125, CDR=0.5, MMSE=27.18±1.97, age 71±7, CDR-SOB=1.18±0.97, 29.6% E4-carriers, and clinical follow-up between 3-16 years); and MCI progressed to ADD (n=307, CDR=0.5, MMSE=25.92±2.78, CDR-SOB=2.04±1.23, age 73±6, 57.33% E4-carriers and progressed to ADD between 1-14 years). Data was split in two subsets: training (481 subjects) and testing (119 subjects). The RF training process showed an averaged Accuracy=0.844 and Kappa=0.739 (averages taken over cross-validation folds). The final model's performance on the testing subset resulted in an overall Accuracy=0.832 (CI95% 0.752-0.894), Kappa=0.711, Sensitivity=0.951, Specificity=0.707, PPV=0.773, NPV=0.932, and F1-score=0.853. The AUC-ROC curve for MCI progressed versus the Rest in the testing subset is 0.903 (CI95% 0.847-0.903). **Conclusion:** ADmit's technology is a cutting-edge technology, that integrates novel blood-based mitochondrial biomarkers and non-invasive clinical features. It represents a useful tool for predicting ADD at MCI stage, optimizing patient stratification and in turn significantly improving AD clinical trials success rate.

P064- MISFOLDING OF ALPHA-SYNUCLEIN AS A DIRECT BIOMARKER FOR PARKINSON'S DISEASE AND SYNUCLEINOPATHIES. K. Gerwert[1] *(1. Ruhr-University Bochum - Bochum (Germany))*

Background: We conducted a discovery and validation study for the investigation of the potential of alpha-synuclein-misfolding as biomarker for Parkinson´s disease (PD) and multiple system atrophy (MSA). 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 [1–4]. **Methods:** For these studies, we analyzed 134 CSF samples from patients with idiopathic and atypical parkinsonian disorders as well as controls consisting mainly of individuals with headache or normal pressure hydrocephalus. For this purpose, we recruited samples from five medical centers. Alpha-synuclein-misfolding was determined by the immuno-infrared-sensor (iRS) indicating protein-biomarker misfolding complementary to concentration changes [1]. **Results:** In our discovery study, we achieved an AUC of 0.92 for the discrimination of PD and non-neurodegenerative controls. In a validation study, we performed a single-center study with of a different cohort. Here we achieved an AUC of 0.88 for the discrimination of alpha-synuclein misfolding positive versus negative cases. The discriminative power could be further increased up to 0.94 by subdividing individuals into high, intermediate, and low according to their misfolding status, like a traffic light scheme. **Conclusion:** We present for the first time a direct alpha-synuclein-misfolding-biomarker in CSF which can discriminate synucleinopathies like PD and MSA from atypical syndromes and other controls. This allows a precise stratification of early-stage-individuals for targeted therapeutic interventions. **Keywords:** body fluid, Alzheimer, Parkinson, ALS, biomarker. **Disclosures:** Klaus Gerwert is founder and CEO of the betaSense GmbH. **References:** [1] Nabers A, et al. J Biophotonics 2016;9(3):224–34. [2] Nabers A, et al. EMBO Mol Med 2018;10(5).[3] Stockmann J, et al. Alzheimer's research & therapy 2020;12(1):1–13. [4] Beyer L, et al. Alzheimers Dement. 2022 Jul 19. doi: 10.1002/alz.12745.

P065- PHENOME-WIDE MENDELIAN RANDOMIZATION ANALYSIS REVEALS SHARED CAUSAL RISK FACTORS AMONG ALZHEIMER'S DISEASE, VASCULAR DEMENTIA, AND STROKE. C.H. Kim[1], J.H. Kim[2], H.S. Kim[2] *(1. Hallym University Sacred Heart Hospital - Anyang (Korea, Republic of), 2. Ilsan Hospital, National Health Insurance Service - Goyang (Korea, Republic of))*

Background: Alzheimer's Disease (AD) shares a similar risk profile with stroke and vascular dementia (VD). Especially causal similarities among these conditions may provide novel therapeutic insights. In this study, we aimed to explore the common causal risk factors for AD, VD, and stroke using a phenome-wide Mendelian randomization (PheW-MR) approach. **Methods:** A two-sample MR design was used to analyze genetic data from large-scale genome-wide association studies (GWAS). We utilized the summary statistics of AD, VD, and stroke and 24,632 phenotype information from MRBase, incorporating MR methods such as the MR Egger, weighted median, inverse-variance weighted, simple mode, and weighted mode. A PheW-MR p value of 7 x 10–5 (FDR p < 0.01) was considered significant. **Results:** Common genetic risk factors among AD, VD, and stroke included body mass index, cholesterol levels, genetic variations related to Apolipoprotein B (involved in lipid metabolism), and increased susceptibility to specific cancers (lung and ovarian). Additionally, shared risk factors for gout and chronic obstructive pulmonary disease suggested a potential role of inflammation and autoimmunity in the development of these conditions. Notably, when stratified by stroke subtypes (large artery, small vessel, and embolic), the strongest genetic overlap was observed between AD and large artery stroke, implying shared mechanisms between these specific conditions. **Conclusion:** Our findings contribute to the understanding of the causal associations among AD, VD, and stroke. By identifying these common causal factors, this study may pave the way for novel treatment strategies and drug repurposing opportunities for these three conditions. **Keywords:** Mendelian randomization, Alzheimer's disease, Vascular dementia, Stroke. **Disclosures:** The authors declare no conflicts of interest.

P066- THE N-GLYCAN STRUCTURE BISECTING N-ACETYLGLUCOSAMINE PREDICTS COGNITIVE DECLINE IN PATIENTS FROM A MEMORY CLINIC COHORT. R. Zhou[1], B. Winblad[1], L.O. Tjernberg[1], S. Schedin Weiss[1] *(1. Karolinska Institutet - Solna (Sweden))*

Background: N-glycosylation of proteins is altered in Alzheimer disease (AD) and the specific N-glycan structure

bisecting N-acetylglucosamine (bisecting GlcNAc) is elevated in AD [1, 2]. The levels of bisecting GlcNAc correlate with levels of phosphorylated Tau (pTau) and total tau (tTau) in cerebrospinal fluid (CSF) already at the subjective cognitive impairment (SCI) stage [1]. Interestingly, our recent study from a longitudinal cohort demonstrated that bisecting GlcNAc correlates with tTau also in blood and that the tTau/bisecting GlcNAc ratio can predict progression to memory decline and dementia a decade before onset of the disease [3]. Here we analyzed bisecting GlcNAc in a memory clinic cohort. **Methods:** CSF levels of bisecting GlcNAc were analyzed by a lectin-based multiwell-plate assay in 251 individuals from the GEDOC cohort, consisting of patients from the memory clinic at Karolinska University Hospital, Sweden. Individuals with higher bisecting GlcNAc levels than average were considered bisecting GlcNAc positive. Patients were classified as amyloid/tau positive or negative based on CSF biomarkers. Cognitive decline, measured by longitudinal Mini-Mental State Examination scores, was followed for an average of 11 ± 4.1 years, and modelled using non-linear mixed effects models. In addition, the distribution of bisecting GlcNAc in postmortem AD brain was measured by lectin-based histochemistry in ten Alzheimer's disease and ten control brains. **Results:** High CSF levels of bisecting GlcNAc predicted earlier cognitive decline in the whole sample. Strikingly, stratification of the samples based on amyloid or tau positivity demonstrated that high levels of bisecting GlcNAc predicted earlier cognitive decline in amyloid negative ($\beta = 2.53 \pm 0.85$ years, $p = 0.003$) but not in amyloid positive patients and in tau negative ($\beta = 2.43 \pm 1.01$ years, $p = 0.017$) but not in tau-positive patients. Finally, histochemical analysis showed increased levels of bisecting GlcNAc in neurons in hippocampus of Alzheimer's disease compared to control brain (fold change = 1.48 – 1.49, $p < 0.001$). **Conclusion:** The bisecting GlcNAc N-glycan structure predicted cognitive decline, especially in amyloid negative and tau negative individuals. Thus, we suggest that this glycan epitope may be altered before amyloid and tau pathology is present and is useful as an early biomarker for AD. **Keywords:** N-glycosylation, Bisecting N-acetylglucosamine, cerebrospinal fluid **Disclosures:** We have nothing to disclose. **References:**
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P067- A PHASE III, RANDOMIZED, DOUBLE-BLINDED STUDY OF THE EFFICACY AND SAFETY OF LEVETIRACETAM TO PREVENT SEIZURES IN SYMPTOMATIC ALZHEIMER'S DISEASE IN ADULTS WITH DOWN SYNDROME: THE LESS-AD TRIAL.

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Background: People with Down syndrome (DS) have a greater predisposition to Alzheimer's disease (AD) and epilepsy than the general population. There is a strong association between these entities, so that as dementia progresses, the development of seizures is more frequent, and conversely epilepsy could accelerate neurological deterioration. Suppression of neural hyperexcitability by drugs such as levetiracetam (LEV), one of the most widely-used anti-seizure medication that has been reported to suppress epileptiform spikes and improve synaptic and cognitive function in mouse models of AD, could improve cognitive dysfunction and overall health outcomes in people with DS associated AD. **Methods:** We present a multi-center, double-blind, placebo-controlled, randomized (1:1) clinical trial on the efficacy and safety of LEV 500mg/12h in 120 patients with DS and AD without epilepsy that will start in mid 2024. The primary objective is to test safety (in terms of incidence of adverse events) and efficacy (in terms of incidence of bilateral tonic-clonic epileptic seizures) in the LEV vs. placebo groups. Secondary objectives include the comparison of time to first bilateral tonic-clonic seizure, the incidence of all-cause mortality and changes on AD-related biomarkers (functionality, cognition, plasma biomarkers -pTau181 and NfL, brain structure- brain MRI, and epileptiform activity- EEG) between LEV and placebo groups. All participants will be monitored for a total of 2 years for the occurrence of bilateral tonic-clonic seizures, all-cause mortality and adverse events. In addition, changes in neuropsychological, serological, imaging and neurophysiological AD-related biomarkers will be collected. **Results:** The trial will start on the third trimester of 2024. **Relevance**: This trial will test the hypothesis whether LEV is safe and can prevent seizures in subjects with DS associated AD and, secondarily, delay the progression of neuronal damage and/or cognitive decline in these individuals. **Funding support**: Study ICI23/00032, funded by "Independent Clinical Research Projects, 2023 (Instituto de Salud Carlos III, Spain).

P068- ASSOCIATION BETWEEN ACCELERATED EPIGENETIC AND INFLAMMATORY AGING AND COGNITIVE FUNCTION IN MEN AND WOMEN: A CROSS-SECTIONAL ANALYSIS FROM THE INSPIRE-T COHORT. S. Thuriot[1], J. Shourick[1], M. Strumia[1], V. Bongard[1], D. Furman[2], J.M. Lemaitre[3], S. Guyonnet[1], H.A. Bischoff-Ferrari[1], B. Vellas[1], S. Andrieu[1], L. Rouch[1] *(1. IHU HealthAge - Toulouse (France), 2. Buck Institute for Research on Aging - Novato (United States), 3. INSERM 1183 Institute of regenerative medicine and Biotherapies - Montpellier (France))*

Background: Biological age has been increasingly recognized as outperforming chronological age in determining age-related outcomes. Epigenetic alterations, specifically DNA methylation (DNAm) patterns, have been employed to develop epigenetic aging clocks as a measure of biological aging. Likewise, an inflammatory aging clock has recently been developed by Furman and colleagues, based on patterns of systemic age-related inflammation, another biomarker of biological aging. To what extent biological aging is associated with cognition in regard to these measures is unclear. Also, gender differences have not been explored, which may be relevant as men may experience faster epigenetic aging. Further, there is limited data on the interplay between epigenetic and inflammatory aging. We therefore aimed to assess the associations between accelerated epigenetic and inflammatory aging, cognition, and potential interactions with sex or between both aging patterns. **Methods:** We included 596 individuals (mean age 49.0 [SD 14.2] years, women 48.8%) from the INSPIRE-T human translational research cohort. At baseline, five measures of epigenetic (DNAm) age accelerations were considered, based on first (Horvath's pan tissue clock [1], Horvath's skin and blood clock [2] and Hannum's clock [3]) and second generation (PhenoAge [4] and GrimAge [5]) epigenetic aging clocks. Inflammatory age acceleration was estimated from Furman iAge clock [6]. Epigenetic age acceleration was the residual from a linear regression model regressing DNAm age on chronological age. Similar method was used to compute inflammatory age acceleration. Baseline global cognition was calculated as a composite measure using the average of Z scores for the Mini Mental State Examination (MMSE) orientation items (orientation), Free and Cued Selective Reminding Test (FCSRT) (episodic memory), Digit Symbol Substitution Test (DSST) (processing speed), Category Naming Test (CNT) (verbal fluency). Each domain was also assessed separately. Linear regressions were used to examine the association between accelerated epigenetic and inflammatory aging and cognition. **Results:** In unadjusted models, only accelerated epigenetic aging based on skin and blood Horvath's and GrimAge clocks was associated with lower global cognition (β = -0.03, 95% CI [-0.04; -0.01], p<0.001). Accelerated inflammatory aging was not associated with global cognition (p=0.13). Skin and blood Horvath's accelerated epigenetic aging was consistently associated with lower cognition on FCSRT (β = -0.33, 95% CI [-0.53; -0.14], p<0.001) and DSST (β = -0.54, 95% CI [-0.82; -0.27], p<0.001). GrimAge accelerated epigenetic aging was also significantly (p<0.001) associated with lower processing speed. After adjustment for chronological age and sex, only GrimAge accelerated epigenetic aging was associated with lower global cognitive function (β = -0.02, 95% CI [-0.03; -0.01], p=0.02). Additional adjustment for education led to non-significant results (p=0.11). Similar findings were obtained on processing speed. Accelerated inflammatory aging was not associated with cognition after adjustment. Interactions with sex or between epigenetic and inflammatory aging were not significant. **Conclusion:** In our cross-sectional study, after adjusting for chronological age, sex, and education, accelerated epigenetic and inflammatory aging were not associated with cognition. Longitudinal studies are urgently needed to investigate how accelerated epigenetic, inflammatory aging and their complex interplay can affect cognitive trajectories, as well as their added predictive value over chronological age on cognitive impairment. **Keywords:** Epigenetic aging clocks, inflammatory aging clock, biological aging, cognition, translational research. **Disclosures:** The authors have no conflicts of interest to declare relevant to the present research. **References:** 1. Horvath S. DNA methylation age of human tissues and cell types. Genome Biol. 2013;14(10):R115. doi: 10.1186/gb-2013-14-10-r115. Erratum in: Genome Biol. 2015;16:96. PMID: 24138928; PMCID: PMC4015143. 2. Horvath S, Oshima J, Martin GM, Lu AT, Quach A, Cohen H, Felton S, Matsuyama M, Lowe D, Kabacik S, Wilson JG, Reiner AP, Maierhofer A, Flunkert J, Aviv A, Hou L, Baccarelli AA, Li Y, Stewart JD, Whitsel EA, Ferrucci L, Matsuyama S, Raj K. 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P069- TOWARDS A CORTICAL MICROSTRUCTURAL SIGNATURE OF NEUROINFLAMMATION IN AD. G. Ridgway[1], M. Torso[1], I. Hardingham[1], S. Chance[1], &. For The Alzheimer's Disease Neuroimaging Initiative[2] *(1. Oxford Brain Diagnostics Ltd - Oxford (United Kingdom), 2. Alzheimer's Disease Neuroimaging Initiative - San Francisco (United States))*

Background: Neuroinflammation is a key aspect of the pathological cascade in Alzheimer's Disease. Recently proposed revised diagnostic criteria for AD (https://aaic.alz.org/diagnostic-criteria.asp) include "Biomarkers of inflammatory/immune processes (I)" (in an expanded ATNIVS version of the ATN framework), but limitations of currently available Inflammation biomarkers are noted. Neuroinflammation is

currently the second most common treatment target in the AD therapeutic pipeline [1], targeted by 25 drugs (20% of the pipeline). In past work, we have shown correlations between neuroinflammation-associated CSF measures and whole-brain diffusion MRI-derived minicolumn-associated cortical microstructural measures [2]. In this work, we aim to extend this analysis towards the idea of a cortical regional signature of neuroinflammation. **Methods:** Data corresponded to that published in Torso et al. (2022), comprising 68 participants from the Alzheimer's Disease Neuroimaging Initiative with diffusion MRI (dMRI) and corresponding values of CSF soluble TREM2 and progranulin (PGRN) concentrations measured by the Haass group using ELISA with the MSD Platform. The data comprised 14 amyloid negative cognitively normal (CN) individuals, 12 amyloid-positive CN, 24 amyloid positive MCI cases, and 18 AD patients). T1-weighted anatomical MRI scans were processed using FreeSurfer v6.0 to obtain Desikan-Killiany cortical parcellations; dMRI were processed using FSL. Proprietary code used dMRI and anatomical information to calculate AngleR [3] – the angle between the radial minicolumnar axis and the principal diffusion direction – in each of the cortical regions. Partial correlations between regional AngleR and CSF sTREM2 adjusting for age were calculated for all regions. A meta-ROI or "signature" was then calculated for the top 10 strongest regions. This sTREM2-derived meta-ROI was then tested using the PGRN data, again calculating the partial correlation adjusted for age. Results: The strongest partial correlation between sTREM2 and regional AngleR was found for left superior parietal cortex ($r = 0.454$, $p < 0.001$). All of the top 10 partial correlations were above 0.25 with $p < 0.05$, and the top 4 regions survived false discovery rate correction over the set of regions. The sTREM2-derived meta-ROI showed a significant partial correlation with CSF PGRN ($r = 0.401$, $p < 0.001$). **Conclusion:** Results show encouraging potential for an MRI signature of neuroinflammation. Acknowledging the limitation that the two neuroinflammation-associated CSF measures studied here are not independent, the relatively strong partial correlations between the CSF measures and the dMRI-derived cortical microstructural measure (AngleR meta-ROI) warrants further investigation in independent datasets and with other measures of neuroinflammation. Comparison of the regions found here with those from earlier work on a microstructural signature of neurodegeneration in AD [4] indicates limited overlap, suggesting the possibility of specific microstructural signatures for neuroinflammation and neurodegeneration. **Keywords:** Neuroinflammation, microstructure, diffusion MRI, imaging biomarkers. **Disclosures:** SC has a patent (WO2016162682A1) related to the diffusion MRI analysis used in this work. SC is a co-founder of a company, Oxford Brain Diagnostics Ltd. All authors are employees of Oxford Brain Diagnostics Ltd.
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P070- ASSOCIATIONS OF LATE-NC WITH PAST MEDICAL HISTORY AND MEDICATION USE: AN EXPLORATORY ANALYSIS USING DATA FROM THE NATIONAL ALZHEIMER'S COORDINATING CENTER.
D. Woodworth[1], J. Wong[1], A.M. Leiby[1], S.A. Sajjadi[1] *(1. University of California, Irvine - Irvine (United States))*

Background: Past medical history and medication use can provide important clues regarding potential pathophysiological pathways or protective mechanisms for Alzheimer's disease and related dementias (ADRD). While Alzheimer's disease (AD) pathology can be assessed in vivo, other important neuropathologic contributors to ADRD can only be assessed at autopsy. Limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC) is one such significant driver of ADRD in older age that cannot be diagnosed during life. Using data from participants in the National Alzheimer's Coordinating Center (NACC), we examined self-reported past medical history and medication use in relation to LATE-NC at autopsy, and contrasted our findings with ADNC and brain atherosclerosis. **Methods:** We selected NACC participants with the necessary neuropathology and clinical information who were cognitively normal at first visit. We excluded participants that developed certain rarer neuropathologies and/or cognitive diagnoses such as frontotemporal dementia. We examined LATE-NC, ADNC, and atherosclerosis, in relation to both self-reported past medical history and medication use at baseline. We examined the following past medical history conditions: hypertension, hypercholesterolemia, diabetes, atrial fibrillation, thyroid disorders, and depression. We examined the following medication classes: antihypertensive, lipid-lowering, anti-diabetic, anti-coagulant, anti-anxiolytic, and anti-depressant medications. We used ordinal logistic regression mixed-effects models (ordinal package, R) with pathology stage/grade as the outcome and a varying intercept for center. We evaluated each measure in separate models, then included selected variables together in a final model for LATE-NC. We adjusted for age at death, interval from last visit to death, sex, years of education, and APOE4 status. Because of the exploratory nature of this study, we set our threshold for reporting at $P<0.1$. **Results:** We included 440 participants in our analysis, of whom 106 (24%) had LATE-NC at autopsy (36 stage 1, 56 stage 2, 14 stage 3). Average age at first visit was 79, and at death 89. The following past medical history variables were associated with a lower burden of LATE-NC: hypertension (OR=0.51, P=0.007), hypercholesterolemia (OR=0.57, P=0.027), and atrial fibrillation (OR=0.40, P=0.039). The following medication classes were associated with lower LATE-NC burden: antihypertensive (OR=0.59, P=0.037), lipid-lowering (OR=0.51, P=0.009), and anti-coagulant (OR=0.61, P=0.098) medications. By contrast, only hypertension (OR=0.62, P=0.008) and antihypertensive use (OR=0.70, P=0.053) were associated with ADNC (lower burden), and only hypertension (OR=1.77, P=0.003) and antihypertensive use (OR=1.55, P=0.022) were associated with atherosclerosis (increased burden). In a model including hypertension, hypercholesterolemia, atrial fibrillation, and antihypertensive, lipid-lowering, and anticoagulant medication use, LATE-NC continued to be associated with hypertension (OR=0.47, P=0.026), atrial fibrillation (OR=0.39,

P=0.045), and lipid-lowering medication use (OR=0.47, P=0.064). **Conclusion:** In this exploratory analysis we found that history of hypertension and anti-hypertensive medication use were consistently associated with a lower burden of both ADNC and LATE-NC, and with a higher burden of atherosclerosis. Additionally, hypercholesterolemia, atrial fibrillation, and lipid-lowering and anticoagulant medication use were associated with a lower burden of LATE-NC. The final model suggests that while history of hypertension and atrial fibrillation may matter more for LATE-NC than antihypertensive and anticoagulant medication use, lipid-lowering medication use may be the more determinant protective factor rather than hypercholesterolemia itself. **Keywords:** limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC), Alzheimer's disease and related disorders. **Disclosures:** The authors declared no competing interests.

P071- ASSOCIATION BETWEEN THE LONG-TERM USE OF HIGH ANTICHOLINERGIC DRUGS AND ITS BURDEN AND THE INCIDENCE OF DEMENTIA IN STROKE. A. Alharthi[1,2], T. Quinn[1], D. Lyall[1] *(1. University of Glasgow - Glasgow (United Kingdom), 2. Umm Al-Qura University - Makkah (Saudi Arabia))*

Background: The effects of anticholinergic drugs on cognitive dysfunction in middle-aged and older adults have been widely studied. However, inconsistent results have been obtained due to heterogeneity in the studies' designs and in the inconsistency of the anticholinergic burden (ACB) scales used. **Aim:** The aim was to assess the association between ACB and the incidence of dementia. **Methods:** The data was obtained from the APPLE (Assessing Post-Stroke Psychology Longitudinal Evaluation) cohort study with inception at time of acute stroke. A multiple regression statistical test using R was performed to measure the relationship between ACB and the incidence of dementia, adjusted for age, gender, comorbidities and smoking status. Four different anticholinergic scoring, the Anticholinergic Risk Scale (ARS), Anticholinergic Cognitive Burden Scoring of drugs (ACB), Clinician- rated Anticholinergic Score (CrAS) and the Anticholinergic Drug Scale (ADS) were implemented. **Results:** 353 patients were included and their ACB was assessed. The participants had a median age of 71 years and around 27% were over 80 years. Most participants were male (55.8%) and categorized without pre-existing dementia (76.5%). Out of the 353 participants included, 120 (34%) were not taking any anticholinergic medication at baseline (scored = 0 in all four anticholinergic burden scales). 233 participants (66%) were taking anticholinergic medications (scored ≥ 1 for any of the scales). In adjusted multiple regression analyses, high anticholinergic burden, measured by all four anticholinergic scores, did not have a statistically significant effect on the incidence of dementia (ARS [OR] 0.98 [95% CI] 0.87 – 1.09, p 0,728; ACB [OR] 0.99 [95% CI] 0.92 – 1.06 p 0.751; CrAS [OR] 0.98 [95% CI] 0.90 – 1.07 p 0.691; ADS [OR] 0.99 [95% CI] 0.91 – 1.07 p 0.820). **Conclusion:** Among an adult stroke population with and without cognitive impairment, the use of anticholinergic drugs was not associated with a greater incidence of dementia.

P072- DIAGNOSTIC PERFORMANCE OF PLASMA ALZHEIMER'S DISEASE BIOMARKERS FOR PREDICTING AMYLOID/TAU/NEURODEGENERATION. H. Cho[1], H.K. Kim[1], J.H. Lee[2], J.H. Lee[1], J.H. Chun[3], T. West[4], K. Kermess[4], P. Verghese[4], D. Connell[4], J. Braunstein[4], Y.H. Ryu[2], C.H. Lyoo[1] *(1. Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine - Seoul (Korea, Republic of), 2. Department of Nuclear Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine - Seoul (Korea, Republic of), 3. Department of Nuclear Medicine, Severance Hospital, Yonsei University College of Medicine - Seoul (Korea, Republic of), 4. C2N diagnostics - St Louis (United States))*

Introduction: Recently, blood-based biomarkers have demonstrated excellent diagnostic performance not only in differentiating Alzheimer's disease (AD) from non-AD but also in predicting amyloid PET and tau PET positivity. However, these findings have been reported in several studies from Europe and the United States, with very few studies conducted on Asian populations. We aim to investigate the diagnostic accuracy of plasma AD biomarkers (amyloid-beta 42 [Aβ42], amyloid-beta 40 [Aβ40], phosphorylated tau 217 [p-tau217], non-phosphorylated tau 217 [np-tau217]) in distinguishing between AD, mild cognitive impairment (MCI), and cognitively unimpaired (CU) individuals, as well as in predicting imaging-based Amyloid/Tau/Neurodegeneration classifications. **Methods:** We enrolled 237 participants (60 CU, 98 with MCI, and 79 with AD) at Gangnam Severance Hospital in Seoul, South Korea from January 2019 to August 2023. All participants underwent 18F-florbetaben PET for amyloid (A), 18F-flortaucipir PET for tau (T), volumetric MRI for neurodegeneration (N), and standardized neuropsychological tests. Plasma biomarkers (Aβ42, Aβ40, p-tau217, np-tau217) were quantified using LC-MS/MS by C2N Diagnostics, and the Aβ42/40 ratio, p-tau217/np-tau217 ratio, and APS2 scores were calculated. A and T positivity (±) were determined based on the SUVR value through a Gaussian mixture model, while N positivity (±) was defined using hippocampal volume as the mean±2SD of A- with CU participants. **Results:** The Aβ42/40 ratio did not significantly differ between the clinical groups (CU, MCI, AD) (p =0.405), whereas p-tau217, p-tau217/np-tau217 ratio, and APS2 scores showed significant differences across all groups (p<0.001). For distinguishing clinical status, p-tau217, p-tau217/np-tau217 ratio, and APS2 demonstrated moderate to good accuracy: CU vs. MCI (AUC = 0.677, 0.701, 0.678), MCI vs. AD (AUC = 0.760, 0.734, 0.736), and CU vs. AD (AUC = 0.890, 0.885, 0.878). For imaging A/Tau/N positivity (±), the plasma Aβ42/40 ratio was significantly lower in the A+ (p<0.001, AUC = 0.720), but no significant differences were observed in T+ (p=0.230, AUC = 0.583) or N+ (p=0.320, AUC = 0.555). Conversely, p-tau217, p-tau217/np-tau217 ratio, and APS2 scores were significantly higher in the A+, T+, and N+ (all p<0.001). These biomarkers showed excellent predictive performance for A+ (AUC = 0.964, 0.965, 0.959) and T+ (AUC = 0.938, 0.928, 0.909), and moderate predictive accuracy for N+ (AUC = 0.818, 0.812, 0.813). **Conclusion:** These findings underscore the potential of plasma p-tau217 and its related biomarkers as non-invasive, cost-effective tools for early and accurate diagnosis of AD. The diagnostic performance to predict imaging biomarker positivity using blood-based tests offers a significant advantage in clinical settings, facilitating early intervention and personalized treatment strategies. This study also addresses a critical gap in the literature by providing data on an Asian population.

P073- SARCOPENIA IS A PREDICTOR FOR ALZHEIMER'S CONTINUUM AND RELATED CLINICAL OUTCOME. S.H. Kang[1], Y.J. Park[1], C.K. Kim[1] *(1. Department of Neurology, Korea University Guro Hospital, Korea University College of Medicine - Seoul (Korea, Republic of))*

Background: Low body mass index (BMI) is closely related to a high risk of Alzheimer's disease (AD) and related biomarkers including amyloid-β (Aβ) deposition. However, the association between sarcopenia and Aβ-confirmed AD remains controversial. Therefore, we investigated the relationship between sarcopenia and the AD continuum. We explored sarcopenia's association with clinical implications of participants on the AD continuum. **Methods:** We prospectively enrolled 142 participants on the AD continuum (19 with preclinical AD, 96 with mild cognitive impairment due to AD, and 28 with AD dementia) and 58 Aβ-negative cognitively unimpaired participants. Sarcopenia, assessed using dual-energy X-ray absorptiometry and hand grip measurements, was considered a predictor. AD continuum, defined by Aβ deposition on positron emission tomography served as an outcome. Clinical severity in participants on the AD continuum assessed using hippocampal volume, Mini-Mental State Examination (MMSE), Seoul Verbal Learning Test (SVLT), and Clinical Dementia Rating Scale Sum of Boxes Scores (CDR-SOB) were also considered an outcome. **Results:** Sarcopenia (odds ratio=4.99, p=0.004) was associated independently with the AD continuum after controlling for potential confounders. Moreover, sarcopenia was associated with poor downstream imaging markers (decreased hippocampal volume, β=−0.206, p=0.020) and clinical outcomes (low MMSE, β=−1.364, p=0.025; low SVLT, β=−1.077, p=0.025; and high CDR-SOB scores, β=0.783, p=0.022) in participants on the AD continuum. **Conclusion:** Sarcopenia was associated with the AD continuum and poor clinical outcome in individuals with AD continuum. Therefore, our results provide evidence for future studies to confirm whether proper management of sarcopenia can effective strategies are required for sarcopenia management to prevent the AD continuum and its clinical implications. **Keywords:** sarcopenia, Alzheimer's disease (AD), AD continuum, amyloid-β (Aβ), clinical

P074- NEUROINFLAMMATORY CSF MARKERS ASSOCIATED WITH CEREBROVASCULAR LESIONS IN ALZHEIMER'S DISEASE. L. Dai[1], Q. Wang[1], F. Gao[1], Y. Shen[1] *(1. University of Science and Technology of China - Hefei (China))*

Background: Neuroinflammation involved in the onset and progression of both cerebrovascular disease and AD. However, the association between cerebrospinal fluid (CSF) markers of neuroinflammation and cerebral small vessel disease (CSVD) features in individuals with and without Alzheimer's disease (AD) pathologies. **Methods:** This study included 52 cognitively unimpaired (CU) individuals, 42 patients with mild cognitive impairment (MCI), 75 patients with AD, and 27 participants with non-AD dementia (Non-ADD). Neuroinflammatory markers in CSF were analyzed including IL-6, MIF, CCL-2, CXCL-8, YKL-40, S100B, and LCN2. The blood-brain barrier (BBB) permeability was assessed using the CSF/plasma albumin quotient (QAlb), and the extent of CSVD was measured using MRI data. **Results:** After adjustment for age, sex, APOE genotype, and Aβ and tau pathologies, participants with CSVD burden exhibited elevated QAlb level (CSVD = 1: P = 0.034; CSVD>1: P = 0.041). CSF IL-6 contributed to exacerbating cerebral microbleeds (CMB), lacunes (LA), and white matter hyperintensities (WMH), as well as impairing BBB integrity. CXCL-8 levels were significantly higher in patients with severe CSVD burden compared to controls (P = 0.013) and individuals with mild CSVD burden (P = 0.003), particularly affecting BBB permeability. The CSF markers related to reactive astrocytes exhibited diverse patterns concerning different cerebrovascular features. YKL-40 was positively correlated with both QAlb and WMH volumes, whereas increased levels of LCN2 were found to be specifically associated with the BBB leakage. Meanwhile, S100B showed a negative contribution to WMH volumes. **Discussion:** Neuroinflammatory CSF markers play a significant role in distinct pathological processes associated with cerebrovascular damage, which is independent with AD pathologies. **Keywords:** Neuroinflammation, Reactive Astrocytes, Alzheimer's Disease, CSF, CSVD. **Disclosures:** All authors declare that they have no competing financial interests.

P075- DISCOVERY OF A NOVEL C3-TARGETING AND CNS ACTIVE SIRNA AS A POTENTIAL THERAPEUTIC FOR ALZHEIMER'S DISEASE. T. Barbour[1], F. Touti[1], Y. Li[1], A. Jain[1], E. Lonie[1], S. Funes[1], A. Carvalho[1], M. Mohr[2], J. Guo[3], M. Poulin[4], A. Geick[5], S. Mandal[5], Z. Zhang[1], K. Lane[1], L. Scheibler[1], D. Eyerman[1] *(1. Apellis Pharmaceuticals - Waltham (United States), 2. Northern Biomedical Research - Norton Shores (United States), 3. Synoligo Biotechnologies - Morrisville (United States), 4. EpigenDx - Hopkinton (United States), 5. Axolabs GmbH - Kulmbach (Germany))*

Background: Complement proteins are key modulators of innate immunity involved in defense against pathogens. The central component, C3, is an attractive therapeutic target for Alzheimer's disease (AD), due to its location at the nexus of the 3 known activation pathways, and key roles in neuroinflammation and synaptic pruning. C3 mRNA is elevated in post-mortem AD brains and correlates with Braak staging; C3 protein and its breakdown products are elevated in AD patient CSF; and C3 gene knockdown in ageing, amyloid, or tauopathy mouse models is synaptoprotective and attenuates measures of cognitive decline. Small interfering (si)RNAs drive post-transcriptional silencing of a gene target through a process known as RNA-interference (RNAi), harnessing the intrinsic machinery of target cells in a catalytic manner, therefore delivery of a small amount of drug can yield a potent pharmacodynamic effect. Thus, siRNAs represent an attractive modality for targeting abundant disease targets, such as C3. **Methods:** siRNAs were synthesized in a library of modification patterns and screened in HepG2 cells. Activity of best performers was confirmed by transfection in human glial and liver cell cultures. Leads were identified by in silico screening for potential off-target liabilities and in vitro immune-stimulation in human PBMCs. Lead siRNAs were synthesized with lipid conjugates to facilitate in vivo delivery. Pharmacology, tolerability, and distribution of a lead siRNA was evaluated in non-naive NHPs following bolus intrathecal administration on D1 and D43. CSF and plasma were collected throughout the in-life phase. Animals were sacrificed on D85, and C3 mRNA levels, relative to a vehicle control treated group, were determined in CNS and peripheral tissues by RT-qPCR. C3 protein in CSF, tissue, and plasma were evaluated by Meso Scale Discovery ELISA. Tissue, CSF, and plasma concentrations of siRNA were determined by IP LC-MS/MS. **Results:** Several siRNAs with single-digit picomolar IC50 values were identified during HepG2-based screening. RNAi activity against C3 was confirmed in primary human astrocytes and hepatocytes, and human iPSC-derived microglial cultures. Several siRNAs tested did not elicit

expression of any cytokines evaluated in the hPBMC screen. In silico analysis further prioritized a lead candidate with low potential for off-target liabilities. Within seven days post-first dose, C3 protein levels were reduced in NHP CSF by ~50% compared to baseline values and remained suppressed for the duration of the study. C3 mRNA (>-75%) and protein levels (>-50%) were significantly reduced in Alzheimer's relevant brain regions, including hippocampal regions, prefrontal cortex, and entorhinal cortex at study terminus, while little effect on peripheral C3 mRNA or protein was observed. The siRNA was detected in all brain regions evaluated. No test article-related findings were observed in exploratory histopathology of brain or spinal tissues. **Conclusion:** Here we describe a novel C3-targeted siRNA, demonstrating potent and durable silencing of C3 in the CNS of NHPs following intrathecal dosing, and is a putative therapeutic for clinical testing against cognitive decline in Alzheimer's disease. **Keywords:** Complement C3, siRNA, NHP, Neuroinflammation. **Disclosures:** By Author Apellis Pharmaceuticals, Waltham MA, 02451 , Northern Biomedical Research, Norton Shores MI, 49456, Synoligo Biotechnologies, Morrisville NC, 27560, EpigenDx, Hopkinton MA, 01748 , Axolabs GmbH, 95326 Kulmbach, Germany. **References:** Stevens, Beth, et al. «The classical complement cascade mediates CNS synapse elimination.» Cell 131.6 (2007): 1164-1178. Wu, Tiffany, et al. «Complement C3 is activated in human AD brain and is required for neurodegeneration in mouse models of amyloidosis and tauopathy.» Cell reports 28.8 (2019): 2111-2123. Litvinchuk, Alexandra, et al. «Complement C3aR inactivation attenuates tau pathology and reverses an immune network deregulated in tauopathy models and Alzheimer's disease.» Neuron 100.6 (2018): 1337-1353. Hong, Soyon, et al. «Complement and microglia mediate early synapse loss in Alzheimer mouse models.» Science 352.6286 (2016): 712-716. Shi, Qiaoqiao, et al. «Complement C3 deficiency protects against neurodegeneration in aged plaque-rich APP/PS1 mice.» Science translational medicine 9.392 (2017): eaaf6295.

LP036- THE AGED TRIAD: A VASCULAR AGING PHENOTYPE AND ITS RELATIONSHIP TO AD BIOMARKERS. A. Noriega De La Colina[1,2], C. Walker[1], M. Ai[3], N. Kaushal[4], M.R. Geddes[2] *(1. Montreal Neurological Institute-Hospital (The Neuro) - Montreal (Canada), 2. Department of Neurology and Neurosurgery, McGill University - Montreal (Canada), 3. Department of Psychology, Northeastern University - Boston (United States), 4. School of Health & Human Sciences - Indianapolis (United States), 5. Montreal Neurological Institute-Hospital (The Neuror) - Montreal (Canada))*

Background: The AGED triad—Apathy, Gait disturbances, and Executive Dysfunction—describes a vascular aging phenotype in older adults, where cognition, mood, and mobility impairments coexist [1]. Damage to vulnerable brain networks from elevated blood pressure (BP), particularly in regions like the basal ganglia and thalamus, underpins this triad. However, the relationship between the AGED triad and Alzheimer's disease (AD) biomarkers like amyloid and tau remains unclear, particularly across different ethnic groups. Recognizing this phenotype could aid clinicians in the early identification of high-risk patients at early clinical stages. **Methods:** The study used a data-driven cluster analysis (k-means/hierarchical clustering examining systolic (SBP) and diastolic blood pressure (DBP), gait speed, and apathy (Apathy Evaluation Scale), in two distinct samples of older adults enrolled in the Daily Activity Study of Health (DASH) at the Center for Cognitive and Brain Health, Northeastern University (Boston, MA) (n=37) and at the Healthy Aging Brain Study (HABS) at The Douglas Research Centre, McGill University (Montreal, Canada) (n=52). Executive functions were evaluated using the Brief Test of Adult Cognition by Telephone (BTACT) Red Go Experimental condition in DASH, and the Digit Span Backwards of the TestMyBrain toolkit in HABS, with mean scored compared per cluster using the Kruskal Wallis Test. Furthermore, we explored the distribution of AD plasma biomarkers across HABS, i.e. ptau 181, Total tau, Amyloid β 40, Amyloid β 42, and the Amyloid 42/40 ratio across each cluster. External validation was performed on the Health and Aging Brain Study: Health Disparities (HABS-HD) at the University of North Texas Health Science Center (Fort Worth, TX), comprising 758 African American, 1196 Mexican-American, and 1196 Non-Hispanic White community-dwelling participants. **Results:** The clustering analysis identified three distinct groups in both DASH and HABS cohorts. Cluster 1 consisted of healthy individuals with normal blood pressure, fast gait speed, no apathy, and the highest executive function scores. Cluster 2, characterized by high blood pressure, slow gait speed, and significant apathy, showed the lowest executive function scores, with statistically significant differences compared to Cluster 1 ($p < 0.05$). Cluster 3 exhibited slow gait speed and apathy without high blood pressure, resulting in moderate executive function scores. In the HABS cohort, Alzheimer's disease (AD) plasma biomarkers were differentially distributed across clusters. Cluster 2 had elevated levels of ptau 181 and Total tau, suggesting a link between vascular aging and AD pathology. Cluster 3 showed higher Amyloid β 42/40 ratios, indicating a potential non-vascular contribution to the AGED phenotype. These patterns were validated in the HABS-HD cohort across African American, Mexican-American, and non-Hispanic White participants, affirming the vascular AGED phenotype's relevance across ethnic groups. **Conclusion:** The AGED triad effectively identifies older adults with a vascular aging phenotype, particularly those with high blood pressure and cognitive impairment (Cluster 2). These individuals demonstrated the strongest association with AD biomarkers, highlighting the role of vascular factors in cognitive decline. Recognizing the AGED triad could improve early detection and intervention, especially in diverse populations. **References:** 1. Hachinski V, Finger E, Pieruccini-Faria F, Montero-Odasso M. The apathy, gait impairment, and executive dysfunction (AGED) triad vascular variant. Alzheimers Dement. 2022 Sep;18(9):1662-1666. doi: 10.1002/alz.12637. **DASH Clinical Trial Registry:** NCT04315363; clinicaltrials.gov. **HABS Clinical Trial Registry:** NCT06038643; clinicaltrials.gov. **Keywords:** aged triad, vascular, neuropsychiatric, phenotype, patient identification. **Disclosures:** The authors report no financial disclosures related to this work. **Acknowledgement:** HABS-HD: Research reported in this publication was supported by the National Institute on Aging of the National Institutes of Health under Award Numbers R01AG054073 and R01AG058533, R01AG070862, P41EB015922 and U19AG078109. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

LP037- INHIBITION OF P38A MAPK PATHWAY IN EARLY ALZHEIMER'S DISEASE. D. Gouilly[1], P. Péran[2], A. Vrillon[3], E. Bertrand[4], M. Goubeaud[4], A. Pistono[5], A. Da Costa[2], A.S. Salabert[2], J. Germain[4], H. Catala[4], M. Rafiq[1], D. Meligne[1], L. Jasse[1], B. Sarton[6], P. Payoux[7], C. Paquet[3], C. Thalams[4], J. Alam[8], J. Pariente[1] *(1. Department of Cognitive Neurology, Epilepsy, Sleep and Movement Disorders, CHU Toulouse Purpan, Toulouse, France. - Toulouse (France), 2. Toulouse Neuroimaging Center, UMR 1214, Inserm/UPS, Toulouse, France. - Toulouse (France), 3. Université de Paris, Cognitive Neurology Center, GHU Nord, APHP, Hospital Lariboisière Fernand Widal, Paris, France. - Paris (France), 4. Center of Clinical Investigation, CHU Toulouse Purpan (CIC 1436), Toulouse, France. - Toulouse (France), 5. Université Toulouse 2 Jean Jaurès, Toulouse, France. - Toulouse (France), 6. Critical Care Unit, CHU Toulouse Purpan, Toulouse, France. - Toulouse (France), 7. Department of Nuclear Medicine, CHU Toulouse Purpan, Toulouse, France. - Toulouse (France), 8. CervoMed Inc (formerly known as EIP Pharma), Boston, Massachusetts, United States of America. - Boston (United States))*

Background: Neuro-inflammation is a mechanistic change of Alzheimer's disease (AD). However, the results of anti-inflammatory interventions have been mostly negative in the early stages. In addition, the short-term effect of suppressing neurotoxic pro-inflammatory activity on neuro-immune biomarkers remained unclear. **Method:** We conducted a phase II monocentric, randomized and placebo-controlled trial to assess the effect of neflamapimod which inhibits the p38α MAPK multicellular pathway. We included 33 participants with clinico-biological evidence of early AD (MMS score >20/30). These participants were followed for 12 weeks to assess the short-term effect of a low dose of neflamapimod (40 mg, BID) versus placebo on the whole brain SUVR on TSPO PET imaging (primary endpoint), and cerebrospinal fluid biomarkers of neuro-inflammation, synaptic and axonal damage including GFAP, sTREM2, YKL-40, IL-6, IL-10, neurogranin, and NfL. Volumetric and neuropsychological changes were also evaluated. An exploratory subgroup analyses were performed to assess the relationship between baseline sTREM2 level and the effect of neflamapimod. **Results:** The results of the analyses will be presented. **Conclusion:** This study is designed to show the short-term effect of an anti-inflammatory intervention on neuro-immune biomarkers, and this might give lines of understanding of the failure of previous anti-inflammatory approaches. **Keywords:** proof-of-concept phase II trial; inflammation; TSPO PET; CSF biomarkers. **Clinical Trial Registry:** NCT03435861; https://clinicaltrials.gov. **Funding:** This study was co-funded by Fondation Alzheimer (Paris, France), and Fondation de l'Avenir (Paris, France; 2022; reference number: AP-RM-21-042). The study treatment and placebo were provided by CervoMed Inc (formerly known as EIP Pharma, Boston, Massachusetts, USA). **Disclosures:** DG received a grant from Fondation de l'Avenir. The other authors declared no financial or non-financial interests related to this study.

LP039- MULTIPLEX CEREBROSPINAL FLUID PROTEOMICS IDENTIFIES BIOMARKERS FOR DIAGNOSIS AND PREDICTION OF ALZHEIMER'S DISEASE. Y. Jin-Tai[1], G. Yu[1], H. Yu-Yuan[1] *(1. Huashan Hospital, Fudan University - Shanghai (China))*

Background: Despite important advances in current biomarker research, the biology of Alzheimer's disease (AD) remains largely unknown [1]. Expanding additional biomarkers becomes essential, especially when disease-modifying therapies targeting Aβ and tau have failed to demonstrate clinical efficacy [2, 3]. Cerebrospinal fluid (CSF) proteomic profiling, possibly directly mirroring biochemical alterations in the brain [3, 4], opens up a golden opportunity to investigate the above concern. **Methods:** This study included 707 participants of cognitively normal, mild cognitive impairment, and AD dementia from the ADNI. CSF proteins were quantified using the SomaScan assay. Multiple linear regressions were run to identify the proteins with differential expression. Those dysregulated proteins were fed into the LGBM classifier[5] and ranked based on their contributions to diagnosing AD. Receiver operating characteristic analyses were performed to assess the discriminative accuracies. Kaplan-Meier survival curves were constructed to evaluate the predictive performance. Enrichment analysis, Mendelian randomization, and druggability profiling were employed to depict enriched pathways, investigate causal links, and explore potential drug targets. **Results:** Among 6,361 CSF proteins, YWHAG performed best in diagnosing both biologically (area under the curve (AUC)=0.969) and clinically (AUC=0.857) defined AD. Four (YWHAG, SMOC1, PIGR, and TMOD2) and five (ACHE, YWHAG, PCSK1, MMP10, and IRF1) protein panels greatly improved the accuracy to 0.987 and 0.975, respectively. Their superior performance was validated in an independent external cohort, and in discriminating autopsy-confirmed AD versus non-AD, rivaling even canonical CSF ATN biomarkers. Moreover, they effectively predicted the clinical progression to AD dementia and were strongly associated with AD core biomarkers and cognitive decline. Synaptic, neurogenic, and infectious pathways were enriched in distinct AD stages. Mendelian randomization didn't support the significant genetic link between CSF proteins and AD. **Conclusion:** Our findings revealed promising high-performance biomarkers for AD diagnosis and prediction, with implications for clinical trials targeting different pathomechanisms. **Keywords:** Alzheimer; proteomics; CSF biomarker; diagnosis; prediction. **Disclosures:** The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article. **References:** 1. Johnson, E.C.B., et al. Large-scale deep multi-layer analysis of Alzheimer's disease brain reveals strong proteomic disease-related changes not observed at the RNA level. Nat Neurosci 25, 213-225 (2022). 2. Sung, Y.J., et al. Proteomics of brain, CSF, and plasma identifies molecular signatures for distinguishing sporadic and genetic Alzheimer's disease. Science translational medicine 15, eabq5923 (2023). 3. Johnson, E.C.B., et al. Cerebrospinal fluid proteomics define the natural history of autosomal dominant Alzheimer's disease. Nat Med 29, 1979-1988 (2023). 4. Del Campo, M., et al. CSF proteome profiling across the Alzheimer's disease spectrum reflects the multifactorial nature of the disease and identifies specific biomarker panels. Nat Aging 2, 1040-1053 (2022). 5. Guolin K, et al. LightGBM: A Highly Efficient Gradient Boosting Decision Tree. Advances in Neural Information Processing Systems 30 (NIPS 2017), 3149-3157 (2017).

LP040- RELATIONSHIP BETWEEN CAREGIVING BURDEN AND ALTERATIONS IN CIRCADIAN RHYTHM AMONG SPOUSAL CAREGIVERS OF COGNITIVE IMPAIRMENT OLDER ADULTS. S.Y. Park[1], J.B. Lee[2], T. Lee[2], Y. Hee Won[1], S.Y. Jeon[3] *(1. Chungnam National University Hospital - Daejeon (Korea, Republic of), 2. Sun Moon University - Asan (Korea, Republic of), 3. Chungnam National University College of Medicine - Daejeon (Korea, Republic of))*

Background: Caregiving for people with dementia can negatively impact the physical and mental health of spousal caregivers (SCGs), leading to disruptions in circadian rhythms. This study investigates how caregiving burden affects sleep-wake cycles and rest-activity rhythms (RARs) in SCGs. **Methods:** We recruited 104 SCGs from a geriatric psychiatry clinic. Participants underwent comprehensive clinical assessments, including the Zarit Caregiver Burden Interview (ZBI) and circadian rhythm evaluations using the Pittsburgh Sleep Quality Index (PSQI) and Fitbit devices. Multiple regression analyses were conducted to assess associations. **Results:** Increased caregiving burden showed a trend-level association with earlier wake times (β = -0.254, p = 0.091) and a significant association with reduced RAR robustness as indicated by lower goodness-of-fit (GoF) values (β = -0.306, p = 0.037), especially among dementia caregivers. PSQI analysis revealed that higher caregiving burden correlated with worsened sleep disturbances (β = 0.203, p = 0.046). **Conclusion:** Caregiving burden significantly affects circadian rhythms in SCGs, with potential implications for cognitive and cardiovascular health. Targeted interventions are needed to mitigate these effects and improve caregiver well-being. **Keywords:** Caregiving burden, circadian rhythms, dementia, spousal caregivers, sleep-wake cycle, rest-activity rhythms.

LP041- MIDDLE AGED AND OLDER ADULTS' KNOWLEDGE, RATINGS, AND PREFERENCES FOR RECEIVING MULTICOMPONENT LIFESTYLE-BASED BRAIN HEALTH INTERVENTIONS. R.L. Ownby[1], G. Cavanaugh[1], J. Caballero[2] *(1. Nova Southeastern University - Fort Lauderdale (United States), 2. University of Georgia - Athens (United States))*

Background: Previous research has evaluated middle-aged and older adults' knowledge of lifestyle factors related to their risk for cognitive impairment but has not studied their preferences for specific intervention activities or how interventions for brain-healthy lifestyles might be delivered. These factors may be critical in developing viable intervention to support patients in developing more brain-healthy lifestyles. The objective of this study was to assess middle-aged and older adults' knowledge of brain health activities and their preferences for multicomponent lifestyle-based brain health interventions. **Methods:** We created a survey assessing respondents' beliefs about the helpfulness of a range of brain health activities such as aerobic exercise, a healthy diet, and other factors such as treatment for depression or the use of supplements. They were also asked about their level of concern regarding their brain health and whether they had a family history of dementia. Finally, they were asked to choose among possible service delivery options for brain health interventions, such as online or in person. The survey was offered via a commercial survey provider to compensated volunteers 40 years of age and older. Ratings of the helpfulness of brain health activities were evaluated by age and gender via MANOVA. Other responses were tabulated. **Results:** The sample comprised 758 individuals with a mean age of 52.6 years; 59% were women. For analyses, individuals were placed into early middle age (40-50 years, n = 380), late middle age (51-64 years, n = 265), and older adult (65 and older, n = 113) groups. Multivariate tests in the MANOVA were significant for an effect of age ($p < 0.001$) and the interaction of gender with age ($p < 0.001$) in ratings of activity effectiveness. Aerobic exercise and mentally stimulating activities were most frequently chosen as the single most important activity for brain health. Early middle-aged men rated aerobic exercise and strength training as more helpful than older adult men and women. Older adult women rated smoking cessation, medical checkups, and meditation as more helpful than older adult men. With respect to the preferred mode of support for brain health interventions, slightly more than half indicated a preference for working with someone who could assess their cognitive status (52%). A substantial number (36%) wanted to have an app on their phone that could assess their memory and thinking. Fewer than 20% of participants chose working in an in-person group. Other preferred modes for receiving support included online (44%) and in-person (29%) education. **Conclusion:** Results show that age and gender may be factors in working with middle-aged and older adults to develop brain-healthy lifestyles. Responses suggested an interest in assessments of cognitive status, perhaps to reduce uncertainty or worry. However, no clear consensus emerger on the preferred way of receiving services. Offering patients several options for them to receive brain health interventions may be needed to optimize their engagement. **Keywords:** Brain health, lifestyle interventions, exercise, diet, intervention delivery, patient preference. **Data Deposition:** Data are available from the first author on request. **Disclosures:** The authors indicate that they have no relevant conflicts to disclose.

LP041BIS- RELATIONSHIP OF ALPHA-SYNUCLEIN CO-PATHOLOGY TO AD BIOMARKERS AND CLINICAL PROGRESSION IN MCI AND MILD AD CLINICAL TRIALS. K. Fraser[1], R. Brown[1], K. Ferber[1], J. Czerkowicz[1], A. Edwards[1], J. Collins[1], G. Dent[1], M. Shulman[1], J. O'gorman[1], C. Rubel[1], D. Graham[1] *(1. Biogen - Cambridge (United States))*

Background: We have previously demonstrated that 28.0% of all CSF sub-study participants with MCI and mild AD in the TANGO study and 25.6% of CSF sub-study participants in the ENGAGE and EMERGE clinical studies are positive on the α-synuclein seed amplification assay (αS-SAA) for presence of α-synuclein co-pathology (ADPD 2024). Recent reports suggest a relationship between occurrence of α-synuclein and patterns of both AD-related biomarkers and clinical progression rates. Here, we evaluated these relationships using data from well-controlled clinical studies. **Methods:** CSF samples collected at baseline from 182 MCI or mild AD participants from the TANGO (NCT03352557) and 203 MCI or mild AD participants from the ENGAGE (NCT02477800) and EMERGE (NCT02484547) studies were evaluated using the αS-SAA from Amprion. Amyloid PET scans were evaluated from a subset of participants in the TANGO, ENGAGE, and EMERGE studies utilizing the florbetapir tracer. Tau PET scans were evaluated in a substudy of participants in the TANGO study utilizing the [18F]MK-6240 tracer. AD-related biomarker levels were quantified in CSF and blood via immunoassay approaches. Baseline levels of AD-related biomarkers across all participants and clinical progression rates from placebo group participants were compared between αS-SAA positive versus negative participants. **Results:** In individuals pooled from the placebo arms of the TANGO, ENGAGE, and EMERGE trials αS-SAA

positive participants showed faster mean progression on the CDR-Sum of Boxes, MMSE, and ADAS COG13 but not ADCS-ADL. No meaningful differences were observed in median baseline amyloid PET SUVR in αS-SAA positive versus negative participants of the TANGO (1.31 vs. 1.36, n=14), ENGAGE (1.43 vs. 1.35, n=46), or EMERGE (1.39 vs. 1.43, n=52) studies. In TANGO, median baseline tau PET SUVR was lower in αS-SAA positive versus negative participants in Braak 1/2 (1.52 vs. 2.29, n=16), 3/4 (1.18 vs. 1.83, n=16), and 5/6 (1.07 vs. 1.50, n=16) regions. No meaningful differences in AD-related biomarkers in CSF or blood were observed. **Conclusion:** A relationship was observed between presence of α-synuclein co-pathology and tau PET but not amyloid PET at baseline. Although sample size is limited, results suggest that MCI or mild AD patients with α-synuclein co-pathology may have a lower burden of tau pathology. While no relationship was observed with baseline amyloid PET, all 3 clinical studies enrolled only patients with confirmed amyloid pathology; therefore, a population that includes amyloid negative participants may be more informative to establish the relationship between α-synuclein and amyloid pathologies. Many AD fluid biomarkers are closely related to amyloid burden, which may explain the lack of differentiation also observed in baseline fluid biomarkers by αS-SAA status. Pooled clinical progression data from the placebo arm of all 3 studies supports the hypothesis that presence of α-synuclein co-pathology in MCI and mild AD populations may be associated with faster rates of clinical progression and suggests value in determining and potentially stratifying by αS-SAA status in clinical studies in this population. **Keywords:** alpha-synuclein, biomarkers, Alzheimer's disease. **Disclosures:** This study was funded by Biogen. All authors are employees of and may hold stock in Biogen.

CLINICAL TRIALS EARLY CAREER INVESTIGATOR SHOWCASE

P076- BUMETANIDE IN PATIENTS WITH ALZHEIMER'S DISEASE (BUMXAD): A PHASE II CLINICAL TRIAL. K. Younes[1], M. Kmiecik[1], M. Huu Chu[1], A. Zhou[1], I. Skylar-Scott[1], N. Samudra[1], P. Tripathi[1], M. Coburn[1], T. Wilson[1], Z. He[1], F. Haddad[1], T. Wyss-Coray[1], S.J. Sha[1], M.D. Greicius[1] *(1. Stanford University - Palo Alto (United States))*

Bumetanide is a potent diuretic administered orally and is FDA approved for the treatment of edema and hypertension. Recently, repurposing Bumetanide as an Alzheimer`s disease (AD) medication was proposed based on data that showed Bumetanide "flipped" the APOE genotype-dependent transcriptomic signatures in AD mouse and human cell culture models [1]. Critically, this finding was then investigated in Electronic Health Record (EHR) cohorts and showed that in individuals over 65 years of age, bumetanide exposure was associated with a significantly lower AD prevalence in three independent dataset [1, 2]. However randomized double blinded trials are needed to investigate the safety, tolerability and benefit of bumetanide in AD. This is a phase II, randomized, double-blind, multi-arm placebo-controlled, parallel group study to evaluate the safety and tolerability of bumetanide in patients with AD. This study aims to investigate bumetanide in patients with biologically confirmed AD. The primary objective is to evaluate the safety and tolerability of bumetanide when administered to participants with biomarker-confirmed AD. The secondary objective is to evaluate the clinical and biomarker effects of bumetanide in participants with mild cognitive impairment or mild dementia due to AD. The inclusion criteria include mild cognitive impairment or mild dementia due to AD, AD medications are planned to remain stable throughout, willingness and ability to complete all aspects of the study including assessments, neuropsychological testing, and MRI. Exclusion criteria includes clinically significant abnormalities in screening laboratory tests, chronic liver disease, renal insufficiency, poorly managed hypertension and participants taking the following concomitant medications, based on the current Prescribing Information for bumetanide: lithium, drugs with ototoxic potential, drugs with nephrotoxic potential, probenecid, and indomethacin. We present the clinical trial protocol and design for a phase II trial evaluating the effect of bumetanide in AD. **References:** 1. Taubes A, Nova P, Zalocusky KA, et al. APOE4 -related Alzheimer ' s disease. 2021;1(October). 2. Graber-Naidich A, Lee J, Younes K, Greicius MD, Le Guen Y, He Z. Loop Diuretics Association with Alzheimer's Disease Risk. Front Aging. 4:1211571.

P077- HIGH PREVALENCE OF BRAIN AMYLOIDOPATHY AMONG FRAIL OLDER ADULTS: ARE THEY ELIGIBLE FOR ANTI-AMYLOID TREATMENTS? SHOULD THEY BE TREATED? EVIDENCE FROM THE REAL-LIFE COGFRAIL COHORT. D. Angioni[1], S. Sourdet[1], J. Delrieu[1], G. Soriano[1], A. Peluso[1], G. Abellan[1], P.J. Ousset[1], B. Vellas[1] *(1. Institut Hospitalo Universitaire HealthAge, Alzheimer's Disease Research and Clinical Center, Toulouse University Hospital - Toulouse (France))*

Background: Recently, Lecanemab has demonstrated efficacy in slowing the progression of Alzheimer's disease. However, concerns have been raised about the generalizability of clinical trial results to underrepresented populations, such as older frail adults. Moreover, the eligibility of this population to Lecanemab has been only sparsely studied. The objectives of our study were to evaluate the prevalence of subjects with a positive amyloid cerebral status in a real-life cohort of older adults presenting frailty criteria and evaluate if this population can be eligible for an anti-amyloid therapy. **Methods:** This is a secondary analysis of the Cogfrail observational cohort, which includes frail and prefrail individuals (as per the Fried criteria) with objective cognitive impairment (CDR 0.5 or 1 – MMSE ≥ 20). Brain amyloidopathy was measured by amyloid-positron emission tomography or cerebrospinal fluid analysis (CSF Aβ42 or CSF Aβ42/Aβ40 ratio values). The Clarity-AD eligibility criteria were applied to identify individuals potentially eligible for Lecanemab treatment. **Results:** Among 215 participants with known amyloid status, 125 (58%) were amyloid-positive (mean age 82.3 ± 4.7 years, 68% women). Twenty-seven (21.6%) of the 125 amyloid-positive participants met the eligibility criteria for Lecanemab in the overall population, and 8% (4 out of 48) in the subgroup of frailty patients (presenting ≥ 3 Fried criteria). Common exclusions were related to neuroimaging abnormalities, the use of prohibited medications, and incompatible medical history. The population of patients eligible for Lecanemab treatment in the Cogfrail cohort was significantly older than that of the Clarity-AD trial (median age 81 [range 73-90] versus 72 [range 50-90], $p < 0.05$), with a higher representation of individuals aged ≥ 80 (63% versus 13%, $p < 0.05$). **Conclusion:** The high prevalence of brain amyloidopathy in frail older patients and their limited eligibility for anti-amyloid clinical trials highlight the necessity for clinical trials specifically designed to include this population. Such trials will be essential to determine the potential benefits of Lecanemab and other anti-amyloid antibodies in older adults with frailty.

Keywords: RCTs, anti-amyloid, older adults, frailty, brain amyloidopathy. **Disclosures:** The authors have no conflict of interest.

LP042- CHARACTERISTICS OF PATIENTS ATTENDING OUR ALZHEIMER'S DISEASE-MODIFYING THERAPY CLINIC IN JAPAN: IMPLICATION FOR CLINICAL TRIALS. M. Kurihara[1], R. Ihara[1], K. Hatano[1], A. Hatakeyama[2], F. Suzuki[3], A.M. Tokumaru[3], K. Ishii[4], K. Furuta[5], A. Iwata[1] *(1. Department of Neurology, Tokyo Metropolitan Institure for Geriatrics and Gerontology - Tokyo (Japan), 2. Dementia Support Center, Tokyo Metropolitan Institure for Geriatrics and Gerontology - Tokyo (Japan), 3. Department of Diagnostic Radiology, Tokyo Metropolitan Institure for Geriatrics and Gerontology - Tokyo (Japan), 4. Research Team for Neuroimaging, Tokyo Metropolitan Institure for Geriatrics and Gerontology - Tokyo (Japan), 5. Department of Psychiatry, Tokyo Metropolitan Institure for Geriatrics and Gerontology - Tokyo (Japan))*

Background: In Japan, lecanemab is approved and covered by health insurance, and its use in clinical practice was launched in December 2023. This has altered not only clinical practice but also the enrollment of patients with early symptomatic Alzheimer's disease (AD) in clinical trials. We aimed to study the characteristics of patients attending our Alzheimer's disease-modifying therapy (DMT) clinic, and consider changes in clinical trial recruitment strategies. **Methods:** We retrospectively reviewed all patients who presented at the DMT clinic between December 2023 and June 2024. Our institution is in urban Tokyo, provides clinical care, and participates in several clinical trials. We established our DMT clinic as part of our memory clinic in December 2023. Patients interested in lecanemab treatment were screened by the Department of Neurology, Psychiatry, or the Memory Clinic. The initial requirement for referral to the DMT clinic included a diagnosis of mild cognitive impairment or mild dementia, a mini-mental state examination (MMSE) score of ≥22, no evidence of disease other than AD primarily causing cognitive impairment, and the ability to undergo MRI scans. Clinical information, test results, and details on clinical trial involvement were obtained through a chart review. **Results:** One-hundred and forty-three patients presented during the period. Three of them were actively participating in a non-anti-Aβ AD clinical trial that permits additional lecanemab treatment. Seven had a history of being screened for a clinical trial. Previous amyloid biomarker positive results were available for 11 patients (4 with cerebrospinal fluid (CSF) analysis, 7 with amyloid PET scans). Of the remaining 132 patients, 39 underwent CSF testing (29.5%), 47 underwent amyloid PET scans (35.6%), 8 were screen failures before biomarker testing (6.1%), and 38 declined further biomarker testing (28.8%). The primary reason for not proceeding was the lack of intention to receive lecanemab after being informed. Of the 86 patients who underwent biomarker testing, 30/39 (76.9%) and 31/47 (66.0%) were amyloid-positive by CSF and PET, respectively. Of the 72 amyloid-positive patients, six showed contraindication on detailed brain MRI, two were considered cognitively normal, three eventually opted out, and the remaining 61 started lecanemab treatment. Of the 82 patients who did not start lecanemab, clinical trial information was given to five patients. The reasons for not starting lecanemab were more than 5 microhemorrhages on MRI in three, high risk of amyloid–related imaging abnormalities due to known ApoE ε4 homozygosity in one, and hesitation due to visiting burden in one. Three were interested and considered screening for a non-anti-Aβ AD clinical trial. None of the lecanemab-eligible patients opted to participate in a clinical trial instead. **Conclusion:** We summarized the characteristics of patients who presented to our Alzheimer's DMT clinic. Since lecanemab is covered by public health insurance and available to many patients in Japan, different strategies—such as allowing patients with slightly lower MMSE scores, more microhemorrhages, or allowing combination therapy—may be needed to recruit a sufficient number of patients for AD clinical trials. However, these strategies have the drawback of increasing bias in the study population. **Keywords:** lecanemab, disease-modifying therapy, biomarkers, CSF, PET, recruitment. **Disclosures:** MK, RI, KH, and AI are investigators in clinical trials conducted by Eisai, Biogen, Eli Lilly, Janssen, Chugai/Roche, and Sound Wave Innovation. RI receives advisory fees from Eisai and Eli Lilly and honoraria for lectures from Eisai and PDRadiopharma. AI receives advisory fees from Eisai, Eli Lilly, Roche, GSK, Otsuka, Soundwave Innovation, and honoraria for lectures from Eisai, Eli Lilly, Chugai/Roche, HU frontier, Fujirebio, Kowa, Sysmex, Ono, Otsuka, Alnylam, DaiichiSankyo, Tokio Marine & Nichido Fire Insurance, PDR pharma, IQVIA, Sumitomo Pharma, and Kyowa Kirin, and is involved in post-marketing surveillance of lecanemab in Japan.

LP043- NOVEL TRIAL DESIGN FOR A TAU-DIRECTED THERAPEUTIC IN PATIENTS WITH CORTICOBASAL SYNDROME. R. Vandevrede[1], R. Snell[1], H. Heuer[1], C. Lane-Donovan[1], P. Ljubenkov[1], J. Rojas[1], A. Boxer[1] *(1. Memory and Aging Center, UCSF Weill Institute for Neurosciences, University of California San Francisco - San Francisco (United States))*

Background: Corticobasal syndrome (CBS) is a devastating, deadly, and untreatable disease that interferes with thinking, movement, and behavior. Currently, no disease-modifying clinical trials are available for CBS, and only a handful of clinical trials have ever been conducted in this population, typically in combined ("basket") trials designed for other tau diseases [1]. The overwhelming majority of CBS cases are caused by tau, but two different types of tau can accumulate: 4R-tauopathy (CBS-4RT) or the tau tangles seen in Alzheimer's disease (CBS-AD) [2]. Recently, we demonstrated that a tau blood test (p-tau217) can distinguish between CBS-AD and CBS-4RT [3], important because different tauopathies may respond differently to therapeutics [4]. This precision diagnosis permits diagnostic refinement of CBS cohorts, justifying a dedicated clinical trial in this underserved population, which has now been funded by the Part the Cloud Initiative through the Alzheimer's Association. **Objectives:** The primary objective is to determine the safety and tolerability of 6 months of treatment with a tau-directed therapeutic in patients with CBS. The secondary objective is to evaluate target engagement in patients with CBS by measuring tau in CSF and plasma. An exploratory objective is to explore the clinical efficacy of a tau-directed therapeutic in patients with CBS using validated clinical, fluid, and imaging endpoints. **Methods:** The proposed trial is a phase 1b/2a, 6-month, randomized, double-blind, placebo-controlled study of the safety/tolerability and preliminary evidence of efficacy of a tau-targeted therapeutic in patients with corticobasal syndrome. A total of N=24 participants with a clinical diagnosis of CBS using Armstrong criteria will be stratified with plasma p-tau217 (goal n=12 per arm) and randomized 2:1 to a tau-directed therapeutics. The study drug will be administered for 6 months, and safety/tolerability, target engagement, and clinical efficacy will be tested in both a primary (CBS-4RT) and a secondary tauopathy

(CBS-AD). Patient visits will be on-site every 3 months. The current study design calls for a single site with an expected launch date in 2025, with the goal of adding a 6-month open-label extension. **Results:** This trial design represents the first dedicated disease-modifying clinical trial for this clinical syndrome, the first "within-syndrome" basket design in CBS stratifying by neuropathological etiology using the plasma p-tau217 biomarker, the first use of a tau-directed therapeutic simultaneously in both an AD and non-AD tauopathy in a single trial, and the first use of several exploratory novel fluid biomarkers of tau engagement. **Conclusion:** A stratified "basket trial" for CBS is an optimized design to enroll clinical subcohorts of tauopathies to test tau-directed therapeutics in this population. **References:** 1. VandeVrede L, Ljubenkov PA, Rojas JC, Welch AE, Boxer AL. Four-Repeat Tauopathies: Current Management and Future Treatments. Neurotherapeutics. 2020;17(4):1563-1581. doi:10.1007/s13311-020-00888-5; 2. Lee SE, Rabinovici GD, Mayo MC, et al. Clinicopathological correlations in corticobasal degeneration. Annals of Neurology. 2011;70(2):327-340. doi:10.1002/ana.22424; 3. VandeVrede L, La Joie R, Thijssen EH, et al. Evaluation of Plasma Phosphorylated Tau217 for Differentiation Between Alzheimer Disease and Frontotemporal Lobar Degeneration Subtypes Among Patients With Corticobasal Syndrome. JAMA Neurol. Published online April 3, 2023:e230488. doi:10.1001/jamaneurol.2023.0488; 4. Tsai RM, Miller Z, Koestler M, et al. Reactions to Multiple Ascending Doses of the Microtubule Stabilizer TPI-287 in Patients With Alzheimer Disease, Progressive Supranuclear Palsy, and Corticobasal Syndrome: A Randomized Clinical Trial. JAMA Neurology. 2020;77(2):215-224. doi:10.1001/jamaneurol.2019.3812.

CLINICAL TRIALS: IMAGING

P079- DIABETES MELLITUS-INDUCED DIFFERENTIAL CEREBELLAR VOLUME REDUCTION ACROSS ALZHEIMER'S DISEASE TRAJECTORY.

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Background: Alzheimer's disease (AD) and diabetes mellitus (DM) are linked to neurodegeneration [1], but their combined effects on the cerebellum are not well understood. While prior research has focused on cortical and hippocampal atrophy in AD, the cerebellum's role has been largely overlooked [2]. As the cerebellum's involvement in cognitive functions gains recognition, it is crucial to explore how DM affects cerebellar volume across different AD stages. This study examines the differential impact of DM on cerebellar volume in normal cognition, preclinical AD, and amyloid-positive MCI. **Methods:** A total of 134 patients with AD pathology and 66 normal controls were recruited for this study. The patients were divided into the following groups: normal control(66 patients), preclinical AD (22 patients), amyloid-positive MCI (37 patients), dementia due to AD (75 patients) with DM or without DM. And we divided cerebellum volume into three regions: anterior lobe, posterior lobe, flocculonodular lobe. Participants were stratified into cognitive groups using CERAD-K assessments and amyloid positivity determined by [18F]flutemetamol PET imaging. MRI scans were acquired, and voxel-based morphometry (VBM) analysis was conducted using the CAT12 toolbox [3]. To achieve precise cerebellar segmentation, the SUIT (Spatially Unbiased Infratentorial Template) atlas was employed, allowing for detailed volumetric analysis of cerebellar subregions across the defined cognitive and amyloid status groups. After that we conducted an ANCOVA with age, sex, and total cranial volume as covariates to examine the relationship between volume of cerebellum and clinical diagnosis. **Results:** In the normal group, a reduction in the volume of the anterior lobe was observed in patients with DM($p=0.042$). However, the cerebellar volume of posterior lobe decreases more significantly in patients with Amyloid-positive MCI who also had DM. ($p=0.045$) after a Bonferroni correction. **Conclusion:** This study reveals that DM affects cerebellar volume differently across the AlD spectrum. Anterior lobe volume reduction in normal cognition suggests early cerebellar vulnerability to DM, while more pronounced posterior lobe atrophy in amyloid-positive MCI indicates that DM may exacerbate cerebellar degeneration as amyloid pathology progresses. The absence of significant changes in preclinical AD suggests that compensatory mechanisms may delay cerebellar involvement. These findings highlight the complex interaction between diabetes and Alzheimer's disease, with DM potentially accelerating cerebellar degeneration in later stages. **Keywords:** Elderly, Diabetes mellitus, Alzheimer's disease, Cerebellum. **Disclosures:** The authors declare that they have no competing interests. **References:** 1. ZHANG, Dongsheng, et al. Frontiers in Neuroscience, 2020, 14: 571210. https://doi.org/10.3389/fnins.2020.571210; 2. LIN, Chi-Ying, et al.The Cerebellum, 2020, 19.2: 217-225. https://doi.org/10.1007/s12311-019-01099-1;3. HOGAN, Michael J., et al.Cortex, 2011, 47.4: 441-450.https://doi.org/10.1016/j.cortex.2010.01.001.

P080- LONGITUDINAL REGIONAL VOLUME CHANGES IN THE CEREBELLUM ACROSS THE ALZHEIMER'S DISEASE SPECTRUM.

Y.H. Yoo Hyun[1], S. Suhyung[1], S.M. Sheng-Min[1], D.W. Dong Woo[1], S. Sunghwan[1], H.K. Hyun Kook[1] *(1. College of Medicine, Catholic University of Korea - Seoul (Korea, Republic of))*

Background: While numerous structural and functional neuroimaging studies have focused on the cerebral cortex in Alzheimer's disease (AD), there is a relative paucity of research on the role and structural changes of the cerebellum across the Alzheimer's disease spectrum. Despite emerging evidence suggesting the cerebellum's involvement in cognitive processes, its contribution and alterations in the context of AD remain underexplored. **Objective:** This study aims to investigate the longitudinal regional volume changes in the cerebellum across different diagnostic stages of the Alzheimer's disease spectrum. We hypothesize that there are significant differences in cerebellar volume changes at each stage, from normal cognition to preclinical AD, amyloid-positive amnestic mild cognitive impairment (aMCI), and Alzheimer's dementia (ADD). **Method:** This longitudinal study included 224 participants categorized into four groups: normal cognition (n=59), preclinical AD (n=58), amyloid-positive aMCI (n=93), and ADD (n=14). Participants underwent repeated neuroimaging assessments over a period ranging from 1 to 3 years, with a maximum of three MRI scans per participant. MRI scans were processed using the Spatially Unbiased Infratentorial Template (SUIT) atlas within the Statistical Parametric Mapping (SPM) framework. Cerebellar regional volumes were segmented

and quantified using this specialized atlas. Longitudinal changes in cerebellar volumes were analyzed using linear mixed-effects models in R, adjusting for potential confounders such as age, sex, and total intracranial volume. **Results:** In the normal cognition group, significant longitudinal volume increases were observed in the following cerebellar regions: Crus I, Crus II, Lobule VIIb, and Lobule IX. In the preclinical AD group, significant longitudinal volume decreases were noted in the following regions: Vermis, Lobule I-IV, Lobule V, Lobule VI, Crus I, and Lobule VIIIa. For the amyloid-positive aMCI group, significant longitudinal volume decreases were found in Lobule V, Lobule VI, Lobule VIIIa, Lobule VIIIb, and Lobule IX. In the ADD group, no significant longitudinal volume changes were observed in any cerebellar regions. **Conclusion:** This study reveals distinct longitudinal cerebellar volume changes across AD spectrum. Individuals with normal cognition showed volume increases in certain cerebellar regions, suggesting potential compensatory mechanisms. In contrast, both preclinical AD and amyloid-positive aMCI groups exhibited significant volume decreases in specific cerebellar regions, reflecting early structural alterations associated with AD pathology. No significant changes were observed in the ADD group, indicating that cerebellar atrophy may stabilize or reach a plateau in advanced stages. These findings underscore the importance of the cerebellum in the progression of AD and suggest that cerebellar volume changes could serve as potential biomarkers for early detection and monitoring of disease progression. **Keywords:** Cerebellar volume; Alzheimer's disease spectrum; longitudinal neuroimaging, biomarkers. **Disclosures:** The authors declared no competing interests.

P081- COMPARISON OF ACCUMULATION RATES OF BETA-AMYLOID TRACERS AND THEIR RELATIONSHIP WITH COGNITIVE CHANGES. S.H. Cho[1], K. Heekyoung[2], H. Hongki[3], M. Seunghwan[4], J. Hyemin[5], Y. Jihwan[6], L. Eun Hye[2], S. Daeun[2], Y. Sohyun[7], K. Hee Jin[2], K. Byeong Chae[1], N. Duk L.[2], S. Sang Won[2], K. Jun Pyo[2] *(1. Department of Neurology, Chonnam National University Hospital, Chonnam National University Medical School - Gwangju (Korea, Republic of), 2. Departments of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine - Seoul (Korea, Republic of), 3. Neuroscience Center, Samsung Medical Center - Seoul (Korea, Republic of), 4. Department of Nuclear Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine - Seoul (Korea, Republic of), 5. Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine, Jongno-gu - Seoul (Korea, Republic of), 6. Department of Neurology, Soonchunhyang University Bucheon Hospital - Gyeonggi-Do (Korea, Republic of), 7. Departments of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine - Seoul (Korea, Republic of) - Seoul (Korea, Republic of))*

Background: 18F-Florbetaben (FBB) and 18F-flutemetamol (FMM) PET scans are used to detect brain beta-amyloid (Aβ). Understanding the differences between these tracers is crucial for interpreting amyloid PET studies. This study compares the rates of Aβ accumulation over time between these tracers and examines whether changes in Aβ uptake are related to cognitive decline differently based on the tracer type. **Methods:** Two cohorts were included: (1) a head-to-head comparison of FBB and FMM tracers in a longitudinal cohort (n=13), and (2) separate longitudinal cohorts for each tracer (n=174 for FMM and n=174 for FBB) matched by propensity score. Aβ uptake was measured in the global, frontal, parietal, cingulate, temporal, occipital cortex, and striatum using regional direct comparison of Centiloid (rdcCL) values. **Results:** In the head-to-head longitudinal cohort, subtracting the changes in FMM rdcCL from FBB rdcCL yielded median values above zero for all regions except the cingulate. In the individual tracer longitudinal cohorts, FBB rdcCL accumulation rates surpassed those of FMM in most cortical regions, but not in the striatum (β [SE] = -2.49 to -1.56 [0.47 to 0.54], $p \leq 0.001$). Differences in Mini-Mental State Examination (MMSE) changes based on annualized FMM rdcCL values were observed in the temporal cortex ($p = 0.02$) and the striatum ($p = 0.01$), but not in the FBB longitudinal study. **Conclusion:** Our findings suggest that longitudinal Aβ PET follow-up studies should consider the different characteristics of tracers depending on the specific context of use. **Keywords:** amyloid tracers, accumulation rates, cognitive changes. **Disclosures:** The author declares no competing interests. **References:** 1. Cho SH, Choe YS, Kim HJ, et al. A new Centiloid method for (18)F-florbetaben and (18) F-flutemetamol PET without conversion to PiB. Eur J Nucl Med Mol Imaging. 2020;47:1938-1948; 2. Cho SH, Shin JH, Jang H, et al. Amyloid involvement in subcortical regions predicts cognitive decline. Eur J Nucl Med Mol Imaging. 2018;45:2368-2376; 3.Cho SH, Choe YS, Kim YJ, et al. Head-to-Head Comparison of 18F-Florbetaben and 18F-Flutemetamol in the Cortical and Striatal Regions. J Alzheimers Dis. 2020;76:281-290; 4. Kim SJ, Ham H, Park YH, et al. Development and clinical validation of CT-based regional modified Centiloid method for amyloid PET. Alzheimers Res Ther. 2022;14:157.

P082- DATA-DRIVEN SUBTYPES OF WHITE MATTER LESIONS ARE DIFFERENTIALLY ASSOCIATED WITH VASCULAR AND ALZHEIMER'S PATHOLOGY. L.E. Collij[1,2], S.E. Mastenbroek[2,3], K. Steijn[2,3], C. Sudre[4], D. Van Westen[3], O. Strandberg[3], N. Mattsson-Carlgren[3], S. Palmqvist[3], E. Stomrud[3], J.E. Vogel[3], R. Ossenkoppele[2,3], O. Hansson[1] *(1. Lund Univeristy - Lund (Sweden), 2. Amsterdam UMC - Amsterdam (Netherlands), 3. Lund University - Lund (Sweden), 4. King's College London - London (United Kingdom))*

Background: White matter hyperintensities (WMHs) is a common pathology in the aging brain and often co-occur with Alzheimer's disease (AD) [1]. Recent work has suggested that the spatial distribution of WMHs is indicative of the underlying etiology, with frontal WMHs associated with vascular risk factors and posterior/occipital WMHs with amyloid-β (Aβ) pathology [2-5]. The effect of vascular co-pathologies on the efficacy and safety of anti-AD treatments is a current focus of the field. Here, we investigated the presence of WMH spatial-temporal subtypes using a data-driven approach. **Methods:** We applied the Subtype and Stage Inference (SuStaIn) model (Mixture Modelling implementation) to regional WMH lesion burden (4 lobes and 4 layers [peri-ventricular to juxta-cortical]) segmented with BaMoS software [6] across 1540 subjects in the BioFINDER-2 cohort (CU=762, MCI=381, dementia=377). SuStaIn provides individual-based assignment of subtype and disease stage [7]. Using logistic regression, SuStaIn-derived WMH-subtypes were compared on demographics, Framingham Risk Score (FRS), CSF-Aβ42/40 status (A+>0.08) [8], continuous amyloid-PET and tau-PET burden (T+: temporal meta-ROI>1.362 [9]), and presence of lacunary infarcts and microbleeds based on MR visual reads. Models were corrected for age, sex, cognitive state, and SuStaIn stage. **Results:** SuStaIn identified two WMH-progression subtypes. The first demonstrated early vascular burden in the deep and periventricular white matter of the frontal lobe, followed by deep parietal and peri-ventricular temporal regions, other

parieto-temporal layers, and finally occipital involvement. The second demonstrated early involvement of the occipital lobe (periventricular and deep layers), followed by deep parietal and frontal regions, and finally temporal and juxtacortical WMH burden. In total, 818 (53.1%) individuals had a high probability assignment (>0.70). Of those, 467 (57.1%) were assigned to the Frontal-subtype and 351 (42.9%) to the Occipital-subtype. Stage-0 subjects (n=607) were considered as a vascular-negative reference population (V-). Compared to the Occipital-subtype, individuals assigned to the Frontal-subtype were more often female (Frontal: 56.%, Occipital: 46.2%, p<0.001), cognitively unimpaired (Frontal: 42.0%, Occipital: 35.6%, p<0.001), had a higher FRS (Frontal: 37.6[±20.2], Occipital: 35.5[±18.4], β=-3.063, p=0.03), and had a higher prevalence of overall, deep, and basal ganglia lacunes (βtotal=1.05[0.26], p<0.001, βdeep=1.46[0.51], p=0.03, βBG=0.96[0.39], p=0.049). There were no differences in APOE-genotype. Subtypes did not differ in Aβ-status based on CSF-Aβ42/40 or in global Aβ-PET burden (Centiloid), but the Occipital-subtype was associated with higher amyloid-PET signal in the occipital cortex compared to the Frontal-subtype (SUVrOcccipital=1.08[±0.21], SUVrFrontal=1.05[±0.17], β=0.04[0.02], p=0.02). This finding was replicated in the A+ group (n=345). In the A+ group with available tau-PET (n=607), the Occipital-subtype had significantly higher tau burden in Braak III-IV (SUVrOcccipital=1.76[±0.67], SUVrFrontal=1.52[±0.50], β=0.16[0.05], p<0.001) and Braak V-VI regions (SUVrOcccipital=1.33[±0.39], SUVrFrontal=1.19[±0.27], β=0.09[0.03], p<0.001), compared to the Frontal-subtype. These findings were replicated in the A+/T+ group (n=304). **Conclusion:** Using a data-driven method, we identified two spatial-temporal patterns of WMHs across the clinical continuum. While the Frontal-subtype was associated with higher vascular risk and lacunary infarcts, the Occipital-subtype was associated with higher occipital amyloid-PET and tau-PET burden beyond medial-temporal regions. These results illustrate that the spatial-temporal pattern of WMH lesions represent distinct etiologies and might have implications for AD risk-stratification and clinical trial design. Future work will include longitudinal measures and cognition. **Keywords:** data-driven, white matter lesions, Alzheimer's disease, tau-PET. **References:** 1. Saridin FN, Hilal S, Villaraza SG, et al. Brain amyloid β, cerebral small vessel disease, and cognition: A memory clinic study. Neurology 2020;95:e2845-e2853. 2. Pålhaugen L, Sudre CH, Tecelao S, et al. Brain amyloid and vascular risk are related to distinct white matter hyperintensity patterns. Journal of Cerebral Blood Flow & Metabolism 2021;41:1162-1174. 3. McAleese KE, Walker L, Graham S, et al. 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SP has acquired research support (for the institution) from ki elements / ADDF and Avid. In the past 2 years, he has received consultancy/speaker fees from Bioartic, Biogen, Esai, Lilly, and Roche. ES reports no relevant disclosures. JV reports no relevant disclosures. RO has received research funding from European Research Council, ZonMw, NWO, National Institute of Health, Alzheimer Association, Alzheimer Nederland, Stichting Dioraphte, Cure Alzheimer's fund, Health Holland, ERA PerMed, Alzheimerfonden, Hjarnfonden (all paid to the institutions). R.O. has received research support from Avid Radiopharmaceuticals, Janssen Research & Development, Roche, Quanterix and Optina Diagnostics, and has given lectures in symposia sponsored by GE Healthcare. He is an advisory board member for Asceneuron and Bristol Myers Squibb. All the aforementioned has been paid to the institutions. He is an editorial board member of Alzheimer's Research & Therapy and the European Journal of Nuclear Medicine and Molecular Imaging. OH has acquired research support (for the institution) from AVID Radiopharmaceuticals, Biogen, Eli Lilly, Eisai, Fujirebio, GE Healthcare, and Roche. In the past 2 years, he has received consultancy/speaker fees from AC Immune, Alzpath, BioArctic, Biogen, Bristol Meyer Squibb, Cerveau, Eisai, Eli Lilly, Fujirebio, Merck, Novartis, Novo Nordisk, Roche, Sanofi and Siemens.

P083- NEUROIMAGING DATA HARMONIZATION IN MULTISITE STUDIES OF ALZHEIMER'S DISEASE AND POTENTIAL IMPLICATIONS ON EFFECT SIZES IN CLINICAL TRIALS.

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Background: Multisite imaging studies increase statistical power and enable the generalization of research outcomes. However, different tau PET tracer properties and inter-scanner technical variability hinders the ability to directly compare multi-scanner and multi-tracer PET data. This is further complicated due to off-target binding characteristic of tau tracers, which can lead to bias in the SUVR estimates and artificially increase or decrease effect sizes in clinical studies of Alzheimer's Disease. In this study, we investigate a scanner harmonization method, ComBat, and its downstream effects on effect size and sample size variability differences in samples of

cognitively unimpaired (CU), mild cognitive impairment (MCI), and Alzheimer's disease (AD) participants in a large multisite study of Alzheimer's disease. **Methods:** 188 participants (114 CU, 58 MCI, 16 AD) received T1 MR, amyloid PET, and 18F-flortaucipir (FTP) (80-100min) and 18F-MK-6240 (MK) (90-110min) tau PET imaging at 6 sites on 6 different scanners under the HEAD study. Tau PET images were smoothed to a common 6mm3 resolution with a scanner-specific Gaussian kernel and processed using a Freesurfer-based pipeline. Braak region (1-6) SUVR outcomes were calculated with inferior cerebellar gray matter as reference. ComBat harmonization(1) was performed on SUVR outcome measures to estimate and remove post-smoothing scanner effects for each tau tracer, FTP and MK, separately. Cohen's d effect sizes, adjusted for unequal sample sizes and variances, were computed for FTP and MK before and after ComBat between CU and AD, MCI and CU and MCI and AD for all 6 Braak region SUVR outcomes. **Results:** For non-harmonized data, Cohen's effect sizes across Braak regions ranged from: 2.73 to 1.35 for MK and 2.59 to 1.28 for FTP between CU and AD, from 1.17 to 0.95 for MK and 1.17 to 0.75 for FTP between MCI and AD, and from 1.25 to 0.52 for MK and 1.11 to 0.53 for FTP between CU and MCI. For harmonized data, Cohen's d effect sizes ranged from: 2.9 to 1.5 for MK and 2.71 to 1.34 for FTP between CU and AD, from 1.24 to 0.98 for MK and 1.24 to 0.75 for the FTP between MCI and AD and from 1.34 to 0.61 for MK and 1.14 to 0.56 for FTP between CU and MCI. ComBat harmonization increased effect sizes across all regions for both tau tracers and across all cognitive status group comparisons, with the exception of FTP Braak 3, in which the CU vs MCI effect size was lowered after harmonization (0.86) compared with before (0.91). **Conclusion:** ComBat harmonization near universally increased effect sizes within each tracer, likely due to reducing within-group variability even after smoothing to a common 6mm3 resolution. These results suggest that Gaussian smoothing may not adequately remove inter-scanner variability in multi-site PET studies. Even so, effect sizes for FTP were consistently lower compared to those from MK. Careful consideration should be given when combining data from different sites and tracers, and harmonization methods should be carefully examined given that effect sizes are standard measures used to determine sample sizes in clinical trials.

P084- NOVEL REGIONAL FLORTAUCIPIR VISUAL READ APPROACHES TO STRATIFY SUBJECTS BY TAU SPREAD: EVALUATION IN TRAILBLAZER-ALZ 2 PHASE 3 STUDY OF DONANEMAB. I. Kennedy[1], M.J. Kim[1], A.K. Arora[1], M. Lu[1], I. Tunali[1], L. Iaccarino[1], J.R. Sims[1], E.C. Collins[1], M.A. Mintun[1], S. Shcherbinin[1] *(1. Eli Lilly and Company - Indianapolis (United States))*

Background: : When visually assessing flortaucipir positron emission tomography (FTP-PET) scans for evidence of Alzheimer's disease (AD), readers interpret regional patterns of tau tracer uptake as either consistent with AD or not. More advanced stratification by regional FTP uptake phenotypes may facilitate staging disease and understanding prognoses. To supplement composite assessments, FTP-PET regional assessments from TRAILBLAZER-ALZ 2 (NCT04437511) were used to create tau spread visual patterns to stratify subjects and compare subgroups in terms of clinical progression. **Methods:** TRAILBLAZER-ALZ 2 was a randomized, double-blind, placebo-controlled phase 3 76-week trial of donanemab in participants with early symptomatic AD with both amyloid and tau pathology [1]. Tau deposition was assessed quantitatively and visually using FTP-PET. In a post hoc study of baseline FTP-PET visual reads, 4 novel methodologies were created to stratify scans as having relatively earlier stage or later stage tau spread. Visual read was based on tracer uptake in the left and right hemispheres of the anterior lateral temporal (ALT), posterior lateral temporal (PLT), occipital, precuneus, parietal excluding precuneus, and frontal regions. Later stage tau spread was defined by presence of increased FTP uptake in all 6 bilateral regions (Method 1); either hemisphere (Method 2) or both hemispheres (Method 3) of the PLT, occipital, parietal/precuneus (combined region), and frontal regions; or the left and/or right frontal region (Method 4). These methods were based on different approaches to assessing extent of FTP uptake (Methods 1, 2, and 3) and the hypothesis that the frontal lobe is expected to be one of the latest regions affected by tau pathology in AD (Method 4). Additionally, Methods 2 and 3 utilize the 4 regions most commonly assessed by readers. Clinical progression was measured by change from baseline to Week 76 in the integrated AD Rating Scale (iADRS; primary analysis) and Clinical Dementia Rating – Sum of Boxes (CDR-SB). Clinical progression was compared between tau visual pattern subgroups within each method using a natural cubic spline model with two degrees of freedom. Results for placebo-treated participants are presented. **Results:** Of 824 baseline FTP-PET scans from placebo-treated participants, later stage tau spread was observed in 33.3%, 54.6%, 35.7%, and 72.3% with Methods 1, 2, 3, and 4, respectively. Across all visual read methods, participants with later stage tau at baseline were younger, had quantitatively more tau and amyloid, and were cognitively more impaired than earlier-stage subgroups. At Week 76 in later-stage vs. earlier-stage subgroups within each method, respectively, least-square mean (standard error) changes in the iADRS were -20.0 (0.8) vs. -9.3 (0.6), -16.5 (0.7) vs. -8.5 (0.7), -19.5 (0.8) vs. -9.2 (0.6), and -15.4 (0.6) vs. -6.4 (0.9). Later-stage subgroups also had faster cognitive decline per the CDR-SB. **Conclusion:** Four novel visual read methodologies of FTP-PET scans were tested as a staging scheme in phase 3 trial placebo-treated participants with early symptomatic AD. Each method demonstrated the ability to visually differentiate stages of tau spread without use of specialized imaging software. Future analyses may determine reliability of visual read methods and assess more nuanced regional phenotypes. **Keywords:** Alzheimer's disease, tau positron emission tomography, flortaucipir, phase 3 clinical trial. **Clinical Trial Registry:** NCT04437511; https://clinicaltrials.gov. **Disclosures:** All authors are employees and shareholders of Eli Lilly and Company. This study was sponsored by Eli Lilly and Company. **References:** 1. Sims et al, 2023. doi:10.1001/jama.2023.13239.

P085- MULTICENTER READER STUDY ASSESSING DIAGNOSTIC ACCURACY OF AMYLOID-B DETECTION COMPARING REAL VERSUS AI-BASED AMYLOID-B PET GENERATED FROM BRAIN MRI. G. Mathoux[1], E. Pirazzo Andrade Teixeira[1], P. Blanc[2], N. Pyatigorskaya[3], D.E. Peretti[4], D. Ioannidou[5], A. Duran[5], G. Temiz[5], S. Belachew[5], N. Paragios[5], J. Touchon[6], B. Vellas[7], A. Gabelle[6], P. Payoux[8], G. Frisoni[9], V. Garibotto[10] *(1. Diagnostic Department, Division of Nuclear Medicine and Molecular Imaging, Geneva University Hospital. - Geneva (Switzerland), 2. Nuclear Medicine Department, Centre Hospitalier d'Albi - Albi (France), 3. Neuroradiology Department, University Hospitals Pitié Salpêtrière - Paris (France), 4. Laboratory of Neuroimaging and Innovative Molecular Tracers (NIMTlab), Faculty of Medicine, Geneva University Neurocenter, University of Geneva - Geneva (Switzerland), 5. Therapanacea - Paris (France), 6. Faculty of Medicine, University of Montpellier - Montpellier (France), 7. Gérontopôle, Centre Hospitalier Universitaire de Toulouse - Toulouse (France), 8. Department of Nuclear Medicine, CHU Toulouse Purpan - Toulouse (France), 9. Department of Rehabilitation and Geriatrics, Memory Clinic, Geneva University Hospitals - Geneva (Switzerland), 10. Diagnostic Department, Division of Nuclear Medicine and Molecular Imaging, Geneva University Hospitals, University of Geneva - Geneva (Switzerland))*

Background: Amyloid-β (aβ) positive profile is mandatory for Alzheimer's disease (AD) diagnosis and aβ-depleting disease-modifying treatment (aβ-DMT) eligibility. Aβ profile measured by aβ positron emission tomography (PET-aβ) imaging is expensive and not scalable. Generating aβ-PET images from MRI scans would offer a cost-effective and easy-to-implement screening solution to fast-track the right patients for early diagnosis and care. We conducted a multicenter reader study assessing the diagnostic accuracy of aβ detection by comparing reader performances on parametric maps (centiloid) derived from real PET scans versus synthetic aβ-PET generated with artificial intelligence (AI)-based models using brain MRI as input. **Methods:** We developed an AI model trained using paired T1w brain MRI and aβ-PET-derived centiloid maps that are obtained from standardized uptake value ratio (SUVr) maps from the EMERGE [NCT02484547] and ENGAGE [NCT02477800] clinical trials. The model consists of a 3D USE-Net and allows to predict centiloid map from MRI. For the reader study, we used an independent external validation set made of aβ-PET and T1w data from the A4 clinical trial [NCT02008357] (n=8) and the Memory Center of Geneva University Hospitals (n=11), involving 12 aβ-positive, 6 aβ-negative, and 1 borderline patient, mean age 70 ± 6.2 years. The ground truth for aβ positivity in the external validation data was established based on CSF measures. Real aβ-PET centiloid maps were created by processing native PET images, including motion correction, static conversion, skull striping, smoothing, resampling, normalization, SUVr maps creation and conversion to centiloid map. The final volumes were then registered in the same atlas space (MIITRA). Synthetic aβ-PET centiloid maps were generated from T1w images with USE-Net. Four readers blindly assessed both real and synthetic aβ-PET centiloid maps for aβ positivity detection for each of the cases. **Results:** The model's performance on the EMERGE & ENGAGE clinical trial test set achieved a 76% balanced accuracy for aβ positivity/negativity assessment. For real aβ-PET centiloid maps, the mean true positives (TP) of reader performances were 77.09%, true negatives (TN) were 87.50%, false positives (FP) were 12.50%, and false negatives (FN) were 31.25%, indicating high accuracy in identifying aβ status. In comparison, reader performances for synthetic aβ-PET centiloid maps showed mean values of 54.17% for TP, 45.83% for TN, 50% for FP, and 56.25% for FN. The inter-reader agreement was moderately strong, with a mean kappa value of 0.47, demonstrating consistent assessments among readers across both real and synthetic maps. Additionally, two readers noted the challenge in distinguishing between real and synthetic aβ-PET images. Two other readers attempted to identify whether the images were real or synthetic. Reader 1 correctly identified 14 out of 19 real images and 19 out of 19 synthetic images, while Reader 2 correctly identified 10/19 real images and 11/19 synthetic images. **Conclusion:** Although the sample size is small, which makes challenging the interpretation of the results, our findings indicate that generating synthetic aβ-PET centiloid maps is feasible, and a promising avenue as software screening tools for computer-assistive detection of aβ in early AD diagnosis, additional efforts in this direction are warranted. **Keywords:** AD, biomarker, generative AI, amyloid beta, amyloid PET.

P086- ROBUSTNESS OF VISUAL AND QUANTITATIVE ASSESSMENT OF [18F]PI-2620 PET SCANS EVALUATED WITH DIFFERENT MASS DOSES. N. Roé-Vellvé[1], H. Barthel[2], L. Howard[1], N. Koglin[1], A. Mueller[1], A. Perrotin[1], A. Jovalekic[1], F.R. Zientek[2], M. Rullmann[2], M. Patt[2], A. Schildan[2], T. Jeschke[2], O. Mishchenko[2], M. Berndt[2], C. Papin[1], J. Castillo-Melean[1], A. Stephens[1], O. Sabri[2], S. Bullich[1] *(1. Life Molecular Imaging GmbH - Berlin (Germany), 2. Nuclear Medicine Department, University of Leipzig Medical Center - Leipzig (Germany))*

Background: [18F]PI-2620 is an increasingly used PET tracer for in vivo tau detection, and shows excellent properties in Alzheimer's disease (AD) studies in terms of signal-to-noise ratio, brain uptake, kinetics, dosimetry, and effect-size, as well as showing a low test-retest variability [1]. Additional clinical studies also indicate the ability of [18F]PI-2620 to detect tau aggregates in 4R tauopathies like progressive supranuclear palsy (PSP). To the best of our knowledge, the possible impact of different tracer mass doses on image characteristics was not assessed for any tau PET tracer so far. **Methods:** Five AD and five PSP patients participated in the study and underwent two PET tracer administrations and dynamic PET data acquisition (10 ± 8 days apart). The first scan was obtained after injection of a low mass dose (0.31 ± 0.12 μg PI-2620), and the second one with a high mass dose (44.56 ± 2.82 μg PI-2620). The injected amount of radioactivity was the same in both instances (180 ± 11 MBq [18F]PI-2620). Three blinded readers independently evaluated the SUVR and DVR images from each session in a pairwise comparison. The sequence of the images displayed (high or low mass dose image first) was randomized. The comparison was performed both globally and at a regional level, using a relevant set of regions of interest (ROIs). DVR values were also calculated for these ROIs and analyzed by Bland-Altman plots. The data were fitted to a target occupancy model [2] to assess the potential biases in quantitative parameters associated to mass dose values. **Results:** All PET tracer administrations and acquisition procedures were well tolerated. Regional and global visual assessments as positive vs. negative were not affected in any case by mass dose neither in SUVR nor DVR images. For SUVR and DVR regional quantitative values, individual differences between the high and low mass dose images were predominantly within or in very close proximity to the 95% confidence interval determined from a prior test-retest variability study of [18F]PI-2620 [1]. This was the case both for the AD and the PSP patients. These results demonstrate a high level of agreement between the PET signals obtained for high and low mass dose images

in the AD and PSP patients studied. The occupancy model further confirmed that the bias in quantitative parameters is negligible when [18F]PI-2620 is used in real-world conditions. **Conclusion:** This study confirmed that [18F]PI-2620 image characteristics are retained at high tracer mass doses. As such, the tracer can be used with high confidence even several half-lives after end of synthesis, as would happen after a longer time of transportation. This further supports the use of [18F] PI-2620 in research studies and clinical evaluations, including longitudinal studies and therapy monitoring. **Keywords:** [18F]PI-2620, Tau PET, Alzheimer's Disease, Progressive Supranuclear Palsy, AD, PSP, Mass dose, Visual assessment, Quantification, SUVR, DVR. **References:** 1. Bullich et al., JNM, 2020;61(6):920-927; https://doi.org/10.2967/jnumed.119.236240. 2. Madsen et al., Nuc MedBiol, 2011; 38(8):1085-1091; https://doi.org/10.1016/j.nucmedbio.2011.04.006. **Disclosures:** Núria Roé-Vellvé, Lorelei Howard, Audrey Perrotin, Andre Mueller, Norman Koglin, Aleksandar Jovalekic, Mathias Berndt, Caroline Papin, Johnny Castillo-Melean, Andrew Stephens and Santiago Bullich are employees of Life Molecular Imaging GmbH, Berlin, Germany. Henryk Barthel, Osama Sabri, Franziska Zientek, Michael Rullmann, Andreas Schildan, Tobias Jeschke and Olena Mishchenko received financial study support from Life Molecular Imaging GmbH, Berlin, Germany. Marianne Patt has nothing to disclose.

P087- EVALUATION OF A SENSITIVE VISUAL READ ALGORITHM FOR ASSESSING TAU PET IMAGES. R. Smith[1], V. Garibotto[2], D. Hägerström[3], J. Jögi[4], T. Ohlsson[5], O. Strandberg[1], M. Tonietto[6], S. Janelidze[1], S. Palmqvist[1], E. Stomrud[1], G. Klein[6], O. Hansson[1] *(1. Lund University, Clinical Memory Research Unit - Malmö (Sweden), 2. Division of Nuclear Medicine and Molecular Imaging, Diagnostic department, University Hospitals of Geneva - Geneva (Switzerland), 3. Skåne University Hospital, Department of Clinical Neurophysiology - Lund (Sweden), 4. Skåne University Hospital, Department of Clinical Physiology and Nuclear Medicine - Lund (Sweden), 5. Skåne University Hospital, Department of Radiation Physics - Lund (Sweden), 6. Hoffman La Roche Ltd. - Basel (Switzerland))*

Background: Developing and validating sensitive visual read algorithms for assessing tau-PET imaging is imperative considering the implementation of the methodology in clinical practice and trials. Our objective of this study was to compare two visual read algorithms for tau-PET images to semiquantitative measurements and plasma phospho-tau217 (p-tau217). **Methods:** The study was conducted in the prospective BioFINDER-2 cohort study (May 2017–Sept 2023). In total 1654 consecutively recruited participants were recruited from secondary Memory and Neurology clinics in southern Sweden. All participants underwent [18F]RO948 PET scans and 37 participants additionally underwent a head-to-head [18F]flortaucipir PET scan. PET scans were read visually according to the BioFINDER visual read protocol1 and the established visual read method for [18F]flortaucipir (FTP-VR)2. Comparative analyses were performed against semiquantitative standardized uptake value ratios (SUVRs) in the entorhinal cortex (ERC) and a temporal meta-ROI, and with the ability to estimate plasma p-tau217 status. The primary endpoints included the sensitivities and specificities of visual read algorithms in detecting increases in semiquantitative SUVRs and p-tau217. Secondary outcomes encompassed the intra-rater and inter-rater reliabilities of the BioFINDER algorithm. **Results:** Both visual read methods exhibited strong concordance with semiquantitative SUVRs. However, the BioFINDER visual read demonstrated superior sensitivity for tau in the ERC compared to FTP-VR ((mean[95%C.I.]) 0.912[0.881-0.936] vs. 0.761[0.719-0.8]; p<0.0001), while maintaining a comparable specificity (0.951[0.937-0.962] vs. 0.949[0.935-0.961]; p=0.77). The BioFINDER visual reads displayed heightened sensitivity (0.952[0.925-0.971] vs. 0.925[0.893-0.95]; p=0.008) albeit with a lower specificity (0.909 [0.891-0.924] vs. 0.955[0.942-0.965]; p<0.0001) for detecting tau in the temporal meta-ROI. Further, the BioFINDER visual reads exhibited higher sensitivity (0.709[0.667-0.749]) compared to FTP-VRs (0.641 [0.597-0.683]; p<0.0001) for detection of p-tau217 abnormality. The inter-rater reliability of the BioFINDER algorithm was excellent (weighted Cohen's kappa [κ]=0.87[0.82-0.93]) and intra-rater reliability almost perfect (κ=0.94[0.89-0.98]). The concordance of visual read assessments of [18F]RO948 and [18F]flortaucipir images was excellent (κ=0.94[0.86-1.00]). **Conclusion:** Visual reads offer a straightforward method for evaluating tau-PET scans. The BioFINDER algorithm provides a more sensitive algorithm for detecting early tau uptake compared to the established FTP-VR algorithm and shows a similar performance when using [18F]RO948 and [18F]flortaucipir images, indicating that the visual read method can easily be applied to [18F] flortaucipir PET scans. **Keywords:** AD, Tau PET, visual read, diagnostic accuracy, biomarkers. **Disclosures:** DH, ES, JJ, OS and SJ report no disclosures. RS has received a speaker fee from Roche. MT and GK are full-time employees of Hoffman-La Roche Ltd. In the last year TO has received consultancy fee from Spago Nanomedical. OH has acquired research support (for the institution) from AVID Radiopharmaceuticals, Biogen, C2N Diagnostics, Eli Lilly, Eisai, Fujirebio, GE Healthcare, and Roche. In the past 2 years, he has received consultancy/speaker fees from AC Immune, Alzpath, BioArctic, Biogen, Bristol Meyer Squibb, Cerveau, Eisai, Eli Lilly, Fujirebio, Merck, Novartis, Novo Nordisk, Roche, Sanofi and Siemens. SP has acquired research support (for the institution) from ki elements / ADDF and Avid. In the past 2 years, he has received consultancy/speaker fees from Bioartic, Biogen, Esai, Lilly, and Roche. VG received through her institution research support and speaker fees from Siemens, GE Healthcare, Janssen and Novo Nordisk. **References:** 1. Smith R, Hagerstrom D, Pawlik D, et al. Clinical Utility of Tau Positron Emission Tomography in the Diagnostic Workup of Patients With Cognitive Symptoms. JAMA Neurol. Jul 1 2023;80(7):749-756. doi:10.1001/jamaneurol.2023.1323; 2. Fleisher AS, Pontecorvo MJ, Devous MD, Sr., et al. Positron Emission Tomography Imaging With [18F]flortaucipir and Postmortem Assessment of Alzheimer Disease Neuropathologic Changes. JAMA Neurol. Jul 1 2020;77(7):829-839. doi:10.1001/jamaneurol.2020.0528.

P088- REGIONAL CEREBRAL HYPOMETABOLISM AND PATHOLOGICAL HETEROGENEITY IN SPORADIC EARLY ONSET ALZHEIMER'S DISEASE USING MULTI-PROBES PET/CT. Z. Zehua[1], S. Jiong[2], W. Shicun[3], L. Xinyi[2], S. Yong[2] *(1. Department of Nuclear Medcine, The First Affiliated Hospital of USTC - Hefei (China) - Hefei (China), 2. Department of Neurology, The First Affiliated Hospital of USTC - Hefei (China), 3. Department of Nuclear Medcine, The First Affiliated Hospital of USTC - Hefei (China))*

Background: Early-onset Alzheimer's disease (EOAD) occurs before 65 years old and accounts for about 10% of all AD cases. Previous studies mainly focused on familial forms of EOAD, while sporadic EOAD (sEOAD) has been under-studied. Technological advancement in molecular imaging and testing of fluid biomarkers has improved our ability to explore

the underlying mechanism of sEOAD. It has been used to compare hypometabolism patterns in sporadic EOAD versus sporadic LOAD patients in several areas of the brain. Multi-probes PET/CT neuroimaging can be used not only to improve sEOAD diagnostic acumen but also enhance our understanding of fundamental pathobiological changes before the onset of symptoms. Throughout this study, we endeavor to integrated multi-probes PET/CT neuroimaging and fluid biomarkers, with the goal of showing how the described approaches can be used to improve our understanding of diagnostic acumen for sEOAD and its heterogeneous clinical presentations. **Methods:** Patients were recruited between 2018 and 2024 from the CANDI study, a prospective cohort study on AD. It included 112 patients with sEOAD, 88 with late-onset AD, 21 young controls, and 11 older controls. All AD patients met the ATN diagnostic criteria. Patients with familial EOAD or non-AD dementia were excluded. Single molecule array technology was used to measure fluid biomarkers, including cerebrospinal fluid (CSF) and plasma amyloid beta (Aβ) 40, Aβ42, phosphorylated tau (p-Tau) 181, total tau (T-tau. Cerebral glucose metabolism and β-Amyloid burden were further assessed by using multi-probes PET/CT (18F-FDG-PET ,18F-AV45-PET and 18F-AV1451-PET) for sEOAD biological definition. PET imaging data were analyzed by SPM12 software implanted in MATLAB 2020b environment. **Results:** Using the FDG-PET scan, the cerebral hypometabolism pattern of sEOAD was observed and limited to bilateral precuneus while the cerebral hypermetabolism pattern was in medial supra- frontal gyrus [$p < 0.05$, family-wise error (FWE) corrected with cluster size (KE) above 20 contiguous voxels]. The same hypermetabolism pattern was also detected in young healthy and older healthy controls. Using the Aβ-PET scan, sEOAD demonstrated lower Aβ burden in the bilateral precuneus, anterior cingulate gyrus, posterior cingulate gyrus, and medial superior frontal gyrus ($p < 0.05$, FWE corrected, KE>2U0). There was no significant Aβ deposition observed in the same cortical areas in healthy control groups. Using the tau-PET scan, sEOAD showed more pronounced tau deposition bilaterally in the precuneus, in contrast to their milder Aβ deposition in the same region ($p < 0.05$, FWE corrected, KE>20). Consistently, CSF P-tau181 levels ($t=3.696$, $p=0.0003$) were elevated in patients with sEOAD, while other AD core biomarkers (plasma P-tau181, plasma T-tau, Aβ42,Aβ40, Aβ42/Aβ40,etc] .) had no statistically significant difference. SUVR values calculated from the precuneus ROI region based on 18F-AV1451 imaging showed the most significant differences ($p <0.0001$) and showed the best efficacy for diagnosing sEOAD from LOAD (AUC=0.878, $p <0.0001$). **Conclusion:** As a result of these preliminary findings, we can conclude that the spatial metabolic profile and Aβ heterogeneity discriminated sEOAD from LOAD. The bilateral precuneus hypometabolic, lower Aβ deposition and higher Tau deposition neuroimaging pattern may integrated as one potential neuroimaging biomarker for characterizing sporadic early-onset Alzheimer's disease.

P089- FIRST-IN-HUMAN PET IMAGING STUDY OF INTRANASAL INSULIN USING THE APTAR CARTRIDGE PUMP SYSTEM. K.K. Solingapuram Sai[1], J.M. Erichsen[1], K. Gollapelli[1], I. Krizan[1], M. Miller[1], C. Cazzola[2], R. Gandhi[2], J. Suman[<é], S. Craft[1] *(1. Wake Forest School of Medicine - Winston Salem (United States), 2. Aptar Pharma - Congers (United States))*

Background: Intranasal insulin (INI) is being explored as a treatment for memory impairment and Alzheimer's disease (AD); improved memory, functional ability, and cerebrospinal fluid (CSF) AD biomarker profiles have been observed following INI administration. However, the method of intranasal delivery has been shown to affect outcomes. Before INI can be fully used clinically, it is essential to identify an intranasal delivery device that reliably and effectively delivers insulin to the brain. We recently demonstrated the whole-body distribution and dosimetry of a novel PET radiotracer, [68Ga] Ga-NOTA-insulin intranasally with the Aptar Cartridge Pump System (CPS) in nonhuman primates. Here, we report our preliminary findings from our first-in-human PET imaging study using [68Ga]Ga-NOTA-insulin with the Aptar CPS intranasal device in 17 cognitively normal and impaired older adults (aged 60-84 years). **Methods:** Chelated NOTA-insulin was radiolabeled with [68Ga]Cl3 in GMP conditions. Aptar CPS was used to intranasally administer [68Ga]Ga-NOTA-insulin (~0.037 ± 0.001 GBq, 6 sprays, 30 sec apart). A dynamic 40-minute brain PET scan, followed by a 15-minute whole-body PET/CT scan were acquired. Vitals including temperature, blood pressure, heart rate, SpO2, and blood glucose were measured at baseline, during, and post-scan. Brain uptake and time-activity curves were determined using the fused PET/MRI images on PMOD software (v4.103). **Results:** Radiochemistry was fully optimized (n=40 runs) for producing high-quality [68Ga]Ga-NOTA-insulin in high radiochemical purity (>99%) and molar activity (95 GBq/μmol). Safety was confirmed: vitals remained stable and blood glucose levels were unchanged in all the participants scanned. PMOD analyses resulted in a whole-brain average SUV(g/mL) of ~0.68 ±0.01 and radioactivity in the brain and whole body were washed away by the end of 40- and 60-min post-radiotracer administration respectively. **Conclusion:** The use of [68Ga]Ga-NOTA-insulin as a PET radiotracer is safe and effective for observing brain uptake in humans. Efficacy and feasibility were shown for the first time i.e., brain penetration was seen in all the subjects scanned following intranasal administration with the Aptar CPS. We are currently working on regional PET/MRI brain analyses and correlations of PET uptake with their associated amyloid loads.

P090- FDG PET FINDINGS ACCORDING TO WANDERING PATTERNS OF PATIENTS WITH DRUG-NAÏVE ALZHEIMER'S DISEASE. Y. Yang[1] *(1. Soonchunhyang University College of Medicine - Cheonan (Korea, Republic of))*

Background and Purpose: To explore anatomic substrate of specific wandering patterns in patients with Alzheimer's disease (AD) by performing positron emission tomography with 18F fluorodeoxyglucose positron emission tomography (FDG PET). **Methods:** Drug-naïve AD patients with wandering (n=80) and without wandering (n=262) were recruited. First, the specific pattern of wandering type was operationally classified according to specific wandering score and clinical assessment. Second, brain FDG PET was performed and fluorodeoxyglucose (FDG) uptake differences of specific brain regions according to wandering patterns were compared to those of non-wanderers. **Results:** In patients with pacing pattern, FDG PET showed significant lower FDG uptake in both middle cingulum and left putamen cluster compared to non-wanderers. The right precuneus and supplementary motor area in patients with random pattern and left calcarine sulcus, right calcarine sulcus, right middle cingulum, and right post central gyrus in patients with lapping pattern had significantly lower FDG uptake compared to non-wanderers. **Conclusion:** This study showed that wandering in patients with AD had three distinct patterns. These specific patterns showed significant lower FDG uptake in specific brain areas compared to non-wanderers.

P091- INDEPENDENT EFFECTS OF WHITE MATTER HYPERINTENSITIES ON FRAILTY FOR PATIENTS WITH ALZHEIMER'S DEMENTIA. W.M. Bahk[1], B.H. Yoon[2], K. Lee[3], H.M. Sung[4], S.Y. Park[5], M.K. Song[6], M.D. Kim[7], H.J. Yang[7], S.Y. Lee[8] *(1. Professor, Department of Psychiatry, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea - Seoul (Korea, Republic of), 2. Psychiatrist, Department of Psychiatry, Naju National Hospital - Naju (Korea, Republic of), 3. Professor, Department of Psychiatry, College of Medicine, Dongguk University - Gyeonju (Korea, Republic of), 4. Professor, Department of Psychiatry, Soonchunhyang University Gumi Hospital, - Gumi (Korea, Republic of), 5. Psychiatrist, Department of Psychiatry, Jeyo Hospital - Uiwang (Korea, Republic of), 6. Psychiatrist, St. Mary's Gon-Gam Mental Health Clinic - Siheung (Korea, Republic of), 7. Professor, Department of Psychiatry, College of Medicine, Jeju National University - Jeju (Korea, Republic of), 8. Professor, Department of Psychiatry, Wokwang University School of Medicine - Iksan (Korea, Republic of))*

Purpose: With an aging global population, there has been a rapid increase in attention to frailty in the recent years. Thus, understanding and determining the potentially modifiable risk factor for frailty is a major concern for health care policy and provision. **Material and method:** Subjects were recruited for the study from the dementia clinic of Jeju National University Hospital between January 2018 and January 2020. All of the subjects were evaluated by using CERAD-K and diagnosed probable AD and possible AD by a panel of two experienced dementia research neuropsychiatrists. WMH volume was calculated using automated segmentation analysis and further partitioned into three categories (Kim, BIOL PSYCHIATRY 2008). Frailty evaluated by Korean Frailty Index (KFI) and classified into three categories according to the cutpoints. Other physical performances such as BMI, muscle mass index, grip strength, and gait speed measures were performed by experienced researchers specialized in geriatric assessment. comorbidity status using the Charlson comorbidity index, and depressive symptoms using GDS was examined. **Results:** In total, 34 subjects (23.6 %) were classified as frail 47 subjects (32.6 %) were classified as prefrail, and 63 subjects (43.8 %) were classified as a non-frail group. The frail group had higher WMH volume compared to the non-frail group (p=0.002), and these trends remained significant after linear regression analyses. According to the new subclassification of WMH, using the non-frail group as a reference, total WMH volume (OR=6.297, p=0.013), JVWMH volume (OR=12.955, p=0.014), and PVWMH (OR=3.382, p=0.025) were associated with frail. Furthermore, according to the path model, only the gait speed mediated the association between WMH and frailty. **Conclusion:** In our study provides evidence of a cross-sectional relationship between WMH and frailty, and there is a difference in the association between the subclassification of WMH volume and frailty. Furthermore, we suggest that gait speed could be a useful biomarker for assessment of the frailty.

P092- OLFACTORY DYSFUNCTION IS ASSOCIATED WITH CEREBRAL AMYLOID DEPOSITION AND COGNITIVE FUNCTION IN THE TRAJECTORY OF ALZHEIMER'S DISEASE. W.M. Bahk[1], B.H. Yoon[2], Y.J. Kwon[3], K. Lee[4], S.Y. Lee[5], H.M. Sung[6], S.Y. Park[7], M.K. Song[8], S.M. Wang[1], H.K. Lim[1] *(1. Department of Psychiatry, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea - Seoul (Korea, Republic of), 2. Department of Psychiatry, Naju National Hospital - Naju (Korea, Republic of), 3. Department of Psychiatry, Soonchunhyang University Cheonan Hospital, Soonchunhyang University - Cheonan (Korea, Republic of), 4. Department of Psychiatry, College of Medicine, Dongguk University, - Gyeongju (Korea, Republic of), 5. Department of Psychiatry, Wonkwang University Hospital, Wonkwang University School of Medicine - Iksan (Korea, Republic of), 6. Department of Psychiatry, Soonchunhyang University Gumi Hospital, College of Medicine, Soonchunhyang University - Gumi (Korea, Republic of), 7. Department of Psychiatry, Keyo Hospital - Uiwang (Korea, Republic of), 8. St. Mary's Gong-Gam Mental Health Clinic - Siheung (Korea, Republic of))*

Background: Olfactory dysfunction is consistently observed in individuals with Alzheimer's disease (AD), but its association with beta-amyloid (Aβ) deposition remains unclear. This study aimed to investigate the relationship among olfactory function, cerebral Aβ deposition, and neuropsychological profiles in individuals with no cognitive impairment (NCI), mild cognitive impairment (MCI), and AD dementia. **Methods:** A total of 164 participants were included, and olfactory function was assessed using the brief smell identification test (B-SIT). Cerebral Aβ deposition was measured using [18F]-flutemetamol PET imaging (A-PET). **Results:** The results show a significant group difference in olfactory function, with the highest impairment observed in the Aβ-positive MCI and AD dementia groups, and the impairment was the lowest in Aβ-negative NCI. Olfactory dysfunction was positively associated with cognitive impairments across multiple domains. Furthermore, individuals with Aβ deposition had lower olfactory function compared to those without Aβ, even within the same neuropsychological stage. The association between olfactory dysfunction and Aβ deposition was observed globally and in specific cortical regions. **Conclusion:** These findings suggest that olfactory dysfunction is associated with both cognitive function and cerebral Aβ pathology in the trajectory of AD. Olfactory deficits may serve as an additional marker for disease progression and contribute to understanding the underlying mechanisms of AD. **Keywords:** Alzheimer's disease; beta-amyloid; mild cognitive impairment; olfaction. **Disclosures:** This research was supported by a grant of the Korea Dementia Research Project through the Korea Dementia Research Center (KDRC), funded by the Ministry of Health & Welfare and Ministry of Science and ICT, Republic of Korea (grant number: HU22C0011). **Conflicts of Interest:** The authors declare no conflict of interest. **References:** 1. Dubois, B.; Villain, N.; Frisoni, G.B.; Rabinovici, G.D.; Sabbagh, M.; Cappa, S.; Bejanin, A.; Bombois, S.; Epelbaum, S.; Teichmann, M.; et al. Clinical diagnosis of Alzheimer's disease: Recommendations of the International Working Group. Lancet Neurol. 2021, 20, 484–496. [CrossRef]; 2. Kurkinen, M.; Fulek, M.; Fulek, K.; Beszlej, J.A.; Kurpas, D.; Leszek, J. The Amyloid Cascade Hypothesis in Alzheimer's Disease: Should We Change Our Thinking? Biomolecules 2023, 13, 453. [CrossRef] [PubMed]; 3. Lloret, A.; Esteve, D.; Lloret, M.A.; Cervera-Ferri, A.; Lopez, B.; Nepomuceno, M.; Monllor, P. When Does Alzheimer's Disease Really Start? The Role of Biomarkers. Int. J. Mol. Sci. 2019, 20, 5536. [CrossRef] [PubMed];

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P093- SEX-RELATED DISPARITIES IN THE RESTING STATE FUNCTIONAL CONNECTIVITY OF THE LOCUS COERUELUS AND SALIENCE NETWORK IN PRECLINICAL ALZHEIMER 'S DISEASE. K. Lee[1], H.K. Lim[2], S.M. Wang[2], W.M. Bahk[2], B.H. Yoon[3], S.Y. Lee[4], H.M. Sung[5], S.Y. Park[6], M.K. Song[7] *(1. Department of Psychiatry, College of Medicine, Dongguk University - Gyeongju (Korea, Republic of), 2. Department of Psychiatry, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea - Seoul (Korea, Republic of), 3. Department of Psychiatry, Naju National Hospital - Naju (Korea, Republic of), 4. Department of Psychiatry, Wonkwang University Hospital, Wonkwang University School of Medicine - Iksan (Korea, Republic of), 5. Department of Psychiatry, Soonchunhyang University Gumi Hospital, College of Medicine, Soonchunhyang University - Gumi (Korea, Republic of), 6. Department of Psychiatry, Keyo Hospital - Uiwang (Korea, Republic of), 7. St. Mary's Gong-Gam Mental Health Clinic - Siheung (Korea, Republic of))*

Background: Recent studies have demonstrated the pivotal role of locus coeruleus (LC) and salience network (SN) resting state functional connectivity (rsFC) changes in the early stage of Alzheimer 's disease (AD). Moreover, sex has been a crucial point of discussion in understanding AD pathology. **Methods:** We aimed to demonstrate the sex-related disparities in the functional connectivity (FC) of the SN and LC in preclinical AD. A total of 89 cognitively normal patients with evidence of amyloid beta (Aβ) accumulation ([18F] flutemetamol +) were recruited in the study. A seed-to-voxel analysis was conducted to measure the LC and SN rsFC differences between sexes. In addition, sex by Aβ interactive effects on FC values were analyzed with a general linear model. **Results:** There were statistically significant sex by regional standardized uptake value ratio (SUVR) interactions in the LC FC with the parietal, frontal, and occipital cortices. Moreover, there was a significant sex by global SUVR interaction in the SN FC with the temporal cortex. **Conclusion:** The findings suggest that there are differential patterns of LC FC and SN FC in males and females with preclinical AD, which interact with regional Aβ deposition. **Keywords:** salience network, locus ceoruleus, Alzheimer 's disease, preclinical, sex.

P094- SEX-SPECIFIC EFFECTS OF APOE E4 GENOTYPE ON LONGITUDINAL HIPPOCAMPAL ATROPHY IN MILD COGNITIVE IMPAIRMENT DUE TO AD OVER A 2-YEAR PERIODSEX-SPECIFIC EFFECTS OF APOE E4 GENOTYPE ON LONGITUDINAL HIPPOCAMPAL ATROPHY IN MILD COGNITIVE IMPAIRMENT DUE TO AD OVER A 2-YEAR PERIOD. H. Lee[1] *(1. Pusan National University Hospital - Busan (Korea, Republic of))*

Background: Hippocampal atrophy is a hallmark of Alzheimer's disease (AD) and also a predictor of AD conversion among patients with mild cognitive impairment (MCI). The risk of AD associated with the apolipoprotein E ε4 (APOE4) allele is greater in females than that in males; however, whether these sex-specific effects of APOE4 genotype are also reflected in longitudinal hippocampal atrophy (ΔHV) remains unclear. We aimed to examine the effects of the interaction between APOE4 genotype and sex on ΔHV in MCI due to AD. **Methods:** This hospital-based prospective longitudinal study included 73 patients with MCI due to AD. ΔHV, the major outcome measure, was assessed using magnetic resonance imaging (MRI) performed at baseline and two years after baseline measurement. We devided all subjects into APOE4 carriers (ε3/ε4) and APOE4 non-carriers (ε3/ε3) (N=73, APOE4 carriers=32, APOE4 non-carriers=41). Two-way analysis of variance was conducted to examine the effects of the interaction between APOE4 genotype and sex on ΔHV over a 2-year period. **Results:** A significant interaction was observed between APOE4 and sex with reference to ΔHV ($p = 0.036$). In the female subjects, ΔHV significantly correlated with APOE4 status. Female APOE4 carriers (ε3/ε4) exhibited 2.3 times greater ΔHV compared to female non-carriers (ε3/ε3) (-0.51 ± 0.28 vs -0.22 ± 0.26, $p<0.001$). However, in males, ΔHV was not linked to APOE4 status ($p=0.599$). **Conclusion:** We identified that APOE4 genotype affected ΔHV in female. Our findings suggest that female APOE4 carriers, unlike males, may be more susceptible than non-carriers to the underlying pathophysiological mechanisms of hippocampal atrophy in MCI due to AD. **Keywords:** APOE, MCI, Hippocampal atrophy. **Data Deposition:** The data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. **Disclosures:** The authors have no potential conflicts of interest to disclose.

P095- MULTICENTER STUDY OF ASSOCIATIONS BETWEEN HARMONIZED TAU-PET CENTAUR VALUES AND ALZHEIMER'S DISEASE NEUROPATHOLOGY AT AUTOPSY: PRELIMINARY SCOPE AND STUDY DESIGN. L. Iaccarino[1,2] *(1. Eli Lilly and Company - Indianapolis (United States), 2. Eli Lilly Italia S.p.A. - Sesto Fiorentino (Italy))*

Background: Multiple studies using tau positron emission tomography (tau-PET) have demonstrated accurate prediction of advanced Braak neurofibrillary tangle stage and Alzheimer's disease (AD) pathology [1]. Although consistent in their findings, studies utilizing tau-PET tracers present methodological differences hindering direct comparisons across findings and cohorts [2]. Recognizing the need for a harmonized tau-PET measurement, researchers developed a standardized methodology for tau-PET quantitation, resulting in the advent of the CenTauR scale [2]. The purpose of the present study is to evaluate diagnostic performance of harmonized Flortaucipir-PET (FTP-PET)-to-autopsy quantitation using the CenTauR scale to predict pathology using both neocortical global and regional data. Utilizing a uniquely large tau-PET-to-autopsy data set, this investigation will aid in the advancement of CenTauR scale adoption for tau-PET quantitation, supporting future research studies and clinical programs employing tau-PET. **Methods:** At the present time, five sites plan to join the CenTauR-to-Pathology Study Group (CTR2PATH) to share data and expertise. The estimated sample size from this collaboration will be $n \geq 300$ individuals. Datapoints collected will include demographics, clinical diagnosis information, biomarkers, autopsy data, FTP-PET data, information detailing intervals of FTP-PET and post-mortem, and clinical and biomarker assessments. Sites will perform FTP-PET imaging analysis locally following recommendations from the Critical Path for Alzheimer's Disease Tau-PET Harmonization Working Group. Statistical analysis will be performed centrally, pooling CTR2PATH datasets following cross-validation. Prior to analysis, CTR2PATH investigators will agree upon the specific statistical approach. **Results:** The primary results of this study will detail the diagnostic performance of harmonized FTP-

PET quantitated values at predicting neuropathology upon autopsy. Assuming enough statistical power, investigators will also evaluate the impact of additional variables on diagnostic performance, including but not limited to comorbid pathologies, other biomarker status (for example, amyloid positivity), and PET-to-autopsy interval. **Conclusion:** The aim of this study is to evaluate the performance of global and regional standardized tau-PET quantitation, such as the CenTauR scale, at predicting pathological scores at autopsy. Considering the sample size, this study is expected to provide robustly determined thresholds in the CenTauR scale, enabling extrapolation to data generated with other tau-PET tracers beyond FTP-PET. Our findings will aid in establishing CenTauR units as a standardized tau-PET measurement for future clinical research, ultimately benefiting the scientific community and advancing AD research. **Keywords:** Tau-PET; CenTauR; Harmonization; Pathology. **Disclosures:** Leonardo Iaccarino is a full-time employee and minor shareholder of Eli Lilly and Company. **References:** 1. Fleisher et al. JAMA Neurol 2020; DOI: 10.1001/jamaneurol.2020.0528; 2. Villemagne et al. Alzheimers Dement 2023; DOI: 10.1002/dad2.12454.

P096- SEX DIFFERENCES IN REGIONAL BRAIN VOLUME CHANGES ASSOCIATED WITH VERBAL MEMORY IN PATIENTS WITH SUBJECTIVE COGNITIVE DECLINE.

H.J. Lee[1], B. Yoon[1], S. Ho[2], Y.J. Hong[3], J.H. Jeong[4], K.H. Park[5], S. Kim[6], M.J. Wang[7], S.H. Choi[8], D.W. Yang[1] *(1. Department of Neurology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea - Seoul (Korea, Republic of), 2. Department of Neurology, Hanyang University Hanmaeum Changwon Hospital - Changwon (Korea, Republic of), 3. Department of Neurology, College of Medicine, The Catholic University of Korea, Uijeongbu St. Mary's Hospital - Uijeongbu (Korea, Republic of), 4. Department of Neurology, Ewha Womans University Mokdong Hospital, Ewha Womans University School of Medicine - Seoul (Korea, Republic of), 5. Department of Neurology, Gachon University Gil Hospital - Incheon (Korea, Republic of), 6. Department of Neurology, Seoul National University College of Medicine, Seoul National University Bundang Hospital - Seongnam (Korea, Republic of), 7. Roa Neurology Clinic - Seongnam (Korea, Republic of), 8. Department of Neurology, Inha University School of Medicine - Incheon (Korea, Republic of))*

Background: Subjective cognitive decline (SCD) is characterized by self-perceived worsening of cognitive function despite normal performance on standardized cognitive tests. Among SCD patients, verbal memory impairment is one of the most common complaints. Notably, sex differences have been reported in SCD concerning clinical manifestation and risk factors for cognitive decline. These differences suggest that underlying neuroanatomical changes may vary between males and females in early stages of cognitive decline. This study aims to investigate regional brain volume changes associated with verbal memory impairment in SCD patients and determine if these changes differ between sexes. **Methods:** This study included 120 Korean individuals diagnosed with SCD following a comprehensive evaluation, which included detailed cognitive function tests, brain MRI, and blood tests. Verbal memory was assessed using the Seoul Verbal Learning Test-Delayed Recall (SVLT-DR), a Korean adaptation of Rey Auditory Verbal Learning Test, which involves memorizing 12 words over three consecutive trials and recalling them after 20 minutes. Percentile scores adjusted for age, sex, and education were used. Brain volumetry was obtained using 3-Tesla MRI, and volumes of 134 specific regions were calculated using AQUA 2.0 program (Neurophet, South Korea). These volumes were normalized by dividing by the intracranial volume. Correlations and associations between the percentile scores of SVLT-DR and normalized regional volumes were analyzed separately for males and females using Pearson correlation and linear regression analysis. **Results:** Of the participants, 69 (57.5%) were females with an average age of 70.1 years for females and 71.8 years for males. In males, SVLT-DR scores positively correlated with the left posterior cingulate cortex, left hippocampus, and left parahippocampal cortex, and negatively correlated with the left medial orbitofrontal cortex. In females, SVLT-DR scores positively correlated with the left cuneus, left pars opercularis, left occipital lobe, and left lateral occipital cortex, and negatively correlated with the right pars orbitalis. Linear regression analysis adjusted for age showed that in females, the right pars orbitalis, left lateral occipital cortex, and left cuneus were significantly associated with SVLT-DR percentile scores. In males, the left hippocampus and left medial orbitofrontal cortex were relevant. **Conclusion:** The volume changes related to verbal memory test in SCD exhibit distinctly different pattern between males and females. These findings underscore the importance of considering sex-specific differences in the neuroanatomical correlates of verbal memory in patients with SCD. **Keywords:** verbal memory, subjective cognitive decline, brain volume, sex difference. **Data Deposition:** Raw data will be made available upon request. **Disclosures:** The authors declare that they have no competing interests. This study was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (2020R1C1C1006121) and the Ministry of Health and Welfare, HI18C0530. The study funders are neither involved in the study design nor its operations.

P097- TSPO PET AS INFLAMMATION BIOMARKER IN DEMENTIA.

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Background: Brain inflammation, a hallmark of neurodegeneration and a potentially important therapeutic target, has been sparsely studied in vivo. Translocator protein 18 kDa (TSPO) positron emission tomography (PET) imaging provides information on the regional brain density of microglia and migrated macrophages, main components of brain inflammation. However, "first-generation" PET tracers exhibit low affinity for TSPO. "Second-generation» tracers, such as a 11C-PBR28 and 11C-ER176 have higher affinity, thus showing a characteristic tracer binding difference depending on the TSPO rs6971 genotype of the participant being studied. In a recent development, 11C-ER176 allows for imaging of all subjects, even those with a low-binder TSPO rs6971 genotype. Furthermore, 11C-ER176 has a favorable metabolite profile compared to other high-affinity tracers (Fujita, 2017). To assess the anatomical specificity of these «second-generation» inflammation biomarkers, we employed TSPO imaging using 11C-PBR28 PET and 11C-ER176 PET in frontotemporal lobar degeneration (FTLD) and Alzheimer's disease (AD) respectively. **Methods:** We studied with MRI and PET 88 patients with FTLD or AD and 37 cognitively unimpaired healthy controls. Sixteen non-fluent variant primary progressive aphasia (nfvPPA) patients (10/16 women, age 67±6.3 years), 10 semantic variant (svPPA) patients (5/10 women, age 65±7.6 years), 9 bvFTD patients (4/9 women, age 63±8.1 years) and 14 healthy controls (5/10 women, age 68±6.1 years) had 11C-PBR28 PET. Fifty-three AD patients (27/26 women, age 66.7±9.0 years) and 23 healthy controls

(5/10 women, age 68±6.1 years) had 11C-ER176 PET. Of the AD patients, 35 had amyloid (Aβ) and 26 tau PET imaging. VT values for 11C-PBR28 and 11C-ER176 were calculated with the Logan plot and a metabolite-corrected arterial input function. All images were corrected for partial volume effect. A full factorial analysis was performed on VT values between patients and controls at the voxel level. For AD, the brain topography of inflammation, Aβ and tau was compared. **Results:** Compared to controls, increased VT values ($p < 0.005$) were found in svPPA (left temporal lobe, anterior right temporal lobe and left insula), nfvPPA (left middle, and inferior frontal gyri, bilateral medial superior frontal gyrus, left putamen and pallidum) and bvFTD (both frontal lobes, particularly orbitofrontal cortex, anterior temporal lobes, insulae, putamen and pallidum). For AD, increased VT values ($p < 0.005$) were found in precuneus and lateral temporal and parietal association cortex; inflammation brain topography correlated most highly with the topography of abnormal tau aggregates. **Conclusion:** 11C-PBR28 PET and 11C-ER176 PET allowed for the identification in FTLD and AD of neuroinflammation in regions known to be involved in the neurodegenerative process for these diseases. Importantly, all subjects with any TSPO genotype could be studied with 11C-ER176. Our data highlight the importance of neuroinflammation as a biomarker of neurodegeneration and as a potential therapeutic target in the FTDL and AD process.

P098- ENHANCING THE EFFECTIVENESS OF ALZHEIMER'S DISEASE DRUG DEVELOPMENT BY ASSESSING TAU PET AS A PROMISING SURROGATE ENDPOINT WITHIN THE PRE-COMPETITIVE CRITICAL PATH FOR ALZHEIMER'S DISEASE (CPAD) CONSORTIUM. Y. Karten[1], D. De Witte[2], M. Irizarry[3], G. Klein[4], A. Leuzy[1,5], K. Romero[1], E. Priest[1], C. Jacobsen[1], A. Ariel Alonso[2,6], G. Molenberghs[2,6], D. Stephenson[1] *(1. Critical Path Institute - Tucson (United States), 2. L-Biostat, KU Leuven - Leuven (Belgium), 3. Eisai - Nutley (United States), 4. F. Hoffmann-La Roche Ltd. - Basel (Switzerland), 5. Enigma Biomedical USA - Knoxville (United States), 6. I-BioStat, Hasselt University - Hasselt (Belgium))*

Background: Drug development in Alzheimer's disease (AD) has recently been transformed thanks to the emergence of robust and reliable biomarkers, in parallel with biological staging of the disease. Tau pathology as measured by positron emission tomography (PET) is strongly linked to neurodegeneration and the emergence of cognitive decline in AD. Longitudinal tau PET is increasingly used to detect drug target engagement or efficacy in AD clinical trials evaluating disease-modifying therapies. Recent work comparing tau PET and cognition as outcomes in clinical trials showed that significantly fewer participants were required to detect a meaningful change in the rate of tau accumulation compared with the rate of cognitive decline. **Method:** A crucial gap exists in drug development during the initial phases of AD for a biomarker that can serve as a surrogate endpoint, providing a reliable indicator of future clinical benefit. Regulatory agencies emphasize the importance of collaborative efforts between public and private entities, involving various stakeholders, to drive the development of data-driven translational tools that target the fundamental pathophysiology of diseases. To that end, the Critical Path for Alzheimer's disease consortium (CPAD) formed a Working Group to explore the potential of tau PET to increase efficiency of AD drug development by providing a reliable surrogate marker that is reasonably likely to predict clinical benefit. To evaluate surrogacy, Buyse et al. (2000) proposed to analyze the data from multiple trials using a meta-analytic approach. We propose to use a similar approach that focuses on two continuous endpoints in a cross-sectional manner, with the possibility of extending it to longitudinal measures as well. By utilizing a novel federated framework, we ensure that trial data remains confidential and secure: sponsors and sites can analyze their own data independently, without the requirement of transferring patient level data for third party analysis. The outcomes of the individual trial analyses are then combined at a central analysis hub, where key metrics for surrogate evaluation are derived. **Results:** We explored the feasibility of the federated meta-analytic approach on a simulated dataset, involving approximately 10 different sites. Moving forward, we will analyze data from natural history studies, which will provide us with valuable insights into the relationship between the surrogate and true endpoint in the longitudinal setting. By combining the results from clinical trial and natural history data, a more precise estimate of individual level surrogacy can be evaluated. In order to allow for the comparison of tau tracer data across different tau tracers, CPAD is also working on a method to harmonize tau PET data. These steps will serve as the foundation for validating the federated analysis on placebo/treatment arm data in relevant disease modifying clinical trials. **Conclusion:** Critical Path Institute's CPAD consortium has core competencies in precompetitive collaboration, legal infrastructure data acquisition and harmonization. Such areas are crucial for the creation of practical quantitative drug development tools that expedite and enhance the process of developing drugs for AD. **Reference:** Buyse, M et al., Biostatistics, 2000 PMID: 12933525. **Disclosures:** Michael Irizarry is an employee of Eisai. Gregory Klein is an employee of F. Hoffmann-La Roche Ltd.

P099- VOXEL-BASED MORPHOMETRIC ANALYSIS OF SELECTED BRAIN REGIONS IN MCI SUBJECTS TREATED WITH CHOLINE ALPHOSCERATE. E. Traini[1], A. Carotenuto[1], M. Hossein[1], V. Andreone[2], A. Francesco[1] *(1. Centro Ricerche Cliniche, Telemedicina e Telefarmacia, Università di Camerino - Camerino (Italy), 2. Neurology and Stroke Unit-Neurology, A. Cardarelli Hospital - Napoli (Italy))*

Background: Assessment of cognitive dysfunctions is mainly based on clinical criteria, although biomarkers can improve the accuracy of diagnosis, and their use is becoming a standard in the evaluation of neurodegenerative diseases and cognitive dysfunctions. Studies of changes in the human brain, through neuroimaging techniques, are in constant development. With MRI it is possible to assess the level of brain atrophy and detect the presence of cognitive alterations by distinguishing mild from more severe forms, such as Alzheimer's disease (AD) and other adult-onset dementias. Cognitive dysfunctions are characterized by a decrease in the weight and volume of the brain, due to cortical atrophy, with widening of the grooves and flattening of the convolutions. Brain atrophy mainly involving the hippocampus is related to the progression of cognitive impairment and the conversion from mild cognitive dysfunction to overt dementia. **Methods:** The CARL (Choline Alphoscerate in miLd cognitive dysfunction) study evaluates the efficacy of choline alphoscerate in patients with mild cognitive impairment (MCI) and associated vascular damage, as the ability to induce stability and/or slowing of hippocampal, entorhinal, cortical atrophy and ventricular dilation. This randomized controlled trial has recruited 60 patients that were randomized in a 1:1 ratio to receive the cholinergic precursor choline alphoscerate (1,200 mg/day) or placebo and were evaluated at the

beginning of the study and after 12 months. Volume (mm3) of hippocampus, entorhinal cortex, neocortex and dilation of lateral ventricles determined from T1-weighted MRI were analyzed, at the baseline and after 12-month, by FreeSurfer v7.4.1 software. Cognitive impairment was measured using the MMSE scale at the final visit compared to baseline. **Results:** The evaluation of the patients that have reached the final endpoint of one year of treatment, have confirmed that the study of mesial temporal and hippocampal atrophy are a sensitive and suitable approach to confirm the presence of dementia. The hippocampal region shows signs of degeneration before the onset of cognitive symptoms and represents the first region to degenerate. The atrophy rate is higher in the group treated with placebo compared to those receiving the cholinergic precursor choline alphoscerate. **Conclusion:** The above findings suggest a possible activity of choline alphoscerate in the treatment of MCI. **Keywords:** Choline alphoscerate; Brain atrophy; Hippocampus; Mild cognitive Impairment. **Clinical Trial Registry:** 2020-000576-38. **Disclosures:** The authors declared no competing interests.

P0100- ASSOCIATION BETWEEN THE NEW SUB-CLASSIFIED WHITE MATTER HYPERINTENSITIES VOLUME AND COGNITIVE FUNCTION IN ELDERLY. Y. Bo-Hyun[1], B. Won-Myong[2], L. Kwanghun[3], L. Sang-Yeol[4], S. Hyung Mo[5], S. Min-Kyu[6], P. Sung-Yong[7], K. Moon-Doo[8], Y. Hyun-Ju[8] *(1. Department of Psychiatry, Naju National Hospital - Naju (Korea, Republic of), 2. Department of Psychiatry, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea - Seoul (Korea, Republic of), 3. Department of Psychiatry, College of Medicine, Dongguk University, - Gyeongju (Korea, Republic of), 4. Department of Psychiatry, Wonkwang University Hospital, Wonkwang University School of Medicine - Iksan (Korea, Republic of), 5. Department of Psychiatry, Soonchunhyang University Gumi Hospital, College of Medicine, Soonchunhyang University - Gumi (Korea, Republic of), 6. St. Mary's Gong-Gam Mental Health Clinic - Siheung (Korea, Republic of), 7. Department of Psychiatry, Keyo Hospital - Uiwang (Korea, Republic of), 8. Department of Psychiatry, College of Medicine, Jeju National University - Jeju (Korea, Republic of))*

Background: White matter hyperintensities(WMH) in brain magnetic resonance imaging(MRI) are common among the elderly. WMH are associated with increased cognitive impairment and risk of Alzheimer`s disease (AD). Although WMH contribute to AD pathology, their clinical implications are not fully understood. **Objective:** This study aimed to assess whether WMH predict AD and investigate the association between WMH classified according to the distance from the ventricular surface and cognitive function in AD. **Methods:** This study enrolled 283 participants, consisting of 171 patients with AD and 112 subjects with normal cognitive function. AD was diagnosed according to the NINCDS-ADRDA criteria with probable AD or possible AD. All participants underwent clinical evaluations including brain MRI study, neuropsychological tests using the CERAD-K neuropsychological assessment battery, and a genetic test. In addition, the Clinical Dementia Rating scale, Charlson comorbidity index, the Korean version of the Geriatric Depression Scale short from were administered. WMH volume was calculated using automated quantification method with SPM and MATLAB image processing software. WMH were classified according to the distance from the ventricular surface. WMH located in juxtaventricular areas, within 3 mm from the ventricular surface, were classified as juxtaventricular with matter hyperintensities (JVWMH). WMH located within 3-13 mm or farther than 13 mm from the ventricular surface were classified as periventricular white matter hyperintensities (PVWMH) or deep white matter hyperintensities (DWMH), respectively. WMH volume data were right-skewed. Consequently, WMH volume data were logarithmic transformed. **Results:** The AD group had a significantly higher mean WMH volume(20.7 ± 18.2 ml) than the NC group (6.8 ± 8.1 ml; $p < 0.001$, t-test). Logistic regression analysis showed that the log total WMH volume was associated with AD (odds ratio = 5.967, 95% CI = 1.550-22.986). Log PVWMH (odds ratio = 4.021, 95% CI = 1.592-10.156) and log DWMH volume (odds ratio = 2.873, 95% CI =1.227-6.731) were also linked to AD. However, JVWMH was not. Multivariate linear regression analysis showed that total WMH volume in AD was associated with poor performance in categorical verbal fluency test ($p = 0.008$) and word list memory test ($p = 0.023$). JVWMH volume in AD was associated with poor performance on categorical verbal fluency test ($p = 0.013$) and digit span test forward ($p = 0.037$). PVWMH volume in AD was associated with poor performance on categorical verbal fluency test ($p = 0.011$) and word list memory test ($p = 0.021$), whereas DWMH volume showed no association with cognitive dysfunction in AD. **Conclusion:** Total WMH, PVWMH, and DWMH were significantly associated with AD risk. Total WMH, JVWMH and PVWMH were associated specifically with executive function, immediate memory, and working memory, independently of hippocampal atrophy in AD. WMH were associated with AD risk and cognitive dysfunction differentially according to the distance from the ventricular surface.

P0101- ALLOPREGNANOLONE PRESERVES WHITE MATTER STRUCTURE INDEPENDENT OF APOE GENOTYPE IN EARLY ALZHEIMER'S DISEASE. A. Raikes[1], G. Hernandez[1], C. Lopez[1], L. Schneider[2], R. Brinton[1] *(1. Center for Innovation in Brain Science, University of Arizona - Tucson (United States), 2. USC School of Medicine - Los Angeles (United States))*

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. The hippocampal findings were specific to APOE-ε4 carriers whereas white matter integrity analyses were APOE genotype agnostic. Herein we addressed the impact of APOE genotype on indicators of white matter integrity. **Objectives:** Determine the impact of APOE genotype indicators of white matter integrity. Methods: A randomized, double-blinded, 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 ≥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. Previously reported exploratory endpoints included change from baseline in measures of microstructural integrity. The analyses here focused on subsets of white matter tracts where the change in fractional (FA) or quantitative anisotropy (QA) differed between Allo and placebo participants. Mean FA and QA were compared APOE-ε4carriers and non-carriers within Allo-treated group. Results are reported for a t-test

between carrier groups and Hedges g as a measure of effect size (positive values indicate carrier > non-carrier). **Results:** These analyses were constrained to 690 tracts with increased fractional anisotropy in Allo participants compared to placebo as well as 1477 white matter tracts where quantitative anisotropy was preserved in Allo treated participants. Allo's impact on indicators of white matter integrity was independent of APOE of genotype with both APOE3 and APOE 4 carriers exhibiting comparable integrity indictors on FA ($p = 0.699$, $g = -0.22$) and QA ($p = 0.852$, $g = -0.13$). **Conclusion:** Preserving white matter microstructural integrity is critical to slowing or reversing progressive neurodegeneration and retaining cognitive capability. Our earlier findings demonstrated that Allo promotes white matter integrity. Findings reported herein indicate Allo's effect on white matter integrity is present in both APOE-ε4 carriers and non-carriers. These findings suggest that Allo holds potential for preserving white matter structural integrity in both APOE-ε4 carriers and non-carriers. **Clinical Trial Registry:** NCT02221622; https://clinicaltrials.gov. **Disclosures:** Adam C. Raikes receives consulting fees for ADM Diagnostics outside the submitted work. Gerson D. Hernandez hold a leadership position with Neutherapeutics. Lon S. Schneider reports grants from Biogen, Roche/Genentech, Eli Lilly and Company, Novartis, and Biohaven; personal fees from Merck, Eli Lilly and Company, and Roche/Genentech for serving on the data and safety monitoring boards; personal fees from Takeda for serving as a consultant and on an adjudication committee; and consulting fees from AC Immune, Avraham Pharmaceuticals, Boehringer Ingelheim, Cognition Therapeutics, Cotexyme, Eisai, Neurim Pharmaceuticals, Neuronix, Tau RX, Toyama, Abbott, and vTv Therapeutics outside the submitted work. Robert D. Brinton holds a leadership position with Neutherapeutics; and patent US8969329B2 for allopregnanolone for the treatment of neurodegenerative diseases. **Acknowledgements:** National Institute on Aging UF1AG046148, U01AG031115, U01AG047222, ADDF to RDB; P30AG066530 Clinical core to LS.

LP045- FRONTAL COGNITIVE DYSFUNCTION CORRESPONDING TO SEVERITY OF CEREBRAL WHITE MATTER HYPERINTENSITIES IN PROBABLE ALZHEIMER'S DISEASE. M.Y. Park[1], H.J. Han[2], J.S. An[3], K.Y. Ahn[1] *(1. Yeungnam Medical University Center - Daegu (Korea, Republic of), 2. Ilsanbrin neurology clnic - Ilsan (Korea, Republic of), 3. university of Ilinois Chicago - Chicago (United States))*

Background: In the past, the presence of white matter hyperintensities(WMHs) on brain MRI in elderly patients was often overlooked and not given much importance. However, recent theories suggest that as Alzheimer's disease(AD) progresses, cerebral amyloid angiopathy(CAA) becomes more pronounced, which in turn exacerbates the degree of WMHs. This has led to increased interest in understanding how WMHs impact cognitive function in AD patients. This study aims to investigate the differences in frontal lobe cognitive function relative to overall cognitive function in AD patients, based on the degree of white matter degeneration. Additionally, it seeks to compare and analyze neuropsychological symptoms and depression scales to understand the impact of WMHs on cognitive function and psychiatric symptoms in AD patients. **Method:** Among the total study population of AD patients (n=50/50~90year old), participants were divided into two groups based on the degree of WMHs: the minimal (n=28) and the moderate to severe (n=22) according to CREDOS (Clinical Research for Dementia of South Korea) rating scale with FLAIR image. Inclusion criteria: 50 to 90 years old being diagnosed with probable mild or moderate AD according to the NINCDS-ADRDA criteria (McKhann et al., 1984), having a Korean Mini-Mental State Examination (KMMSE) score between 10 and 26, a Clinical Dementia Rating (CDR) score of 1 or less. Memory, word fluency, and frontal function tests were administered, along with the Neuropsychiatric Inventory (NPI) and the Geriatric Depression Scale (GDS) for assessing depression. **Results:** · The average age in the minimal LA group was 74 years, while in the moderate to severe LA group it was 79 years, indicating that patients in the moderate to severe group were older. Both groups had a higher number of women than men (Age: p=0.002, Gender: p=0.04). · There was no significant difference in years of education between the two groups (p=0.31). Although there was a tendency for higher frequency of hypertension in the moderate to severe LA group, it did not reach statistical significance (p=0.07). · There were no statistically significant differences in KMMSE and CDR scores between the two groups (KMMSE: p=0.62, CDR: p=0.72). · When comparing neuropsychological test results (SNSB-II, KMMSE, CDR) between the minimal LA group (n=28) and the moderate to severe LA group (n=22), there were no significant differences in any cognitive function domains (attention, language & related function, visuospatial function, memory function, frontal/executive function) (p>0.05). However, the Digit Span Forward test, which assesses frontal lobe function, showed a trend towards decreased performance in the moderate to severe LA group compared to the minimal LA group, although this was not statistically significant (p=0.06). There were no significant differences between the two groups in depression scales or neuropsychiatric symptoms (p=0.16, p=0.76). Detailed results of the comparisons of cognitive functions and neuropsychiatric symptoms between the groups.

LP046- CONCORDANCE BETWEEN FDA-APPROVED VISUAL INTERPRETATION OF [18F]FLORTAUCIPIR PET IMAGES AND THE CENTAUR SCALE. S. Karagianni[1,2], A. Moscoso[3,4,5], M. Van Essen[6], I. Mainta[7], V. Camacho[8], O. Rodríguez-Fonseca[9], J. Silva-Rodríguez[10,11], A. Perissinotti[12,13], N. Franzmeier[14,15,16], M.J. Grothe[17,18], G.B. Frisoni[19,20], V. Garibotto[7,21], M. Schöll[1,16,22,23] *(1. Wallenberg Centre for Molecular and Translational Medicine, University of Gothenburg - Gothenburg (Sweden), 2. Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy - Gothenburg (Sweden), 3. Wallenberg Centre for Molecular and Translational Medicine, University of Gothenburg, - Gothenburg (Sweden), 4. Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg - Gothenburg (Sweden), 5. Nuclear medicine department and Molecular Imaging Group, Instituto de Investigación Sanitaria - Santiago De Compostela (Spain), 6. Department of Clinical Physiology, Sahlgrenska University Hospital - Gothenburg (Sweden), 7. Division of Nuclear Medicine, Geneva University Hospitals - Geneva (Switzerland), 8. Department of Nuclear Medicine, Hospital de la Santa Creu i Sant Pau - Barchelona (Spain), 9. Lucus Augusti University Hospital - Lugo (Spain), 10. Instituto de Salud Carlos III - Madrid (Spain), 11. Reina Sofía Alzheimer's Centre, CIEN Foundation - Madrid (Spain), 12. Hospital Clínic Barcelona - Barcelona (Spain), 13. (CIBER-BBN), ISCIII - Barcelona (Spain), 14. Institute for Stroke and Dementia Research - Munich (Germany), 15. Munich Cluster for Systems Neurology - Munich (Germany), 16. Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg - Gothenburg (Sweden), 17. Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas, Instituto de Salud Carlos III - Madrid (Spain), 18. Reina Sofía Alzheimer's Centre, CIEN Foundation, ISCIII - Madrid (Spain), 19. Geneva Memory Center - Geneva (Switzerland), 20. Laboratory of Neuroimaging of Aging, University of Geneva - Geneva (Switzerland), 21. Faculty of Medicine, University of Geneva and Center for Biomedical Imaging (CIBM) - Geneva (Switzerland), 22. Sahlgrenska University Hospital - Gothenburg (Sweden), 23. Laboratory of Neuroimaging of Aging (LANVIE), University of Geneva,Geneva, Switzerland. - Geneva (Switzerland))*

Objectives: Positron emission tomography (PET) imaging with [18F]flortaucipir allows for in-vivo visualization of aggregated tau in Alzheimer's disease (AD). The FDA-approved label for [18F]flortaucipir PET provides a standardized, clinically applicable definition of tau-PET positivity by visual interpretation. The goal of the present study was to study the concordance between this clinically approved definition of tau PET positivity and a recently proposed methodology—CenTauR—for the standardized quantification of abnormal tau aggregates using different tau PET ligands. **Method:** We included 2011 participants (cognitively unimpaired [CU] and impaired [CI, MCI or AD dementia]) from four cohorts (A4 study, ADNI, OASIS-3, Geneva Memory Center, and HABS) with available [18F]flortaucipir PET scans. Three trained readers rated each [18F]flortaucipir PET scan as positive/negative using an FDA-approved visual interpretation method. Visual reads were compared to [18F]flortaucipir PET quantification using the CenTauRz scale in different regions of interest (ROI) as defined in the CenTauR project (https://www.gaain.org/centaur-project). Specifically, we analysed concordance by 1) performing a receiver operating characteristic (ROC) curve analysis of continuous CenTauRz (CTRz) values discriminating between positive/negative visual reads; and 2) computing sensitivity and specificity when using a previously proposed cut-point of 2 CTRz. **Results:** The ability of continuous CTRz measures to distinguish between visually positive and negative cases was relatively limited (AUC = 0.7–0.86 for CU and AUC = 0.83–0.96 for CI), with all ROIs performing similarly except for the frontal ROI, which exhibited significantly lower performance (AUC = 0.7 for CU and AUC = 0.83 for CI). When using the previously proposed cut-point of 2 CTRz for the Universal ROI, there were more visually-positive cases than CenTauR-positive cases (185 vs 166 in CU and 281 vs 253 in CI). This quantitative approach yielded a sensitivity of 53% [95% CI, 46% to 60%] and a specificity of 95% [93% to 96%] in CU individuals and a sensitivity of 83% [95% CI, 78% to 87%] and a specificity of 93% [95% CI, 89% to 96%] in CI individuals. Visually-positive, CenTauRz-negative individuals were more frequently Aβ-positive than visual-negative, CenTauRz-positive individuals (86% vs 48%, $p<0.001$). Similar results were found when analyzing other CenTauR ROIs. **Conclusion:** Visual interpretation of [18F]flortaucipir PET images and quantification using the CenTauR methodology limited agreement, particularly among CU individuals. Tau-PET positivity based on visual interpretation aligns better with the presence of Aβ-pathology. Visual interpretation may be more sensitive to early tau aggregation compared to quantitative approaches. Future analyses will compare clinical outcomes associated to each definition of tau-PET positivity.

LP047- FUNCTIONAL CONNECTIVITY, CEREBRAL BLOOD FLOW, AND CORTICAL THICKNESS CHANGES EVALUATED IN PATIENTS WITH ALZHEIMER'S DISEASE RECEIVING ANTI-AMYLOID THERAPY. A. Hone-Blanchet[1], T. Sun[1], G. Dent[1], C. Rubel[1], J. Dubois[1], J. Murphy[1], R.M. Hutchison[1], J. O'gorman[1] *(1. Biogen - Cambridge (United States))*

Background: The ENGAGE/EMERGE (NCT02477800/NCT02484547) phase 3 clinical trials assessed the efficacy and safety of aducanumab, a human IgG1 amyloid-β (Aβ)-directed monoclonal antibody in patients with early Alzheimer's disease (AD) [1]. These studies provided evidence of Aβ removal and reduced p-tau181 levels, with biomarker changes correlating with the slowing of clinical decline. Further, there was evidence of reducing neurofibrillary tangle accumulation as assessed with tau PET. Here, we use exploratory MRI-derived measurements to evaluate potential pathophysiological changes that can also be captured in response to anti-amyloid treatment. **Methods:** Data from the ENGAGE/EMERGE placebo (n=545/n=548), low-dose (n=547/n=543), and high-dose (n=555/n=547) arms were obtained at baseline, week-30, and week-78. Resting-state functional MRI (rs-fMRI), arterial spin labelling (ASL), and volumetric MRI were used to assess functional connectivity, cerebral blood flow, and atrophy, respectively. Data were collected on 1.5T and 3T MRI systems with sequences harmonized across scanner manufacturers. Sample sizes varied across imaging modalities and site capabilities due to centrally performed quality assessments. Change from baseline was analyzed using a mixed model for repeated measures (MMRM) with 'time' and 'treatment group' as factors, and age, APOE status, and MMSE as covariates. Regions of interest across measurements included frontal, medial temporal, parietal, posterior, and anterior cingulate cortex. **Results:** Longitudinal change from baseline (CFB) in the placebo group in prespecified rs-fMRI, ASL, or cortical thickness metrics at week 78 showed decreases over time as expected based on prior reports of age- and disease related effects [2, 3, 4, 5]. For example, for study ENGAGE, rs-fMRI default-network functional connectivity

(mean CFB±SD) was -0.011±0.06, ASL posterior cingulate cortex was -7.25±43.80mL/100g/mi for, and whole cortex thickness was -0.044±0.051mm. However, the changes from baseline were small relative to standard deviation. The range of mean change to standard deviation ratio values at week-78 across metrics showed no ratio value >|1|. MMRM analyses showed no significant differences of exploratory MR-derived metrics between treatment (low- or high- dose) and placebo groups from baseline at week-78 in either trial. There were within trial trends [p=0.051-0.1] in rs-fMRI and ASL at week-30 but these failed to reach statistical significance and were not consistent across trials or groups. **Conclusion:** Evaluation of exploratory MRI measurements in the ENGAGE/EMERGE clinical trials showed no significant effect of aducanumab on indices of functional connectivity, cerebral blood flow, or atrophy. This lack of effect was evident in both trials. Anti-amyloid therapies may have limited effect on these measures, but given the observed effects on PET, fluid, and clinical measures, it is difficult to reconcile the lack of pathophysiological alterations. Given the variable placebo arm progression, it is likely that these biomarkers are too variable to capture reliable change and/or drug effects over time. Additional analyses from other contemporary AD trials will be informative to better understand if slowing amyloid-associated pathology can impact these biomarkers and may further require improving the signal-to-noise properties through enhanced sequences or analysis approaches. **Keywords:** Alzheimer's disease, aducanumab, arterial spin labelling, functional MRI, cortical thickness. **Disclosures:** The study was funded by Biogen. All authors are employees of and may own stock in Biogen. **References:** 1. Budd Haeberlein, S., Aisen, P. S., Barkhof, F., Chalkias, S., Chen, T., Cohen, S., ... & Sandrock, A. (2022). Two randomized phase 3 studies of aducanumab in early Alzheimer's disease. J Prev Alzheimers Dis. 2. Li, H. J., Hou, X. H., Liu, H. H., Yue, C. L., Lu, G. M., & Zuo, X. N. (2015). Putting age-related task activation into large-scale brain networks: a meta-analysis of 114 fMRI studies on healthy aging. Neuroscience & Biobehavioral Reviews, 57, 156-174. 3. De Vis, J. B., Hendrikse, J., Bhogal, A., Adams, A., Kappelle, L. J., & Petersen, E. T. (2015). Age-related changes in brain hemodynamics; A calibrated MRI study. Human brain mapping, 36(10), 3973-3987. 4. Liu, Y., Zhu, X., Feinberg, D., Guenther, M., Gregori, J., Weiner, M. W., & Schuff, N. (2012). Arterial spin labeling MRI study of age and gender effects on brain perfusion hemodynamics. Magnetic resonance in medicine, 68(3), 912-922. 5. Fjell, A. M., Westlye, L. T., Amlien, I., Espeseth, T., Reinvang, I., Raz, N., ... & Walhovd, K. B. (2009). High consistency of regional cortical thinning in aging across multiple samples. Cerebral cortex, 19(9), 2001-2012.

CLINICAL TRIALS: BIOMARKERS INCLUDING PLASMA

P102- DETERMINATION OF PLASMA BIOMARKERS FOR THE EARLY AND SPECIFIC DETECTION OF ALZHEIMER'S DISEASE.

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Background: Patients with Alzheimer's disease (AD) could suffer similar initial symptoms to other neurocognitive diseases (Lewy body disease (LBD) and frontotemporal dementia (FTD)). The aim of this study is to analyze plasma biomarkers as early and specific AD detection method, and the utility for distinguish between other dementias. **Methods:** The patients were selected in the cognitive memory clinic of hospital la Fe, in Valencia. The clinical criteria were ages between 50-80 in both sexes, with cognitive symptoms (subjective or objective). The classification was made using the cerebrospinal fluid (CSF) biomarker for AD, according to criteria of National Institute of Aging-Alzheimer's Association (NIA-AA); for the patient with DFT were diagnosed according to International Behavioural Variant FTD Criteria Consortium (FTDC); and for LBD patients, were used LBD Consortium criteria. The group of subjective cognitive complains (SCI) was composed by patient with normal values of CSF biomarkers and normal performance in the neurocognitive testing. Plasma p-Tau181, neurofilament light (NfL), and glial fibrillary acid protein (GFAP) were determined by Single Molecule Assay (SIMOA® Quanterix, Billerica, MA, USA) in patients with mild cognitive impairment due to AD (MCI-AD, n = 50), AD dementia (n = 10), FTD (n = 20), LBD (n = 5), and subjective cognitive impairment (SCI (n = 21)). **Results:** The levels of plasma p-Tau181 and GFAP were highest in AD dementia, and significant correlations with clinical AD characteristics were showed; meanwhile, plasma NfL levels were highest in FTD, without significant correlations with AD. The partial least squares (PLS) diagnosis model developed between the AD and SCI groups showed good accuracy with a receiver operating characteristic (ROC) area under curve (AUC) of 0.935 (CI 95% 0.87–0.98), sensitivity of 86%, and specificity of 88%. NfL plasma levels could be helpful to identify FTD patients among subjects with cognitive impairment. **Conclusion:** The developed PLS model including p-Tau181 and GFAP plasma levels could identify AD patients.

P103- EVALUATING THE PERFORMANCE OF PLASMA PHOSPHORYLATED-TAU 181 AND APOLIPOPROTEIN E4 IN EARLY DETECTION OF AMYLOID PATHOLOGY IN A MULTI-CENTER STUDY REFLECTIVE OF ROUTINE CLINICAL PRACTICE.

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Background: Blood-based biomarkers have emerged as a promising avenue for detecting amyloid pathology at an early stage. In particular, the combination of phosphorylated-Tau 181 (pTau181) and apolipoprotein E4 (ApoE4) has shown potential in accurately identifying patients with a low likelihood of amyloid pathology before confirmatory diagnostic evaluation. This study aims to determine the clinical performance of

pTau181 and ApoE4 in the detection of amyloid pathology in relation to Alzheimer's Disease (AD) diagnosis, which will be confirmed in an ongoing, independent validation study. **Methods:** A minimum of 450 patients aged 55-80, with either subjective cognitive decline (SCD), mild cognitive impairment (MCI), or mild dementia as defined as MMSE>19 and QDRS≥0.5 with ≥0.5 in the memory domain, were enrolled in a prospective multicenter study. Plasma from eligible patients was measured with the Elecsys® pTau181 and ApoE4 plasma assays (Roche Diagnostics International Ltd, Rotkreuz, Switzerland). The levels of pTau181 and ApoE4 were analyzed with respect to amyloid PET status, using [18F]Florbetapir, [18F]Florbetaben, or [18F]Flutemetamol and assessed by expert visual read, and with respect to CSF pTau181/Abeta42 binary readout, measured with the Elecsys β-Amyloid (1-42) II CSF and Elecsys Phospho-Tau (181P) CSF (Roche Diagnostics International Ltd). ApoE4 plasma levels were compared to APOE genetic status. Clinical performance was assessed for the combination of pTau181 and ApoE4 and for pTau181 alone, with a focus on high negative predictive value. Subgroup effects, based on cognitive performance, comorbidities, or demographics, were assessed as part of exploratory analyses. **Results:** Performance data are still being analyzed and full results will be available at CTAD. **Conclusion:** This study determines the potential of pTau181 and ApoE4 as powerful tools to accurately rule out individuals with a low likelihood of amyloid pathology, which may ultimately contribute to improved patient care and outcomes in the field of AD. Further research and validation is ongoing.

P104- PLASMA PTAU181 AND PTAU217 SIMILARLY PREDICT ASYMPTOMATIC AMYLOID ACCUMULATION WITH PERFORMANCES COMPARABLE TO AMYLOID-PET. S. De Meyer[1], J. Schaeverbeke[1], E. Luckett[1], E. Blujdea[2], P. Dupont[1], K. Van Laere[3], J. Vanbrabant[4], E. Stoops[4], E. Vanmechelen[4], G. Di Molfetta[5], H. Zetterberg[5], N. Ashton[5], C. Teunissen[6], K. Poesen[3], R. Vandenberghe[3] *(1. KU Leuven - Leuven (Belgium), 2. UMC Amsterdam - Amsterdam (Netherlands), 3. UZ Leuven - Leuven (Belgium), 4. ADx NeuroSciences - Ghent (Belgium), 5. Sahlgrenska Academy - Mölndal (Sweden), 6. UMC Amsterdam - Amsterdam (Sweden))*

Background: Blood-based phosphorylated tau (pTau) immunoassays can detect asymptomatic cerebral amyloid-β (Aβ) pathology with relatively high accuracy, with pTau217 recommended as the preferred epitope due to its higher fold changes. In the current study, we evaluated the ability of plasma pTau217 to predict the dynamic phase of Aβ accumulation, an early window of opportunity for Aβ lowering therapies, and compared it to the best-performing plasma pTau181 assay and Aβ-PET. **Methods:** Seventy-five cognitively unimpaired (CU) elderly from the Flemish Prevent Alzheimer's disease Cohort KU Leuven (F-PACK, mean age = 70 years, 48% female) were included based on the availability of plasma samples obtained at baseline as well as two serial Aβ-PET scans (average time interval = 5 years, range 2 - 10 years). Plasma pTau217 and pTau181 were quantified using the ALZpath and ADx NeuroSciences Simoa assays, respectively. Serum glial fibrillary acidic protein (GFAP), neurofilament light (NfL) and Aβ1-42/Aβ1-40 were measured using the Quanterix Neurology 4-Plex E Simoa assay. Participants were classified as Aβ-accumulators if their Aβ rate of change exceeded an empirically defined cut-off of a 2.62 Centiloid (CL) increase per year. The ability of biomarkers to discriminate Aβ-accumulators from non-accumulators was evaluated using receiver operating characteristic analyses. Predictive abilities for Aβ rate of change were investigated through Pearson correlations and linear regression models using respectively baseline pTau217, pTau181 and Aβ-PET CLs as predictors and the Aβ rate of change as outcome. The regions in which each of these biomarkers predicted Aβ rate of change was determined using voxelwise linear mixed-effects models (VoxelStats package) including the Aβ-PET scans as outcome. Clusters were considered significant if the cluster-level PRFT<0.05 and voxel-level Puncorrected<0.001. All models were adjusted for age, sex and APOE-ε4 carriership. **Results:** Sixteen CU elderly were Aβ accumulators. Plasma pTau217 as well as pTau181 levels and Aβ-PET CLs were higher in Aβ accumulators compared to non-accumulators and discriminated the two groups with comparable, moderate performance (area under the curve (AUCs) = 0.75, 0.72 and 0.72, respectively, all PDeLong = 0.94). Plasma pTau181 and pTau217 strongly correlated with each other (r=0.93, PFDR<0.001) and similarly correlated with Aβ rate of change, as did baseline Aβ-PET (r=0.33-0.36, all PFDR≤0.01). Serum GFAP, NfL and Aβ1-42/Aβ1-40 could not discriminate accumulators from non-accumulators and did not correlate with Aβ rate of change. Addition of either plasma pTau217, pTau181, or Aβ-PET to a linear demographic model including age, sex and APOE-ε4 carriership similarly improved the prediction of Aβ accumulation (ΔAkaike Information Criterion≤4.1). The spatial distribution of regions demonstrating associations between pTau217 or pTau181 plasma levels and Aβ rate of change mainly involved clusters within the temporal (peak MNI coordinates: x/y/z=-50/-4/-34) and frontal (x/y/z=6/50/-24mm) cortices and the precuneus (x=-6/-41/45 for pTau217 and -8/-40/46 for pTau181). **Conclusion:** Plasma pTau217, plasma pTau181 and Aβ-PET convey overlapping information and predict the dynamic phase of asymptomatic amyloid-β accumulation with comparable, moderate accuracy. Given this moderate accuracy, future studies should investigate whether integrating plasma pTau species with other factors can improve performance and thus enhance clinical and research utility. **Keywords:** blood, pTau217, pTau181, amyloid accumulation, Alzheimer's disease, PET. **Disclosures:** SDM, JMS, ESL, MR, ERB, IC, PD, GDM and KP report no disclosures. JV and ES are full-time paid employees and EV is co-founder of ADx Neurosciences. KVL has performed contract research through UZ/KU Leuven as principal investigator for GE Healthcare and received speaker fees from GE Healthcare. HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZpath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Alzecure, Biogen, Cellectricon, Fujirebio, Lilly, Novo Nordisk, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). NJA has given lectures in symposia sponsored by Eli-Lilly, Roche Diagnostics, and Quanterix. NJA has declined paid opportunities from ALZpath. CET performed contract research for Acumen, ADx Neurosciences, AC-Immune, Alamar, Aribio, Axon Neurosciences, Beckman-Coulter, BioConnect, Bioorchestra, Brainstorm Therapeutics, Celgene, Cognition Therapeutics, EIP Pharma, Eisai, Eli Lilly, Fujirebio, Grifols, Instant Nano Biosensors, Merck, Novo Nordisk, Olink, PeopleBio, Quanterix, Roche, Toyama, Vivoryon. She serves on

editorial boards of Medidact Neurologie/Springer, Alzheimer's Research and Therapy and Neurology: Neuroimmunology & Neuroinflammation. RV's institution has had a clinical trial agreement for phase 1 and 2 studies with GE Healthcare, which provided [18F]flutemetamol for this study as well as with Biogen, Denali, Eli Lilly, J&J, Roche/Genentech, Wave and UCB. RV's institution has consultancy agreements for participation in DSMB (RV as consultant) with AC Immune and Novartis.

P105- USE OF NON- GENETICALLY MODIFIED NATURAL KILLER CELLS (SNK01) WITH ENHANCED ACTIVITY IN SUBJECTS WITH ACTIVE ALZHEIMER'S DISEASE. FURTHER BIOMARKER ANALYSIS AND IMPLICATIONS FOR USE IN PREVENTION. P. Song[1], C.H. Zúñiga Gil[2], B.I. Acosta Gallo[3], C.A. Amescua[3], R. Menchaca Díaz[3], S. Hong[1], J. Mata[1], K. Betito[1], H. Lee[1], Y. Kang[1], L. Hui[1] *(1. NKGen Biotech - Santa Ana (United States), 2. Tijuana General Hospital - Tijuana (Mexico), 3. Hospital Angeles - Tijuana (Mexico))*

Background: Dementia remains an enormous global problem of which Alzheimer's disease (AD) is the leading cause. By 2030, the number of cases is expected to exceed 80 million. Due to the lack of disease modifying therapies, more emphasis is being placed on pre-emptive diagnosis and developing preventative therapies. A recent study by Guo correlated elevated serum plasma levels of GFAP, NF-L, GDF15 and LTBP2 with a 2.32 times greater risk of developing dementia in the U.K., while a study by Cai found that AB42, p-tau181, and NF-L could be detected 8 years before clinical onset of AD in Chinese populations. SNK01 is an autologous non-genetically modified NK cell product with highly enhanced cytotoxicity and activating receptor expression which has been previously shown to cross the blood brain barrier to reduce neuroinflammation and improve protein levels in CSF and plasma. We reanalyzed our biobank to see if SNK01 had any effect on these additional implicated biomarkers associated with increased AD risk. **Methods:** In this Phase 1 study, SNK01 was administered IV every three weeks for a total of 4 treatments using a 3+3 dose escalation design (1, 2 and 4 x 109 cells) in subjects with either mild, moderate, or severe AD (Median MMSE of 14). Cognitive assessments and CSF and plasma biomarker analyses were performed at baseline and at 1 and 12 weeks after the final dose. The primary endpoint was safety and secondary endpoints included changes in cognitive assessments and biomarker levels. Samples were re-analyzed for GDF-15 and LTBP2. **Results:** Eleven subjects (5 males and 6 females) were enrolled and 10 were evaluable. Median age was 79 years (56 to 85 years). No treatment related adverse events were observed. Despite 70% of subjects being treated at relatively low doses of SNK01, 90% of all evaluable subjects had either stable or improved (±0.1) composite ADCOMS scores at week 11 (one-week after the final dose). Additionally, one-week post-final dose, improvement in CSF biomarkers were observed in 70% p-Tau181, 60% AB42/40 ratio, 60% GFAP, 40% GDF-15, 30% LTBP2, and 30% NF-L. **Conclusion:** SNK01 was very safe and despite suboptimal dosing for 2/3 of subjects, SNK was able to positively affect biomarkers associated with increased AD development suggesting SNK01 could potentially be a safe preventative intervention for high-risk individuals.

P106- ANALYTICAL VALIDATION OF AN ULTRASENSITIVE IMMUNOASSAY FOR DETECTION OF PHOSPHORYLATED TAU217 IN HUMAN BIOFLUIDS. J. Surls[1], K. Janzen[1], H. Rawlins[1], R. Vega Ibanez[1], L. Brown[1], J. Kemp[1] *(1. Rules-Based Medicine, a Q Squared Solutions Company - Austin (United States))*

Background: Phosphorylated Tau 217 (pTau217) is increasingly recognized as a significant indicator for Alzheimer's disease (AD), indicative of the presence of neurofibrillary tangles [1]. Precise measurement of pTau217 levels in human biological fluids such as EDTA plasma, serum, and cerebrospinal fluid (CSF) is essential for the early detection and tracking of AD and holds great value in preliminary research trials. These initial trials, despite not aiming for therapeutic or diagnostic outcomes, are vital for the integrity and advancement of clinical research. Consequently, the generation of results that are accurate, consistent, and repeatable is of utmost importance. The goal here was to confirm the effectiveness of a highly sensitive immunoassay designed to measure pTau21, in compliance with the standards set by the Clinical and Laboratory Standards Institute (CLSI). **Methods:** Using the Quanterix® Simoa® technology (Billerica, USA) (HD-X) platform, pTau217 was analytically validated in human serum, EDTA plasma, and CSF per CLSI standards. We employed a novel immunoassay with enhanced sensitivity for pTau217, conducting a rigorous analytical validation. The assay's performance was evaluated through parameters such as specificity, precision, accuracy, linearity, and robustness. In addition, to confirm the assay's consistency and reliability across different assays, instruments, and laboratories, a correlation study was performed with a cohort of forty donor samples. The Rules-Based Medicine's (RBM) pTau217 assay was compared to a commercially-available pTau217 assay, resulting in a correlation coefficient (R) of 0.97, indicating a strong agreement of the results. **Results:** We have developed and analytically validated a novel Simoa immunoassay to detect pTau217 in human serum, EDTA plasma, and CSF. The assay met acceptance criteria for sensitivity, precision, stability, interference, and linearity. Endogenous levels of serum, EDTA plasma, and CSF were linear when diluted through the calibration curve range. The three quality controls met inter-assay precision with %CV of 10%, 11%, and 9% for the low ($\bar{x}$=0.18 pg/mL), middle ($\bar{x}$=2.1 pg/mL), and high ($\bar{x}$=21 pg/mL) levels, respectively. No interference was observed with bilirubin, hemoglobin, or triglyceride. The stability of pTau217 was demonstrated under various conditions, such as freeze-thaw cycles, refrigerated and ambient short-term and frozen long-term storage. The immunoassay demonstrated exceptional specificity and sensitivity, with a lower limit of quantification of 0.027 pg/mL, suitable for detecting low endogenous concentrations of pTau217 in serum, EDTA plasma, and CSF. The results were consistent with established CSF biomarkers, supporting the assay's clinical utility [2]. **Conclusion:** Different pTau217 assays may offer unique advantages, such as varying sensitivity levels, which can be customized to specific research or clinical needs. The presence of multiple assays for pTau217 not only strengthens the immunodiagnostic framework for AD but also propels the field towards more innovative and accurate resources and solutions. In summary, this analytically-validated pTau217 assay for detection in human serum, EDTA plasma, and CSF demonstrated acceptable performance for exploratory clinical implementation as research use only. **Keywords:** Plasma, Serum, CSF, pTau217, Tau. **Disclosures:** No competing disclosures. **References:** 1. Janelidze S, et al. Nat Commun 2020;

11: 1683. Cerebrospinal fluid p-tau217 performs better than p-tau181 as a biomarker of Alzheimer's disease. https://doi.org/10.1038/s41467-020-15436-0; 2. Bayoumy S, et al. Alz Res Therapy 2021; 13: 198. Clinical and analytical comparison of six Simoa assays for plasma P-tau isoforms P-tau181, P-tau217, and P-tau231. https://doi.org/10.1186/s13195-021-00939-9.

P107- PLASMA P-TAU217 CONCENTRATIONS IN PATIENTS UNDERGOING EVALUATION FOR ANTI-AMYLOID THERAPY. A. Algeciras-Schimnich[1], S. Ashrafzadeh Kian[1], J. Bornhorst[1], D. Figdore [1], J. Graff-Radford[1], R. Petersen[1], V. Ramanan[1] *(1. Mayo Clinic - Rochester (United States))*

Background: Alzheimer's disease (AD) blood biomarkers (BBMs) are noninvasive tools that can aid in the evaluation of patients with mild cognitive impairment (MCI) or dementia. Additionally, they may be used to determine eligibility for disease-modifying therapies when access to advanced testing, such as cerebrospinal fluid (CSF) biomarker evaluation or positron emission tomography (PET), is limited. Among AD BBMs, p-tau217 is a leading biomarker demonstrating high diagnostic accuracy and disease specificity when evaluated retrospectively in memory clinic-based cohorts. In this study, the performance of a clinically validated p-tau217 assay was prospectively evaluated in patients seen at a tertiary care subspecialty clinic for consideration of lecanemab therapy. **Methods:** Patients with MCI or dementia being evaluated for lecanemab therapy were asked to provide an EDTA-plasma sample during the initial evaluation or first infusion visit, but before treatment initiation. For patients receiving lecanemab therapy, longitudinal samples were also collected. Blood samples were collected in EDTA tubes, plasma was separated within 2 hours of collection, and the samples were aliquoted and frozen. Plasma p-tau217 was measured using the Lumipulse p-tau217 assay on the Fujirebio Lumipulse G1200 analyzer. The p-tau217 (pg/mL) results were classified as negative (< or = 0.185), positive (> or = 0.325), or intermediate (0.186–0.324). Patients had office examination, neuropsychological assessment, structural magnetic resonance imaging (MRI), amyloid PET (with either 11C-Pittsburgh compound B or 18F-florbetapir), CSF AD biomarkers (Elecsys p-tau181/Aβ42), and apolipoprotein E (APOE) allele typing as part of the evaluation. Concordance between the plasma p-tau217, amyloid PET, and/or CSF p-tau181/Aβ42 was evaluated. **Results:** Twenty-six patients participated between November 2023 and May 2024. Of these, 14 patients had both amyloid PET and CSF p-tau181/Aβ42 measurements, 6 patients had only amyloid PET and 6 patients had only CSF p-tau181/Aβ42 to assess for the presence of amyloid pathology. In the amyloid-PET positive individuals (n=17), plasma p-tau217 was positive in 16 cases and intermediate in 1 case. In the amyloid-PET negative individuals (n=3), plasma p-tau217 was negative in 1 case and positive in 2 cases. The p-tau217 overall concordance with amyloid PET was 85%. For CSF p-tau181/Aβ42 positive patients (n=18), plasma p-tau217 was positive in 15 cases and intermediate in 3 cases; in CSF p-tau181/Aβ42 negative patients (n=2), plasma p-tau217 was positive. Plasma p-tau217 overall concordance with CSF p-tau181/Aβ42 was 75%. The two cases which were CSF p-tau181/Aβ42 negative and plasma p-tau217 positive were both amyloid-PET positive. The overall concordance between CSF p-tau181/Aβ42 and amyloid PET was 79% (11/14). **Conclusion:** This study represents one of the initial assessments of real-world practical clinical experience of the p-tau217 association with amyloid pathology. In this initial evaluation of the study data, plasma p-tau217 showed a higher overall concordance with amyloid PET (85%) than with CSF p-tau181/Aβ42 (75%). Patient recruitment is ongoing to further understand the performance of plasma p-tau217 for the selection of patients who could benefit from disease-modifying therapies.

P108- INTEGRATIVE ANALYSIS OF CLINICAL STAGES, PLASMA BIOMARKERS, AND COGNITIVE TRAJECTORIES ACCORDING TO AT CLASSIFICATION IN ALZHEIMER'S DISEASE RELATED COGNITIVE IMPAIRMENT, SUBCORTICAL VASCULAR COGNITIVE IMPARIMENT, AND FRONTOTEMPORAL DEMENTIA. S. Yoon[1], M.Y. Chun[2], J. Yun[3], D. Shin[1], E.H. Lee[1], H. Jang[4], J.P. Kim[1], H.J. Kim[1], D.L. Na[1], S.W. Seo[1] *(1. Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine - Gangnam-Gu, Seoul (Korea, Republic of), 2. Department of Neurology, Yonsei University College of Medicine - Seoul (Korea, Republic of), 3. Department of Neurology, Soonchunhyang University Bucheon Hospital - Gyeonggi-Do (Korea, Republic of), 4. Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine - Jongno-Gu, Seoul (Korea, Republic of))*

Background: The effects of amyloid-β(A) and tau protein(T) in various dementias remain relatively under-examined. This study aimed to examine the distribution of biological and clinical stages in Alzheimer's Disease related cognitive impairment(ADCI), subcortical vascular cognitive impairment(SVCI), and frontotemporal dementia(FTD). Additionally, plasma biomarker levels and cogintive trajectories in various dementias according to AT classification were investigated. **Methods:** A total of 275 participants (169 ADCI, 78 SVCI, and 28 FTD) underwent detailed neuropsychological tests, Aβ and Tau positron emition tomography, and plasma biomarker analysis (p-tau217, GFAP, and NfL). The distribution of biological and clinical stages were examined across ADCI, SVCI, and FTD. Plasma biomarkers were compared between dementia types according to AT classification. To investigate the effects of Aβ and tau on cognitive trajectories, a linear mixed effects model was applied with adjustment for age, sex, education, and APOE genotype. **Results:** In ADCI, progression from A-T- to A+T+ correlated with increasingly severe clinical stages, while SVCI and FTD showed more advanced clinical stages relative to biological stages. Plasma p-tau217 was lower in SVCI compared to ADCI within the A+T+ group ($p = 0.021$), while plasma GFAP was highest in FTD within the A-T- group (FTD vs ADCI, $p = 0.004$). Cognitive decline was faster in SVCI and FTD than in ADCI in the A-T- group (SVCI vs ADCI, $p < 0.008$; FTD vs ADCI, $p < 0.001$). **Conclusion:** This integrative study reveals distinct patterns of clinical progression, plasma biomarker profiles, and cognitive decline in ADCI, SVCI, and FTD based on AT classification. These findings highlight the heterogeneity in pathophysiological mechanisms across dementia types, underscoring the need for personalized diagnostics and therapies. **Keywords:** Amyloid-β, Tau, Alzheimer's Disease, Subcortical vascular cognitive impairment, Frontotemporal dementia, Positro emission tomography, Plasma biomarkers, Phosphorylated tau, Glial fibrillary acidic protein, Neurofilament light chain, Cognitive trajectory.

P109- ASSOCIATION OF PLASMA AB42/AB40 WITH BRAIN AMYLOIDOSIS AND CONVERSION TO MILD COGNITIVE IMPAIRMENT AFTER A 5-YEAR FOLLOW-UP IN INDIVIDUALS WITH SUBJECTIVE COGNITIVE DECLINE: DATA FROM THE FACEHBI COHORT.

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Introduction: Blood-based biomarkers have recently emerged as powerful tools for the in-vivo diagnosis of Alzheimer's disease (AD). Identifying individuals who are cognitively unimpaired but at risk of clinical progression to mild cognitive impairment (MCI) remains a critical challenge, especially now that novel disease-modifying therapies are becoming available. This study examines the ability of plasma Aβ42/Aβ40 to predict longitudinal changes in cognition and brain amyloidosis in individuals with subjective cognitive decline (SCD). **Methods:** Data from 200 cognitively unimpaired individuals with SCD from Fundació ACE Healthy Brain Initiative (FACEHBI) were analysed [1]. Participants underwent 18F-Florbetaben (FBB)-PET scans, blood draw and clinical assessment at baseline, two-year, and five-year follow-up visits. Amyloid positivity was determined by FBB-PET using a 13.5 centiloid cut-off for early amyloid deposition [2]. Baseline plasma Aβ42/Aβ40 values were measured with ABtest-MS, an antibody-free HPLC-MS/MS method developed by Araclon Biotech [3]. Cognition was assessed using the Neuropsychological battery of Fundació ACE (NBACE) [4]. A diagnosis of MCI was established when any of the NBACE test scores was impaired according to published cut-offs[4]. Cox proportional hazards modelling assessed time to event based on plasma Aβ42/Aβ40 status, according to a previously published cut-off value of 0.2415[3]. Differences in the rates of brain amyloid accumulation were analysed using linear mixed-effects modelling using random intercepts and slopes. **Results:** At baseline, median age of the cohort was 67.0 years (IQR 60.0–70.0). Aβ-PET(+) individuals (18%) were older than those Aβ-PET(–) (P< 0.001). Sex and APOE ε4 allele distribution differed between Aβ-PET(+) and Aβ-PET(-) groups (P=0.02 and P<0.001, respectively). Among the 164 individuals who were Aβ-PET(–) at baseline, 24 (15.6%) converted to Aβ-PET(+) at the end of the follow-up period. Subjects with plasma Aβ42/Aβ40<0.2415 at baseline presented significantly increased conversion risk to Aβ-PET(+) (Hazard Ratio [HR]=3.3 [95% CI 1.4-7.6], P=0.0036), remaining significant after adjusting for age, sex, and APOE status (HR=3.3 [95% CI 1.3-8.5], P=0.016). Cox models were also applied to evaluate conversion to MCI due to AD, that is, individuals who converted to MCI and were Aβ-PET(+) at the end of the follow-up. Out of 200 individuals, 23 (11.5%) converted. Individuals with plasma Aβ42/Aβ40<0.2415 at baseline showed significantly increased conversion risk (HR=7.0 [95% CI 2.8-17.0], P<0.001), remaining significant after covariates inclusion (HR = 3.4 [95% CI 1.2-8.5], P=0.019). Regarding conversion to all-cause MCI, individuals with baseline plasma Aβ42/Aβ40 below the threshold value did not show higher conversion risk. A negative and significant association between baseline plasma Aβ42/Aβ40 and the rate of brain amyloid accumulation was found. Individuals with plasma Aβ42/Aβ40<0.2415 at baseline showed a faster accumulation (3.2-fold, P<0.0001) than their counterparts. **Conclusion:** In this study, baseline plasma Aβ42/Aβ40 was a useful tool for identifying cognitively unimpaired individuals with SCD with high risk of conversion to AB-PET+ and to MCI due to AD. However, as expected, it was not a good predictor of conversion to MCI due to other underlying etiologies in which amyloid pathology is not present. **Keywords:** ABtest-MS, FACEHBI, amyloid-PET, conversion to MCI, plasma Aβ42/Aβ40, subjective cognitive decline, amyloid deposition. **Disclosures:** JAA, MPL, LS and NF are full time employees at Araclon Biotech-Grifols. JT is a full time employee at Grifols. MES is the founder of CAEBI (Centro Andaluz de Estudios Bioinformáticos). AR is member of scientific advisory board of Landsteiner Genmed and Grifols SA. AR has stocks of Landsteiner Genmed. MM has consulted for F. Hoffmann-La Roche Ltd and is a member of the Scientific Advisory Board of Biomarkers of Araclon. MB has consulted for Araclon, Avid, Grifols, Lilly, Nutricia, Roche, Eisai and Servier. She received fees from lectures and funds for research from Araclon, Biogen, Grifols, Nutricia, Roche and Servier. She reports grants/research funding from Abbvie, Araclon, Biogen Research Limited, Bioiberica, Grifols, Lilly, S.A, Merck Sharp & Dohme, Kyowa Hakko Kirin, Laboratorios Servier, Nutricia SRL, Oryzon Genomics, Piramal Imaging Limited, Roche Pharma SA, and Schwabe Farma Iberica SLU, all outside the submitted work. She has not received personal compensations from these organizations. The FACEHBI study was supported with funds from Ace Alzheimer Center Barcelona, Grifols, Life Molecular Imaging, Araclon Biotech, Alkahest, Laboratorio de análisis Echevarne and IrsiCaixa. **References:** 1. Rodriguez-Gomez O, et al. J Prev Alzheimer's Dis. 2017;4:100–8. http://dx.doi.org/ 10.14283/jpad.2016.122; 2. Bullich S, et al. Alzheimers Res Ther. 2021; 13(1):179. https://doi.org/10.1186/s13195-021-00807-6; 3. Pascual-Lucas M, et al. Alzheimers Res Ther. 2023; 15:2. https://doi.org/10.1186/s13195-022-01143-z; 4. Alegret M, et al. PLoS One. 2013;8. https://doi.org/10.1371/journal.pone.0076436.

P110- PREDICTION OF ALZHEIMER'S DISEASE USING AN AI DRIVEN SCREENING PLATFORM: PREDICTOM STUDY DESIGN.

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Background: Early prediction of Alzheimer's disease (AD) is an urgent health challenge. Technological developments in (neuro-)physiological and digital biomarkers suggest that the early diagnostic process can take place in the home-setting. The PREDICTOM study aims to evaluate promising biomarkers in the home-setting via an artificial intelligence (AI) driven platform. **Method:** The PREDICTOM (Prediction of AD using an AI-driven Screening Platform) study includes the development and evaluation of a cloud-based platform, which is used to digitally collect, store and analyse data using AI algorithms to provide an individual risk assessment for the development of AD. It includes participants from 7 European

sites (Norway, UK, Belgium, France, Switzerland, Germany, Spain). In the first cohort phase (Level 1), participants (N=4000, >50y) with an increased risk of developing AD will undergo home-based screening including digital (cognition, hearing, eye-tracking, questionnaires) and physiological (finger-prick blood, saliva, stool) biomarkers. In the second phase, participants whose risk was identified as being high (N=415) versus low (N=200) will undergo a simple in-clinic assessment, which can be implemented in a GP setting, including EEG, MRI, blood, cognition, hearing, and eye-tracking (Level 2). A diagnostic evaluation including cerebrospinal fluid, plasma, or amyloid PET measures (Level 3) to confirm or rule out AD pathology will be completed. A subset of participants will complete a follow-up visit after 12 months. The study protocol received feedback from lay people involved in the project's Advisory Board and we aim to implement a feedback system for participants and care providers. **Result:** First results are expected to be disseminated in 2025. **Conclusion:** PREDICTOM will develop and evaluate AI-driven algorithms for the early detection of AD using existing and novel home-based biomarkers with the aim of incorporating its use into the clinical pathway for the early screening and stratification of individuals at risk of AD. **Conflicts of interest:** Dr Aarsland has received research support and/or honoraria from Astra-Zeneca, H. Lundbeck, Novartis Pharmaceuticals, Evonik, Roche Diagnostics, and GE Health, Sanofi, and served as paid consultant for H. Lundbeck, Eisai, Heptares, Eli Lilly, Enterin, Acadia, EIP Pharma, Biogen, and Takeda.

P111- CEREBROSPINAL FLUID LEVELS OF VAMP-2 AND SNAP-25 ARE ASSOCIATED WITH EXECUTIVE FUNCTION IN DEMENTIA WITH LEWY BODIES, AN EFFECT THAT IS COFOUNDED BY ALZHEIMER COMORBIDITY. A. Cervantes González[1,2], J. Goosens[3], N. Dewit[4], L. Lidón[1,2], D. Perlaza[1,2], J. Fortea[1,2], D. Alcolea[1,2], A. Lleo[1,2], E. Vanmechelen[3], O. Belbin[1,2] *(1. Sant Pau Memory Unit, Neurology Department and IIB-Sant Pau, Hospital de La Santa Creu I Santa Pau, Universitat Autonoma de Barcelona - Barcelona (Spain), 2. Network Center for Biomedical Research in Neurodegenerative Diseases (CIBERNED), - Madrid (Spain), 3. ADx NeuroSciences NV, Zwijnaarde - Ghent (Belgium), 4. Medpace Reference Laboratories (A.A.), Flow Cytometry Unit - Louvain (Belgium))*

Background: Synaptic proteins in cerebrospinal fluid (CSF) could represent much-needed objective biomarkers of cognitive impairment, disease progression and drug efficacy in Dementia with Lewy Bodies (DLB) patients. Soluble N-ethylmaleimide-sensitive factor attachment proteins receptors (SNARE) proteins, such as VAMP-2 and SNAP-25, are implicated in α-synuclein pathophysiology and were associated with pathophysiological biomarkers and cognitive decline in Alzheimer's disease (AD) CSF. The objective is to compare CSF levels of VAMP-2 and SNAP-25 in patients with DLB to cognitively unimpaired controls and AD patients and study their association with AD pathophysiological biomarkers and cognitive performance. **Methods:** VAMP-2 and SNAP-25 were quantified in CSF from cognitively normal controls (n=62), DLB (n=44) and AD (n=114) patients from the Sant Pau Initiative for Neurodegeneration cohort using Single Molecular Array assays (ADx Neurosciences). The DLB group was stratified into "pure DLB" (n=16) and "DLB+AD" (n=28) using our validated cut-off for the CSF p-tau/Aβ42 ratio. We tested group differences using linear regression adjusting for age and association with AD biomarkers and cognitive performance using linear regression. To evaluate the association with cognitive performance we used standardized W-scores and composite scores for each cognitive domain adjusting for age, sex and years of education. **Results:** CSF VAMP-2 and SNAP-25 (1) directly correlated across all groups (r=0.71-0.9, p<0.001), (2) were decreased in pure DLB (p<0.001, p=0.01) but increased in DLB+AD (p= 0.01, p=0.02) compared to controls (3) discriminated pure DLB from DLB+AD (AUC=0.84-0.85), (4) correlated with CSF p-tau and t-tau across all groups (adj.r2= 0.49-0.88, p<0.001) and with the Aβ42/40 ratio in DLB+AD (adj.r2= 0.29-0.36, p<0.001) and in AD (adj.r2= 0.12-0.23, p<0.001) and (5) directly correlated with Phonemic Fluency (executive domain) in pure DLB (adj. r2= 0.44-0.37, p=0.04-0.07). **Conclusion:** CSF VAMP-2 and SNAP-25 may reflect distinct pathophysiological process in DLB, dependent on AD comorbidity, and could be used as surrogate measures of executive dysfunction in pure DLB and in the discrimination of pure DLB and comorbid forms. **Keywords:** biomarker, synapse, cerebrospinal fluid, dementia with Lewy bodies. **Disclosures:** E.V. is co-founder of ADx NeuroSciences NV, Zwijnaarde (Ghent), Belgium, J.G. is employee at ADx NeuroSciences NV, N. D. was an employee at ADx NeuroSciences at the time of this research work and is now employee at Medpace Laboratories. D.A. participated in advisory boards from Fujirebio- Europe and Roche Diagnostics and received speaker honoraria from Fujirebio Europe, Roche Diagnostics, Nutricia, Krka Farmacéutica S.L., Zambon S.A.U., Lilly and Esteve Pharmaceuticals. D. A, J.F., A.L. and O.B. declare a filed patent application (WO2019175379 A1 Markers of synaptopathy in neurodegenerative disease).

P113- NOVEL PLASMA ASSAY FOR P-TAU217: EVALUATION IN A COHORT OF INDIVIDUALS WITH CEREBRAL AMYLOIDOSIS AND ALZHEIMER'S DISEASE. E. Mondesert[1], A.M. Dupuy[1], P. Wynveen[2], C. Carlson[2], M. Szabo[2], K. Ley[2], C. Knutson[2], J.S. Blanchet[3], C. Delaby[1], G. Busto[4], C. Hirtz[1], J.P. Cristol[5], S. Lehmann[1] *(1. LBPC-PPC, Univ Montpellier, CHU Montpellier, INM INSERM - Montpellier (France), 2. Beckman Coulter Diagnostics - Chaska (United States), 3. Beckman Coulter France - Villepinte (France), 4. CMRR, Univ Montpellier, CHU Montpellier, INM INSERM - Montpellier (France), 5. Biochimie Lapeyronie, Univ Montpellier, CHU Montpellier - Montpellier (France))*

Background: Blood biomarkers (BBM) represent a major hope for accurate and timely diagnosis of Alzheimer's disease (AD), particularly with a view to disease-modifying therapies. Plasma tau protein phosphorylated at position 217 (p-Tau217) is considered one of the best biomarkers for predicting cerebral amyloidosis and diagnosing Alzheimer's disease. Before using this biomarker in clinical practice, it is essential to validate the various tests used to measure them and to support their implementation in medical laboratories. Here, we evaluate for the first time a new research-use only p-Tau217 assay implemented on a high-throughput clinical-grade immunoassay platform, the DxI 9000 analyzer (Beckman Coulter Diagnostics). **Methods:** The study consisted of the evaluation of a cohort of 90 individuals: 20 controls (CTRL) with subjective cognitive impairment, 45 with Alzheimer's disease (AD), and 25 with other neurodegenerative diseases (OND), including frontotemporal dementia and Lewy body disease. Cerebrospinal fluid (CSF) core biomarkers were available for all patients. Plasma p-Tau217 was measured with SIMOA (Quanterix), Lumipulse (Fujirebio), and DxI 9000 platforms. Receiver operating characteristic analyses were used to assess the performance of the different assays to detect amyloid status

(based on CSF Aβ42/40) and to distinguish AD from CTRL and OND in this population. The corresponding areas under the curve (AUCs) were compared using the Delong method. Spearman correlations and Bland-Altman plots were used to compare assays. **Results:** Mean patient age was not significantly different among groups (ANOVA P=0.265; AD: 71.0 (SD 5.7); CTRL: 68.6 (SD 9.2); OND: 71.4 (SD 3.4)). Cognitive assessment result (MMSE) was lower in AD (21.7 (SD 4.2)) and OND (23.9 (SD 3.5)) than in CTRL (26.7 (SD 2.9)) (ANOVA P<0.001). In this study population, concentration (pg/mL) of p-Tau217 values were statistically different between non AD and AD patients ((Quanterix: 0.434 (SD 0.222) vs 1.392(SD 0.817); Lumipulse: 0.118(SD 0.074) vs 0.711(SD 0.493); DxI 9000: 0.323(SD 0.250) vs 1.344(SD 0.769)). The three p-Tau217 assays showed similar AUCs in distinguishing amyloid status: 0.96, 0.96, and 0.95 for SIMOA, Lumipulse, and DxI 9000 platforms, respectively. AUCs for distinguishing AD from CTRL and OND in this cohort were 0.95, 0.94, and 0.93 for the SIMOA, Lumipulse, and DxI 9000 platforms, respectively. These AUCs did not differ following Delong comparison. Correlations in the disease population (excluding controls) of MMSE score and p-Tau217 values were significant for the three assays (Quanterix: r=-0.353, P=0.0052; Lumipulse r=-0.363, P=0.0041; DxI 9000 r=-0.353, P=0.0052). Correlations between the assays' measures were all significant ($p < 0.001$), with coefficients ranging from 0.93 to 0.96. Bland-Altman plots also revealed good agreement between assays (in the 95% confidence interval). **Conclusion:** In a cohort of AD and non-AD individuals, our results indicated a good correlation between amyloid status and plasma p-Tau217 levels as measured using the DxI 9000 assay, results similar to those from the SIMOA and Lumipulse assays. Significant correlation with MMSE score in diseased population also suggest that p-Tau217 might be interesting for cognitively staging patients. **Keywords:** blood biomarkers, p-Tau217, amyloid peptides. **Disclosures:** WP, CC, SM, LK, KC, BJS are Beckman Coulter Employees. The other authors declared no competing interests.

P114- PLASMA P-TAU217 MEASUREMENT AS A SCREENING TOOL FOR FUTURE AD NEUROPATHOLOGY PROXY STATUS IN DEMENTIA-FREE INDIVIDUALS FROM THE BRITISH 1946 BIRTH COHORT. A. Keshavan[1], W. Coath[1], D.M. Cash[1], F. Barkhof[2,3,4], A. Heslegrave[5], H. Zetterberg[5,6,7,8], J.M. Schott[1] *(1. Dementia Research Centre, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology - London (United Kingdom), 2. Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centre - Amsterdam (Netherlands), 3. Centre for Medical Image Computing, University College London - London (United Kingdom), 4. Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, Queen Square - London (United Kingdom), 5. UK Dementia Research Institute, University College London, London - London (United Kingdom), 6. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital; Department of Psychiatry and Neurochemistry, Institute of Neuroscience & Physiology, the Sahlgrenska Academy at the University of Gothenburg - Molndal (Sweden), 7. Hong Kong Center for Neurodegenerative Diseases, Science Park - Hong Kong (China), 8. School of Medicine and Public Health, University of Wisconsin-Madison - Madison, Wisconsin (United States))*

Background: In an interim analysis of the Insight46 neuroimaging sub-study of the population-based British 1946 birth cohort enriched for amyloid positivity [1], we examined whether plasma p-tau217 measured in dementia-free individuals at baseline (age 69-71) predicted AD neuropathology proxy status derived from amyloid PET at ~2 years and tau PET at ~6 years post-baseline. **Methods:** We measured baseline plasma p-tau217 in singlicate using a single batch of ALZpath assay reagents on the Quanterix Simoa HD-X platform. Amyloid status (A-/A+) was defined by a cut-point of 11.9 centiloids, derived from Gaussian mixture modelling of 18F-florbetapir PET cortical composite standardized uptake value ratio (SUVR, whole cerebellum reference region, partial volume correction) values across the cohort. We used a similar approach with MK-6240 PET (90-110 mins post-injection, inferior cerebellar grey matter reference region) to derive cut-points in Braak regions to categorize individuals as T-, T+Braak1-2, and T+Braak3-6. AD neuropathology proxy status (Jack et al. 2023 [2]) was determined from amyloid PET at 2 years and tau PET at 6 years, by grouping A-T-, A+T-, A-T+Braak1-2 and A+T+Braak1-2 into "no/low severity AD", and grouping A-/T+Braak3-6 and A+/T+Braak3-6 into "intermediate/high severity AD". Differences in plasma p-tau217 by AD severity were assessed using median fold change and Wilcoxon rank sum tests. Ability of plasma p-tau217 (with/without covarying for age, sex and APOE-ε4 status) to predict AD severity was examined with logistic regression, and areas under the receiver operating characteristics curves (AUROC) and the precision recall curves (AUPRC). We ascertained the predictive value of two pre-defined plasma p-tau217 cut-points (lower 0.4 pg/ml, upper 0.63 pg/ml) from an independent dataset from Ashton et al. 2024 [3]. **Results:** We included 140 dementia-free participants with mean baseline age 70.5 years (range 69.3–71.7). 56.4% were male, 35% were APOE-ε4 positive, and 43% were amyloid positive at 2 years. Among 129 individuals with no/low severity AD, 77 (55%) were A-T- and 52 (37%) were A+T-, A-T+Braak1-2 or A+T+Braak1-2; 11 (8%) were intermediate/high severity AD. Median baseline plasma p-tau217 was 2.5-fold higher in the intermediate/high severity AD group than the no/low severity group (p<0.0001). Baseline plasma p-tau217 discriminated well between those subsequently developing intermediate/high severity vs no/low severity AD (AUROCptau-217=0.895, AUROCptau-217+covariates=0.921; AUPRCptau-217=0.485, AUPRCptau-217+covariates=0.551). Results were unchanged by additionally covarying for baseline serum creatinine or body mass index. Applying the pre-defined cut-points, plasma p-tau217<0.4pg/ml had 100% negative predictive value and plasma p-tau217>0.63 pg/ml had 38% positive predictive value for intermediate/high severity AD ~6 years later. Of 19/140 (14%) individuals who had plasma p-tau217 values between 0.4-0.63 pg/ml, 18 (95%) were A+, but only 5 (26%) had intermediate/high severity AD. The data-driven Youden's index cut-point of 0.43 pg/ml (100% sensitivity, 82% specificity) was close to the pre-defined lower cut-point. **Conclusion:** In this interim analysis of a population-based cohort enriched for amyloid positivity, no dementia-free individual with plasma p-tau217<0.4pg/mL at age ~70 (75% of included participants) had intermediate/high severity AD pathology ~6 years later. Most individuals with intermediate p-tau217 values were A+ but had low severity AD. These findings have significant implications for population-based screening for pre-clinical AD. **Keywords:** Plasma; p-tau; amyloid, tau PET. **Disclosures/** AK and JS receive funding from the ARUK Blood biomarker challenge grant (ARUK-BBC-02), and NIHR UCL/H Research Centre. JS receives funding from the Wolfson Foundation, Alzheimer's Research UK, Brain Research UK, Weston Brain Institute, Medical Research Council, British Heart Foundation, UK Dementia Research Institute, and Alzheimer's Association. J.S. has

received research funding from Avid Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly); consulted for Roche Pharmaceuticals, Biogen, Merck, and Eli Lilly; given educational lectures sponsored by GE Healthcare, Eli Lilly, and Biogen; and is Chief Medical Officer for ARUK. HZ is a Wallenberg Scholar and a Distinguished Professor at the Swedish Research Council supported by grants from the Swedish Research Council (#2023-00356; #2022-01018 and #2019-02397), the European Union's Horizon Europe research and innovation programme under grant agreement No 101053962, Swedish State Support for Clinical Research (#ALFGBG-71320), the Alzheimer Drug Discovery Foundation (ADDF), USA (#201809-2016862), the AD Strategic Fund and the Alzheimer's Association (#ADSF-21-831376-C, #ADSF-21-831381-C, #ADSF-21-831377-C, and #ADSF-24-1284328-C), the Bluefield Project, Cure Alzheimer's Fund, the Olav Thon Foundation, the Erling-Persson Family Foundation, Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden (#FO2022-0270), the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 860197 (MIRIADE), the European Union Joint Programme – Neurodegenerative Disease Research (JPND2021-00694), the National Institute for Health and Care Research University College London Hospitals Biomedical Research Centre, and the UK Dementia Research Institute at UCL (UKDRI-1003). H.Z. has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Alzecure, Biogen, Cellectricon, Fujirebio, Lilly, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). FB serves on the steering committee or data safety monitoring board member for Biogen, Merck, ATRI/ACTC and Prothena. Consultant for Roche, Celltrion, Rewind Therapeutics, Merck, IXICO, Jansen, and Combinostics. FB also has research agreements with Merck, Biogen, GE Healthcare, Roche. FB is the co-founder and shareholder of Queen Square Analytics LTD. WC, DC and AH have no relevant disclosures. **References:** 1. Murray-Smith H, Barker S, Barkhof F, et al. Updating the study protocol: Insight 46 - a longitudinal neuroscience sub-study of the MRC National Survey of Health and Development - phases 2 and 3. BMC neurology 2024;24(1):40. doi: 10.1186/s12883-023-03465-3; 2. Jack CR, Wiste HJ, Algeciras-Schimnich A, et al. Predicting amyloid PET and tau PET stages with plasma biomarkers. Brain : a journal of neurology 2023;146(5):2029-44. doi: 10.1093/brain/awad042; 3. Ashton NJ, Brum WS, Di Molfetta G, et al. Diagnostic Accuracy of a Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer Disease Pathology. JAMA Neurology 2024;81(3):255-63. doi: 10.1001/jamaneurol.2023.5319.

P115- LEVELS OF P-TAU217 IN BLOOD AND ITS CAPACITY TO PREDICT PATTERNS CHANGE OF COGNITIVE TRAJECTORIES IN ELDERLY: 10 YEARS FOLLOW-UP VALLECAS PROJECT.

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Aim: Longitudinal trajectories of cognitive performance in older adults are non-homogeneous across time. For this reason, one approach to capturing that heterogeneity is the estimation of patterns of change or latent classes (LC) that explain the formation of groups of subjects with stable or changing cognitive trajectories. We conducted this study to analyse the effect of baseline plasma p-tau217 levels on cognitive change patterns in the elderly. **Methods:** 913 participants, cognitively healthy at baseline, from the Vallecas Project, were selected (583 women, 64%) with a mean baseline age of 73.8±3.8 years and an average follow-up of 10.2±0.6 years. Patterns of change based on the non-linear trajectories of 5 cognitive domains were analysed using Growth Mixed Models (GMM), and adjusting for educational level, baseline age, sex and number of drugs in the medication list. Three LC explaining individual cognitive change were obtained, then the distribution of baseline plasma p-tau217 levels and other relevant clinical variables were examined according to the previously established LCs. **Results:** The group with a stable pattern of their cognitive trajectory shows significantly lower concentrations of p-tau217 than the groups with slight cognitive decline or markedly declining, in domains such as delayed verbal memory (P<.001), semantic fluency (P<.001), and processing speed ($p < 0.001$). In addition, a lower number of drugs in the medication list consumed, a greater speed and motor control ability, lower depression indicators and other clinical variables characterize the group with stable patterns in their cognition. **Conclusion:** Significantly lower concentrations of plasma p-tau217 are associated with a stable longitudinal change pattern and therefore a lower probability of accumulation of AD pathology. **Keywords:** blood biomarkers, p-tau217, cognitive changes pattern, growth mixture model.

P116- USING NEURAL DERIVED EV-BOUND BIOMARKERS IN BLOOD FOR THE ACCURATE CLASSIFICATION OF ALPHA SYNUCLEIN AGGREGATION IN THE BRAIN.

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Background: We currently face challenges in early diagnosis and prognosis prediction of Parkinson's disease due to the lack of accessible, non-invasive, and cost-effective diagnostic tests for alpha-synuclein aggregation in the brain. If this were to change, it could lead to more efficient clinical trial recruitment. For instance, pre-screening with EV bound aggregated Aβ in blood for trial entry could offer over half (57%) reduction in costs[Tanaka, 2021]. Emerging research suggests that Glial and Neuronal extracellular vesicles (NDEVs) play a crucial role in transferring alpha-synuclein aggregates throughout the brain [Danzer, 2012; Guo, 2020]. EVs carrying proteins can freely traverse the blood-brain barrier, either through transcytosis or targeted uptake by endothelial cells. Our early clinical studies indicate that direct measurement of biomarkers associated with neural derived EVs in the bloodstream provide a more

accurate measure of brain-related abnormalities compared to soluble proteins. **Methods:** Blood samples were collected from Parkinson's Disease diagnosed patients (n=16) and age matched healthy controls (n=24) with informed consent. Blood samples were collected by venipuncture into EDTA tubes using sterile techniques. Blood samples were centrifuged at 1500 x g for 10 minutes to separate plasma from cellular components. Plasma was then aspirated into sterile tubes and stored at -80°C until further analysis. In-house developed assays were performed to measure the amounts of neural EV-bound forms of alpha synuclein, GFAP, and NfL and soluble forms of the same proteins in the plasma samples. **Results:** We found that the combination of EV-associated alpha synuclein forms, and GFAP in the plasma was able to distinguish between healthy and PD patients (AUC: 0.86). Soluble (non-EV bound) forms of the same biomarkers in blood were unable to do so (AUC: 0.56). **Conclusion:** Neural derived EVs that are measured directly in blood contain forms of biomarkers relevant to their state in the brain in diseases such as AD and PD, and allow easy access to screening. **Keywords:** alpha synuclein, blood biomarker, neural extracellular vesicle, Parkinson's Disease. **Disclosures:** Authors are employees of Sunbird Bio and own shares/options in Sunbird Bio. **References:** Tanaka, T., Ruifen, J.C., Nai, Y.-H., Tan, C.H., Lim, C.Z.J., Zhang, Y., Stephenson, M.C., Hilal, S., Saridin, F.N., Gyanwali, B., Villaraza, S., Robins, E.G., Ihara, M., Schöll, M., Zetterberg, H., Blennow, K., Ashton, N.J., Shao, H., Reilhac, A. and Chen, C. Head-to-head comparison of amplified plasmonic exosome Aβ42 platform and single-molecule array immunoassay in a memory clinic cohort. Eur J Neurol, 28: 1479-1489 (2021). Danzer, K. M., Kranich, L. R., Ruf, W. P., Cagsal-Getkin, O., Winslow, A. R., Zhu, L., Vanderburg, C. R. & McLean, P. J. Exosomal cell-to-cell transmission of alpha synuclein oligomers. Mol Neurodegener 7, 42 (2012). Guo, M., Wang, J., Zhao, Y., Feng, Y., Han, S., Dong, Q., Cui, M. & Tieu, K. Microglial exosomes facilitate α-synuclein transmission in Parkinson's disease. Brain 143, 1476-1497 (2020).

P117- PLASMA PTAU181 PREDICTS CLINICAL PROGRESSION IN MILD ALZHEIMER'S DISEASE IN A RANDOMIZED CONTROLLED TRIAL. D. Hilt[1], J. Taylor[1], M. Jaros[2], C. Chen[3], J. Harrison[4,5,6] *(1. Actinogen Medical - Sydney (Australia), 2. Summit Analytical - Chicago (United States), 3. Memory Aging and Cognition Centre, Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore - Singapore (Singapore), 4. Scottish Brain Sciences, Edinburgh, United Kingdom - Edinburgh (United Kingdom), 5. King's College - London (United Kingdom), 6. Alzheimercentrum, AUmc - Amsterdam (Netherlands))*

Background: Phosphorylated tau (pTau) protein species measured in the blood are biomarkers with high diagnostic accuracy, disease sensitivity, and correlation with pathologically proven Alzheimer's Disease (AD), as well as potentially predictive of future progression rate. Evidence suggests plasma pTau181 is a useful biomarker in the staging of AD. Prospective longitudinal studies can elucidate the relationship between plasma pTau181 and clinical progression. Xanamem® is a brain-penetrant inhibitor of 11β-HSD1, which acts to reduce brain cortisol. Chronically elevated cortisol is strongly associated with cognitive dysfunction, neurotoxicity, and Alzheimer's Disease (AD). Thus, reducing cortisol levels in the brain may be an important therapeutic goal in the treatment of AD. The Phase 2a XanADu biomarker trial identified patients with elevated plasma pTau181 and explored their clinical progression and potential efficacy of Xanamem. **Methods:** The XanADu biomarker extension trial used a prespecified, double-blind analysis. 72 participants with clinically diagnosed AD and available plasma samples from baseline to Week 12 of the "XanADu" phase 2a trial of Xanamem vs. placebo were studied. The analysis prespecified plasma pTau181 > median to identify patients more likely to have AD ("H", >6.74pg/mL, n = 34). Efficacy variables assessed included four clinical scales: ADAS-Cog v14, AD COMposite Scores (ADCOMS), Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB), and Mini Mental State Exam (MMSE). Other endpoints were the Rey Auditory Verbal Learning Test (RAVLT), Neuropsychiatric Inventory (NPI), NTB – Executive Domain (NTB-exec), and ADAS-Cog167 (a composite of ADAS-Cog items 1 [word recall], 6 [orientation], and 7 [word recognition]). To control for varying endpoint scoring properties and compare clinical progression across different endpoints, individual participant responses at baseline and Week 12 were z-transformed using the pooled baseline means and standard deviations (SD). The analysis was designed to evaluate the benefit of Xanamem treatment and defined a potentially clinically meaningful improvement as a Cohen's d (d) statistic ≥ 0.2. **Results:** In the H pTau181 placebo group, participants displayed clinically significant worsening over 12 weeks compared to the L pTau181 group on the CDR-SB, and the ADCOMS with a Cohen's d 0.63 and 0.55, respectively. There was also clinical worsening on the MMSE and ADAS-Cog with Cohen's d of 0.52 and 0.53, respectively. Xanamem largely prevented clinical progression over 12 weeks, displaying a clinically significant benefit (Cohen's d of 0.41) on the CDR-SB compared to placebo in the H group but not in the L group. In both L and H groups improvements were seen favouring Xanamem in tests of executive function (Cohen's d=0.34 and 0.26, respectively) and the MMSE (Cohen's d=0.32 and 0.16, respectively). **Conclusion:** Together, these data suggest elevated plasma pTau181 may have utility for patient enrichment in future AD trials of patients with mild AD more likely to progress. Enrichment in this way may reduce sample size, cost, and duration of clinical trials. Xanamem showed evidence of potentially clinically meaningful benefits in these patients which is being explored in an on-going study (XanaMIA).

P118- INTRODUCTION OF MULTI-DIMENSION BIOMARKERS APPLICATION FOR A RANDOMIZED, DOUBLE-BLIND, SINGLE-SIMULATED CLINICAL TRIAL OF SODIUM OLIGOMANNATE ON ALZHEIMER'S DISEASE. W. Qiong[1], D. Linbin[2], G. Feng[2], S. Jiong[2], S. Yong[2] *(1. The first Affiliated Hospital of USTC - Hefei (China), 2. The first Affiliated hospital of USTC - Hefei (China))*

Background: Dementia has been declared a global challenge. However, solutions to address this problem are far from global (Parra et al., 2019). A key factor precluding the validity and generalizability of novel developments in the field of early diagnosis is their cultural bias. The Professional Interest Area on Diversity and Disparities from ISTAART highlighted the urgent need to harmonise assessments across the global north and global south if we are to better understand and detect these globally devastating disorders earlier (Babulal et al., 2019). The novel ViewMind AI Solution which combines state of the art cognitive markers, high precision eye-tracking metrics (ET), and AI has been subjected to the investigation of these outstanding needs. Here we present preliminary results from a large population-based study in southern regions of Colombia aimed at investigating the validity of a novel digital neurocognitive biomarkers to detect dementia risk in underrepresented populations. **Methods:** The ViewMind AI Solution records ET variables during memory binding (Parra et al., 2011). The task

assesses low-level integrative memory abilities, and it has been proposed as a novel memory marker for AD (Costa et al., 2017). We analysed a small sample of 29 individuals of whom 8 met criteria for Mild Cognitive Impairment (MCI). Healthy control (HC) and MCI participants were matched according to age (HC: 61.8±6.68, MCI: 62.5±5.2, p=0.398) but were significantly different with regard to years of education (HC: 12.3±6.0, MCI: 5.87±5.6, p=0.007). They all underwent standard clinical, functional, and neuropsychological assessments. Multivariate analyses were conducted to investigate if groups differed in the neuropsychological (i.e., a battery comprising memory, attention, language, praxis, and executive functions tests), cognitive (i.e., behavioural responses during the integrative memory task), and biomarker (i.e., ET metrics) domains, when education was and was not added to the models as a confounding factor. **Results:** The non-controlled model addressing the neuropsychological domain yielded significant group effects [F=2.69, p=0.034, β=83%], but these disappeared when we covaried for education [F=1.78, p=0.143, β=61%]. The cognitive domain proved uninformative. The biomarker domain revealed group differences with the non-controlled model which were significant [F=3.83, p=0.007, β=94%] and increased after removing the variance accounted for by years of education [F=4.10, p=0.005, β=95%]. These ET findings emerged during the memory encoding phase of the integrative memory task only. **Conclusion:** Traditional neuropsychological assessments proved uninformative to detect dementia risk among individuals with very low education. As we have previously shown, biological data drawn from ET metrics taken during the memory encoding phase outperformed pure behavioural scores drawn from the integrative memory task (Fernandez et al., 2018; Fernández & Parra, 2021). This profile mirrors that seen in patients with or at risk of Alzheimer's disease dementia. Of note, such ET metrics detected significant group differences with statistical power above 80% whether models controlled for years education or not. These results support our proposal of ViewMind AI Solution as a culture-free neurocognitive biomarker for the early detection of dementia in underrepresented populations. **Key words:** Dementia, Diversity and Disparity, Eye-Tracking, Cognitive Markers, AI, Biomarkers, Preclinical Detection. **Disclosures:** MAP is a consultant for ViewMind serving as Neuroscientific Officer. GF is ViewMind Chief Scientific Officer. **References:** Babulal, G. M., Quiroz, Y. T., Albensi, B. C., Arenaza-Urquijo, E., Astell, A. J., Babiloni, C., Bahar-Fuchs, A., Bell, J., Bowman, G. L., Brickman, A. M., Chetelat, G., Ciro, C., Cohen, A. D., Dilworth-Anderson, P., Dodge, H. H., Dreux, S., Edland, S., Esbensen, A., Evered, L., . . . O'Bryant, S. E. (2019). Perspectives on ethnic and racial disparities in Alzheimer's disease and related dementias: Update and areas of immediate need. Alzheimers Dement, 15(2), 292-312. https://doi.org/10.1016/j.jalz.2018.09.009; Costa, A., Bak, T., Caffarra, P., Caltagirone, C., Ceccaldi, M., Collette, F., Crutch, S., Della Sala, S., Demonet, J. F., Dubois, B., Duzel, E., Nestor, P., Papageorgiou, S. G., Salmon, E., Sikkes, S., Tiraboschi, P., van der Flier, W. M., Visser, P. J., & Cappa, S. F. (2017). The need for harmonisation and innovation of neuropsychological assessment in neurodegenerative dementias in Europe: consensus document of the Joint Program for Neurodegenerative Diseases Working Group. Alzheimers. Res. Ther, 9(1), 27. https://doi.org/10.1186/s13195-017-0254-x [doi];10.1186/s13195-017-0254-x [pii]; Fernandez, G., Orozco, D., Agamennoni, O., Schumacher, M., Sanudo, S., Biondi, J., & Parra, M. A. (2018). Visual Processing during Short-Term Memory Binding in Mild Alzheimer's Disease. Journal of Alzheimer's Disease, 63(1), 185-194. https://doi.org/10.3233/jad-170728; Fernández, G., & Parra, M. A. (2021). Oculomotor Behaviors and Integrative Memory Functions in the Alzheimer's Clinical Syndrome. Journal of Alzheimer's Disease, 82(3), 1033-1044. https://doi.org/10.3233/JAD-201189; Parra, M. A., Butler, S., McGeown, W. J., Brown Nicholls, L. A., & Robertson, D. J. (2019). Globalising strategies to meet global challenges: the case of ageing and dementia. J Glob Health, 9(2), 020310. https://doi.org/10.7189/jogh.09.020310; Parra, M. A., Della Sala, S., Abrahams, S., Logie, R. H., Mendez, L. G., & Lopera, F. (2011). Specific deficit of colour-colour short-term memory binding in sporadic and familial Alzheimer's disease. Neuropsychologia, 49(7), 1943-1952. https://doi.org/S0028-3932(11)00154-0 [pii];10.1016/j.neuropsychologia.2011.03.022 [doi]

P119- PLASMA P-TAU AND AMYLOID BIOMARKERS DISCRIMINATION ACCURACY OF BIOLOGICALLY-DEFINED ALZHEIMER'S DISEASE IN A MEMORY CLINIC SETTING: A HEAD-TO-HEAD STUDY. F. Anastasi[1], A. Fernández-Lebrero[1], N.J. Ashton[2], P. Ortiz-Romero[1], E. Jiménez-Moyano[1], J. Torres-Torronteras[1], M. Milà-Alomà[1], J. Contador[1], G. García-Escobar[3], O. Grau-Rivera[1], H. Zetterberg[2], M. Del Campo[1], K. Blennow[2], A. Puig-Pijoan[3], M. Suárez-Calvet[1] *(1. BarcelonaBeta Brain Research Center - Barcelona (Spain), 2. Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, University of Gothenburg, Mölndal, Sweden - Gothenburg (Sweden), 3. Hospital del Mar Research Institute, Barcelona, Spain - Barcelona (Spain))*

Background: Blood-based biomarkers offer a non-invasive and cost-effective means for Alzheimer's disease (AD) pathology detection. In this study, we performed a direct comparison of these novel biomarkers in a memory clinic population to facilitate their implementation into clinical practice. **Methods:** We included a total of 197 patients with cognitive complaints from the BIODEGMAR cohort at Hospital del Mar (Barcelona). CSF was used as standard-of-truth for the definition of amyloid pathology and patients were categorized as having an AD-CSF profile defined by Lumipulse CSF Aβ42/p-tau181<10.25. The following biomarkers were measured in paired plasma and CSF samples: Aβ42, p-tau181, p-tau217 (Lumipulse Fujirebio), Aβ42 and p-tau181 (measured using the NeuroToolKit [NTK], a panel of exploratory robust prototype assays [Roche Diagnostics International Ltd, Rotkreuz, Switzerland]), p-tau181, p-tau217, p-tau231 and MAP-T (NULISA, Alamar) and p-tau217 (AlzPath). P-value and effect size of the group comparison (AD vs non-AD CSF profiles) were calculated using a Mann-Whitney U test. ROC curve analysis evaluated plasma biomarkers accuracy to discriminate AD from non-AD CSF profiles. Spearman test was used to assess the correlation between plasma and CSF biomarkers. Analyses were repeated defining AD-CSF profile as having Elecsys® CSF p-tau181/Aβ42>0.022 (N=157). Sex-effect in AD-CSF profile prediction was assessed. **Results:** All plasma biomarkers were significantly different between the AD and non-AD CSF profile groups, but the effect size varied among them. NULISA p-tau217, Lumipulse p-tau217 and NTK p-tau181 reported the greatest effect. ROC curve analysis revealed that the p-tau217 assays performed best in predicting AD-CSF vs non-AD-CSF profile group. The highest discrimination accuracy (AUC) values were for Lumipulse p-tau217 (AUC=0.96, CI:0.94-0.99), NULISA p-tau217 (AUC=0.96, CI:0.92-0.99), and AlzPath p-tau217 (AUC=0.93, CI:0.9-0.98). In comparison to the p-tau assays, Aβ42 reported modest effect size and AUCs. Lumipulse p-tau217 and NULISA p-tau217 had the highest correlation between plasma and CSF (Spearman ϱ=0.79 and ϱ=0.72, respectively, with both FDR corrected p-values<0.001). P-tau

and amyloid biomarkers performed consistently using the Elecsys CSF p-tau181/Aβ42 thresholds. P-tau 217 biomarkers showed higher effect size between AD-CSF and non-AD-CSF in woman with respect to men, although no significant differences in AD-CSF profile prediction accuracy have been detected. **Conclusion:** In a memory clinic population, various plasma p-tau plasma biomarkers, targeting different epitope and using different platforms, demonstrated high performance in distinguishing patients with biologically defined AD from those without, consistently for men and women. **Keywords:** plasma biomarkers; amyloid; tau; Alzheimer's disease; memory clinic; head-to-head. **Disclosures:** MS-C has given lectures in symposia sponsored by Almirall, Eli Lilly, Novo Nordisk, Roche Diagnostics, and Roche Farma; received consultancy fees (paid to the institution) from Roche Diagnostics; and served on advisory boards of Roche Diagnostics and Grifols. He was granted a project and is a site investigator of a clinical trial (funded to the institution) by Roche Diagnostics. In-kind support for research (to the institution) was received from ADx Neurosciences, Alamar Biosciences, Avid Radiopharmaceuticals, Eli Lilly, Fujirebio, Janssen Research & Development, and Roche Diagnostics. ELECSYS is a trademark of Roche. All other product names and trademarks are the property of their respective owners. The NeuroToolKit is a panel of exploratory prototype assays designed to robustly evaluate biomarkers associated with key pathologic events characteristic of AD and other neurological disorders, used for research purposes only and not approved for clinical use (Roche Diagnostics International Ltd, Rotkreuz, Switzerland).

P120- ASSOCIATIONS OF DEMENTIA RISK SCORES WITH GLUCOSE AND LIPID-RELATED METABOLIC BLOOD BIOMARKERS IN THE PERSONS AT-RISK OF DEMENTIA. S. Ana Lopez Rocha[1], R. Stephen[1], A. Solomon[2], T. Ngandu[3], J. Lehtisalo[3], T. Laatikainen[3], P. Mecocci[4], J. Tuomilehto[5], M. Kivipelto[1], F. Mangialasche[1] *(1. Karolinska Institutet - Stockholm (Sweden), 2. University of Eastern Finland - Kuopio (Finland), 3. Finnish Institute for Health and Welfare - Helsinki (Finland), 4. Università di Perugia - Perugia (Italy), 5Univeristy of Helsinki - Helsinki (Finland))*

Background: The Cardiovascular risk factors, aging, and dementia (CAIDE) risk score [1] and LIfestyle for BRAin Health (LIBRA) [2] are validated tools for estimating future dementia risk. CAIDE assessment is based on both non-modifiable and modifiable factors (age, sex, education, blood pressure, body mass index (BMI), cholesterol, physical activity) while LIBRA is solely based on modifiable factors (blood pressure, cholesterol, diet, diabetes, heart disease, chronic kidney disease, physical inactivity, depression, obesity, smoking, alcohol use). We investigated the cross-sectional associations of CAIDE and LIBRA scores with 12 markers of glucose and lipid metabolism in persons at-risk of dementia. **Methods:** The FINGER trial had 1259 participants, aged 60–77 years, without substantial cognitive impairment or dementia [3]. At baseline, a panel of 12 glucose and lipid metabolism blood markers (adiponectin, adipsin, c-peptide, ghrelin, gastric inhibitor polypeptide (GIP), glucagon-like-peptide (GLP-1), glucagon, insulin, leptin, plasminogen activator in plasma (PAI-1), resistin, and visfatin) were measured using Bio-Plex-200. CAIDE and LIBRA scores were calculated at FINGER baseline. Linear regression models were fit using dementia scores as the outcome and metabolic markers as predictors. Initially, dementia scores were tested with each metabolic marker separately, following which the metabolic markers with significant associations were added to a mutually adjusted model. Analyses were adjusted for APOE4 in models with CAIDE as outcome, and additionally for age, sex, education in models with LIBRA as outcome. Interactions between the metabolic markers and APOE4 were also assessed. **Results:** The participants with the metabolic markers (n=812) were younger (p=0.02), had lower high-density lipoprotein (HDL) (p=0.005), higher systolic blood pressure (p=0.02), glycated hemoglobin (HbA1c) (p=0.001), BMI (p=0.00), CRP (p=0.02) triglycerides (p<0.001), CAIDE score (p=0.01), and better memory (p=0.005) compared to those without the metabolic markers (n=447). Higher CAIDE score was associated with lower adiponectin (β coefficient= -0.01, p=0.005), ghrelin (β = -0.109, p=0.002), and higher insulin (β =0.16, p<0.001), leptin (β=0.14 p<0.001), PAI-1 (β =0.132, p<0.001) and c-peptide (β=0.15 p<0.001). No interactions between metabolic markers and APOE were significant except for glucagon x APOE4 (β= -2.109, p=0.019). Next, the metabolic markers with the significant associations were added to a mutually adjusted model where associations of CAIDE score with ghrelin (β= -0.22, p<0.001), glucagon (β=0.105, p=0.038) and glucagon x APOE4 (β=-2.190, p=0.013)and insulin (β=0.124, p=0.03) remained significant. Higher LIBRA was associated with higher levels of C-peptide (β=0.176, p<0.001), insulin (β=0.190 p<0.001), leptin (β =0.207, p<0.001), PAI-1 (β =0.152, p<0.001) and resistin (β = 0.085, p=0.18). The only significant interaction between metabolic markers and APOE4 was GLP-1x APOE4 (β =-1.463, p=0.025). In the mutually adjusted model, GLP-1x APOE4 remained significant (β -1.363, p=0.035). **Conclusion:** Increased dementia risk in older people is linked to glucose and lipid imbalance. The identification of phenotypes through different metabolic markers and the role of genetic factors on these metabolic markers can lead to a better stratification of the population at risk of developing dementia. **Disclosures:** None. **References:** 1. Kivipelto M. Lancet Neurol. 2006 Sep;5(9):735-41. 2. Schiepers. Int J Geriatr Psychiatry. 2018 Jan;33(1):167-175. 3. Ngandu T. Lancet. 2015 Jun 6;385(9984):2255-63.

P121- ACCELERATION OF EPIGENETIC AGE AS A BIOMARKER FOR COGNITIVE IMPAIRMENT: FINDINGS FROM THE DIET AND HEALTHY AGING COHORT. K. Ye[1] *(1. National University of Singapore - Singapore (Singapore))*

Background: Dementia and cognitive impairment have been associated with accelerated cellular aging that is reflected in changes at the molecular level. Epigenetic alterations, such as changes in DNA methylation patterns, have emerged as potential estimators of biological age and are implicated in the pathogenesis of dementia. Here, we examine the association between accelerated epigenetic age, measured by six DNA methylation-based (DNAm) epigenetic clocks, and cognitive impairment (CI) risk. **Methods:** epigenetic clocks (PCHorvath1, PCHorvath2, PCHannum, PCPhenoAge, PCGrimAge, Dunedin PoAm and Dunedin PACE) were estimated in blood from 323 community dwelling adults aged ≥60, enrolled in the Diet and Healthy Aging (DaHA) study. Epigenetic age acceleration (EAA) was calculated as the residual from regressing epigenetic age against chronological age. Several cognitive assessment tools, including a modified Singapore version of the original Mini-Mental State Examination (SM-MMSE), Clinical Dementia Rating (CDR), and a battery of standard neurocognitive tests, were utilized to diagnose CI. **Results:** It was found that a greater PCGrimAge relative to chronological age was associated with greater risk of CI (B = 0.102, p= 0.035). This association remained significant even after accounting for other known risk factors, such as smoking, physical inactivity and

cardiovascular diseases. Estimates of EAA of other clocks did not show association with CI. **Conclusion:** Findings suggests that PCGrimAge might make a better biomarker for identifying individuals at risk for dementia than other epigenetic clocks. Further research with larger sample size and follow-up is needed to elucidate the underlying mechanisms and establish the clinical utility of GrimAge as a predictive biomarker for dementia onset and progression. **Keywords:** cognitive impairment, epigenetic age, biomarker, aging. **Disclosures:** The study is supported by the National Medical Research Council of Singapore. The authors declared no competing interests.

P122- THE CLINICAL IMPACT OF BLOOD-BASED BIOMARKERS: THE PLASMAR STUDY. G. Iaccarino[1,2], J.M. Contador[1,3,4], I. Estragués[5,3,6], L.D. Martìnez[7,4,3], A. Fernandez Lobrero[5,8,3], I. Navalpotro-Gomez[5], G. García-Escobar[3], R.M. Manero[9], O. Grau-Rivera[5,4,10], J.J. Hernandez-Sanchez[11], A. Padròs-Fluvià[11], P. Ortiz-Romero[5], J. Torres-Torronteras[5], M. Del Campo[5,12,3], A. Puig-Pijoan[3,4], M. Suárez-Calvet[5,3,4,10] *(1. Barcelonaβeta Brain Research Center (BBRC), Pasqual Maragall Foundation - Barcelona (Spain) - Barcelona (Spain), 2. Università Campus Bio-Medico - Roma (Italy), 3. Hospital del Mar Research Institute - Barcelona (Spain), 4. Servei de Neurologia, Hospital del Mar - Barcelona (Spain), 5. Barcelonaβeta Brain Research Center (BBRC), Pasqual Maragall Foundation - Barcelona (Spain), 6. Servei de Neurologia, Hospital del Mar, - Barcelona (Spain), 7. Barcelonaβeta Brain Research Center (BBRC) - Barcelona (Spain), 8. Cognitive Decline and Movement Disorders Unit, Neurology Department - Barcelona (Spain), 9. Hospital del Mar Research Institute - Barcelona (Spain) - Barcelona (Spain), 10. Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable (CIBERFES), Instituto de Salud Carlos III - Madrid (Spain), 11. Laboratori de Referència de Catalunya - Barcelona (Spain), 12. Departamento de Ciencias Farmacéuticas y de la Salud, Facultad de Farmacia, Universidad San Pablo-CEU, CEU Universities - Madrid (Spain))*

Background: Blood-based biomarkers (BBMs) are emerging as promising tools for cost-effective and non-invasive detection of Alzheimer's disease (AD) pathology. Before BBMs can be used in routine clinical practice, they must be validated in real-world settings. The PLASMAR study is a prospective, single center, unblinded, randomized controlled trial designed to compare the impact and costs of early versus late BBMs utilization on the etiological diagnosis, diagnostic confidence, and clinical management of patients in a public hospital memory clinic. Additionally, the relationship between BBMs and other biomarkers, confounding factors, or cognition will be analyzed, as well as cost-savings in patient management. **Methods:** In 2024, the study is enrolling 200 prospective patients referred to the memory clinic at Hospital del Mar (Barcelona, Spain) with cognitive or behavioral complaints. Eligibility criteria include age between 18 and 85 years, a GDS score of ≤4, and availability of routine diagnostic work-up (neuropsychological evaluation, CT/MRI scan, and blood tests for treatable conditions). Patients with existing biomarkers or etiological diagnoses are excluded. The baseline visit involves blood sampling for BBMs, and questionnaires to assess emotional impact (HADS, PSS), quality of life (EQ-5D-5L), discomfort, and neurologist diagnostic confidence and work-up. Patients are classified into low, intermediate, or high risk of AD pathology based on plasma p-tau217 and internal cut-offs for PPA or PPN=90%. Neurodegeneration risk is assessed using plasma NfL with age-adjusted cut-offs [1]. Participants will be randomly assigned to either an early (BBMs disclosed at 3 months) or late (BBMs disclosed at 9 months) arms. **Results:** By May 2024, 101 patients have been enrolled. The average age was 71 years (SD=10), 73.2% female, 93% Caucasian and 25.7% APOE-ε4 carriers. The mean MMSE score was 24.6 (SD= 4.15), the median CDR score was 0.5 (IQR 0-0.5), and GDS score was 2.5 (IQR 2-3). Common comorbidities included dyslipidemia (59.4%), hypertension (52.4%), diabetes (27.7%), and depression/anxiety (25.7%). Additionally, 40.6% of participants reported a family history of cognitive impairment. Based on plasma p-tau217, 48.5% of patients were classified as high-risk, 24.7% as intermediate-risk, and 25.7% as low-risk for AD pathology. Using plasma NfL, 30.7% were classified as high-risk and 68.3% as low-risk for neurodegeneration. Linear regression models indicated a significant association between age and plasma p-tau217 or NfL levels ($p<0.001$ and $p<0.05$, respectively). Higher creatinine or urea levels were associated with increased plasma p-tau217 and NfL after adjusting for sex and age ($p<0.05$). Plasma NfL levels were also associated to proton pump inhibitor use ($p<0.05$). **Conclusion:** The PLASMAR study will offer insights into how BBMs adoption in real-world settings affects neurologist diagnostic confidence and clinical work-up. Furthermore, the PLASMAR cohort and its study design make the findings applicable to the general population. **Keywords:** Blood-based biomarkers, clinical trial, real-world setting. **Clinical Trial Registry:** NCT06246019. **Disclosures:** MS-C has given lectures in symposia sponsored by Almirall, Eli Lilly, Novo Nordisk, Roche Diagnostics, and Roche Farma; received consultancy fees (paid to the institution) from Roche Diagnostics; and served on advisory boards of Roche Diagnostics and Grifols. He was granted a project and is a site investigator of a clinical trial (funded to the institution) by Roche Diagnostics. In-kind support for research (to the institution) was received from ADx Neurosciences, Alamar Biosciences, Avid Radiopharmaceuticals, Eli Lilly, Fujirebio, Janssen Research & Development, and Roche Diagnostics. **References:** 1. Simrén J,et al. Establishment of reference values for plasma neurofilament light based on healthy individuals aged 5-90 years. Brain Commun. 2022 Jul 4;4(4):fcac174. doi: 10.1093/braincomms/fcac174. PMID: 35865350; PMCID: PMC9297091.

P123- IS SERUM P-TAU217 A VIABLE BLOOD SOURCE AS A BIOMARKER FOR ALZHEIMER'S DISEASE? A. L. Benedet[1], B. Arslan[1], K. Tan[1], H. Hulbert[1], I. Pola[1], G. Di Molfetta[1], K. Blennow[1], H. Zetterberg[1], N. J. Ashton[2] *(1. Gothenburg University - Gothenburg (Sweden), 2. Banner Health - Phoenix (United States))*

Background: Several studies on both research and clinical cohorts have confirmed the high accuracy of plasma pTau217 assays in identifying individuals in the Alzheimer's disease pathway. However, it is worth noting that while these blood tests rely strictly on EDTA plasma, clinical settings and some bio-banked research environments often prefer serum matrices, as dictated by established clinical chemistry protocols for other targets. Yet, the performance of pTau217 assays in serum remains uncertain, prompting the need to determine if serum results are comparable to plasma. **Methods:** This study evaluated the performance of six high-performing pTau217 assays (Simoa, ALZpath; Simoa, Janssen; Nulisa, Alamar; Lumipulse, Fujirebio; MSD, Lilly; MSD, S-plex) in plasma and serum. Patient samples were collected concurrently from 100 participants with known amyloid PET status (35 CU-, 15 CU+, 15 MCI+, 5 ADD, and 30 MCI-; TRIAD cohort) and analyzed in duplicate. **Results:** Initial results on the Janssen and Lumipulse show comparable group separation of serum pTau217 as to plasma p-tau217 as well as comparable fold mean in relation

to the respective CU- quantifications. High concordance was shown between the matrices, but better agreement was observed for Lumipulse. Further data will compare to Simoa, ALZpath; Nulisa, Alamar; Lumipulse ,Fujirebio; MSD, Lilly and MSD, S-plex. **Conclusion:** Despite limited data, serum is often disregarded as source of p-tau measures. Our preliminary data suggests a good agreement between serum and plasma results with similar diagnostic accuracy. However, serum levels are lower and are at the limit of detection in controls. **Keywords:** biomarker, pTau217, plasma, serum.

P124- A TWO-STAGE APPROACH TO RISK STRATIFICATION IN EARLY-STAGE ALZHEIMER'S DISEASE: UTILIZING MRI AND PLASMA P-TAU217.

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Background: With the recent introduction of amyloid-β (Aβ) targeting therapies for mild cognitive impairment (MCI) and early-stage dementia of Alzheimer's type (DAT), the need for accurate detection of Aβ status in at-risk individuals has increased to guide early intervention and treatment strategies. The primary objective of this study was to evaluate a two-step diagnostic workflow utilizing brain MRI and plasma p-Tau217 as cost-effective and less invasive methods to identify brain Aβ positivity in patients with MCI and early-stage dementia. This approach aimed to improve the accuracy of risk stratification while reducing the number of individuals requiring further invasive screening tests, thereby facilitating earlier intervention and management strategies. **Methods:** We enrolled 807 participants diagnosed with MCI and early-stage dementia (CDR 0.5) at Samsung Medical Center. Participants had complete data on Aβ status, plasma p-tau217 levels, and brain volume. Aβ positivity was determined through visual reading of Aβ positron emission tomography (PET). Plasma p-tau217 levels were measured using the ALZpath assay, and brain volumes were assessed via increases in cerebrospinal fluid (CSF) volumes in specific regions of interest (ROIs). We developed a two-step workflow using a random forest model, with APOE ε4 status, regional brain volume and plasma p-tau217 as predictors. The first step, based on brain volume and APOE ε4 status, stratified patients into low-, intermediate-, or high-risk groups for Aβ positivity. The thresholds were set at 95% sensitivity (low-risk) and 95% specificity (high-risk) to ensure a clinically relevant balance between accuracy and minimizing false positives and negatives. In the second step, plasma p-tau217 was tested exclusively in the intermediate-risk group identified in the first stage, and positive and negative predictive values were evaluated. **Results:** For the first step, the brain volume-based risk stratification identified 65.1% of patients as either high-or low-risk. The accuracy for identifying Aβ negativity was 90.2%, while the accuracy for identifying Aβ positivity was 94.4%. Among the remaining 34.9% in the intermediate-risk group, plasma p-Tau217 testing demonstrated a positive predictive value of 84.5% for Aβ positivity on PET and a negative predictive value of 84.2% for Aβ negativity on PET. The overall accuracy of the entire two-step diagnostic workflow was 90.7% (95% CI = 88.5-92.9%). **Conclusion:** Our study demonstrates that the two-step diagnostic workflow integrating brain MRI and plasma p-Tau217 effectively stratified individuals with MCI and early dementia into low-, intermediate-, and high-risk groups for Aβ positivity. This two-step workflow not only maintained high diagnostic accuracy but also significantly reduced the number of patients requiring additional confirmatory testing. Thereby, it holds potential for broader application in clinical setting, improving access to early intervention strategies for AD while considering both clinical and economic factors. **Keywords:** amyloid-β (Aβ), mild cognitive impairment (MCI), early-stage dementia, plasma p-Tau217, brain MRI, risk stratification. **Disclosure:** The authors declare no competing interests.

P125- FLUID BIOSPECIMENS AND GENETIC DATA COLLECTION AND DISSEMINATION: NEW PIPELINES TO SERVE THE DEMENTIA RESEARCH COMMUNITY FROM THE UCSF MEMORY AND AGING CENTER.

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Background: Collection, storage, and distribution of human fluid biospecimens in a scientifically rigorous manner is challenging. It requires physical space availability and robust infrastructure. Nonetheless, it is key to contribute to research in Alzheimer's Disease and Related Disorders, including Frontotemporal Dementia (FTD). These specimens facilitate fluid biomarker discovery and validation studies. At the UCSF Memory and Aging center (MAC) we support 31 protocols. Of those, up to a dozen are clinical trials led by 5 different investigators. The rest of them are observational studies, some of them international (e.g. ALLFTD) and some of broad national interest (e.g. the MAC is an ADRC center). Besides specimens, our Biospecimens and Genetics Program (BsGP) stores and shares fluid biomarker and genetic data associated with specimens collected under such studies. Here, we aim to report results of a single center's operational efforts to create a platform for biospecimens and biospecimens-related data management that functions seamlessly allowing for collaborative research. **Methods:** Over the past three years, we developed infrastructure to support biospecimen research, both locally and internationally. Our program is led by a PhD neuroscientist and supported by

four faculty members. We have a dedicated data manager, an administrative coordinator, and five members in our processing lab. We doubled our laboratory equipment (acquired two centrifuges) and implemented a superior version of our Laboratory Information Management System. We maintained and expanded partnerships with entities like UCSF-IHG, UCLA, NCRAD, ATRI. We strengthened our technological infrastructure by hiring a dedicated programmer. We transitioned towards a de-centralized biobanking strategy. **Results:** During 2023, the BsGP supported 16 investigators who submitted 20 genetic data requests. We supported our Fibroblast, Genetic, and Neuropathology Cores by providing quarterly customized genetic datasets. Our BsGP Committee reviewed 31 biospecimens requests, including 11 from non-UCSF affiliated investigators (from academic institutions and industry). They all required heavily leveraging internal resources to provide additional clinical and biomarker data. We began to build a bespoke bioinformatics solution for our program: BEAM (BiospecimEn dAta Metarepository). BEAM will facilitate tracking and searching for biospecimens (and associated fluid biomarker and genetic data) easily, so that accessing existing resources is not a roadblock for research. Since we adopted our de-centralized biobanking strategy, we increased the capacity of our processing lab in terms of new studies by 10.5% and 24.7% in terms of participants. Of the 1,436 visits that required sample processing during the last year, 4.6% were clinical trials visits, and 52.9% were visits associated with our ADRC. **Conclusion:** The MAC is a center where clinical trials and observational studies coexist and collaborate to provide the highest quality of care for individuals with cognitive problems, to conduct research on causes and cures for degenerative brain diseases, and to educate health professionals, patients and their families. Its Biospecimen and Genetics Program can serve as a model for centers interested in improving their biospecimen research programs, which requires dedicated investments in infrastructure, especially hiring and supporting qualified personnel.

P126- ASSOCIATIONS BETWEEN COGNITIVE IMPAIRMENT, APOE GENOTYPE AND PLASMA P-TAU BIOMARKERS IN EUROPEAN MCI POPULATIONS: INSIGHTS FROM THE AI-MIND PROJECT. G.M. Giuffrè[1,2], A. Perez[3], S. Alfonsin[4,5], C. Hatlestad-Hall[3], T. Saarinen[6], N. Caraglia[1], E. Christensen[7], G. Kollmorgen[8], K. Blennow[9,10], H. Zetterberg[9,10], F. Maestú[4,5], H. Renvall[6,11], I.H. Haraldsen[3], P.M. Rossini[12], C. Marra[1,2] *(1. Memory Clinic, Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Rome (Italy), 2. Department of Neuroscience, Catholic University of the Sacred Heart - Rome (Italy), 3. Department of Neurology, Oslo University Hospital - Oslo (Norway), 4. Centre for Cognitive and Computational Neuroscience, Universidad Complutense de Madrid - Madrid (Spain), 5. Department of Experimental Psychology, Cognitive Psychology and Speech and Language Therapy, Universidad Complutense de Madrid - Pozuelo De Alarcón (Spain), 6. BioMag Laboratory, HUS Medical Imaging Centre, Helsinki University Hospital, Helsinki University and Aalto University School of Science - Helsinki (Finland), 7. Pre Diagnostics AS - Oslo (Norway), 8. Roche Diagnostics GmbH - Penzberg (Germany), 9. Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg - Mölndal (Sweden), 10. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital - Mölndal (Sweden), 11. Department of Neuroscience and Biomedical Engineering, Aalto University - Helsinki (Finland), 12. Department of Neuroscience and Neurorehabilitation, IRCCS San Raffaele - Rome (Italy))*

Background: Dementia presents an escalating global challenge, with nearly 10 million new cases yearly, largely driven by Alzheimer's disease. Mild cognitive impairment (MCI) is a crucial transitional stage between typical brain aging and dementia, affecting over 10 million Europeans. This condition is of significant clinical and scientific interest due to its heightened risk of progressing to dementia compared to the general population. The AI-Mind project, funded by a European Research and Innovation Action, offers a pioneering approach to early-risk assessment using advanced artificial intelligence. The primary aim is to develop an automated tool for predicting the progression from MCI to dementia through cost-effective, widely available, accurate, and non-invasive measures such as blood biomarkers, APOE genotyping, high-density electroencephalography and cognitive assessments. This study aims to investigate the association between biological data and neuropsychological assessments in the AI-Mind MCI cohort. **Methods:** Operating across five clinical sites in four European nations (Norway and Finland in Northern Europe, Italy and Spain in Southern Europe), the AI-MIND project enrolled 1023 MCI subjects from 2022 to 2024. Baseline investigations included extensive neuropsychological assessments, encompassing tasks that evaluate verbal and visuospatial episodic memory, language, attention/executive function, and visual-constructive ability. Additionally, blood samples were collected for APOE genotype determination and plasma phosphorylated tau (p-tau181 and p-tau 217) biomarkers quantification: p-tau181 levels were measured using the NeuroToolKit, a panel of exploratory robust prototype assays (Roche Diagnostics International Ltd, Rotkreuz, Switzerland), while p-tau217 levels were measured using the MesoScale S-PLEX Human Tau (pT217) Kit on a MESO QuickPlex SQ 120MM instrument. To explore the associations between these variables, regression model analyses were performed, including age, sex, and education level as covariates. **Results:** APOE ε4 carriers constituted 32.17% of the analyzed subjects (including 15.3% homozygotes), with 67.83% being non-carriers. As expected,

regional variations in APOE ε4 prevalence were noted, with higher rates observed in Northern Europe (41.3% vs. 23.59%), while the prevalence of APOE ε2 carriers was similar. Both plasma p-tau biomarkers exhibited significant associations with APOE genotype, with higher levels in APOE ε4 carriers. Among the neuropsychological assessments, measures of episodic memory (RAVLT delayed recall) and psychomotor speed and set-shifting (TMT-B) emerged as the most significant independent predictors of both p-tau181 and p-tau217 levels. Additionally, RAVLT delayed recall was also identified as the most significant independent predictor of APOE genotype. **Conclusion:** In recent years, various studies using different assays and technologies have demonstrated that plasma biomarkers such p-tau181 and p-tau217 can accurately and specifically identify AD pathology in vivo, with performance metrics that could rival the gold standards of Aß-PET and CSF. Our findings reveal the associations of these novel plasma p-tau biomarkers measured through fully-automated technologies with ApoE genotype and cognitive impairment in different cognitive domains in a large multicentric European MCI cohort. These results underscore the potential of these cost-effective and non-invasive methods and encourage their future use in routine clinical practice in large and diverse populations. Future studies will further investigate these associations and the role of these biomarkers in predicting the progression from MCI to dementia. **Keywords:** AI-Mind, mild cognitive impairment, Alzheimer's disease, p-tau. **Clinical Trial Registry:** Not applicable. **Data Deposition:** Not applicable. **Disclosures:** This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 964220. The abstract reflects views of author, and the European Commission is not responsible for any use that may be made of the information it contains. The NeuroToolKit is a panel of exploratory prototype assays designed to robustly evaluate biomarkers associated with key pathologic events characteristic of AD and other neurological disorders, used for research purposes only and not approved for clinical use (Roche Diagnostics International Ltd, Rotkreuz, Switzerland). GK is a full-time employee of Roche Diagnostics GmbH. The remaining authors declare no competing interests.

P127- FULLY AUTOMATED ULTRASENSITIVE SIMOA ASSAY FOR BRAIN-DERIVED TAU: ENHANCING THE CHARACTERIZATION OF ALZHEIMER'S DISEASE-RELATED NEURODEGENERATION IN BLOOD. J. Shi[1], C. Sheehy[1], J. Herrera[1], D. Wilson[1], P. Gawande[1], M. Miller[1], K. Malyavantham[1] *(1. Quanterix - Billerica (United States))*

Background: The amyloid beta, tau, and neurodegeneration (AT(N)) framework offers a cost-effective and scalable solution for diagnosing Alzheimer's Disease (AD) and other dementias. While phosphorylated tau is a powerful AD diagnostic marker, total tau in cerebrospinal fluid (CSF) remains essential for pathological staging, reflecting AD-specific neurodegeneration. However, plasma total tau measurements lack specificity due to the predominant presence of peripheral tau. This study addresses this challenge by developing ultrasensitive Simoa assay on the fully automated HD-X platform that utilizes a monoclonal antibody targeting brain-derived tau (BD-Tau) specific to a fragment on exon 4a, which is absent in peripheral tau (1). **Methods:** The Simoa BD-Tau assay is a two-step digital sandwich immunoassay employing paramagnetic beads with capture antibodies and biotinylated detector antibodies. Digital detection is mediated by Streptavidin-ß-galactosidase (SβG) and Resorufin-β-D-Galactopyranoside (RGP), amplifying specific BD-Tau immune complexes immobilized on the bead surface. Clinical samples included healthy controls, MCI, and mild AD specimens from the BioHermes cohort. **Results:** The Simoa BD-Tau assay reliably measured BD-Tau in human serum and plasma. Average BD-Tau levels in normal serum and plasma (N=20) were 5.1 and 7.2 pg/ml, respectively, with %CVs of 5.8% and 5.0%. Serum and plasma measurements correlated well, although plasma levels were consistently higher. The assay exhibited a limit of detection (LOD) of 0.02 pg/ml and a lower limit of quantification (LLOQ) of 0.130 pg/ml. Intra- and inter-assay precision were 2.7% and 9.4%, respectively. Spike recovery experiments showed an average recovery of 75% (range: 65.2-89.4%) for both serum and plasma, with good dilution linearity (2X to 64X). The assay, validated in the BioHermes cohort, demonstrated excellent precision, enabling better characterization of BD-Tau in AD. Additional clinical data from ongoing work will be reported at the meeting. **Conclusion:** BD-Tau is an emerging biomarker that outperforms blood total tau and neurofilament light (NF-L) in distinguishing AD from other neurodegenerative diseases. While CSF measurements of BD-Tau are invasive, blood-based detection offers a major advantage with reduced risk. The Simoa BD-Tau assay effectively measures BD-Tau in serum and plasma with high precision, providing a valuable tool for evaluating AD patients in both diagnostic and clinical trial settings. This assay enhances our ability to characterize BD-Tau's role in AD, representing a significant advancement in the non-invasive monitoring of neurodegeneration. **Keywords:** Brain derived Tau (BD-Tau), Tau, Simoa, Alzheimer's Disease, Ultra-sensitive. **Disclosures:** All authors are primary employees of Quanterix Corporation.

P128- EVALUATION OF THE EFFECTS OF REPEATED LUMBAR PUNCTURES ON ALZHEIMER'S DISEASE CSF AND BLOOD BIOMARKERS. A. Biever[1], Y. Zou[1], C. Arneja[1], S. Stephen[1], C. Emilia[1], C. Ryan[1], G. Kollmorgen[2], T. Bittner[3], L. Jew[4], T. Kremer[3], V. Machado[3], B. Zinnhardt[3], C. Nicholas[5], K. Blennow[6], E. Teng[1] *(1. Genentech Inc - San Francisco (United States), 2. Roche Diagnostics - Penzberg (Germany), 3. Roche - Basel (Switzerland), 4. Genentech Inc - San Francisco (Switzerland), 5. New Zealand Clinical Research - Christchurch (New Zealand), 6. Department of Psychiatry and Neurochemistry - Gothenburg (Sweden))*

Background: Cerebrospinal fluid (CSF) and blood biomarker measurements are critical early indicators of central nervous system (CNS) pharmacodynamic activity in Phase I studies, which are most frequently conducted in healthy volunteers. However, repeated sampling of CSF through lumbar punctures (LPs) may cause fluid biomarker levels to transiently deviate from baseline, which can complicate the evaluation of pharmacodynamic effects of investigational products. We sought to characterize the impact of different LP intervals on CSF and blood biomarkers. **Methods:** Healthy volunteers underwent two LPs separated by either 3, 7, 14 or 28 days. CSF and plasma or serum β-amyloid 1–40 (Aβ40), β-amyloid 1–42 (Aβ42), total Tau, phosphorylated-Tau 181 (pTau181), synaptosomal associated protein 25kDa (SNAP25), α-synuclein (SNCA), apolipoprotein E4 (APOE4), glial fibrillary acidic protein (GFAP), neurofilament light chain (NfL), soluble triggering receptor expressed on myeloid cells 2 (sTREM2), neuronal pentraxin 2 (NPTX2), chitinase 3 like protein 1 (CHI3L1, aka YKL40), S100 calcium-binding protein B (S100B) and interleukin 6 receptor (IL6R) were measured using the Roche Elecsys® NeuroToolKit assay panel. **Results:**

A 29-42% median increase in CSF Aβ40, Aβ42, total Tau, pTau181, SNCA, SNAP25 and NPTX2 was observed in the 3-day cohort but not the 7-,14- and 28-day interval cohorts. Other CSF biomarkers (i.e., GFAP, Nfl, sTREM2, S100B and YKL40) and plasma biomarkers did not display significant differences in the changes from baseline across 3-,7-,14- and 28-day interval cohorts. Consistent with the prior literature, the most common LP-related adverse events (AEs) were headache, back pain/discomfort, and pain at the LP site. No consistent relationships between AE frequency and inter-LP interval were observed. Fewer AEs were associated with the second LP than with the first. **Conclusion:** Prior CSF sampling can impact the concentrations of a subset of CSF AD biomarkers when samples are collected by repeated LPs separated by less than 7 days. This effect may be due to disturbed CSF dynamics the days following the LP, which normalizes in 7 days. Inter-LP intervals should be carefully considered in both the design and interpretation of Phase 1 trials focused on longitudinal CSF pharmacodynamic endpoints. **Keywords:** Repeated CSF sampling, Alzheimer's Disease biomarkers, Elecsys® NeuroToolKit. **Disclosures:** AB, YZ, CA, SS, EC, LZ, VM, BZ, RC, JK, LJ and ET are full-time employees of Genentech/Roche. TB is a full-time employee of F. Hoffmann-La Roche and Genentech. AB, YZ, CA, SS, EC, LZ, VM, BZ, RC, JK, LJ, TB and ET are shareholders in F. Hoffmann-La Roche. GK is a full-time employee of Roche Diagnostics GmbH. KB has served as a consultant and at advisory boards for Abbvie, AC Immune, ALZPath, AriBio, BioArctic, Biogen, Eisai, Lilly, Neurimmune, Novartis, Ono Pharma, Prothena, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program.

P129- CONCORDANCE BETWEEN THE UPDATED ELECSYS CSF IMMUNOASSAYS AND AMYLOID PET FOR THE DIAGNOSIS OF ALZHEIMER'S DISEASE: FINDINGS FROM THE APOLLO STUDY. H. Schinke[1], M. Förnvik Jonsson[2,3], M. Gummesson[2], R. Nilsson[2], S. Gaupp[1], E. Manuilova[1], S. Mcilwrick[1], M. Carboni[4], E. Stomrud[5,6] *(1. Roche Diagnostics GmbH - Penzberg (Germany), 2. Department of Clinical Chemistry and Pharmacology, Skåne University Hospital - Lund (Sweden), 3. Department of translational medicine, Lund university - Lund (Sweden), 4. Roche Diagnostics Int. AG - Rotkreuz (Switzerland), 5. Clinical, Memory Research Unit, Department of Clinical Sciences Malmö - Malmö (Sweden), 6. Memory Clinic, Skåne University Hospital - Malmö (Sweden))*

Background: Cerebrospinal fluid (CSF) biomarkers play a crucial role in the timely and accurate diagnosis of Alzheimer's disease (AD). The Elecsys® β-Amyloid(1-42) CSF II, Elecsys® Phospho-Tau(181P) CSF and Elecsys® total-Tau CSF (Roche Diagnostics Int. AG, Rotkreuz, Switzerland), are electrochemiluminescence immunoassays that use a quantitative sandwich principle to detect amyloid pathology. The aim of this study was to assess the concordance between amyloid status classification based on the Elecsys Abeta42 and its ratios with pTau and tTau, and the visual evaluation of amyloid positron electromagnetic tomography (PET) scans. Methods: The Apollo study is a prospective study designed to verify clinical performance of the updated Abeta42, pTau and tTau Elecsys assays in samples prepared according to the routine-use pre-analytical procedure [1]. Participants with a diagnosis of subjective cognitive decline (SCD) or mild cognitive impairment (MCI) were recruited from the Swedish BioFINDER2 study, following the previously described eligibility criteria [2]. Eligible participants were required to have their amyloid status tested via Elecsys CSF assays and an amyloid PET scan. The main study objectives were to demonstrate concordance of the Elecsys CSF pTau/Abeta42 and tTau/Abeta42 ratios with visual amyloid PET. Cutoff values for biomarker classification were determined previously (pTau/Abeta42 ratio > 0.023, tTau/Abeta42 ratio > 0.28), and amyloid PET results were assessed by three blinded independent expert readers. The Acceptance Criterion for the point estimates of positive and negative percent agreement (PPA and NPA) was set at >0.75. Elecsys measurements were performed in fresh CSF samples. After the measurements, some samples were frozen at -20°C and re-measured to investigate the effect of freezing. **Results:** A total of 108 subjects were enrolled in the study, out of which 91 met the eligibility criteria. The mean age of the participants was 70.3 (43-90). At the time of the visit, 31 participants (34.1%) were diagnosed with MCI, and 41 (45.1%) were diagnosed with SCD. The primary analysis population consisted of 40 PET+ (44.0%) and 51 PET- (56.0%) subjects. For the Elecsys CSF pTau/Abeta42 ratio, the PPA was 0.800 (95% CI: 0.652-0.895) and the NPA was 0.882 (95% CI: 0.766-0.945). For the Elecsys CSF tTau/Abeta42 ratio, the PPA was 0.775 (95% CI: 0.625-0.877) and the NPA was 0.902 (95% CI: 0.790-0.957). 33 out of the 91 samples (36%) were frozen at -20°C and re-measured after 1-13 weeks of storage. In samples (n=6) stored 1-8 weeks, the concentration recoveries were within 100% ±10%. **Conclusion:** Both pTau/Abeta42 and tTau/Abeta42 ratios showed evident concordance with amyloid PET. The new routine-use pre-analytical procedure, along with the adjusted cutoffs for the updated Elecsys assays, are recommended for use in clinical practice. CSF samples can be stored at -20°C for up to 8 weeks before testing, as they maintain good stability under such conditions. **Disclosures:** HS, EM and SM are employees of Roche Diagnostics GmbH and hold shares in F. Hoffmann-La Roche. MC is an employee of Roche Diagnostics Int. AG and hold shares in F. Hoffmann-La Roche. The authors declared no competing interests. **References:** 1. Hansson O, et al. Alzheimers Dement (Amst). 2020;12(1):e12137. doi: 10.1002/dad2.12137. Erratum in: Alzheimers Dement (Amst). 2021;13(1):e12176. 2. The Swedish BioFINDER 2 Study (BioFINDER2). Study details, eligibility criteria. Accessible: https://classic.clinicaltrials.gov/ct2/show/NCT03174938 Last accessed: May 2024.

P130- UNRAVELING THE ENIGMA IN CEREBRAL AMYLOID ANGIOPATHY, PLASMA ALZHEIMER'S DOWNSTREAM MARKERS, AND COGNITIVE DECLINE: IN RELATION TO AMYLOID UPTAKES. S.H. Kang[1], E.H. Lee[2], J.P. Kim[2], S.W. Seo[2] *(1. Department of Neurology, Korea University Guro Hospital, Korea University College of Medicine - Seoul (Korea, Republic of), 2. Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine - Seoul (Korea, Republic of))*

Background: As amyloid-targeted therapies have become commercially available, their side effects, amyloid-related imaging abnormalities (ARIA) and its important risk factor, cerebral amyloid angiopathy (CAA), have received increasing attention. In particular, plasma biomarkers have recently been emphasized in the diagnosis of patients with Alzheimer's disease (AD). Therefore, in the present study, we aimed to determine whether CAA markers affect plasma AD downstream markers in relation to β-amyloid (Aβ) uptakes on positron emission tomography (PET) and their interplay impacts cognitive changes. **Methods:** In total, 1,708 participants

(438 with cognitively unimpaired [CU], 762 with mild cognitive impairment [MCI], and 508 with dementia of the Alzheimer's type [DAT]) were recruited from 25 hospitals participating in the "Korea-Registries to Overcome and Accelerate Dementia". All participants underwent plasma phosphorylated tau (p-tau)217, glial fibrillary protein (GFAP), and neurofilament light chain (NfL) level measurements and either 18F-florbetaben or 18F-flutemetamol PET. In addition, we assessed CAA and vascular markers including cerebral microbleeds (CMB), cortical superficial siderosis (cSS), white matter hyperintensities (WMH), lacunes, and enlarged perivascular spaces on magnetic resonance imaging (MRI). **Results:** CAA markers including lobar MBs, cSS, and WMH were associated with p-tau 217, GFAP and NfL levels ($p<0.001$). Lobar MBs counts and the presence of CAA were associated with plasma downstream markers including p-tau217, GFAP, and NfL with the mediation of Aβ uptakes ($p<0.05$, for all) as well as without the mediation ($p<0.001$, for all). Aβ uptakes fully mediated the relationships between cSS and plasma downstream markers including p-tau217, GFAP, and NfL ($p<0.005$). In contrast, hypertensive arteriosclerotic CSVD markers including lacunes, deep CMB, and enlarged perivascular spaces in basal ganglia were associated with only NfL levels regardless of Aβ uptakes on PET. Finally, there were interactive effects of lobar microbleeds in conjunction with p-tau217 ($\beta=-0.50$, $p<0.001$) and GFAP ($\beta=-0.42$, $p=0.001$) on annual MMSE changes. **Conclusion:** Our findings have uncovered novel association between CAA markers, plasma downstream markers, and cognitive declines, taking into account Aβ burdens in the brain. Futhermore, understanding the relationship between ARIA-like CAAs markers, plasma downstream markers and cognitive decline is critical as amyloid-targeted therapies may become widely available in the near future.

P131- DETECTION OF CEREBRAL AMYLOID ANGIOPATHY (CAA) IN ALZHEIMER'S DISEASE (AD) USING BLOOD BIOMARKERS. M. Ricciardi[1], E. Valeriano-Lorenzo[1], M.A. Zea-Sevilla[1], M. Valentí[1], B. Frades[1], A. Ruiz-González[1], A.B. Pastor[1], F. López-González[1], P. Ruiz[1], L. Saiz[1], I. Burgueño-García[1], M.J. López-Martínez[1], A. Rábano[1], T. Del Ser[1], P. Sánchez-Juan[1] *(1. Alzheimer's Centre Reina Sofía-CIEN Foundation-ISCIII - Madrid (Spain))*

Background: The Amyloid-Related Imaging Abnormalities (ARIA) produced by anti-amyloid drugs and the clinical repercussions of the disease raise the need for earlier biomarkers than MRI in CAA [1-4]. This research aims to evaluate in patients with pathologically confirmed AD the correlation between CAA severity, serum biomarker levels and APOE genotypes. **Methods:** Cases with a pathological diagnosis of AD according to NIA-AA criteria were selected [5]. In each case, CAA was assessed according to the criteria of Vonsattel et al. (grade 0 to 3) [6], APOE was genotyped, and serum levels of Ab40, Ab42, Tau-total, and p-Tau181 were determined using SIMOA. A descriptive, correlation (Spearman coefficient) and comparison (Mann-Whitney U test) analysis of the data were performed. Using a Kruskal-Wallis analysis, biomarker levels and APOE genotypes were compared among the 3 groups of CAA severity (grade 0-1, grade 2, and grade 3). **Results:** A total of 104 cases were included: 10 grade 0, 36 grade 1, 46 grade 2, and 12 grade 3 CAA. 97% had a high Braak stage (5 or 6). A higher grade of CAA correlated with lower levels of Ab40 ($rs= -0.225$, $p= 0.02$) and p-Tau181 ($rs= -0.251$, $p= 0.01$) and was associated with a higher frequency of APOEε4 ($U= 865.5$, z-score 3.20281, $p= 0.00069$). Ab40 levels showed an inverse gradient to the degree of CAA severity in the 3 groups (medians: 235 pg/mL, 212 pg/mL and 190 pg/mL), with a significant difference between groups ($H= 6.407$, $p= 0.04$). **Conclusion:** The severity of CAA is associated with decreasing serum levels of Ab40 and increased presence of APOEε4. **Keywords:** Cerebral Amyloid Angiopathy, Alzheimer's Disease, Blood Biomarkers, APOE. **Disclosures:** This work has been supported by the Reina Sofia Foundation, ISCIII and Next Generation funding UE. The authors report no competing interests. **References:** 1. Hampel H, Elhage A, Cho M, Apostolova LG, Nicoll JAR, Atri A. Amyloid-related imaging abnormalities (ARIA): radiological, biological and clinical characteristics. Brain. 2023;146(11):4414-4424. doi:10.1093/brain/awad188; 2. Koemans EA, Chhatwal JP, van Veluw SJ, et al. Progression of cerebral amyloid angiopathy: a pathophysiological framework. Lancet Neurol. 2023;22(7):632-642. doi:10.1016/S1474-4422(23)00114-X; 3. Charidimou A, Boulouis G, Frosch MP, et al. The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. Lancet Neurol. 2022;21(8):714-725. doi:10.1016/S1474-4422(22)00208-3; 4. Charidimou A, Boulouis G, Gurol ME, et al. Emerging concepts in sporadic cerebral amyloid angiopathy. Brain. 2017;140(7):1829-1850. doi:10.1093/brain/awx047; 5. Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. Acta Neuropathol. 2012;123(1):1-11. doi:10.1007/s00401-011-0910-3; 6. Vonsattel JP, Myers RH, Hedley-Whyte ET, Ropper AH, Bird ED, Richardson EP Jr. Cerebral amyloid angiopathy without and with cerebral hemorrhages: a comparative histological study. Ann Neurol. 1991;30(5):637-649. doi:10.1002/ana.410300503.

P132- DAVOS ALZHEIMER'S COLLABORATIVE HEALTHCARE SYSTEM PREPAREDNESS: ACCURATE DIAGNOSIS PROJECT METHODOLOGY. A. Deckert[1], K.J. Selzler[1], M. Zigman Suchsland[1], T. Macleod[1], A. Kurzman[1], K. Weyrauch[1] *(1. Davos Alzheimer's Collaborative - Wayne (United States))*

Background: Achieving accurate and timely detection of mild cognitive impairment (MCI) symptoms and Alzheimer's disease (AD) pathology at early stages continues to be a significant barrier to delivering optimal care, providing supportive services, and accessing disease-modifying therapies. Blood biomarker (BBM) tests are emerging as promising tools for detecting AD in its early stages. The availability of these innovations is promising only if healthcare systems are adequately prepared and able to integrate them into routine clinical practice. The Davos Alzheimer's Collaborative Healthcare System Preparedness (DAC-SP) program launched the Accurate Diagnosis project to support the real-world use of Alzheimer's BBMs and confirmatory pathology diagnostics (cerebral spinal fluid [CSF] and/or amyloid PET imaging) and evaluate their impact on the ADRD diagnostic pathway in primary and specialty care settings. **Methods:** The DAC-SP Accurate Diagnosis implementation project will assess real-world differences between a group of participants that receive BBM and a comparison group that does not receive BBM on rates of BBM use, time between diagnostic milestones, resource utilization, and estimated cost at baseline, mid- and post-program. Core elements of the Accurate Diagnosis project include operational funding, in-kind BBM (n=8000 max) and CSF (n=3000 CSF max) test kits, technical assistance, and a

Community of Practice (CoP) as an embedded forum for peer expertise. Two concurrent research streams will be led by sites (site-level clinical data collection across diagnostic milestones) and DAC-SP (cross-site program evaluation) to assess and document the process and outcomes of using ADRD biomarker tests in existing care pathways in primary and specialty care across diverse settings. The CoP will co-design a practical, digital blueprint to share the implementation challenges and learnings from the Accurate Diagnosis project to help other healthcare systems adopt diagnostic innovations in ADRD clinical practice. **Results:** The ongoing DAC-SP Accurate Diagnosis project includes eight healthcare institutions across 5 countries (Germany, Japan, Netherlands, UK, and four sites in the US). Sites were selected to participate based on their scientific and clinical capabilities in primary and brain health specialty care. The intervention effect will be modeled using site-specific clinical data. Model results will inform clinical and health services outcomes of BBM use in the ADRD care pathway. 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 of their use in clinical practice. The impact of individual and contextual factors across clinical practice settings will be explored at baseline, mid-point, and post-program through questionnaires, structured documentation, and semi-structured interviews with participating clinicians, implementation team members, and site leaders. **Conclusion:** The DAC-SP Accurate Diagnosis project is the first global implementation study of the real-world use of Alzheimer's blood biomarkers for triaging patients with suspected ADRD. Findings from this project will accelerate the development of standard processes and uptake of new innovations in the Alzheimer's care pathway, so that patients and families can benefit from a timely and accurate diagnosis. **Keywords:** Blood biomarkers, early detection, primary care.

P133- PRELIMINARY EVALUATION OF PLASMA ALZPATH P-TAU217 FOR DETECTING AMYLOID PATHOLOGY IN A DIVERSE COMMUNITY-BASED COHORT. M. Mielke[1] *(1. Wake Forest University School of Medicine - Winston Salem (United States))*

Background: Recent studies suggest excellent performance of plasma ALZpath phosphorylated tau 217 (p-tau217) for detecting elevated amyloid PET. Studies incorporating more diverse populations are needed to further validate the previously examined cutpoints and develop a range of biomarker thresholds. **Methods:** Participants (n=588) were enrolled in the Wake Forest Alzheimer's Disease Research Center clinical core and included 313 cognitively unimpaired (CU), 212 with mild cognitive impairment (MCI), and 63 with dementia (DEM). Plasma p-tau217 (pg/mL) was measured at baseline exam 1 visits using the ALZpath assay on the Simoa HD-X platform. A subset of participants had neuroimaging data and amyloid PET (global PiB [Aβ]: Visual Read, SUVr, Centiloids). APOE-ε4 carrier status, demographics (age, sex, race, education), and kidney functioning (estimated glomerular filtration rate [eGFR]) were assessed. Wilcoxon rank sum tests and corresponding effect sizes (ES) were used for group comparisons. General linear models, receiver-operating curve (ROC) analyses were performed. **Results:** Baseline plasma p-tau217 was positively associated (r2=0.58; p<0.001) with Aβ-PET deposition and accurately classified Aβ-PET positivity (ROC: 91-94%) across thresholds (Aβ-PET+: Visual Read: ROC=93% [CI=0.88-0.95]; SUVr >= 1.2; ROC=91% [CI=.87-.94]; PMOD-SUVr >= 1.2: ROC=92% [CI=0.89-0.95]; CL>=22: ROC=94% [CI=0.91-0.96]; CL>=24: ROC=94% [CI=0.91-0.96]). P-tau217 was negatively associated with eGFR (rho= -0.26, p<0.001) and elevated in: (1) males compared to females (Median: Male=0.472, Female=0.419; p=0.006; ES=0.113); (2) White versus Black participants (Mean: White (n=461)=0.468, Black (n=122)=0.332; p=0.006; ES=0.198); and (3) APOE-ε4 carriers (Mean: Carrier (n=171)=0.536, Non-Carrier (n=370)=0.386; p=0.006; ES=0.215). P-tau217 remained significantly associated with a continuous measure of Aβ-PET (b = 96.05, 95% CI [87.98, 104.11], t(382) = 23.41, p<0.001; Std. beta = 0.77, 95% CI [0.70, 0.83]) and a dichotomous measure of Aβ-PET positivity status (OR = 2.73, 95% CI [2.24, 3.43], p<0.001) after adjusting for age, sex, race, APOE status, and eGFR (all p < .05). A 4-tier system was used to further stratify p-tau217 (e.g., amyloid) positivity to identify intermediate zones. Specifically, binary (Youden index = .338) and two-point ROC detection[1,2,3] thresholds (max sensitivity cutoff=0.247; max specificity cutoff=0.474) were combined: (1) Negative [<0.274; N~39%]; (2) Intermediate-Low [0.274-.338; N~20%]; (3) Intermediate-High [0.338-.474; 13%]; and (4) Positive [>0.474; 28%]. Longitudinally, ~9% (N=32 of 344 with 2+ sessions) of p-tau217 negative individuals (baseline < .474) converted to and remained p-tau217 (e.g., amyloid) positive at follow-up 2 to 4 years later. The majority converted (N=21; 66%) from the INT-HIGH zone. **Conclusion:** ALZpath p-tau217 is a highly accurate index of amyloid pathology. Intermediate zones capture subthreshold p-tau217 accumulators who convert to amyloid positivity at follow-up. Additional longitudinal analyses assessing how vascular and metabolic factors may impact disease progression captured by p-tau217 are planned. **Keywords:** Plasma P-tau217, amyloid PET, Biomarkers, Dementia, Risk. **References:** Ashton NJ, et al. (2024). JAMA Neurology. https://doi.org/10.1001/JAMANEUROL.2023.5319; Benedet AL, et al. (2022). Alzheimer's Research and Therapy, 14(1), 1–11. https://doi.org/10.1186/s13195-021-00942-0; Mattsson-Carlgren N, et al. (2023). JAMA Neurology. https://doi.org/10.1001/JAMANEUROL.2023.4596. **Disclosures:** Drs. Chaby and Jeromin are employees of ALZpath. Dr. Mielke consults for or serves on advisory boards for Biogen, Eisai, Lilly, Merck, Novo Nordisk, Roche, and Siemens Healthineers. Dr. Craft reports disclosures for: vTv Therapeutics, T3D Therapeutics, Cyclerion Inc, and Cognito Inc. There are no additional disclosures to report.

P134- ADVANCING DETECTION OF NEUROLOGICAL BIOMARKERS IN BLOOD USING A NOVEL ULTRASENSITIVE SINGLE MOLECULE COUNTING TECHNOLOGY. R. Tobias[1], P. Wagner[1], J. Sandlund[1], K. Moriyama[2], M. Imaizumi[2], Y. Kawada[2], K. Hamano[2], F. Zaugg[1], G. Dave[1], D. Inaoka[1], H. Kimura[1], K. Kobayashi[1], V. Brachet[1] *(1. Fluxus, Inc. - Sunnyvale (United States), 2. Fujirebio, Inc. - Tokyo (Japan))*

Background: We have developed a novel optofluidic ultrasensitive immunoassay technology capable of measuring extremely low concentrations of biomarkers across various sample types. Traditionally, neurological biomarkers are measured in cerebrospinal fluid, a process that involves highly invasive sample collection. Detecting lower levels of these biomarkers circulating in blood has been challenging for traditional, less sensitive immunoassay technologies. Fluxus'

ultrasensitive single molecule counting technology has the potential to enable the accurate detection and measurement of these biomarkers at lower concentration levels in plasma, offering a less invasive and more accessible method for diagnosing Alzheimer's disease and other neurological conditions. Here, we present analytical performance data for three neurological biomarker immunoassays: pTau181, Aβ1-40, and Aβ1-42, developed on a fully-automated benchtop analyzer with an integrated ultrasensitive detector. We also describe the correlation of these assays with the fully validated and commercially available immunoassay system, Lumipulse G1200 (Fujirebio Diagnostics, Inc., USA). **Methods:** Fluxus' ultrasensitive immunoassays for pTau181, Aβ1-40, and Aβ1-42 were developed using high-performing monoclonal antibodies (Fujirebio Europe, Belgium). Capture antibodies were immobilized on magnetic beads and detection antibodies were conjugated to a proprietary fluorescent reporter construct (reporter-Ab). Multiple incubation and wash steps were followed by dissociation of immune complexes and separation of reporter-Ab molecules from the beads. Released reporter-Ab molecules were injected into the ultrasensitive detector for single molecule counting. We performed analytical evaluations of each of the three assays, determining limits of detection (LoD) and lower limits of quantification (LLoQ), linearity, parallelism, precision, and reproducibility using endogenous analytes spiked into a plasma matrix across multiple concentration levels. We also performed a correlation study with the Lumipulse G1200, comparing the quantified levels of pTau181, Aβ1-40, and Aβ1-42 across the dynamic range of the assay, as measured by both our ultrasensitive assays and Lumipulse G1200. **Results:** The LoDs for the pTau181, Aβ1-40, and Aβ1-42 assays were calculated to be <0.1, 0.06, and 0.1 pg/mL, respectively. The LLoQs for pTau181, Aβ1-40, and Aβ1-42 were estimated to be 0.2, 0.5, and 0.5 pg/mL, respectively. Comparison of biomarker levels quantified with the Lumipulse G1200 showed correlation coefficients greater than 0.998 across an assay working range of >4 logs. **Conclusion:** We have developed a novel ultrasensitive single molecule counting platform with the ability to accurately measure neurological biomarkers at sub-pg/mL levels in blood, and measured concentrations levels in samples of all three biomarkers correlated well with Lumipulse G1200 results. This offers the potential for a less invasive, more accessible, and scalable method for early detection and monitoring of neurological diseases, facilitating early intervention, better disease management, and improved outcomes. **Key words:** blood biomarkers, ultrasensitivity, neurology. **Conflict of interests:** All authors are employees of either Fluxus, Inc. or Fujirebio, Inc., Japan.

P135- A TWO-STAGE MACHINE LEARNING MODEL PREDICTS AMYLOID B POSITIVITY ACCURATELY AND COST EFFECTIVELY. W. Zhu[1], L. Sun[1], S.Y. Shin[1], J. Donahue[1], J. Latourelle[1] *(1. Aitia - Somerville (United States))*

Background: The detection of brain β-Amyloid plagues (Aβ+) is critical to both diagnosis and treatment of Alzheimer's disease [1]. The 'gold-standard' method to diagnose Aβ+ in living people is PET scan, which is radioactive, expensive, and not universally accessible [2]. Machine learning models using blood biomarkers for the timely and accurate Aβ+ detection have been developed recently [3, 4]. However, barriers still exist as blood tests, due to the high cost, may be limited to individuals covered by insurance. Thus, a more affordable and accessible approach for Aβ+ screening would benefit clinical practice. **Methods:** GAP's Bio-Hermes [5] study provided high-dimensional data from more than 1,000 volunteers; covering demographics, APOE genotype, proteomics, blood biomarkers, cognitive scores, amyloid PET centiloid values, etc. Our training dataset included ~9000 features from 686 multi-ethnoracial participants (47% cognitively normal, 32% MCI and 21% probable AD). The prevalence of Aβ+ (centiloid value > 25) was 35% in full population, 56% in AD subset, and 29% in normal/MCI subset. Aitia's REFSTM platform [6] was used to develop a series of predictive ensemble models using different combinations of features to predict Aβ+. Considering the tradeoff between prediction accuracy and the cost of features such as blood biomarkers, a two-stage Aβ+ screening scheme integrating two of the predictive models is proposed. The effectiveness of the screening scheme is measured by the number of initial screens, blood tests and PET scans performed to reach a certain number of Aβ+ individuals with reasonable PET scan failure rate and overall NPV (Negative Predictive Value) in different populations with different Aβ+ prevalence. **Results:** Two predictive models built using Aitia's causal machine learning platform were selected to construct a two-stage screening scheme. The stage-1 model including only easily accessible features (demographics, cognitive tests and speech analysis scores) achieves an out-of-sample AUC (Area Under ROC Curve) of 0.75. The stage-2 model includes APOE4 status and blood biomarkers (Aβ ratio, p-tau 181, p-tau 217) in addition to stage-1 features and improves the out-of-sample AUC to 0.94. Using this screening scheme to identify 250 true Aβ+ individuals from a population similar to the original mixed normal/MCI/AD cohort with 35% Aβ+ prevalence, 1032 digital screenings, 724 blood draws, and 273 PET scans need to be done. In an AD population with 56% Aβ+ prevalence, 505 digital screenings, 461 blood draws, and 270 PET scans are needed. In a normal/MCI population with 29% Aβ+ prevalence, 1450 digital screenings, 985 blood draws, and 273 PET scans are needed. **Conclusion:** A two-stage Aβ+ screening scheme was proposed to achieve comparable overall performance with other blood biomarker-based predictive models but at lower cost. Screening performance largely depends on the Aβ+ prevalence of the population, and can be tuned by adjusting the cutoffs of the two embedded models. Knowing APOE4 at initial screen can further reduce number of blood draws. **Keywords:** REFS, Amyloid positivity, Centiloid, blood biomarkers, causal inference, two-stage screening. **References:** 1. Pleen J, et al. Practical Neurol. 2024. 23(2):27-29,35-39. Available: https://practicalneurology.com/articles/2024-mar/blood-based-biomarkers-in-alzheimer-disease-clinical-implementation-and-limitations; 2. Tosun D, et al. Brain communications. 2021. 3(2), fcab008. https://doi.org/10.1093/braincomms/fcab008; 3. Fogelman I, et al. Ann Clin Transl Neurol. 2023. 10(5), 765–778. https://doi.org/10.1002/acn3.51763; 4. Zhu W, et al. Prediction of Amyloid PET positivity from blood-based biomarkers and clinical data using AI-based Digital Twins. [Poster Presentation]. 2023. CTAD, Boston; 5. https://globalalzplatform.org/biohermesstudy/; 6. Latourelle JC, et al. Lancet Neurol. 2017. PMID: 28958801. https://doi.org/10.1016/S1474-4422(17)30328-9.

P136- USE OF CSF STREM2/TOTAL-TAU RATIO AS A POTENTIAL PROGNOSTIC BIOMARKER TO IDENTIFY FAST PROGRESSORS IN EARLY ALZHEIMER'S DISEASE. J. Sorinas[1], N. Coello[2], N. Pezous[2], E. Khokhlovich[3], A. Rogojina[2], J. Curcic[1], H. Kocherla[2], K. Hannesdottir[3] *(1. Biomedical Research, Novartis - Basel (Switzerland), 2. Novartis Pharma AG - Basel (Switzerland), 3. Biomedical Research, Novartis - Cambridge (United States))*

Background: Brain inflammation has gained attention as a potential target in Alzheimer's disease (AD) [1]. Recent evidence links microglial activation through triggering receptor expressed on myeloid cells 2 (TREM2) to a potential neuroprotective pathway in AD and other neurodegenerative diseases [2]. Soluble TREM2 (sTREM2) is elevated in the cerebrospinal fluid (CSF) of AD patients and is currently regarded as a potential candidate biomarker for microglial activation [3]. High sTREM2 CSF levels have been hypothesized as predictive of slower cognitive decline, lower β-amyloid (Aβ) accumulation and reduced changes in tau pathology in AD [4-6]. The aim of the current work is to assess sTREM2 as a prognostic biomarker of cognitive decline in early AD. **Methods:** Early AD patients (N=460; mean age 73.6 (SD 7.6); mean years of education 15.8 (SD 2.9); 42.2% female; 21.3% APOE4 homozygotes, 49.8% APOE4 heterozygotes) from the Alzheimer's Disease Neuroimaging Initiative* (ADNI) database (adni.loni.usc.edu) were selected for this study. Early AD was defined as clinical diagnosis of mild cognitive impairment or AD, Aβ positivity [7-8] and mild cognitive decline based on the mini-mental state examination clinical scale (MMSE≥20). We performed ordinary least squares regression to evaluate associations between sTREM2 and CDR-SB (clinical dementia rating scale – sum of boxes) at baseline. Models were corrected by the conventional cofactors used in AD, such as age, gender, number of years of education and APOE4 genotype. Additionally, we included CSF biomarkers of amyloid (Aβ42) and tau (phospho-tau181, total-tau) pathology to better understand how brain inflammation relates with the underlying AD pathology. **Results:** CSF sTREM2 was not a statistically significant (p-value>0.05) cofactor in our regression model, suggesting that sTREM2 CSF baseline levels alone are not associated with cognition in early AD patients. However, when including AD pathology markers as cofactors in the models, specifically tau but not amyloid, sTREM2 contribution turned out statistically significant. sTREM2 showed a negative relationship with CDR-SB, whereas tau markers showed a positive relationship. The opposite relationship of sTREM2 and tau with CDR-SB suggests an interplay between the hallmarks; high levels of sTREM2 and low levels of tau might be associated with lower cognitive decline. To confirm these findings, we split the patients into two subgroups by the median of sTREM2/total-tau CSF levels at baseline and evaluated their progression over two years throughout a set of cognitive assessments. The group below the median progressed statistically significantly faster than the group with higher baseline levels of CSF sTREM2/total-tau. **Conclusion:** Our findings show that the sTREM2 CSF levels are inversely related to the tau CSF levels, suggesting an interplay between the shedding of TREM2 and the levels of tau. Moreover, low sTREM2 CSF levels combined with high total-tau CSF levels were associated with a worse clinical prognosis, with faster clinical progression. We propose the ratio between sTREM2 and total-tau as a potential prognostic biomarker to identify fast progressors in early AD. Nevertheless, the performance of the sTREM2/total-tau CSF ratio should be further validated in additional datasets. **Keywords:** early Alzheimer's disease, prognostic biomarkers, sTREM2, total-tau. **Disclosures:** All co-authors are employees and N.C., N.P., E.K., J.C., H.K., K.H. are shareholders of Novartis Pharma AG. The authors declared no competing interests. **References:** 1. Calsolaro V, et al. Alzheimer's Dement 2016; 12(6):719-732. https://doi.org/10.1016/j.jalz.2016.02.010. 2. Qin J, et al. Front. Neurol. 2023; Vol 14. https://doi.org/10.3389/fneur.2023.1103416; 3. Li Y, et al. Biomed Pharmacother 2023; 165, 115218. https://doi.org/10.1016/j.biopha.2023.115218; 4. Ewers M, et al. Sci Transl Med 2019;11(507):eaav6221. doi: 10.1126/scitranslmed.aav6221; 5. Hu WT, et al. Nat Commun 2021 ; 12, 4001. https://doi.org/10.1038/s41467-021-24220-7; 6. Pereira JB, et al. Nat Aging 2022; 2, 1138–1144. https://doi.org/10.1038/s43587-022-00310-z; 7. Johnson KA, et al. Alzheimer's Dement 2013; 9(0): S72–S83. Doi: 10.1016/j.jalz.2012.10.007; 8. van Harten AC, et al. Alzheimer's Dement 2022; 2022; 18:635–644. https://doi.org/10.1002/alz.12406; *Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

P137- EXPLORING THE ASSOCIATION BETWEEN P-TAU217 AND PERFORMANCE-BASED DIGITAL ASSESSMENT OF COGNITIVE FUNCTIONING IN MILD COGNITIVE IMPAIRMENT. A. Perez[1,2], S. Afonsin[3,4], G. Giuffrè[5], E. Christensen[6,2], F. Maestú[3,7], H. Renvall[8,4], C. Marra[5], P. Rossini[4], C. Hatlestad-Hall[1], I. Haraldsen[1,9] *(1. Department of Neurology, Oslo University Hospital - Oslo (Norway), 2. Department of Experimental Psychology, Cognitive Psychology and Speech and Language Therapy, Universidad Complutense de Madrid - Madrid (Spain), 3. Centre for Cognitive and Computational Neuroscience, Universidad Complutense de Madrid - Madrid (Spain), 4. Department of Neuroscience and Neurorehabilitation, IRCCS San Raffaele - Rome (Italy), 5. Memory Clinic, Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Rome (Italy), 6. Pre Diagnostics AS - Oslo (Norway), 7. BioMag Laboratory, HUS Medical Imaging Centre, Helsinki University Hospital, Helsinki University and Aalto University School of Science - Helsinki (Finland), 8. Department of Neuroscience and Biomedical Engineering, Aalto University - Helsinki (Finland), 9. Institute of Clinical Medicine, Faculty of Medicine, University of Oslo - Oslo (Norway))*

Background: The measurement of phosphorylated tau (p-tau) proteins is emerging as a promising biomarker for diagnosing Alzheimer's disease (AD) and other dementias. P-tau may be measured in blood plasma and cerebrospinal fluid and is associated with disease presence and progression. The Cambridge Neuropsychological Test Automated Battery (CANTABTM) is a digital assessment that offers robust performance-based measures of cognitive functions. Here, we explore the relationship between levels of p-tau217 and performance on CANTABTM tests in a multicentre cohort of individuals with mild cognitive impairment (MCI) aged 60-80 years. The work is part of the AI-Mind project [1]. **Methods:** p-tau217 levels were measured in blood plasma using highly sensitive immunoassays from 486 individuals with MCI using the MesoScale S-PLEX Human Tau (pT217; Meso Scale Discovery) on a MESO QuickPlex SQ 120MM instrument.

Each participant underwent a battery of CANTABTM tests, including Paired Associates Learning (PAL), Rapid Visual Information Processing (RVP), Spatial Working Memory (SWM), Delayed Matching to Sample (DMS), and Pattern Recognition Memory (PRM). We selected one key variable from each test and explored their relationship with p-tau levels. First, partial correlation coefficients were calculated between each CANTABTM outcome variable and the p-tau level. The p values associated with the correlation coefficients were corrected for multiple comparisons with the Bonferroni method. Second, a general linear model (GLM) was constructed with the p-tau level serving as the dependent variable and the five CANTAB™ outcome variables as independent predictors. Additional covariates included in the model were age, sex, and education level. **Results:** These preliminary analyses reveal significant correlations ($p < 0.05$) of low to medium magnitude ($r = 0.13$-0.20) between p-tau and selected CANTABTM outcome variables, controlled for age, sex, and education. Higher levels of p-tau217 were associated with lower performance on the test for visual information processing (RVP) and the learning-memory function test (PAL). In the GLM, among the CANTAB variables, only the RVP performance demonstrated a significant effect on p-tau217 levels. **Conclusion:** In this exploratory analysis of the AI-Mind cohort, we observed that measures of cognitive functioning obtained from digital assessment varies across cognitive domains in their association with p-tau217 levels in blood plasma. The RVP test displayed the strongest association with p-tau217 levels. To elucidate the nature of this association and its potential value in predicting dementia risk remains an important target for future work. **Keywords:** AI-Mind, mild cognitive impairment, p-tau217, cognition. Clinical Trial Registry: Not applicable. **Data Deposition:** Not applicable. **Disclosures:** This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 964220. The abstract reflects views of author, and the European Commission is not responsible for any use that may be made of the information it contains. The authors have no competing interests to declare. **References:** 1. Haraldsen, IH, et al. Front Neurorobot. 2023; 17: 1289406. doi:10.3389/fnbot.2023.1289406.

P138- NEW HIGH-THROUGHPUT, FULLY AUTOMATED IMMUNOASSAY FOR PLASMA NEUROFILAMENT LIGHT CHAIN. J. Todtleben[1], D. Unruh[1], M. Szabo[1], C. Carlson[1], K. Curtis[1], K. Hoffmann[1], L. Mediger[1], J. Mendoza[1], M. Nichova-Doseva[1] *(1. Beckman Coulter Inc - Chaska, Mn (United States))*

Background: Neurofilament light chain (NfL) is a marker of neuroaxonal injury. Elevated levels of NfL are detected in blood in multiple neurodegenerative diseases, including Alzheimer's disease (AD). Given the low abundance of NfL in blood (picomolar and sub-picomolar levels), improvement in the sensitivity of NfL assays is necessary for accurate detection. Additionally, the availability of high-throughput assays will allow for reliable and widespread use in clinical trials and practice. Here, we describe the performance of a highly sensitive plasma NfL assay on the DxI 9000 and Access 2 Immunoassay Analyzers. **Methods:** The prototype NfL assay is a one-step sandwich assay utilizing an anti-NfL monoclonal antibody (MAb)/alkaline phosphatase conjugate and paramagnetic particles coated with a complementary anti-NfL MAb. Sample and reactants are incubated and washed, then a chemiluminescent substrate is added. The light generated is directly proportional to the NfL concentration in the sample. Samples were screened on the DxI 9000 and Access 2 Immunoassay Analyzers, capable of analyzing up to 450 and 100 tests/hour, respectively. The assay's time to first result is ~26 minutes on the DxI 9000 and ~31 minutes on the Access 2 Immunoassay Analyzers. For this study, 40 EDTA plasma samples from 20 AD patients (53–85 years) and 15 age-matched (56–74 years) and 5 young (30–39 years) healthy controls were evaluated. Analytical sensitivity (lower limit of quantitation) and discrimination between AD-positive and healthy control populations were evaluated. A method comparison was performed between the DxI 9000 and Access 2 Immunoassay Analyzers and two commercially available NfL immunoassays using the same EDTA plasma samples described above. **Results:** The prototype NfL assay had an approximated analytical measuring range of 1.5 to 10,000 pg/mL (DxI 9000) and 2.0 to 10,000 pg/mL (Access 2). NfL was detected and quantified in all (100%) samples on both analyzers, and a 20% within-run lower limit of quantitation (LLOQ) was estimated at ~1.5 pg/mL for the DxI 9000 and ~2.0 pg/mL for the Access 2 analyzers. The intra-assay coefficient of variation was ≤8% on both analyzers. Cross-reactivity was performed on proteins with high homology with NfL—neurofilament medium and heavy chain, alpha-internexin, and peripherin—all of which did not cross-react. A comparison of the prototype NfL assay, performed on the DxI 9000 and Access 2 Immunoassay analyzers, against two commercially available NfL assays yielded correlations between r=0.92 and 0.98. The median concentration of NfL in the AD samples (39.9 pg/mL) was compared with age-matched healthy controls (21.8 pg/mL) and young healthy controls (12.0 pg/mL). **Conclusion:** The prototype NfL assay provided fast, highly sensitive, and precise results in an automated immunoassay on the Beckman Coulter DxI 9000 and Access 2 Immunoassay Analyzers. The assay was able to detect NfL in 100% of samples on both analyzers, even the young healthy controls, and had high correlation with commercially available NfL assays. **Keywords:** Neurofilament light chain, biomarker, immunoassay, Alzheimer's Disease. **Disclosures:** J. Todtleben, D. Unruh, M. Szabo, C. Carlson, J. Mendoza, and M. Nichova-Doseva are full-time employees and hold stocks of Beckman Coulter/Danaher. All other authors are full-time employees of Beckman Coulter/Danaher.

P139- CLINICAL AND ANALYTICAL VALIDATION OF LUCENTAD COMPLETE, MULTI-MARKER ALGORITHMIC LAB DEVELOPED TEST (LDT) FOR HIGH ACCURACY PLASMA DETECTION OF AMYLOID PATHOLOGY. D. Wilson[1] K. Copeland[2] M. Khare[1], M. Wolfe[1], P. Sheehy[1], L. Hesterberg[3], A-J. Vasko[1], W. van der Flier[4], A. van Harten[4], I. Verberk[4], C. Teunissen[4], M. Miller[1] *(1. Quanterix Corporation - Billerica (United States), 2. Boulder Statistics - Steamboat Springs (United States), 3. HCS, Inc - Denver (United States), 4. Amsterdam UMC, Vrije Universiteit Amsterdam -Amsterdam, (Netherlands))*

Background: 217 is considered the most accurate single plasma biomarker for detecting amyloid pathology. Recent draft Alzheimer's Association criteria for diagnosing Alzheimer's recommends that plasma p-Tau 217 tests be designed with two cutoffs in recognition of signal overlap between amyloid positive and negative patients. Two cutoffs maximizes the accuracy of the test, but leaves a diagnostic intermediate zone with uncertainty of amyloid status. It is desirable to minimize the intermediate zone to reduce the number of patients receiving uncertain results. We investigated whether application of a multi-marker logistic regression model including p-Tau 217, amyloid b42/40 ratio, NfL, and GFAP

to intermediate range samples would improve classification of these borderline cases and reduce the overall number of uncertain test results. **Methods:** We first tested 735 MCI and AD plasma samples from two independent cohorts (Bio-Hermes, n=238, Amsterdam Dementia Cohort, n=497) using the Simoa LucentAD 217 test which has two cutoffs optimized for ≥ 90% accuracy. These cohorts represent divergent clinical settings, comparator methods (CSF and amyloid PET) and geographic/ethnic/racial/mean age samplings. 228 (31.0%) of the samples fell into the intermediate range between the lower and upper cutoffs. Next we applied a multivariate logistic regression model with all five biomarkers to the intermediate results, and examined potential re-classification of these samples as amyloid positive or negative. The p-Tau 217 results below and above the intermediate range were combined with the multivariate model results within the intermediate range to generate a full range probability scale with two new cutoffs optimized for accuracy and a reduced intermediate range. **Results:** Applying the multi-marker model to the 228 intermediate range samples enabled re-classification of 140 samples (61.4%) to either amyloid positive (67.9%) or negative (32.1%) with an overall accuracy of 87.1%. The multivariate re-classification reduced the intermediate range from 31% to 12%, a 2.6-fold reduction. The AUC of the multi-marker test across all 735 samples was 0.917 (0.89-0.94). Excluding samples remaining in the new intermediate range, sensitivity was 90.5% (87.5-92.9%), specificity was 90.7% (85.6-94.1%), and accuracy was 90.6% (88.1-92.6%). At the amyloid prevalence in this study of 70.2%, PPV was 96.1%, and NPV was 79.0%. With an assumed prevalence of 50% (representative of MCI patients), PPV and NPV was estimated as 90.7% and 90.5% respectively with a 13.3% intermediate rate. **Conclusion:** Previous studies have found no benefit to combining additional AD-relevant biomarkers with p-Tau 217 to enhance plasma test accuracy. We show for the first time that the addition of amyloid ratio, NfL, and GFAP to p-Tau 217 allows accurate amyloid classification of over one-half of intermediate cases that could not be classified with p-Tau 217 alone while preserving high overall test accuracy. This finding can help provide amyloid status certainty for a greater number of symptomatic patients undergoing evaluation for Alzheimer's. **Keywords:** p-Tau 217, multi-marker, algorithm, intermediate range. **Disclosures:** DW, MK, MW, PS, AV, and MM are employees of and shareholders in Quanterix. KC and LH are contracted consultants for Quanterix.

P140- THE DIAGNOSTIC IMPACT OF PLASMA P-TAU217 COMBINED WITH STRUCTURAL MAGNETIC RESONANCE IMAGING IN A MEMORY CLINIC COHORT.

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Background: Blood-based biomarkers for Alzheimer's disease (AD) are emerging alternatives to established cerebrospinal fluid biomarkers and molecular neuroimaging(1). Plasma phosphorylated (p)-tau217 has shown promising results, with a relatively high association with both cerebral amyloid- and tau-pathology. The clinical utility of plasma p-tau217 in diagnosing predementia AD should be clarified, also whether additional diagnostic tools increase diagnostic accuracy. We examined (1) the diagnostic value of plasma p-tau217 in the diagnosis of predementia AD in a memory clinic cohort, and (2) the added diagnostic value of structural imaging. **Methods:** Plasma p-tau217 was measured using the The University of Gothenburgh p-tau 217 assay on the Simoa HD-X platform. We used a logistic regression model to evaluate the association of p-tau217 with the diagnosis of AD in 164 participants from the Norwegian Dementia Disease Initiation study at baseline. Participants were classified as cognitively normal (CN) or with mild cognitive impairment (MCI) based on a standardized cognitive test battery. Presence (+) or absence (-) of amyloid (A) pathology was determined using amyloid-beta42/40-ratio [CN A- (n=52), CN A+ (n=21), MCI A- (n=44) and MCI A+ (n=47)]. In addition, Medial Temporal Atrophy (MTA) scores (0-4) from Magnetic Resonance Imaging (MRI) were evaluated as predictors in separate models. Area Under The curve (AUC), Positive- and Negative Predictive values (PPV/NPV) were computed for each model and resulting diagnostic accuracies were compared using Delong's test. **Results:** The AUC for plasma p-tau217 when comparing MCI A- vs MCI A+ was .860, All A- vs All A+ (.828) and CN A- vs CN A+ (.743). Adding MTA-scores as a predictor in the models, resulted in a significant improvement in AUC for All A- vs All A+ (from .828 to .855, $p<.05$), and an improvement in PPV (from .814 to .862), but slight reduction in NPV (from .746 to .727). Similarly, an improved AUC was seen for CN A- vs MCI A+ (from .876 to .922, $p<.05$) and improvements in both PPV (from .813 to .857) and NPV (from .843 to .900). No significant improvement in AUC was observed between CN A- and CN A+ (from .743 to .748, $p=.650$), nor for MCI A- vs MCI A+ (from .860 to .888, $p=.167$). However, improvements in both PPV (from .787 to .848) and NPV (from .772 to .822) for MCI A- vs MCI A+ were nevertheless observed. **Conclusion:** p-tau217 performed well at separating A+ from A-, but positive and

negative predictive values were improved when MTA scores were included in models aimed at identifying MCI A+ from MCI A, leading to less false positive and negative diagnoses. We did not observe any improvement in positive or negative predictive values when adding MTA scores to models aimed at identifying CN A+ from CN A-. Thus, combining blood-based biomarkers and MRI in the diagnosis of prodromal AD may be a cost-effective way identify prodromal AD cases eligible for treatment and inclusion in clinical trials. For future studies we will incorporate MRI based AI-metrics. **Keywords:** Prodromal Alzheimer's disease; blood biomarkers; diagnostic utility; magnetic resonance imaging. **Disclosures:** BEK has served as a consultant for Biogen and advisory board for Eisai. KB has served as a consultant and at advisory boards for Acumen, ALZPath, AriBio, BioArctic, Biogen, Eisai, Lilly, Moleac Pte. Ltd, Novartis, Ono Pharma, Prothena, Roche Diagnostics, and Siemens Healthineers; has served at data monitoring committees for Julius Clinical and Novartis; has given lectures, produced educational materials and participated in educational programs for AC Immune, Biogen, Celdara Medical, Eisai and Roche Diagnostics; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, outside the work presented in this paper. HZ has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Alzecure, Biogen, Cellectricon, Fujirebio, Lilly, Novo Nordisk, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). TF has served as a consultant and at the advisory boards for Biogen, Eisai, Novo Nordisk, Eli Lilly and Roche. **References:** 1. Zabala-Findlay A, Penny LK, Lofthouse RA, Porter AJ, Palliyil S, Harrington CR, et al. Utility of Blood-Based Tau Biomarkers for Mild Cognitive Impairment and Alzheimer's Disease: Systematic Review and Meta-Analysis. Cells 2023;12:1184. https://doi.org/10.3390/cells12081184.

P141- GEOGRAPHIC ACCESS TO AMYLOID PET SCANS IN THE U.S.: IMPLICATIONS FOR CLINICAL TRIALS AND REAL-WORLD TREATMENT. M. Hanson[1], Y. Liu[1], H. Yin[1], S. Mattke[1] *(1. University of Southern California - Los Angeles (United States))*

Background: Several disease-modifying Alzheimer's disease (AD) treatments are available or in various stages of clinical trials. Participation in these trials and access to approved treatments often requires amyloid positron emission tomography (PET) scans, sometimes repeatedly. In a vast country like the U.S., the question arises whether this requirement excludes segments of the population living in sparsely populated areas, and how these segments differ from the overall population. Geographic access to amyloid PET is further complicated by the fact that the radioactive amyloid tracer has a short half-life, and the PET scanner must be within a reasonable driving distance from a cyclotron that can produce the tracer. We estimate the size and composition of the U.S. population that faces likely geographical obstacles to access due to these constraints. **Methods:** From published data for the U.S., we extracted 2,371 geocoded sites that offer PET scans1 and 117 cyclotron locations from the International Atomic Energy Agency website. We assumed that a qualifying PET site must be within a three-hour drive time, one-way, from a cyclotron, regardless of whether the site is currently offering amyloid PET scans since it could do so in the future. We compared the population of age 65 and older living in a census tract within one-hour drive time, one-way, of such sites to those living farther away by their demographic characteristics using the 2017-2021 5-yr estimates of the American Community Survey. Drive times were estimated based on major U.S. roads at average highway speed using street network data from the U.S. Bureau of Transportation Statistics. Geographic analysis was performed using QGIS software. **Results:** Among the 2,371 PET scan sites, 2311 (97.5%) were located within a three-hour drive time from a cyclotron. From a qualifying PET site, 2,440 (2.9%) of the 83,611 census tracts were outside of the one-hour drive range. These tracts are mostly located in the Intermountain West (including Idaho, Wyoming, Montana, Utah, Colorado, Nevada and Arizona) and in rural parts of the Southern and Northern borders and of the West Coast. Further, 2.8% (1,479,277 out of 52,549,644) of the population aged 65+ residing in the tracts more than one-hour drive from a qualifying PET site, leaving 97% residing in a reasonable proximity. On average, tracts farther have higher percentage of population below the Federal Poverty Level (11% vs 9%, p<.01), non-Hispanic white (71% vs. 65%, p<.01), and American Indian (4% vs. 1%, p<.01), compared to tracts in a reasonable proximity. **Conclusion:** The vast majority of the elderly U.S. population lives within reasonable proximity to a site that could conduct amyloid PET scans for AD clinical trials and approved treatments. However, the composition of the remaining 1.5 million with likely geographic barriers to access raises concern for disparities in healthcare, in particular regarding access to clinical trials, which often require multiple PET scans. AD treatments that do not require amyloid PET scans could alleviate such disparities. **Keywords:** Amyloid PET, diagnosis, disease-modifying treatment, geographic access, disparities. **Disclosures:** Mark Hanson reports no potential conflicts of interest. **References:** 1. Lam J, Jun H, Cho SK, Hanson M, Mattke S. Projection of budgetary savings to US state Medicaid programs from reduced nursing home use due to an Alzheimer's disease treatment. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2021;13(1) doi:10.1002/dad2.12159.

P142- IMPLEMENTATION OF P-TAU181/AB42 AND TOTAL-TAU/AB42 ROCHE ELECSYS RATIOS: EVALUATION OF CUT-OFFS FOR P-TAU181, TOTAL-TAU AND AB42. J. Colon-Franco[1], L. Bekris[2], S. Zilka[1], K. Troike[1], M. Khrestian[2], T. Babak[3], E. Tuason[2], J. Leverenz[3] *(1. Laboratory Medicine, Diagnostic Institute, Cleveland Clinic - Cleveland (United States), 2. Genomic Medicine Institute, Cleveland Clinic - Cleveland (United States), 3. Lou Ruvo Center for Brain Health, Neurological Institute, Cleveland Clinic - Cleveland (United States))*

Background: Cerebrospinal fluid (CSF) amyloid and tau biomarkers are diagnostic for Alzheimer's disease (AD). The ratios Aβ42/ABeta40, p-tau181/Aβ42 and total-tau/Aβ42 correlate with amyloid PET scans and outperform individual biomarkers concentrations. We recently implemented the US Food and Drug Administration (FDA)-cleared Roche Elecsys p-tau181/Aβ42 and total-tau/Aβ42 ratios in a US hospital laboratory. Co-reporting the ratios and individual AD biomarkers concentrations is a common and preferred practice, as these offer independent clinical information in the differential diagnosis across the AD continuum. Reporting

the individual biomarkers has limitations. For example, when deviating from the test intended use or if diagnostic cut-offs information from the assay manufacturer is lacking. Only population-based reference intervals in an apparently healthy population are listed in the Roche US package inserts. The aim of this study was to evaluate concordance between various cut-off approaches for Aβ42, p-tau181 and total-tau in our patient population. **Methods:** Cut-offs for the ratios and biomarkers were derived using ROC and Youden-index analyses on 35 CSF samples (n=11 PET negative, n=24 PET positive) from the Cleveland Alzheimer's Disease Research Center and Cleveland Clinic Lou Ruvo Center for Brain Health Aging and Neurodegenerative Disease Biobank; referred to as CADRC. Consecutive CSF samples (n=30, 9 males/21 females, 53-84 years of age) with clinical orders for p-tau181/Aβ42 and total-tau/Aβ42 tests at the Cleveland Clinic were classified as positive/negative using these cut-offs: approved by the FDA (0.023 and 0.28, respectively) [1], established for p-tau181/Aβ42 in another US population (0.028) [2] and CADRC-derived. We evaluated the concordance between ratio classification and these cut-points for Aβ42, p-tau181 and total-tau: reference intervals (RI, 95th percentile, FDA-cleared package inserts [1])->564.3, ≤31.3 and ≤375.4 pg/mL, respectively; cut-offs for predicting amyloid PET status (non-US package inserts [3])->1030, ≤27.0 and ≤300 pg/mL, respectively; Bornhorst-derived [2] cut-offs->834 and ≤21.6 pg/mL for Aβ42 and p-tau181, respectively; and CADRC-derived cut-offs. **Results:** The CADRC-derived cut-offs are: Aβ42 >846 pg/mL, p-tau181 ≤21.7 pg/mL, total-tau ≤278.3 pg/mL, p-tau181/Aβ42 ≤0.024 and total-tau/Aβ42 ≤0.27. The ratios correlated well (y=7.619x+0.1044, R2 0.9241, p-value <0.0001) and classification matched in 28 (93.3%) of the 30 clinical cases. The Aβ42 RI resulted in 53.3% classification discrepancies (p-tau181/Aβ42 positive-Aβ42 normal) (p-value 0.2720, Fisher's exact test). The cut-offs >834 or >846 pg/mL decreased the discordant cases to 10% (p<0.0001). The Aβ42 cut-off >1030 pg/mL resulted in only 3% of samples misclassified as p-tau181/Aβ42 negative-Aβ42 decreased (p-value <0.0001). The RI for p-tau181 and total-tau resulted in 50-70% of discrepant classifications. Clinical cut-offs for p-tau181 (≤27 or ≤21.7 pg/mL) increased concordance 2-fold but there was no significant improvement for total-tau clinical cut-offs (≤300 or ≤278.3 pg/mL). **Conclusion:** The cut-offs derived from the CADRC cohort performed similarly in our patient population than cut-offs previously reported for PET concordance, despite the small sample size. Interpretation of AD biomarkers using the 95th percentile RI results in many discrepancies with the ratio classification. Applying clinical cut-offs significantly improved the classification concordance for Aβ42, and modestly for p-tau181. Our findings highlight the need to establish and validate cut-off values to support widespread introduction of AD biomarkers in clinical practice. **Keywords:** biomarkers, cerebrospinal fluid, cut-offs, reference interval. **Disclosures:** none. **References:** 1. Elecsys Method Sheets (US): 08846634501V2.0; 08821909501V3.0; 08846693501V2.0; 2. Bornhorst J, et al. J Prev Alz Dis 2023;10(S1):S132; 3. Elecsys Method Sheets (non-US): 08846634500V2; 08821909500V3.0; 008846693500V2.0.

P143- EXPLORING THE UTILITY OF PLASMA MICRORNA FOR EARLY DIAGNOSIS OF ALZHEIMER'S DISEASE. J. Williams[1], D. Guevremont[1], C. Fowler[2], C. Masters[2], R. Martins[3], W. Abraham[1], W. Tate[1], N. Cutfield[1] *(1. University of Otago - Dunedin (New Zealand), 2. The Florey Institute - Melbourne (Australia), 3. Macquarie University - New South Wales (Australia))*

Background: A class of regulatory RNA, microRNA, control a wide range of neuronal functions which are dysregulated in Alzheimer's disease (AD). MicroRNA are highly stable in blood plasma and can be measured by routine technologies. Accordingly, they may represent robust, stable, and easily accessible biomarkers capable of reflecting amyloid pathology, as well as multiple other aspects of AD physiology. Indeed, in previous work we identified specific plasma microRNA that change with AD progression. **Method:** Focusing on a group of cognitively normal individuals from the AIBL cohort, we have explored the expression of these microRNA in association with amyloid-β (Aβ) load as determined by positron emission tomography. The group was stratified by centiloid score where n=84 individuals (73.4 ± 4.4 years; 43:41 female:male) were considered Aβ-positive (69.26 ± 32) and n=93 (73.8 ± 5.0 years; 47:46 female:male) were considered Aβ-negative (-0.64 ± 6.3). MicroRNA expression was assessed using custom TaqMan microfluidics arrays. Following data normalisation, and identification of differentially expressed microRNA (empirical Bayes moderated t-tests; fold change > ± 0.2; $p < 0.05$), multiple logistic regressions were performed using the Backward: Wald method and goodness of fit was evaluated using the Hosmer-Lemeshow test ($p > 0.05$). The receiver-operating characteristic curve, area under the curve (AUC) was calculated to assess the ability of specific microRNA to predict membership of the groups ($p < 0.05$). **Results:** We found 13 differentially expressed microRNA, nine of which significantly contributed to the model. The diagnostic ability (AUC) of the nine microRNA was determined as 0.877 which increased to 0.910 with inclusion of ApoE status in the predictive model. **Discussion:** These results suggest that this microRNA signature alone or in combination with ApoE status may be a useful additional tool for detecting the earliest stages of AD.

P144- THE PLASMA PTAU181/217 RATIO IS HIGHLY SENSITIVE TO DISCRIMINATE ALZHEIMER´S DISEASE FROM OTHER DEMENTIAS– A PILOT STUDY IN A MEMORY CLINIC POPULATION. M. Defrancesco[1], A. Hofer[1], C. Humpel[1] *(1. Medical University of Innsbruck - Innsbruck (Austria))*

Background: The growing number of people with dementia and new ways to treat people with mild cognitive impairment due to Alzheimer's disease (AD) necessitate the development of non-invasive and cost-effective biomarkers. Elevated levels of pTau-181 and pTau-217 are generally associated with tau pathology in AD. However, these levels may also be indicative of other tauopathies, albeit often in different concentrations or patterns of elevation [1]. Blood-based biomarkers of tau (pTau 181 and pTau 217) showed good correlation with amyloid PET and CSF markers. However, the use of the pTau181/217 ratio has not been evaluated and valid cut-offs for clinical routine are lacking [2]. **Methods:** Data of 45 patients with positive or negative AD biomarkers (CSF or Amyloid PET [18F-florbetaben]) and a clinical diagnosis of major neurocognitive impairment were included. Levels of cerebrospinal fluid beta-amyloid-42, beta-amyloid -40, total Tau and pTau181 as well as plasma pTau 181 and plasma pTau 217 were analyzed with the commercial automated

Lumipulse G600II (Fujirebio). Binomial logistic regression and linear discriminant analysis were performed to determine the diagnostic accuracy of plasma pTau 181, pTau 217, and the ratio pTau181/217 to discriminate AD from other dementias. The Youden index of the ratio was calculated to determine the optimal threshold in a receiver operating characteristic (ROC) curve analysis. **Results:** Analysis of plasma tau 181, pTau 217 and the ratio pTau181/217 in memory clinic outpatients with major neurocognitive impairment due to Alzheimer's disease (N= 35, pTau 181: 2.8±1.4 pg/ml, pTau 217: 0.7±0.5 pg/ml, pTau181/217 ratio: 4.9) and due to other dementias (N= 10, pTau 181: 1.6±0.7 pg/ml, pTau 217: 0.2±0.2pg/ml, pTau181/217 ratio: 9.1) showed significantly lower levels of both plasma tau measures and a higher ratio in the latter group. The binomial logistic regression model was statistically significant,($\chi^2(3) = 30.305$, $p < .001$, Nagelkerke's $R^2 = .750$). The Ratio ptau181/217 had the highest diagnostic accuracy in the stepwise logistic regression analysis (p=<.001, OR = 0.493 (95%-CI [0.332 - 0.737]). LDA with pTau 181 and 217 alone correctly classified 77.8 % of patients. Adding the pTau181/217 ratio improved the diagnostic accuracy to 91.1%. The area under the curve for correctly classifying AD was 0.894 (95% CI 0.753 to 1.0) with a ratio cut-off of 5.7. **Conclusion:** Our results indicate that the use of plasma pTau-181 and 217 can effectively distinguish AD from other neurodegenerative dementias. However, the combination of both in one ratio significantly increases their validity. This is particularly useful in clinical settings where early and accurate differentiation of dementia etiology is critical for appropriate management and treatment planning. **Keywords:** Alzheimer's disease, tauopathies, Aβ pathology, tau pathology, blood-based biomarkers. **Disclosures:** The authors declare no competing interests. **References:** 1. Therriault J, et al. JAMA Neurol 2023;80(2):188-99. doi:10.1001/jamaneurol.2022.4485. 2. Lehmann S, et al. J Neurol Neurosurg Psychiatry 2024. doi:10.1136/jnnp-2024-333467.

LP048- PLASMA OLIGOMER BETA-AMYLOID IS ASSOCIATED WITH DISEASE SEVERITY AND CEREBRAL AMYLOID DEPOSITION IN ALZHEIMER'S DISEASE SPECTRUM. S.M. Wang[1], D.W. Kang[1], Y.H. Um[1], S. Kim[1], C.U. Lee[1], P. Scheltens[1], H.K.L. Lim[1] *(1. Department of Psychiatry, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea - Seoul (Korea, Republic of))*

Background: Multimer detection system-oligomeric amyloid-β (MDS-OAβ) is a measure of plasma OAβ, which is associated with Alzheimer's disease (AD) pathology. However, the relationship between MDS-OAβ and disease severity of AD is not clear. We aimed to investigate MDS-OAβ levels in different stages of AD and analyze the association between MDS-OAβ and cerebral Aβ deposition, cognitive function, and cortical thickness in subjects within the AD continuum. **Methods:** In this cross-sectional study, we analyzed a total 126 participants who underwent plasma MDS-OAβ, structural magnetic resonance image of brain, and neurocognitive measures using Korean version of the Consortium to Establish a Registry for Alzheimer's Disease, and cerebral Aβ deposition or amyloid positron emission tomography (A-PET) assessed by [18F] flutemetamol PET. Subjects were divided into 4 groups: N=39 for normal control (NC), N=31 for A-PET-negative mild cognitive impairment (MCI) patients, N=30 for A-PET-positive MCI patients, and N=22 for AD dementia patients. The severity of cerebral Aβ deposition was expressed as standard uptake value ratio (SUVR). **Results:** Compared to the NC (0.803 ± 0.27), MDS-OAβ level was higher in the A-PET-negative MCI group (0.946 ± 0.137) and highest in the A-PET-positive MCI group (1.07 ± 0.17). MDS-OAβ level in the AD dementia group was higher than in the NC, but it fell to that of the A-PET-negative MCI group level (0.958 ± 0.103). There were negative associations between MDS-OAβ and cognitive function and both global and regional cerebral Aβ deposition (SUVR). Cortical thickness of the left fusiform gyrus showed a negative association with MDS-OAβ when we excluded the AD dementia group. **Conclusion:** These findings suggest that MDS-OAβ is not only associated with neurocognitive staging, but also with cerebral Aβ burden in patients along the AD continuum.

LP049- A MULTIOMIC BLOOD BIOMARKER PANEL TO ENHANCE AD PATIENT SELECTION AND THERAPY OUTCOMES. B. Souchet[1], E. Fountis[2], R. Popp[3], A.M.C. Pimenta[4], B. Billoir[1], E.V. Petrotchenko[4], C.H. Borchers[4], D. Petinataud[2], J. Braudeau[1] *(1. AgenT - Paris (France), 2. Inovie - Marseille (France), 3. MRM proteomics - Montreal (Canada), 4. McGill University - Montreal (Canada))*

Background: Significant progress has been made in the search for treatments that can slow or prevent the onset of Alzheimer's (AD) dementia symptoms, leading to the approval of Aducanumab (US), Lecanemab (US, Japan, China, Israel, and Australia), and Donanemab (US). However, challenges remain due to the use of amyloid or tau biomarkers as binary inclusion criteria, which fails to capture the complexity of AD at the individual level and hinders the development of precision medicine [1]. This issue has sparked considerable debate, especially with Aducanumab, where conflicting clinical trial outcomes have raised doubts about its efficacy [2]. The European Medicines Agency's recent recommendation against approving Lecanumab further highlights the controversy, as concerns over balancing clinical benefits with the risk of serious adverse events persist [3]. To address these challenges, a blood biomarker platform capable of accurately identifying patients most likely to benefit from specific treatments—or those less likely to experience adverse drug events—could significantly enhance the success of AD clinical trials. Such an approach would also facilitate acceptance by regulatory bodies and prescribing physicians. To develop this platform, a panel of blood biomarkers was pre-identified using the patented AAV-AD rat model [4-6], with their relevance confirmed in humans [7]. The aim of this study was to extend, optimize and industrialize this biomarkers panel platform. **Methods:** Two multiplexed targeted mass spectrometry methods—one for proteins and one for metabolites—were developed by MRM proteomics researchers and validated at Inovie's ISO15189-certified facility. The analysis requires only 150 μL of EDTA plasma to quantify 100 blood biomarkers (50% proteins, 50% metabolites). Both methods underwent rigorous analytical validation in accordance with FDA guidelines [8], encompassing key parameters such as calibration curves, quality controls, selectivity, specificity, carryover, sensitivity, accuracy and precision. This comprehensive validation ensures the methods robustness and reliability for high-throughput clinical applications. **Results:** The mass spectrometry assays successfully met FDA criteria for analytical validation at Inovie's laboratory. Interestingly, these biomarkers are involved in the pathophysiology of several major age-related diseases, including cardiovascular diseases, neurodegenerative disorders and cancers. The panel enables comprehensive and simultaneous analysis of nine critical biological pathways (Bioenergetics, Innate Immune Response, Lipid Metabolism,

Oxidative Stress, Blood Coagulation, Purine Metabolism, Cell Protection, Hormonal System, and APP/Aβ Metabolism). This multi-pathway approach offers deep insights into the complex mechanisms driving age-related diseases, enhancing the precision of therapeutic interventions. **Conclusion:** This groundbreaking 100-biomarker multiomic panel represents the first of its kind to achieve full scientific and analytical validation, marking a significant milestone in the field of precision medicine. Its integration into routine clinical trials heralds a transformative shift toward personalized healthcare, offering the potential for more targeted and effective treatments for AD and other age-related conditions. The utility of this biomarker panel is being further explored in an ongoing international retrospective study across more than 35 hospitals, involving 3,500 participants with mild cognitive impairment or no cognitive issues. This study aims to identify individuals that will develop AD dementia symptoms, providing a critical tool for early intervention and improving therapeutic outcomes. **Keywords:** Blood biomarker, Multiomic panel, Age-related disease, Mass spectrometry. **Disclosures:** BS, BB and JB are AgenT employees, EF and DP are Inovie employees, RP, AP, EVP and CHB are MRM proteomics employees. **References:** 1. Souchet B, Michail A, Billoir B, Braudeau J. Biological Diagnosis of Alzheimer's Disease Based on Amyloid Status: An Illustration of Confirmation Bias in Medical Research? Int J Mol Sci. 2023;24(24). 2. Maulden A. Ignoring the Experts: Implications of the FDA's Aduhelm Approval. Am J Law Med. 2022;48(1):108-33. 3. https://www.ema.europa.eu/en/documents/smop-initial/questions-answers-refusal-marketing-authorisation-leqembi-lecanemab_en.pdf. 4. Audrain M, Souchet B, Alves S, Fol R, Viode A, Haddjeri A, et al. betaAPP Processing Drives Gradual Tau Pathology in an Age-Dependent Amyloid Rat Model of Alzheimer's Disease. Cereb Cortex. 2018;28(11):3976-93. 5. Souchet B, Audrain M, Alves S, Fol R, Tada S, Orefice NS, et al. Evaluation of Memantine in AAV-AD Rat: A Model of Late-Onset Alzheimer's Disease Predementia. J Prev Alzheimers Dis. 2022;9(2):338-47. 6. Souchet B, Audrain M, Gu Y, Lindberg MF, Orefice NS, Rey E, et al. Cerebral Phospho-Tau Acts Synergistically with Soluble Abeta42 Leading to Mild Cognitive Impairment in AAV-AD Rats. J Prev Alzheimers Dis. 2022;9(3):480-90. 7. Souchet B, Michail A, Heuillet M, Dupuy-Gayral A, Haudebourg E, Pech C, et al. Multiomics Blood-Based Biomarkers Predict Alzheimer's Predementia with High Specificity in a Multicentric Cohort Study. J Prev Alzheimers Dis. 2024;11(3):567-81. 8. https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf.

LP050- DEVELOPMENT OF BLOOD-BASED PTAU217 ASSAY USING A NOVEL ULTRASENSITIVE SINGLE-MOLECULE COUNTING TECHNOLOGY. K. Hamano[1], Y. Kawada[1], M. Imaizumi[1], G. Dave[2], K. Kobayashi[2], M. Soban[2], H. Kimura[2], K. Moriyama[1], K. Aoyagi[1], F. Zaugg[2], P. Wagner[2], J. Sandlund[2], R. Tobias[2], V. Brachet[2] *(1. Fujirebio, Inc., - Tokyo (Japan), 2. Fluxus, Inc. - Sunnyvale (United States))*

Background: Phosphorylated tau at threonine 217 (pTau217) correlates with hallmarks of Alzheimer's disease (AD) pathology, such as amyloid status. Blood-based detection is less invasive and more accessible compared to evaluations via imaging or in cerebrospinal fluid and may offer a scalable tool for clinical evaluation and trial management. Here, we present analytical performance of a novel ultrasensitive pTau217 immunoassay that utilizes flow-based single-molecule detection in an optofluidic chip (Fluxus, Inc., Sunnyvale, CA, USA). **Methods:** Using high-performing anti-pTau217 monoclonal antibodies developed by Fujirebio, Inc. (Tokyo, Japan), the pTau217 assay was designed with capture antibodies immobilized on magnetic beads and detection antibodies conjugated to a proprietary fluorescent reporter construct (reporter-Ab). Multiple incubation and wash steps were followed by dissociation of immune complexes and separation of reporter-Ab molecules from the beads. Released reporter-Ab molecules were then injected into an ultrasensitive detection device with optofluidic chip for single molecule counting. Limits of detection (LoD) and quantification (LoQ), dynamic range, linearity, and precision for the assay were evaluated. Testing in clinical samples from patients diagnosed with AD is ongoing. **Results:** The LoD and LoQ for the pTau217 assay were calculated to be 0.002 and 0.0067 pg/mL, respectively, with a working range of greater than four logs (0.0125–512 pg/mL). Intraassay and interassay precision were 4.3% CV (0.7%–10.3%) and 7.0% CV (5.6%–8.5%), respectively. **Conclusion:** We have developed an ultrasensitive assay for measurements of pTau217 at sub-pg/mL levels in blood using a novel single-molecule counting platform. This advancement can potentially provide a less invasive, more accessible, and scalable method for detection, enabling earlier intervention and more frequent monitoring in AD clinical trials.

LP051- ANALYTICAL PERFORMANCE OF THE LUMIPULSE G PTAU 217/B-AMYLOID 1-42 PLASMA RATIO. L. Buitrago[1], F.I. De Simone[1], N. Benina[1], R.R. Radwan[1], J. Junfola[1], A. Graney[1], N. Goepfert[1], E. Jones[1], M.C. Miller[2], A. Moghekar[3], W.T. Hu[4], D. Dickson[1] *(1. Fujirebio Diagnostics Inc. - Malvern, Pa (United States), 2. Statistical Consultant, Fujirebio Diagnostics Inc. - Quakertown, Pa (United States), 3. Department of Neurology, Johns Hopkins School of Medicine - Baltimore, Md (United States), 4. Department of Neurology, Rutgers-Robert Wood Johnson Medical School and Center for Healthy Aging, Rutgers Institute for Health, Health Care Policy, and Aging Research - New Brunswick, Nj (United States))*

Background: Blood-based biomarkers hold significant promise in aiding in the assessment of amyloid pathology by offering a more accessible option (compared to amyloid PET and CSF testing) for patients with cognitive impairment. To ensure clinical utility, a reliable biomarker must demonstrate minimal variability across different measurements to reduce the risk of patient misclassification. This study evaluated the LoB/LoD/LoQ, linearity, within-laboratory, lot-to-lot, and site-to-site reproducibility of the Lumipulse G pTau 217/β-Amyloid 1-42 Plasma Ratio. **Methods:** The Lumipulse G pTau 217/β-Amyloid 1-42 Plasma Ratio LoBDQ, linearity, and precision studies were conducted according to CLSI guidelines1,2,3. For the precision studies, a 5-sample panel set was prepared to achieve target concentrations of plasma pTau 217 and β-Amyloid 1-42 that cover the measuring ranges of the individual assays (pTau 217: 0.047 pg/mL – 10.000 pg/mL; β-Amyloid 1-42: 0.8 pg/mL – 1000 pg/mL). The within-laboratory precision was evaluated by testing each panel sample (n=80) in replicates of two, at two separate times of the day, for 20 days, using one instrument and one reagent lot. Lot-to-lot precision studies were performed by testing all panel samples at a single site (Malvern, Fujirebio Diagnostics, Inc. (FDI)), using one instrument and three paired reagent lots (n=90). A paired reagent lot consists of specific lots of Lumipulse G pTau 217 and β-Amyloid 1-42-N Plasma Immunoreaction Cartridges along with their corresponding calibrators. Each sample within the panel was tested in replicates of three at two separate times of the day for 5 days.

To evaluate site-to-site reproducibility, each panel sample was assayed in replicates of three, at two separate times of the day, for 5 days, at three different sites (FDI, Johns Hopkins University (JHU) and Rutgers-Robert Wood Johnson Medical School (Rutgers)), using one instrument and one reagent lot at each site (n=90 for each panel sample). **Results:** For the Lumipulse G pTau217, LoB, LoD, and LoQ were 0.025 pg/mL, 0.0407 pg/mL, and 0.0472 pg/mL; linearity was demonstrated from 0.037 to 11.326 pg/mL. For the Lumipulse G β-Amyloid 1-42 LoB, LoD, and LoQ were 0.128 pg/mL, 0.2074 pg/mL, and 0.4488 pg/mL; linearity was demonstrated from 0.8 to 1012 pg/mL. The Lumipulse G pTau 217/β-Amyloid 1-42 Plasma Ratio demonstrated strong precision. Within-run precision ranged from 2.1% to 9.8%, while between-run and between-day precisions were 0.0% to 3.9% and 0.0% to 2.8%, respectively. The overall total precision for these conditions ranged from 3.1% to 10.2%. In the lot-to-lot analysis, the total precision of the Lumipulse G pTau 217/β-Amyloid 1-42 Plasma Ratio for the five-panel sample in the study ranged from 7.3% to 16.3%. Excursions outside of ± 10% from the baseline did not impact the test results when evaluating the ratio's interpretation per its intended use. Between-lot precision was measured at ≤12.8%. Site-to-site analysis revealed a total within laboratory precision of ≤12.1% (% CVs ranging from 5.1% to 12.1%). Between-site precision values ranged from 0.0% to 5.6%. **Conclusion:** The Lumipulse G pTau 217/β-Amyloid 1-42 Plasma Ratio demonstrated high sensitivity, good linearity, and robust precision. **Keywords:** Lumipulse G1200 System, pTau217/Aβ1-42 Plasma Ratio, Blood-based Biomarkers, Analytical Performance. **Disclosures:** Luna Buitrago, Francesca I. De Simone, Natalya Benina, Rachel R. Radwan, Jessica Junfola, Andie Graney, Natalie Goepfert, Eric Jones, and Diana Dickson are employed by Fujirebio Diagnostics Inc.; M Craig Miller is a statistical consultant for Fujirebio Diagnostics Inc.; Abhay Moghekar receives research support from Fujirebio Diagnostics, Inc.; William T. Hu has received research support from Fujirebio Diagnostics Inc. and has also served as a consultant for the company. **References:** CLSI. Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline-Second Edition. CLSI Document EP17-A2. Wayne, PA: Clinical and Laboratory Standards Institute; 2012. CLSI. Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline – Second Edition. CLSI document EP06-Ad2. Wayne, PA: Clinical and Laboratory Standards Institute; 2020. CLSI. Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition. CLSI document EP05-A3. Wayne, PA: Clinical and Laboratory Standards Institute; 2014.

LP052- EXPLORING THE ASSOCIATION BETWEEN BLOOD-BASED BIOMARKERS AND COGNITIVE-RELATED OCULOMOTOR BEHAVIOURS IN ASYMPTOMATIC CARRIERS OF THE AUTOSOMAL DOMINANT MUTATION E280A-PSEN1.

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(1. Glasgow University - Glasgow (United Kingdom), 2. Harvard - Massachussets (United States), 3. Universidad de Antioquia - Medellin (Colombia), 4. ViewMind - Copenhagen (Denmark), 5. ViewMind - Bahia Blanca (Argentina))

Background: Oculomotor behaviours recorded during the Visual Short-Term Memory Binding (VSTMB) Task have been found to be affected in cognitively-unimpaired carriers of the mutation E280A-PSEN1 which leads to early familial Alzheimer's disease (FAD) (Fernandez et al., 2022). Performance on the VSTMB Task has been linked to brain pathology (specifically Amyloid-β and Tau) in individuals within these families (Norton et al., 2020). Research indicates that blood-based biomarkers (BBB) can differentiate between carriers and non-carriers of the mutation long before symptoms appear (Quiroz, et al. 2020). Most recently, Aguillon et al., 2023 found that baseline levels of plasma p-tau217 can forecast future memory performance and brain pathology in mutation carriers. We investigated whether a novel digital neurocognitive biomarker drawn from oculomotor behaviours recorded during the VSTMB Task correlates with BBB in cognitively impaired mutation carriers. **Methods:** We collected eye-tracking data during the VSTMB task from 19 cognitively unimpaired carriers recruited from the Colombia-Boston (COLBOS) Biomarker Study (Age: 37+7 years old, Education: 11+3 years, F/M ratio: 12/7). They all underwent standard clinical, functional, and neuropsychological assessments. The oculomotor activity was recorded synchronised with the VSTMB task. The task assesses the ability to temporarily hold bicoloured objects whose colours were remembered individually (Unbound Colours – UC) or integrated (Bound Colours – BC). We ran FDR-corrected correlations (Pike, 2011) to explore associations between oculomotor variables and BBB (β40, β42, β42/B40, GFAP, NFL, pTau181, pTau217, tTau, YKL40, CRP, sTREM2). **Results:** All significant correlations were found either with YKL40 or GFAP. Of these, only one correlation survived FDR correction: YKL40 was associated with the number of target visits during memory retrieval of the UC condition, $q<0.001$. We then investigated uncorrected correlations (at $p < 0.01$). YKL40 also showed associations with several oculomotor variables during the BC condition, including the number of target visits ($p=0.002$) and the number of fixations during the retrieval phase of the UC ($p=0.007$) and BC condition ($p=0.01$). GFAP was correlated with saccadic amplitude during the encoding phase of the BC condition ($p=0.005$) and the number of target visits during the retrieval of UC ($p=0.005$). Finally, B40 was correlated with saccadic amplitude during the encoding phase of the BC ($p=0.012$, at the limit of the allowed threshold). **Conclusion:** Associations with markers of astrocyte activation (GFAP) and neuroinflammation (GFAP and YKL40) emerged. Previous studies have confirmed the presence of VSTMB in preclinical AD before episodic memory impairments become apparent. A plausible hypothesis is that BBB and Neurocognitive markers share a temporal gradient (i.e., astrocyte and neuroinflammation > Aβ or Tau BBB, and Visual WM Memory > Episodic Memory Markers). High YKL40 (CSF or plasma) has been found in MCI patients who progressed to dementia, independently of their amyloid, tau, and neurodegeneration status (Muszyński et al., 2017; Pase et al., 2024), and astrocyte reactivity, as informed by elevated plasma GFAP, appears to mediate the association of Aβ with early tau phosphorylation in preclinical AD (Bellaver et al., 2023). The preliminary findings reported here warrant further investigation of the association between neurocognitive biomarkers and BBB in the preclinical stages of AD. **Keywords:** Blood-based biomarkers, Eye-Tracking, Familial Alzheimer's disease, AI, Biomarkers, Preclinical Detection. **Disclosures:** MAP is a consultant for ViewMind and serves as its Neuroscientific Officer. YTQ is a consultant for Biogen. DV is ViewMind's Chief Medical Officer and Chief Operating Officer. GF is ViewMind's Chief Scientific Officer. **References:** Aguillon, D., Langella, S., Chen, Y., Sanchez, J. S., Su, Y., Vila-Castelar, C.,…Quiroz, Y. T. (2023). Plasma p-tau217 predicts in vivo brain pathology and cognition in autosomal dominant Alzheimer's disease. Alzheimers Dement, 19(6), 2585-2594. https://doi.org/10.1002/alz.12906.

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LP053- IMPACT OF PREANALYTICAL FACTORS ON THE LUMIPULSE G PTAU 217/B-AMYLOID 1-42 PLASMA RATIO. L. Buitrago[1], F.I. De Simone[1], N. Benina[1], R.R. Radwan[1], A. Calabro[1], J. Junfola[1], N. Goepfert[1], A. Moghekar[2], D. Dickson[1] *(1. Fujirebio Diagnostics Inc. - Malvern, PA (United States), 2. Department of Neurology, Johns Hopkins School of Medicine - Baltimore, MD (United States))*

Background: Blood-based biomarkers for Alzheimer's disease (AD) have the potential to be implemented as non-invasive aid tools for the assessment of amyloid pathology. However, there is an urgent need to understand further how pre-analytics affect plasma biomarker values to define standard procedures to guarantee the quality of the results. This study evaluated the impact of pre-analytics on the Lumipulse G pTau 217/β-Amyloid 1-42 Plasma Ratio. **Methods:** Whole blood was collected from subjects within the intended use population at Johns Hopkins University (JHU) in K2EDTA tubes. Blood was centrifuged for 10 min at 1800 × g at room temperature (RT) 30 minutes after collection (reference condition). To assess the impact of time between collection and centrifugation, plasma samples were collected into three separate tubes and stored at RT for 30 min, 1 hour, and 2 hours before centrifugation. The impact of multiple F/T cycles (n=4) was also assessed and analyzed against the reference sample. To evaluate the impact of storage conditions, plasma samples were stored at four different temperatures (25°C, 5°C, -20°C and -60°C) over multiple time points. The percentage difference (% Diff) for each experimental condition was calculated for each analyte relative to the reference mean concentration. A mean concentration recovery change of ±10% was considered significant. Long-term stability (17 years) for the Lumipulse G pTau 217/β-Amyloid 1-42 Plasma Ratio was also assessed by analyzing paired CSF and plasma samples from 96 individuals with no change in their CSF Aβ42/Aβ40 ratio longitudinally. The log-transformed ratio of the plasma pTau217/Aβ42 ratio between visits was calculated, and linear regressions and a Rocke-Lorenzato1 variance profile model were used to evaluate whether time gaps affected the mean or variability of the plasma pTau217/Aβ42 ratio. **Results:** This study shows that plasma samples can be centrifuged up to 2 hours after collection without significant changes in the pTau217/Aβ42 ratio levels. The mean percentage difference was 11% one hour after collection and 10% two hours after collection. Plasma samples can undergo 4 freeze-thaw cycles (mean change of 1% at FT 4). Storage stability studies demonstrated that the plasma pTau217/Aβ42 ratio was unstable at 25°C ± 2°C 1 day after collection (mean change of 33%), while acceptable %Diff was observed in the 2 days storage at 5°C ± 3°C (mean change of 22%), one month at -20°C ± 10°C (mean change of -6%), and one month at ≤ -60°C (mean change of -11%) conditions. When evaluating the ratio's interpretation per its intended use, excursions outside of ± 10% from the baseline did not impact the test results. Long-term stability of pTau217/Aβ42 was confirmed, with no significant time-dependent drift or increased variability over 17 years. **Conclusion:** Our data indicates that the Lumipulse G pTau 217/β-Amyloid 1-42 Plasma Ratio is a robust biomarker ratio, able to withstand pre-analytical variability within the following recommendations: centrifugation delays of up to 2 hours, 4 freeze-thaw cycles, and various storage conditions, including long-term stability at -80°C, for up to 17 years. **Keywords:** Lumipulse G1200 System, pTau 217/β-Amyloid 1-42 Plasma Ratio, Blood-based Biomarkers, Pre-analytical variability. **Disclosures:** Luna Buitrago, Francesca I. De Simone, Natalya Benina, Rachel R. Radwan, Amanda Calabro, Jessica Junfola, Natalie Goepfert, and Diana Dickson are employed by Fujirebio Diagnostics Inc.; Abhay Moghekar receives research support from Fujirebio Diagnostics, Inc. **References:** Hawkins, D. M. (2013). A general variance model in methods comparison. Journal of Chemometrics, 27(11), 414-419.

LP054- BIOMARKER EVALUATION IN YOUNG ONSET DEMENTIA FROM DIVERSE POPULATIONS (BEYONDD). E. Barragan[1], H. Heuer[1], R. Nosheny[2,3], M. Camacho[2,4], K. Navarra[2,4], P. Aisen[5], A. Rahman-Filipiak[6], J.S. Roberts[6,7], A. Ajayi[8], D. Byrd[9], M. Rivera-Mindt[8,10], G. Rabinovici[1], A. Boxer[1] *(1. Memory and Aging Center, UCSF Weill Institute for Neurosciences, University of California, San Francisco - San Francisco (United States), 2. VA Advanced Imaging Research Center, San Francisco Veteran's Administration Medical Center - San Francisco (United States), 3. Department of Psychiatry, University of California San Francisco - San Francisco (United States), 4. Northern California Institute for Research and Education (NCIRE) - San Francisco (United States), 5. VA AdvancedAlzheimer's Therapeutic Research Institute, University of Southern CaliforniaImaging Research Center, San Francisco Veteran's Administration Medical Center - San Diego (United States), 6. Michigan Alzheimer's Disease Research Center, University of MichigandAlzheimer's Therapeutic Research Institute, University of Southern CaliforniaImaging Research Center, San Francisco Veteran's Administration Medical Center - Ann Arbor (United States), 7. Department of Health Behavior and Health Education, School of Public Health, University of Michigan - Ann Arbor (United States), 8. Department of Neurology, Icahn School of Medicine at Mount Sinai - New York (United States), 9. Department of Psychology, Queens College - Flushing (United States), 10. Departments of Psychology, Latin American Latino Studies, and African and African American Studies, Fordham University - New York (United States))*

Background: Early onset dementia (EOD) affects people at the peak of their personal and professional responsibilities and economic productivity. Alzheimer's disease (AD) and Frontotemporal Dementia (FTD) are the most common EOD etiologies in Non-Latinx White adults (NLW). Black and Latinx older adults bear a disproportionate burden of dementia

compared to NLW, likely due to vulnerabilities that confer increased risk, such as cardiovascular factors, socioeconomic stressors, and structural racism. Little is known, however, about the prevalence and causes of EOD in Black, Latinx, and other diverse populations (DP) because most EOD studies have primarily recruited NLW individuals. Many barriers impede research participation in DP, but community-engaged research (CER) strategies to collect diagnostic data, like blood-based biomarkers and digital assessments, may increase access and convenience of research participation in DP. **Methods:** The BEYONDD study (www.beyonddproject.org), a new NIH-funded study, is recruiting 200 DP individuals to evaluate the use of remote assessments and the impact of returning diagnostic information to participants as a more accessible research framework to understand the etiology of EOD in DP. Participants are recruited using CER strategies and screened via online platform for eligibility (age 40-64, with concerns about cognitive or behavioral function). Participants complete the following procedures remotely and receive gift cards after completion: online questionnaires, self-administered, tablet-based cognitive testing (Brain Health Assessment), and an in-home blood draw for standard labs and plasma biomarkers of AD and neurodegeneration (Aβ and P-tau217 ratios, NfL). Participants can learn their results remotely or in person. Participants are invited for more comprehensive onsite evaluation at one of 10 BEYONDD clinical centers, followed by appropriate referral to other NIH-funded research programs. **Results:** In just 8 weeks of deployed social media ads, over 1000 potential participants registered for BEYONDD via the study website. Of the registered participants, 518 (51%) have completed the online screening survey. Of the 173 (33%) eligible participants, 148 (86%) have enrolled in the online procedures. All participants that completed the online assessments agreed to an in-home blood draw and over 74 (69%) blood draws have already been completed across 14 states. Enrollment continues and analyses of digital and blood biomarker data are underway. **Conclusion:** The importance of surmounting historic barriers to DP participation in EOD research is clear. We plan to build on the experience of this project to improve DP enrollment into ongoing and future observational research and clinical trials. **Keywords:** early-onset dementia. **Disclosures:** n/a.

LP055- CLINICAL PERFORMANCE OF THE LUMIPULSE G PTAU 217/B-AMYLOID 1-42 PLASMA RATIO.

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Background: Plasma biomarker tests currently available for use in the Alzheimer's disease (AD) field have significant diagnostic capabilities that would allow them to act as a triage tool alongside clinical and neurological investigations to aid in the assessment of amyloid burden in the early stages of AD. It is suggested that a rule-out test should have a negative predictive value (NPV) of > 90% in the intended use population, whereas a rule-in test would need to have a positive predictive value (PPV) of > 90% in the intended use population [1]. Furthermore, the BBM Workgroups recommended that a blood-based biomarker test should result in an indeterminate value for no more than 20% of individuals in a typical clinical population [2]. This study evaluated the performance of the Lumipulse G pTau 217/β-Amyloid 1-42 Plasma Ratio and the Lumipulse G pTau 217 Plasma test in predicting the amyloid positivity as defined by amyloid PET/CSF results in a symptomatic population. **Methods:** This study included 500 human biobanked K2EDTA plasma samples from Real World Data, pharmaceutical, and observational studies. The study patient population had a median age of 73 years, presenting with symptoms of cognitive decline and with amyloid positivity confirmed by historic amyloid PET, FDA-cleared tracer, and/or FDA-cleared amyloid CSF ratio. The performance of the Lumipulse G pTau 217/β-Amyloid 1-42 Plasma Ratio test and the Lumipulse G pTau 217 Plasma test is described by PET and/or CSF predictive value (PV) and by the frequency of test results (FR) of the tested samples for positive, indeterminate and negative test results. The goal of this analysis was to obtain a minimum positive PV (PPV) ≥85% and a corresponding minimum negative PV (NPV) of 95% to the corresponding PET or CSF result. In this exercise, Positive and negative likelihood ratios (PLR and NLR, respectively) were also calculated. All plasma assays were run on the LUMIPULSE G1200 system (Fujirebio). **Results:** Of the 296 subjects with a positive PET/CSF result, 242 subjects had a positive Lumipulse G pTau 217/β-Amyloid 1-42 Plasma Ratio result, leading to a PPV of 93.1% and a FR of 52.0%. Of the 204 subjects with a negative PET/CSF result, 134 subjects had a negative Lumipulse G pTau 217/β-Amyloid 1-42 Plasma Ratio result, leading to an NPV of 95.7% and a FR of 28.0%. Of the 100 subjects with an indeterminate Lumipulse G pTau 217/β-Amyloid 1-42 Plasma Ratio result, 48 had a positive PET and/or CSF scan result, resulting in a PV for an indeterminate test result of 48.0% and an FR of 20.0%. On the other hand, the Lumipulse G pTau 217 Plasma test categorized 66% of patients as positive (46%) and negative (20%), while 34% of patients remained in the indeterminate group. **Conclusion:** The Lumipulse G pTau217/β-Amyloid 1-42 Plasma Ratio reduces the uncertainty of a patient to have amyloid pathology, allowing for better classification of true positive or true negative patients. **Keywords:** Lumipulse G1200 System, pTau217/β-Amyloid 1-42 Plasma Ratio, Blood-based Biomarkers, Amyloid Pathology Assessment. **Disclosures:** Francesca I. De Simone, Luna Buitrago, Natalya Benina, Jessica Junfola, Stephen Menkes, James Koch, and Rachel R. Radwan are employed by Fujirebio Diagnostics Inc.; Douglas Hawkin is a statistical consultant for Fujirebio Diagnostics Inc.; James Rock is a full-time employee of AriBio, Oskar Hansson has acquired research support (for the institution) from AVID Radiopharmaceuticals, Biogen, C2N Diagnostics, Eli Lilly, Eisai, Fujirebio, GE Healthcare, and Roche. In the past 2 years, he has received consultancy/speaker fees from Alzpath, BioArctic, Biogen, Bristol Meyer Squibb, Eisai, Eli Lilly, Fujirebio, Merck, Novartis, Novo Nordisk, Roche, Sanofi, and Siemens; Erik Stomrud has nothing to disclose; Richard C. Mohs is the Chief Science Officer for the Global Alzheimer's Platform (GAP) Foundation and Vice President for Clinical Development at Agenebio, Inc.; Elaine Peskind receives research support from Fujirebio Diagnostics, Inc.; Jefferson Kinney has nothing to disclose, Sterling

Johnson is a consultant for Alzpath and Enigma Biomedical. **References: 1.** Blennow K, Galasko D, Perneczky R, Quevenco FC, van der Flier WM, Akinwonmi A, Carboni M, Jethwa A, Suridjan I, Zetterberg H. The potential clinical value of plasma biomarkers in Alzheimer's disease. Alzheimers Dement. 2023 Dec;19(12):5805-5816. doi: 10.1002/alz.13455. Epub 2023 Sep 11. PMID: 37694991. 2. Schindler SE, Galasko D, Pereira AC, Rabinovici GD, Salloway S, Suárez-Calvet M, Khachaturian AS, Mielke MM, Udeh-Momoh C, Weiss J, Batrla R, Bozeat S, Dwyer JR, Holzapfel D, Jones DR, Murray JF, Partrick KA, Scholler E, Vradenburg G, Young D, Algeciras-Schimnich A, Aubrecht J, Braunstein JB, Hendrix J, Hu YH, Mattke S, Monane M, Reilly D, Somers E, Teunissen CE, Shobin E, Vanderstichele H, Weiner MW, Wilson D, Hansson O. Acceptable performance of blood biomarker tests of amyloid pathology - recommendations from the Global CEO Initiative on Alzheimer's Disease. Nat Rev Neurol. 2024 Jul;20(7):426-439. doi: 10.1038/s41582-024-00977-5. Epub 2024 Jun 12. PMID: 38866966.

LP057- INVESTIGATING PERSONALIZED GENOMIC PROFILING IN ALZHEIMER'S DISEASE USING SYNCHRONIZED CELLS FROM AUTOPSY-VALIDATED SKIN AND BLOOD SAMPLES. F. Chirila[1], D.L. Alkon[2] *(1. Spot Dx - Morgantown (United States), 2. Synaps Dx - Rockville (United States))*

A gene expression profile has not been identified for late-onset Alzheimer's Disease (LOAD) in more than 95% of cases. However, autosomal dominant genes are known for early onset (EOAD). Moreover, the genetic convergences between familial EOAD and sporadic LOAD have not previously been identified despite the common neuropathology. Our research, based on synchronized skin fibroblast samples from individuals with LOAD, confirmed by autopsy, has revealed 36 statistically significant (P<0.05) LOAD-dysregulated genes. Significantly, 26 of these genes show an essential gap with non-Alzheimer's disease (non-ADD) dementia patients. Notably, five LOAD-dysregulated genes in the skin - FAM149B, NHLH1, SHISA5, URB2, and WASF2 - were also dysregulated in synchronized blood B-lymphocytes. The fact that an additional 18 LOAD-dysregulated gene families in the skin were validated in the blood confirms the reliability of our findings. 23 of the 36 LOAD-dysregulated genes and gene families in the skin were confirmed in the blood, providing a solid foundation for our research. An intriguing and novel aspect is the genetic convergence between late-onset and early-onset Alzheimer's disease, demonstrated by dysregulated gene families ADAM, IL, and RAB. Here, we compared the gene expression of skin and blood of individual patients with late-onset Alzheimer's disease (LOAD) to non-AD dementia groups using Z-scores. Our findings indicate that most genes dysregulated in LOAD(>52%) are specific to each patient, highlighting the need for personalized diagnostics and therapeutics. Additionally, we observed changes in the genetic signature of primary skin fibroblasts after the tenth cell passage. The gene expression profile aligns remarkably well with prior autopsy-validated biomarkers: Morphometric Imaging, PKC epsilon/AD index, Cell Size, Growth Rate, and Protein Amount, providing a solid genetic foundation. Our findings indicate a promising potential for personalized genomic profiling in LOAD diagnosis and treatment, offering hope for more effective and targeted approaches. **Competing interests:** FVC owns shares of Synaps Dx and owns Spot DX.

LP059- NON-INVASIVE DETECTION OF DEMENTIA USING PLASMA CELL-FREE DNA SEQUENCING AND ARTIFICIAL INTELLIGENCE. J. Wan[1], J. Ganbat[1], T. Liu[1], H. Thompson[1], H. Babikir[1], A. Jhutty[1], A. Surani[1], H. Zetterberg[1], S. Tonniolo[1], H. Masud[1], I. Koychev[1], R. Solanki[1] *(1. cfdx - London (United Kingdom))*

Background: Dementia is the seventh leading cause of death globally and a significant cause of morbidity [1]. Effective drug development for its leading cause, Alzheimer's disease (AD), requires early detection and molecular characterisation of both early and advanced stages of pathology. However, analysis of the brain at a molecular level is limited by the difficulty of sampling healthy and diseased brain tissue directly [2]. Recently, highly sensitive protein-based assays for AD in plasma have emerged, enabling non-invasive detection [3,4]. However, such approaches do not provide molecular characterisation on a genomic, epigenomic or transcriptomic level. Advances in oncology have demonstrated the potential utility of liquid biopsies sequencing circulating tumour DNA for detecting and studying early-stage disease [5,6]. In this study, we hypothesised that whole-genome sequencing of plasma cell-free DNA (cfDNA) may allow early disease detection as well as uncover disease stage-specific pathophysiological mechanisms that can provide novel drug development avenues. **Methods:** Plasma was collected from 145 individuals, including individuals with a historical diagnosis of dementia or cognitively healthy controls collected either in the United Kingdom or Sweden. Briefly, plasma was extracted, and then cfDNA underwent methylation conversion and library preparation. Whole-genome sequencing was performed using NovaSeq X to a mean depth of 15x. Data were demultiplexed, aligned using Bismark and quality filtered. For data analysis, the samples originating from different studies were treated as separate batches. **Results:** In this exploratory analysis, we sought to both characterise and suppress noise and characterise and boost dementia-specific signals in cfDNA. First, we identified stereotyped noise signatures in plasma sequencing data; a bespoke filtering approach was developed to suppress noise by over an order of magnitude relative to raw sequencing data. By applying machine learning-based classifiers to filtered data, we developed several methods to characterise generated data. Across our pilot methods (version 0.1), we show a median AUC for dementia detection of 0.70 (range 0.56-0.80). We also demonstrate the generalisation of these methods into a second cohort with an AUC of 0.82. These approaches leverage multiple parameters of cfDNA biology, and development is ongoing for version 0.2. Next, we studied tissue and plasma sequencing data to identify specific differentially methylated regions in dementia. We developed a method that may identify putative genes preferentially expressed in the brain using tissue sequencing ($p = 0.054$). Using plasma sequencing, we identified 3,746 regions across the genome that were significantly differentially methylated between cases and controls. **Conclusion:** In this proof-of-concept study, we provide evidence to suggest that plasma cfDNA sequencing may allow the detection of dementia and AD and may identify genomic regions that may be relevant for therapeutic development in dementia. Ongoing data analysis, including the use of large AI models, combined with an exploration of cfDNA biology using experimental methods, are expected to improve performance in a subsequent version of these methods by boosting the signal and reducing noise further. **Keywords:** cell-free DNA; Alzheimer's disease; liquid biopsy. **Data Deposition:** N/A. **Disclosures:** J.C.M. Wan is an inventor of patents for methods

for cancer detection. He is a co-founder and stockholder of cfdx, an AI neuroscience company. He has served as a consultant for Delfi Diagnostics, Rostrum and Cleary Gottlieb. R. Solanki. is a co-founder and stockholder of cfdx. **References:** 1. World Health Organization. Dementia. (2023). 2. Solanki, R. Human pluripotent stem cell-derived models of cortex for the study of frontotemporal dementia. (2019). 3. Thijssen, E. H. et al. Highly specific and ultrasensitive plasma test detects Abeta(1-42) and Abeta(1-40) in Alzheimer's disease. Sci Rep 11, 9736 (2021). 4. PreclivityAD. C2N Data Release for New Blood Test Combining p-tau217 Ratio with Amyloid beta 42/40. (2022). 5. Wan, J. C. M. et al. Liquid biopsies come of age: towards implementation of circulating tumour DNA. Nat Rev Cancer 17, 223–238 (2017). 6. Im, Y. R., Tsui, D. W. Y., Diaz, L. A. & Wan, J. C. M. Next-Generation Liquid Biopsies: Embracing Data Science in Oncology. Trends Cancer 7, 283–292 (2021).

LP060- PLASMA P-TAU217, PET AND COGNITION IN AN AFRICAN AMERICAN SAMPLE: RESULTS FROM THE AA-FAIM STUDY. R. Langhough[1], L. Du[2], R. Wilson[1], R. Reyes[1], G. Ennis[1], F. Carter[1], N. Norris[1], D. Gooding[3], L. Mclester-Davis[1], C. Van Hulle[1], N. Chin[1], M. Zuelsdorff[4], H. Zetterberg[1], S. Johnson[1], C. Gleason[1] *(1. University of Wisconsin School of Medicine and Public Health - Madison (United States), 2. Rush University - Chicago (United States), 3. Dept of Psychology, University of Wisconsin, Madison - Madison (United States), 4. University of Wisconsin School of Nursing - Madison (United States))*

Background: While PET is a gold standard for establishing presence of amyloid or tau proteinopathies, plasma p-tau217 is emerging as a viable AD pathology indicator. For African Americans and other under-included groups, it is crucial to clarify whether p-tau217, PET and cognition associations studied in mostly non-Hispanic, white participant samples, are generalizable to racialized groups. This study investigated these questions: in African Americans with amyloid PET, does plasma p-tau217 vary across amyloid positive and negative (A+/-) PET statuses?; what are ROC-related characteristics?; what is the distribution of estimated ages at which p-tau217 values indicate amyloid positivity onset?; and, in a larger set, does baseline p-tau217 risk group predict longitudinal cognition? **Methods:** The African Americans Fighting Alzheimer's in Midlife (AA-FAIM) study is a meta-cohort that combines data from predominantly baseline unimpaired participants in the Wisconsin Registry for Alzheimer's Prevention (WRAP) and Wisconsin ADRC studies. In this study, N=237 AA-FAIM participants had at least one plasma p-tau217 (ALZpath SIMOA assay) value and a subset (n=70) had >=1 amyloid PET (PiB) scan with visually-determined A+/- status. ROC analyses identified and characterized potential plasma p-tau217 cut-points, comparing AA-FAIM-based cut-points to recently published ROC results of n=323 WRAP participants (21.1% A+; ~95% non-Hispanic White; Ashton et al., 2024). We used sampled iterative local approximation (SILA) modeling to estimate age at amyloid-related p-tau217 elevation in the PET A+ subset and linear mixed effects models to examine longitudinal cognition (primary outcome: Preclinical Alzheimer's Cognitive Composite (PACC), comprised of AVLT learning, Delayed Story Recall and phonemic fluency; secondary: Digit Symbol Substitution (DSS), Semantic Fluency, and Trails B). Models retained significant person-level random intercepts and slopes; fixed effects included relevant covariates and investigated interactions between age and p-tau217 risk group (low, intermediate, high). **Results:** 16 of 70 (22.9%) were PET A+ (mean(sd) age at scan=67.1(7.9)). Median[Q1, Q3] plasma p-tau217 pg/mL was 0.256[0.204, 0.342] for PET A-, compared with 0.569[0.457, 0.919] for PET A+ (2-sample Wilcoxon p-value<0.0001). ROC characteristics based on n=70 in AA-FAIM [with the corresponding published values in brackets] included: AUC, .90[.93]; binary cut (Youden's J) indicating A+ if >0.374[>.42] pg/mL; 3-level A+ risk grouping of low (<0.355 [<.40]); intermediate, or high (>0.659 [>.63]). For binary thresholds and observed PET A+ prevalence, positive and negative predictive values were .70[.71] and .96[.92], respectively, using AA-FAIM[or published] cut-offs. Minimum, median, and maximum estimated ages of amyloid-related plasma elevations were 46, 60 and 80 in the sixteen PET A+ African Americans. Simple slopes comparisons following significant interactions indicated that average age-related cognitive decline in one or both elevated risk groups was 2-5 times faster relative to low p-tau217 risk group for PACC (n=220) and DSS (n=171). **Conclusion:** These preliminary results suggest the plasma ALZpath pTau217 assay is sensitive to amyloid PET positivity in African Americans and elevated levels are associated with greater cognitive decline. Data collection toward a larger dataset of paired amyloid plasma and PET data continues in AA-FAIM to ensure generalizable screening criteria and to power studies to detect clinically meaningful responses to treatment for African Americans.

LP061- NULISA ASSAYS FOR INFLAMMATORY MARKERS IN FECAL SAMPLES FROM PATIENTS WITH OR AT RISK FOR AD. S. Harding[1], B. Bendlin[1], M. Heston[1], J.W. Kang[1], A. Braceros[1], J.L. Wheeler[1], S. Shankar [1], A. Mickol[1], H. Chow[1], E. Zhang[1], E. Clements[1], F. Taylor[1], A. Mushtaque[1], D. Peter[1], S. Johnson[1], S. Asthana[1], H. Zetterberg[2], B. Kaj[2], T.K. Ulland[1], F. Rey[1] *(1. University of Wisconsin - Madison (United States), 2. University of Gothenburg - Gothenburg (Sweden))*

Background: Alzheimer's disease (AD) dementia and preclinical AD are associated with decreased microbial diversity and altered composition of the gut microbiome. Moreover, older age and dementia are associated with intestinal inflammation. Microbial changes may play a role in the immune activation and systemic inflammation seen in AD. However, the extent to which intestinal inflammation is associated with AD pathology is still largely unknown. To address gaps in understanding the role of the brain-gut axis in AD, an assay for inflammatory markers in gut-derived samples is needed. Here we evaluated a multiplex immunoassay as a potential tool for discovering AD-associated gut inflammation profiles using stool samples. **Method:** Using NULISA technology and the 250-plex NULISAseq Inflammation Panel, we measured levels of inflammatory biomarkers in fecal samples collected from 20 AD biomarker phenotyped participants (10 healthy controls who were amyloid negative, and 10 with AD and amyloid positivity) from the Microbiome Alzheimer's Risk Study (MARS). Participants were recruited from the Wisconsin Alzheimer's Disease Research Center and Wisconsin Registry for Alzheimer's Prevention, comprising longitudinally followed and well-phenotyped participants with and without AD. Samples were prepared with diluent buffer (including protease/DNAse inhibitors). This was followed by gentle shaking for 1 hour and centrifugation to remove debris. Fluid from extracted samples was stored at -80C until testing. **Results:** 45 (18%) of 250 targets in the inflammation panel were detectable in stool (above the limit of detection in >50% of samples). Markers detected included CRP as well as several cytokines. 206/250 showed >0% detectability (above the limit of detection in at least one sample). Preliminary results show

MMP9 and IL16 were upregulated in AD vs controls, whereas IL13 and FGF2 were downregulated (unadjusted, p-value cut-off). Factors influencing detectability included sample concentration; matrix effects were seen at higher concentrations. Lowering sample input reduced matrix effects but also reduced detectability. Other potential confounding variables including consumption of nutritional supplements (biotin) and stool consistency (Bristol scale) were considered, but were not found to explain matrix effects. **Conclusion:** Inflammatory targets were detected in stool using the NULISA platform. Further, stool levels of several targets varied between AD and cognitively unimpaired participants, which may reflect changes to the gut immune environment in AD. While initial analysis shows promising preliminary results, preanalytic protocol optimization is needed to improve NULISA outputs with stool samples. Future directions will include using an extraction protocol tailored for tissue homogenization rather than the biofluid protocol used here and optimization of methods for data normalization. **Keywords:** microbiome, inflammation, inflammatory, NULISA. **Disclosures:** The authors declared no competing interests. **References:** 1. Heston M, et al. Sci Rep. 2023 Nov 14;13(1):18924.doi: 10.1038/s41598-023-45929-z. 2. Vogt NM, et al. Sci Rep. 2017 Oct 19;7(1):13537. doi: 10.1038/s41598-017-13601-y. 3. Feng W, et al. Nat Commun. 2023 Nov 9;14(1):7238. doi: 10.1038/s41467-023-42834-x.

LP062- ADVANCING ALZHEIMER'S DISEASE STRATIFICATION: INTEGRATING APOE GENOTYPING WITH AI-DRIVEN BIOMARKER ANALYSIS. M. Casanova[1], S. Kuhl[1], N. Scalzitti[2], L. Pham-Van[1], G. Sanchez[3], S. Boutillier[1], J.C. Bier[4], T. Demiralp[5], F. Blanc[6], F. Sellal[7], B. Dubois[8], H. Firat[1] *(1. AMONETA - Huningue (France), 2. FIRALIS - Huningue (France), 3. FMP - Huningue (France), 4. ERASME Hospital - Brussels (Belgium), 5. Istanbul Faculty of Medicine - Istanbul (Turkey), 6. CHU Strasbourg - Strasbourg, France (France), 7. Hopitaux civils de Colmar - Colmar (France), 8. AP-HP) - Paris (France))*

Introduction: Alzheimer's disease (AD) is a multifaceted neurodegenerative disorder influenced by both genetic and environmental factors. While the APOE gene variants E2, E3, E4 are critical in understanding genetic risk, they alone do not provide a complete picture of disease progression. In this study, we present a comprehensive approach that combines genetic signatures, with dynamic biomarker signatures (lncRNA, miRNA) to refine patient stratification and better predict disease trajectory and treatment response. **Methods:** Our approach begins with a focus on APOE genotyping to establish a baseline genetic risk profile. We then develop a targeting sequencing tool (Neurodegene panel) incorporating multiple AD-related genetic variants. Our preliminary results using modeling (LASSO, XGB, PLS, ND, RF) offer a promising avenue for stratifying patients based on their genetic profile. To enhance this genetic framework, we integrate dynamic signatures derived from various biomarkers, including long non-coding RNAs (lncRNA), and microRNAs (miRNA), measured longitudinally in patient samples for AD but also 5 NAD (Corticobasal Degeneration, Dementia with Lewy Bodies, Progressive Supranuclear Palsy, Parkinson's Disease Dementia, Frontotemporal Dementia from the ADDIA multicenter clinical study (NCT03030586). These biomarkers provide real-time insights into the physiological state of the patient, reflecting ongoing disease processes and potential responses to treatment. Advanced AI algorithms are used to combine these dynamic and static data, enabling the identification of complex interactions that might otherwise go unnoticed. **Expected Results:** Our preliminary observations suggest that combining genetic and biomarker data can provide a more accurate stratification and comprehensive characterization of patient subgroups with dementia. The dynamic biomarker signatures have the potential to complement the static genetic data, offering real-time assessments that may improve the prediction of disease progression and treatment outcomes. This combined approach is expected to enhance patient stratification, allowing for more tailored and effective therapeutic interventions. **Discussion:** The integration of static genetic risk factors with dynamic biomarker profiles represents a paradigm shift in Alzheimer's disease management. By moving beyond a purely genetic framework to include dynamic indicators of disease state, we can better understand the complex interplay between genes and the environment. This dual approach not only improves patient characterization but also provides a foundation for precision medicine in dementia disorders. **Conclusion:** Our study introduces a novel strategy; by combining static and dynamic data, we propose a more comprehensive and accurate model for early diagnosis, disease progression and better stratification of patients. This approach improves the precision of patient stratification, identifying those who are most likely to benefit from new disease-modifying therapies. **Keywords:** APOE genotyping, lncRNA, miRNA, Modeling signature. **Acknowledgment:** We would like to thank the ADDIA consortium, Renaud David (Centre Hospitalier Universitaire de Nice), Jean-François Démonet (Centre Hospitalier Universitaire Vaudois), Erdinc Dursun (Istanbul University), Giovanni B. Frisoni (Hôpitaux Universitaires de Genève), Audrey Gabelle (Centre Hospitalier Universitaire de Montpellier), Hakan I. Gurvit (Istanbul Faculty of Medicine), Eloi Magnin (Centre Hospitalier Universitaire de Besançon), Moira Marizzoni (IRCCS Centro San Giovanni di Dio Fatenenefratelli), Florence Pasquier (Centre Hospitalier Universitaire de Lille), Adrian Ivanoiu (Centre Hospitalier Universitaire de Bruxelles), for their valuable contributions to this study. **Disclosure Statement:** AMONETA confirms that the content of this poster includes proprietary and confidential information and should not be shared without prior authorization from the company.

LP063- ELEVATED P-TAU217 IS MORE STRONGLY ASSOCIATED WITH CHANGES IN TAU-PET AND COGNITION IN YOUNGER ADULTS: FINDINGS FROM THE A4 AND LEARN STUDIES. G. Coughlan[1], H. Klinger[1], M. Seto[1], C. Birkenbihl[1], M. Farrell[1], R. Rissman[2], M. Properzi[1], D. Townsend[1], H.S. Yang[1], K. Johnson[1], O. Langford[2], M. Donohue[2], R. Sperling[1], R. Buckley[1], S.T. A4/learn[1] *(1. Mass General Hospital/Harvard Medical School - Boston (United States), 2. Alzheimer's Therapeutic Research Institute, University of Southern California - San Diego (United States))*

Background: The pathophysiological cascade of Alzheimer's Disease (AD) is characterized by amyloid-β(Aβ) related secretion of soluble phosphorylated tau (p-tau), followed by the aggregation of tau tangles and cognitive decline. Previous literature suggests that tau aggregation is more aggressive at younger ages, but the extent to which this is true within the context of plasma markers remains unclear. We examined whether age interacts with soluble p-tau217 (measured with electrochemiluminescence immunoassay) to predict rates of regional tau-PET accumulation and Preclinical Alzheimer Cognitive Composite (PACC) decline in individuals with elevated Aβ. **Methods:** Participants were 376 clinically normal individuals (mean age 72.1; 213 women [57%]; 209 APOEε4-

carriers [56%]; mean years of education 16.3, 339 Aβ positive [90%]) with baseline p-tau217 and longitudinal tau-PET from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4; N=339) trial and the companion Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN; N=37) study. Seven apriori cortical and neocortical brain regions were selected as longitudinal tau-PET outcomes (rostral middle frontal gyri, fusiform gyrus, inferior temporal and parietal gyri, the superior parietal lobule, precuneus and lateral occipital cortex). Corresponding PACC scores represented the longitudinal cognition outcome. The average tau-PET and PACC follow-up time was 3.4 years (SD=1.6 years, range=1.3-7.1 years) and 3.6 years (SD=1.6 years, range=1.4-7.2 years) respectively. Random-effects regression estimated the interaction between baseline age and baseline p-tau217 on each longitudinal tau-region and PACC score, adjusting for sex and years of education (including participant-specific intercepts and slopes). βs are standardized and P values are FDR corrected (7 comparisons). **Results:** Age moderated the association between baseline p-tau217 and all apriori tau-PET regions over time (β's=-0.03 - -0.09, P's=0.029 - 0.004), such that the effects of elevated p-tau217 on faster rates of tau accumulation were stronger at younger ages. The influence of elevated p-tau217 on worsening PACC performance was also exacerbated at a younger age (β=0.05, P=0.032). In Post-hoc analysis covarying baseline Aβ-burden, the interactive effects of age and p-tau217 concentrations remained significant. **Conclusion:** In the A4 and LEARN studies, there is evidence for more aggressive tau-related processes in younger individuals. If replicated, these findings highlight the critical need for early identification and enrollment in AD clinical trials, potentially using plasma biomarkers in primary care and secondary care. **Keywords:** Younger age, ptau217, tau-PET, cognition, longitudinal. **Disclosures:** Sperling has received grants or contracts from National Institute on Aging, Eli Lilly (public-private partnership trial funding), Eisai (public-private partnership trial funding), Alzheimer's Association and GHR Foundation. She has received consulting fees from Abbvie, AC Immune, Acumen, Alector, Biohaven, Bristol-Myers Squibb, Ionis, Janssen, Oligomerix, Prothena, Roche, Shionogi, and Vaxxinity. Rissman has research support from the National Institute on Aging, the Alzheimer's Association and is a consultant for Amydis Inc, Bioivt, Lexeo, Keystone Bio, Allyx, DiamiR, Ionis and PrecisionMed.

LP064- PLASMA PTAU217 AS A SINGLE RULE-IN BIOMARKER TO DIAGNOSE UNDERLYING AD IN EARLY DEMENTIA PATIENTS. T. Wegehaupt[1], P. Sommer[1], O. Goldhardt[1], J. Priller[1], H. Dennis[1], Y. Igor[1], T. Grimmer[1] *(1. Technical University of Munich, School of Medicine and Health, TUM University Hospital - Munich (Germany))*

Background: Plasma pTau217 appears to be a specific marker for Alzheimer's disease (A9. High NPV of plasma pTau217 has been proposed as a rule-out test for AD with high certainty. However, a negative test result does not inform on whether a patient is suffering from a non-amyloid neurodegenerative disease instead limiting its added value in diagnostic work-up. The aim of this study was to evaluate the performance of plasma pTau217 as a specific rule-in test for the individual diagnosis of AD. **Methods:** PTau217 in plasma has been measured on a fully automated chemiluminescent enzyme immunoassay (CLEIA) platform (Lumipulse G pTau217 Plasma) in subjectively and objectively healthy controls with negative CSF AD biomarkers (HC; n=24, age: 64.8±9.65, MMSE: 29.2±0.92; CDR SOB: 0.0±0.00), patients with early dementia due to AD confirmed by typical CSF AD biomarkers (AD; n=47, age: 64.4±8.38; MMSE: 21.5±5.97; CDR SOB: 4.4±1.87), and patients with non-fluent primary progressive aphasia with typical FDG-metabolic pattern and negative CSF AD biomarkers (nfvPPA; n=16, age: 64.8±8.80, MMSE: 22.7±5.86; CDR SOB: 3.7±1.71) as a non-amyloid neurodegenerative disease group, at the Centre for Cognitive Disorders, Technical University of Munich. **Results:** AUC of AD vs. (HC+nfvPPA) was 0.956 [0.905-1.007]. At a cut-off of ≥0.666 pg/mL Positive Predictive Value (PPV) was highest with 0.97 (sensitivity: 0.66, specificity 0.975). **Conclusion:** High specificity of plasma pTau217 in differing AD from other neurodegenerative diseases and healthy controls was confirmed. Plasma pTau217 positively identified patients with AD with very high likelihood meeting needs for individual diagnosis in a memory clinic with high true prevalence of AD implying its potential use as a single biomarker to confirm underlying AD pathology in early dementia patients. This approach could help to overcome the bottleneck of AD biomarker work-up constraints. **Keywords:** Alzheimer's disease, AD, plasma, pTau217, CLEIA. **Disclosures:** No disclosures with regards to the submitted work. Outside the current work, TG received consulting fees from AbbVie, Alector, Anavex, Biogen, BMS; Cogthera, Eisai, Eli Lilly Functional Neuromodulation, Grifols, Iqvia, Janssen, Novo Nordisk, NoselabNuiCare, Orphanzyme, Roche Diagnostics, Roche Pharma, UCB, and Vivoryon; lecture fees from Anavex, Biogen, Eisai, Eli Lilly, Grifols, Medical Tribune, Novo Nordisk, Roche Pharma, Schwabe, and Synlab; and has received grants to his institution from Biogen, Eisai, and Roche Diagnostics.

LP065- REVAMPING ALZHEIMER'S DISEASE DIAGNOSTICS: EVALUATING FUTURE IVD PLASMA P-TAU 181 AND APOE4 IMMUNOASSAYS FOR AMYLOID DETECTION IN A MULTI-CENTER STUDY REFLECTIVE OF ROUTINE CLINICAL PRACTICE. I. Kirste[1], S. Hortsch[2], S. Baez-Torres[3], M. Boada[4], M. Crane[5], F.K. Steen[6], K. Hanson[7], J. Liss[8], J. Norton[9], M. Suárez-Calvet[10], C. Ritchie[11], S. Rutrick[12], D. Watson[13], K. Yokum[14], C. Quijano-Rubio[15] *(1. Roche Molecular Solutions - Indianapolis (United States), 2. Roche Diagnostics GmbH - Penzberg (Germany), 3. K2 Medical Research - Maitland (United States), 4. ACE Alzheimer Center - Barcelona (Spain), 5. Genesis Neuroscience Clinic/Tennessee Memory Disorders Foundation - Knoxville (United States), 6. Danish Dementia Research Centre, Department of Clinical Medicine - Copenhagen (Denmark), 7. Eastside Research Associates - Redmond (United States), 8. Columbus Memory Center - Columbus (United States), 9. Charter Research Lady Lake - The Villages (United States), 10. Barcelona Beta Brain Research Center - Barcelona (Spain), 11. Brain Health Scotland - Edinburgh (United Kingdom), 12. Adams Clinical - Watertown (United States), 13. Alzheimer's Research and Treatment Center - Wellington (United States), 14. K2 Medical Research, LLC - Tampa (United States), 15. Roche Diagnostics International Ltd - Rotkreuz (Switzerland))*

Background: Early detection of amyloid pathology is a critical step in the Alzheimer's Disease (AD) patient journey. Blood-based biomarkers have emerged as powerful tools in accurately identifying individuals' amyloid pathology. This study investigates the clinical performance of plasma tau phosphorylated at threonine 181 (pTau181) in combination with plasma apolipoprotein E4 (ApoE4) as a potential In Vitro Diagnostics to detect amyloid pathology, and addresses gaps in evidence by providing blood-based biomarkers data gathered from a broad population as seen in routine clinical practice. **Methods:** In this prospective multicenter study, we enrolled

492 patients aged 55-80 with subjective cognitive decline (SCD), mild cognitive impairment (MCI), or mild dementia being evaluated for Alzheimer's disease or other causes of cognitive decline. Plasma samples from eligible patients were analyzed using Elecsys® pTau181 and ApoE4 plasma assays (Roche Diagnostics International Ltd, Rotkreuz, Switzerland). The study population was recruited at 12 clinical sites in the US and Europe. The discriminative ability of pTau181 and ApoE4 with respect to amyloid PET visual read status and to CSF ratio of the Elecsys Phospho-Tau (181P) and Elecsys Amyloid (1-42) II CSF (Roche Diagnostics International Ltd) was evaluated. Additionally, we examined the relationship between ApoE4 plasma levels and APOE4 genetic status. The clinical performance of the combination of pTau181 and ApoE4, as well as pTau181 alone, was assessed with a focus on high negative predictive value. Exploratory analyses examined subgroup effects based on cognitive status, comorbidities, and demographics. **Results:** The study population was heterogeneous regarding sex, race, and comorbidities, which allowed for an assessment of pTau181 and ApoE4 performance in a real-world setting. The area under the curve (AUC) of a combination of pTau181 and ApoE4 was 0.894, while pTau181 alone achieved an AUC of 0.884 (AUCs with respect to amyloid PET positive versus negative). Based on an amyloid positivity prevalence of 23.4% (based on amyloid PET), the negative predictive value (NPV) was 96.2%, paired with a positive predictive value of 47.9% (sensitivity: 91.0%, specificity: 69.8%). The performance was only minimally impacted by age, sex, body mass index or impaired kidney function. The rule-out performance of pTau181 alone was similar (NPV: 97.6%, PPV: 46.1%). However, the combination with ApoE4, a major genetic risk factor for Alzheimer's disease and for adverse events of amyloid modifying therapies, made the clinical performance more robust towards analytical variability. The study also showed 100% concordance of plasma ApoE4 results with genetic APOE4 carrier status. **Conclusion:** The observed clinical performance in this study highlights the potential of plasma pTau181 with the combination of ApoE4 as robust and accurate tools for ruling out individuals with a low likelihood of amyloid pathology in the early stages of the AD continuum. Paired with high analytical performance of the plasma assays, further IVD development is being pursued in an ongoing independent, prospective validation cohort.

LP066- NOVEL B-SYNUCLEIN SPECIFIC ASSAYS.

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Background: Beta-synuclein (β-synuclein) is an emerging biomarker for synaptic degeneration in cerebrospinal fluid (CSF), although most results rely on direct mass-spectrometry methods. immunoassays might accelerate insights on how this biomarker relates to the disease pathology. Low-invasive matrices such as plasma/serum, which could offer novel opportunities for disease monitoring and screening. Yet, cross-reactivity of existing antibodies with other synucleins present in blood is a challenge in this context (Halbgebauer et al., 2022). Our goal is to develop a highly specific β-synuclein immunoassay for both CSF and blood. **Methods:** New monoclonal antibodies specific for β-synuclein with which prototype immunoassays were developed based on colorimetric ELISA, for CSF studies and on the Simoa HD-X platform to explore more sensitive formats in plasma and serum. Several ELISA formats, targeting different proteoforms/fragments of β-synuclein,were already compared with a format that was previously published.160 samples from the Amsterdam Dementia Cohort included four groups of 40 samples in each group: (1) controls, (2) individuals with subjective cognitive decline (SCD), (3) mild cognitive impairment due to AD (MCI-160 AD) and (4) AD dementia (AD-Dem) based on CSF biomarker (phosphorylated tau181, pTau181/amyloid-β(1-42) profiles. **Results:** Two new high-affinity antibodies (RD116 and RD123) were further characterized for their specificity on peptides that mimic the differences between alpha- and β -synuclein. RD116 is dependent on Glutamine 78 for its β-specificity, while RD123 relies on Proline 123 for optimal recognition, a residue that has also been found mutated in Lewy body dementia (Ohtake et al., 2004). Clinical studies on the 160 samples from the Amsterdam Dementia cohort had a similar clinical performance, suggesting that the proteoforms/fragments targeted by the different antibodies are not influenced by post-translational modifications. Finally, in paired plasma-serum samples from healthy volunteers, we found a high correlation between both matrices. **Conclusion and perspectives:** Based on β -specific monoclonal antibodies, we confirmed the increase of β -synuclein in CSF of the AD continuum with ELISA. An ongoing pilot study in paired plasma-CSF samples and further spiking-recovery experiments will confirm specificity of the serum-plasma signals and the use of this blood-based immunoassay will be further optimized for clinical studies. Such assays will help to explore the clinical potential of β-synuclein in cohorts with respect to established blood biomarkers such as ptau217, GFAP and neurofilament light, not only for synaptopathy in AD, but also in other neurological conditions.

LP067- HIGH-THROUGHPUT, FULLY AUTOMATED IMMUNOASSAY FOR DETECTING ZYGOSITY OF APOLIPOPROTEIN E4 (APOE E4) IN EDTA PLASMA.

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Background: Apolipoprotein E (APOE) and its isoforms (APOE2/3/4) shuttle lipids between cellular compartments and organs. The APOE4 isoform is associated with increased risk of developing Alzheimer's disease (AD), with higher risk for homozygous APOE ε4+/+ individuals. Availability of high-throughput assays to determine APOE ε4 zygosity would enable reliable and widespread use by researchers. We describe the performance of a prototype high-throughput APOE ε4 zygosity assay on the DxI 9000 and Access 2 Immunoassay Analyzers. **Methods:** The prototype APOE ε4 assay is a multiplex of 2 two-step sandwich assays using paramagnetic particles coated with anti-PanAPOE monoclonal antibody (MAb) APOE and complementary anti-PanAPOE MAb/alkaline phosphatase conjugate or an anti-APOE4 MAb/alkaline phosphatase conjugate. Sample and reactants are incubated and washed, then a chemiluminescent substrate is added. The light generated is processed through an algorithm that provides a result indicating the APOE ε4 zygosity of the sample. Samples screened on the DxI 9000 analyzer have a time-to-first result of ~20 minutes, with up to 400 tests/hour. Samples screened on the Access 2 analyzer have a time-to-first result of ~25 minutes, with up to 100 tests/hour. EDTA plasma samples were evaluated for imprecision and interferences (n=43), as well as concordance with PCR genotyping and a commercially available research-use only (RUO) APOE ε4 immunoassay

(n=300). **Results:** The prototype APOE ε4 assay demonstrated an intra-assay coefficient of variation of ≤9% on both analyzers. Cross-reactivity of the APOE4-specific assay to the APOE2 and APOE3 isoforms was negligible. Minimal interference was observed from other AD biomarkers, AD drugs, and endogenous interferents. A comparison of the DxI 9000 and Access 2 analyzer prototype assays against a commercially available APOE ε4 RUO assay had correlations of r=0.95 and 0.90 (n=43), respectively. Concordance with PCR genotype data was 99.3% (n=300). **Conclusion:** This prototype RUO APOE ε4 assay currently in development provided fast and precise results in an automated immunoassay on the Beckman Coulter DxI 9000 and Access analyzers. The assay had excellent concordance with PCR genotyping and commercially available immunoassays. **Keywords:** Apolipoprotein E, biomarker, immunoassay, Alzheimer's Disease. **Disclosures:** B. Engel is a full-time employee of Beckman Coulter/Danaher. M. Szabo is a full-time employee and holds stocks of Beckman Coulter/Danaher. B. Schlichtmann is a full-time employee of Beckman Coulter/Danaher. K. Curtis is a full-time employee of Beckman Coulter/Danaher. K. Hoffmann is a full-time employee of Beckman Coulter/Danaher. L. Mediger is a full-time employee of Beckman Coulter/Danaher. C. Carlson is a full-time employee and holds stocks of Beckman Coulter/Danaher. J. Mendoza is a full-time employee and holds stocks of Beckman Coulter/Danaher. M. Nichkova-Doseva is a full-time employee and holds stocks of Beckman Coulter/Danaher.

LP068- PLASMA PTAU-217 VERSUS PLASMA PTAU-217/AB1-42 RATIO PERFORMANCE IN PREDICTING AMYLOID POSITIVITY COMPARED TO CSF AB42/40 RATIO OR PET IN A SCREENING COHORT FROM A PHASE 3 REGISTRATION STUDY: IMPLICATIONS FOR A TRIAGE MODEL. S. Sha[1], J. Rock[2], F. Kim[2], R. Radwan[3], F. De Simone[3], N. Benina[3], D. Hawkins[4] *(1. Neurology & Neurological Sciences, Stanford University - Palo Alto (United States), 2. AriBio Co., Ltd. - San Diego (United States), 3. Fujirebio Diagnostics, Inc. - Malvern (United States), 4. Scottsdale Scientific LLC - Austin (United States))*

Background: Currently acceptable diagnostics to verify amyloid plaque in a dementia population are positron emission tomography (PET) or cerebral spinal fluid (CSF) ratios with FDA/EMA-approved assays and amyloid tracers. Recently, blood-based biomarkers (BBMs) showed promising concordance with amyloid PET and CSF ratios. The use of BBMs to triage screening patients into two groups--1) amyloid positive or amyloid negative; and 2) to be confirmed--can be considered. To achieve a model that is adequately robust for triaging, only a small number of participants should require confirmation. This model would limit time-consuming and difficult to schedule procedures and help democratize the diagnostic pathway. By referring fewer patients for lumbar puncture, which is needed to obtain CSF, and with limited access to PET scans and/or amyloid tracers, both of which can prolong the confirmatory Alzheimer's disease pathway, significant cost and time saving can be realized. Phosphorylated tau variants, specifically pTau-217 and/or pTau-217/Aβ1-42 ratio, have demonstrated the best accuracy to detect amyloid pathology with results similar to CSF or PET. **Methods:** To test triage models and determine assay performance, samples collected during screening from an early AD phase 3 registrational trial were analyzed. Plasma pTau-217 and pTau-217/Aβ1-42 ratio assays were run with pre-determined cut-offs and compared to CSF or PET results obtained within the 6-week screening period. The Lumipulse G pTau-217 and β-Amyloid 1-42 Investigational Use Only (IUO) plasma kits from Fujirebio were used to test 272 unique screening plasma samples. Samples were tested in singlicate on a Lumipulse G1200 analyzer. Results for pTau-217 and pTau-217/β-Amyloid 1-42 ratio were compared to FDA cleared Lumipulse® G β-Amyloid Ratio (1-42 /1-40) with > 0.073 considered a negative result and < 0.072 a positive result. Triage models were analyzed in aggregate, and by age (>71), sex, race (African American versus Caucasian), and ethnicity (Hispanic versus non-Hispanic). **Results:** 272 samples were collected and 265 (97.4%) were evaluable for pTau 217 (excluded if no Lumipulse CSF ratio) and 256 (94.1%) were evaluable for pTau-217/β-Amyloid 1-42 ratio (excluded if no Lumipulse CSF ratio or pTau-217 result below range of assay). The pTau-217/β-Amyloid 1-42 ratio resolves 78.9% of patients – 45.3% positive and 33.6% negative, leaving 21.1% to be confirmed by PET or CSF for amyloid positivity. The positives have a positive predictive value (PPV) of 91% and a positive likelihood ratio (PLR) of 9, suggesting that the PPV is an informative statistic in predicting positivity. Predictive value (PV) of negative samples is 2% which constitutes a negative predictive value (NPV) of 98% and a PLR of 0.020, indicating that NPV is an informative statistic in predicting negativity. Plasma pTau-217 alone resolves fewer patients, 66.7% with slightly better PV for positive results and slightly worse PV for negative results. Overall, when results were analyzed by age, sex, race, and ethnicity, lower assay triage lower performance was noted with pTau-217 only assay. **Conclusion:** Plasma pTau-217/β-Amyloid 1-42 ratio demonstrated a robust triage model capable of being applied to a diverse early AD population that deserves further investigation.

LP069- HEAD-TO-HEAD COMPARISON OF THE FULLY AUTOMATED ELECSYS PTAU217 PLASMA ASSAY AND THE LUMIPULSE PTAU217 PLASMA ASSAY. R. Perneczky[1,2,3,4,5], L. Stoeckl[6], M. Carboni[7], S. Hortsch[6], C. Rabe[8], A. Jethwa[6], T. Bittner[8,9] *(1. University Hospital of Munich - Munich (Germany), 2. German Center for Neurodegenerative Diseases - Munich (Germany), 3. Munich Cluster for Systems Neurology - Munich (Germany), 4. Ageing Epidemiology Research Unit, - London (United Kingdom), 5. Sheffield Institute for Translational Neuroscience - Sheffield (United Kingdom), 6. Roche Diagnostics GmbH - Penzberg (Germany), 7. Roche Diagnostics International Ltd - Rotkreuz (Switzerland), 8. Genentech Inc. - San Francisco (United States), 9. F. Hoffmann-La Roche Ltd - Basel (Switzerland))*

Background: Blood tests are a non-invasive and cost-effective method for detecting Alzheimer's disease pathology, including amyloid deposits. Plasma phosphorylated tau 217 (pTau217) is a biomarker with high clinical utility in detecting amyloid pathology. The Elecsys® Phospho-Tau 217 plasma prototype immunoassay (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) identifies amyloid pathology by quantitatively determining plasma pTau217 levels and has received United States Food and Drug administration Breakthrough Device Designation.1 The Lumipulse G pTau217 plasma assay is a research use only assay from Fujirebio. Here, we performed a head-to-head comparison of the Elecsys and Lumipulse pTau217 assays. **Methods:** This head-to-head, blinded, method comparison study compared plasma pTau217 levels measured using the Elecsys and Lumipulse pTau217 assays in samples from a selected subset of patients from the amyloid screening population of the CREAD2 study (NCT03114657). Amyloid status was determined by amyloid-positron emission

tomography imaging with visual read or, if not available, by the Elecsys cerebrospinal fluid Phospho-Tau 181/Amyloid beta (1–42) ratio. The area under the receiver operating characteristic curve (AUC) with respect to amyloid status was calculated. A dual cutoff approach assessed the cutoffs at sensitivity and specificity of 90%. Positive predictive values (PPV) and negative predictive values (NPV) were calculated. The Pearson correlation coefficient between the two assay results was calculated. **Results:** This analysis included samples from 264 patients (184 [69.7%] were amyloid positive and 80 [30.3%] were amyloid negative). Mean age was 71.3 years (range: 50.0–85.0), 146 (55.3%) were female, 34 (12.9%) carried two copies of Apolipoprotein E4, and the mean Mini-Mental State Examination score was 24.7 (range: 22.0–30.0). Baseline demographics were consistent across amyloid-positive and negative subgroups. For the Elecsys pTau217 assay, six (2.27%) measurements were below the corresponding limits of quantification versus one (0.38%) measurement for the Lumipulse pTau217 assay. For the Elecsys pTau217 assay, there were no measurements that exceed the measuring range versus two (0.76%) measurements for the Lumipulse pTau217 assay. The AUC for pTau217 with respect to amyloid status was 0.907 (95% confidence interval [CI]: 0.858–0.957) with Elecsys and 0.862 (CI: 0.805–0.920) with Lumipulse. For the Elecsys assay, at the 90% sensitivity cutoff, the PPV was 91.7% and the NPV was 78.3%; at the 90% specificity cutoff, the PPV was 94.8% and the NPV was 65.5%; 10.2% were in the intermediate zone between the two cutoffs. For the Lumipulse assay, at the 90% sensitivity cutoff, the PPV was 87.4% and the NPV was 75.7%; at the 90% specificity cutoff, the PPV was 93.1% and the NPV was 48.6%; 28.0% were in the intermediate zone between the two cutoffs. Plasma pTau217 levels between the Elecsys and Lumipulse assays were positively correlated (Pearson's r=0.883; ten outliers identified by Generalized Extreme Studentized Deviate were removed). **Conclusion:** The Elecsys pTau217 assay detects amyloid pathology with high accuracy and is highly correlated with the Lumipulse pTau217 assay. The fully automated Elecsys and Lumipulse pTau217 assays have clinical potential for detecting amyloid pathology. However, the assays need to be fully validated and approved by regulatory bodies before clinical use. **Keywords:** Amyloid pathology; Alzheimer's disease; head-to-head comparison; plasma phosphorylated tau 217. **Disclosures:** R.P. has received honoraria for advisory boards and speaker engagements from Roche, EISAI, Eli Lilly, Biogen, Janssen-Cilag, Astra Zeneca, Schwabe, Grifols, Novo Nordisk, GSK, Bristol Myers Squibb and Tabuk. L.S., S.H. and A.J. are full-time employees of Roche Diagnostics GmbH. M.C. is a full-time employee of Roche Diagnostics International Ltd and a shareholder in Roche. C.R. is a full-time employee of Genentech Inc., a member of the Roche Group and shareholder in F. Hoffmann-La Roche AG. T.B. is a full-time employee of F. Hoffmann-La Roche Ltd and Genentech Inc., a member of the Roche Group and shareholder in F. Hoffmann-La Roche AG. This study was funded by Roche Diagnostics International Ltd (Rotkreuz, Switzerland). Third-party medical writing assistance for the development of this abstract, under the direction of the authors, was provided by Tiffany Blythe, BSc, of Ashfield MedComms, an Inizio company (London, UK), and funded by Roche Diagnostics International Ltd (Rotkreuz, Switzerland). **Reference:** 1. Roche. Roche granted FDA Breakthrough Device Designation for blood test to support earlier Alzheimer's disease diagnosis; 2024. Available at: https://www.roche.com/media/releases/med-cor-2024-04-11.

LP070- LP070 BIOMARKERS OF NEUROPATHOLOGY IN PATIENTS SCREENED FOR CLINICAL TRIALS WHO HAVE COGNITIVE IMPAIRMENT BUT ARE AMYLOID PET NEGATIVE.

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Background: Screening for AD clinical trials yields many persons with clinical signs of Mild Cognitive Impairment (MCI) or mild AD but who do not have amyloid deposits as assessed by PET scan. Characterizing these people with biomarkers may identify neurobiological abnormalities worth targeting with non-amyloid therapies. **Methods:** The Bio-Hermes study [1] enrolled over 1000 ethnically diverse participants, assessed by clinical history, cognitive tests and functional assessment as cognitively normal (CN), MCI or mild AD; clinical assessment was followed by an amyloid PET scan just as is done in screening for clinical trials. 296 were MCI or mild AD clinically but were negative on clinical read of amyloid PET (MCI/AD Ab-). We compared biomarkers in these persons with other groups: cognitively normal (CN) and amyloid PET negative (N=313) (CN Ab-), CN and amyloid PET positive (N=84) (CN Ab+), clinical MCI or mild AD and amyloid PET positive (N=258) (MCI/AD Ab+). **Results:** Regional amyloid PET [2] showed no brain regions with elevated amyloid in the clinical MCI/AD persons who were amyloid negative by visual read; plasma p-Tau 217 also was not elevated. In blood the MCI/AD-Ab- persons had elevated levels of NfL, GFAP, and total tau relative to the CNAb- group. Cytokine analysis found Eotaxin-3 reduced in MCI/ADAb- relative to all other groups and IL-23 higher in CN Ab- persons relative to all other groups; other cytokines did not distinguish the MCI/AD Ab- participants relative to CN Ab- participants. Proteomics analysis [3] showed differences in several biological processes; some reflecting cellular regulation were different in persons with MCI/AD Ab- compared with CN Ab- persons. Proteomics reflecting inflammation pathways differed between MCI/AD Ab+ persons and CN Ab- participants. Other analyses looking at biomarkers of alpha-synuclein and vascular disease are in process. **Conclusion:** Persons with clinical signs MCI or mild AD who are Ab- show biomarker evidence of neurodegeneration and evidence of dysregulation in some cytokines. They also have proteomics profiles suggesting cellular dysregulation. These finding may point to biological pathways that differ in non-amyloid related cognitive dysfunction relative to AD with amyloid and tau deposits. **Keywords:** Clinical trials, biomarkers including plasma, proteomics, methodology. **Clinical Trial Registry:** NCT04733989; https://clinicaltrials.gov. **Disclosures:** RCM, DB and JRD are employees of the Global Alzheimer's Platform Foundation. Robin Wolz is employed by IXICO. JC, JN-J and SH are employed by Pentara. KP is employed by EMTherapro. The authors declared no competing interests. **References:** 1. Mohs RC, et al. Alzheimer's Dement. 2024;1-14. 2. Grothe MJ, et al. Neurology. 2017;89:2031-2038. 3. Rayaprolu S, et al. Neuropsychopharm. 2021;46:98-115.

LP071- GLYMPHATIC DYSFUNCTION AFFECTS PLASMA DOWNSTREAM MARKERS FOR ALZHEIMER'S DISEASE AND CLINICAL PROGRESSION. S.H. Kang[1], S. Kim[2,3], B. Sohn[4], S.W. Seo[2,5,6,7] *(1. Department of Neurology, Korea University Guro Hospital, Korea University College of Medicine - Seoul (Korea, Republic of), 2. Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine - Seoul (Korea, Republic of), 3. Alzheimer's disease convergence research center, Samsung Medical Center - Seoul (Korea, Republic of), 4. Department of Radiology and Center for Imaging Sciences, Samsung Medical Center, Sungkyunkwan University School of Medicine, - Seoul (Korea, Republic of), 5. Alzheimer's Disease Convergence Research Center, Samsung Medical Center, - Seoul (Korea, Republic of), 6. Department of Digital Health, SAIHST, Sungkyunkwan University, - Seoul (Korea, Republic of), 7. Department of Health Sciences and Technology, SAIHST, Sungkyunkwan University, - Seoul (Korea, Republic of))*

Background: Growing evidence has shown that increased cerebral small vessel disease (CSVD) burdens affect the glymphatic dysfunction, and it is closely associated with amyloid deposition in the brain, respectively. However, whether glymphatic system may interplay the association between CSVD burdens and Alzheimer's disease (AD) downstream markers remains unclear. In the present study we aim to determine whether glymphatic dysfunction, assessed by diffusion tensor imaging analysis along the perivascular space (ALPS) index, mediated the relationship between CSVD markers and AD downstream markers. Furthermore, we examined whether glymphatic dysfunction was related to cognitive decline and whether AD downstream markers mediate the relationship. **Methods:** We enrolled 1,249 participants (262 cognitively unimpaired [CU], 489 mild cognitive impairment [MCI], and 352 dementia of the Alzheimer's type [DAT], 146 subcortical vascular cognitive impairment [SVCI]) from the Korea-Registries to Overcome and Accelerate Dementia Research (K-ROAD) project, in collaboration with 25 nationwide university affiliated hospitals in South Korea between 2016 and 2023. All participants underwent Aβ PET and brain MRI. ALPS index was calculated by measuring diffusivity along the x, y, and z axes which highlights water diffusion along the perivascular space. Additionally, all participants underwent plasma phosphorylated tau 217 (p-tau 217), glial fibrillary protein (GFAP), and neurofilament light chain (NFL) level measurements. To determine whether ALPS index mediates the relationship between CSVD markers and downstream markers, we conducted mediation analyses with each CSVD markers as a predictor, ALPS index as a mediator, and each downstream markers as an outcome after controlling for age, sex, BMI status, APOE genotype, and centiloid (CL) value. To explore whether downstream markers mediate the effect of the ALPS index on cognitive decline, we conducted mediation analyses with ALPS index as a predictor, each downstream markers as a mediator, and annual MMSE change as an outcome after controlling for age, sex, BMI status, APOE genotype, CL value, and education years. **Results:** ALPS index fully mediated the relationship between the relationship between CSVD markers and downstream markers: CSVD score and CAA for p-tau 217 (CSVD score, p for indirect effect=0.002, p for direct effect=0.655; CAA, p for indirect effect=0.042, p for direct effect=0.158) and GFAP (CSVD score, p for indirect effect<0.001, p for direct effect=0.779; CAA, p for indirect effect=0.020, p for direct effect=0.056). ALPS index partially mediated the relationship between CSVD markers and NFL (CSVD score, p for indirect effect<0.001, p for direct effect<0.001; CAA, p for indirect effect=0.012, p for direct effect=0.012). Regarding cognitive decline, p-tau 217 affects annual MMSE change without mediation of ALPS (p for indirect=0.054, p for direct effect<0.001). GFAP and NFL partially mediated the relationship of ALPS index and annual MMSE change (GFAP, p for indirect effect<0.001, p for direct effect<0.001; NFL, p for indirect effect<0.001, p for direct effect=0.001). **Conclusion:** Our findings have uncovered novel association between glymphatic dysfunction indicated by ALPS index, CSVD markers, plasma AD downstream markers, and cognitive declines. Furthermore, understanding the relationship between glymphatic function and AD biomarkers provides an opportunity for further research to discover new markers for treating AD. **Keywords:** Glymphatic dysfunction, cerebral small vessel disease (CSVD), Alzheimer's disease (AD), downstream markers. **Disclosures:** The authors declared no competing interests.

LP072- CAPS PLUS: A CLINICAL BIOMARKER SCORING SYSTEM TO PREDICT AB POSITIVITY AND FACILITATE ENROLMENT IN ANTI-AMYLOID CLINICAL TRIALS. D. Lahiri[1], J. Cooper[2], B. Seixas-Lima[3], C. Roncero[3], C. Wellington[2], H. Chertkow[3] *(1. Queen's University - Kingston (Canada), 2. University of British Columbia - Vancouver (Canada), 3. University of Toronto - Toronto (Canada))*

Background: A critical step towards determining treatment eligibility and enrolment in clinical trials for anti-amyloid therapies in Alzheimer's Disease (AD) is to select appropriate subjects having a high likelihood of being Aβ+. This step ensures better allocation of resources, such as amyloid PET scanning, especially in resource constrained settings. We hereby propose a clinical-biomarker composite score, named Clinical Amyloid Positivity Prediction Score Plus (CAPS plus), incorporating total neuropsychology inventory quantitative (NPI-Q) score, rapidity of decline in mini mental status examination (MMSE) score over time, the magnitude of cerebrovascular disease burden as measured by Fazekas score, and plasma p-tau217, for Aβ+ prediction in people presenting with clinical Alzheimer's syndrome including both prodromal and mild AD. **Methods:** The original CAPS included 0-2 points for total NPI-Q score, 1 point for an MMSE loss of >2 per year, and 1 point for a Fazekas score of ≤1 (Lahiri et al, 2024). Plasma p-tau217 was measured using the Simoa HD-X and AlzPATH p-tau217 advantage Plus assay. To incorporate p-tau217 into CAPS plus, an intra-cohort cut off (>0.698 pg/ml) for p-tau217 was generated using logistic regression and Yoden's index. A score of +1 was assigned to individuals with a plasma level above this cut off, making the maximum possible score as 5, with those ≥4 indicating a high probability of being Aβ+. The accuracy of Aβ positivity classification based on this novel scheme named CAPS plus was computed through logistic regression and area under the receiver operating curve (AUROC) analysis. **Results:** Complete dataset for final analysis was available for n=45 patients, among which n=25 (55%) were Aβ+. The Aβ+ group had significantly lower baseline MMSE scores (p=0.04) and total NPI-Q scores (p=0.001) than the Aβ- group. Plasma level of p-tau217 was significantly higher in the Aβ+ subgroup (1.36 vs 0.46 pg/mL, p<0.001). The AUROC was 0.89 for a CAPS plus score of 4 or more, suggesting excellent discrimination and improving the accuracy of original CAPS (0.86). CAPS plus has a notably better specificity than the original CAPS (95% vs 80%). **Conclusion:** CAPS plus is potentially a useful screening tool for enrolment in anti-Aβ clinical trials for AD, specifically addressing people

with prodromal and mild AD. Adding p-tau217 to CAPS can improve prediction accuracy of Aβ status, especially in subjects with a borderline negative CAP Score, owing to a better specificity of CAPS plus. While p-tau217 alone has a high accuracy in Aβ+ predictivity, CAPS plus can potentially put this powerful blood-based biomarker in the right clinical context. **Keywords:** anti-amyloid trials: clinical biomarker; CAPS plus; screening. **Disclosures:** HC is supported by a Chair in Cognitive Neurology and Innovation from the Baycrest Academy for Research and Education, Baycrest Health Sciences, Toronto. HC has been supported by a Foundation Grant from the Canadian Institutes for Health Research (CIHR), along with operating funds from the Weston Foundation, Weston Brain Institute, and the National Institute of Health (United States) [(Aging Research)—Phase II clinical trial of transcranial direct current stimulation in the treatment of primary progressive aphasia—1R01AG075111-01A1]. HC has participated as a site PI in the past 5years for pharmaceutical clinical trial activities sponsored by the following companies: Hoffmann-La Roche Limited, TauRx, Eli Lilly Corp., Anavex Life Sciences, Alector LLC, Biogen MA Inc., IntelGenX Corp., and Immunocal. HC has participated as an unpaid advisor in 2020 for establishment of an international database by Biogen. HC has received honoraria for sitting on advisory boards for Eisai, Biogen, and Lilly Inc. in Canada. HC is scientific director (unpaid) for the Canadian Consortium on Neurodegeneration in Aging (CCNA), which receives funding from the Canadian Institutes for Health Research, along with partner support from a set of partners including not for profit organizations: Brain Canada, Alzheimer Society of Canada, Womens Brain Health Initiative, Picov Family Foundation, New Brunswick Health Research Foundation, Saskatchewan Health Research Foundation, and Ontario Brain Institute. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. **References:** Lahiri, D., Seixas-Lima, B., Roncero, C., Verhoeff, N. P., Freedman, M., Al-Shamaa, S., & Chertkow, H. (2024). CAPS: a simple clinical tool for β-amyloid positivity prediction in clinical Alzheimer syndrome. Frontiers in neurology, 15, 1422681. https://doi.org/10.3389/fneur.2024.1422681.

LP073- INTRODUCTION OF MULTI-DIMENSION BIOMARKERS APPLICATION FOR A RANDOMIZED, DOUBLE-BLIND, SINGLESIMULATED CLINICAL TRIAL OF SODIUM OLIGOMANNATE ON ALZHEIMER'S DISEASE. Q. Wang[1], L. Dai[1], F. Gao[1], J. Shi[1], Y. Shen[1] *(1. The first Affiliated Hospital of USTC - Hefei (China), 2. The first Affiliated hospital of USTC - Hefei (China) - Hefei (China))*

Background: The Alzheimer's disease (AD) continuum is a chronic neurodegenerative disease, which is characterized by deposit of amyloid plaquesand neurofibrillary tangles (NFTs) through the brain. Previous studies of sodium oligomannate of phase II and phase III clinical trials demonstrated significant efficacy in improving cognition on mild to moderate Alzheimer's dementia. However, the big limitation of these trials was the lack of requirement for the presence of a diagnostic biomarkers at screening. Furthermore, these studies have not explored the effects of sodium oligomannate on biomarkers. Then, we enrolled individuals with Alzheimer's disease continuum diagnosed based on biomarkers, administrating with sodium oligomannate to evaluate its effect on cognition and biomarkers. **Methods:** We conducted a 36-week, double-blind, placebo-controlled involving individuals 50-79 years of age with Alzheimer's disease (mild cognitive impairment or mild/moderate dementia due to Alzheimer's disease) with evidence of amyloid on positron-emission tomography (PET) imaging. Participants were randomly assigned in a 1:1 ratio to receive sodium oligomannate or placebo with all administrated with donepezil (Eisai). The primary end point was the change from baseline at 36 weeks in the score on the Clinical Dementia Rating-Sum of Boxes (CDR-SB; range, 0 to 18, with higher score indicating greater impairment). Key secondary end points were the change in amyloid burden and tau burden or brain metabolism (fluorodeoxyglucose, FDG) on PET, the score on the Minimum Mental State Examination (MMSE; range, 0 to 30; lower scores indicate greater impairment), the score on the 12-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog12; range, 0 to 75; higher scores indicate greater impairment), and the score on the Alzheimer's Disease Cooperative Study Activities of Daily Living Scale (ADCS-ADL; range, 0 to 54; lower scores indicate greater impairment). Plasma biomarker Assessments of AD that may include amyloid isoforms, tau, metabolites and other protein biomarkers (eg, GFAP, NFL), the brain volume assessments in whole brain, hippocampal, ventricular and cortical thickness et al. Exploratory end points were the change in gut microbiota metagenomics and periphery immune cells and related inflammatory cytokines. **Results:** A total of 60 participants were enrolled, with randomly assigned to 1:1 to receive sodium oligomannate and placebo. The mean CDR-SB score was approximately 4.06 in total participants. Currently, 46 participants are completed the trial and had the data available on the primary end point. The remaining participants will complete the trial by the end of this year. Subsequently, clinical characteristics, imaging and biological biomarkers will be fully analyzed. **Conclusion:** The biomarkers driven study will be provide the rigorous data on the effect and mechanism of sodium oligomannate in the treatment of AD. Importantly, subgroup analysis will also be analyzed to provide a reference for the pathogenesis and treatment exploration of different AD subtypes.

LP074- BIOMARKER DATA SHOWED BUNTANETAP REDUCED NEUROTOXIC PROTEINS, IMPROVED AXONAL INTEGRITY, REDUCED INFLAMMATION, AND NEURONAL FUNCTIONS IN ALZHEIMER'S CLINICAL STUDIES. C. Fang[1], D. Feng[2], M. Gaines[1], E. Damiano[1], M. Maccecchini[1] *(1. Annovis Bio - Malvern (United States), 2. TCM - Princeton (United States))*

Background: Neurotoxic aggregating proteins, such as Tau and amyloid, can inhibit axonal transport, induce inflammation, cause neuronal death and eventual loss of functions [1-4]. Buntanetap/Posiphen can regulate the translation of multiple neurotoxic proteins and therefore reverse the toxic cascade caused by these proteins [5]. **Method:** the biomarker results from 4 randomized, double blind, placebo-controlled studies in AD patients were summarized here. **Results:** Biomarkers were measured in four double-blind, placebo-controlled Alzheimer's (AD) clinical studies: In the phase 1b Stable Isotope Labeling Kinetic (SILK) analysis study (NCT02925650), lumbar and venous catheters were placed in AD patients who were 13C6-leucine infused for 9 hours with dosing of placebo or buntanetap according to their dose arm (placebo, 60mg QD, 60mg BID and 60mg TID for 21 days). CSF and venous blood were collected every two hours for over 36 hours. Pharmacokinetics of the drug metabolites was assessed in plasma and CSF. Pharmacodynamics of Aβ38, Aβ40 and APP

were evaluated and showed that with increasing dose the translation starts later, the slope is flatter, the Cmax is lower, the Tmax is longer resulting in an overall much smaller area under the curve. Buntanetap showed a statistically significant and dose-dependent reduction of Aß38, Aß40, and APP production [6]. In a phase 1b MCI POC study (NCT01072812) buntanetap decreased APP and its by products, tau, and alpha-synuclein in CSF after 10 days treatment [7]. In our phase2a study (NCT04524351), buntanetap reduced AD patients' total tau and phosphorylated tau (pTau181), reduced inflammation as shown by YKL-40, sTREM2, GFAP, and complement C3, protected axonal integrity as shown by NFL and protected neuronal function as shown by neurogranin after 28 days treatment [8]. In our recent Phase2/3 study (NCT05686044), plasma biomarker data showed that buntanetap reduced total Tau, TDP43, GFAP and NFL in patients treated for 3. Importantly, we also observed similar and consistent biomarker data in our two double-blind, placebo-controlled Parkinson's (PD) studies. In our phase 2a Parkinson's study(NCT04524351) buntanetap reduced neurotoxic proteins alpha-synuclein and TDP43, reduced inflammatory makersYKL-40, sTREM2, GFAP, and complement C3, protected axonal integrity as shown by NFL and protected neuronal function as shown by neurogranin. We also tested TDP43, GFAP and NFL in plasma and saw the same pattern as in CSF. **Conclusion:** Biomarker data from various clinical studies in Alzheimer's and Parkinson's patients reproducibly showed that buntanetap reduced multiple neurotoxic aggregating proteins, reduced inflammation, and preserve neuronal functions. All these biomarker data support buntanetap's clinical efficacy in improving AD patients' cognitive function. **Keywords:** Alzheimer, Parkinson, SILK, CSF and plasma biomarkers. **Disclosures:** Cheng Fang, Melissa Gaines, Eve Damiano, and Maria Maccecchini are employees of Annovis Bio. The authors declared no competing interests.

LP075- LEVELS OF AGE-RELATED CD8 T CELLS BINDING HLA TRACK WITH ALZHEIMER'S DISEASE STATUS IN HLA-A2+ AND HLA-A2- PATIENTS: EXPANSION OF A FLOW CYTOMETRIC BLOOD BIOMARKER ASSAY TO ALL PATIENTS. C. Wheeler[1], V.D. Debbie[2], V. Yannick[3], D.R. Hans[4], D.D. Peter Paul[2] *(1. T-Neuro Pharma, Inc., Albuquerque, NM 87123; NovAccess Global and StemVax LLC, Cleveland, OH 44023; Society for Brain Mapping & Therapeutics, World Brain Mapping Foundation, Pacific Palisades, CA 90272; Department of Chemistry & Biochemistry, University of California, Santa Cruz, CA 95064 - Aptos (United States), 2. Department of Biomedical Sciences, Institute Born-Bunge, Laboratory of Neurochemistry and Behavior, University of Antwerp, Antwerp 2610, Belgium; Department of Neurology and Alzheimer Research Center, University of Groningen and University Medical Center Groningen, Groningen AB 9700, Netherlands - Antwerp (Belgium), 3. Department of Biomedical Sciences, Institute Born-Bunge, Laboratory of Neurochemistry and Behavior, University of Antwerp, Antwerp 2610, Belgium; Faculty of Medicine and Health Sciences, Vaccine and Infectious Disease Institute, Laboratory of Experimental Hematology, University of Antwerp, Antwerp 2 - Antwerp (Belgium), 4. Faculty of Medicine and Health Sciences, Vaccine and Infectious Disease Institute, Laboratory of Experimental Hematology, University of Antwerp, Antwerp 2610, Belgium - Antwerp (Belgium))*

Background: We recently developed a 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). As this model is induced by age-related self-reactive CD8 T cells, identification of the peptide antigen to which these T cells responded, a non-Aβ epitope on mouse Amyloid Precursor Protein (APP470-478), also allowed us to quantify levels of analogous T cells in humans (responsive to human APP471-479). Levels of these cells in blood, quantified via binding to a APP471-479/Human Leukocyte Antigen(HLA)-A2 (pHLA) multimer reagent recognizing T cell receptors specific for the peptide antigen in flow cytometry, distinguished AD and related MCI from normal aging controls with high accuracy in multiple patient cohorts (AUC: 0.883-0.892). While more extensive validation of this "T-Track" biomarker is underway, it is currently suitable only for HLA-A2-positive patients, or about half the otherwise eligible population. It was thus desirable to examine whether similar metrics coincide with disease status in HLA-A2-negative patients, which could extend biomarker assay suitability to all patients. **Methods:** In this context, levels of age-related T cells binding to a separate control pHLA (ALIAPHAV/HLA-A2) whose peptide human CD8 T cells do not recognize paralleled those binding to APP-specific pHLA, even in HLA-A2-negative individuals (0.42-0.58x relative to APP/HLA-A2; $r = 0.81$, $n = 79$; $P < 0.001$), suggesting T cell binding to HLA independent of both peptide and HLA subtype. Since this could be useful in developing an AD biomarker for HLA-A2-negative individuals, we quantified levels of age-related, KLRG1+ CD8 T cells binding to control pHLA multimer in HLA-A2-negative subjects by flow cytometry in Alzheimer's disease (AD) and normal aging control cohorts ($n = 23$ and 21, respectively). **Results:** Levels of T cells binding pHLA-A2 were significantly diminished in AD relative to normal aging controls ($P < 0.015$ by 2-sided T-Test). We next analyzed the levels of the pHLA-bound cells' correspondence to disease status. In receiver operating characteristic (ROC) analysis, area under the curve (AUC) was 0.878 for AD ($P < 0.0001$) with 79.4% sensitivity and 98.6% specificity, nearly identical to APP-specific CD8 T cells in HLA-A2-positive individuals (AUC 0.88; 72.2% sensitivity, 97.2 specificity). **Conclusion:** A modified T cell-based blood test for peptide- and subtype-independent binding of age-related CD8 T cells to HLA corresponds with AD status in HLA-A2-negative individuals with nearly equal metrics as the APP-specific T-Track test in HLA-A2-positive individuals. This provides a basis for expanding T cell-based biomarker test development beyond the roughly 50% of patients expressing HLA-A2, to potentially all patients. Further work is needed to determine the nature of HLA subtype-independent binding by T cells, and increasing binding sensitivity, which may allow us to increase the utility of the assay for HLA-A2-negative individuals in particular. **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.

LP076- MONITORING TREATMENT EFFECTS OF SODIUM SELENATE IN ALZHEIMER'S DISEASE AND BEHAVIOURAL VARIANT FRONTOTEMPORAL DEMENTIA USING FLUID BIOMARKERS. F. Gonzalez-Ortiz[1], C. Marotta[2], H. Zetterberg[1], M. Turton[3], P. Harrison[3], C.M. Hovens[4], T.J. O'brien[2], K. Blennow[1], L. Vivash[4] *(1. Gothenburg University - Gothenburg (Sweden), 2. Monash University - Melbourne (Australia), 3. Bioventix - Farnham (United Kingdom), 4. University of Melbourne - Parkville (Australia))*

Background: Sodium selenate is a potential disease-modifying anti-tau therapy for Alzheimer's disease (AD)

and behavioural variant frontotemporal dementia (bvFTD) which reduces hyperphosphorylated tau through activation of the protein phosphatase 2A enzyme (PP2A). We have shown sodium selenate to be safe and well tolerated in a 24-week, phase 2a double-blind placebo-controlled randomised controlled trial, also reporting sodium selenate reduced neurodegeneration on diffusion-weighted MRI. In this study we aimed to determine if cerebrospinal fluid (CSF) levels of brain-derived tau (BD-tau) and p-tau217 could be potential biomarkers of treatment effect in clinical trials of sodium selenate and compared results against standard CSF biomarkers. **Method:** We evaluated biomarker changes in two clinical trials of AD and bvFTD (Trial Registration: ACTRN12611001200976 and ACTRN12617001218381). CSF BD-tau and p-tau217 were measured using the Gothenburg University previously validated assays. CSF T-tau, p-tau181 and Amyloid-beta42 analyses were performed using ELISA (AD trial) or Simoa (bvFTD trial). For the AD trials, participants received either sodium selenate at 10mg (n=10), 320μg (n=5) or placebo (n=6) three times a day for 24 weeks. CSF samples included in this analysis are from the baseline and week 24 visits. In the bvFTD cohort serum, plasma and CSF samples were included from 11 subjects at baseline and after 52 weeks' treatment with sodium selenate. **Results:** In the AD trial, we observed the following changes in CSF BD-tau after 24 weeks compared to baseline: the placebo group from 277.0 (210.6 – 425.5) pg/ml to 297.5 (249.9 – 380.5) pg/ml (2.2%, p>0.8); the group receiving 320μg from 319.2 (259.7 – 434.2) pg/ml to 296.1 (257.1 – 373.4) pg/ml (-1.91%, p>0.06) and from 410.5 (265.3 – 530.4) pg/ml to 349.6 (239.6 – 433.3) pg/ml (-8.27%) (p<0.01) in the 10mg group. Moreover, we found a significant correlation between CSF BD-tau and change in right hippocampal volume in the AD trial (Spearman's rho = -0.4541, p-value = 0.04428). There were no changes in T-tau, p-tau181, AB-42 or p-tau217 in any of the treatment groups. In the bvFTD trial, change in CSF biomarkers levels after 52 weeks of sodium selenate treatment did not reach statistical significance despite small reductions in BD-tau levels being observed in all participants. **Conclusion:** The decrease in concentrations of CSF BD-tau agrees with our previous findings where we observed reduced neurodegeneration on diffusion-weighted MRI in AD patients after treatment with sodium selenate. CSF BD-tau demonstrated potential as an effective biomarker for assessing treatment effects in Alzheimer's disease patients. Additional research is required to explore the viability of plasma BD-tau and its applicability in other drug trials. **Keywords:** Fluid biomarkers; treatment monitoring; tau; sodium selenate. **Disclosures:** This study was funded by Velacor Therapeutics, the Royal Melbourne Hospital Neuroscience Foundation, and Medical Research Future Fund grant from the Australian Government (#MRF1170276). LV has received consultancy and scientific advisory board fees from Steminent for unrelated work and has a current patent pending (PCT/AU2023/050497) for unrelated work. KB and HZ have served as a consultant and at advisory boards for Acumen, ALZPath, AriBio, BioArctic, Biogen, Eisai, Lilly, Moleac Pte. Ltd, Novartis, Ono Pharma, Prothena, Roche Diagnostics, and Siemens Healthineers; have given lectures in symposia sponsored by Alzecure, Biogen, Cellectricon, Fujirebio, Lilly, Novo Nordisk, and Roche.

LP077- EXPLORING THE LINK BETWEEN DIFFERENCES IN SPECTRAL POWER ACROSS OCULAR STATES IN RESTING-STATE EEG AND P-TAU181 LEVELS IN MILD COGNITIVE IMPAIRMENT. C. Hatlestad-Hall[1], L. Gemein[2], F. Ramirez-Toraño[3,4], R. Bruña[3,5], G. Kollmorgen[6], M. Carboni[6], J. Hipp[2], K. Blennow[7,8], H. Zetterberg[7,8], F. Maestú[3,4], H. Renvall[9,10], C. Marra[11,12], P.M. Rossini[13], D. Engemann[2], I.H. Haraldsen[1] *(1. Dept. of Neurology, Oslo University Hospital - Oslo (Norway), 2. Roche Pharma Research and Early Development, Neuroscience and Rare Diseases, F. Hoffmann–La Roche Ltd. - Basel (Switzerland), 3. Centre for Cognitive and Computational Neuroscience, Universidad Complutense de Madrid - Madrid (Spain), 4. Department of Experimental Psychology, Cognitive Psychology and Speech and Language Therapy, Universidad Complutense de Madrid - Pozuelo De Alarcón (Spain), 5. Department of Radiology, Rehabilitation and Physiotherapy, School of Medicine, Universidad Complutense de Madrid - Madrid (Spain), 6. Roche Diagnostics GmbH - Penzberg (Germany), 7. Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg - Mölndal (Sweden), 8. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital - Mölndal (Sweden), 9. BioMag Laboratory, HUS Medical Imaging Centre, Helsinki University Hospital, Helsinki University and Aalto University School of Science - Helsinki (Finland), 10. Department of Neuroscience and Biomedical Engineering, Aalto University - Helsinki (Finland), 11. Memory Clinic, Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Rome (Italy), 12. Department of Neuroscience, Catholic University of the Sacred Heart - Rome (Italy), 13. Department of Neuroscience and Neurorehabilitation, IRCCS San Raffaele - Rome (Italy))*

Background: Individuals with mild cognitive impairment (MCI) have a significantly increased risk of developing dementia within a five-year period [1]. In the AI-Mind study [2], 1023 individuals with MCI are longitudinally studied with state-of-the-art blood biomarkers (p-tau181 and p-tau217), APOE genotyping, high-density electroencephalography (EEG), cognitive assessment, and clinical progression evaluation. Here, we present the first results from the AI-Mind baseline data, demonstrating that the differences in spectral power between ocular states (open/closed) during resting EEG are associated with p-tau levels. It has been consistently reported that EEG power spectra, in particular the frequency range typically known as alpha (8-12 Hz), are dependent on the ocular state during recording. Based on these findings, there is a general consensus that these ocular states represent two functionally different brain states, of which the eyes closed paradigm is the most investigated in dementia. Recent findings suggest that subtle synaptic pathology and network disruption, possibly fuelled by amyloid deposition and tau protein phosphorylation, may be observable before any clinical manifestation of dementia. In the current work, we hypothesised that a less clear distinction between the two brain states characterised by opened and closed eyes during wakeful resting may be an accessible and straightforward probe for such early dementia-related synaptic pathology. To explore this concept, we examined the relationship between the absolute difference in EEG power spectra across ocular states and p-tau181 levels, another biomarker for dementia risk in MCI. **Methods:** The current analyses included 642 participants with complete p-tau181 and 126-channel EEG recordings. EEG spectral features were calculated using the MEEGLET package, based on Morlet wavelets [3,4]. Spectral power was averaged across all channels, and consequently, we did not investigate

topographic effects. p-tau181 levels were measured using the NeuroToolKit, a panel of exploratory robust prototype assays (Roche Diagnostics International Ltd, Rotkreuz, Switzerland), and log transformed to approximate a normal distribution. To explore the associations between these data, a General Linear Model was fitted for each EEG frequency with p-tau181, age, and sex as independent variables. The interaction effect between sex and p-tau181 was also considered. As the analysis was considered exploratory, significance levels were not adjusted for multiple comparisons. Coefficients associated with a p value below 0.05 were considered significant. **Results:** A significant effect of p-tau181 level on power difference between ocular states was observed in the frequency range 7.3-11.3 Hz. Higher p-tau181 levels were associated with a smaller difference between ocular states during resting-state EEG. Additionally, a significant interaction effect between p-tau181 and sex was evident in the frequency range 6.7-9.5 Hz. In males, high p-tau181 levels were more markedly associated with lower differences between ocular states than in females. **Conclusion:** In this exploratory analysis, we observed a significant association between p-tau181 levels and the difference in power across ocular states in frequencies overlapping with the alpha band. These preliminary findings suggest that the quality of the distinction between wakeful resting with eyes closed and eyes open may be related to tauopathy and dementia risk. **Keywords:** AI-Mind, MCI, EEG, p-tau. **Clinical Trial Registry:** Not applicable. **Data Deposition:** Not applicable. Disclosures: This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 964220. This presentation/publication reflects the views of the authors, and the European Commission is not responsible for any use that may be made of the information it contains. The NeuroToolKit is a panel of exploratory prototype assays designed to robustly evaluate biomarkers associated with key pathologic events characteristic of AD and other neurological disorders, used for research purposes only and not approved for clinical use (Roche Diagnostics International Ltd, Rotkreuz, Switzerland). GK and MC are full-time employees of Roche Diagnostics GmbH. LG is an intern of the RiSE programme (Roche). JH and DE are full-time employees of F. Hoffman - La Roche Ltd. The remaining authors declare no competing interests. **References:** 1. Manly, JJ, et al. Ann Neurol. 2008; 63: 494–506. doi:10.1002/ana.21326; 2. Haraldsen, IH, et al. Front Neurorobot. 2023; 17: 1289406. doi:10.3389/fnbot.2023.1289406; 3. Hipp JF, et al. Nat Neurosci. 2012; 15: 884–890. doi:10.1038/nn.3101; 4. Bomatter P, et al. bioRxiv [preprint]. 2024. doi:10.1101/2023.12.15.571864.

PROOF OF CONCEPT/TRANSLATIONAL RESEARCH FOR AD DEVELOPMENT INTERVENTIONS

P145- APOE-TARGETED EPIGENOME THERAPY FOR ALZHEIMER'S DISEASE.

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Background: : Apolipoprotein E gene (APOE) is the strongest and most reproducible genetic risk factor for late-onset AD (LOAD). Moreover, 50% reduction in APOE levels showed beneficial effects in AD cellular and mouse models. Thus, APOE gene holds promise as an emerging therapeutic target for LOAD. In this study, we developed an epigenome therapy platform to reduce APOEe4 expression by targeted modification of the epigenome landscape across APOE locus. **Methods:** Our epigenome therapy platform is based on all-in-one AAV vector comprises of CRISPR/deactivated(d)Cas9, fused with a synthetic repressor molecule. We 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 models from a LOAD patient homozygote for the APOEe4 allele including, cholinergic neurons, cerebral organoids and microglia like cells. 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:** The therapeutic AAV vector showed a robust decrease, amounting to ~50%, in APOE-mRNA levels in hiPSCs-derived cholinergic neurons, microglia, and cerebral organoids models. Further examination of the transduced e4/4 cerebral organoids demonstrated that the specific reduction in APOEe4 expression led to significant decrease in the level of phosphorylated-Tau (pTau). Moreover, the repression of APOEe4 expression in the hiPSC-derived microglia resulted in a significant increase in Aβ clearance such that the improved Aβ 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 neuroinflammation, characteristic of APOEe4 microglia cells. Next, we moved onto animal studies and administrated the therapeutic AAV-dCas-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. **Conclusion:** Collectively, our results provided in vitro and in vivo proof-of-concept for the utility, efficacy, and specificity of the APOE-targeted epigenome therapy approach and demonstrated the capability to fine-tune APOEe4 expression. Furthermore, our therapeutics based on dCas9 technology offers the opportunity to refine the platform for the development of gene-specific and even allele- and cell-type- specific therapies, and by that enables 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.

P146- NASAL IMMUNOTHERAPY CLEARS INTRACELLULAR TAU PATHOLOGY THROUGH TRIM21 AND IMPROVES COGNITIVE FUNCTIONS IN AGED TAUOPATHY MICE.

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Background: Pathological tau aggregates cause cognitive decline in neurodegenerative tauopathies, including Alzheimer's disease (AD). These aggregates are prevalent within intracellular compartments. Current tau immunotherapies have shown limited efficacy in clearing intracellular tau aggregates and improving cognition in

clinical trials. **Methods:** In this study, we developed toxic tau conformation–specific monoclonal antibody-2 (TTCM2) that selectively recognized pathological tau aggregates in brain tissues from patients with AD, dementia with Lewy bodies (DLB), and progressive supranuclear palsy (PSP). TTCM2 potently inhibited tau-seeding activity, an essential mechanism underlying tauopathy progression. To effectively target intracellular tau aggregates and ensure rapid delivery to the brain, TTCM2 was loaded in micelles (TTCM2-ms) and administered through the intranasal route. **Results:** We found that intranasally administered TTCM2-ms efficiently entered the brain in hTau-tauopathy mice, targeting pathological tau in intracellular compartments.Moreover, a single intranasal dose of TTCM2-ms effectively cleared pathological tau, elevated synaptic proteins levels, and improved cognitive functions in aged tauopathy mice. Mechanistic studies revealed that TTCM2-ms cleared intracellular, synaptic, and seed-competent tau aggregates through tripartite motif-containing 21 (TRIM21), an intracellular antibody receptor and E3 ubiquitin ligase known to facilitate proteasomal degradation of cytosolic antibody-bound proteins. TRIM21 was found to be essential for TTCM2-ms–mediated clearance of tau pathology. **Conclusion:** Our study collectively provides evidence of the effectiveness of nasal tau immunotherapy in targeting and clearing intracellular tau pathology through TRIM21 and enhancing cognition in aged tauopathy mice. This study could be helpful in designing effective tau immunotherapies for AD and other tauopathies. **Keywords:** Tau, immunotherapy , Oligomers. **Conflict of interests:** Rakez Kayed is the inventor on patents involving the compositions and methods related to tau oligomers and antibodies.

P147- MEDIATION OF BETA-AMYLOID PATHOLOGY FOR THE ASSOCIATION BETWEEN SERUM CORTISOL, NEURODEGENERATION, AND COGNITIVE IMPAIRMENT. G. Byeon[1], J. Kim[2], D. Yi[3], H. Ahn[3], G. Jung[3], J.H. Jung[4], Y.Y. Chang[5], K. Kim[6], H. Choi[6], J. Choi[6], Y.K. Kim[2], J. Lee[2], K.M. Kang[6], C.H. Sohn[6], Y. Lee[6], M.S. Byun[6], D.Y. Lee[6] *(1. Seoul St. Mary's Hospital - Seoul (Korea, Republic of), 2. SMG SNU Boramae Medical Center - Seoul (Korea, Republic of), 3. Institute of Human Behavioral Medicine, Medical Research Center Seoul National University - Seoul (Korea, Republic of), 4. Chungbuk National University Hospital - Cheongju (Korea, Republic of), 5. Inje University Sanggye Paik Hospital - Seoul (Korea, Republic of), 6. Seoul National University Hospital - Seoul (Korea, Republic of))*

Objectives: While elevated blood cortisol has frequently been linked to Alzheimer's disease (AD) dementia and related cognitive decline, the underlying pathological mechanisms remain poorly understood. Here, we aimed to investigate the associations between serum cortisol and AD pathologies including beta-amyloid (Aβ) and neurodegeneration, as well as their impact on cognitive outcomes. Additionally, we examined whether Aβ mediates the relationships between cortisol, neurodegeneration, and cognitive decline. **Methods:** This study was conducted as part of the Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease (KBASE), a prospective cohort study. A total of 502 older adults, including cognitively normal individuals and those with mild cognitive impairment and AD dementia, underwent comprehensive clinical assessments and multi-modal neuroimaging including PET imaging, MRI, as well as blood cortisol measurement. **Results:** We observed a significant positive association between serum cortisol levels and global cerebral Aβ deposition. Additionally, cortisol levels exhibited significant inverse associations with cerebral glucose metabolism in the AD-signature region (AD-CM) and hippocampal volume (HV). Mediation analysis showed Aβ deposition partially mediated the cortisol and AD-CM association, and fully mediated the cortisol and HV association. Cortisol levels were significantly negatively associated with global cognition. Furthermore, in a double mediation analysis, cortisol levels were linked to cognitive impairment through increased Aβ deposition and subsequent neurodegeneration, including reduced AD-CM and HV, and also through an Aβ-independent pathway. **Interpretation:** Our findings suggest that elevated serum cortisol may contribute to cognitive impairment through both Aβ-dependent and Aβ-independent brain injury in older adults.

P148- BRAIN HEALTH SERVICES FOR THE PREVENTION OF DEMENTIA: EVIDENCE FROM PILOT EXPERIENCES. F. Ribaldi[1] , G.B. Frisoni[1] *(1. UNIGE - Geneva (Switzerland))*

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Background: The European Task Force for Brain Health Services for the prevention of dementia (dBHS) has developed a framework for the evidence-based and ethical secondary prevention of dementia in individuals with intact cognition who are at high risk. dBHS has four primary missions: risk assessment, risk communication, personalized risk reduction, and cognitive enhancement. Recommendations for implementing these four pillars have been published, and pilot BHS projects are underway in Stockholm, Scotland, Geneva, Amsterdam, Monza, Barcelona, Cologne, Paris, and New York. The insights gained from these pilot experiences will facilitate progress toward clinical deployment. **Methods:** We reviewed the activities of each pilot experience, including those that have transitioned into clinical practice and those still confined to research due to high costs, limited feasibility, or insufficient evidence. **Results:** Risk assessment includes evaluating 12 lifestyle risk factors, APOE ε4 status, Alzheimer's pathology (amyloid, tau), neurodegeneration, and cerebrovascular disease (via MRI). While lifestyle risk factors and APOE ε4 assessments are increasingly integrated into clinical settings, biological risk assessments largely remain within research projects. Risk communication should involve visual aids explained in plain language, ideally through digital tools, though currently, this is mostly limited to research. In contrast, in-person, semi-structured disclosure of dementia risks is now common in academic memory clinics. Lifestyle risk reduction is limited by high costs and need for specialized personnel. Initiatives such as MET-FINGER and Geneva's multidomain biological intervention (including multivitamins, tramiprosate, Souvenaid, probiotics) are progressing but remain in the research stage. Cognitive enhancement includes non-invasive brain stimulation (NIBS) and cognitive training. While evidence for cognitive training is growing, NIBS techniques require further research before clinical implementation. **Conclusion:** To successfully integrate an optimal dBHS patient journey into clinical practice, more research, technological development, and resource allocation are necessary. The development and widespread adoption of dBHS will help fight dementia and reduce the burden on patients, their families, and society. **Keywords:** Prevention; Brain Health Services; Dementia.

P149- DE NOVO DESIGNED TFR1 BINDING PEPTIDE TO SHUTTLE ANTIBODY THERAPEUTICS ACROSS BLOOD BRAIN BARRIER. H. Wu[1], Y. Qiu[1], F. Sheng[1], Y. Wu[1] *(1. ChainGen Bio - Shanghai (China))*

Background: Antibody clearing Aβ plaque has been approved for Alzheimer's Disease, but its efficacy is limited by poor penetration across blood brain barrier. TfR1 binding shuttles including antibodies, antibody fragments, single domain antibodies have been widely explored to enhance delivery of therapeutics into the brain. Trontinemab, taking advantage of a Fab shuttle, is the first brain penetrating antibody entering clinic and shows promise in early clinical trials. However, the existing shuttles suffer from large sizes, poor protein expressions and solely rely on N-terminal complementary determining regions for TfR1 binding. Here we reported an de novo designed TfR1 binding peptide with small size, differentiated paratope, optimal protein expression and efficient delivery of gantenerumab across the blood brain barrier. **Methods:** Over 200,000 TfR1 binding peptides were de novo designed by Alphafold 2 and screened by yeast display. A lead peptide of ~70aa was selected and expressed alone or as gantenerumab-peptide fusion protein. The binding epitope and paratope was determined by HDX-MS and validated by ELISA. The brain transport capability of gantenerumab-peptide fusion protein was tested in vitro by transcytosis assay and in vivo in human TfR1 transgenic model. **Results:** The lead peptide showed single-digit nM binding affinity with a desired "fast-on,fast off" kinetics to hTfR1. The peptide bound with its C-terminal to the apical domain of human TfR1 receptor in a unique beta extension conformation. The gantenerumab-peptide fusion protein was expressed at higher titer than trontinemab. The fusion protein retained hTfR1 binding affinity and the ability to bind and clear human Aβ plaque. In a hTfR1 transgenic mouse model, intravenous injected gantenerumab-peptide fusion protein showed substantial parenchymal delivery. The delivery efficiency of gantenerumab-peptide fusion protein is similar to that of trontinemab. **Conclusion:** De novo designed TfR1 binding peptide offers an alternative approach of shuttling antibody therapeutics across blood brain barrier. Peptide is smaller, easy for protein engineering, flexible in epitope/paratope design, and shows optimal developability and superior parenchymal delivery efficiency. It may develop into a a platform technology for drug delivery into the brain. **Keywords:** De novo design, peptide, TfR1, blood brain barrier. **Disclosures:** HW, YQ, FS and YW are employees and receive compensation and stock options from ChainGen Bio. The authors declared no competing interests.

P150- TAU PET MEASURES OPTIMIZED FOR DETECTING TREATMENT EFFECTS ON TAU SPREAD IN ALZHEIMER DISEASE. J. Wong[1], T. Wang[2], R. Datta[2], D. Henley[3,4], H.C. Kolb[2], Z.S. Saad[2] *(1. Janssen Research & Development, LLC - Cambridge, Massachusetts (United States), 2. Janssen Research & Development, LLC - La Jolla, California (United States), 3. Janssen Research & Development, LLC - Titusville, New Jersey (United States), 4. Indiana University School of Medicine, Psychiatry - Indianapolis, Indiana (United Kingdom))*

Background: Many anti-tau therapies under investigation for Alzheimer disease (AD) are hypothesized to slow cognitive decline by inhibiting spread of pathological tau seeds that lead to eventual formation of paired helical filaments (PHF), neurofibrillary tangles (NFT) and neuronal death. Tau PET, which provides in vivo topographic quantification of PHF and NFT, has potential as a reasonably likely surrogate biomarker for demonstrating treatment effect on tau spread. While anti-tau therapies may reduce or halt transcellular spread of tau seeds to new brain regions, they may do so without impacting continued aggregation of tangles where they have already formed. Tau PET assessments using Standardized Uptake Value Ratio (SUVR) change over anatomically defined region of interests (ROIs) may be dominated by this continuing aggregation, thereby masking treatment effects on spread. The objective of this study is to describe two tau PET estimates optimized for detecting treatment effect on tau spread. **Methods:** In the first method, spatial spread is measured by subtracting the fraction of cortex with high uptake at the follow-up visit from the fraction of cortex with high uptake at baseline. SUVR threshold for high uptake is set uniformly across the brain at 1.2 for both Flortaucipir and MK6240 tracers. Those thresholds correspond to median+2 standard deviations (SD) of cortex-wide SUVR observed in tracer-matched cognitively normal amyloid-negative (CNTRL) cohorts. To reduce outlier effects, SD is estimated using median absolute deviation. The second method measures spread as the change in tau PET SUVR assessed over voxels without NFT evidence at baseline. This tau naïve ROI is a participant-specific composite consisting of the aggregate of cortical voxels where baseline SUVR is within 1 SD of the average SUVR in CNTRL cohorts. We examine the performance of these two methods in observational cohorts from ADNI (Flortaucipir) and Cerveau/AIBL (MK6240) in CNTRL, cognitively normal amyloid-positive (CN A+), and MCI A+ participants. **Results:** Using the spatial spread method, spread estimates produced comparable effect sizes to SUVR change measures amongst CN A+ and MCI A+ groups. While spread measures at higher SUVR thresholds may yield more pronounced differences between diagnostic categories, they may not be optimal for detecting treatment effects in participants with lower tau levels. Using the tau naïve ROI method, measurable annualized change in SUVR was detected in CN A+ and MCI A+, but not in CNTRL participants. Those changes were comparable in effect size to changes in anatomically defined ROIs. In A+ participants that would meet the intermediate tau PET inclusion criteria for the Phase 2 Autonomy study investigating posdinemab – a tau monoclonal antibody – in early AD [1], effects sizes for SUVR change in tau naïve ROI ranged from 0.76 to 1.2. In both methods, results were qualitatively consistent across PET tracers. **Conclusion:** Spatial spread and tau naïve ROI are methods optimized for detecting cortex-wide treatment related effects on tau spread and should be considered in addition to SUVR change measures from anatomically based ROIs to capture treatment effects on both aggregation and spread. **Keywords:** Alzheimer's disease, detection methods, tau PET, treatment effect. **Disclosures:** All authors are or were employees or contractors of Janssen Pharmaceuticals and may hold stock or stock options in Johnson & Johnson. **References:** Henley et al. Design, Population, and Lessons Learned from Screening for the Phase 2 Autonomy Trial of Posdinemab for Early Symptomatic Alzheimer's Disease. Presented at AD/PD 2024 Alzheimer's & Parkinson's Diseases Conference; March 5-9, 2024; Lisbon, Portugal.

P151- PREDICTION OF COGNITIVE OUTCOME AND PROGRESSION TO DEMENTIA USING POLYUNSATURATED FATTY ACIDS OMEGA6/3 RATIO. V. Andrade[1,2], L. Kleineidam[1,2], H. Wagner-Thelen[1], R. Campos[1], T. Ballarini[2,3], S. Egert[4], P. Martino-Adami[1], L. Weinhold[5], S. Guyonnet[6], B. Vellas[7], F. Jessen[3,8], M. Schmid[3,9], A. Schneider[2,3], M. Wagner[2,3], A. Ramirez[1,2] *(1. Division of Neurogenetics and Molecular Psychiatry, Department of Psychiatry and Psychotherapy. University of Cologne, Medical faculty - Köln (Germany), 2. Department of Neurodegenerative Diseases and Geriatric Psychiatry, University Hospital Bonn - Bonn (Germany), 3. DZNE - Bonn (Germany), 4. Department of Nutrition and Food Sciences, Nutritional Physiology, University of Bonn, Bonn (Germany), 5. Department of Medical Biometry, Informatics and Epidemiology, University Hospital Bonn - Bonn (Germany), 6. Centre d'Epidémiologie et de Recherche en santé des POPulations de Toulouse - Toulouse (France), 7. Gérontopôle & Department of Geriatric Internal Medicine at the Toulouse University Hospital - Toulouse (France), 8. Department of Psychiatry, Medical Faculty, University of Cologne, Cologne (Germany), 9. Department of Medical Biometry, Informatics and Epidemiology, University Hospital Bonn, Bonn (Germany))*

Background: Previous research reported the association between circulating Omega-3 polyunsaturated fatty acids (PUFA-ω3) in blood, cognitive performance and the risk of dementia and dementia of the Alzheimer's type (DAT) [1-3]. However, a large intervention trial supplementing Omega-3 found only a marginal improvement in cognitive performance after the supplementation [4-5]. Since PUFA metabolism shares the processing enzymes, we explored whether the balance between the two main families of PUFA, i.e., PUFA-ω3 and PUFA-ω6, might be associated with cognitive performance and progression to DAT. **Methods:** Two independent cohorts were used for this study: i) the primary care-derived cohort AgeCoDe (n=1378); ii) the Multidomain Alzheimer Preventive Trial (MAPT study) cohort (n=1679). PUFA levels were quantified in plasma from each cohort with previously reported methods. COX regressions and linear mixed models were applied to evaluate the effect of the PUFA ratio on cognitive decline and progression to dementia. **Results:** The PUFA-ω6/PUFA-ω3 ratio is associated with the risk of progressing to DAT in AgeCoDe. In MAPT, the improvement of this ratio is associated with a significant improvement in cognitive performance after PUFA-ω3 supplementation. Molecular analysis revealed that levels of PUFA-ω3 in blood modulate the methylation of genes coding for key desaturases of PUFA metabolism. However, this modulation has no impact on its effect in the risk of DAT. Finally, PUFA-ω6 shifts the preference of PUFA enzyme FADS1 for PUFA-ω6 precursors reducing the metabolism and protective effect of PUFA-ω3 precursors. **Conclusion:** Our data suggest that the balance between PUFA-ω6 and PUFA-ω3 is more relevant in predicting cognitive performance and the risk of progressing to DAT than each PUFA independently. Thus, keeping a healthy low-PUFA-ω6/high-PUFA-ω3 ratio offers a real alternative to protect against cognitive decline and progression to dementia. Herein, our data suggest that diet is the main mediator of this effect. Hence, future interventions should focus on modulating dietary PUFA consumption to keep a healthy ratio. **Keywords:** Alzheimer's disease, fatty acids, Omega3, Omega6, prevalent neurological disorders. **Disclosures:** No conflicts of interest. **References:** 1. Scarmeas, N., Anastasiou, C. A. & Yannakoulia, M. Nutrition and prevention of cognitive impairment. Lancet Neurol 17, 1006–1015 (2018). doi: 10.1016/S1474-4422(18)30338-7. 2. Lee, S. J. et al. Circulating metabolites and general cognitive ability and dementia: Evidence from 11 cohort studies. Alzheimer's & Dementia 14, 707–722 (2018). doi: 10.1016/j.jalz.2019.01.002. 3. Melo van Lent, D. et al. Eicosapentaenoic Acid Is Associated with Decreased Incidence of Alzheimer's Dementia in the Oldest Old. Nutrients 13, 461 (2021). doi: 10.3390/nu13020461. 4. Vellas, B. et al. MAPT STUDY: A MULTIDOMAIN APPROACH FOR PREVENTING ALZHEIMER'S DISEASE: DESIGN AND BASELINE DATA. J Prev Alzheimers Dis 1, 13–22 (2014). http://dx.doi.org/10.14283/jpad.2014.34. 5. Andrieu, S. et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. Lancet Neurol 16, 377–389 (2017). doi: 10.1016/S1474-4422(17)30040-6.

P152- MRI MONITORING OF ALZHEIMER DISEASE PATIENTS IN THE NEW ERA OF DISEASE-MODIFYING THERAPIES: A REAL-WORLD CASE STUDY. S. Napoli[1], C. Maes[2], R. Khan[2], A. Tanghe[2], S. Catuara Solarz[2], J. Claes[2], N.P. De Barros[2], D. Sima[2], W. Van Hecke[2], D. Smeets[2], A. Ribbens[2] *(1. Neurology and Infusion Center of New England - Foxborough (United States), 2. icometrix - Leuven (Belgium))*

Background: The use of anti-amyloid targeting therapies for Alzheimer's Disease requires repeated MRI scanning for safety monitoring, i.e. the assessment of amyloid-related imaging abnormalities (ARIA). **Methods:** We present a real-world case study and show how automated MRI quantification could support improved patient assessment. Post-hoc analysis was performed using icobrain aria, which quantifies relevant brain abnormalities and provides ARIA severity assessment based on the FDA safety label. **Results:** In November 2021, a 66-year old female diagnosed with dementia, was referred to a specialized neurology center. A full biomarker assessment including lumbar puncture and MRI confirmed the suspicion of Alzheimer's Disease. The patient had an MMSE of 26/30, and had the Apoe ε4/ε4 genotype. The patient showed interest in being treated with aducanumab, the currently available anti-amyloid targeting therapy, despite her higher risk profile. However, treatment was not initiated due to lack of reimbursement. By June 2022, the patient showed clinical worsening, confirmed by the MMSE dropping to 22/30. Thus, the patient was enrolled in a free-access aducanumab program. By January 2023, she developed occipital headaches and visual problems. The headache resolved, but vision in the left eye was severely limited. An MRI was performed, and the radiological report indicated diffuse sulcal FLAIR bright signal within the posterior parietal-occipital sulci, and new sulcal FLAIR bright signals within at least one left frontal sulcus. It was unclear if these findings were new, or the long-term evolution of previous FLAIR signal abnormalities. Although these findings are suggestive of ARIA-E, the report did not mention ARIA. The SWI image for the assessment of ARIA-H was not discussed. icobrain aria confirmed the presence of moderate ARIA-E (longest axis = 83mm), and also indicated moderate ARIA-H (2 microhemorrhages and 2 areas of superficial siderosis). Treatment was suspended and monthly MRI scans were performed to track the evolution of ARIA. By February 2023, the radiological report indicated that the occipital ARIA-E had resolved, while a new region with ARIA-E was noted in left frontal regions. These results were corroborated by the icobrain aria report, which showed an overall reduction of 21.7ml in ARIA-E, including an increase of 3.5ml ARIA-E in left frontal regions. ARIA-H was not mentioned in the radiological report.

The radiological report from an MRI in April 2023 indicated that the hyperintense FLAIR signal (ARIA-E) had resolved, and one area of ARIA-H was detected. icobrain aria generally agreed with the radiological report, although it indicated that resolution of ARIA-E was incomplete, as three regions of ARIA-E were identified. As the patient became clinically asymptomatic by April 2023, treatment was resumed in May 2023, when MMSE was 23/30. **Conclusion:** Safety monitoring of patients with Alzheimer's Disease on anti-amyloid targeting therapies can be uniquely challenging. Considering the novelty of ARIA, radiological reading may be incomplete and/or lack standardization. This use case demonstrates the utility of icobrain aria supporting radiologists in the detection and quantification of ARIA findings, providing more confidence in clinical decision-making for the neurologists, ultimately contributing to optimized patient care. **Keywords:** ARIA, safety monitoring, real-world, radiological reporting. **Disclosures:** Dr. Napoli has received personal compensation for serving as a Consultant for biogen, genentech, genzyme, bristol myers and serono. Dr. Napoli has received personal compensation for serving on a Speakers Bureau for biogen, bristol myers, serono and genzyme. Dr. Napoli has received personal compensation for serving as an Expert Witness for vaccine injury. C. Maes, A. Tanghe, S. Catuara Solarz, J. Claes, N.P. de Barros, D. Sima, W. Van Hecke, D. Smeets and A. Ribbens are employees of icometrix.

P154- MILD BEHAVIORAL IMPAIRMENT: BUILDING THE KILLIFISH-MOUSE-HUMAN PIPELINE IN THE INSPIRE-T COHORT. E. Gonzalez-Bautista[1,2,3], B. Guiard[3,4], I. Ader[3,5], S. Guyonnet[2,3], J. Shourick[6], A. De Mauleon[1], E. Dubus[1], M. Mommeja[1], J.P. Pradere[3,5], M. Soto[1,2,3] *(1. Research and Clinical Alzheimer's Disease Center, CMRR, CHU Toulouse, Toulouse (France), 2. Maintain Aging Research team, CERPOP, Inserm, Université Paul Sabatier, Toulouse (France), 3. Institut Hospitalo-Universitaire HealthAge, IHU HealthAge, Inserm, CHU Toulouse, Toulouse (France), 4. Equipe REMEMBeR. Centre de Recherches sur la Cognition Animale, CRCA, Univ. P. Sabatier. Toulouse (France), 5. Institut RESTORE - UMR 1301- Inserm/5070-CNRS/EFS/ Université Paul Sabatier, Toulouse (France), 6. Maintain Aging Research team, CERPOP, Inserm, Université Paul Sabatier, Toulouse (France))*

Background: The MBI are persistent late-onset neuropsychiatric symptoms (NPS) in dementia-free people, concomitant/prodromal to cognitive impairment. MBI represents a high-risk condition for accelerated cognitive decline and a dementia predictor. Furthermore, NPS are often the most disturbing aspect of Alzheimer's disease (AD) and other dementias, yet with few drugs approved for their management. The MBI-C clinical scale has been validated for diagnosing MBI assessing five behavioral domains, i.e.,emotional dysregulation (mood or anxiety symptoms). The pathophysiology of MBI is not fully understood. We recently found that MBI was associated with metabolic/inflammatory disruptions in humans [1]. These associations suggest that the hallmarks of aging can play a role in the development or progression of these pre-dementia conditions. Our objective is to study the pathophysiology of MBI from the perspective of Geroscience using translational research. **Methods:** The INSPIRE-T cohort methodology has been published elsewhere clinicaltrials.gov NCT04224038. [2] This cohort is composed of 1000 subjects aged 20 to 102, followed annually since 2019. A composite cognitive score and the MBI-C scale will be evaluated from October 2024 and annually (self- and hetero-assessment). We will include all participants, regardless of age, to study the biology of aging across the life course; excluding participants diagnosed with dementia or psychiatric illness. In humans, we will address senescence via circulating SASP (plasma) to facilitate translation into clinical practice: GDF15, TNFR1, IL-15, IL-6, ICAM1, VEGF-A, GFAP, and metabolism using IGF1 and the HOMA index. Blood samples will be obtained yearly. We will analyze whether baseline levels of SASP/metabolic biomarkers are related to the MBI incidence and time evolution (moderated or not by cognitive function) using mixed effects models. Translational study T1. Using new cohorts of mice and fish, the MBI-C scale will be "translated" and validated in mice and killifish. We will use equivalent items between MBI-C and existing behavioral tests in mice and killifish. E.g.,anxiety in mice will be assessed using the elevated cross maze based on mice's innate aversion to empty spaces; and in killifish by the unknown tank diving test. We will validate the MBI-C in mice using the Alzheimer's model (Tg2576) and in killifish via their AD-type neurodegeneration experienced at age 4-6 months. This validated animal score will allow us to test MBI-C associations with SASP/metabolic biomarkers by measuring and mapping the same SASP/metabolic proteins in mice and killifish as in humans, plus further molecular tissue characterization. Finally, we will test the effect of pharmacological (senolytic) and non-pharmacological (caloric restriction and physical activity) interventions targeting senescence/metabolism on these preclinical models of MBI. **Expected results:** • Proof of concept on the implication of cellular senescence and metabolism on MBI pathophysiology. • Identify a battery of biomarkers to support the MBI diagnostic and monitoring response to interventions. • Test innovative pharmacological and non-pharmacological management options for MBI. **Conclusion:** The use of translational Geroscience research can be useful to bridge the gap of the lack of pharmacological and non-pharmacological management options for MBI, notably opening the door to molecules different from currently available psychotropic drugs and thus reducing their serious adverse effects [3]. **Keywords:** Mild behavioral impairment, agitation, mood, pre-dementia, translational research, Geroscience. **Disclosures:** EGB declares no conflict of interest. MS has served on advisory boards/consultancies Acadia, Otsuka, Avanir, Medesis Pharma, Servier, Eisai, Roche, Biogen, Lilly and Ethypharm. **References:** 1. Gonzalez-Bautista E, et al. Alzheimer's Dement. 2024;in Press(ADJ-D-23-01417). 2. Guyonnet S, et al. J frailty aging. 2021;10(2):110-120. doi:10.14283/JFA.2020.38. 3. Soto M, Rosenberg P, Ballard C, et al. J Prev Alzheimer's Dis. 2024;11(1):56-64. doi:10.14283/jpad.2023.125.

P155- ADDITION-MCI: A CLINICAL TRIAL TO FULLY EXCHANGE THE BLOOD PLASMA OF OLDER COGNITIVELY IMPAIRED INDIVIDUALS WITH YOUNG DONOR PLASMA. S. Nygaard[1,2], L.N. Karim[3], A. Engvik[4], H. Ihle-Hansen[5], P. Holland[1], A. Søraas[1] *(1. Dept. of Microbiology, Oslo University Hospital - Oslo (Norway), 2. Dept. of Acute Medicine, Oslo University Hospital - Oslo (Norway), 3. Dept. of Immunology and Transfusion Medicine, Oslo University Hospital - Oslo (Norway), 4. Dept. of Endocrinology, Obesity and Preventive Medicine, Oslo University Hospital - Oslo (Norway), 5. Dept of Medicine, Bærum Hospital, Vestre Viken Hospital Trust - Drammen (Norway))*

Background: The age of the circulating blood influences aging processes within organs, demonstrated by connecting the circulatory systems of old and young rodents (heterochronic

parabiosis). Our recent findings show that epigenetic aging of human cells is influenced by the age of the circulating environment in vivo, suggesting that these effects on aging processes may also apply to humans [1]. **Methods:** Our clinical trial will emulate heterochronic parabiosis in humans; removing an older individual's blood plasma and replacing it with young healthy donor plasma. One treatment cycle involves 10 plasma exchange treatments of 1.8L each using the Spectra Optia Apheresis System, performed every 2-3 days. **Results:** Our first patient successfully completed one treatment cycle without any severe adverse events or procedure challenges. **Conclusion:** The assumption is that rejuvenation of the circulating environment stops or reverses aging processes that are driving the progression of mild cognitive impariment toward Alzheimer's disease. **Keywords:** Alzheimer's disease, Plasma exchange, Mild cognitive imparment, Heterochronic parabiosis. **Disclosures:** The authors declare no conflicts of interest. **References:** 1. Holland P, Istre M, Ali MM, Gedde-Dahl T, Buechner J, Wildhagen M, et al. Epigenetic aging of human blood cells is influenced by the age of the host body. Aging Cell. 2024 Mar 4;e14112.

P156- EXPANDING IMPACT-AD TO INCLUDE INTERNATIONAL TRAINEES: A PILOT PROGRAM. M.D. Mastrolorenzo[1], R. Raman[1], J. Grill[2], M. Carrillo[3], H. Snyder[3] *(1. Alzheimer's Therapeutic Research Institute (ATRI), University of Southern California - San Diego, CA (United States), 2. Institute of Memory Impairment and Neurological Disorders, Department of Psychiatry & Human Behavior, Department of Neurobiology & Behavior, University of California at Irvine - Irvine, CA (United States), 3. Alzheimer's Association - Chicago, IL (United States))*

Background: The Institute on Methods and Protocols for Advancement of Clinical Trials in Alzheimer's Disease Related Dementias (AD/ADRD) (IMPACT-AD) [1] is a novel multi-disciplinary training program for individuals seeking expertise in designing and conducting these studies. The mission of IMPACT-AD is to train and diversify the next generation of AD/ADRD clinical trialists. IMPACT-AD leverages the interdisciplinary expertise of the Alzheimer's Clinical Trials Consortium (ACTC), the NIA-funded AD/ADRD clinical trials network, and offers a Fellowship Track for future AD/ADRD clinical trial principal investigators. In 2023, IMPACT-AD, originally open only to investigators at institutions in the United States, launched a partnership with the Alzheimer's Association to establish a pilot international program in this Fellowship Track. The purpose of this program was to identify and train scientists outside of the United States who were interested in building careers in AD/ADRD clinical trials and establishing clinical trials infrastructure in their respective countries. **Methods:** This pilot program was open to researchers funded by the Alzheimer's Association and global programs such as the Global Brain Health Initiative (GBHI). Applications from international investigators were reviewed using criteria identical to those for US-based applicants. After completion of the in-person program, trainees were asked their satisfaction with the course, with responses ranging from "not satisfied" to "very satisfied". Other metrics of evaluation for the pilot program included a self-evaluation of the value of participation to their research and patient care in their careers. **Results:** Across two years of this pilot program, eight investigators participated in IMPACT-AD's Fellowship Track representing seven countries outside of the United States across four continents. IMPACT-AD international alumni-scholars included investigators from North America (Canada), South America (Brazil, Argentina), Africa (Nigeria), Europe (Spain), and Asia (South Korea, India). Of these scholars, five (63%) were female and one (13%) indicated being first in their families to attend college. Of the 7 (88%) international alumni-scholars who responded, all reported being "very satisfied" with the course. They unanimously reported that the course increased their knowledge of clinical trials; that the information was relevant to and would improve their practice of medicine; and that the course content was relevant to trials conducted in their country, with a few areas that may require specific tailoring (e.g., recruitment, IRB issues, availability of technology). **Conclusion:** Data from this pilot program demonstrate the feasibility of extending a US-centric training program to an international community of investigators. Preliminary data support the utility of this unique training approach to building a global network of AD/ADRD clinical trialists and enhancing the global AD/ADRD research capacity. **Acknowledgements:** IMPACT-AD is supported by National Institute on Aging (NIA) grant numbers R25AG076392 and U13AG067696, Alzheimer's Clinical Trial Consortium (ACTC) NIA grant number U24AG057437, and the Alzheimer's Association (grant number SG-20-693744). We thank Laurie Ryan, PhD, and Kristina McLinden, PhD, of the National Institute on Aging (NIA) for their key contributions in leadership and scientific guidance to IMPACT-AD. **Keywords:** Alzheimer's Disease, clinical trials, training and education, capacity-building. **References:** 1. Berkness, T., Carrillo, M.C., Sperling, R. et al. The Institute on Methods and Protocols for Advancement of Clinical Trials in ADRD (IMPACT-AD): A Novel Clinical Trials Training Program. J Prev Alzheimer's Dis (2021). https://doi.org/10.14283/jpad.2021.12. **Disclosures:** Margaret D. Mastrolorenzo receives research support from the NIA and the Alzheimer's Association. Maria C. Carrillo, PhD, and Heather Snyder, PhD, are full-time employees of the Alzheimer's Association, which is a funder of the IMPACT-AD course. Joshua Grill, PhD, receives research support from the NIA, Alzheimer's Association, BrightFocus Foundation, Eli Lilly, Biogen, Genentech, and Eisai; and personal editorial service fees from Alzheimer's & Dementia. Rema Raman, PhD, receives research support from the NIA, Alzheimer's Association, American Heart Association, and Eisai.

P157- IMPLANTABLE DEVICE FOR INTRATHECAL PSEUDODELIVERY OF IMMUNOTHERAPIES: PRECLINICAL TESTING OF A PROTOTYPE FOR HUMANS. E. Perez-Martin[1], M. Rodiguez-Cañon[1], G. Alvarez[1], C. Prado[1], C. Tomas-Zapico[2,3], M. Menendez-Gonzalez[2,3,4] *(1. Neuroscience Innovative Technologies - Llanera (Spain), 2. Universidad de Oviedo - Oviedo (Spain), 3. Instituto de Investigación Sanitaria del Principado de Asturias - Oviedo (Spain), 4. Hospital Universitario Central de Asturias - Oviedo (Spain))*

Introduction: Immunotherapy for neurodegenerative diseases often induces severe side effects due to the interaction of mAb with the immune and nervous systems. We introduce a novel platform for administering mAb, based on an intrathecal device enabling clearance of target molecules from the CSF without releasing mAb to the organism (pseudodelivery) that may provide important advantages in terms of efficacy and safety [1, 2]. This pilot non-GLP study aims to evaluate the feasibility and safety of implanting a prototype for humans in a porcine model. **Methods:** We designed and manufactured a fully implantable medical device according to regulations for humans (class III device). The pumpless device comprises a tricameral subcutaneous reservoir with three independent ports

and an intrathecal catheter, creating a system for continuous CSF flow. Seven female pigs were randomly allocated into three experimental groups: implanted with the device containing solutions of mAb (n=3) or artificial CSF (n=3), and a naïve control (n=1). The surgery involved inserting a catheter via lumbar puncture at the L4-L5 level and advancing it to T7-T8. The reservoir was connected to the catheter and implanted in a subcutaneous pocket. Solutions were exchanged every 4 weeks percutaneously. Animals were monitored daily for behavior; while body weight, temperature, and hematology analyses were performed every two weeks until termination at week 13. **Results:** At baseline, all animals exhibited a healthy state with a mean body weight of 61.92±1.03, and a slight deviation in some hematological parameters that normalized after one month. Body weight remained stable over time, with a minimal reduction in two animals (<15%). The main complications included pain, slight gait loss, and subcutaneous pocket infections. **Conclusion:** Implantation of a medical device in regulatory compliance of class III medical device for intrathecal pseudodelivery of immunotherapies is feasible and safe in pigs, with surgery-related infections and distress as the main complications. Refining the surgery protocol and further research are needed to ascertain device functionality and efficacy before progressing to clinical development. Since this is a combination therapy, partnerships with pharmaceutical companies interested in this therapeutic approach are necessary. **References:** 1. Menendez-Gonzalez M, Tamba BI, Leclere M, Mabrouk M, Schreiner TG, Ciobanu R, Cristina TZ. Intrathecal Pseudodelivery of Drugs in the Therapy of Neurodegenerative Diseases: Rationale, Basis and Potential Applications. Pharmaceutics. 2023 Feb 25;15(3):768. doi: 10.3390/pharmaceutics15030768; 2. Coto-Vilcapoma MA, Castilla-Silgado J, Fernández-García B, Pinto-Hernández P, Cipriani R, Capetillo-Zarate E, Menéndez-González M, Álvarez-Vega M, Tomás-Zapico C. New, Fully Implantable Device for Selective Clearance of CSF-Target Molecules: Proof of Concept in a Murine Model of Alzheimer's Disease. Int J Mol Sci. 2022 Aug 17;23(16):9256. doi: 10.3390/ijms23169256.

P158- ONESTX-01, A POTENT INHIBITOR OF STEROID SULPHATASE (STS), THAT RESTORES NEURON CHOLINERGIC ACTIVITY AND DECREASES COGNITIVE IMPAIRMENT: DESIGN OF A PHASE IIA CLINICAL STUDY. V. Andrés-Simón[1], J. Valle-Galisteo[2], J.A. Fernández-Cabrera[3], A. Ramos-Pozo[2], J.M. Hernández-Curiel[3], S. Gavaldá-Martín[1], C. García-Gutierrez[2], I. Sánchez Romero[3], M. Pérez-Jiménez[2], E. Rodríguez Sandoval[3], A. Aires-Trapote[1], M.J. Muñoz-Ruíz[2], A.M. Carrión[3], A. Cebolla-Ramírez[1] *(1. Olavide Neuron STX SL - Seville (Spain), 2. Universidad Pablo de Olavide, Centro Andaluz de Biología del Desarrollo (CABD), CSIC, JA - Seville (Spain), 3. Universidad Pablo de Olavide, Department of Physiology, Anatomy and Cellular Biology - Seville (Spain))*

Background: ONESTX-01 (Irosustat/STX64) is a small molecule that inhibits steroid sulfatase (STS), which showed a good safety and tolerability profile in patients with cancer in Phase I-II clinical trials. ONESTX-01 activity produced an increase in sulfated steroids. Some of them are called neurosteroids for its role in Central Nervous System (CNS). The administration of ONESTX-01 increased the ratio of sulfated/free steroids which expanded the lifespan of C. elegans, decreased the b-amyloid accumulation and recovered memory in Alzheimer Disease's (AD) models (mice) [1]. The drug appeared to act on the biology of aging. According to this idea, old mice showing cognitive impairment, treated up to 6 months with ONESTX-01, showed histological and molecular changes compatible with neuroprotection mechanism, such as increase of microglial response, decrease of inflammation markers, and improvement in cognition. We investigated whether the activity of ONESTX-01 on the cholinergic neuron was involved in the dependent cognition restoration in aged or in the Alzheimer's models. **Methods:** On the one side, we have studied the cholinergic response in C. elegans using aldicarb, an acetylcholinesterase inhibitor, which generate a time-dependent paralysis due to the excess of acetylcholine. Then paralysis time depend on the amount of acetylcholine. On the other hand, to investigate the cholinergic activity in a mammal model, we tested the anti-amnesic effects of ONESTX-01 in a scopolamine-induced amnesia rat model. Animals were orally treated with ONESTX-01 (1 and 4mg/Kg) for 16 consecutive days before receiving scopolamine administration. **Results:** In C elegans, the simultaneous treatment with ONESTX-01 and aldicarb produced an earlier paralysis than aldicarb treatment alone, indicating a synergic cholinergic response. In the rat model of amnesia induced by acetylcholine deficiency, chronic oral administration of ONESTX-01 was effective in the prevention of memory impairments induced by acute administration of scopolamine, similarly to donepezil treatment. Our results suggest that the mechanism of action is due to changes in neuron functions and/or neuroprotection. **Conclusion:** ONESTX-01 oral treatment reduced symptoms in neurodegenerative diseases and decreased the cognitive impairment associated to aging in different "in vivo" models. Histological, genetic, pharmacological, and behavioural analysis pointed out that ONESTX-01 treatment increased cholinergic activity in different animal models, which may underlie the observed beneficial effect on neurodegeneration. A Phase IIa clinical trial, double-blind, multicenter, randomized, parallel group, placebo-controlled to assess the safety, tolerability and clinical benefit of treatment with ONESTX-01 in subjects mild to moderate AD that have abandoned anti-acetylcholinesterase treatments is being planned. **Keywords:** cholinergic activity, neuroprotection, clinical trial phase. **Disclosures:** A. Cebolla, A.M Carrión, M.J Muñoz, and M. Pérez-Jiménez have ONESTX company shares. The rest of authors declare no competing interests. **References:** 1. Pérez-Jiménez M. et al. Nature Communications 2021. https://doi.org/10.1038/s41467-020-20269-y.

P159- NOVEL CYCLODEXTRINS WITH REDUCED CELLULAR TOXICITY: APPLICATION IN TREATING PATHOLOGIC TAU-RELATED LIPID ACCUMULATIONS. J.Y. Lee[1], H. Kim[2], S.A. Park[1,3,4] *(1. Lab of Neurodegenerative Dementia, Department of Anatomy, Ajou University School of Medicine - Suwon (Korea, Republic of), 2. Renatus - Daejeon (Korea, Republic of), 3. Neuroscience Graduate Program, Department of Biomedical Sciences, Ajou University Graduate School of Medicine, - Suwon (Korea, Republic of), 4. Department of Neurology, Ajou University School of Medicine - Suwon (Korea, Republic of))*

Background: Alzheimer's disease (AD) and related tauopathies are characterized by the increased accumulation of hyperphosphorylated tau proteins in neurons. Remarkably, it has been proposed that dysregulated intracellular cholesterol levels may contribute to the aggravation of tau pathology, underscoring the potential significance of cholesterol regulation in retarding the advancement of AD. 2-hydroxypropyl-β-cyclodextrin (HPβCD), a cyclic oligosaccharide derivative, is recognized for its ability to facilitate cholesterol efflux, and

its use in Niemann-Pick Type C disease, a lysosomal storage disease characterized by lipid accumulation in lysosome, has been granted Orphan Drug Designation by the U.S. Food and Drug Administration. Currently, its potential application in AD is under investigation (NCT05607615). However, HPβCD has been associated with ototoxicity, particularly at high doses or prolonged exposure, and its narrow therapeutic window is attributed to the high dose requirement for efficacy. Herein, we delineate a novel synthetic cyclodextrin, RN005, which mediates cellular cholesterol efflux with less toxicity compared to HPβCD. **Methods:** N2a-tau 0N4R P301S stable cell line, transiently overexpression SH-SY5Y cells and primary neurons were used for the experiment. Neutral lipid and cholesterol levels were assessed using HCS LipidTOX and Filipin III staining. Cell viability was checked by trypan blue staining and MTT assay. Transcripts related to a lipid or cholesterol regulation were quantified via RT-qPCR. The changes in tau pathology were validated through western blot, immunocytochemistry, and aggregation assay, etc. **Results:** The overexpression of tau 2N4R P301S significantly heightened both neutral lipid and cholesterol signals. HPβCD and RN005 reduced intracellular lipid levels in SH-SY5Y and N2a cells in a dose-dependent manner. On cell viability assay, RN005 exhibited a significantly lower toxicity than HPβCD. Whereas both cyclodextrins reversed intracellular lipid accumulation, they also induced distinctive mRNA expression profiles in genes associated with cholesterol metabolism. These findings suggest that they have differential modes of action in modulating lipid levels, which will be further investigated. In terms of tau pathology, both cyclodextrins reduced tau spreading and uptake when conditioned medium from N2a cells treated with tau K18 preformed fibril was supplied to recipient cells. **Conclusion:** The newly introduced agent, RN005, effectively mitigated the intracellular cholesterol levels, comparable to the existing drug, HPβCD, in cell models with pathologic tau 2N4R P301S overexpression. Moreover, compared to HPβCD, RN005 demonstrated reduced cytotoxicity, suggesting its potential to minimize ototoxicity and thereby widen the therapeutic window. This benefit suggests that RN005 can be a drug of choice as a candidate for diminishing lipid accumulations in tauopathy. Further investigation is needed to determine to what extent cholesterol-lowering modulation would be effective in improving and preventing tau pathology in vivo and in humans. **Keywords:** Alzheimer's disease, tauopathy, lipid accumulation. **Disclosures:** SAP is the scientific advisor of Renatus Inc. HK is the CEO of Renatus and an inventor of the RN005. SAP received the grants from NRF of Korean government (2019R1A5A2026045 and 2022R1A2C1092672) and Hospital-based Business Innovation Center of Ajou University, Korea. The authors have disclosed no conflicts of interest.

P160- ENHANCED IMAGING TECHNIQUES FOR ARIA DETECTION AND TREATMENT EFFICACY MONITORING IN LECANEMAB THERAPY FOR ALZHEIMER'S DISEASE.

J.P.N. Okafor[1], J. Stefanko[1], H. Shimony[1], A. Mccullough[1], N. Jana[1], N. Jospeh-Mathurin[1], S. Jarman[1], E. Knopp[2], T. Benzinger[1] *(1. Washington University School of Medicine - Saint Louis (United States), 2. Hyperfine Inc. - Guilford (United States))*

Background: Alzheimer's disease (AD) stands as a formidable challenge in modern healthcare. While current immunotherapy directed at beta-amyloid (Aβ) signifies a notable stride forward, it may bring along potential complications, including amyloid-related imaging abnormalities (ARIA). Monitoring ARIA through high-field MRI encounters practical obstacles, compounded by regulatory requirements for frequent MRI surveillance. This investigation delves into the incorporation of a portable ultra-low field MRI into AD patient monitoring during immunotherapy, aiming to refine ARIA detection, streamline workflow, and enhance treatment outcomes.Alzheimer's disease (AD) stands as a formidable challenge in modern healthcare. While current immunotherapy directed at beta-amyloid (Aβ) signifies a notable stride forward, it may bring along potential complications, including amyloid-related imaging abnormalities (ARIA). Monitoring ARIA through high-field MRI encounters practical obstacles, compounded by regulatory requirements for frequent MRI surveillance. This investigation delves into the incorporation of a portable ultra-low field MRI into AD patient monitoring during immunotherapy, aiming to refine ARIA detection, streamline workflow, and enhance treatment outcomes. **Methods:** This prospective observational study recruits participants with mild cognitive decline from esteemed neuroclinics. Baseline pre-lecanemab therapy utilizing a 3T MRI serves as a reference for subsequent assessments. Participants undergo Hyperfine Swoop MRI scans at 0.064 tesla alongside their baseline and subsequent sessions, covering T1-weighted, T2-weighted, FLAIR, and DWI-ADC sequences. Data comparison with high-field images evaluates ARIA-E detection reliability, while workflow improvement is also assessed. Monitoring extends for 12 months post-imaging within the lecanemab clinic, allowing real-time treatment response evaluation. Approximately 50 scans annually ensure comprehensive neuroimaging monitoring throughout treatment. This prospective observational study recruits participants with mild cognitive decline from esteemed neuroclinics. Baseline pre-lecanemab therapy utilizing a 3T MRI serves as a reference for subsequent assessments. Participants undergo Hyperfine Swoop MRI scans at 0.064 tesla alongside their baseline and subsequent sessions, covering T1-weighted, T2-weighted, FLAIR, and DWI-ADC sequences. Data comparison with high-field images evaluates ARIA-E detection reliability, while workflow improvement is also assessed. Monitoring extends for 12 months after the initial clinic visit, enabling real-time treatment response evaluation. Each participant will undergo ~5 paired imaging visits, according to the therapy FDA label. **Data analysis plan:** This study aims to compare the efficacy of longitudinal imaging sessions conducted at both high-field and low-field strengths in detecting and assessing moderate and severe ARIA-E (edema). A randomized, blinded assessment methodology will be employed to analyze discrepancies in radiologist evaluations and treatment strategies across different field strengths. Additionally, the enhancement of patient imaging workflow will be evaluated through a comprehensive survey. **Discussion:** The Hyperfine Swoop MRI, distinguished by its portability and accessibility, emerges as a promising and cost-effective alternative to the conventional 3T MRI, offering the added advantage of workflow optimization. However, further investigation is warranted to validate these advantages in larger cohorts and ascertain their long-term reliability. This study underscores the potential of innovative imaging technologies in advancing patient care and monitoring neurodegenerative conditions, ultimately fostering a more equitable framework for healthcare delivery. **Reference:** Alzheimer's Association. 2023 Alzheimer's disease facts and figures. Alzheimer's & Dementia. 2023;19(4). doi:https://doi.org/10.1002/alz.13016; DeTure MA, Dickson DW. The Neuropathological Diagnosis of Alzheimer's Disease. Molecular Neurodegeneration.

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P161- CRISPR-CAS9-MEDIATED UPREGULATION OF MELATONIN RECEPTOR 1 ATTENUATES COGNITIVE IMPAIRMENT IN ALZHEIMER'S DISEASE. J. Kim[1]
(1. Dongguk University - Seoul (Korea, Republic of))

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the accumulation of neurotoxic beta-amyloid (Aβ) in the brain. Recent research has highlighted the association between melatonin receptors and both aging and AD, with receptor expression decreasing as the disease progresses. This study explores a novel therapeutic approach for AD by investigating the potential of overexpressing melatonin receptors to mimic melatonin's beneficial effects and alleviate AD symptoms. **Methods:** The research employed a cutting-edge approach utilizing a Cas9 activator to upregulate the type 1 melatonin receptor (Mt1) in vivo in the brain. This innovative strategy aimed to activate the endogenous Mt1 gene efficiently. The study was conducted using 5xFAD AD mouse models to evaluate the effects of Mt1 activation on various AD-related parameters. **Results:** The stuy yielded several significant findings: Gene Activation: The Cas9 activator successfully and efficiently activated the endogenous Mt1 gene in the brain. Anti-amyloidogenic and Anti-inflammatory Effects: Activation of Mt1 via Cas9 activators demonstrated modulation of anti-amyloidogenic and anti-inflammatory roles in the brains of 5xFAD AD mice. Cognitive Improvement: The activation of Mt1 using the CRISPR/Cas9 activator resulted in improved cognitive function in the AD mouse model. **Conclusion:** This research provides compelling evidence for the therapeutic potential of melatonin receptor activation via CRISPR/Cas9 activator technology in the treatment of Alzheimer's disease. The successful activation of Mt1 and its subsequent effects on amyloid pathology, inflammation, and cognitive function demonstrate a promising new avenue for AD therapeutics. These findings contribute significantly to the field of neurodegenerative disease research and open up possibilities for novel gene therapy approaches in AD treatment. **Keywords:** Alzheimer's disease, melatonin receptors, CRISPR/Cas9 activator, gene therapy, beta-amyloid, neuroinflammation, cognitive function, 5xFAD mouse model. **Disclosures:** The authors declared no competing interests. **References:** Park et al., J Pineal Res . 2022 Apr;72(3):e12787. doi: 10.1111/jpi.12787.

LP078- BRAIN SHUTTLES TO NOVEL RECEPTORS TO OVERCOME LIABILITIES OF FIRST-GENERATION SHUTTLED ANTI-AMYLOID THERAPEUTICS. S. Lofgren[1]
(1. Manifold Bio - Boston (United States))

Background: After several decades of pioneering research, brain shuttling technologies are poised to revolutionize the treatment of neurological disease. Enhanced with delivery moieties that are able to target and cross the blood-brain barrier, brain shuttle-enabled medicines have been shown to significantly improve the dosing, tolerability, accessibility, and efficacy of diverse therapeutic modalities. Notably, early evidence suggests that shuttles against the transferrin receptor (TfR1) can enhance the properties of anti-amyloid beta (anti-Aβ) antibodies for the treatment of Alzheimer's disease. Despite the promise of this approach, TfR1-based shuttles are known to have significant peripheral binding and introduce safety liabilities such as hematologic toxicity. Shuttles against novel BBB receptors ("portals") have the potential to further improve upon the safety and efficiency of first-generation TfR1-based shuttles, leading to enhanced delivery of anti-Aβ antibodies and other neuromedicines. **Methods:** Here, we introduce a high-throughput in vivo screening methodology based on Manifold's mCodeTM technology to identify novel brain shuttles and target "portals" and examine the performance of these shuttles on a clinically validated anti-Aβ antibody. Using mCodesTM, we evaluated the uptake of over 1000 nanobody shuttle candidates across multiple known and novel BBB portals in up to 100-plexed pooled reactions in mice. Novel portals were prioritized based on factors like strength and specificity of BBB gene expression: favoring portals that are enriched on brain endothelial cells versus peripheral cell types. Top shuttle hits were further validated in terms of brain and

plasma kinetics, and performance when expressed in fusion with anti-Aβ. **Results:** Our approach reveals novel portals, shuttles, and shuttle-anti-Aβ fusion molecules with diverse molecular properties. By characterizing dozens of binders per BBB target using high-throughput in vivo screening, we were able to validate the shuttling potential of novel portals while simultaneously nominating lead shuttling candidates against these targets. In particular, shuttles against novel portal PX1 exhibited pharmacokinetic and biodistribution profiles in brain, blood, and other peripheral tissues that are distinct from TfR1-based shuttles. Shuttles against novel portals enhanced the delivery of an anti-Aβ antibody versus unshuttled controls and benchmark shuttle molecules, and were shown to avoid the hematological toxicity - most notably reticulocyte depletion - associated with traditional TfR1-shuttled anti-Aβ antibodies. **Conclusion:** In sum, our work significantly expands the the pool of known shuttles and portals capable of shuttling therapeutic payloads across the BBB, demonstrates the utility of these molecules to develop shuttled anti-Aβ therapeutics, and highlights how multiplexed in vivo screening in the early stages of drug discovery can lead to improved biologic designs.

LP080- THERAPEUTIC POTENTIAL OF NOVEL GAS6 FUSION PROTEIN (GAIA) - OVERCOMING NEUROINFLAMMATION VIA EFFEROCYTOSIS IN ANTI-AB IMMUNOTHERAPIES. J.K. Lee[1], S. Ji[1], S. Park[1], C.H. Kim[2], W.S. Chung[3] *(1. Illimis Therapeutics., Inc. - Seoul (Korea, Republic of), 2. College of Pharmacy, Seoul National University - Seoul (Korea, Republic of), 3. Department of Biological Sciences, Korea Advanced Institute of Science and Technology (KAIST) - Daejeon (Korea, Republic of))*

Background: Aβ immunotherapy has been acknowledged as a promising approach in treating Alzheimer's disease (AD) and several antibody therapeutics including Lecanemab and Donanemab have been recently approved by the FDA. The approved Aβ-antibodies have shown significant reduction of Aβ burden in the brain together with slowing down of cognitive decline, proving Aβ as a promising biomarker in Alzheimer's disease. Yet, the limitations such as adverse reactions including antibody-induced inflammation, subsequent amyloid-related imaging abnormalities (ARIA), and cerebral microbleeding remain to be improved [1]. GAIA platform is a novel chimeric protein which utilizes Tyro3, Axl, and Mer-TK (TAM) receptors. The platform was designed to utilize efferocytosis mediating phagocytosis without inflammatory response to mitigate limitations seen in Aβ immunotherapies [2]. Here we have applied the GAIA platform to Aβ-antibodies to explore their efficacy and pharmacokinetics for evaluation of its therapeutic potential. **Methods:** We have developed GAIA-based novel chimeric proteins (GAIA-Aβ) with two distinct functional domains; Aβ-specific fragments fused with engineered GAS6, a TAM receptor-binding domain. ELISA methods were utilized to examine the specific binding of GAIA-Aβ to oligomeric Aβ (oAβ), as well as the binding to TAM receptors. Cell-based assay by using HMC3 (human microglial cell line without FcγR) was used to evaluate the TAM receptor-mediated phagocytosis, leading to oAβ clearance. iPSC-derived monocytes were employed to determine anti-inflammatory responses of GAIA-Aβ. Pharmacokinetic properties of GAIA-Aβ were also evaluated in mice. **Results:** The specific binding of GAIA-Aβ towards oAβ as well as the platform's intended binding to TAM receptors were confirmed. In addition, their ability to activate TAM receptor was shown in dose dependent manners. Further evaluation of GAIA-Aβ through cell-based phagocytosis assay has shown clearance of oAβ, while reduction in inflammatory cytokines demonstrated efferocytosis-mediated activities of GAIA-Aβ. Pharmacokinetic properties of the GAIA-Aβ have shown comparable PK parameters observed from monoclonal antibody therapeutics. **Conclusion:** The intended amyloid clearance coupled with anti-inflammatory response of the GAIA-Aβ has been elaborated, while PK properties of the GAIA-Aβ were comparable to PK of monoclonal antibody therapeutics. In light of the confirmed data, the efficacy of GAIA-Aβ is currently being evaluated using in vivo disease models and will be further characterized. Those data of GAIA-Aβ may provide comparable therapeutic efficacy in reduction of Aβ burden with favorable safety profile prevailing the limitations seen from currently approved immunotherapies including vascular damage as well as subsequent ARIA. **Keyword:** ARIA, Alzheimer's disease, Anti-inflammation, GAS6, TAM, Efferocytosis. **Disclosures:** Dr. Won-suk Chung and Dr. Chan Hyeok Kim are the scientific co-founders of Illimis Therapeutics. All other authors are employees of Illimis Therapeutics. **References:** 1. Cummings., Drugs, 2023, PMID: 37060386. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10195708/; 2. Chung et al., Nature Medicine, 2022, PMID: 35927581. https://www.nature.com/articles/s41591-022-01926-9.

LP081- TARGETING DISULFIDE-LINKED PROTEIN AGGREGATION WITH SMALL MOLECULES: A POTENTIAL STRATEGY FOR NEURODEGENERATIVE DISEASE THERAPY. N. Lukianenko[1,2], L. Sungsu[1], Y.K. Kim[1,2] *(1. Center for Brain Disorders, Korea Institute of Science and Technology, Seoul, Republic of Korea - Seoul (Korea, Republic of), 2. Division of Bio-Medical Science & Technology, University of Science and Technology (UST), Daejeon, Republic of Korea - Daejeon (Korea, Republic of))*

Background: Neurodegenerative disorders such as Alzheimer's disease (AD), Amyotrophic Lateral Sclerosis (ALS), and Frontotemporal Lobar Degeneration (FTLD) are characterized by the accumulation of misfolded proteins, leading to neuronal damage and cognitive decline. FTLD, a leading cause of early-onset dementia, often involves the aggregation of Tau and TDP-43 proteins. Disulfide bond-linked TDP-43 and Tau aggregates have been observed in patients with AD, ALS, and FTLD. Despite advancements in understanding these diseases, effective therapies targeting these protein aggregations remain elusive. This study aims to (1) generate a TDP43-BiFC cell line for visualizing and analyzing TDP-43 aggregation and mislocalization, which are central to FTLD and ALS pathology, and (2) investigate Levosimendan-derived small molecules as inhibitors of disulfide bond formation, directly targeting protein aggregation. The ultimate goal is to develop novel therapeutic strategies for neurodegenerative diseases, particularly AD, ALS, and FTLD. **Methods:** The Bimolecular Fluorescence Complementation (BiFC) technique was employed to visualize protein aggregation. BiFC involves fusing proteins of interest with non-fluorescent fragments of the Venus protein. When BiFC-tagged molecules interact, they form a fluorescent Venus complex, indicating protein aggregation. Previously, we visualized Tau aggregation using a Tau-BiFC cell line and a TauP301L-BiFC mouse model, identifying Levosimendan as a lead compound. Building on this, we developed a TDP43-BiFC cell line to analyze TDP-43 aggregation and mislocalization. Levosimendan derivatives were then tested for their ability to inhibit TDP-43 and Tau aggregation. The TDP43-BiFC model

was validated using various aggregation activators. TDP-43 aggregation and mislocalization were visualized over time using Operetta CLS and Leica microscopy. Immunoblot analysis confirmed the presence of SDS-resistant TDP-43 aggregates and high molecular weight aggregates under non-reducing conditions. We conducted a high-throughput screening of a thiol-reactive drug library derived from Levosimendan. These compounds were tested at concentrations of 1, 3, and 10 μM, alongside a TDP-43 pathology activator at 3 μM, to assess their effectiveness in preventing TDP-43 aggregation. Promising candidates were further evaluated in dose-dependent studies to determine their therapeutic potential. **Results:** The study demonstrated significant TDP-43 accumulation and oligomerization, particularly in response to Pan-HDAC inhibitors, which correlated with the presence of cross-linked aggregates. Immunoblot analysis confirmed both SDS-resistant and non-resistant TDP-43 aggregates. Several thiol-reactive Levosimendan-based compounds were identified that effectively inhibited disulfide bond formation, disrupting both TDP-43 and Tau aggregation. Specific compounds showed distinct efficacy for each protein. These findings suggest that targeting disulfide bond formation with Levosimendan-based compounds offers a promising approach to mitigating protein aggregation, a key factor in the progression of neurodegenerative diseases. The efficacy of these small molecules in reducing pathological protein accumulation and mislocalization underscores their potential as targeted therapies. **Conclusion:** This study highlights the potential of Levosimendan-based small molecules in inhibiting disulfide bond-linked aggregation of TDP-43 and Tau proteins, which are critical to the pathology of neurodegenerative diseases like AD, ALS, and FTLD. Future research will focus on in vivo validation, with the TDP-43A315T transgenic mouse model, which is known to express an ALS phenotype, and the newly generated TauP301L-BiFC/TDP-43A315T transgenic mouse model, which is expected to exhibit an FTLD-like phenotype, potentially resembling behavioral variant FTD (bvFTD). This approach aims to develop new treatments for neurodegenerative disorders. **Keywords:** Alzheimer's disease, Frontotemporal Lobar Degeneration, TDP-43, Tau protein, Neurodegenerative diseases, Protein aggregation, Levosimendan, Disulfide bond. **Disclosures:** The authors declared no competing interests.

CLINICAL TRIALS EARLY CAREER INVESTIGATOR SHOWCASE

P162- PET IMAGING OF MICROTUBULES IN COGNITIVELY NORMAL AND IMPAIRED OLDER ADULTS: A PILOT STUDY. B. Bhoopal[1], M. Miller[1], N. Damuka[1], K. Gollapelli[1], I. Krizan[1], S. Lockhart[1], A. Mintz[2], S. Craft[1], K.K. Solingapuram Sai[1] *(1. Wake Forest School of Medicine - Winston Salem (United States), 2. Columbia University School of Medicine - New York (United States))*

Introduction: Disruption of the structural integrity of the microtubule (MT) network and impairment of MT function are critical to the pathophysiology of Alzheimer's disease (AD) and related disorders. Our lab reported the first brain-penetrant PET radiotracer [11C]MPC-6827 to image MTs in both rodent and non-human primate models of AD, showing [11C]MPC-6827 uptake is elevated with destabilized tubulins. We also reported the dosimetry of [11C]MPC-6827 in healthy adults. Here we report the first clinical [11C]MPC-6827 PET imaging study in age-matched cognitively normal and impaired older adult subjects from the Wake Forest Alzheimer's Disease Research Center (ADRC) Clinical Core Cohort (Craft, PI). **Methods:** Eighteen older (66-90 y, 7 male and 11 female) cognitively normal ([11C]PiB negative, n=11) and impaired ([11C]PiB positive, n=7) adults with brain MRI, [11C]PiB Aβ PET, and [18F]FTP tau PET scans were recruited from the WF ADRC Clinical Core. [11C]MPC-6827 was produced from the corresponding phenol precursor following our reported methods. Dynamic 0-60 min brain PET imaging was obtained following intravenous injection of [11C]MPC-6827 (0.37 GBq, < 10 μg) using the GE Discovery MI PET/CT scanner. Vitals including temperature, blood pressure, and SpO2 were measured before, during, and after the [11C]MPC-6827 PET scans. Regions of interest were drawn for whole-brain, cortical regions (frontal, occipital, parietal, and temporal lobes), thalamus, putamen, cerebellum, corpus callosum, and hippocampus from the fused [11C]MPC-6827 PET/MR DICOM images using PMOD software (v 4.304). Standard uptake values with reference to corpus callosum (SUVR) were calculated, and examined in association with age, PiB Aβ PET global SUVR, and FTP tau PET meta-temporal SUVR using Pearson correlation coefficients, computed using GraphPad Prism (v10.1.2). **Results:** [11C]MPC-6827 was produced with high radiochemical purity (>99.8%) and molar activity (146 ± 10 GBq/μmol). Vitals remained unchanged in all the subjects scanned. Whole-brain [11C]MPC-6827 SUVR demonstrated positive (r=0.25 to 0.57, p=0.13 to 0.31) trends with age, PiB, and FTP—validating its relevance with existing AD biomarkers. While all the [11C]MPC-6827 brain regional SUVRs showed a positive trend with age (r=0.28 to 0.44, p=0.07 to 0.21), significant positive correlations were observed in putamen (r=0.581; *p= 0.014) and thalamus (r=0.533; *p=0.027). Similarly, significant positive correlations were seen between [11C]MPC-6827 uptake in cortical regions (i.e., average frontal, occipital, parietal, and temporal lobes, r=0.615; *p=0.011) and global PiB SUVR. No significant differences were seen in uptake between male and female subjects. **Conclusion:** These preliminary results suggest that MT destabilization is closely associated with Aβ and tau loads even among older adults without dementia. We are currently collecting data on more subjects to exploit the clinical significance of MT-based PET imaging in AD, including fluid biomarkers, MRI, and behavioral correlations.

LP082- EFFECT OF EGB761 ON BLOOD MARKERS OF INFLAMMATION AND OXIDATIVE STRESS IN A COHORT OF PATIENTS WITH MILD COGNITIVE IMPAIRMENT (ACE-2020-EGB761). X. Morató[1], J.P. Tartari[1], M.E. Saez[2], M. Capdevila-Bayo[1], A. Cano[1], L. Montoliu-Gaya[3], H. Huber[3], A. Lafuente[1], M. Ibarria[1], S. Diego Gullon[1], Y. Cantero Fortiz[1], N. Aguilera[1], S. Jofresa[1], L. Cañada[1], N. Tantinya[1], M. Marquié[1], S. Valero[1], H. Zetterberg[3], A. Ruiz[1], M. Boada[1] *(1. FUNDACIO ACE - Barcelona (Spain), 2. Andalusian Bioinformatics Research Centre (CAEBi) - Sevilla (Spain), 3. University of Gothenburg - Mölndal (Spain))*

Background: Mild cognitive impairment (MCI), is an intermediate state between normal aging and dementia and a premorbid risk factor for dementia. In MCI, the appearance of inflammation, oxidative stress, and metabolic alterations are common pathways of neurotoxicity and neurodegeneration. Preclinical studies showed that the standardized extract of Ginkgo biloba EGb761 interferes with the pathogenic mechanisms involved in both the development of cognitive impairment due to Alzheimer's disease and vascular pathology (1). This study investigated the effect of EGb761 on blood

markers of inflammation and oxidative stress in individuals with MCI, to enhance our understanding of its potential therapeutic benefits in this population. **Methods:** ACE-2020-EGb761 is a Phase IV, single-center, randomized, open-label, parallel-group clinical trial involving 100 participants with MCI. The study consisted of a 12-month follow-up, examining changes in blood markers of inflammation and oxidative stress quantified using the Olink Proteomics panel of Inflammation and Neurology markers (2). **Results:** A Linear mixed model was used, adjusting for sex, age, and ApoE. Analysis shows that 3 proteins from the Inflammation (CD8A, CX3CL1 and CSF1) and 12 from the Neurology panel (CDH6, CLM6, EFNA4, GCSF, GDF8, GMCSFR-α, NMNAT1, NRP2, PDGFR-α, RGMA, ROBO2 and TNFRSF21) showed larger decreases in the EGb761 group compared with the control group ($p<0.05$) after 12 months of treatment. These reductions in biomarkers were positively correlated with decreases in neurodegenerative biomarkers (i.e. GFAP, NfL). While the analysis of cognitive performance did not showed significant changes (measured by MMSE, NBACE), some statistically significant changes were observed in neuropsychiatric symptoms measured using the Neuropsychiatric Inventory via a chi-squared test. **Conclusion:** Our findings demonstrate a significant reduction in inflammatory and neurology plasma biomarkers among patients with MCI following 12 months of treatment with EGb761, as measured using Olink Proteomics. These results suggest the potential use of EGb761 as a therapeutic intervention for reducing inflammation and oxidative stress in MCI, potentially preventing its progression to dementia. **Clinical Trial Registry:** NCT05594355. **Keywords:** MCI, EGb761, inflammation, plasma biomarkers. **Disclosures:** Full time employee at Ace Alzheimer Center (Fundació ACE). Received research grant support from KERN Pharma, The Siesta Group, Novo Nordisk, Sengenics Corporation LLC and Schwabe Farma Ibérica S.A.U. (this last one to support Olink Proteomic analysis of the ACE-2020-EGb761 study).

LP083- DIFFERENTIATING UNDERLYING PATHOLOGIES IN EARLY ALZHEIMER'S CLINICAL PHENOTYPES: INTEREST OF ACOUSTIC MARKERS FOR PREDICTING CSF BIOMARKERS AND CLINICAL EVOLUTION.

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Background: Accurate early detection and specific classification of Alzheimer's disease (AD) is a critical challenge in neurogeriatrics. Diagnosing this condition often requires invasive procedures to analyze cerebrospinal fluid (CSF) biomarkers such as B-amyloid and tau proteins. Logopenic primary progressive aphasia (lvPPA), a syndrome primarily affecting language with an AD-like phenotype, frequently progresses to AD [1]. However, the current diagnostic process is insufficient to differentiate lvPPA from AD and predict the clinical course of lvPPA patients. Recent research indicates that automated acoustic analysis of sentence repetition task can discriminate lvPPA and AD at onset time [2]. Therefore, this study explores the potential of acoustic markers to predict CSF biomarkers in lvPPA and their clinical evolution. **Methods:** This longitudinal study included 26 patients: 14 with an initial diagnosis of lvPPA and 12 with AD. All patients underwent CSF analysis. AD biomarkers were present in all AD patients and in 7 lvPPA patients (lvPPA+), while the remaining 7 lvPPA patients (lvPPA-) did not exhibit AD biomarkers. Patients performed a sentence span task, targeting the phonological loop, at the time of diagnosis (3). A total of 67 prosodic and temporal features were extracted from these speech recordings. Subsequently, their clinical evolution was assessed over 12 to 18 months. Following this, a multinomial logistic regression was performed to predict the final diagnostic classification, considering both CSF results and clinical diagnostic evolution. This classification resulted in three groups: AD patients with a CSF-confirmed diagnosis, lvPPA patients with AD biomarkers who progressed to AD, and lvPPA patients without AD biomarkers who retained an lvPPA diagnosis. To refine the model, 39 parameters with adapted variance inflation factors (VIF) were selected. Cross-validation with a 70/30 train-test split was used to evaluate model performance. **Results:** The first multinomial logistic regression model with 67 acoustic covariates demonstrated strong predictive performance, with an overall accuracy of 80%, an AUC of 0.89 and a R^2 of 0.53. Precision scores were 0.71 (AUC=0.88) for predicting progression to lvPPA+, 0.77 (AUC = 0.86) for lvPPA-, and 0.88 (AUC = 0.89) for AD. In a refined model using 39 significant predictors, 16 variables significantly improved prediction accuracy, leading to an increased R^2 of 0.73 and a highly significant Likelihood Ratio Test (LLR p-value = 3.5e-51). Although the general predictive accuracy of the test set decreased to 76%, these results highlight a significant predictive model for CSF biomarkers and clinical evolution in the context of Alzheimer's-like phenotype. Therefore, this exploratory analysis suggests that acoustic speech markers could serve as valuable predictors of both CSF biomarkers and the pathological progression of neurodegenerative diseases. **Conclusion:** This study suggests that acoustic markers could serve as accessible predictive indicators for the pathological evolution of Alzheimer-like clinical phenotypes at the onset of neurodegeneration. These findings highlight the potential of acoustic classification as a non-invasive tool to enhance early diagnosis and improve patient's care orientation. To confirm these results, further research with larger datasets and advanced classification techniques is warranted to validate these promising results. **Keywords:** Alzheimer's Disease, Primary Progressive Aphasia, Acoustic markers, Cerebrospinal Fluid. **Clinical Trial Registry:** This study was registered and approved by CPP Ile de France X (N° IDRCB: 2019-A00342-55 accepted on 11 September 2019). **Disclosures:** The authors declared no competing interests. **References:** 1. Gorno-Tempini, & al. Neurology. 2011 76, 1006–1014. https://doi.org/10.1212/WNL.0b013e31821103e6; 2. Da Cunha E, & al. Life. 2022; 12(7):933. https://doi.org/10.3390/life12070933; 3. Arslan, S., & al. Front. Commun., Volume 7 - 2022. https://doi.org/10.3389/fcomm.2022.934487.

LP084- POTENTIAL ROLE OF MRI TO OPTIMIZE THE DESIGN OF CLINICAL TRIALS FOR PSP AND CBD. I. Illan-Gala[1], J. García-Castro[1], L. Vandevrede[2], H. Heuer[2], R. Raman[3], M. Donohue[3], B. Eden[2], J. Rojas[2], A.M. Wills[4], L. Irene[5], A. Boxer[2] *(1. Hospital de la Santa Creu i Sant Pau - Barcelona (Spain), 2. Memory and Aging Center, University of California San Francisco - San Francisco (United States), 3. Alzheimer's Therapeutic Research Institute (ATRI) Keck School of Medicine, University of Southern California - San Diego (United States), 4. Department of Neurology, Massachusetts General Hospital, Harvard Medical School - Boston (United States), 5. Department of Neurosciences, University of California San Diego - San Diego (United States))*

Background: Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are neurodegenerative disorders characterized by the accumulation of insoluble, predominantly 4R-tau protein aggregates (4R-tauopathies) [1]. The design of clinical trials for these conditions is challenged by their phenotypic overlap [2], and imperfect clinical-pathological correlations [3, 4]. Recently, we demonstrated that MRI-derived models, validated in a large autopsy-confirmed cohort, can predict PSP and CBD pathology [5]. This study explored the impact of selecting participants based on MRI-derived models and using MRI measures as outcomes on sample size estimates in hypothetical clinical trials. **Methods:** We included 102 participants from the 4 Repeat Tauopathy Neuroimaging Initiative (4RTNI) with baseline and longitudinal MRI data and clinical assessments at 6 or 12 months. Among these, 51 (50%) were diagnosed with Richardson syndrome (RS), and 51 (50%) with corticobasal syndrome (CBS) without Alzheimer's disease (AD), as determined by amyloid-PET or plasma pTau-217 status. Using previously validated MRI-derived models [5], we predicted PSP, CBD, or other pathologies at baseline (MRI-PSP, MRI-CBD, MRI-Other, respectively). Disease progression was measured using the PSP Rating Scale (PSPRS) and midbrain volume reduction. We applied linear mixed-effects models to predict changes in PSPRS and midbrain volume at 12 months and calculated sample sizes required for hypothetical clinical trials to detect a small effect (20% mean change reduction) in PSPRS or midbrain volume at month 12 (power = 0.8, $\alpha = 0.05$) [6]. **Results:** At baseline, MRI predicted MRI-PSP, MRI-CBD, and other pathologies in 43 (42.2%), 28 (27.5%), and 31 (30.4%) participants, respectively. Among those diagnosed with RS, 31 of 43 (72%) were predicted to have PSP. Among CBS participants without AD, 17 of 28 (61%) were expected to have CBD. In a hypothetical PSP trial using PSPRS as the outcome, the model estimated a total sample size of 382 when selecting participants based solely on clinical phenotype (RS). An MRI-based diagnosis (MRI-PSP) reduced the required sample size to 353 (an 8% reduction). Using midbrain volume as the outcome further reduced the sample size estimates: 50 participants when selecting by clinical diagnosis (RS) and 91 participants when using MRI-based diagnosis (MRI-PSP). In a hypothetical CBS trial using PSPRS as the outcome, 525 participants would be needed when selecting based on clinical diagnosis (CBS), compared to 539 participants using MRI-based diagnosis (MRI-CBD). When midbrain volume was the outcome, 102 participants were needed with clinical diagnosis (CBS), whereas only 50 were required when employing MRI-based diagnosis (MRI-CBD), representing a 49% reduction. **Conclusion:** Preliminary analyses of this sample suggest that selecting participants with increased diagnostic certainty for PSP and CBD based on baseline MRI, combined with using MRI measures as outcomes, could enhance the efficiency of future phase 2 clinical trials for 4R tauopathies. **Keywords:** 4R-tauopathy, clinical trial, magnetic resonance imaging, sample size. **Disclosures:** The authors declare no relevant disclosures related to the present work. **References:** 1. Stamelou M, Respondek G, Giagkou N, Whitwell JL, Kovacs GG, Höglinger GU. Evolving concepts in progressive supranuclear palsy and other 4-repeat tauopathies. Nat Rev Neurol 2021;17:601–20. https://doi.org/10.1038/s41582-021-00541-5. 2. Boxer A, Yu J, Golbe L, Litvan I, Lang A, Höglinger G. Advances in progressive supranuclear palsy: new diagnostic criteria, biomarkers, and therapeutic approaches. Lancet Neurology 2017;16:552–63. 3. Ali F, Martin PR, Botha H, Ahlskog JE, Bower JH, Masumoto JY, et al. Sensitivity and Specificity of Diagnostic Criteria for Progressive Supranuclear Palsy. Movement Disorders 2019;34:1144–53. https://doi.org/10.1002/mds.27619. 4. Dutt S, Binney RJ, Heuer HW, Luong P, Attygalle S, Bhatt P, et al. Progression of brain atrophy in PSP and CBS over 6 months and 1 year. Neurology 2016;87:2016–25. https://doi.org/10.1212/WNL.0000000000003305. 5. Illán-Gala I, Nigro S, Vandevrede L, Falgàs N, Heuer HW, Painous C, et al. Diagnostic Accuracy of Magnetic Resonance Imaging Measures of Brain Atrophy Across the Spectrum of Progressive Supranuclear Palsy and Corticobasal Degeneration. JAMA Netw Open 2022;5:E229588. https://doi.org/10.1001/jamanetworkopen.2022.9588. 6. Staffaroni AM, Weintraub S, Rascovsky K, Rankin KP, Taylor J, Fields JA, et al. Uniform data set language measures for bvftd and ppa diagnosis and monitoring. Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring 2021;13. https://doi.org/10.1002/dad2.12148.

CLINICAL TRIALS: COGNITIVE AND FUNCTIONAL ENDPOINTS

P163- IMPAIRMENTS OF VISUAL INFORMATION PROCESSING IN DEMENTIA. M. Stemmler[1], M. Daseking[2] *(1. Friedrich-Alexander University of Erlangen-Nuremberg - Erlangen (Germany), 2. Helmut-Schmidt-University Hamburg - Hamburg (Germany))*

Background: Visual perception proves to be a fundamental ability that plays a central role in the perception of the external environment. Deficits can lead to impairments in everyday activities. It is known that visual perception is impaired in Alzheimer's disease (AD). To date, however, the extent to which visual perception is deficient in mild cognitive impairment (MCI), the prodromal state of AD, has been insufficiently investigated. A study with healthy, older people has already shown that visual perceptual performance decreases with increasing age (Kim et al., 2014). There is also evidence that dementia-related diseases, including AD, are associated with deficits in visual perception (Mosimann et al., 2004). With regard to MCI, two studies investigate visuo-motor integration in terms of a sub-area of visual perception (Malloy et al., 2003; Rattanavichit et al., 2022). Both studies found significant group differences in visuo-motor integration performance in MCI vs. AD (Malloy et al., 2003; Rattanavichit et al., 2022). Malloy et al. (2013) conclude that visuo-motor integration performance differs between individuals with MCI and AD may discriminate. This study investigates the functionality of visual perception in people with MCI, mild AD and a healthy control group. This will provide new insights into the study of MCI and visual perception. **Methods:** Persons with MCI, mild AD and healthy control subjects are examined for cognitive deficits using the Short Cognitive Performance Test (SKT;

Erzigkeit, 2001). Visual perceptual performance will be assessed using the Frostig's Developmental Test of Visual Perception - Adolescents and Adults (FEW-JE:2; Daseking et al., in press). In addition, practical everyday skills, executive functions and intelligence will be assessed. An ethics vote from the ethics committee of Helmut Schmidt University has been obtained. **Results:** The degree of impairment of visual-motor integration performance depends on the degree of cognitive impairment. **Conclusion:** The results will be discussed whether in clinical trials new cognitive and functional endpoints need to be discussed, e.g., maybe in terms whether the parietal processing stream including object localization and motion perception («where» pathway) or the temporal processing stream including object recognition («what» path) will be affected. **References:** Daseking, M., Jaščenoka, J., & Waldmann, H.-C. (in press). FEW-JE:2 Frostigs Entwicklungstest der visuellen Wahrnehmung – Jugendliche und Erwachsene 2. Auflage. Hogrefe. Erzigkeit, H. (2001). Manual zum Syndrom-Kurztest (SKT). Geromed, Germany. Kim, E., Park, Y.-K., Byun, Y.-H., Park, M.-S., & Kim, H. (2014). Influence of aging on visual perception and visual motor integration in Korean adults. Journal of Exercise Rehabilitation, 10(4), 245–250. https://doi.org/10.12965/jer.140147. Malloy, P., Belanger, H., Hall, S., Aloia, M., & Salloway, S. (2003). Assessing visuoconstructional per-formance in AD, MCI and normal elderly using the Beery Visual-Motor Integration Test. The Clinical Neuropsychologist, 17(4), 544–550. https://doi.org/10.1076/clin.17.4.544.27947. Mosimann, U. P., Mather, G., Wesnes, K. A., O'Brien, J. T., Burn, D. J., & McKeith, I. G. (2004). Visual perception in Parkinson disease dementia and dementia with Lewy bodies. Neurology, 63(11), 2091–2096. https://doi.org/10.1212/01.WNL.0000145764.70698.4E. Rattanavichit, Y., Chaikeeree, N., Boonsinsukh, R., & Kitiyanant, K. (2022). The age differences and effect of mild cognitive impairment on perceptual-motor and executive functions. Frontiers in Psychology, 13, 906898. https://doi.org/10.3389/fpsyg.2022.906898. **Keywords:** visual-motor integration, cognitive impairment, Alzheimer's disease. **Disclosures:** The authors declared no competing interests.

P164- HOME-BASED TRANSCRANIAL ALTERNATING CURRENT STIMULATION OVER THE PRECUNEUS IN ALZHEIMER'S DISEASE: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL FOLLOWED BY AN OPEN LABEL PHASE.

V. Cantoni[1], E.P. Casula[2], C. Cupidi[3], D. Altomare[4], E. Premi[5], E. Zummo[3], R. Esposito[2], N. Huber[6], E. Solje[7,8], M.S. Cotelli[1], A. Martorana[9], G. Koch[2,10,11], A. Haapasalo[12], A. Benussi[13], B. Borroni[1,10]

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Background: Gamma (γ) brain oscillations are involved in neural communication and synaptic plasticity, and are dysregulated in Alzheimer's disease (AD). Brain oscillations can be modulated using transcranial alternating stimulation (tACS). Here, we describe a study assessing safety, feasibility, clinical and biological efficacy, and predictors of outcome of a home-based intervention consisting of γ-tACS over the precuneus. **Methods:** Sixty consecutive AD patients have been screened, and 53 randomized into two arms: ARM1, γ-tACS (frequency: 40 Hz, intensity: 2 mA; duration: 5 sessions/week 60-minutes/each; target region: precuneus) for 8 weeks; and ARM2, sham tACS (same parameters as the real γ-tACS, with the current being discontinued 5 seconds after the beginning of the stimulation) for 8 weeks. In a second phase, all participants have received γ-tACS (same parameters as the real γ-tACS in the first phase) for 8 weeks. The study outcomes will be collected at several timepoints till 24 weeks and include safety and feasibility as well as changes in cognitive functions (assessed through neuropsychological assessment), brain entrainment (electroencephalography), and biomarkers. Imaging markers (functional MRI) and cholinergic neurotransmission (transcranial magnetic stimulation) were considered as well. **Results:** As of May 2024, 46 out of 53 participants successfully completed the first phase of the study, and 36 the second, with the end of the study estimated in October 2024. The intervention has been demonstrated safe and feasible so far. **Conclusion:** If our expected results are achieved, home-based γ-tACS, either alone or in combination with other therapies, may become a reality for treating AD. **Keywords:** Alzheimer disease, TACS, clinical trial, cognition, blood markers, imaging, brain entrainment. **Disclosures:** All authors declare that they have no conflicts of interest. **References:** 1) Home-based transcranial alternating current stimulation (tACS) in Alzheimer's disease: rationale and study design. Altomare D, Benussi A, Cantoni V, Premi E, Rivolta J, Cupidi C, Martorana A, Santarnecchi E, Padovani A, Ko ch G, Borroni B. Alzheimers Res Ther. 2023

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P165- ASSESSING INFORMAL CAREGIVERS´ SELF-PERCEIVED SENSE OF COMPETENCE IN MILD COGNITIVE IMPAIRMENT: PSYCHOMETRIC EVALUATION OF THE 7-ITEM SENSE OF COMPETENCE QUESTIONNAIRE (SCQ). P. Sanchez-Juan[1], E. Garcia-Arcelay[2], M. Balasa[3], G. Piñol-Ripoll[4], M. Boada[5], L. Landete[6], E. Navarro[7], I. Abellán[8], A. Berbel[9], B. Espejo[10], M. Almagro[11], J. Rodrigo[11], J. Maurino[2], S. Manzano-Palomo[12], J. Ballesteros[13] *(1. Fundación CIEN (Centro de Investigación de Enfermedades Neurológicas) - Madrid (Spain), 2. Medical Department, Roche Farma - Madrid (Spain), 3. Alzheimer´s Disease and Other Cognitive Disorders Unit, Hospital Clínic, IDIBAPS - Barcelona (Spain), 4. Unitat Trastorns Cognitius, Hospital Universitari Santa Maria de Lleida, Institut de Recerca Biomédica de Lleida (IRBLLeida) - Lleida (Spain), 5. Ace Alzheimer Center Barcelona – Universitat Internacional de Catalunya. - Barcelona (Spain), 6. Department of Neurology, Hospital Universitario Dr. Peset - Valencia (Spain), 7. Department of Neurology, Hospital Universitario Infanta Leonor, - Madrid (Spain), 8. Behavioral Neurology and Dementia Unit Hospital San Vicente del Raspeig, - Alicante (Spain), 9. Department of Neurology. Hospital de la Cruz Roja Madrid - Madrid (Spain), 10. Cognitive-Behavioral Neurology Unit Hospital Clínico San Cecilio - Granada (Spain), 11. Confederación española de Alzheimer y otras demencias (CEAFA) - Madrid (Spain), 12. Department of Neurology, Hospital Universitario Infanta Leonor - Madrid (Spain), 13. Department of Neurosciences, University of Basque Country (UPV/EHU), CIBERSAM, - Leioa (Spain))*

Background: The Sense of Competence Questionnaire (SCQ) is a self-report tool designed to evaluate a caregivers´ perception of their ability to handle a particular care situation and their confidence in caring for the patient. The SCQ is validated in caregivers of patients with dementia and comprises three distinct domains: satisfaction with the care recipient, with ones performance as a caregiver, and consequences of involvement in personal life. However, it has not been evaluated in caregivers of patients with mild cognitive impairment (MCI). **Objectives:** This study aimed to assess the dimensional structure and item distributions of the 7-item SCQ in informal caregivers of patients with MCI, and obtain evidence on its concurrent validity with burden and psychological assessments, and its potential to discriminate across levels of burnout. **Methods:** A non-interventional, cross-sectional study was conducted at 19 memory clinics in collaboration with the Spanish Confederation of Alzheimer´s Disease (CEAFA). Individuals providing informal care for patients diagnosed of MCI (National Institute on Aging and the Alzheimer´s Association clinical criteria) and a Global Deterioration Scale score of 3 were included. The short SCQ consists of seven items, each rated according to a 5-point Likert scale. Higher scores meant more sense of competence. A non-parametric item response theory procedure, Mokken analysis, assessed the underlying dimensional structure and scalability of items and the overall questionnaire. Each item was required to have a scalability coefficient (Hi) of ≥0.30 and an overall scale scalability index (H) of ≥0.30. Associations between the 7-item SCQ and Zarit Burden Interview (ZBI-22), Hospital Anxiety and Depression Scale (HADS), and a single-item burnout measure from the Physician Work Life Study were analyzed to assess concurrent and discriminant validity with Pearson correlations and linear regression models. **Results:** A total of 196 caregivers were studied. Mean (SD) age was 63.5 (13.1) years and 63% were female. Mean (SD) SCQ score was 26.1 (6.1). Items with the highest agreement were "I wish that my… and I had a better relationship" (38.9%), "I feel stressed between trying to give up my ... as well as to other family responsibilities, job" (31.7%). The SCQ showed high internal reliability (Cronbach's alpha=0.86, 95% CI 0.83 to 0.89), and a unidimensional structure according to Mokken analysis. All items presented appropriate scalability (>0.30), and the scalability index for the total scale indicated a strong scale (H=0.52). The SCQ fitted a monotone homogeneity model with different item discrimination on the caregiver´s perception of their ability to handle everyday situations. The linear correlation of SCQ with ZBI-22 validated the association between the caregiver's perception of the ability to handle situations and burdens (r=-0.66, p-value <0.01). The SCQ was further associated with the anxiety subscale of the HADS (r=-0.52, p-value <0.01), but not with its depression subscale (r=-0.11, p-value=0.89). The SCQ mean scores presented a linear trend across categories of the single-item of emotional exhaustion (p-value <0.001). **Conclusion:** The 7-item SCQ is a unidimensional scale with appropriate psychometric characteristics to evaluate the caregiver's burden associated with the management of everyday situations with patients presenting MCI.

P166- THE EFFECT OF HIGH-DEFINITION TRANSCRANIAL DIRECT CURRENT STIMULATION (HD-TDCS) ON COGNITIVE FUNCTION IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT: A RANDOMIZED, TRIPLE-BLIND, SHAM-CONTROLLED, STUDY. C.S. Chu[1], C.C. Pan[1], C.H. Chang[1], Y.C. Chiang[1], H.Y. Kuo[1], S.L. Chen[2], C.S. Chen[2] *(1. Department of Psychiatry, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan - Kaohsiung (Taiwan, Republic of China), 2. Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan - Kaohsiung (Taiwan, Republic of China))*

Background: Few studies examined the high-definition transcranial direct current stimulation (HD-tDCS), targeting in more focal simulation of selected brain regions than tDCS, in individuals with mild cognitive impairment (MCI). The study aimed to assess the safety and efficacy of HD-tDCS on cognitive functioning, mood condition, and subjective cognitive function in patients with MCI. **Methods:** The study was a two-arm, parallel, triple-blind (participants, outcomes assessor, principal investigator), randomized, and sham-controlled trial. We recruited patients with MCI with inclusion criteria as follows: (1) aged 60- to 85-year-old; (2) cognitive impairment did not interfere with capacity for independence in everyday activities; (3) no history of dementia (4) clinical dementia rating scale 0.5 or mini-mental state examination score less than 24 (out of 30); (5) and right-handed. An Eldith DC stimulator (Neuroconn DC Stimulator Plus, GmbH, Ilmenau, Germany) was used for stimulation. Based on the

10-20 EEG system, the cathode was placed Fp1, Fz, C3, and F7 and anode was located on F3, presumably corresponding to left dorsolateral prefrontal cortex. A current of 2.0 mA for 25 minutes for 10 sessions with once daily for 2 weeks were performed for each patient. The cognitive function changes from pre-intervention to post-intervention measurements (i.e., 2nd week, 6th week, and 14th week) between the study groups were compared using a linear mixed model (LMM). Cognitive abilities screening instrument (CASI), Wechsler memory scale (WMS), Wechsler adult intelligence scale (WAIS), Wisconsin card sorting test (WCST), and frontal assessment battery (FAB) were conducted to evaluate global and specific sub-domain cognitive function. The LMM included the main effects of the study groups, time points, and the interaction terms between study groups and time points. The random intercept in the LMM was set to account for repeated measurements within each subject. The change between groups was considered different when the interaction effects were significant. Since there were multiple outcome variables, the alpha level was adjusted using the Bonferroni correction to avoid inflation of type I error. Data analyses were conducted using SPSS 26 (IBM SPSS Inc, Chicago, Illinois). **Results:** Total of 51 participants were recruited. Among them, 26 (mean age, 73.2 ± 5.9 years; percentage of female: 53.9%) and 25 (mean age, 74.3 ± 6.6 years; percentage of female: 48.0%) received active and sham stimulation, respectively. After 10 HD-tDCS anodal stimulation, we did not group-time interaction for global cognitive function measured by CASI nor other secondary outcomes such as WMS-III-verbal paired associates, WMS-III-visual reproduction, WAIS-IV-digit span, WAIS-IV-digit symbol coding, WAIS-IV-vocabulary, WCST, and FAB. No serious adverse effects were reported. There were no significant differences between groups regarding adverse events. **Conclusion:** The current study identified insignificant improvement in cognitive performance with active HD-tDCS treatment as compared to sham HD-tDCS among people with MCI. **Keywords:** cognitive function, high-definition transcranial direct current stimulation, mild cognitive impairment, randomized controlled trial. **Clinical Trial Registry:** NCT04121156; https://clinicaltrials.gov/study/NCT04121156?cond=Mild%20Cognitive%20Impairment&term=kaohsiung&intr=direct%20current%20stimulation&rank=1. **Conflict of interest:** None

P167- THE LONGITUDINAL RELATIONSHIP BETWEEN CARDIORESPIRATORY FITNESS, AMYLOID-B, AND COGNITIVE PERFORMANCE IN ADULTS AT RISK FOR ALZHEIMER'S DISEASE. A.J. Paulsen[1,2], B.M. Breidenbach[1,3], M. Glittenberg[1,3], S. Asthana[1,3,4], S.C. Johnson[1,3], T.J. Betthauser[1], D.B. Cook[5,6], O.C. Okonkwo[1,2,4] *(1. Wisconsin Alzheimer's Disease Research Center, Department of Medicine, University of Wisconsin-Madison, School of Medicine and Public Health - Madison (United States), 2. Wisconsin Alzheimer's Institute, Madison, WI, USA. - Madison (United States), 3. Wisconsin Alzheimer's Institute, - Madison (United States), 4. Geriatric Research Education and Clinical Center, William S. Middleton VA Hospital - Madison (United States), 5. Department of Kinesiology, University of Wisconsin-Madison - Madison (United States), 6. William S. Middleton Memorial Veterans Hospital - Madison (United States))*

Background: Identifying primary preventative strategies and targets of clinical trials for Alzheimer's disease (AD) is paramount to stem a growing public health crisis. This study investigates longitudinal impacts of cardiorespiratory fitness (CRF) on accumulation of amyloid-β (Aβ), an AD hallmark, and potential modification of the effect of Aβ on cognitive decline by CRF. **Methods:** Two hundred forty-one longitudinally followed adults (mean baseline age=63 years, mean follow-up=5.7 years) from the Wisconsin Alzheimer's Disease Research Center (WADRC) and the Wisconsin Registry for Alzheimer's Prevention (WRAP) participated in this study. They underwent serial 11C-Pittsburgh compound B (PiB) PET imaging and 18F-MK-6240 imaging of tau (T) pathology. Sex-specific estimated CRF (eCRF) tertiles were created using a validated equation incorporating age, sex, BMI, resting heart rate, and physical activity. Cognition was assessed with a three-test Preclinical Alzheimer's Cognitive Composite (PACC-3) score. Linear mixed effects (LME) models estimated associations between time-varying eCRF and Aβ accumulation, including an interaction term for eCRF by time indicating differing accumulation rates. LME models were used to investigate potential modification of Aβ's impact on PACC3 score change by time-varying eCRF category using a three-way interaction term including eCRF, z-scored cortical PiB DVR, and time. Analyses were stratified by Aβ (A)/tau (T) status, with A+ defined as a cortical PiB DVR>1.19 and T+ defined as entorhinal cortex MK-6240 SUVR>1.27 or positive for any level of Braak staging during follow-up. Analyses were adjusted for baseline age, sex, education, APOEε4 carrier status, and parental history of AD. Sensitivity analyses included practice effects and A+ duration. **Results:** There were 145 A-/T-, 31 A+/T-, 21 A-/T+, and 44 A+/T+ individuals in the analytic sample. The A-/T+ group was omitted from modeling due to sample size. No protective effect of eCRF on Aβ accumulation was observed among participants who were A+/T- or A+/T+ during follow-up. However, a significant protective association was observed between eCRF and cognitive change over the course of follow-up independent of baseline age, sex, education, and AD risk conferred by APOEε4 carriage or family history of AD. Among participants who were A+/T+, those with Aβ 1 SD above within group mean and low fitness had an estimated decline in PACC-3 score of -0.22 per year. In contrast, among A+/T+ persons with the same Aβ burden, those in the middle or high fitness group displayed a significantly slower or no annual decline in PACC-3 score [0.00 ($p<0.001$) and -0.02 ($p<0.001$), respectively]. This eCRF modification of the impact of Aβ on cognitive trajectory was not observed in the A-/T- or A+/T- group. Inclusion of practice effects and A+ duration did not affect results. **Conclusion:** These findings suggest that while cardiorespiratory fitness may not influence Aβ accumulation among those at risk of developing clinically significant levels of amyloid, it may impart resistance to cognitive decline due to AD neuropathology. These findings could help inform clinical trials aimed at using exercise as intervention strategies and imply that trials focused on functional outcomes rather than protection against Aβ accumulation may be the more likely to observe protective effects. **Keywords:** Cognition, cognitive resilience, cardiorespiratory fitness, amyloid-β. **Disclosures:** This work was supported by grants awarded by the National Institutes of Health: R01AG062167 (Dr. Okonkwo), P30AG062715 (Dr. Asthana), RF1AG027161 (Dr. Johnson), and an NIH National Center for Advancing Translational Sciences grant UL1TR002373 awarded to the UW-Madison ICTR CTSA program. All authors report no conflict of interest directly 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.

P168- EVALUATING THE PERFORMANCE OF PARTICIPANT-REPORT, STUDY PARTNER-REPORT, AND PERFORMANCE-BASED ASSESSMENTS OF DAILY FUNCTIONING IN OLDER ADULTS AS FUNCTIONAL ENDPOINTS IN ALZHEIMER'S DISEASE CLINICAL TRIALS. H. Truitt[1,2], R.E. Amariglio[1,2,3], S. Wang[3], O. Udeogu[3], A. Brathwaite[3], D.M. Rentz[1,2], G.A. Marshall[1,2,3], M.A. Dubbelman[1,2,3] *(1. Brigham and Women's Hospital - Boston (United States), 2. Harvard Medical School - Boston (United States), 3. Massachusetts General Hospital - Boston (United States))*

Background: Instrumental activities of daily living (IADL) encompass a range of complex tasks integral to an individual's functional independence, including managing finances, taking medications, and completing household responsibilities [1]. Functional impairment in older adults can be a sign of a major neurocognitive disorder, such as Alzheimer's disease (AD) [2], which is why IADL are routinely assessed in clinical trials for all stages of AD. There is no clear consensus on the ideal IADL assessment modality, as participant-report, study partner-report, and performance-based measures each provide unique information on an individual's functioning. Certain assessments may be more sensitive to early functional decline than others [3]. This will be particularly important for AD prevention trials [4]. The present study sought to clarify this by examining how measures of IADL perform among older adults across cognitive statuses. **Methods:** Our sample (n=143, 71±6 years, 62% female), comprised of n=127 (89%) cognitively unimpaired (CU) individuals and n=16 (11%) with mild cognitive impairment (MCI), was recruited from the general community and two memory disorders clinics and completed a comprehensive battery of IADL assessments, including the self- and informant-reported Alzheimer's Disease Cooperative Study Activities of Daily Living-Prevention Instrument (ADCS ADL-PI), the Cognitive Function Index (CFI), the performance-based Financial Capacity Instrument Short Form (FCI), the Czaja Functional Assessment Battery (CFAB), and the Harvard Automated Phone Task (Harvard APT). Cognitive performance was assessed using the Preclinical Alzheimer's Cognitive Composite (PACC). IADL measures' distributions were evaluated for ceiling effects and linear regressions, adjusted for age, sex, and years of education, were used to analyze cross-sectional inter-modality associations. We also included interactions with cognitive status. **Results:** Among cognitively unimpaired participants, ceiling effects were apparent in participant-reported and study partner-reported ADCS ADL-PI and study partner-reported CFI (27-59% of responses at maximum score), but not in performance-based measures. Linear modeling found several intra-modality, but fewer inter-modality associations, including between FCI-SF and self- and study partner-reported ADCS ADL-PI (Z=-8.27, p<.001; Z=-3.88, p<.001, respectively) and between a CFAB task and self-reported ADCS ADL-PI (Z=3.19, p=.002). PACC related to measures in all modalities (e.g., the primary care physician task of H-APT (Z=4.97, p<.001); self-reported ADCS-ADL-PI (Z=2.66, p=.009); study partner-reported CFI (Z=-6.07, p<.001)). Cognitive status modified the relationship between IADL measures, such that several associations were no longer significant when examined among only CU participants. **Conclusion:** Different IADL assessments appear to measure distinct aspects of functioning, as evidenced by the low number of inter-modality associations, particularly among only CU individuals. Performance-based measures may be particularly useful instruments when assessing CU persons, as they did not produce a pronounced floor or ceiling effect. The current study upholds prior research suggesting a strong relation between study partner-reported assessments and cognitive functioning, which may be particularly helpful when aiming to detect early signs of decline [5]. Altogether, these findings underscore the necessity of a multifaceted approach to IADL assessment and affirm the utility of these instruments among CU persons, which is critical for early detection and monitoring of treatment response. **Keywords:** instrumental activities of daily living, functional endpoints, self-report, informant-report, performance-based assessments, cognition. **Disclosures:** Authors have no conflicts of interest to disclose. **References:** 1. Edemekong PF, Bomgaars DL, Sukumaran S, Levy SB (2022) Activities of Daily Living. In StatPearls, Treasure Island (FL). 2. Dubbelman, M. A., Jutten, R. J., Tomaszewski Farias, S. E., Amariglio, R. E., Buckley, R. F., Visser, P. J., Rentz, D. M., Johnson, K. A., Properzi, M. J., Schultz, A., Donovan, N., Gatchell, J. R., Teunissen, C. E., Van Berckel, B. N. M., Van Der Flier, W. M., Sperling, R. A., Papp, K. V., Scheltens, P., Marshall, G. A., & Sikkes, S. A. M. (2020). 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P169- MAPPING ALZHEIMER'S DISEASE PROGRESSION VIA CHANGES IN THE CDR-GLOBAL FOR ACCURATE CLINICAL TRIAL DESIGN. R.C. Canovas[1], C.J.F. Fowler[2], S.M.L. Laws[3,4,5,6], S.R.S. Rainey-Smith[7,8,9,10], C.L.M. Masters[2], R.N.M. Martins[7,11], P.M. Maruff[2], J.D.D. Doecke[12] *(1. Australian E-Health Research Centre, CSIRO - Parkville (Australia), 2. Florey Institute, The University of Melbourne - Parkville (Australia), 3. Centre for Precision Health, Edith Cowan University - Joondalup (Australia), 4. Collaborative Genomics and Translation Group, Edith Cowan University, - Joondalup (Australia), 5. School of Medical and Health Sciences, Edith Cowan University, - Joondalup (Australia), 6. Curtin Medical School, Curtin University - Bently (Australia), 7. School of Medical and Health Sciences, Edith Cowan University - Joondalup (Australia), 8. School of Psychological Science, University of Western Australia - Crawley (Australia), 9. Centre for Healthy Ageing, Health Futures Institute, Murdoch University - Murdoch (Australia), 10. Australian Alzheimer's Research Foundation, Sarich Neuroscience Research Institute - Nedlands (Australia), 11. Department of Biomedical Sciences, Macquarie University - Macquarie (Australia), 12. Australian E-Health Research Centre, CSIRO - Herston (Australia))*

Background: As the volume of data collected in natural history studies of Alzheimer's disease (AD) increases so too there is improvement in the accuracy of estimates of the

trajectory of AD-related cognitive and clinical decline. There is also improvement in understanding about how confounders can influence age of onset (AO) and trajectories of decline. Statistical modelling of the disease process via longitudinal assessment of PET Aβ scans has provided accurate estimates of AO based on a sigmoidal disease process (Budgeon et al., 2017). Estimates of AO in specific subgroups can be used to inform clinical trial design. The aim of this study was to combine sigmoidal disease processes estimates with time to event modelling to understand the nature of cognitive decline from the prodromal (e.g. Clinical Dementia Rating scale global score [CDR] = 0.5) to mild dementia (i.e. CDR = 1) and from being cognitively unimpaired (CDR = 0) to prodromal dementia (CDR = 0.5). Such estimates can provide a basis for modelling natural disease related changes and provide a basis for estimating rates of decline over the shorter time intervals used typically in clinical trials. **Methods:** CDR, APOE ε4 genotype, gender, baseline age (<70yrs, 70-80yrs, >80yrs), and PET-Aβ status (Aβ+ >20 centiloid) were collected among 1,905 participants from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of ageing. Time to progression was modelled using Kaplan Meier (univariate) and Cox proportional hazards (multivariate) modelling. **Results:** For progression from CDR=0 to CDR=0.5, 1321 participants were available (all, CU). Of these, ~41% were male, 28% carried at least 1 APOE ε4 allele, with a mean age was 70.95 (SD:6.59). For progression of CDR0.5 to CDR1 605 participants were available. Of this sample approximately 51% were male, 57% carried at least 1 APOE ε4 allele, with a mean age of 73.41 (SD:7.99). Across the 16 years 213 progressed from CDR0 to CDR0.5 (~16%), and 140 progressed from CDR0.5 to CDR1. Univariate models indicated that age group, carriage of APOE ε4 genotype and PET-Aβ status each influenced time to progression in the CDR0-CDR0.5 and CDR0.5-CDR1 progressors. For CDR0-CDR0.5 males had a shorter time to progression but this was not present for the CDR0.5-CDR1 progressors. Multivariate models showed that for the CDR0-CDR0.5 progressors, participants carrying 2 APOE ε4 alleles had a hazard ratio (HR, compared to participants with no APOE ε4 alleles) nearly twice as large as compared with those carrying only one allele (3.78 vs 1.45). This sizable difference however was not evident in the CDR-0.5-CDR1 progressors. **Conclusion:** The data presented here provide estimates of the rate of clinical disease progression in the largest sample studied over the longest period to date. The data suggest that median time to progress from the CU to prodromal AD is 16.5 years, and 3.6 years for from prodromal to mild dementia. Both of these estimates varied due to age group, PET-Aβ status and APOE ε4 allele status. **Keywords:** Cognitive decline, CDR-Global, Biostatistics, Progression. **Disclosures:** The authos have nothing to disclose. **References:** Budgeon CA, Murray K, Turlach BA, Baker S, Villemagne VL, Burnham SC; and for the Alzheimer's Disease Neuroimaging Initiative. Constructing longitudinal disease progression curves using sparse, short-term individual data with an application to Alzheimer's disease. Stat Med. 2017 Jul 30;36(17):2720-2734.

P170- TIME-SAVED DUE ON TREATMENT: VALIDATION IN A REAL-WORLD POPULATION STUDY. R.C. Canovas[1], M.C. Cespedes[2], C.J.F. Fowler[3], S.R.S. Rainey-Smith[4,5,6,7], C.L.M. Masters[3], R.N.M. Martins[4,8], P.M. Maruff[3], J.D.D. Doecke[2] *(1. Australian E-Health Research Centre, CSIRO - Parkville (Australia), 2. Australian E-Health Research Centre, CSIRO - Herston (Australia), 3. Florey Institute, The University of Melbourne - Parkville (Australia), 4. School of Medical and Health Sciences, Edith Cowan University - Joondalup (Australia), 5. School of Psychological Science, University of Western Australia - Crawley (Australia), 6. Centre for Healthy Ageing, Health Futures Institute, Murdoch University - Murdoch (Australia), 7. Australian Alzheimer's Research Foundation, Sarich Neuroscience Research Institute - Nedlands (Australia), 8. Department of Biomedical Sciences, Macquarie University - Macquarie (Australia))*

Background: Recent successful outcomes from phase III clinical trials of anti-amyloid drugs in symptomatic Alzheimer's disease now raises the issue of how such positive effects can be communicated meaningful to patients, health care providers and governments. There is growing acceptance of the concept of time-saved as way of expressing an absence of disease progression. To date, estimates of time-saved have been generated from clinical trial data. Thus, the extent to which these estimates reflect true changes in the disease course are potentially biased by the clinical trial context (e.g., sample restriction, confounding by placebo or practice effects, high frequency of clinical assessment). Understanding of estimates of time-saved generated from clinical trials would therefore be improved by access to information from non-interventional natural history studies of equivalent patient groups. While such data is available natural history studies have typically not expressed estimates of change in terms of time. The aim of this study was to identify of adults enrolled in the AIBL study who would have met the inclusion criteria for the phase III Lecanemab study design. Estimates of time lost were then computed for the AIBL PACC and the clinical dementia rating sum of boxes (CDR-SB) over a three-year period. This data was then used to derive estimates of the change necessary for a 20, 25 and 30% improvement in time-saved over 3 years. **Methods:** From 3,358 AIBL participants, N=451 who were PET-Aβ+ (centiloid>25), had MMSE of between 22 and 30, were classified as having either mild cognitive impairment (MCI) or AD, and were aged between 55 and 90 years were selected for follow up. The PACC score (CVLT, LM-II, digit symbol coding and MMSE), and CDR-SB were modelled using linear mixed effects models using a random slope and random intercept, and adjusting for number of visits. Using the slopes derived from participants for each score, conjugate slopes were created over a 3-year period, whereby a 20, 25 and 30% decrease in cognitive decline was used to calculate time-saved at 6 monthly intervals. **Results:** For the AIBL PACC, time-saved computed after 36 months of follow up demonstrated savings of 6.6, 8.2 and 9.9 months for a 20, 25 and 30% reduction in cognitive decline. For CDR-SB, these values were slightly higher saving approximately, 7.2, 9 and 11 months for a 20, 25 and 30% reduction in cognitive decline. Using a 20% reduction in the final PACC score equated to an 80% reduction in the slope over 36 months, whilst a 20% reduction in the final CDR-SB score equated to an approximate 50% reduction in the slope over 36 months. **Conclusion:** Use of population data collected over long periods of time from natural history studies can provide a high precision estimate of time lost to AD over a greater amount of the disease course. Therefore expressing rates of decline on clinical outcome measures as estimates of time lost

provides a strong context for understanding, contextualizing and even potentially adjusting, estimates of time-saved derived from clinical trial. **Keywords:** Time saved, CDR-SB, PACC score, Longitudinal progression. **Disclosures:** The authors have nothing to disclose.

P171- STREAMLINING RECRUITMENT FOR AD CLINICAL TRIALS: CONCURRENT DETECTION OF COGNITIVE IMPAIRMENT AND AMYLOID-BETA PET STATUS WITH A MACHINE LEARNING-ENABLED DIGITAL COGNITIVE ASSESSMENT. A. Jannati[1], K. Thompson[1], C. Toro-Serey[1], C. Higgins[1], R. Banks[1], P. Jeff[1], S. John[1], B. David[1], T. Sean[1], P.L. Alvaro[1] *(1. Linus Health - Boston (United States))*

Background: Identifying suitable participants for clinical trials of disease-modifying treatments (DMTs) for Alzheimer's disease (AD) is impeded by high screen failure rates and costly prescreening. Such identification requires both early detection of cognitive impairment and abnormal brain amyloid-beta (Aβ) status. Therefore, an efficient and cost-effective solution to streamline the process of early AD identification can significantly streamline the process of participant recruitment for clinical trials of DMTs for AD. In this study, we assessed the accuracy of a brief digital cognitive assessment, the Linus Health Digital Clock and Recall (DCR), to identify cognitive impairment and predict brain amyloid-beta (Aβ) status on positron emission tomography (PET). **Methods:** 930 participants (mean age 72.0±6.7; 56.8% female; 23% minorities) in the Bio-Hermes-001 study were classified as cognitively unimpaired, mild cognitive impairment, or probable Alzheimer's dementia, and 35.1% were Aβ+ on 18F-florbetapir PET scan. A DCR-based algorithm (LinusAD) used age, APOE status, drawing metrics, speech and acoustic features, and temporal-spatial features of stylus manipulation. LinusAD was compared with MMSE and blood-based biomarkers (BBMs) Lilly pTau-217, Quanterix pTau-181, C2N Aβ42/40, and C2N Amyloid Probability Score (APS). Superiority or non-inferiority was established if 95% confidence interval of the bootstrapped AUC difference between two tests was higher than or within ΔAUC±0.1. **Results:** Cognitive-impairment identification by the DCR (AUC=0.85) was superior to Aβ42/40, pTau-181, and pTau-217 (AUCs=0.63, 0.66, 0.72) and non-inferior to RAVLT and MMSE (AUCs=0.89, 0.82). Aβ-status prediction by LinusAD (AUC=0.882) was equivalent to BBMs (AUC range: 0.775–0.887; average AUC=0.82) and superior to MMSE (AUC=0.71) (see Table and Figure). Combining the DCR with Aβ42/40, pTau-181, and pTau-217 improved their Aβ-status prediction performance to AUCs of 0.882, 0.835, and 0.905, respectively. **Conclusion:** The 3-minute DCR was superior to BBMs in detecting cognitive impairment and boosted their Aβ-PET prediction ability to levels comparable to CSF biomarkers of AD. By leveraging AI process metrics the DCR enables cost-effective identification of most suitable participants for novel DMTs and can decrease high screen-failure rates in AD clinical trials. **Keywords:** digital cognitive assessment; Alzheimer's disease; mild cognitive impairment; dementia; recruitment; clinical trials. **Disclosures:** DJB is a co-founder of Linus Health and declares ownership of shares or share options in the company. AJ, KT, CTS, JGO, RB, JP, CH, JS, and ST 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., TetraNeuron, Skin2Neuron, and MedRhythms. APL, DJB, ST, AJ, and JGO are listed as inventors on a pending patent assessing central nervous system functionality using a digital tablet and stylus. APL is further listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging, and applications of noninvasive brain stimulation in various neurological disorders, as well as digital biomarkers of cognition and digital assessments for early diagnosis of dementia.

P173- NEUROGENESIS HYPOTHESIS- CLINICAL TRIALS OF NA-831 FOR ALZHEIMER'S DISEASE AND NA-901 FOR MAJOR DEPRESSIVE DISORDER. L. Tran[1], F. Vu[1], Z. Tran[1] *(1. Biomed Industries, Inc. - San Jose (United States))*

Adult Hippocampal Neurogenesis (AHN) is persistent through the tenth decade of human life and is detectable in patients with Alzheimer's disease (AD). There was a marked and progressive decline of DCX+ cell numbers in AD patients as compared with neurologically healthy individuals. AHN impairment compromises hippocampal function in AD and MCI. This indicates that reduced AHN causes memory impairments and cognitive deterioration in the disease. AHN is crucial for the regulation of mood. If disturbed, it can have severe consequences for mental health. AHN has been shown to be involved in Major Depressive Disorder (MDD) and Alzheimer's disease pathology. The clinical trials of a new drug, NA-831 for the treatment of Alzheimer's Disease and NA-901 for Major Depressive Disorder presented here provide some evidence that AHN is involved in both AD and MDD. NA-831 and its analog, NA-901 are small drug molecules, exhibiting neuroprotection, neurogenesis and memory enhancing properties. Both can readily cross the blood brain barrier. NA-831 and NA-901 are administered orally. Phase 2 Clinical Trials of NA-831 for the treatment of Alzheimer's Disease. NA-831 is a small drug molecule, easily crosses the blood brain barrier with excellent bioavailability. The drug exhibits neuroprotection, neurogenesis and memory enhancing properties. A randomized clinical trial of NA-831 was performed in 112 participants with mild and moderate Alzheimer's disease, half received the drugs and half received placebo. The patients with MCI received 10 mg of NA-831 or placebo orally per day. The patients with mild and moderate Alzheimer's disease received 30 mg of NA-831 or placebo orally per day. Subjects with MCI to meet the NIA-AA core clinical criteria for mild cognitive impairment due to Alzheimer's disease. CDR score of 0.5 and a Memory Box score of 0.5 or greater at Screening and Baseline. MMSE score ≥22. Subjects with mild & moderate Alzheimer's disease to meet the NIA-AA core clinical criteria for probable Alzheimer's disease dementia. MMSE: 17-21. 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). mNA-831 was well-tolerated at 30 mg/day. There were no serious adverse events observed. Phase 1B Clinical Trials of NA-831 for Major Depressive Disorder (MDD). We completed a Phase 1B pilot study, which was a randomized, double-blind, fixed-dose, placebo-controlled, active reference study to investigate the efficacy, safety, and tolerability of two fixed doses (20 and 40 mg/d) of NA-831 vs. that of placebo after 6-week treatment in 32 adult patients with major depressive disorder (MDD). Venlafaxine XR was used as the active reference. The most common adverse effects reported in the active NA-831

treatment groups were mild headache and dry mouth. Both doses of NA-831 resulted in a significant improvement compared to placebo on the primary efficacy analysis. The difference between active treatment and placebo of ~7 points on the MADRS translates into a clinically relevant difference in response rates of 32.5 % units, compared to an average of 16% units for antidepressants approved by the USA and European health authorities. Treatment with NA-831 for 6-week was well tolerated and efficacious in reducing depressive and anxious symptoms in patients with MDD. The Neurogenesis Hypothesis has been shown to be a viable approach for further research for Alzheimer's disease (AD) and Major Depressive Disorder (MDD). Biomed is in the process of conducting a Phase 2B/Phase 3 trials of NA-831 for the treatment of AD and MDD.

P174- PRELIMINARY FINDINGS ON THE EFFECTS OF DONEPEZIL ON VISUOSPATIAL ABILITIES IN AMYLOD PET-POSITIVE MILD COGNITIVE IMPAIRMENT ASSESSED USING EYE-TRACKING. K.W. Kim[1], Q. Wang[2], S.J. Wang[3], B.S. Shin[3] *(1. Jeonbuk National University Medical School and Hospita - Jeonju (Korea, Republic of), 2. Jeonbuk National University Medical School - Jeonju (Korea, Republic of), 3. Jeonbuk National University Hospital - Jeonju (Korea, Republic of))*

Introduction: Cholinesterase inhibitors (ChEIs) have demonstrated efficacy in slowing cognitive decline in patients with Alzheimer's disease (AD) over extended periods. Nonetheless, evidence regarding their impact on cognitive test outcomes in patients with mild cognitive impairment (MCI) attributed to AD remains sparse. Conventional evaluation methods, such as cognitive tests, may lack the sensitivity needed to identify subtle therapeutic effects in MCI patients. Therefore, we propose a randomized controlled trial using eye-tracking to investigate the effects of donepezil in individuals with MCI due to AD. **Methods:** We enrolled 25 participants with MCI, all of whom tested positive for amyloid using positron emission tomography (PET). The participants were divided into two groups: 13 in the donepezil group and 12 in the control group. We utilized eye-tracking metrics and digital pen data during the execution of a simplified version of the Rey Complex Figure Test (RCFT). Eye-tracking data was collected while participants copied the simplified RCFT. Following standard gaze mapping, we measured eye-tracking metrics, including the number and duration of fixations within the perceptual and working spaces. The primary outcome measure focused on changes in the ratio of fixations (working space/perceptual space) from baseline to 12 weeks, assessed via eye-tracking metrics. Statistical analysis of the primary outcome was conducted using the paired Wilcoxon test to compare the donepezil and control groups between the baseline and follow-up sessions. **Results:** The eye-tracking metrics revealed a significant increase in the ratio of the first fixation duration (working space/perceptual space) in the donepezil group at the follow-up visit compared to the baseline visit ($P = 0.005$). Conversely, the control group showed no significant changes in the first fixation duration. **Conclusion:** This study highlights the potential utility of eye-tracking metrics as valuable digital biomarkers for detecting subtle cognitive changes. The significant alterations observed in the donepezil group suggest that eye-tracking could be a sensitive tool for assessing the efficacy of treatments in patients with mild cognitive impairment due to Alzheimer's disease. These findings underscore the need for further research to validate and expand the use of eye-tracking metrics in clinical settings, potentially offering a non-invasive and precise method for monitoring cognitive changes over time. This research was supported by Eisai Korea Inc. **Trial registration:** Clinical Research Information Service, Republic of Korea (CRIS, cris.nih.go.kr) KCT0006236. Registered on June 10, 2021. **References:**
1. Kim KW, Wang Q, Koo SH, Shin BS. A single-center, randomized, parallel design study to evaluate the efficacy of donepezil in improving visuospatial abilities in patients with mild cognitive impairment using eye-tracker: the COG-EYE study protocol for a phase II trial. Trials. 2022 Sep 27;23(1):813. doi: 10.1186/s13063-022-06781-0.

P175- UNDERSTANDING THE EARLY ALZHEIMER'S DISEASE EXPERIENCE: PERSPECTIVES FROM PATIENTS AND CAREGIVERS. J. Dine[1], J. Lee[2], A. Shewale[2], J. Stokes[2], B. Basnyat[1], M. Brown[1], A. Greenblatt[1], E. Shirneshan[2] *(1. RTI International - Research Triangle Park (United States), 2. AbbVie - North Chicago (United States)*

Background: Alzheimer's disease (AD) profoundly affects not only the patients, but also their caregivers. Additionally, given the nature of the disease, both patients and caregivers are in unique positions to provide their own perspectives on how AD presents, especially in early-stage AD. This research aims to explore the experiences of patients with early-stage AD as reported by affected individuals and their caregivers, to gain a more holistic understanding of the disease. **Methods:** This qualitative study involved individual interviews with adult caregivers (n = 24) and patients (n = 24) diagnosed with mild cognitive impairment due to AD, mild AD, and moderate AD in the United States. To qualify, caregivers had to provide direct or informal (unpaid) support for ≥10 hours per week to AD-diagnosed patients. Patient participants were required to have a physician-provided diagnosis of AD and dementia stage confirmed in the past 6 months. Semi-structured interviews, approximately 60 minutes in duration, were conducted, audio-recorded, and transcribed for qualitative analysis. Both patients and caregivers were asked to describe the patient's current symptoms or problems. This study was reviewed and granted exemption by the Research Triangle Institute Institutional Review Board. **Results:** The most frequently reported symptoms by both patients and caregivers were associated with instrumental activities of daily living such as difficulty with household chores [PT = 18 (75%); CG = 23 (96%)], food preparation [PT = 15 (63%); CG = 20 (83%)], driving [PT = 17 (71%); CG = 17 (71%)], and remembering appointments [PT = 20 (83%); CG = 21 (88%)]. Patients reported mood-related symptoms, particularly anxiety/stress [PT = 14 (58%); CG = 2 (8%)] and irritation/agitation [PT = 22 (92%); CG = 7 (29%)], more frequently than caregivers did. Specific memory-related problems such as word recall [PT = 14 (58%); CG = 3 (13%)] and misplacing/losing items [PT = 23 (96%); CG = 9 (38%)] were also reported more often by patients. Caregivers on the other hand were more likely to report problems related to patients' independence, such as their inability to be left alone [PT = 4 (17%); CG = 14 (58%)] or stay safe [PT = 1 (4%); CG = 11 (46%). Caregivers also reported difficulties with other daily activities, including grooming [PT = 10 (42%); CG = 18 (75%)], taking medication correctly [PT = 12 (50%); CG = 21 (88%)], and appointment planning [PT = 3 (13%); CG = 14 (58%)]. **Conclusion:** This research underlines that while patients and caregivers align in many aspects of their perspectives on the AD disease experience, their individual perspectives provide unique insights that can help in developing more personalized and effective strategies for managing AD. These distinct perspectives

provide a more comprehensive view of the early stages of AD, highlighting the importance of considering multiple viewpoints in understanding and managing the disease. **Keywords:** Endpoints, qualitative research. **Disclosures:** AbbVie funded this study and participated in the study design, research, analysis, interpretation of data, reviewing, and approval of this publication. All authors participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. Jae Lee, Anand Shewale, Jonathan Stokes, and Elaheh Shirneshan are employees of AbbVie and may hold AbbVie stock/option. Jennifer Dine, Bonita Basnyat, Michelle Brown, and Amy Greenblatt are employees of RTI. RTI services used to conduct the study research and analysis was funded by AbbVie.

P176- IMPACT OF RATER CHANGE ON CLINICAL DEMENTIA RATING DATA: A RETROSPECTIVE ANALYSIS. D. Miller[1], X. Wang[1], A. Kott[2] *(1. Signant Health - Blue Bell, PA (United States), 2. Signant Health - Prague (Czech Republic))*

Background: Rater change is inevitable in often lengthy clinical trials in Alzheimer's disease. We have previously reported that rater change significantly increased the magnitude of MMSE change between screening and baseline in 6 out of 13 clinical trials in early AD. In the current post-hoc analysis we wanted to assess whether rater change impacts CDR data after randomization. **Methods:** A total of 20,925 baseline, first and second post-baseline CDR-Sum of Boxes (CDR-SB) data (reflecting 6975 patients) were obtained from 12 Alzheimer's disease clinical trials. We analyzed the impact of rater change on the absolute CDR-SB change separately at the first and the second post-baseline visits. Given differences in protocol design and visit windows, data were analyzed separately for each protocol. General linear models and ANOVA models were used to analyze the data. **Results:** Out of the 12 analyzed protocols, at the first post-baseline visit, rater change did significantly increase the magnitude of CDR-SB change in 5 protocols, ranging between 0.2 to 0.4 CDR-SB points. In the remaining 7 protocols, the results were not significant. At the second post-baseline visit the results were mixed depending on the type of scenario that occurred. In the 4 of 11 protocols where three different raters rated the three visits, a significant increase in the magnitude of CDR-SB change from baseline ranging between 0.5 to 2.4 CDR-SB points was identified. On the other hand, rater change that happened only between the first and second post-baseline visits did not significantly impact any of the tested protocols. Two protocols were affected when the rater change occurred between baseline and first post-baseline visits, but the second post-baseline visit was assessed by the baseline CDR rater. In these instances, the magnitude of CDR-SB change from baseline decreased between 0.6 to 1.0 points. **Conclusion:** Our post-hoc analyses indicate that CDR rater change has the potential to impact on CDR variability, but the results are inconsistent. Not surprisingly, having different CDR raters at all assessed visits had the largest impact on the magnitude of CDR-SB change from baseline. Given the results, rater change should be considered a risk factor to assessment reliability and adequate steps should be taken to limit the frequency of rater change. In instances where rater change is inevitable, mitigation strategies including robust initial calibration and when possible, co-rating before the actual change should occur. The key limitations of our findings are driven by the post-hoc nature of the analyses and the fact that all analyses were conducted on blinded data, preventing us to assess the actual impact of rater change on signal detection.

P177- A STRATEGIC APPROACH TO RIGOROUS CLINICAL ENDPOINT STRATEGIES IN DRUG DEVELOPMENT – AN EXAMPLE FROM A PHASE 2 TRIAL IN EARLY ALZHEIMER´S DISEASE (EXPLAIN-AD). F. Loreto[1], A. Sverdlov[2], N. Pezous[1], N. Coello[1], A. Murphy[3], P. Allred[4], P. Rock[1], G. Erdemli[3], J. Whittle[5], J. Saleh Subaie[6], J.G. Snædal[7], J. Curcic[8], K. Hannesdottir[4] *(1. Novartis - Basel (Switzerland), 2. Novartis - East Hanover (United States), 3. Novartis - Cambridge (United States), 4. Novartis Biomedical Research - Cambridge (United States), 5. Novartis Biomedical Research - Chicago (United States), 6. Novartis - Mexico City (Mexico), 7. National University Hospital of Iceland | LSH · Department of Geriatrics - Reykjavik (Iceland), 8. Novartis Biomedical Research - Basel (Switzerland))*

Background: Drug development in neuroscience is complex, with over 70% of late-stage trials failing due to efficacy-related reasons (Hwang et al. 2016). The low probability of success in this space may lead to companies reducing investments, thus slowing down advancements in the field and the delivery of new treatments to patients. In Alzheimer's disease (AD), a disease area that has historically seen a high rate of trial failure, the number of new chemical entities in development declined disproportionately, registering a 13% drop between 2023 and 2024 (Cummings et al. 2024). While the understanding of AD has been rapidly evolving in the last decades, relatively little progress has been made with respect to clinical outcome assessments, which might contribute to the high trial failure rate (Jutten et al. 2023). At Novartis, the Neuropsychology eXpert Team (NeXT) aims to tackle this issue by adopting a systematic data-driven approach to clinical endpoint strategies across neuroscience indications. This presentation will provide a step-by-step description of building a rigorous clinical endpoint strategy for a 6-month phase 2 trial in early AD (EXPLAIN-AD; NCT04795466). **Methods:** NeXT is an internal cross-functional team of experts bringing together neuropsychology, analytics, strategic, and regulatory expertise to support clinical endpoint strategies across neuroscience indications. This team follows a systematic approach. Firstly, once the target patient population and objective of the trial have been defined, the team determines what are clinically relevant domains, and what treatment effects can be expected on those domains with the mode of action of the drug. Secondly, the team identifies relevant endpoints and appropriate internal and external datasets to test the psychometric properties of these endpoints. Finally, the team rank orders the performance of the endpoints, based on a predefined success criteria, including site and patient acceptance and burden, as well as regulatory acceptance. This multi-disciplinary strategic approach incorporates thorough assessments of the available literature, consultations with external experts and when needed, reports from patient insight panels. In the example of EXPLAIN-AD, all of the aforementioned steps were taken to build the clinical endpoint strategy. A patient advisory board was conducted during early protocol development in order to get patient and study partner feedback on the clinical endpoint strategy, and both internal and external historical trials were used to interrogate psychometric properties including ceiling and floor effects, sensitivity to change and variability in the target patient population. **Results:** Through the application of the aforementioned approach, NeXT ensures the selection of clinical endpoints that are not only sensitive to the cognitive and functional deficits characteristic of AD, but that maximize the likelihood of detecting the clinically relevant effects of investigational drugs. EXPLAIN-AD included measures on cognition, function and neuropsychiatric

symptoms. The Neuropsychological Test Battery (NTB) ranked the highest on a predefined success criteria and was selected as the primary endpoint for the trial. Additional computerized tests were included to address day-to-day fluctuations and to more thoroughly assess cognitive domains related to the drug's mode of action. Remote at-home assessments were included based on patient feedback. Measures of function were selected based on internal and external datasets, and study partners were allowed to remotely monitor neuropsychiatric symptoms via a tablet in order to avoid recall bias. **Conclusion:** Given the complexity and heterogeneity of AD, the dramatically high failure rate, and the different mechanisms of action of drug candidates for AD, a thorough and data-driven evaluation is essential for selecting fit-for-purpose neuropsychological measures when designing clinical endpoint strategies. Novartis' NeXT approach underscores its mission to ensure that clinical trials do not produce inconclusive results due to unreliable endpoints. Efforts to unveil the complex biology of AD must go hand-in-hand with efforts to improve methods to accurately measure the clinical manifestations of the disease. This imperative need in AD drug development is instrumental in advancing effective treatments for patients living with AD. The NeXT approach to tailored clinical endpoint strategies across neuroscience indications underlines Novartis' commitment to driving innovation and promoting reliable and meaningful outcomes in clinical trials. **Keywords:** Clinical drug trials, Neuropsychology, Clinical endpoint strategies, Alzheimer's disease. **Clinical Trial Registry:** NCT04795466; https://clinicaltrials.gov. **Disclosures:** All authors, apart from F.L. and J.G.S., are shareholders of Novartis Pharma AG. **References:** Cummings, J., Lee, G., Zhong, K., Fonseca, J., & Taghva, K. (2021). Alzheimer's disease drug development pipeline: 2021. Alzheimer's & Dementia: Translational Research & Clinical Interventions, 7(1), e12179. Hwang, T. J., Carpenter, D., Lauffenburger, J. C., Wang, B., Franklin, J. M., & Kesselheim, A. S. (2016). Failure of investigational drugs in late-stage clinical development and publication of trial results. JAMA internal medicine, 176(12), 1826-1833. Jutten, R. J., Papp, K. V., Hendrix, S., Ellison, N., Langbaum, J. B., Donohue, M. C., ... & Sikkes, S. A. (2023). Why a clinical trial is as good as its outcome measure: A framework for the selection and use of cognitive outcome measures for clinical trials of Alzheimer's disease. Alzheimer's & Dementia, 19(2), 708-720.

LP085- COGNITIVE ASSESSMENT AND WEARABLE SENSOR-BASED GAIT AND BALANCE ASSESSMENT IN STUDIES OF ALZHEIMER'S DISEASE AND MILD COGNITIVE IMPAIRMENT: A PRELIMINARY REVIEW. Rebecca Lydon[1], Adam Jagodinsky[1], Reina Davis-Aoki[1], Prateek Verma[1], Kristen Sowalsky[1,] *(1. Clario, Philadelphia, PA, (United States))*

Background: Gait and balance deficits are present in patients with diminished cognitive function due to overlapping cortical networks in the central nervous system [1, 2]. Given the interplay between gait and cognition, quantitative gait measures show potential as clinical measures of cognitive impairment and dementia [3,4,5]. Wearable sensor-based gait assessment offers a feasible approach to monitor gait impairment in large studies, however a better understanding of the concurrent use of sensor-based gait assessment with traditional measures of cognitive function in mild cognitive impairment (MCI) and Alzheimer's Disease (AD) populations is important for determining utility for clinical trials. **Methods:** A literature review was conducted in PubMed to assess studies that incorporated cognitive assessment and wearable sensor-based gait or balance assessment in AD and MCI populations. The search was conducted using the following inclusion criteria: 1) MCI or AD populations. 2) Cognitive assessment (i.e. Mini-Mental Status Examination: MMSE, Montreal Cognitive Assessment: MoCA). 3) Wearable sensor. 4) Gait or balance assessment. Review articles and studies not utilizing wearables for gait or balance assessment were excluded. **Results:** Out of 56 studies identified, only 17 included cognitive assessment and wearable- based analysis of gait or balance. The indications included AD (1), MCI (12), and both (4). Cognitive assessments reported include MMSE (11), MoCA (9), and both (3). The most common instrumented tests were walk tests (13: 6 MMSE, 5 MoCA, 2 Both) and Timed Up and Go (TUG) (4: 1 MMSE, 2 MoCA, 1 Both), in addition to daily monitoring (2: 1 MMSE, 1 MoCA) and balance (1: 1 MoCA). Sensor location included lumbar (7: 5 MMSE, 2 MoCA), wrist/arms (2: 1 MMSE, 1 Both), feet/ankles (3: 1 MMSE, 1 MoCA, 1 Both), and multiple sensor configurations (5: 1 MMSE, 3 MoCA, 1 Both). Inertial measurement units (IMUs) were implemented most frequently (13: 6 MMSE, 4 MoCA, 3 Both), followed by accelerometers (4: 2 MMSE, 2 MoCA). Two studies reported a significant association between gait parameters and MoCA scores. **Conclusion:** In AD and MCI studies using both wearable sensors and cognitive assessments, gait was measured most using a single sensor on the lumbar region, although multi-sensor configurations were also implemented to assess movement in the extremities. Walk tests were the most common form of instrumented gait assessment used together with cognitive assessments, followed by the instrumented TUG. Only two studies implemented daily monitoring, and one study assessed balance. There was no major distinction between use of MoCA and MMSE when considering the sensor location, wearable sensor type, and instrumented test. This review provides insights into concurrent implementation of cognitive assessment and wearable sensor-based gait/balance measurement in AD and MCI studies. Further investigation is needed to explore the interrelationship between cognitive assessments and wearable sensor-based gait outcomes, as well as implications for test selection and sensor placement. **Keywords:** wearable sensors, gait and balance, cognitive assessment, clinical outcome assessment. **Clinical Trial Registry:** N/A. **Data Deposition:** N/A. **Disclosures:** All authors are employees of Clario. **References:** 1. Morris R, et al. Neuroscience & Biobehavioral Reviews 2016; 64: 326-345. https://doi.org/10.1016/j.neubiorev.2016.02.012; 2. Rosso A, et al. Neurology 2017; 89 (4): 336-342. https://doi.org/10.1212/WNL.0000000000004153; 3. Montero-Odasso M, et al. The Journals of Gerontology 2019: Series A, 74(6), 897-909. https://doi.org/10.1093/gerona/gly148; 4. Valkanova V, et al. Gait & Posture 2017; 215-223. https://doi.org/10.1016/j.gaitpost.2017.01.024; 5. Buckley C, et al. Brain Sciences 2019; 9(2), 34. https://doi.org/10.3390/brainsci9020034.

LP086- ASSOCIATIONS BETWEEN CENTRAL AND PERIPHERAL BIOMARKERS FOR ALZHEIMER'S DISEASE IN COMMUNITY-DWELLING OLDER ADULTS AT RISK OF DEMENTIA. M.A.P. Parra[1], A. Gonzalez Hernandez[2], J. Bonilla Santos[2], R. Gonzalez Montealegre[2], Y. Cala[2], D. Verge[3], G. Fernandez[4] *(1. Glasgow University - Glasgow (United Kingdom), 2. Surcolombiana - Neiva (Colombia), 3. ViewMind - Copenage (Denmark), 4. ViewMind - Bahia Blanca (Argentina))*

Background: Electrophysiological activity drawn from the Visual Short-Term Memory Binding (VSTMB) Test (Parra et al., 2022), has identified older adults at risk of Alzheimer's

disease (AD) dementia in clinic-based samples (Pietto et al., 2016) and more recently in community-based underrepresented samples from southern Colombia (Gonzalez-Montealegre et al., under revision). We recently demonstrated that oculomotor behaviours evaluated by ViewMind Atlas, a novel digital biomarker assessing Eye-tracking and Pupillometry (ETP) linked to VSTMB also identified risk profiles in similar populations (Parra, Gonzalez-Hernandez, et al., 2023; Parra, Lopera, et al., 2023). We investigated whether such central (EEG) and peripheral (ETP) biomarker profiles are associated. **Methods:** Following (Bonilla-Santos et al., 2023)'s procedures, 65 adults met the clinical criteria for Mild Cognitive Impairment (MCI - Age: 62.83±6.11, Education: 8.05±5.83), and 71 for healthy controls (HC - Age: 59.31±6.01, Education: 11.84±5.76). They all underwent standard clinical, functional, and neuropsychological assessments (i.e., a battery comprising memory, attention, language, praxis, and executive functions tests). Electrophysiological (EEG) and oculomotor activity (ETP) were also recorded synchronised with the VSTMB Test. Groups were compared using t-tests controlling for type-I error. Regression models were used to explore whether oculomotor behaviours linked to VSTMB were associated with Event-Related Potentials also linked to this memory function. Age and education were added as predictors for all these models. **Results:** Patients with MCI presented with a predominant amnestic profile. As previously reported, they displayed significant VSTMB deficits. Analysis involving the entire sample revealed that pupil behaviours during both the encoding [R2=9.7, F=3.41 p=0.023] and retrieval [R2=10.2, F=3.52 p=0.020] stages of the VSTMB Test were significantly predicted by a Late Processing Positivity (LPP) elicited over the right frontocentral region. Further analysis involving groups separately revealed that such an association was driven by MCI patients only [Encoding: HC: R2=5.8, F=0.394 p=0.758, MCI: R2=36.67, F=7.36 p<0.001; Retrieval: HC: R2=7.4, F=0.241 p=0.867, MCI: R2=38.7, F=7.94 p<0.001]. We included additional models accounting for fixations during a Go/No-Go task to explore this frontal association further. Similar results were found but only reached marginal significance. **Conclusion:** Community-dwelling older adults at risk of dementia who had not sought medical advice at the time of testing but met MCI criteria were found to display cognitive and biomarker profiles similar to those seen in MCI patients recruited and tested in clinics. Our sample was, therefore, in earlier stages of MCI. The pattern of associations here reported suggests the potential involvement of compensatory mechanisms linked to this cognitive marker. Pupils' responses are related to cognitive load (Sekar et al., 2024) and are severely affected in patients with AD dementia when they perform the VSTMB test (Fernández & Parra, 2021). The frontal activity underpinning pupil behaviours during VSTMB in the very early stages of MCI seemingly suggests a functional reorganisation which might aim at compensating for the impact that neurodegenerative changes are exerting on such brain circuits. Further studies will need to explore the mechanistic and diagnostic value of these findings. **Keywords:** Mild Cognitive Impairment, Eye-Tracking, EEG, Cognitive Markers, AI, Biomarkers, Preclinical Detection. **Disclosures:** MAP is a consultant for ViewMind and serves as its Neuroscientific Officer. DV and GF are ViewMind Chief Medical Officer and ViewMind Chief Scientific Officer, respectively. **References:** Bonilla-Santos, J., González-Hernández, A., Cala-Martínez, D. Y., Gómez-Morales, D. F., Calceto-Garavito, L. N., Forero-Aldana, A. E.,…Parra, M. A. (2023). Prevalence of Mild Cognitive Impairment in Southern Regions of Colombia. Journal of Alzheimer's Disease Reports, 7, 1455-1464. https://doi.org/10.3233/ADR-230041; Fernández, G., & Parra, M. A. (2021). Oculomotor Behaviors and Integrative Memory Functions in the Alzheimer's Clinical Syndrome. Journal of Alzheimer's Disease, 82(3), 1033-1044. https://doi.org/10.3233/JAD-201189; Parra, M. 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Journal of Alzheimer's Disease, 53(4), 1325-1340; Sekar, A., Panouillères, M. T., & Kaski, D. (2024). Detecting Abnormal Eye Movements in Patients with Neurodegenerative Diseases: Current Insights. 16, 3-16.

LP087- THE EFFECT OF EDUCATION ON ATN BIOMARKERS OF ALZHEIMER'S DISEASE. K. Yeshin[1], K. Sunghoon[1], K. Sungheon[1] *(1. Kangwon National University Hospital - Chuncheon (Korea, Republic of))*

Background and Objective: Education, a commonly used proxy for cognitive reserve, is believed to provide protective effects against cognitive decline in Alzheimer's disease (AD). Individuals with higher education may resist the pathological burdens of AD through alternative neural mechanisms, such as brain network reorganization. However, the direct association between education and pathological burden—specifically related to ATN (Amyloid, Tau, and Neurodegeneration) biomarkers—is not fully understood. This study aimed to evaluate the relationship between education and ATN biomarkers, with a focus on the influence of the APOE4 allele, a known genetic risk factor for AD. **Methods:** This cross-sectional study utilized data from 1,076 participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI), divided into four groups: cognitively normal (CN; n=336), early amnestic mild cognitive impairment (aMCI; n=279), late aMCI (n=279), and AD (n=182). ATN biomarkers were assessed using cerebrospinal fluid (CSF) levels of Aβ1-42 and p-Tau, and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) to measure brain metabolism. Multiple linear regression models were applied to examine the association between education levels and these biomarkers, adjusting for age, sex, and APOE4 status. **Results:** Significant differences in biomarker levels were observed across diagnostic groups. CSF Aβ1-42 levels were significantly lower, and CSF p-Tau levels significantly higher in the AD group compared to other groups. FDG-PET results showed a progressive decline in brain metabolism, with lower FDG-PET values observed in the AD group. The presence of the APOE4 allele was associated with an increased pathological burden across all groups. Significantly, in APOE4 carriers within the early aMCI group, higher education levels were associated with lower tau pathology, suggesting a protective effect against neurodegeneration. **Conclusion:** This study suggests that education may confer resistance to Alzheimer's disease pathology, particularly in APOE4 carriers at the early aMCI stage, by reducing p-Tau burdens. These

findings highlight the potential role of education in delaying neurodegenerative changes in the early stages of cognitive decline. However, the underlying biological mechanisms remain to be elucidated, and further research is necessary to explore how education influences the progression of AD pathology.

LP089- VALIDATION OF A PRECISION MEASURE OF COGNITIVE CHANGE IN A PHASE II CLINICAL TRIAL IN EARLY AD: THE EARLY AND MILD ALZHEIMER'S COGNITIVE COMPOSITE (EMACC). S. Barnum[1], J. Jaeger[2], K. Lisle[3] *(1. Cognition Metrics LLC - Lake Orion (United States), 2. Cognition Metrics LLC - Hixson (United States), 3. Consultant Neuropsychologist - Geneva (United States))*

Background: Cognitive measures with higher precision produce more robust and replicable signals with smaller sample sizes. The Early and Mild Alzheimer's Cognitive Composite (EMACC, Jaeger 2017) is an empirically derived composite of validated clinical neuropsychological tests statistically optimized for amyloid associated cognitive decline in early AD. Building on its development using multiple longitudinal aging cohorts, we report data from an ongoing phase two clinical trial that confirms feasibility and examines replicability and validation as compared to other endpoints. **Methods:** Data from an ongoing phase II, double-blind, placebo-controlled trial of early Alzheimer's disease sponsored by INmune Bio were used in these analyses (ClinicalTrials.gov ID NCT05318976). Sites from Australia, UK, Poland, Spain, France, Germany and Canada are represented. Screening and baseline data for the EMACC, CDR, and MMSE (screening only), were included in the analyses. The EMACC was computed by averaging the z-scores for 6 variables: Digit Symbol Coding Total Score, Average of Trail-Making Test Parts A and B, Average of Digit Span-Forward and Backward, Letter Fluency, Category Fluency, and a measure of Verbal Learning (International Shopping List Task), using each test's baseline mean and standard deviation. Psychometric analyses include descriptive statistics to examine normality of distributions, Pearson correlations to evaluate test-retest reliability between screening and baseline visits and construct validity by way of associations with CDS-SB and MMSE. Paired-sample t-tests were used to evaluate practice effects between screening and baseline and ANOVA was used to estimate the difference on EMACC as a function of baseline CDR Global rating. **Results:** Screening and baseline data from 140 participants (48% Female) with a mean age of 73 years (SD = 6.47), meeting Alzheimer's disease diagnostic criteria at Jack stage 3 (MCI) or 4 (Mild AD) were available for this interim analysis. The EMACC score was normally distributed with no evidence of floor or ceiling effects. Statistically significant practice effects were evident on Digit Symbol-Coding, but not EMACC score. Mean duration between screening and baseline was 33 days (SD 10.7). Test-retest correlations for each EMACC component were medium to high (0.74 to 0.92), with an overall test-retest correlation of 0.93 for the EMACC score. Correlations between EMACC and CDR-SB and MMSE (at screening), were highly significant (both $p<.001$), and EMACC distinguished CDR Global Score levels of .5 vs. 1.0 (effect size=0.87, $p<.001$). Additional available cases will be included in the final presentation. **Conclusion:** The EMACC is being successfully administered in a global clinical trial with high data integrity. Component measures demonstrate high levels of test-retest reliability from screening to baseline, with slight anticipated practice effects noted on one scale. The EMACC z-score composite shows high test-retest reliability and outstanding validity. There is a significant and clinically consistent relationship with overall dementia severity on CDR-SB. EMACC robustly distinguishes between CDR Global ratings of 0.5 and 1. Adoption of the EMACC has the potential to streamline clinical trials, reducing patient burden and sponsor cost while advancing development of new therapies by using precise and clinically meaningful cognitive measures in early AD. **Keywords:** Clinical outcome assessments, Cognitive testing, Psychometrics. **Disclosures:** This work was supported by INmune Bio. Sarah Barnum and Lisle Kingery are independent consultants working with INmune Bio. Judith Jaeger is the president and owner of Cognition Metrics, LLC which received funding from INmune Bio to support this work. **References:** Jaeger, J., Hagen, C.E., Loft, H., Lim, YY., Aschenbrenner, A., Segerdahl, M., Tong, G., Mielke, M., Hassenstab, J, Stricker, N. The Early AD/ MCI Alzheimer's Cognitive Composite (EMACC): Development and preliminary validation across four longitudinal cohorts of a cognitive endpoint for clinical trials in the MCI and Early AD stage of disease. (Abstract) Journal of Prevention of Alzheimer's Disease:4(4): 415-417, 2017.

LP090- PILOT STUDY OF A CONVERSATIONAL AI VOICEBOT TO ADMINISTER THE AUTOBIOGRAPHICAL RECALL QUESTIONS OF THE CLINICAL DEMENTIA RATING. R. Nosheny[1], J. Weston[2], E. Fristed[2], J. Fockler[1], J. Eichenbaum[1], D. Flenniken[1], K. Moulder[3], J. Morris[3], M. Weiner[1] *(1. University of California, San Francisco - San Francisco (United States), 2. Novoic, Ltd. - London (United Kingdom), 3. Knight Alzheimer's Disease Research Center, Department of Neurology, Washington University School of Medicine - St. Louis (United States))*

Background: The Clinical Dementia Rating® (CDR®) is well-validated and widely used to detect and stage cognitive and functional impairment due to Alzheimer's Disease (AD), and as an AD clinical trial outcome measure. The need for a trained assessor for administration and scoring limits its scalability. The objective of this pilot study was to determine feasibility, usability, and user acceptance of an artificial intelligence (AI) powered conversational voicebot to administer the autobiographical recall questions of the CDR memory domain to participants and their study partners in a remote, unsupervised setting. **Methods:** Participant-study partner pairs (dyads; all spouses with a participant age 55+) were enrolled from the UCSF Brain Health Registry and emailed unique links to separately interact with the voicebot. The voicebot first instructed the study partner to describe two recent events involving the participant and to provide event details (e.g., location, time of day, duration, who was involved, when it ended, how the participants got there). Then the voicebot asked the participant to describe the same events, providing cues to orient the participant to correct events if necessary, and collected the same event details. After study completion, dyads completed an online questionnaire about their experience. An objective memory metric (ranging from 0 to 1, where 1 indicates near-perfect recall) was automatically extracted based on the proportion of event details correctly recalled by the participant. **Results:** Out of 542 dyads invited, 30 (6%) enrolled. Of those enrolled, 22 study partners (73%) and 16 complete dyads (53%) completed the assessment. Participants had a mean age of 74.8 ± 5.9 (range: 66 - 90+), 17.4 ± 1.2 (range: 16-20) years of education, 38% were female, and 6% self-reported a diagnosis of Mild Cognitive Impairment (MCI), AD, or dementia. Study partners had a mean age of 72.8 ± 8.6 (range: 56 - 90+), 17.6 ± 1.8 (range: 13-20) years of education, and 62% were female. Duration of voicebot interview was 6.1 ± 1.6

(range: 4.3-9.5) minutes for study partners and 5.5 ± 1.2 (range: 3.8-7.9) minutes for participants. The mean automated recall score was 0.651 ± 0.137 (range: 0.384-0.905). Of those who completed a feedback questionnaire (N=33), 29 (88%) rated the difficulty of completing the task as 1 or 2 on a five point scale (1=least difficult, 5=most difficult); 32 (97%) would agree to participate in a similar study; 12 (36%) would prefer to complete this task with a voicebot versus a real person; and 10 (30%) would prefer a voicebot versus an online questionnaire. **Conclusion:** This study supports the feasibility, usability, and acceptance of a conversational AI voicebot to obtain data about autobiographical recall of recent events from dyads, which is important for accurately assigning the memory box score of the CDR and identifying those with MCI. Future work will develop and validate a complete, voicebot-based CDR (vCDR) with novel, automated scoring. The vCDR could be used for efficient, scalable, automated, accurate detection of impairment and screening and staging of dementia in clinical research and trials, healthcare settings, and for population-based screening. **Keywords:** Alzheimer's Disease, remote assessment, digital assessment, voice/speech-based assessment, cognitive decline, activities of daily living, Clinical Dementia Rating® (CDR®). **Disclosures:** RLN reports grants to institution from NIH, California Department of Public Health, and Genentech, Inc. JW is an employee, director, and shareholder of Novoic Ltd. EF is an employee, director, and shareholder of Novoic Ltd. JF reports no disclosures. JE reports no disclosures. DF reports no disclosures. KM reports no disclosures. JCM reports grant to institution from NIH (grants # P30 AG066444; P01AG003991; P01AG026276). MWW reports grants from National Institutes of Health (NIH), grants from Department of Defense (DOD), grants from Patient-Centered Outcomes Research Institute (PCORI), grants from California Department of Public Health (CDPH), grants from University of Michigan, grants from Siemens, grants from Biogen, grants from Hillblom Foundation, grants from Alzheimer's Association, grants from The State of California, grants from Johnson & Johnson, grants from Kevin and Connie Shanahan, grants from GE, grants from VUmc, grants from Australian Catholic University (HBI- BHR), grants from The Stroke Foundation, grants from Veterans Administration, personal fees from Acumen Pharmaceutical, personal fees from Cerecin, personal fees from Dolby Family Ventures, personal fees from Eli Lilly, personal fees from Merck Sharp & Dohme Corp., personal fees from National Institute on Aging (NIA), personal fees from Nestle/Nestec, personal fees from PCORI/PPRN, personal fees from Roche, personal fees from University of Southern California (USC), personal fees from NervGen, personal fees from Baird Equity Capital, personal fees from BioClinica, personal fees from Cytox, personal fees from Duke University, personal fees from Eisai, personal fees from FUJIFILM-Toyama Chemical (Japan), personal fees from Garfield Weston, personal fees from Genentech, personal fees from Guidepoint Global, personal fees from Indiana University, personal fees from Japanese Organization for Medical Device Development, Inc. (JOMDD), personal fees from Medscape, personal fees from Peerview Internal Medicine, personal fees from Roche, personal fees from T3D Therapeutics, personal fees from WebMD, personal fees from Vida Ventures, personal fees from The Buck Institute for Research on Aging, personal fees from China Association for Alzheimer's Disease (CAAD), personal fees from Japan Society for Dementia Research, personal fees from Korean Dementia Society, outside the submitted work; and I hold stocks or options with Alzheon Inc., Alzeca, and Anven.

LP091- CLINICAL MEANINGFULNESS OF COGNITIVE DECLINE MEASURED USING THE PRECLINICAL ALZHEIMER'S DISEASE COGNITIVE COMPOSITE SCORE (PACC), IN THE PRECLINICAL STAGE OF ALZHEIMER'S DISEASE. R. Canovas[1], R. Shishegar[1], M. Cespedes[2], C. Fowler[3], H. Sohrabi[4], J. Fripp[2], Y.Y. Lim[5], J. Hassenstab[6], P. Maruff[7], J. Doecke[2], A. Adopic Resesarch Group[8] *(1. Australian E-Health Research Centre, CSIRO, - Melbourne (Australia), 2. Australian E-Health Research Centre, CSIRO, - Brisbane (Australia), 3. The University of Melbourne - Melbourne (Australia), 4. Murdoch University - Perth (Australia), 5. Monash University - Melbourne (Australia), 6. Washington University - Saint Louis (United States), 7. Cogstate - Melbourne (Australia), 8. ADOPIC - Melbourne (Australia))*

Background: Clinical trials of disease modifying therapy (DMT) drugs in preclinical AD raises new design challenges, including how best to determine the clinical meaningfulness of any benefits observed. One approach is to compare rates of progression from preclinical to symptomatic AD in active and placebo groups. While disease progression is clinically meaningful, the number of events may be low necessitating use of large samples, or long follows. Smaller and shorter trials of DMT may require different benchmarks for understanding the meaning of any effects observed. Changes in cognitive composite scores, such as the Preclinical Alzheimer's Cognitive Composite (PACC), may be sensitive to effects of DMTs, particularly over short study periods (i.e. 3 years), although criteria for clinical meaningfulness of PACC changes are not developed. This study estimated clinically meaningful change and minimal within person change (MWPC) in preclinical AD. **Methods:** Demographic, clinical and biomarker data was obtained from the pooled ADNI, AIBL and OASIS preclinical AD cohorts. A harmonized ADCS-PACC was computed per subject in each cohort and visit. The global Clinical Disease Rating Scale (CDR) score was also collected. Clinical disease progression was defined when CDR increased from 0 to >/=0.5 (i.e. progressors) and PACC data for three years prior to progression was submitted to analyses. Participants whose CDR rating did not change were classified as stable, and PACC data for three years was submitted to analyses. Estimates of PACC stability were obtained by computing the mean and SD of slope of three-year change in the stable group. Second, responsiveness to change was estimated by comparing three-year change in PACC between stable and progressor groups. The reliability of the PACC in the stable group was determined using ICCs and the mean and SD of the stable group were used to develop criteria for small (-0.5SD) medium (-1SD) and large (-1.5 SD) meaningful within person change (MWPC). Fourth, proportions of the progressor group with small, medium and large decline on the PACC were computed. **Results:** Three-year data on the PACC was available for 203 stable and 91 progressor participants. In the stable group, rate of three-year change on the PACC was slightly negative (-0.002, SD= 0.147). Three-year PACC decline prior to clinical disease progression was -0.19 (SD = 0.241, Hedges effect size g = -1.31: 95%CIs = -1.57, –1.03). Distributions of PACC decline slopes were significantly smaller in the progressor than stable group (p<0.0001). Reliability of the PACC in the stable group was high (ICC = 0.733). Of the progressor group, 74%, 56% and 30% showed small, medium and large three-year PACC decline. **Conclusion:** Clinical disease progression was used as an anchor for determining the meaningfulness of PACC decline over three years. In the stable group, PACC scores did not change and were reliable. In contrast, progressors showed large three-year decline (mean -0.19). Of the progressor group a MWPC of </= -0.076 was

evident in 74% of participants. These estimates can provide a guide to intepretation of change on the PACC in clinical trials of DMT in preclinical AD.

LP092- INCORPORATING PERSONALLY DEFINED BRAIN HEALTH PRIORITIES IN CLINICAL TRIALS OUTCOMES: THE ELECTRONIC PERSON SPECIFIC OUTCOME MEASURE APPROACH IN THE US. S. Saunders[1,2], A. Jannati[1,3], S. Sheehan[2], S. Tobyne[1], Á. Pascual-Leone[1,3,4] *(1. Linus Health - Boston (United States), 2. Usher Institute, University of Edinburgh - Edinburgh (United Kingdom), 3. Department of Neurology, Harvard Medical School - Boston (United States), 4. Hinda and Arthur Marcus Institute for Aging Research and Deanna and Sidney Wolk Center for Memory Health, Hebrew SeniorLife - Boston (United States))*

Background: While a limited number of disease-modifying treatments have been approved in the US, providers are moving with appropriate caution in adopting these new treatments in clinical use. One of the key considerations in developing new treatments is demonstration of sufficient beneficial effects. The electronic Person Specific Outcome Measure (ePSOM) tool was recently developed to establish whether new treatments not only modify underlying Alzheimer's disease (AD) pathology but also offer clinically meaningful treatment effects in areas that matter the most to an individual. Here, we report findings from a study capturing individual-level brain health priorities in the US population and participants' self-reported confidence in managing these priorities. **Methods:** We conducted an online nationwide study to understand what matters to people aged 50 and older about their brain health in the US. The ePSOM US survey (May 2023-Jan 2024) collected primarily free-text responses in personally defined brain health priorities, alongside self-reported confidence in managing these priorities (total score 5-25, item score 1-5; lower scores indicate lower confidence). We used natural language processing (K-means clustering of GloVe vectors) to embed the free text responses and cluster them into themes. We used a Mann Whitney U-test to compare the mean confidence ratings between participants with and without a self-reported diagnosis of neurodegenerative disease. We also identified themes where individuals who reported a neurodegenerative disease diagnosis frequently reported below average confidence scores. **Results:** Our analysis included 764 participants with a total of 9,010 free text responses; mean age 63.1 (SD=8.47), 68.8% female, 64.08% had higher education; of whom 53 individuals (6.90%) reported neurodegenerative disease diagnosis. The free text responses clustered into 102 themes, the most common themes across the sample were 'Driving', 'Staying active', 'Reading', 'Chatting with friends and family' and 'Socialising'. The following themes with at least five participants' answers had at least one SD lower confidence ratings in those with a diagnosis than the sample mean: Driving (3.8), Reading (3.3), Socialising (3.8). Those with a diagnosis rated their confidence significantly lower (median score 21, IQR=17-23) than those without a diagnosis (median score 24, IQR=22-25), U=8908, p<0.01. There were no statistically significant differences in confidence ratings in individual themes between the two groups with and without a diagnosis. **Conclusion:** Our study demonstrates there is heterogeneity in individual-level brain health priorities in the US. Our findings indicate that self-reported confidence in managing personally meaningful priorities may be an appropriate construct to incorporate the person's voice in study outcomes. In our study, the diagnosis group was overall significantly less confident in managing personally meaningful priorities. However, there were no specific themes impaired in the diagnosis group but rather similar heterogeneity as in the no-diagnosis group. The ePSOM tool is now being validated in other global populations. **Keywords:** clinical meaningfulness, patient reported outcomes. **Disclosures:** StS, AJ, ST and ÁPL are employees of Linus Health and declare ownership of shares or share options in the company. ÁPL is a co-founder of Linus Health and declares ownership of shares or share options in the company. ÁPL serves as a paid member of the scientific advisory boards for Neuroelectrics, Magstim Inc., TetraNeuron, Skin2Neuron, and MedRhythms.ShS receives consulting fees from Linus Health.

COGNITIVE ASSESSMENT AND CLINICAL TRIALS

P178- NEUROPSYCHOLOGICAL TESTING IN PATIENTS WITH CONVERTED AND STABLE MILD COGNITIVE IMPAIRMENT. Y.J. Lee[1], J.S. Kim[2], H.J. Kim[1] *(1. Hanyang University - Seoul (Korea, Republic of), 2. Konkuk University Medical Center - Seoul (Korea, Republic of))*

Background: Alzheimer's disease (AD) is characterized by the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles, leading to progressive cognitive decline and dementia [1]. Mild cognitive impairment (MCI) is a prodromal stage of AD, with variable trajectories: some individuals remain stable (sMCI), while others progress to AD (cMCI). This study investigates neuropsychological test across four groups distinguished by Aβ status: sMCI Aβ-positive (sMCI Aβ(+)), sMCI Aβ-negative (sMCI Aβ(-)), converted MCI Aβ-positive (cMCI Aβ(+)), and converted MCI Aβ-negative (cMCI Aβ(-)). we aim to delineate how early amyloid deposition and its absence influence cognitive functions, potentially identifying early indicators of progression to AD. **Methods:** In this retrospective hospital-based cohort study, 195 participants diagnosed with MCI through 18F-Florbetaben Brain PET scans and neuropsychological assessments were included. Inclusion criteria were based on the NIA-AA Diagnostic Criteria for Dementia, utilizing clinical and biological markers to define and stage Alzheimer's disease [2]. Participants, classified post-follow-up into sMCI Aβ(+) (n=41), sMCI Aβ(-) (n=87), cMCI Aβ(+) (n=48), and cMCI Aβ(-) (n=19), underwent neuropsychological evaluations over a period of two to eight years. Exclusion criteria encompassed major cardiovascular diseases, stroke, malignancies, severe psychiatric disorders, and neurological disorders such as Parkinson's disease and multiple sclerosis [3]. Cognitive functions were assessed with the Seoul Neuropsychological Screening Battery, 2nd edition (SNSB-II), measuring memory, executive function, language, and visuospatial abilities. Scores were standardized to Z-scores, adjusting for age, gender, and education. Statistical analyses utilized the stats sub-package of the SciPy library. ANCOVA controlled for age, sex, and education was employed to compare neuropsychological test results across groups. Multiple comparisons were adjusted using Tukey's HSD test, with significance defined at $p < 0.05$. **Results:** The Rey Complex Figure Test (CFT) Copy Score showed differences with cMCI Aβ(+) 0.18±1.82, sMCI Aβ(-) 0.14±0.89, sMCI Aβ(+) 0.15±0.97, and cMCI Aβ(-) 0.32±0.78 (p=0.000). RCFT Delayed Recall scores were lower in cMCI Aβ(+) compared to sMCI Aβ(-), sMCI Aβ(+), and cMCI Aβ(-) (p=0.000). RCFT Immediate Recall scores were also lower in cMCI Aβ(+) relative to the other groups (p=0.000). RCFT Recognition Scores and Discriminability Index were reduced in cMCI Aβ(+) compared to sMCI Aβ(-), sMCI Aβ(+), and cMCI Aβ(-) (p=0.000). SVLT Delayed Recall scores were lower in cMCI Aβ(-) compared to sMCI Aβ(+), sMCI

Aβ(-), and cMCI Aβ(+) (p=0.000). Naming Korean Boston Naming Test (K-BNT) scores were lower in cMCI Aβ(+) compared to the other groups (p=0.000). In the Tukey's HSD post-hoc analysis, significant cognitive differences were observed between the cMCI Aβ(-) and cMCI Aβ(+). CFT was significantly lower in the cMCI Aβ(+), with a mean difference of -1.55 (95% confidence interval: -2.77 to -0.34; adjusted p-value = 0.006). RCFT Delayed Recall showed lower in the cMCI Aβ(+), with a mean difference of -0.75 (95% confidence interval: -1.47 to -0.02; adjusted p-value = 0.043). **Conclusion:** The differential performance on the CFT between Aβ(+) and Aβ(-) within cMCI underscores its critical role as an indicator of amyloid pathology. Furthermore, CFT proves to be a sensitive tool for assessing visuospatial and memory functions that are affected in the early stages of Alzheimer's disease. **Keywords:** Neuropsychological Test, Alzheimer's Disease, cMCI, sMCI, Amyloid-β. **Clinical Trial Registry:** Data Deposition DOI: 10.13140/RG.2.2.26876.55683. **Disclosures:** This research was supported by the [Bio&Medical Technology Development Program] of the National Research Foundation (NRF) funded by the Korean government (MSIT) (No.RS-2023-00226494). **References:** 1. Scheltens, P., De Strooper, B., Kivipelto, M., Holstege, H., Chetelat, G., Teunissen, C. E., ... & van der Flier, W. M. (2021). Alzheimer's disease. The Lancet, 397(10284), 1577-1590. https://doi.org/10.1016/S0140-6736(20)32205-4; 2. Jack, C. R., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., ... & Silverberg, N. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's & Dementia, 14(4), 535-562. https://doi.org/10.1016/j.jalz.2018.02.018; 3. Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: Clinical characterization and outcome. Archives of Neurology, 56(3), 303-308. https://doi.org/10.1001/archneur.56.3.303.

P179- LONGITUDINAL ANALYSIS OF THE FACTOR STRUCTURE OF A MULTIDOMAIN COGNITIVE TASK BATTERY IN AGEING AND PRECLINICAL AD.

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Background: Three lines of research warrant investigation into the latent structure of cognitive decline in healthy ageing and preclinical Alzheimer's disease. Firstly, no individual cognitive test has provided high levels of sensitivity to dementia risk at the preclinical stage, leading to widespread use of compound measures of cognition and recommendations by regulators for compound endpoints in clinical trials. Secondly, subtypes in the cognitive phenotype of Alzheimer's disease are poorly indexed by performance in individual cognitive tasks. Finally, scalable cognitive testing in healthcare and clinical trials requires well designed cognitive batteries that are not burdensome to patients and that minimize redundant information. **Methods:** We analyzed data from the digital cognitive testing battery in the AI Mind study. 724 participants aged 60-80 (mean age 72) across four European clinical sites, were tested at four time points and across two years with digital cognitive tests, neuroimaging and blood-based biomarkers. The battery compromised motor screening (MOT), delayed match to sample (DMS), paired associate learning (PAL), pattern recognition memory task (PRM), spatial working memory (SWM) and rapid visual processing (RVP); collectively thought to index attention, short-term and working memory, executive function and speed of processing. We used factor analysis, at baseline, to perform dimensionality reduction, using varimax rotation to aid interpretability. We then applied the baseline factor model to visits 2 (month 8), 3 (month 16) and 4 (month 24) and examined the change in factor scores over the visits using mixed linear effects modeling controlling for age, sex and level of education. **Results:** Visual inspection of an elbow plot of factor eigenvalues revealed six factors accounting for 55% of the variance of cognitive test performance at baseline. Factors 1, 4 and 6 principally loaded onto outcome measures from the DMS, SWM and PAL tasks respectively. The remaining factors loaded mainly onto measures from the PRM task, which cumulatively explained nearly 30% of the variance. Longitudinal analysis of the factors over the three subsequent visits showed different patterns of decline in the different factors. There were no significant changes in the factors between visits 1 and 2. However between the first and last visits, the decline in factors 1, 4 and 6, relating primarily to DMS, SWM and PAL met significance, with an effect size of -0.18, -0.25 and -0.19 respectively. **Conclusion:** We analyzed the facture structure of a battery of six cognitive tasks, and examined how these factors change over the course of the study. There was considerable variation in sensitivity to change between the factors. While the factors relating to PRM and DMS explained more variance at baseline, factors relating to the SWM and PAL tasks were more sensitive to change, suggesting these tasks may be of greater utility in longitudinal studies of MCI populations. Further work will examine the relationship between these factors and clinical variables such as CDR and biomarkers of AD, and their sensitivity to baseline differences and change over time. This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 964220. This presentation/publication reflects the views of the authors, and the European Commission is not responsible for any use that may be made of the information it contains.

P180- INTERPERSONAL EFFECTS OF ADRD SCREENING ON OLDER PRIMARY CARE PATIENTS AND THEIR FAMILY MEMBERS WELLBEING: RESULTS FROM THE CAREGIVER OUTCOMES OF ALZHEIMER'S DISEASE SCREENING (COADS) TRIAL.

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Background: Since 1996 the United States Preventive Services Task Force (USPSTF) has reviewed the literature four times to evaluate the evidence for the benefits, harms, and risks of screening for Alzheimer's disease and related dementias (ADRD). In the latest review the USPSTF stated that the evidence for ADRD screening is lacking and graded the data as "I" or insufficient to assess. They recommended additional evidence from longer-term trials that test both behavioral and pharmacological interventions that measure benefits and harms for patients and caregivers. In an effort

to fill that gap, we conducted the Caregiver Outcomes of Alzheimer's Disease Screening (COADS) trial to measure the effects of ADRD screening on patient and family member dyadic outcomes. This dyadic approach is important given the impact of ADRD on both the patient and their family and potential alignment or discordance of benefits, harms, and risks. This study explores the interpersonal mechanism behind ADRD screening. **Methods:** COADS is a multi-center, three-arm, randomized controlled trial evaluating the impact of ADRD screening on older primary care patient's family members' quality of life (SF-36), depressive symptoms (PHQ-9), and anxiety (GAD-7) at 24 months post-screening. Dyads were randomized into three groups- no ADRD screening ("Control"), ADRD screening with notification of results to the dyad and the patient's PCP ("Screening Only"), and screening with same notification and follow-up diagnostic assessment for determination of ADRD if positive ("Screening Plus"). We used mediation analysis to investigate whether ADRD screening affects family members' outcomes through spillover effects on patient outcomes. We hypothesized that the patient's awareness of a positive screening test may increase their depressive symptoms, and then result in increased depressive symptoms in family members. Also, that the effects of a positive screening on patients' and family members' depressive symptoms may be mitigated in the "Screening Plus" group as they received more information and resources about ADRD. **Results:** A total of 1822 dyads were randomized, and 1808 dyads completed the baseline assessment. A total of 1,489 dyads completed the 24-month assessment. At baseline, there were no statistically significant differences among patients or family members. The mean patient age was 73.7 years (SD 5.7); 968 (53.1%) were female and 1547 (85.1%) were white. The mean family age was 64.1 years (SD 13); 1234 (67.8%) were female, 1532 (84.5%) were white, and 1171 (64.7%) were a spouse/partner and 506 (28%) were an adult child of the patient. At 24 months, we were unable to detect significant differences in depressive symptoms of both dyad members between the control group and two screening groups. At 24 months, a positive IQCODE significantly increased family members' depressive symptoms (ß=1.96, p<0.001) via increased patients' depressive symptoms (mediating effect=0.58, p<0.01). The significant mediating effect explained 29.42% of the impact of positive screening on caregivers' depressive symptoms in all dyads. Upon further stratified analyses, we found that this mediating path was only significant in the two treatment groups. **Conclusion:** Awareness of a positive ADRD screen negatively influences family members' wellbeing through patients' depressive symptoms.

P181- ADVANCEMENTS IN IDENTIFYING STAGE 2 PRECLINICAL ALZHEIMER'S DISEASE: RELIABLE METHODS TO DEFINE OBJECTIVE MEMORY DECLINE ASSOCIATED WITH CEREBROSPINAL FLUID AND PLASMA BIOMARKERS. D. López-Martos[1], M. Suárez-Calvet[1], A. González-Escalante[1], M. Milà-Alomà[1], J.D. Gispert[1], C. Minguillon[1], C. Quijano-Rubio[2], G. Kollmorgen[3], H. Zetterberg[4], K. Blennow[4], O. Grau-Rivera[1], G. Sánchez-Benavides[1]
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Background: Objective Subtle Cognitive Decline (Obj-SCD) can be identified through standardized neuropsychological tests and may precede the development of Mild Cognitive Impairment (MCI). Nevertheless, current clinical and research criteria lack a standardized definition of Obj-SCD. Besides cognitive complaints and behavioral changes occurring at the preclinical stage, Obj-SCD might be more reliable in identifying otherwise Cognitively Unimpaired (CU) individuals, with evidence of Alzheimer's disease (AD) pathophysiology - NIA-AA Stage 2 of transitional decline. This study introduces a standardized protocol to define Obj-SCD. We aimed to explore the association of Obj-SCD with Cerebrospinal Fluid (CSF) and plasma biomarkers in CU individuals at increased risk of AD dementia. **Methods:** From the ALFA+ cohort study, 350 CU individuals (mean age: 60.93, SD: 4.72) with a 3-year follow-up were included. AT(N) profiles were defined at baseline with CSF biomarkers, excluding from the present sample profiles defined with suspected non-AD pathophysiology (i.e., A-T+). AD biomarker-based reliable change indices adjusted for practice effect (using A-T-[N]- longitudinal cognitive performance as reference) were computed for 11 variables from 3 episodic memory tests (Free-Cued Selective Reminding Test, Memory Binding Test, and Wechsler Memory Scale-IV). Obj-SCD was categorically defined as AD biomarker-based longitudinal cognitive change below -1.28 SD (≤10th percentile) in at least 3 out of the 11 cognitive variables included. These criteria considered the non-linear relationship between the number of neuropsychological measures and the base rate of impaired scores to capture clinically meaningful deviations from the expected normal cognitive trajectory. Chi-square (χ^2) test was used to evaluate the prevalence of Obj-SCD across AT profiles. ANCOVAs were used to evaluate differences in CSF (amyloid-β42/40, p-tau181, p-tau181/Aβ42, t-tau/Aβ42, NfL, and GFAP), and plasma (p-tau217, NfL, and GFAP) biomarkers by Obj-SCD groups, adjusting through stepwise backward selection for age, sex, education, and APOE-ε4 genotype. **Results:** A-T- was defined in 228 (65%), A+T- in 93 (27%), and A+T+ in 29 (8%) individuals. According to the above-defined criteria, 51 (15%) individuals exhibited Obj-SCD. Frequency of Obj-SCD across AT profiles was 23 (10%) in A-T-, 16 (17%) in A+T-, and 12 (41%) individuals in A+T+. The distribution of Obj-SCD revealed significant differences across AT profiles (χ^2= 20.94, p= <0.001). The contrast control – Obj-SCD was associated with baseline CSF amyloid-β42/40 (d= 0.589, p= <0.001), CSF p-tau181 (d= -0.411, p= 0.007), CSF p-tau181/Aβ42 (d= -0.539, p= <0.001), and CSF t-tau/Aβ42 (d= -0.577, p= <0.001), but not with CSF NfL (d= -0.217, p= 0.155) and CSF GFAP (d= -0.145, p= 0.342). Similarly, Obj-SCD was associated with plasma p-tau217 (d= -0.337, p= 0.027), but not with plasma NfL (d= -0.170, p= 0.270) and plasma GFAP (d= -0.221, p= 0.155). **Conclusion:** It is necessary to identify patients at the early NIA-AA Stage 2. This study aimed to contribute with the definition of Obj-SCD, capturing an episodic memory decline indicative of AD pathology in CU individuals. The identification of individuals falling outside the expected normal trajectory with positive AD pathophysiological markers - NIA-AA Stage 2 of transitional decline - might inform about the optimal population for secondary preventive strategies in AD. **Keywords:** Preclinical Alzheimer's disease, NIA-AA stage 2, objective subtle cognitive decline, episodic memory, amyloid-β, p-tau. **Disclosures:** The presenting author has no conflicts of interest. CSF (amyloid-β42, amyloid-β42/40, NfL, and GFAP) and plasma (NfL, and GFAP) were measured with the NeuroToolKit, a panel of exploratory prototype assays designed to robustly evaluate biomarkers associated with key pathologic events characteristic of AD and other neurological disorders, used for research purposes only and not approved

for clinical use (Roche Diagnostics International Ltd, Rotkreuz, Switzerland). CSF (p-tau181, and t-tau) were measured with ELECSYS, a trademark of Roche. Elecsys® Phospho-Tau (181P) CSF and Elecsys Total-Tau CSF assays are approved for clinical use. Eli Lilly and Company provided the measurements of the in-house assay for plasma p-tau217 using the Meso Scale Discovery platform (MSD).

P182- IDENTIFICATION OF COGNITIVE IMPAIRMENT IN ALZHEIMER'S DISEASE WITH DRAWING AND SPEECH-BASED ASSESSMENTS AND METRICS. T. Talkar[1], K. Thompson[1], A. Jannati[1,2], R. Banks[1], J. Showalter[1], D. Bates[1], A. Pascual-Leone[1,2,3], S. Tobyne[1] *(1. Linus Health - Boston (United States), 2. Department of Neurology, Harvard Medical School - Boston (United States), 3. Hinda and Arthur Marcus Institute for Aging Research and Deanna and Sidney Wolk Center for Memory Health, Hebrew SeniorLife - Boston (United States))*

Background: Maximizing the benefits of disease-modifying treatments (DMTs) for Alzheimer's disease (AD) requires early diagnosis. According to the FDA approval for lecanemab, CMS coverage necessitates identification of both cognitive impairment and abnormal brain amyloid-beta (Aβ) status. Emerging blood-based biomarkers have shown promise for simplifying the process of determining the presence of AD-related pathology but do not mitigate the need to establish the presence of cognitive impairment. Thus there is an urgent need for efficient cognitive assessments that can be readily deployed in both clinical trials and in healthcare settings to reduce screen failure rates and streamline the process of identifying individuals who most benefit from emerging treatments. This study aims to assess the accuracy of the combination of two brief digital cognitive assessments, Linus Health's Digital Clock and Recall (DCR) and Aural Analytics' Speech Vitals (SV), in identifying cognitive impairment. **Methods:** All participants were recruited through the Bio-Hermes-001 study. There were a total of 1001 participants, split across three cohorts: Healthy Controls (n=417, 248 females; age 71.30±6.53), Mild Cognitive Impairment (MCI) (n=312, 166 females; age 71.79±6.62), Probable AD/dementia (pAD) (n=272, 147 females; age 73.56±6.66). The study recruited individuals from traditionally underrepresented populations across 13 sites in the United States. A DCR-based algorithm was generated to detect the presence of cognitive impairment, defined as MCI or pAD cohort status, using age, APOE status, drawing metrics, speech and acoustic features, and temporal-spatial features of stylus manipulation. An SV-based algorithm was similarly generated to detect cognitive impairment using acoustic and linguistic features based on audio recordings of sentence reading, sustained phonation, picture description, repeated phrases, and a series of memory-based tasks. The outputs of the two algorithms were combined for a final prediction of cognitive impairment. **Results:** Cognitive impairment identification by DCR (AUC=0.88) and SV (AUC=0.83) improved when the two algorithms were combined to result in an AUC of 0.91. Model performance with DCR, acoustic, and linguistic features (AUC=0.91) was similar to performance with just DCR and linguistic features (AUC=0.91) or DCR and acoustic features (AUC=0.90). The final model created from DCR, acoustic, and linguistic features additionally had a specificity of 0.96, a sensitivity of 0.79, a positive predictive value (PPV) of 0.89, and a negative predictive value (NPV) of 0.91. **Conclusion:** The combination of drawing- and process-based metrics from the DCR along with acoustic and linguistic features from recall in the DCR and speech and language tasks in SV aid in the identification of cognitive impairment, and improve performance over the use of metrics from any sub-group within the protocol. Brief digital assessments that combine the use of process metrics, such as the DCR, as well as speech- and language-based metrics, such as the remote-capable SV, can be easily administered by medical/research assistants in clinical and remote settings to provide a cost-effective and highly accurate screening tool for AD clinical trials and evaluation for DMTs. **Keywords:** cognitive impairment, Alzheimer's disease, machine learning, speech. **Trial Registration:** NCT04733989; https://www.ClinicalTrials.gov. **Data Deposition:** The data that support the findings of this study were collected as part of the Bio-Hermes-001 study (ClinicalTrials.gov Identifier: NCT04733989) and are governed by the Global Alzheimer's Platform (GAP) consortium agreement. Data will be made available via the Alzheimer's Disease Data Initiative (ADDI) Workbench in the future and at the discretion of GAP. All requests for data access should be made directly to GAP. The code used to calculate the reported results is available from Linus Health, Inc. upon reasonable request and with the permission of Linus Health, Inc. Usage restrictions apply to the availability of this code, which is not immediately publicly available. **Disclosures:** TT, KT, AJ, RB, JS, and ST are employees of Linus Health and declare ownership of shares or share options in the company. DJB is a co-founder of Linus Health and declares 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., TetraNeuron, Skin2Neuron, MedRhythms, and Hearts Radiant.

P183- EXPLORING NOVEL RT-BASED MEASURES CALCULATED FROM DETAILED PAIRED ASSOCIATE LEARNING TASK DATA: PRELIMINARY ANALYSES. A. Kaula[1], N. Taptiklis[1], F. Cormack[1,2], N. Stang[3], A. Perez[3], S. Alfonsín[4], T. Saarinen[5], F. Maestú[4], H. Renvall[5], C. Marra[6], P. Rossini[7], C. Hatlestad-Hall[3], I. Haraldsen[3] *(1. Cambridge Cognition - Cambridge (United Kingdom), 2. Department of Psychiatry, University of Cambridge - Cambridge (United Kingdom), 3. Dept. of Neurology, Oslo University Hospital - Oslo (Norway), 4. Centre for Cognitive and Computational Neuroscience, Universidad Complutense de Madrid - Madrid (Spain), 5. BioMag Laboratory, HUS Medical Imaging Centre, Helsinki University Hospital, Helsinki University and Aalto University School of Science - Helsinki (Finland), 6. Memory Clinic, Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Rome (Italy), 7. Department of Neurosciences & Neurorehabilitation. IRCCS San Raffaele - Rome (Italy))*

Background: The CANTAB Paired Associates Learning (PAL) is a digital task of learning and memory and has been used extensively in both academic and clinical settings to assess MCI and AD patients. During the PAL task, response-time (RT) data from each touch interaction is collected but not typically analysed. We hypothesise that this detailed data can yield insights about cognition in addition to standard outcome measures. Here we present preliminary work exploring psychometric properties and relations of such new measures to existing CANTAB measures in a large cohort of well-characterised MCI patients. **Introduction:** The AI-Mind study is a large, multicentric (4 clinical centres in Europe), longitudinal study of patients with MCI assessed four times over two years. The study has collected clinical, biological, electrophysiological measures and cognitive assessments using

both pencil and paper and CANTAB computerised tasks. This provides a unique dataset in which to evaluate the sensitivity of novel measures to clinical change and disease biomarkers. As part of this effort, the present work explores the development of novel digital measures from PAL, a well-established task of memory and learning, with the ultimate goal of increasing the discriminative and predictive sensitivity of the task without increasing burden associated with the task. Within this cohort we are exploring the psychometric properties of novel PAL RT-based measures, their relationship to standard PAL measures and other CANTAB tasks, to understand whether novel RT features, derived from an un-speeded memory task, are related to other domains of cognition. **Methods:** Participants from the AI-Mind study (N=724 MCI patients) completed a battery of CANTAB tasks (MOT, PAL, PRM, RVP, SWM, DMS) at four timepoints. Novel RT-based candidate measures were calculated using detailed data obtained from the administration of the PAL task at baseline and eight month follow up timepoints. In total, 21 features were generated, representing different aspects of task performance (e.g. Fastest Correct RT). We applied a systematic evaluation framework to the novel measures, examining the distributional properties of the measures (floor and ceiling effects, normality and reliability). Construct validity was evaluated through correlation of new measures to existing CANTAB tasks. We evaluated the summed rankings of correlation coefficients to explore the relationship between novel RT measures and 1) CANTANB PAL outcome measures 2) measures of processing speed from other CANTAB tasks and 3) measures accuracy from other CANTAB tasks. **Results:** Our measure evaluation produced a set of candidate measures which met our criteria, suggesting that reaction time measures could be reliably estimated from the PAL task. A subset of the measures derived from PAL were found to be more correlated with CANTAB measures of processing speed from speeded tasks than accuracy measures from PAL. In contrast, standard PAL measures of memory were consistently better correlated with other CANTAB measures of accuracy than the new RT-based measures. **Conclusion:** This work suggests some new RT-based measures from PAL may provide additional information regarding aspects of processing speed, independent of memory. In future work we will explore the relationship with clinical measures of MCI, such as the CDR, and sensitivity of these measures to change over time. **Funding/Disclosures:** This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 964220. This presentation/publication reflects the views of the authors, and the European Commission is not responsible for any use that may be made of the information it contains.

P184- THE COGNIVUE AMYLOID RISK MEASURE (CARM): A NOVEL METHOD TO DETECT THE PRESENCE OF AMYLOID IN CLINICAL SAMPLES WITH COGNIVUE CLARITY®. J. Galvin[1], M. Kleiman[1], P. Estes[2], H. Harris[2], E. Fung[2] *(1. University of Miami Miller School of Medicine - Boca Raton (United States), 2. Cognivue, Inc - Victor (United States))*

Background: Detection of the early stages of Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI) in the community has been challenging, and in clinical practice, many patients first come to medical attention at the moderate stage. Preclinical Alzheimer's disease (pAD) is defined by amyloid positivity in the absence of cognitive impairment. Clinical detection of individuals who have amyloid in their brain at the present time is not possible. As its primary objective, the Bio-Hermes Study, funded by the Global Alzheimer's Platform Foundation [1], investigated the relationship between emerging blood-based and digital biomarkers and the presence of amyloid measured by PET scan. We explored the ability of Cognivue Clarity® (Cognivue, Inc, USA) [2] to detect the presence of amyloid in individuals with and without cognitive impairment. **Methods:** Bio-Hermes recruited 1001 individuals who completed Cognivue Clarity and had amyloid PET scan and plasma biomarkers (ptau181, ptau217, ab42/40 ratio, and amyloid prediction score or APS). Three Cognivue Clarity subtests (Adaptive Motor Control, Visual Salience, Shape Discrimination) were statistically significantly different between cognitively normal biomarker-positive (pAD) and True Control individuals and between cognitive impairment due to AD pathology from cognitive impairment due to non-AD processes [3]. This finding was leveraged to determine whether an amyloid-specific marker could be developed. The 3 subtests plus age were combined and used to train gradient boosted regression of amyloid PET Centiloid levels, which was then thresholded based on specificity, sensitivity, and Youden J metrics to create the 4-point Cognivue Amyloid Risk Measure (CARM). **Results:** Cognivue Clarity total scores discriminate cognitively normal from cognitively impaired individuals ($p<.001$, Cohen's $d=0.732$). The CARM discriminates individuals with amyloid from individuals without amyloid ($p<.001$, Cohen's $d=0.618$). Amyloid positivity increased across the 4 CARM thresholds (CARM1: 19%, CARM2: 12%, CARM3: 26%, CARM4: 43%, $p<.001$). Cognitive impairment also increased across CARM thresholds (CARM1: 40%, CARM2: 47%, CARM3: 64%, CARM4: 75%, $p<.001$). Dichotomizing the CARM into low likelihood of amyloid (CARM1, CARM2) and high likelihood of amyloid (CARM3, CARM4) provided excellent discrimination for amyloid positivity by PET (OR 3.67, 95%CI: 2.76-4.89). CARM thresholds also differentiated by increasing levels of plasma biomarkers: APS, Ab42/40 ratio, ptau181 and ptau217 (all ANOVA $p<.001$). CARM categories differentiated True Controls, pAD, MCI due to AD, AD, and cognitive impairment due to non-AD etiologies ($c2=137.6$, $p<.001$) with the majority of True Controls and non-AD etiologies being in CARM1 and CARM2, and the majority of pAD, MCI due to AD, and AD being in CARM3 and CARM4. **Conclusion:** Cognivue Clarity detects individuals with cognitive impairment and a derivation of Cognivue scores was used to develop the CARM to predict the presence of amyloid. Combining the CARM and the Cognivue Clarity total score could help identify individuals with and without cognitive impairment due to AD or non-AD etiologies. Cognivue Clarity could be used to help screen older adults for treatment protocols with anti-amyloid therapies, enrich clinical trial recruitment before obtaining expensive biomarkers, and identify individuals likely to have pAD for prevention studies in a valid, brief, and cost-effective fashion. **Keywords:** Cognivue Clarity, amyloid, preclinical AD, cognitive screening. **Disclosures:** JEG and MJK are paid consultants for Cognivue. EF, HMH, and PWE are employees of Cognivue. The authors declared no competing interests. **References:** 1. Mohs RC, et al. Alzheimers Dement 2024 Feb 28. Doi: 10.1002/alz.13722. Online ahead of print; 2. Galvin JE et al. J Alz Dis, In Press 2024; 3. Jack CR, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018; 14(4): 535-562.

P185- EVALUATING COGNITION ACROSS LATIN AMERICA: INSIGHTS FROM THE LATAM-FINGERS STUDY. L. Crivelli[1], N. Corvalán[1], R.F. Allegri[1], I.L. Calandri[1], P. Caramelli[2], M.A. Espeland[3], F. Lopera[4], R. Nitrini[5], K.V. Papp[6], G.E. Sevlever[1], R.M. Salinas[7], A.L. Sosa[7], C.K. Suemoto[8], M. Sanches Yassuda[9], L. Baker[10] *(1. Fleni - Buenos Aires (Argentina), 2. Faculty of Medicine - Universidade Federal de Minas Gerais - Belo Horizonte (Brazil), 3. Departments of Internal Medicine and Biostatistics and Data Science,Wake Forest University School of Medicine,Winston-Salem - North Carolina (United States), 4. Grupo de Neurociencias de Antioquia, Universidad de Antioquia - Medellín (Colombia), 5. Cognitive and Behavioral Neurology Unit - University of São Paulo - São Paulo (Brazil), 6. Brigham and Women's Hospital, Harvard Medical School - Massachusetts (United States), 7. Dementias Laboratory, National Institute of Neurology and Neurosurgery - Ciudad De México (Mexico), 8. Division of Geriatrics, Department of Internal Medicine, University of Sao Paulo Medical School - São Paulo (Brazil), 9. University of São Paulo - São Paulo (Brazil), 10. Wake Forest University School of Medicine - Winston-Salem, North Carolina (United States))*

Background: LatAm-FINGERS is the first non-pharmacological RCT aimed at preventing cognitive decline and dementia across Latin America. Its primary outcome is the feasibility and efficacy of a multidomain lifestyle intervention in improving cognitive function, assessed by the Latin American Neuropsychological Test Battery (LatAm-NTB). This study aimed to assess validity properties of LatAm-NTB within the LatAm-FINGERS cohort. **Methods:** The Latin American Neuropsychological Battery (LatAm-NTB) was developed, including tests such as the Free and Cued Selective Reminding Test, Logical Memory, Digit Span, Stroop Test, Concept Shifting Test, Trail Making Test, Symbol Digit Modalities Test, and semantic and phonological fluency. Associations between LatAm-NTB scores and the Framingham Risk Score, sex, age, and education were assessed through regression modeling. Additionally, in order to test convergent validity the correlation between LatAm-NTB and the PACC-5, FINGER, and PmNTB composites was calculated. **Results:** Since recruitment began in December 2021, 1,186 participants have been enrolled. The mean age is 67.41 years (SD = 4.65), with an average educational level of 12.9 years (SD = 3.7) and an average Mini-Mental State Examination (MMSE) score of 27.2 (SD = 2.17). Women comprise 73.8% of the cohort and ethnicity is heterogeneous (56% Mestizo). A multivariate regression model, which included sociodemographic variables, non-modifiable risk factors, and cardiovascular risk, was constructed to explain cognitive performance. This model demonstrated better fit parameters (BIC: 734.649, AIC: 793.661) compared to the reduced model (BIC: 1041.591, AIC: 1051.426). Higher education (β = 0.04, SE = 0.003, $p < .001$), younger age (β = -0.01, SE = 0.002, $p < .001$), and a lower Framingham Risk Score (β = -0.01, SE = 0.003, $p < .001$) were associated with better cognitive performance. Being male was not significantly associated with cognitive outcomes (β = -0.01, SE = 0.02, p = 0.57). Significant correlations were also observed between LatAm-NTB and the PACC-5 composite (rho = 0.78, $p < .001$), FINGER NTB (rho = 0.82, $p < .001$), and PmNTB (rho = 0.94, $p < .001$). **Conclusion:** The LatAm-NTB is strongly associated with cognition-related variables such as education, age, and cardiovascular risk. Additionally, its correlation with established cognitive composites underscores its valuable comparability. It is crucial to identify neuropsychological tools that are harmonized with research from high-income countries and validated across Latin America's diverse demographics. This will facilitate precise assessments of underserved multicultural populations and ensure their equitable representation in upcoming clinical trials. **Keywords:** Neuropsychology, LatAm-FINGERS, Cognition, Validity. **Disclosures:** The authors declared no competing interests. The LatAm-FINGERS project is fully funded by the Alzheimer's Association.

P186- EXPLORING THE ROLE OF EDUCATION ON COGNITIVE OUTCOMES IN HISPANIC/LATINO ADULTS IN SOUTHERN CALIFORNIA: INSIGHTS FROM COMMUNITY BASED INTERVENTION, SERVE-OC. A. Kurzman[1], B. Albala[1], A. Chavez[1], J. Wing[2], D. Gutierrez[3], D. Draughter[3], B. Boden-Albala[3] *(1. University of California Irvine - Irvine (United States), 2. Ohio State University - Columbus (United States), 3. University of California, Irvine - Irvine (United States))*

Background: The aging population in the U.S. is increasing rapidly, with significant public health implications. Currently, ~6.2 million Americans aged 65+ years live with Alzheimer's disease and related dementias (ADRD), projected to nearly triple to 13.8 million by 2060. ADRDs begin ~20 years before symptom onset, with the accumulation of key biomarkers associated with the disease (amyloid and tau). Racial and ethnic minority groups, particularly Hispanic/Latinos are disproportionately impacted by ADRDs with 11.1% living with mild cognitive impairment (MCI) and 5.3% living with mild dementia due to ADRD. The recent approval of disease-modifying treatments for MCI underscores the importance of timely and accurate screening for early intervention. Cognitive assessments are vital for cognitive decline screening; however, performance may be influenced by educational attainment or cultural factors. This may lead to challenges in accurately differentiating cognitively impaired individuals from individuals with low educational status. Previous studies of the Montreal Cognitive Assessment (MoCA) note that scores are significantly affected by education and literacy levels, potentially leading to biases in diagnosis. Yet little research has focused on the distinct relationship between education attainment and performance in each domain of the MoCA, particularly among Hispanic/Latino populations. The purpose of this study is to assess the relationship between education and cognitive outcomes within the Hispanic/Latino cohort of SERVE-OC, aiming to identify which MoCA domains are significantly associated with education attainment. **Methods:** Data from the community-based study, Skills-Based Educational strategies for Reduction of Vascular Events in Orange County, California (SERVE-OC) trial were used (NIMHD P50MD017366). Study participants were restricted to individuals 18+ years who self-identified as Hispanic/Latino and completed the MoCA at baseline between December 2022 and April 2024 (n=262). Statistical analysis utilized multivariable linear regressions to examine associations between education attainment and MoCA score (adjusted for education per instrument protocol), and MoCA domain, controlling for age, sex, language of assessment and years living in the United States. **Results:** Participants were an average of 44.8 years (SD=14.65) with 105≥50 years; 64.89% of participants were female and 60.63% had ≤8 years of formal education. Average MoCA scores were 22.87 (SD=4.03) and 21.17 (SD=4.70) for individuals <50 and ≥50years respectively; 210 (80.15) MoCA assessments were administered in Spanish. Having ≥8 years of formal education was significantly associated with higher MoCA scores (B=2.62; p<0.001). Additionally, having ≥8 years of formal education was significantly associated with better performance on the following domains: visuospatial/executive

function (B=0.57; p<0.05); attention (B=0.75; p<0.05); and language (B=0.49; p<0.05). Completing the MoCA assessment in Spanish was significantly associated with lower MIS scores (B=-2.95; p<0.001). **Conclusion:** Results show that educational attainment is significantly associated with performance on cognitive assessments among community-based Hispanic/Latino individuals, with specific MoCA domains being more influenced by education than others. These results underscore the importance of developing, validating and utilizing culturally appropriate and comprehensive cognitive assessments that better adjust for or mitigate the confounding effects of education. Such assessments are necessary for enabling equitable and accurate cognitive screening across diverse populations, while differentiating cognitively impaired individuals from individuals with low educational status.

P187- LONGITUDINALLY DEFINED OBJECTIVE SUBTLE MEMORY DECLINE IN COGNITIVELY UNIMPAIRED INDIVIDUALS IS ASSOCIATED WITH TAU DEPOSITION IN BRAAK I/II REGIONS. G. Sánchez-Benavides[1,2,3], D. López-Martos[1,2], M. Shekari[1], E. Borroni[4], G. Klein[4], M. Tonietto[4], M. Suarez-Calvet[1,2,3,5], J.D. Gispert[1,2], O. Grau-Rivera[1] *(1. Barcelonaβeta Brain Research Center (BBRC), Pasqual Maragall Foundation - Barcelona (Spain), 2. Hospital del Mar Medical Research Institute (IMIM) - Barcelona (Spain), 3. Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable, Instituto de Salud Carlos III, - Madrid (Spain), 4. Roche Pharma Research and Early Development, Neuroscience and Rare Disease, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd - Basel (Switzerland), 5. Servei de Neurologia, Hospital del Mar - Barcelona (Spain))*

Background: Although a transitional stage between healthy cognition and Mild Cognitive Impairment has been recognized by clinical and research criteria, this has not been yet fully operationalized [1, 2]. The use of cognitive trajectories obtained from individuals without evidence of Alzheimer's disease (AD) pathophysiological biomarkers as reference norms, while accounting for the expected base-rates of low scores in cognitively unimpaired (CU) individuals, could provide a reliable framework to define this stage. In the present study, we explored the associations between tau deposition and a new definition of Objective Subtle Cognitive Decline (Obj-SCD) in CU individuals at increased risk of AD dementia. **Methods:** We analyzed data from 97 CU participants from the ALFA+ cohort study (mean[SD] age: 61.5[4.9]; 57.7% women, 62.9% APOE-e4 carriers, 53.7% amyloid-b [Ab]+) with 18F-RO-948 tau PET and three-year cognitive follow-up data available. Regional SUVR of 18F-RO-948 PET was calculated in entorhinal (Braak I/II), limbic (Braak III/IV), and neocortical (Braak V/VI) regions using the inferior cerebellum as reference region. ObjSCD in memory was defined through cerebrospinal fluid (CSF) AD biomarker-based reliable change indices (RCI) adjusted for practice effect (using A-T-[N]- longitudinal cognitive performance as reference). RCIs were computed for 11 variables from 3 episodic memory tests (Free-Cued Selective Reminding Test, Memory Binding Test, Wechsler Memory Scale-IV) and Obj-SCD was labeled when a cognitive change below -1.28 SD (≤10th percentile) in at least 3 of the 11 memory variables included was found. CSF Ab42/40 ratio was measured using the NeuroToolKit, a panel of exploratory robust prototype assays (Roche Diagnostics International Ltd). The Ab+ group was defined as Ab42/40<0.071 [3]. We used linear models, with SUVRs as dependent variables, presence/absence of ObjSCD as predictor of interest, and age, education and sex as covariates, to explore the associations between regional and global tau deposition and objective memory decline. Interactions with sex and Ab status were also explored. **Results:** Twenty-three participants (23.7%) were classified as Obj-SCD. ObjSCD and control groups did not differ (p>0.1) in age (61.9[5.7] vs. 61.3[4.7], education (12.3[3.9] vs. 13.7[3.7]), number of females (58.1% vs. 56.5%) or Ab status (59.1% vs. 52.1%). We found significant associations between ObjSCD status and the SUVRs in entorhinal (Braak I/II) regions (t=2.168, p=0.032), a trend in limbic (Braak III/IV) regions (t=1.714, p=0.0899), and non-significant associations in neocortical (Braak V/VI) regions (t=0.445, p=0.657) and global measures (t=1.108, p=0.271). A significant interaction (p=0.018) between ObjSCD and Ab status was observed for the SUVRs levels in entorhinal (Braak I/II), being the association only observed in Ab+ individuals (t=3.174, p=0.002) in stratified analyses (Ab-, t=-1.275, p=0.211). **Conclusion:** We found higher deposition of tau in entorhinal (Braak I/II) regions in CU individuals showing a memory decline falling outside the expected trajectory based on references obtained from A-T-N- individuals. Such associations were driven by individuals harboring Ab pathology. Our results support that ObjSCD is sensitive to detect early AD-related subtle cognitive decline in the early AD continuum. This approach may help operationalize the NIA-AA transitional decline (stage 2) for the selection of individuals at higher risk of AD for enrollment in research and prevention trials. **Keywords:** Preclinical Alzheimer's disease, tau-PET, objective subtle cognitive decline, episodic memory, amyloid-β. **Disclosures:** Edilio Borroni, Gregory Klein, and Matteo Tonietto are Roche Pharma employees. The rest of authors have nothing to disclose. **References:** 1. Sperling et al., 2011 doi: 10.1016/j.jalz.2011.03.003; 2. Jack et al., 2018 doi: 10.1016/j.jalz.2018.02.018; 3. Milà-Alomà et al., 2020 doi : 10.1002/alz.12131.

P188- SEVERE COVID-19 LEADS TO ACCELERATED DEMENTIA ONSET. S. Mukhij[1,2,3], M. Suno[1,2], C. Magdamo[1,2], M.W. Albers[1,2] *(1. Harvard Medical School - Boston (United States), 2. Massachusetts General Hospital - Boston (United States), 3. University Hospital of Zurich - Zurich (Switzerland))*

Background: COVID-19, a global pandemic, has affected about 700 million people worldwide [1]. Despite its widespread impact, there is limited information available on the long-term consequences of this disease. Cognitive symptoms are well-established as a consequence of COVID-19 [2]. However, it remains unclear whether the severity of this disease influences the likelihood of a physician diagnosing cognitive impairment (CI). The entry of SARS-CoV-2 into the body triggers a neuroinflammatory immune response, leading to neuronal and glial dysregulation. This process can result in neural injury and cognitive impairment [3]. The hypothesis of our study is that individuals with severe COVID-19 symptoms requiring hospitalization would have a higher incidence of newly diagnosed cognitive impairment. **Methods:** To investigate the causal effects of COVID-19 on cognitive impairment, data from Mass General Brigham (MGB) was used. Diagnosis of CI is based on ICD-codes and prescription of drugs for cognitive impairment. We employed inverse propensity score weighting to balance hospitalized and non-hospitalized patients for age, sex, vaccination status, level of education and COVID-19 strain. Exclusion criteria included age < 55 years, no or < 6 month follow-up, prior cognitive impairment diagnosis and no primary care physician at MGB. The competing risk of death was accounted for [4]. Data was collected from March 1 2020, through April 10, 2024. **Results:** Among the 30'448 COVID-19

patients included in our study at Mass General Brigham mean age at COVID-19 positive results was 68 (9) with 56% female. Of these, 2'316 (7.6%) were hospitalized due to the severity of their COVID-19 symptoms. There was a significant difference ($p < 0.001$) between the hospitalized group and the non-hospitalized groups in terms of age and certain comorbidities including obesity, overweight status and diabetes. Our results indicate that patients with severe COVID-19 leading to hospitalization have a significantly higher incidence of dementia compared to non-hospitalized COVID-19 patients (Hazard Ratio 2.68 [1.99-3.62], $p < 0.001$). When accounting for the competing risk of death, where we acknowledge the possibility of death occurring before diagnosing CI, a significant difference in dementia incidence remained. After 3.5 years since the beginning of the COVID-19 pandemic, our data suggests that the probability of being diagnosed with dementia among individuals who were hospitalized due to COVID-19 is 7.7% [5.7-9.5], compared to 3.6% [2.8-4.5] for non-hospitalized individuals. **Conclusion:** This study suggests a significant association between severe COVID-19 that leads to hospitalization and the increased incidence of dementia diagnosis. The findings suggest that the neurological impact of severe COVID-19 may accelerate the onset of dementia symptoms, prompting earlier clinical recognition and diagnosis. This underscores the importance of monitoring cognitive function in patients recovering from severe COVID-19, as timely identification and intervention for dementia can potentially improve patient outcomes. **Keywords:** Covid-19, dementia, pandemic, cognitive impairment. **Disclosures:** Grant received from NIH. The authors declare no competing interests. **References:** 1. https://www.worldometers.info/coronavirus/; 2. Atchison, C.J., Davies, B., Cooper, E. et al. Long-term health impacts of COVID-19 among 242,712 adults in England. Nat Commun 14, 6588 (2023). https://doi.org/10.1038/s41467-023-41879-2; 3. Monje M, Iwasaki A. The neurobiology of long COVID. Neuron. 2022 Nov 2;110(21):3484-3496. doi: 10.1016/j.neuron.2022.10.006. Epub 2022 Oct 7. PMID: 36288726; PMCID: PMC9537254; 4. Charpignon, ML. et al. Causal inference in medical records and complementary systems pharmacology for metformin drug repurposing towards dementia. Nat Commun 13, 7652 (2022).

P189- EFFECT OF DISEASE STAGE AND AMYLOID LEVEL ON HARMONIZED DATA FROM NEUROPSYCHOLOGICAL TESTS IN THREE NATURAL HISTORY STUDIES. R. Shishegar[1], V. Dore[1], P. Bourgea[2], S. Laws[3], T. Porter[3], S. Burnham[4], A. Feizpour[5], M. Weiner[6], J. Hassenstab[7], C. Row[5], V. Villemagne[8], C. Masters[5], J. Fripp[2], J. Doecke[2], H. Sohrabi[9], P. Maruff[10] *(1. The Australian e-Health Research Centre, CSIRO, Melbourne (Australia), 2. The Australian e-Health Research Centre, CSIRO, Brisbane (Australia), 3. School of Biomedical Sciences, Faculty of Health Sciences, Curtin University, Bentley (Australia), 4. Avid, Eli Lilly and Company, Indianapolis, Boston (United States), 5. Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Melbourne (Australia), 6. Center for Imaging of Neurodegenerative Diseases, University of California-San Francisco, San Francisco, San Francisco, (United States), 7. Institute of Clinical and Translational Sciences, Washington University School of Medicine, St Louis (United States), 8. Department of Psychiatry, University of Pittsburgh, Pittsburgh (United States), 9. Centre for Healthy Ageing, Health Futures Institute, Murdoch University, Murdoch, Perth (Australia), 10. Cogstate Ltd, Melbourne, Melbourne (Australia))*

Background: Understanding of clinical-pathological relationships across the AD spectrum is improved by the measurement precision and statistical power afforded by large study samples. The ability to harmonize neuropsychological data is limited by use of different tests to measure the same cognitive domains. This can be overcome through application of data science techniques, although optimal methods are still being sought. Here we report the sensitivity to AD-related disease cognitive decline of composite scores harmonised from across the AIBL, ADNI and OASIS studies that extends to multiple neuropsychological tests from three samples, a machine learning (ML) data harmonisation method [1]. **Methods:** Data utilized in the harmonization method longitudinal clinical/pathological data from the AIBL (N=1765), ADNI (N=1779) and OASIS (N=440) cohorts. The harmonization processes involved three stages. First, neuropsychologists defined cognitive domains of interest and nominated the neuropsychological tests that assessed each in each cohort. Second, a standardized scoring and naming convention was established for demographic and neuropsychological outcomes. Third, the ML harmonisation approach [1] was applied. Test scores present in one cohort, but not another, were treated as missing and imputed using ML [2] before calculating composite scores of episodic memory, executive function, language and attention. Imputation utilized data from neuropsychological tests, age, gender, education years and APOE-ε4 status. To determine the extent to which the composite sores, computed from harmonized neuropsychological test data remained sensitive to AD clinical disease status and AS biomarker levels, linear mixed models (LMMs) were used to model trajectory of change on each composite score. Each LMM included time, CDR-global score, and amyloid status (AB-/AB+) interactions as fixed effects with sex and age at baseline included as covariates. Variation in baseline and decline in each composite score was modelled using random intercepts and slopes. For each composite score the magnitude of difference in slope between each clinical group and the amyloid negative cognitively unimpaired (CUAB-) group was expressed as an effect size (Cohen's d). **Results:** For the harmonized episodic memory composite, compared to the CUAB- adults, performance declined in the amyloid positive CU adults (d=0.20), prodromal AD (d=0.25) and AD dementia (d=0.13) groups. For the harmonized executive function composite, compared to the CUAB- adults, performance declined in the amyloid positive CU adults (d=0.14), prodromal AD (d=0.28) and AD dementia (d=0.36) groups. For the harmonized language composite, compared to the CUAB- adults, performance declined in the amyloid positive CU adults (d=0.14), prodromal AD (d=0.44) and AD dementia (d=0.96) groups. For the harmonized attention composite, compared to the CUAB- adults, performance declined in the amyloid positive CU adults (d=0.06), prodromal AD (d=0.09) and AD dementia (d=0.27) groups. **Conclusion:** The results show that the memory, executive function, language and attention composites computed from the harmonized data show the expected effects of AD clinical disease stage. These data provide initial validation of the harmonization method and a foundation for use of these to improve understanding of clinical pathological relationships using data integrated from across multiple prospective natural history studies. **References:** 1. doi: 10.1002/alz.044302; 2. doi:10.1093/bioinformatics/btr597

P191- CLINCLOUD SUCCESSFULLY DEMOCRATIZES

POLARIS-AD PHASE 3 EARLY ALZHEIMER'S DISEASE STUDY TO MAXIMIZE TRIAL EXPOSURE TO DIVERSIFIED AND UNDERSERVED POPULATIONS. M. Biban[1], J. Rock[2], J. Branning[1], C. Skirrow[3], G. Marino[1], L. Estes[1], K. Sapp[1], N. Gadea[1] *(1. ClinCloud, LLC - Maitland (United States), 2. AriBio Co., LTD - San Diego (United States), 3. Novoic LTD - London (United Kingdom))*

Background: Enrolling diverse populations into clinical trials helps ensure that diagnostics and treatments are safe and effective across groups. Building inclusive clinical trial infrastructure in underserved communities is important for achieving this goal and will benefit those communities by providing access to treatments and accelerating the adoption of medical advances. ClinCloud designed and implemented pilot clinical trial prescreen programs with the assistance of Novoic and AriBio that incorporated innovative recruitment initiatives and new engagement strategies to increase enrollment in POLARIS-AD phase 3 clinical trial for early Alzheimer's disease. ClinCloud recruited participants from diverse communities with a focus on Black/African American and Hispanic/Latino participants, who are at higher risk of developing dementias than Whites within the US. Our teams identified strategic partnerships with walk-in laboratories, pharmacies, and large provider networks to educate patients, providers, and community partners on clinical research. We used on-site community-based screening with the Montreal Cognitive Assessment (MoCA) and Storyteller by Novoic, a self-guided assessment technology administered followed by telehealth services to verify study eligibility. **Method:** ClinCloud deployed this strategy at pharmacies, laboratory facilities, and large provider networks, serving as recruitment and education hubs providing integrated educational materials and awareness campaigns. In addition, we implemented self-guided memory assessments via telehealth to enhance accessibility while minimizing staffing burdens often required for enrollment. These collaborative, transdisciplinary approaches to engage, educate, and motivate played an important role not only in recruitment but also in retention of these subjects. We provided training sessions for external providers to enhance their understanding of clinical trial benefits and access to electronic medical records systems for seamless integration of clinical research into practice workflows, which improved participant adherence to the research. We also used a follow-up conversation with a clinician after the prescreening cognitive assessments to discuss the potential subject's performance and obtain commitments to attend a study screening visit. **Results:** During the 4-month recruiting period, 140 potential subjects responded to these recruitment efforts and completed the MoCA and Storyteller evaluations. Forty-six (33%) potential subjects were tentatively qualified, of which 21 (46%) were Hispanic/Latino, 6 (13%) were Black/African American, and 7 (15%) were other ethnicities. Of these 34 (74%) subjects were screened and 5 (11%) enrolled in POLARIS-AD clinical trial. Through our recruitment strategies utilizing Storyteller by Novoic self-guided memory assessment and telehealth services, we have increased the participation rate of diverse populations in clinical trial screening to 24% compared with the 2% participation rate obtained historically. **Conclusion:** These strategic partnerships utilizing pharmacies and laboratories with walk-in blood draw stations provided a valuable source of potential subjects from diverse backgrounds. Potential subjects reviewed the educational materials and participated in the self-guided memory assessments while follow-up telehealth services minimized staff burden and facilitated enrollment. **Keywords:** Alzheimer's disease, Early Detection, Cognitive Assessment, Recruitment, Clinical Trials, Pre-Screening. **Disclosures:** Maria Emanuela Biban, Jessica Branning, Geraldine Marino, Landon Estes, Karem Sapp, and Natalie Gadea are employees of ClinCloud LLC, James Rock is employed by and a shareholder of AriBio Co. LTD, Caroline Skirrow is an employee of Novoic LTD.

P192- ASSOCIATIONS BETWEEN BODY COMPOSITION METRICS, CLINICAL DEMENTIA RATING SCALE (CDR©) SCORES, GENDER, AND RACE/ETHNICITY AMONG OLDER ADULTS WITH AND WITHOUT COGNITIVE IMPAIRMENT. G. Pilonieta[1], D. Geldmacher[1] *(1. The University of Alabama at Birmingham - Birmingham (United States))*

Background: Gender-related differences in the associations between body composition metrics (BCMs) and Alzheimer's disease (AD) clinical profiles have been observed. However, whether there are differential race and gender effects on body composition metrics that correlate with cognitive performance remains unclear. We therefore evaluated the associations of different BCMs (measured by bioelectrical impedance) and a composite measure of cognition and daily function for race and the gender-related effects in a cohort of older adults. **Methods:** We analyzed five BCM variables (visceral fat level, body fat mass, body fat percentage, skeletal muscle mass, and BMI), composite measures of cognition and daily function (Clinical dementia rating global scores (CDR-GS) and CDR-sum of boxes (CDR-SB)) obtained from 153 individuals from the UAB Alzheimer's Disease Research Center clinical cohort. Participants included non-Hispanic White (NHW) (N=69; 45.10 %) and non-Hispanic Black (N=84; 54.90%) adults with clinical diagnoses of normal cognition, mild cognitive impairment (MCI), or dementia. Participants who had an MCI or dementia clinical diagnosis were grouped as cognitively impaired (n=87, 56.86%). Spearman's rank partial correlation analyses examined the associations between CDR-GS, CDR-SB, and BCMs by race and controlling by gender. **Results:** Among 153 participants (64.05% women, mean age 69.5 yrs.± 8.03., mean education 15.45±2.6 yrs., mean BMI 29.66±7.41), NHB participants had higher BMI, body fat percentage, and visceral fat level in both diagnosis groups ($p<0.05$) compared to NHW participants. There were no differences in CDR-GS and CDR-SB scores among unimpaired participants by race, but cognitively impaired NHB participants were less impaired on CDR-GS ($p<0.05$) than NHW participants. Spearman's correlation analyses showed significant associations between CDR-GS, CDR-SB, and all BCMs ($p<0.05$) except skeletal muscle mass in the NHB cognitively impaired subsample. There were statistically significant negative associations between CDR-GS, CDR-SB, and BCMs after controlling by gender among cognitively impaired NHB participants. **Conclusion:** Our study found differences by self-reported race/ethnicity on cross-sectional analyses of CDR severity ratings and body composition metrics among NHB participants diagnosed as cognitively impaired. Future research exploring the influence of cardiometabolic factors, genetic ancestry, and correlations with imaging biomarkers in members of groups underrepresented in research may provide new insights into factors differentially influencing AD risk. Such studies could improve understanding of gender and race-related disparities in AD risk factors, pathogenesis, clinical expression, and progression. **Keywords:** Alzheimer's disease, race, body composition, cognitive impairment. **Funding:** The National Institute of Aging supported this work through the Alzheimer's Disease Center

at the University of Alabama at Birmingham under the award number 5P20AG068024-02. **Disclosures:** Dr. Pilonieta reports no disclosures. Dr. Geldmacher has received research funding paid to his employer from Biogen, Cognition Therapeutics, Eisai, Janssen, NIH, Vaccinex. He has received consulting income from. Eisai, Genentech/Roche, HMP/CME, Lilly, Medscape, MedLearning Group, Premier Applied Science.

P193- RELATIONSHIP BETWEEN BODY COMPOSITION METRICS AND PERFORMANCE ON THE DEMENTIA RATING SCALE (DRS-2) IN OLDER ADULTS WITH AND WITHOUT COGNITIVE IMPAIRMENT. D. Geldmacher[1], G. Pilonieta[1] *(1. The University of Alabama at Birmingham - Birmingham (United States))*

Background: While race and obesity are well-studied risk factors for dementia, there is little information about the associations between body composition metrics (BCMs) and cognitive impairment by race. Moreover, most studies of these used composite measures of cognition and daily function measures such as the CDR® Dementia Staging Instrument (CDR®) to establish severity of impairment. Few studies have employed broad-based objective cognitive measures such as the Dementia Rating Scale-2 (DRS-2). The DRS-2 is used to assess cognitive status in both clinical practice and research settings. It comprises tests in five cognitive domains: attention, initiation/perseveration (I/P), construction, conceptualization, and memory. This study investigates associations between DRS-2 total score and body composition measures (BCMs) in the UAB Alzheimer's Disease Research Center (UAB eADRC) clinical cohort by race and gender-related effects. **Methods:** Individuals enrolled in the UAB eADRC (n=135; non-Hispanic White (NHW) (N=61, 45.19; %) and non-Hispanic Black (NHB) (N=74; 54.81%) with baseline cognitive status of normal cognition, mild cognitive impairment (MCI), or dementia completed the DRS-2 as part of their initial neuropsychological assessment. For this analysis, we grouped individuals with a clinical diagnosis of MCI and dementia as "cognitively impaired". Bivariate analyses compared DRS-2 total score and the BCMs (BMI, skeletal muscle mass, body fat mass, body fat percentage, and visceral fat level) among cognitively normal (n=56, 41.48%) and impaired individuals (n=79, 58.51%) by race. Spearman's partial rank correlation examined the relationships between DRS-2 total score and BCMs by self-reported race and adjusting for gender. **Results:** Of 135 participants, 90 (66.67%) were women, mean age was 69.31 (SD 8.1), and mean education was 15.30 (SD 2.60) years. There were race related differences in BCMs but no differences in DRS-2 scores by race. When analyzed by race, spearman's correlations showed significant positive associations between DRS-2 total score, BMI and visceral fat level in the NHB cognitively impaired subsample. After adjusting for gender effects, in the NHW subsample, there were significant positive relationships between skeletal muscle mass and DRS-2 in both diagnostic groups. Among NHB cognitively unimpaired and impaired participants, there were positive significant associations between DRS-2 and body fat percentage. **Conclusion:** In this study, we found that associations between DRS-2 scores and body composition measures varied by racial group among community-dwelling older adults with and without cognitive impairment. These findings - in a sample with high representation of NHB individuals - support prior research on the associations between obesity and cognitive impairment. The relationship between DRS-2 performance and non-invasive anthropometric measures of body composition requires further studies in larger and more diverse populations, with consideration of genetic ancestry in conjunction with self-reported race and ethnicity. **Keywords:** Dementia Rating Scale-2, cognitive impairment, Alzheimer's disease, obesity, body composition metrics. **Funding:** This work was supported by the National Institute of Aging through the Alzheimer Disease Center at the University of Alabama at Birmingham under the award number 5P20AG068024-02. **Disclosures:** Dr. Pilonieta reports no disclosures. Dr. Geldmacher has received research funding paid to his employer from Biogen, Cognition Therapeutics, Eisai, Janssen, NIH, Vaccinex. He has received consulting income from Eisai, Genentech/Roche, HMP/CME, Lilly, Medscape, MedLearning Group, Premier Applied Science.

P194- EFFECTS OF THE DAVOS ALZHEIMER'S COLLABORATIVE EARLY DETECTION OF COGNITIVE IMPAIRMENT PROGRAM ON CLINICIAN ATTITUDES AND CONFIDENCE. S. Mattke[1], T. Ozawa[1], V. Baldivieso[2], O. Corrêa Dos Santos Filho[3], I. Govia[4], H. Kowa[5], M. Lopez-Ortega[6], A. Mckean[7], D. Willis[8], A. Deckert[9], K. Selzler[9] *(1. University of Southern California - Los Angeles (United States), 2. AdventHealth - Orlando (United States), 3. State University of Rio de Janeiro - Rio De Janeiro (Brazil), 4. Jamaica Mental Health Advocacy Network - Kingston (Jamaica), 5. Kobe University - Kobe (Japan), 6. National Institute of Geriatrics - Mexico City (Mexico), 7. Brain Health Scotland - Edinburgh (United Kingdom), 8. Indiana University School of Medicine - Indianapolis (United States), 9. Davos Alzheimer's Collaborative - Wayne (United States))*

Background: Early detection of cognitive impairment remains a challenge across global healthcare systems, with obstacles to accessing new innovations, including diagnostics and disease-modifying Alzheimer's treatments. The Davos Alzheimer's Collaborative Healthcare System Preparedness launched the Early Detection Program to improve early detection of cognitive impairment in primary care and non-specialty settings. The program tests the feasibility and effects of training clinicians and providing them with diagnostic tools, such as digital cognitive assessments and a blood biomarker test for Alzheimer's pathology. It was conducted in seven healthcare systems across six countries (Brazil, Jamaica, Japan, Mexico, Scotland, two US sites). Here, we report the effects of the interventions on clinicians' confidence in clinical abilities, attitudes to care, and engagement. **Methods:** The General Practitioners Attitude and Confidence Scale for Dementia (GPACS-D) was completed by 109 clinicians before and 68 clinicians after the intervention. GPACS-D is a validated scale of 15 items with three subscales: confidence in clinical abilities, attitude to care, and engagement. Results are expressed in a 5-point Likert scale that range from "strongly disagree" to "strongly agree" (some reverse scored). Pre and post intervention scores were compared with two-tailed t-tests. Results for Japan could not be included in these analyses because the existence of an ongoing early detection program meant that no baseline data were available. **Results:** Female respondents accounted for 61.5% and 61.8% and physicians for 75.2% and 70.6% of the pre- and post-intervention samples, respectively. Average years in practice were 11.96 (STD: 13.26) and 15.52 (STD: 13.41), respectively. The mean average score on the attitudes scale changed from 4.27 to 4.42 (p=0.07), on the engagement scale from 2.85 to 2.88 (p=0.79), and on the confidence scale from 2.98 to 3.27 (p=0.014). The overall score increased significantly from 3.47 to 3.65 (p=0.001). **Conclusion:** The intervention was associated with an overall increase in the GPACS-D score, mostly driven by a significant increase in clinicians' confidence in diagnosing dementia and providing post-diagnostic support. Attitudes towards dementia care

improved non-significantly from a high baseline, whereas engagement scores remained virtually unchanged at an equivocal level. Future research is needed to understand the long-term impact of this program on earlier detection of patients with cognitive impairment. **Keywords:** Cognitive impairment, early detection, primary care. **Disclosures:** Soeren Mattke serves on the board of directors of Senscio Systems, Inc., and the scientific advisory board of AiCure Technologies, Alzpath, and Boston Millennia Partners. He has received consulting and speaker fees from Biogen, C2N, Eisai, Eli Lilly, Novartis, Novo Nordisk and Roche/Genentech.

P195- DAVOS ALZHEIMER'S COLLABORATIVE HEALTHCARE SYSTEM PREPAREDNESS EARLY DETECTION PROGRAM: KEY ROLES FOR SUCCESSFUL DCA IMPLEMENTATION. A. Deckert[1], K.J. Selzler[1], L. Chavira-Razo[1], A. Kurzman[1], T. Macleod[1] *(1. Davos Alzheimer's Collaborative - Wayne (United States))*

Background: Global healthcare systems are not prepared to care for the increasing prevalence of Alzheimer's disease and related dementias (ADRD). The Davos Alzheimer's Collaborative Healthcare System Preparedness (DAC-SP) program aims to drive transformative changes in healthcare systems worldwide, accelerating access to groundbreaking innovations and treatments for individuals with Alzheimer's and their families. In 2021, DAC-SP launched the Early Detection program in seven healthcare systems across six countries, with the objective of increasing detection rates for cognitive impairment and gaining insights into the barriers and facilitators to integrating digital cognitive assessments (DCA) into primary care and non-specialty settings. **Methods:** A qualitative implementation evaluation of the DAC-SP Early Detection program was completed, guided by the Consolidated Framework for Implementation Research (CFIR; Damschroder et al., 2009). In-depth interviews were conducted at baseline, mid- and post-program with implementation team members and participating clinicians. Transcribed interviews were analyzed using a directive content analysis. We report here two key recommendations focused on individual factors that contributed to successful DCA implementation as part of the DAC-SP Early Detection program. **Results:** Qualitative interviews were completed with 87 clinicians and 14 implementation team members. Clinician participants were predominantly primary care physicians. Our inductive analysis of the CFIR model revealed three levels of influential factors contributing to implementation progress and outcomes across sites: brain health ecosystem (e.g., contextual factors such as policy and regulatory environment, clinical guidelines), healthcare institution, and individuals (i.e., patients and clinicians). Overall findings underscore the critical role of the brain health ecosystem in successful DCA implementation across DAC-SP Early Detection program sites. We highlight in this presentation the unique skills and characteristics of two key roles at the individual level that emerged as important enablers of DCA adoption across global sites. First, we outline the skillset and key activities of a patient-facing role, and second, those of an implementation lead in designing and supporting the program within their healthcare institution. **Conclusion:** Despite the emphasis in our findings on the profound influence of the existing brain health ecosystem on early detection attitudes and behaviours at the individual clinician level, we identified two key roles that characterized successful DCA implementation across sites. Our findings suggest that the skills and experience of brain health navigators and primary care-oriented implementation leaders can facilitate navigating complex organizations and brain health ecosystems to support DCA adoption in primary care settings. **Keywords:** Digital cognitive assessments, early detection, primary care, implementation.

P196- REPEATABLE BATTERY FOR THE ASSESSMENT OF NEUROPSYCHOLOGICAL STATUS (RBANS) CHANGES ANCHORED WITH CDR PROGRESSION IN A PRECLINICAL AD POPULATION. C. Cunha[1], R. Blattner[1], B. Echevarria[1], S. Negash[1], C. Randolph[1] *(1. WCG Clinical Research Solution - Princeton (United States))*

Background: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a brief neuropsychological battery that evaluates multiple cognitive domains [1]. It has been used as an endpoint in multiple preclinical Alzheimer disease (AD) trials [2,3]. To date, characterization of neurocognitive decline in preclinical AD trials has been limited due to the discontinuation of many of these trials for various reasons [4]. We sought to determine the nature and magnitude of changes on the RBANS associated with progression from a Clinical Dementia Rating scale (CDR) global score of 0 to 0.5, as well as to examine any differences at baseline on the RBANS for the sample that progressed versus those that did not in the available data. **Methods:** Data from 2310 subjects that participated in four preclinical AD multinational double-blind, placebo controlled clinical trials were available for analysis. All participants had a CDR global score of 0 at baseline. We examined data from the first visit at which participants had a change in their CDR global score of 0 to 0.5. RBANS data from baseline to this visit were compared, and the baseline data from this group was compared to the baseline data for the group that remained at a CDR global score of 0, to explore any baseline differences between the groups. **Results:** Independent samples t-tests were performed to assess the differences at baseline in the RBANS scores between the groups. 2043 subjects remained cognitively normal, while 267 subjects progressed to a CDR global score of 0.5. At baseline, the group that progressed scored numerically lower across all RBANS index scores, with this difference reaching statistical significance for the Visuospatial/Constructional index. Within the group that progressed, RBANS index scores also dropped from baseline to the visit where a CDR global score of 0.5 was assigned, with statistical significance on the RBANS Immediate Memory index. **Conclusion:** There appear to be subtle neurocognitive differences at baseline between individuals who later exhibit clinical progression versus those that do not within this preclinical population. Additionally, immediate memory appears to be the domain within the RBANS that is most sensitive to early progression. This may be due to the combination of demands of both working memory and anterograde memory for the subtests within this domain, but this requires clarification from further investigation. **Keywords:** Alzheimer's disease; Preclinical, RBANS; CDR global score. **Disclosures:** The authors declare that they have no conflicts of interest related to this study. CR is the author of the RBANS and receive royalty payments from the publisher and copyright holder of the test, Pearson, Inc. **References:** 1. Randolph, C. et al. Journal of Clinical and Experimental Neuropsychology 1984;20(3),310-319. https://doi.org/10.1076/jcen.20.3.310.8231. 2. Ritchie, K. et al. Alzheimer's and Dementia 2017; 13, 186-195. https://doi.org/10.1016/j.jalz.2016.07.1542. 3. Karantzoulis , S. et al. Archives of Clinical Neuropsychology 2013; 28, 837-844. http://doi.org/10.1093/arclin/act057. 4.

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P197- AN ASSESSMENT OF THE UTILITY OF THE MONTREAL COGNITIVE ASSESSMENT (MOCA) IN PREDICTING AMYLOID PET POSITIVITY IN ALZHEIMER'S DISEASE (AD) CLINICAL TRIALS. E. Sosa[1] *(1. Irvine Clinical Research - Irvine (United States))*

Background: The Montreal Cognitive Assessment (MoCA) is a commonly used tool to assess for cognitive impairment. The assessment has been used in both clinical and research settings. Prior studies have found that lower MoCA scores are related to amyloid positron emission topography (PET) positivity. There is also some supportive evidence that specific domains within the MoCA may be useful for identifying Alzheimer's Disease (AD). For example, impaired clock drawings, particularly errors with hand setting, can represent early signs of AD. The current research extends prior studies by examining the predictive utility of MoCA domain scores (in addition to overall score). Findings provide insight on practices for identifying cognitive impairment among prospective clinical trial participants. **Methods:** Participants were administered the MoCA as part of a clinical trial pre-qualification process. Those who were deemed suitable and interested proceeded to screen for an industry-sponsored trial. Data from the MoCA and amyloid PET scans (positive/negative) were analyzed to determine the predictive value of the MoCA (and its domains) on amyloid status. **Results:** Multiple binary logistic regression was conducted to test whether overall MoCA and domain scores of the assessment (i.e., visuospatial/executive, naming, attention, language, abstraction, delayed recall, and orientation) were predictive of amyloid PET status. Findings indicated that total MoCA score was not predictive of amyloid positivity, B = 0.001 (0.06), p = .983. The domains scores also were not significantly predictive of amyloid positivity, Bvisuo = 0.12 (0.20), p = .540, Bnaming = 0.07 (0.38), p = .859, Battention = 0.02 (0.19), p = .933, Blanguage = 0.28 (0.20), p = .176, Babstraction = 0.05 (0.30), p = .876, Bdelayedrecall = -0. 20 (0.15), p = .175, Borientation = -0.19 (0.28), p = .493. **Conclusion:** The MoCA may not be as useful of a pre-screening tool for discerning amyloid status among clinical trial participants, particularly those with minimal cognitive impairment. Alternate cognitive assessments for selecting prospective participants should be considered. **Keywords:** Alzheimer's Disease, MoCA, Amyloid PET, Eligibility, Recruitment, Pre-Screening.

P198- DEVELOPMENT AND VALIDATION OF A 4-YEARS ALL-CAUSE DEMENTIA PREDICTION TOOL BASED ON SLEEP-RELATED SYMPTOMS USING A SCORE RISK PREDICTION MODEL. H. Lee[1], J.W. Han[1], J.B. Bae[1], D.G. Moon[1], J. Shin[2], D.J. Oh[3], E. Lim[4], B.J. Kim[5], D.W. Lee[6], J.L. Kim[7], J.H. Park[8], J.J. Lee[9], K.P. Kwak[10], S.B. Lee[9], K.W. Kim[11] *(1. Department of Neuropsychiatry, Seoul National University Bundang Hospital - Seongnam (Korea, Republic of), 2. Department of Neuropsychiatry, Seoul National University Bundang Hospital, - Seongnam (Korea, Republic of), 3. Workplace Mental Health Institute, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, - Seoul (Korea, Republic of), 4. Department of Neuropsychiatry, Gyeongsang National University Changwon Hospital - Changwon (Korea, Republic of), 5. Department of Psychiatry, Gyeongsang National University, School of Medicine - Jinju (Korea, Republic of), 6. Department of Neuropsychiatry, Inje University Sanggye Paik Hospital - Seoul (Korea, Republic of), 7. Department of Psychiatry, School of Medicine, Chungnam National University - Daejeon (Korea, Republic of), 8. Department of Neuropsychiatry, Jeju National University Hospital - Jeju (Korea, Republic of), 9. Department of Psychiatry, Dankook University Hospital - Cheonan (Korea, Republic of), 10. Department of Psychiatry, Dongguk University Gyeongju Hospital - Gyeongju (Korea, Republic of), 11. Department of Psychiatry, Seoul National University, College of Medicine - Seoul (Korea, Republic of))*

Background: Dementia poses a major global health challenge with profound socio-economic impacts [1, 2]. Existing dementia prediction models have inadequately incorporated sleep-related symptoms, which are pivotal in predicting cognitive decline [3]. **Objective:** This study aims to develop and validate a score risk prediction model based on sleep-related symptoms for all-cause dementia among the Korean population. **Methods:** Data were sourced from the Korean Longitudinal Study on Cognitive Aging and Dementia, involving 2984 participants aged over 60 [4]. Participants were stratified into a young-old group (aged 60-74) and an old-old group (aged 75 and above). We employed LASSO regression and multivariate logistic regression to construct a score risk prediction model, incorporating variables from sleep symptom scales such as the Pittsburgh Sleep Quality Index, the Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire, the STOP Questionnaire, and the Cambridge-Hopkins Restless Legs Syndrome Questionnaire. **Results:** The original model demonstrated strong predictive capabilities with an area under the curve (AUC) of 0.881 in the training set and 0.875 in the validation set. The score risk prediction model, transformed from the logistic model, showed modest performance with AUC values of 0.868 (95% CI: 0.787-0.920) in the training set and 0.878 (95% CI: 0.704-0.988) in the validation set. For participants aged 75 and older, the model did not show significant differences compared to an age-only model. **Conclusion:** The score risk prediction model effectively identifies the risk of dementia based on sleep-related symptoms in individuals aged 60-74. This model holds significant potential for early intervention and may help delay the onset of dementia, emphasizing its utility in clinical settings. **Keywords:** Dementia, Score risk prediction model, Sleep related symptoms. **Data Deposition:** The data that support the findings of this study are available from the corresponding author upon reasonable request. **Disclosures:** The authors declared no competing interests. **References:** 1. Nichols, E., et al., Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. The Lancet Public Health, 2022. 7(2): p. e105-e125. 2. Organization, W.H., Dementia: a public

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P199- SEQUENTIAL ADMINISTRATION OF DIGITAL TESTING TO SCREEN FOR COGNITIVE IMPAIRMENT FOLLOWED BY BLOOD BASED BIOMARKERS TO ASSIST WITH TIMELY DETECTION AND ACCURATE DIAGNOSIS OF ALZHEIMER'S DISEASE IN ADVENTHEALTH. V. Baldivieso[1], S.R. Smith[1], R.E. Pratley[1], M. Baksh[1], G. Shepherd[1], J. Lopez[1] *(1. AdventHealth - Orlando (United States))*

Background: Alzheimer's disease (AD) diagnosis continues to be a challenge. One of the main obstacles is to identify AD pathology early and reliably, in those who have the condition. Leading to significant hurdles in delivering optimal care, providing supportive services, treatment with disease-modifying therapies and access to clinical research. **Methods:** This study involved older adults 65+, who agreed to take part in the collection of data and samples related to their health, cognition, and other biological markers. We utilized two pathways to recruit participants; Primary Care Providers (PCP) referral and a direct-to-consumer (DTC) approach via social media. The participants completed a digital cognitive test (DCT) online to check for possible cognitive impairment. Those who had abnormal and borderline results qualified to visit our Translational Research Institute. At this in-person visit, the participants completed a second cognitive test, MoCA and blood tests including a blood-biomarker (BBM) test, the PrecivityAD® blood test, a CLIA-certified laboratory developed test that uses mass spectrometry to analyze biomarkers to identify brain amyloid plaques (reported by the Amyloid Probability Score-APS) in individuals with Cognitive Impairment (CI). Those who tested positive on MoCA for cognitive impairment were advised to follow-up with a neurologist or gerontologist. **Results:** Over 2,300 participants expressed interest. Of 2,001 eligible, 1076 (96% social media, 4% PCP) e-consented. 742 completed the Cogstate Brief Battery (CBB) of which 211 (28%) were borderline, 113 (15%) abnormal, and 418 (56%) were negative for CI. Of the 324 with borderline or abnormal CBB scores, 219 (67%) completed the MoCA (59% Normal range, 38% Mild CI range, 2% Moderate CI range, and 0.5% Severe CI range). Of the 324, 218 (67%) received BBM: 18.8% had High APS, 67.9% Low APS, and 13.3% Intermediate (e.g. non-informative) APS. The APS result for participants with a normal MoCA showed 20% with High APS, 12% with an Intermediate APS, and 69% with Low APS. Of those with an impaired MoCA 18% had High APS, 15% Intermediate and 67% low APS. A Fisher's Exact test determined there was no statistically significant relationship between MoCA impairment and APS category (p-value 0.68). **Conclusion:** This study revealed the opportunities and difficulties of early detection of Alzheimer's, with insights into PCP and DTC referral routes. Both DCAs and blood-based biomarkers (BBMs) are useful in early detection for cognitive decline and a preliminary step in finding patients who could gain from future treatments. A more comprehensive clinical evaluation of AD can be enhanced with the addition of a BBM leading to better disease-modifying strategies.

P200- CLINICAL MANAGEMENT DURING THE DAVOS ALZHEIMER'S COLLABORATIVE EARLY DETECTION OF COGNITIVE IMPAIRMENT PROGRAM IN SIX COUNTRIES. S. Mattke[1], T. Ozawa[1], J. Chen[1], V. Baldivieso[2], O. Corrêa Dos Santos Filho[3], I. Govia[4], H. Kowa[5], M. Lopez-Ortega[6], A. Mckean[7], D. Willis[8], A. Deckert[9], K. Selzler[9] *(1. University of Southern California - Los Angeles (United States), 2. AdventHealth - Orlando (United States), 3. State University of Rio de Janeiro - Rio De Janeiro (Brazil), 4. Jamaica Mental Health Advocacy Network - Kingston (Jamaica), 5. Kobe University - Kobe (Japan), 6. National Institute of Geriatrics - Mexico City (Mexico), 7. Brain Health Scotland - Edinburgh (United Kingdom), 8. Indiana University School of Medicine - Indianapolis (United States), 9. Davos Alzheimer's Collaborative - Wayne (United States))*

Background: As new diagnostic tools and disease-modifying Alzheimer's disease (AD) treatments are becoming available, there is an increased urgency to detect early-stage cognitive impairment. The Davos Alzheimer's Collaborative Healthcare System Preparedness Early Detection Program aimed to improve early detection of cognitive impairment by implementing digital cognitive assessments (DCA) and a blood biomarker (BBM) tests for Alzheimer's pathology in primary care and non-specialty settings. The program was conducted in seven sites across six countries (Brazil, Jamaica, Japan, Mexico, Scotland, and two US sites). **Methods:** Participants were included in the program if they came to any type of appointment at a site, were at least 60 or 65 years old (site-specific age eligibility) and had no prior documented diagnosis of cognitive impairment. Patients with borderline and/or abnormal DCA were offered a BBM. Participant data were collected and extracted from electronic health records or abstracted from charts, including: patient age and sex, DCA and BBM test uptake and results, subsequent diagnostic tests (i.e., laboratory tests for addressable causes, structural brain imaging, confirmatory biomarker testing, cognitive testing, or AD specialist referral), and, if relevant, changes in management (i.e., symptomatic medications prescribed or referral to an AD support organization). For each data point, we report the sample-wide results with the across-site range in parentheses. **Results:** Of the 4,455 patients in the Early Detection Program across sites (across-site range = 46 to 1,722), the average age was 72 (69 to 74) years and 61% (36 to 71%) were female. The DCA was administered in 90% (69 to 100%) of included patients and the result was normal in 33% (17 to 44%), borderline in 33% (19 to 46%), and abnormal in 23% (11 to 45%) of the 4,000 tested patients. The BBM test was conducted in 433 (0 to 218) patients and the result was negative in 48% (0 to 68%), indeterminate in 12% (8 to 18%), and positive in 23% (16 to 82%) of the 4,000 tested patients. Uptake of BBM tests among those with non-normal DCA was 17% (0 to 100%). Of 2,508 (25 to 864) patients with non-negative DCA, lab tests were conducted in 66% (0 to 100%), imaging in 14% (0 to 69%), confirmatory biomarker testing in 1% (0 to 3%) and cognitive testing in 2% (0 to 5%) cases; 10% (0 to 100%) patients were referred to a specialist. Symptomatic drugs were prescribed in 5% (0 to 100%) cases and 2% (0 to 49%) patients were referred to a support organization. Overall, 60% (0 to 100%) underwent at least one additional diagnostic assessment or change in management. **Conclusion:** The DCA completion rates were high and 67% had a borderline or abnormal score. Of those eligible for BBM, only 17% underwent blood biomarker testing for AD pathology. The majority of patients with borderline or abnormal DCA results received subsequent diagnostic assessments or changes in clinical management. Findings from the Early

Detection Program demonstrate that DCAs and BBMs can be implemented into existing workflows and commonly inform clinical decisions. **Keywords:** Cognitive impairment, early detection, primary care. **Disclosures:** Soeren Mattke serves on the board of directors of Senscio Systems, Inc., and the scientific advisory board of AiCure Technologies, Alzpath, and Boston Millennia Partners. He has received consulting and speaker fees from Biogen, C2N, Eisai, Eli Lilly, Novartis, Novo Nordisk and Roche/Genentech.

P201- ACCOUNTING FOR WORDLIST FEATURE DIFFERENCES ACROSS ALTERNATE FORMS OF THE ADAS-COG WORD RECALL TEST. J. Bock[1,2], J. Hara[1,3], D. Fortier[1], T. Mangrola[1], M. Lee[2] *(1. Embic Corporation - Newport Beach (United States), 2. Dept. of Cognitive Sciences, University of California at Irvine - Irvine (United States), 3. Pickup Family Neuroscience Institute, Hoag Memorial Hospital - Newport Beach (United States))*

Background: When assessing performance on a wordlist memory (WLM) test (e.g., ADAS-Cog, AVLT, EVLT, and CERAD) to characterize cognition or identify impairment with item response data, it is essential to account for each test's specific features. Such features vary across tests and alternative forms within a test, including the words presented and the order of presentation. These variabilities greatly and differently impact the way that individuals learn and remember the words' episodic presentation, thus affecting test performance. The ADAS-Cog WLM test presents the list of 10 words in a different order for each of its three immediate free recall tasks, and all respondents are presented this same set of orders. This shuffled presentation obscures the per-task serial position effects of primacy and recency when examined across the full test, and it limits the ability to measure the impact of serial position effects on memory. Additionally, there are three different wordlists used as alternate forms. While at the level of total scores and sub-scores, there is little effect on the number of words recalled across the lists, it is necessary to account for their effect on recall behavior at the item level, such as for measuring underlying (latent) cognitive processes. This study compares quantified cognitive process (qCPs) differences across three different wordlists used in the Alzheimer's Disease Neuroimaging Initiative (ADNI) and presents a solution to adjust for such differences. **Methods:** We applied a hierarchical Bayesian cognitive processing (HBCP) model to item responses for the ADAS-Cog WLM tests from 1,538 assessments (across 888 cognitively normal participants) to generate penalty values for each word presentation position for each of three wordlists. These position penalties are the proportion of an individual's qCPs that can be applied to encoding or retrieving a word presented in a given position. There are seven base qCPs, each representing the probability of information processing through different encoding (One-shot, Transient, Consolidated, and Testing Effect Encoding) or retrieval (Transient, Durable, and Delayed Retrieval) pathways, to and from three distinct storage states (Pre-task, Transient, and Durable storage states). The generated position penalties were used in a subsequent HBCP model that multiplicatively applied them, along with prior data, to generate latent qCPs with each ADAS-Cog assessment of a larger set of ADNI participants (n = 2,366; assessments = 10,868) for comparison. **Results:** Position by position, the three wordlists were found to differ. In one example, the word presented second on the first task for List 1 ("Arm") very weakly penalizes One-shot Encoding (99% of a participant's ability can be used), while the List 2 word in the same position ("Potato") significantly penalizes it (43%). After separating out the impact of wordlist features, individuals' qCPs are comparable across alternate forms. **Conclusion:** This study has identified differences in how individuals process information with respect to the effect of the ADAS-Cog WLM test's alternate forms. Additionally, adjusting for these differences enables characterization of latent ability for encoding and retrieval, independent of the presented list words, and enables comparison in latent ability across these alternate forms.

LP093- COMPARABILITY AND USABILITY OF CAMBRIDGE NEUROPSYCHOLOGICAL TEST AUTOMATED BATTERY (CANTAB®) TESTS DELIVERED VIA A SMARTPHONE. E. Thorp[1], A. Kaula[1], N. Taptiklis[1], E. Wragg[1], F. Cormack[1,2] *(1. Cambridge Cognition Ltd. - Cambridge (United Kingdom), 2. Department of Psychiatry, University of Cambridge - Cambridge (United Kingdom))*

Background: Delivering cognitive tests on smartphones supports increased accessibility across diverse health settings and can improving access to screening tools. CANTAB ® Spatial Working Memory (SWM) is a short (4-6 minute) measure of working memory and executive functioning, and CANTAB® Match to Sample Visual Search (MTS) is a short (7 minute) task of attention. All CANTAB ® tasks are currently validated for delivery on tablet, laptop or desktop devices. We have recently adapted the Paired Associates Learning (PAL) task, assessing learning and memory, for use on smartphones, work that has now been extended to include SWM and MTS tasks. It is important to understand and quantify differences between versions of the tasks carried out on different devices. In addition, for tasks delivered direct to the home of the patient, where quality of support may vary, usability is especially important. This study was therefore designed to compare task performance on smartphone and desktop devices, and usability of SWM and MTS on smartphones. **Methods:** In separate SWM and MTS studies with the same design, healthy volunteers, (SWM: N=108, age M=58, SD=6.48, 44% male, MTS: N=99, age M=57, SD=5.79, 43% male) were recruited through the Prolific online platform to complete both smartphone and desktop versions of the studied task on two consecutive days followed by a usability questionnaire. A cross-over design was used with 50:50 participants smartphone-first: desktop-first to counterbalance for exposure to the task. Participants used their own devices for assessment. Performance across Device and Visit was assessed in key outcome measures for each task using a two-way ANOVA, and reliability and bias were explored using Pearson correlation and Bland-Altman plots. **Results:** SWM showed no effect of device on strategy or error scores, although a Visit (i.e. practice) effect was found. MTS showed no significant effects of Device or of Visit. Performance in smartphone and desktop versions showed good inter-device correlation (SWM: $r = .58$, $p < .001$, MTS: $r = .55$, $p < .0001$). Inspection of Bland-Altman plots showed good agreement between devices of both tasks. Task usability was rated highly by participants, with most participants strongly agreeing that task instructions were clear and easy to follow (89% SWM, 70% MTS) and they could see symbols easily on their smartphones (80% SWM, 70% MTS). When asked which version of the task they would prefer to complete if they had to do the task again 48% of SWM and 52% of MTS participants indicated either no preference or preference for smartphone. **Conclusion:** This preliminary study comparing smartphone with other remote versions of SWM and MTS showed overall good comparability between the smartphone and desktop used at home, supporting

remote use of CANTAB ® tasks on widely available devices as a viable method of cognitive testing. This comparability suggests norms and other measures associated with existing variants of the tasks should be relevant to the smartphone format. Useability answers suggested that the smartphone versions did not provide worse experiences for healthy volunteers. Future work will investigate repeated administration of batteries combining multiple smartphone CANTAB ® tasks. **Keywords:** Working Memory, Attention, Cognitive impairment, smartphone assessments, usability. **Disclosures:** ET, AK, NT, EW and FC are employees of Cambridge Cognition Ltd. One or more authors report potential conflicts which are described in the program.

LP094- EVALUATION OF A MULTICOMPONENT PFAS ASSAY IN BLOOD SAMPLES TO ASSESS THE IMPACT OF COGNITIVE FUNCTION. H. Eun[1], H. Hata[1], M. Ohnishi-Kameyama[1], J. Yoon[2] *(1. National Agriculture and Food Research Organization (NARO) - Tsukuba (Japan), 2. University of Tsukuba - Tsukuba (Japan))*

Background: Currently, there is great concern worldwide about the toxicity and persistence of perfluoroalkyl substances (PFAS) on human health. It is known that exposure to certain levels of PFAS can reduce fertility, increase hypertension, developmental disorders, increased risk of some cancers such as prostate, kidney and testicular cancer, interference with the body's natural hormones, increased cholesterol levels and/or obesity. Furthermore, accumulation of PFAS in the human central nervous system has been suggested to be associated with Alzheimer's disease [1]. Although water and food are the major routes of human exposure to PFAS, they are also known to be associated with a variety of causes, including age, gender, lifestyle, geographic region of residence, and occupation. Exposure and concentrations of PFAS due to confiscation of fish and shellfish in food groups are of particular concern in countries where confiscation of fish and shellfish is relatively common. However, information on the effects of various PFAS other than PFOS and PFOA on human blood is limited, especially in Japan. Therefore, a method to investigate the effects of PFAS accumulation on humans, including Alzheimer's disease, is urgently needed in Japan, which has a super-aging society. However, accurate and precise measurement of a wide variety of PFAS in blood matrix is an analytical challenge. The purpose of this study was to evaluate 30 PFAS in whole blood and serum in order to develop a simpler, lower cost, and higher performance analytical method. **Methods:** The rabbit whole blood and serum for the test were purchased and stored frozen (≤−20 ◦C). To evaluate a simpler, lower cost, higher performance analytical method for 30 PFAS in whole blood and serum, conventional 6cc150mg WAX, 1cc30mg WAX, 1cc30mg HLB, and protein precipitation medium type 96-well plate type solid phase columns were used. For 6cc150 mg WAX, the sample volume was 200 μL, while the other solid phase columns were tested with 100 μL of sample. Conditioning and fractionation processes for 6cc150mg WAX were the same as for NARO DRAFT METHOD 202201 [2]). The other columns were run by modifying some of the general processing protocols for each solid-phase column. 30 PFAS mixed ISO 21675 standards were used to evaluate the analytical process for each solid phase column. 100 μL of 10 ng/mL surrogate (labeled 24 PFAS) was added to each sample to evaluate the overall process recovery. The calibration curve was a 7-point calibration curve from 0.02 ng/mL to 100 ng/mL and the internal standard method was adopted. **Results:** The recovery of native compounds in the purification process on all columns of whole blood and serum samples ranged from 67% to 128% for PFHxS, 86% to 110% for PFOS, 99% to 115% for PFOA, and 103% to 111% for PFNA. Recoveries of surrogates for those compounds ranged from 77% to 192% for PFHxS, 80% to 108% for PFOS, 79% to 128% for PFOA, and 79% to 121% for PFNA. Although the solid-phase columns tested were of different types, volumes, and purification methods, the native and surrogate recoveries of the four major PFAS (PFHxS, PFOS, PFOA, and PFNA) out of 30 PFAS added to whole blood and serum samples were found to be acceptable. However, it was suggested that the proposed pretreatment modifications are necessary for some compounds such as PFTeDA, PFHxDA, PFOcDA and MeFOSAA, HFPO-DA and 8:2diPAP, which are long chain PFAS in some columns. **Conclusion:** The recoveries of native and surrogates of 30 PFASs on commercially available solid-phase columns for PFAS analysis in blood were investigated using the rabbit whole blood and serum. Although high recoveries were obtained for the four major PFAS (PFHxS, PFOS, PFOA, and PFNA) without any special treatment, it was suggested that some pretreatment is necessary for long-chain PFAS and some compounds. **Acknowledgments:** This work was supported by NARO Innovation Creation Program (N.I.P.) 2024 and JST COI-NEXT Support Project (JPMJPF2017). **Keywords:** 30 PFAS, whole blood, serum. References: 1. Delcourt et. al., First Observations of a Potential Association Between Accumulation of Per- and Polyfuoroalkyl Substances in the Central Nervous System and Markers of Alzheimer's Disease, The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences, 2024, 79(3), 1–6. 2. NARO DRAFT METHOD 202201, Determination of perfluoroalkyl and polyfluoroalkyl substances (PFAS) in soil, https://forms.office.com/Pages/ResponsePage.aspx?id=MBzgSGhzkUq9DL7StxstrydBQT-yXn9Plcify-E6he1UODJaRFRTRERLQ0NNS0xVUjJFN0hESDU4NS4u&lang=en.

LP095- PSYCHOMETRIC VALIDITY OF NEUROCOGNITIVE BIOMARKERS FROM VIEWMIND: INSIGHTS FROM CLASSICAL COGNITIVE SCREENINGS. G. Fernandez[1], A. Gonzalez Hernandez[2], J. Bonilla Santos[2], R. Gonzalez Montealegre[2], Y. Cala[2], V. Barco[1], D. Verge[3], M. Parra[4] *(1. ViewMind - Bahia Blanca (Argentina), 2. SurColombiana - Neiva (Colombia), 3. ViewMind - Copenhage (Denmark), 4. Glasgow University - Glasgow (United Kingdom))*

Background: According to the data provided by the WHO, people over 60 years of age have a prevalence rate of dementia between 5% and 8%, which can rise up to 45% in those over 80 years of age. Mild Cognitive Impairment (MCI) is a heterogeneous entity that implies a high risk of progression to dementia: without treatment, more than 50% progress to Dementia (ADI, 2024). The detection of and intervention in MCI patients is an objective of current prevention initiatives. We need affordable and culturally unbiased assessments that can help identify MCI. We present a clinical validation of ViewMind Atlas, in a large population-based study in southern regions of Colombia. **Methods:** To validate ViewMind (VM) two visual tasks were used: the Visual Short-Term Memory Binding Task (VSTMBT) [1] and the Go/No-Go task (GNGT) [2]. We derived cognitive domains and composite scores from oculomotor behaviours recorded during these tasks. The VSTMBT assesses low-level integrative memory abilities, and it has been proposed as a novel memory marker for AD [3]. The GNGT assesses selective attention, processing speed and executive functions. We analysed a sample of 201 community dwellers, of whom 91 met the criteria for Mild

Cognitive Impairment (MCI) [4]. Healthy control (HC) and MCI participants showed significant differences in both age (HC: 59.7±6.3, MCI: 63.1±6.9, p=0.003) and years of education (HC: 11.8±6.9, MCI: 7.6±5.9, p=0.0008). Correlation analyses and ROC curves were conducted to investigate VM Atlas Clinical Validity relative to Addenbrooke's Cognitive Examination (ACE-R) [5]. **Results:** Correlations between VM Atlas and ACE-R when considering comparable cognitive domains were significant: a) Memory (r=0.24, p =0.0002), b) Attention (r=0.26, p=0.00002) and c) Visuo-Spatial (r=0.28, p=0.000002). Composite Score VM vs.ACE-R Total (r=0.39, p=0.000001). The cognitive domains also showed similar results when classifying HC and MCI using VM and ACE-R: a) Memory (sensitivity=58 vs. 69, specificity=68 vs. 67, balanced accuracy=63 vs. 67, respectively), b) Attention (sensitivity=59 vs.69, specificity=62 vs. 67, balanced accuracy=60 vs. 67, respectively) and c) VisuoSpatial (sensitivity=57 vs. 72, specificity=78 vs. 69, balanced accuracy=67 vs. 67, respectively). VM Atlas Composite Score (sensitivity=77, specificity=64, balanced accuracy=70) vs. ACE-R Total (sensitivity=65, specificity=88, balanced accuracy=76). **Conclusion:** We compared VM Atlas and ACE-R convergent clinical validity and classification accuracy in a community-dwelling sample of older adults, some of whom met MCI criteria (Petersen et al., 2014). VM Atlas appears to be more accurate when seeking to maximise sensitivity and number of true positives, especially in situations where the aim is to detect the greatest possible number of positive cases and avoid false negatives. ACE-R offers greater specificity, making it a good option for situations where it is important to reduce false positives. Of note is that VM Atlas was able to classify MCI similarly to ACE-R. However, it is worth noting that VM has proved unbiased in terms of age and years of education. These results support our proposal of VM Atlas as a culture-free neurocognitive biomarker for MCI detection in underrepresented populations. **Keywords:** Cognitive Screening, ViewMind, Psychometric Properties, Cognitive Domains, MCI, Early detection. **Disclosures:** MAP is a consultant for ViewMind serving as its Neuroscientific Officer. DV and GF are ViewMind Chief Medical Officer and ViewMind Chief Scientific Officer, respectively. **References:** 1. Parra, M. A., Della Sala, S., Abrahams, S., Logie, R. H., Mendez, L. G., & Lopera, F. (2011). Specific deficit of colour-colour short-term memory binding in sporadic and familial Alzheimer's disease. Neuropsychologia, 49(7), 1943-1952. https://doi.org/S0028-3932(11)00154-0 [pii];10.1016/j.neuropsychologia.2011.03.022 [doi] (Not in File); 2. Pereira, Tiago & Castro-Caldas, Alexandre & Abreu, Ana Maria. (2014). Age-related Gender Differences in Motor and Inhibitory Learning and Consolidation. Journal of Advanced Neuroscience Research. 1. 10-21. 10.15379/2409-3564.2014.01.01.2. 3. Costa, A., Bak, T., Caffarra, P., Caltagirone, C., Ceccaldi, M., Collette, F., Crutch, S., Della Sala, S., Demonet, J. F., Dubois, B., Duzel, E., Nestor, P., Papageorgiou, S. G., Salmon, E., Sikkes, S., Tiraboschi, P., van der Flier, W. M., Visser, P. J., & Cappa, S. F. (2017). The need for harmonisation and innovation of neuropsychological assessment in neurodegenerative dementias in Europe: consensus document of the Joint Program for Neurodegenerative Diseases Working Group. Alzheimers. Res. Ther, 9(1), 27. https://doi.org/10.1186/s13195-017-0254-x [doi];10.1186/s13195-017-0254-x [pii] (Not in File); 4. Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. J Intern Med. 2014 Mar;275(3):214-28. doi: 10.1111/joim.12190. PMID: 24605806; PMCID: PMC3967548; 5. Mioshi, E., Dawson, K., Mitchell, J., Arnold, R., & Hodges, J. R. (2006). The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. Int. J. Geriatr. Psychiatry, 21(11), 1078-1085. http://www.ncbi.nlm.nih.gov/pubmed/16977673 (Not in File).

LP096- REMOTE AND UNSUPERVISED DIGITAL MONITORING OF MEMORY DECLINE IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT. S.E. Polk[1], K. Basche[2], L. Kleineidam[3], W. Glanz[1], R. Pernecky[4], A. Spottke[3], A. Schneider[3], J. Wiltfang[5], S. Teipel[6], M. Wagner[3], S.C. Johnson[2], L.R. Clark[2], F. Jessen[3], E. Düzel, D. Berron[1] *(1. German Center for Neurodegenerative Diseases (DZNE) - Magdeburg (Germany), 2. University of Wisconsin School of Medicine and Public Health - Madison (United States), 3. German Center for Neurodegenerative Diseases (DZNE) - Bonn (Germany), 4. German Center for Neurodegenerative Diseases (DZNE) - München (Germany), 5. German Center for Neurodegenerative Diseases (DZNE) - Göttingen (Germany), 6. German Center for Neurodegenerative Diseases (DZNE) - Rostock (Germany))*

Background: Measuring cognitive change in clinical trials is challenging since there are only subtle changes in cognition during the earliest stages of Alzheimer's disease that are difficult to capture using traditional pen-and-paper neuropsychological assessments. Remote and unsupervised digital cognitive assessment using mobile devices holds promise for detecting such subtle cognitive changes, as it offers novel test formats as well as the ability to repeat cognitive assessments at high frequency over shorter periods of time. **Methods:** Here, we investigated episodic memory trajectories using remote and unsupervised digital assessments in 202 participants (52–85 years old) with and without amyloid positivity from the German DELCODE and US-based WRAP cohorts. Participants repeatedly completed three different visual memory tasks in the neotivTrials app over a period of at least 30 weeks: the Mnemonic Discrimination Task for Objects and Scenes (MDT-OS), a task that engages pattern separation and recruits the perirhinal, parahippocampal, and entorhinal cortices, the Object-in-Room Recall (ORR) task, a delayed recall task primarily engaging pattern completion and targeting medial temporal lobe structures and the retrosplenial cortex, and the Complex Scene Recognition (CSR) task, a recognition task that relies on a broader network of temporal and parietal brain regions. In addition, all participants completed in-clinic assessments comprising tests included in the Preclinical Alzheimer's Cognitive Composite (PACC5) at least every two years. We used linear mixed modeling to examine main effects of cognitive status, n = 152 cognitively unimpaired (CU), n = 50 with mild cognitive impairment (MCI), and interaction effects of cognitive status by time in weeks. **Results:** At baseline, MCI patients performed worse than the CU group on the ORR, MDT-OS, and CSR. Over time, MCI patients showed greater decline across repeated assessments over 30 weeks than the CU group on the CSR and MDT-OS, but not on the ORR. The pattern of memory impairment and decline across the three memory tasks was in line with the progression of Alzheimer's disease pathology across the respective functional memory networks in the human brain. Model-extracted individual slopes on the CSR positively correlated with change in the PACC5 over eight years. **Conclusion:** These findings suggest that high-frequency remote and unsupervised digital cognitive assessments are able to capture short-term changes in episodic memory in MCI patients. Furthermore, our results suggest that digital cognitive assessments that are tailored towards specific episodic memory brain networks show disease-stage specific memory decline in Alzheimer's disease. Future analyses will

investigate whether this approach yields increased sensitivity to cognitive change in preclinical AD. **Keywords:** Monitoring, digital biomarkers, Alzheimer's, episodic memory, longitudinal trajectories, cognitive outcome measure, smartphone-based cognitive assessments. **Disclosures:** Emrah Düzel and David Berron are co-founders and shareholders of neotiv GmbH.

BEHAVIORAL DISORDERS AND CLINICAL TRIALS

P202- EHR-BASED IDENTIFICATION AND PRE-QUALIFICATION OF PATIENTS WITH BEHAVIORAL SYMPTOMS OF ALZHEIMER'S DISEASE FOR NEUROPSYCHIATRIC CLINICAL TRIALS.

S. Mahesh[1], E. Beck[1], D. Gautieri[1] *(1. SiteRx - New York (United States))*

Background: Behavioral and neuropsychiatric symptoms, including Agitation, Psychosis, and Apathy, are common in advanced Alzheimer's disease (AD) and significantly complicate disease management. Estimates suggest that up to 90% of AD patients experience one or more of these symptoms, which accelerates cognitive decline and increases caregiver burden. While most research in AD has focused on disease-modifying treatments (DMTs) for early-stage patients, there has been less emphasis on managing progressed disease for patients with advanced cognitive impairment. Accurate identification of these patients for neuropsychiatric research is challenging due to the lack of visibility into symptom timing and severity, often documented in physician and caregiver notes. Moreover, health record annotation and coding in the clinical care community have not been standardized, and neuropsychiatric evaluations vary across providers. SiteRx's data-driven platform integrates structured and unstructured data from provider Electronic Health Records (EHRs) and HCP chart reviews to pre-qualify patients for neuropsychiatric AD trials. **Objective:** This analysis assesses the efficacy of the SiteRx platform in improving patient recruitment for neuropsychiatric AD trials through the structuring and analysis of comprehensive patient EHR data and ancillary notes. This research aims to inform targeted recruitment strategies for neuropsychiatric research in AD. **Methods:** SiteRx employed a two-pronged approach by structuring and analyzing data captured in treating providers' EHRs (e.g. ICD coding and unstructured clinical notes) and coordinating with caregivers to capture detailed documentation of neuropsychiatric symptoms. SiteRx's clinical intelligence platform is embedded into EHR workflows across its neurology-focused Real-World Database (RWD) to support real-time identification and pre-qualification of AD patients with Behavioral and neuropsychiatric symptoms. Recruitment outcomes were analyzed across 4 trials to evaluate the platform's ability to match patients with trial eligibility criteria, including presentation and occurrence of behavioral symptoms and cognitive status. Performance metrics included time from referral to informed consent screening and screen fail rates. **Results:** The SiteRx platform improved recruitment efficacy for clinical trials targeting patients with advanced behavioral symptoms. Across 4 trials, SiteRx's structuring and analysis of EHR data and physician notes reduced screen-fail rates by 10%- 22% (e.g., 72.8% screen-fail rate in AD Psychosis, 52.7% in AD Agitation). A 4x increase in the screening of SiteRx referred patients was observed compared to non-SiteRx patients, due to medical history based pre-qualification and geographical mapping of patients to proximal research sites. SiteRx increased the velocity from referral to informed consent form (ICF) screening by 1 - 2 weeks (on average 21 days for AD Psychosis, 28 days for AD Agitation), allowing for the timely activation of eligible candidates ahead of disease or symptomatology progression. **Conclusion:** The SiteRx platform improved recruitment outcomes when used to identify and recruit patients with behavioral and neuropsychiatric symptoms in AD. Its ability to integrate and structure EHR data provides a more comprehensive assessment of patients' symptom severity and cognitive status. The reduction in screen failures and increased velocity underscore SiteRx's transformative recruitment approach for specialized AD research. We call for broader adoption of standardized provider notes across clinical care to facilitate timely referral to research settings.

P203- BASELINE DEMOGRAPHICS OF THE ECT-AD TRIAL: ELECTROCONVULSIVE THERAPY FOR THE MANAGEMENT OF TREATMENT-REFRACTORY AGITATION AND AGGRESSION IN ADVANCED DEMENTIA.

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Background: Advanced dementia with severe and treatment refractory agitation and aggression profoundly deteriorates the quality of life and results in challenges in clinical management, increasing the burden on patients, caregivers, and healthcare systems alike. The ECT-AD is an ongoing multi-site NIA-funded trial that aims to investigate the effectiveness of electroconvulsive therapy (ECT) for this population. In this abstract we describe demographic and clinical characteristics of our patient population at baseline, alongside the initial ECT treatment parameters. **Methods:** We collected baseline demographic and clinical data and summarized ECT treatment parameters at baseline. Assessments included cognitive function (Mini-Mental State Examination [MMSE], Severe Impairment Battery [SIB-8]), functional impairment (Barthel Index [BI]), and severity of agitation (Cohen-Mansfield Agitation Inventory [CMAI], Neuropsychiatric Inventory [NPI], Pittsburgh Agitation Scale [PAS]). ECT parameters recorded were the number of stimulations at first ECT, dose (% energy) and charge (mC) of electrical stimulus, and duration of motor and central seizures (seconds). Descriptive statistics were used to summarize demographics, using frequencies and percentages for categorical variables and means and standard deviations for continuous variables. **Results:** There are 22 participants enrolled to date, with a mean age of 74.1 years, and 61.1% male. Race is predominantly White (94.4%) with 5.6% Asian and 11.1% identifying as Hispanic or Latino. Dementia subtypes are predominantly Alzheimer's disease (AD, 77.8%), followed by vascular dementia (VaD, 16.7%), and frontotemporal dementia (FTD, 5.6%). At baseline, participants exhibited significant cognitive (MMSE 4.0 ± 4.6, SIB-8 2.9 ± 3.8) and functional (BI 52.2 ± 21.8) impairments, and severe agitation and aggression (CMAI 75.8 ± 23.8, NPI agitation 15.1 ± 7.1, NPI aggression 9.2 ± 5.4, PAS 7.8 ± 4.3). Twelve of the 22 patients received ECT and had ECT data available. For the first ECT session, the mean number of stimuli delivered is 1.3 ± 0.8 (range 1-3), with mean 7.4 ± 5.0 % energy and 35.1 ±

24.2 mC. Mean duration of seizures were 34.3 ± 14.6 for motor and 43.9 ± 23.1 for EEG indicating adequate seizure duration. **Conclusion:** Baseline data from the ECT-AD trial underscores the profound cognitive and functional impairments, along with severe agitation and aggression, in our study population with advanced dementia. Adequate seizure durations observed during the first ECT session are crucial for therapeutic efficacy, indicating a promising role for ECT in managing severe, treatment-refractory agitation in this demographic. The ECT-AD trial offers a potential to enhance the management of severe and treatment-refractory agitation in advanced dementia. **Keywords:** late-stage dementia, behavioral disturbances, brain stimulation. **Clinical Trial Registry:** NCT03926520; https://clinicaltrials.gov. **Disclosures:** This work is supported by the National Institute on Aging (AG061100) and conducted with an Investigational Device Exemption from the U.S. Food and Drug Administration (G190121) held by Brent P. Forester, MD as Sponsor Investigator. The authors declare no competing interests.

P204- CAREGIVING-RELATED DEPRESSION INCREASES NEUROINFLAMMATION IN SPOUSAL CAREGIVERS OF INDIVIDUALS WITH COGNITIVE IMPAIRMENT: A LONGITUDINAL STUDY. S.Y. Jeon[1], H.W. Yang[1], J.L. Kim[1] *(1. Chungnam National University Hospital - Daejeon (Korea, Republic of))*

Background: Caregiving burden of spousal caregivers (SCGs) for individuals with cognitive impairment poses public health challenges with adverse psychosocial and physiological effects, potentially leading to increased dementia risks and all-cause mortality. However, no study has yet investigated the neurobiological impact of caregiving, particularly through the investigation of neuroinflammation and neurodegeneration. **Method:** A longitudinal cohort from Chungnam National University Hospital examined the relationship between the impact of caregiving burden and neuroinflammation and neurodegeneration plasma biomarkers GFAP and NfL in thirty-eight older adults couples over 16 month, using regression analyses adjusted for various factors including age, sex, APOE4 status, follow-up interval and vascular risk factors. **Results:** Changes in depressive symptom correlated with higher increased in GFAP levels among SCGs ($\beta = 0.787$, $p = 0.003$) over 16 month, suggesting SCG's experience greater depressive symptoms during caregiving, neuroinflammation correspondingly increases. However, no significant correlations were observed between the degree of cognitive decline in care-recipients and plasma biomarkers, nor between SCGs' depression and NfL levels. **Conclusion:** The study highlights the psychological stress experienced by SCGs caring for partners with cognitive impairment actively contributes to neuroinflammation, a well-known risk factor for various diseases. It emphasized the need to attentively address the psychological stress felt by these elderly caregivers.

P205- PREDICTING SUICIDE RISK IN INDIVIDUALS WITH COGNITIVE DECLINE: INTEGRATING SOCIODEMOGRAPHIC AND CLINICAL PREDICTORS. E. Vidovic[1], J.R. Finžgar[2], A. Kokalj Palandacic[1], P. Rus Prelog[1,3] *(1. University Psychiatric Clinic Ljubljana - Ljubljana (Slovenia), 2. Technical University Munich, School of CIT, Department of Computer Science - Garching (Germany), 3. Faculty of Medicine, University of Ljubljana - Ljubljana (Slovenia))*

Background: Suicidal behavior is a significant global health concern, especially among the elderly, where attempts often result in fatal outcomes [1, 2]. Active suicidal ideation (SI) notably increases the risk of suicide attempts [3], necessitating the identification of at-risk individuals for timely preventive measures. Cognitive decline is a critical risk factor for SI [4, 5]. Current clinical models are unable to capture the complex data patterns that can be used for suicidal risk assessment. Although some studies have explored complex models for predicting suicide risk [6], few have focused on the elderly with cognitive decline [7, 8]. This study aims to address this gap by identifying risk factors and developing predictive models for individuals with cognitive decline using advanced statistical methods. **Methods:** The study included 1216 patients (718 females, 498 males) diagnosed with Alzheimer's disease and mild cognitive impairment (MCI) admitted to the University Psychiatric Clinic Ljubljana from January 2019 to April 2024. Suicide risk was assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS), categorizing patients into high risk (HiR; active SI; C-SSRS 3-5; total 136; 86 females, 50 males) and low risk (LoR; absent or passive SI; C-SSRS 0-2; total 1080; 632 females, 448 males). Demographic and clinical factors, cognitive, and functional status were evaluated. Univariate logistic regression identified clinical correlates of active SI, followed by multivariate logistic regression (LR) and extreme gradient boosting (XGB) for predictive model construction, using backward feature selection. **Results:** Univariate analysis showed depressive symptoms (coef. 2.33, $p < 0.001$), psychiatric history (coef. 0.76, $p < 0.001$), and mini-mental state exam scores (coef. 0.46, $p < 0.001$) as the strongest correlates of active SI. Other significant positive correlates included MCI diagnosis, number of somatic diseases, clock drawing test results, living alone, and functional status (grip strength and the de Morton Mobility Index - DEMMI) (coef. 0.2-0.5, $p < 0.05$). Acetylcholinesterase inhibitors and duration of cognitive decline were negatively associated with HiR (coef. -0.67, $p = 0.001$ and coef. -0.49, $p = 0.002$). Key features in predictive models included depressive symptoms (coef. 2.21), ability to walk without help (coef. -2.24), needing a walker or rolator (coef. -1.77), DEMMI (coef. 0.49), newly diagnosed cognitive decline (coef. -0.77), number of somatic diseases (coef. 0.29), acetylcholinesterase inhibitor use (coef. -0.66), and age (coef. 0.24), all with $p < 0.05$. The achieved area under receiver operating curve scores were 0.78 and 0.79 for LR and XGB, respectively. **Conclusion:** This study identifies key predictors of suicide risk in cognitive decline: early cognitive decline, shorter diagnosis duration, psychiatric history, multiple comorbidities, and low social support increase the risk, while acetylcholinesterase inhibitors reduce it. Functional status shows a nuanced impact: grip strength and DEMMI indicate higher risk in early stages, whereas walking independently protects against active SI. The strong performance of predictive models highlights advanced analytics' potential in improving suicide risk assessment. Implementing these models in clinical settings could enhance early detection and prevention efforts, reducing suicide rates in this vulnerable population. **Keywords:** suicide ideation,

prevention, mild cognitive decline, Alzheimer's disease. **Disclosures:** The authors declare no conflicts of interest. **References:** 1. Naghavi M. Global, regional, and national burden of suicide mortality 1990 to 2016: systematic analysis for the Global Burden of Disease Study 2016 BMJ. 2019; 364 :l94 doi:10.1136/bmj.l94. 2. De Leo D. Late-life suicide in an aging world. Nat Aging. 2022 Jan;2(1):7-12. doi: 10.1038/s43587-021-00160-1. 3. Klonsky ED, et al. Suicide, Suicide Attempts, and Suicidal Ideation. Annu Rev Clin Psychol. 2016;12:307-30. doi: 10.1146/annurev-clinpsy-021815-093204. 4. Stott J., et al. Suicide ideation, attempts and deaths in people living with dementia (PLWD): A systematic review and meta-analysis of prevalence and risk factors. Alzheimer's Dement., 19: e074734. doi: 10.1002/alz.074734. 5. Günak MM, et al. Risk of Suicide Attempt in Patients With Recent Diagnosis of Mild Cognitive Impairment or Dementia. JAMA Psychiatry. 2021 Jun 1;78(6):659-666. doi: 10.1001/jamapsychiatry.2021.0150. 6. Pigoni, A., et al. Machine learning and the prediction of suicide in psychiatric populations: a systematic review. Transl Psychiatry 14, 140 (2024). doi:10.1038/s41398-024-02852-9. 7. Cho S-E, et al. Development of a Suicide Prediction Model for the Elderly Using Health Screening Data. International Journal of Environmental Research and Public Health. 2021; 18(19):10150. doi:10.3390/ijerph181910150. 8. Zheng S, et al. Can cognition help predict suicide risk in patients with major depressive disorder? A machine learning study. BMC Psychiatry 22, 580 (2022). doi:10.1186/s12888-022-04223-4.

HEALTH ECONOMICS AND CLINICAL TRIALS

P206- RISK PREDICTION MODELS OF MILD COGNITIVE IMPAIRMENT USING ELECTRONIC HEALTH RECORD DATA. G. Li[1], V. Devanarayan[1], R. Halpern[2], S. Borentain[1], S. Desanti[1], J. Vandercappellen[1], A. Khachaturian[3], R. Crislip[2], J. Meyerhoff[2], J. Bell[1], M. Soeren[4], H. Hampel[1] *(1. Eisai - Nutley (United States), 2. Optum - Prairie (United States), 3. PAD2020 - Washington (United States), 4. University of Southern California - Los Angles (United States))*

Background: Timely identification of mild cognitive impairment (MCI) is crucial for early intervention and potential treatment with novel monoclonal antibodies. Primary care providers (PCPs) play a critical role in detecting early signs of MCI, yet detection rates by PCPs in clinical practice are reported to be only 6-15%. To improve these detection rates, we augmented previous claims data analyses with electronic health record (EHR) data to identify additional risk factors and develop new prediction models for MCI risk. **Methods:** This retrospective analysis uses the Optum EHR database that contains >100 million records from across the U.S. Individuals ≥40 years old were identified from January 2016 to March 2021. The MCI cohort had ≥1 diagnosis record of diagnosis code for MCI; the first record set the index date. For the non-MCI cohort, the index date was set on randomly selected non-MCI condition diagnosis records. All individuals were observed for 2 years before the index date. The MCI cohort had no diagnosis or natural language processing (NLP)-derived abstracted note records for MCI, Alzheimer's disease or related dementias (ADRD) before the index date; non-MCI cohort had no records of MCI/ADRD in the entire study period. Potential predictors of MCI were identified from literature review: demographic and health status characteristics; laboratory test results, and a spectrum of medical conditions measured with diagnostic records and with NLP-derived records. Prediction models were constructed with Bayesian logistic lasso regression with spike-and-slab mixture double-exponential prior, a machine-learning algorithm, to discriminate between MCI and non-MCI individuals. Model performance was evaluated via 10-fold cross-validation using a 70% random sample of subjects and then validated in the remaining 30%. **Results:** The analysis sample included 5,838 MCI and 100,565 non-MCI individuals. Mean (standard deviation) ages in the MCI and non-MCI cohorts were 71.1 (12.0) and 59.1 (11.9), respectively. The female representation in the MCI and non-MCI cohorts were 61% and 59%, respectively. Models with demographics, health status, laboratory results, and medical conditions were tested. The model with medical conditions from diagnosis records, plus two NLP-derived selected for parsimony and simpler execution. Top ten predictors in the model include age, stroke, depression, gait, bipolar disorder, and concussion. This model performs best among individuals aged 50-64 years (AUC=0.78), followed by those aged 65-79 years (AUC=0.72) and ≥80 years (AUC=0.65). **Conclusion:** The MCI risk model established in this study worked best for individuals aged 50-64 years and detected MCI risk similarly to screening measures used in clinical practice (e.g. MoCA : AUC 0.77). We aim to use the final prediction model to develop a triage tool for PCPs to identify individuals at elevated risk for MCI for further workup.

P207- DEVELOPMENT OF A SIMULATION MODEL OF ALZHEIMER'S DISEASE TO EVALUATE DISEASE MODIFYING TREATMENTS IN A MEMORY CLINIC POPULATION. P.J. Van Der Veere[1,2,3], H.M. Broulikova[4,5], J. Hoogland[6], E.G.B. Vijverberg[1,3], W.M. Flier[1,2,3], J. Berkhof[2] *(1. Alzheimer Center and Department of Neurology, Amsterdam Neuroscience, VU University Medical Center - Amsterdam (Netherlands), 2. Department of Epidemiology and Biostatistics, Amsterdam Neuroscience, VU University Medical Center - Amsterdam (Netherlands), 3. Amsterdam Neuroscience, Neurodegeneration - Amsterdam (Netherlands), 4. Department of Health Science, Faculty of Science, Vrije Universiteit Amsterdam - Amsterdam (Netherlands), 5. Department of Public Mental Health, National Institute of Mental Health - Klecany (Czech Republic), 6. Department of Epidemiology and Biostatistics, Amsterdam Neuroscience, VU University Medical Center - Amsterdam (Netherlands) - Amsterdam (Netherlands))*

Introduction: Recent trials showed anti-amyloid medications slow cognitive decline in mild cognitive impairment (MCI) and mild dementia Alzheimer's Disease (AD) patients during 18-month of follow-up. Many questions remain regarding their application in real-world settings. Simulations models can be used to evaluate and compare potential benefits, harms and costs. The current aim is to develop a simulation model for AD memory clinic patients and show natural disease trajectories, with the overall aim to assess the cost-effectiveness of AD treatments in memory clinic patients with MCI or mild dementia due to AD. **Methods:** We constructed a microsimulation model of the AD disease trajectory from MCI, via the mild, moderate, and severe dementia stages to institutionalisation and/or death. The parameters for the model were estimated with data from the Amsterdam Dementia Cohort, including 397 amyloid-positive MCI patients with baseline visit from 2000 onwards and 330 amyloid-positive dementia patients with baseline visits between 2014 and 2023. Mini-mental state examination (MMSE) and progression from MCI to dementia (n=244) were assessed longitudinally. Institutionalisation (n=143) and death (n=130) dates were extracted from Statistics Netherlands. Joint models for MMSE decline and progression to dementia in MCI

patients, and institutionalisation and/or dead in dementia patients, were fitted to data collected in the first five years of follow-up. Gamma clock-reset survival models were fitted to data collected beyond five years of follow-up. Time from institutionalisation to death was estimated using a Weibull model. Treatment effects will be modelled as modifications of the cognitive decline trajectories. Mild, moderate and severe dementia stages were defined as an MMSE >20, 10-20, and <10, respectively. To quantify model fit, we calculated a three-fold cross-validated area under the curve (AUC) at five years for the joint models. Subsequently, we provided a proof-of-principle microsimulation of 1000 MCI patients (66±7yr, 47%F, MMSE 26±2) and reported the estimated time in MCI and the dementia stages, percentage institutionalised, and time in institution. **Results:** The five-year cross-validated AUC of the joint model for progression from MCI to dementia was 0.63. The five-year cross-validated AUC of the dementia joint model was 0.73 for institutionalisation and 0.74 for death. The microsimulation of 1000 sampled MCI patients yielded a mean time from MCI to dementia of 3.8 years. In the dementia state, 232 died without being institutionalised and 768 were institutionalised before death. Time outside of an institution in the mild, moderate and severe dementia stages was, 2.3, 1.9, and 0.8 years. Time in an institution was 3.2 years. Overall survival time from MCI to death was 11.3 years. **Conclusion:** We developed a simulation model for disease progression from MCI and mild dementia due to AD and show how this model can be used to evaluate decline trajectories. As a next step, we will simulate long-term outcomes of anti-amyloid medications in memory clinic patients. We are currently including costs and utilities in the model, and will show initial cost-effectiveness analyses. **Keywords:** Alzheimer's Disease, cost-effectiveness, simulation, anti-amyloid therapies. **Disclosures:** Dr W.M. van der Flier reported grants from Nederlandse Organisatie voor Wetenschappelijk Onderzoek, Alzheimer Nederland, Cardiovascular Research Netherlands, Hersenstichting, Health Holland Topsector Life Sciences & Health, Stichting Dioraphte, Gieskes-Strijbis Fonds, Stichting Equilibrio, Edwin Bouw Fonds, Philips, Biogen, Novartis-NL, Life-MI, Avid Radiopharmaceuticals, Roche-BV, Fujifilm, Eisai, Combinostics, and ZonMW. Dr. W.M. van der Flier has done consulting work for to Oxford Health Policy Forum, Roche, Biogen, and Eisai. Dr. E.G.B. Vijverberg is senior researcher at the Brain Research Center and Amsterdam UMC sponsor-initiated studies: DIAN trials, ACI, Alnylam, CogRX, New Amsterdam Pharma research on Obicetrapib, research on JNJ-63733657 (Janssen), research on Trontinemab (Roche), research on varoglutamstat (Vivoryon), research on IBC- AB002 antibody (ImmunoBrain), research on AL002 (Alector), research on BMS-986446 (BMS – prothema), research on AL101 (GSK), research on Gentherapie for PRGN FTD (Aviadobio), research on edaravone (Treeway) Dr. E.G.B. Vijverberg has done consulting work for New Amsterdam Pharma, Treeway, Vivoryon, Biogen, Vigil Neuroscience, ImmunoBrain Checkpoint, Roche, Eli Lilly en Eisai.

P208- ESTIMATION OF LONG-TERM CARE UTILIZATION AND LIFETIME DISTRIBUTION OF MEDICAL COST FOR DEMENTIA IN KOREA. J.H. Lee[1] *(1. NHIS Ilsan Hospital - Goyang-Si (Korea, Republic of))*

Background & Objective: To investigate the current status of long-term care services for patients with dementia and lifetime medical costs for dementia in South Korea. **Methods:** This study utilized the National Health Insurance Service-National Health Information Database (NHIS-NHID) from January 2018 to December 2022. The prevalence and incidence of dementia was estimated by extracting people who were diagnosed and treated with dementia (age ?45 years) from the database. The use of long-term care services for the elderly with newly diagnosed dementia was also investigated. Additionally, the lifetime medical expenses for dementia were estimated using data on single year's medical costs, population data, and a life table from Statistics Korea. **Results:** The prevalence of dementia increased over three years from 2020 to 2022, while the incidence of dementia gradually decreased. Among the patients with newly diagnosed dementia, approximately 30% used the long-term care services, while 4th graders accounted for the highest proportion every year. The older the age and the lower the income quartile, the shorter the time it took to apply for long-term care services after diagnosis of dementia. The total medical expenses per capita increased steadily every year, and the lifetime medical expenses were higher for females than males. Half of the lifetime medical costs of dementia occurred after 67 years of age for males and 83 years for females. **Conclusion:** This study suggests that medical, social, and political measures are needed to effectively manage long-term care service recipients and prepare for rising medical costs for dementia.

P209- USE OF A MOBILE RESEARCH UNIT TO ADDRESS HEALTH DISPARITIES IN ALZHEIMER'S CLINICAL TRIALS. S. Santelis[1], S. Carmona Torres[1], R. Rittichier[1], G. Kautz[1], L. Lenox[1], B. Quaning[2] *(1. K2 Medical Research - Orlando (United States), 2. MetroHealth Inc. - Orlando (United States))*

Background: Alzheimer's disease (AD) remains a significant public health challenge, with a critical need for early intervention and prevention strategies. Recruitment for Alzheimer's clinical trials is often hindered by barriers faced by underserved populations, leading to a lack of diversity and generalizability in research findings [1, 2]. This study examines the efficacy of a Mobile Research Unit (MRU) in reaching and engaging diverse populations for Alzheimer's clinical trials, targeting individuals who are asymptomatic but interested in participating in AD prevention measures. **Methods:** A retrospective study was conducted from October 2023 to April 2024. Following the implementation of engagement strategies, including community partnerships, local media campaigns, and bilingual support staff, the MRU was deployed across various areas in the state of Florida that voluntarily expressed interest in participating. The MRU provided education, memory screenings, and information about Alzheimer's clinical trial participation. We collected demographics from participants, including race, ethnicity, age, and sex. The Area Deprivation Index (ADI) [3] was determined to assess the diversity of populations reached by the MRU. The database was reviewed for errors while ensuring patient confidentiality. Basic statistical analyses were calculated using data expressed in percentages. **Results:** The MRU engaged with 703 individuals across 73 communities in Florida. Among these, 207 were screened for an asymptomatic Alzheimer's clinical trial. The mean age of participants was 70.18 years. The demographic composition of the interested participants was predominantly female (71%), with a significant representation of Hispanic individuals (37.2%). Most participants self-identified as Caucasian (73.4%), followed by African Americans at 18.8%. For all asymptomatic participants, ADI was determined, revealing a state decile mean of 5.5, ranging from 2 to 10. The national percentile

average is 50.7, ranging from 11 to 99. **Conclusion:** These data highlight the expansive diversity of populations reached via an MRU. The MRU enhanced participation from historically underrepresented populations in clinical trials and addressed health disparities, including issues such as limited access to transportation and reliable information on AD. This approach broadened the diversity of AD clinical trial participants while improving community trust and education concerning AD and the importance of clinical research. Future efforts should focus on sustaining these outreach activities. Additionally, integrating mobile health units into more comprehensive clinical trial recruitment strategies will ensure ongoing engagement with the underserved communities at higher risk for AD. **Keywords:** Alzheimer's Disease, Clinical trials, Diversity, Recruitment. **Disclosure:** Authors have no conflict of interest to declare. **References:** 1. Ritchie M, Gillen DL, Grill JD. Recruitment across two decades of NIH-funded Alzheimer's disease clinical trials. Alzheimers Res Ther. 2023;15(1):28. Published 2023 Feb 2. doi:10.1186/s13195-023-01177-x; 2. Lin PJ, Daly AT, Olchanski N, et al. Dementia Diagnosis Disparities by Race and Ethnicity. Med Care. 2021;59(8):679-686. doi:10.1097/MLR.0000000000001577; 3. Kind AJH, Buckingham W. Making Neighborhood Disadvantage Metrics Accessible: The Neighborhood Atlas. New England Journal of Medicine, 2018. 378: 2456-2458. DOI: 10.1056/NEJMp1802313. PMCID: PMC6051533. AND University of Wisconsin School of Medicine Public Health. 2022 Area Deprivation Index v4.0.1. Downloaded from https://www.neighborhoodatlas.medicine.wisc.edu/ May 30, 2024.

LP097- COST-EFFECTIVENESS OF DIAGNOSING AND TREATING PATIENTS WITH EARLY ALZHEIMER´S DISEASE WITH ANTI-AMYLOID TREATMENT. A. Wimo[1], R. Handels[2], K. Blennow[3], J. Bon[4], A. Emersic[4], B.E. Kirsebom[5], F. Gonzalez-Ortiz[3], M. Gregoric Kramberger[4], A. Speh[4], P. Selnes[6], A. Sköldunger[1], S. Timón-Reina[6], P. Jelle Visser[2], E. Vromen[7], B. Winblad[1], T. Fladby[6] *(1. Karolinska Institutet - Solna (Sweden), 2. Maastricht Univertsity - Maastricht (Netherlands), 3. University of Gothenburg - Gothenburg (Sweden), 4. University Medical Centre Ljubljana - Ljubljana (Slovenia), 5. The Arctic University of Norway - Tromsø (Norway), 6. University of Oslo - Oslo (Norway), 7. Vrije Universiteit Amsterdam - Amsterdam (Netherlands))*

Introduction: The introduction of anti-amyloid treatments (AAT) for Alzheimer's Disease (AD) has put the cost-effectiveness of treatment into focus. The aim was to estimate the cost-effectiveness of diagnostic pathways combined with AAT for early AD. Two research questions were analyzed: First, is BBM testing cost-effective as a replacement or add-on to CSF compared to the CSF testing, both in combination with AAT? Second, is CSF testing in combination with AAT cost-effective compared to standard of care. **Methods:** Based on data of blood-based (BBM) and cerebrospinal fluid (CSF) biomarkers in Norwegian memory clinics, the diagnostic accuracy was calculated, using positron emission tomography (PET) as reference standard. In a health-economic model the cost-effectiveness of three diagnostic strategies was estimated relying either on BBM (p-tau 217), CSF (Aβ42/40-ratio) and BBM with CSF confirmatory testing. The model starts with a decision tree that reflects the diagnostic strategies. The decision tree is linked to 16 Markov cohort branches starting at MCI due to AD, representing true positive, true negative, false positive and false negative outcomes of the diagnostic strategies. All diagnostic strategies are combined with AAT including costs of treatment (assumed €5,000/year), infusions and monitoring and are compared to standard of care. **Results:** The incremental cost-effectiveness ratio (ICER) for the BBM-CSF-AAT diagnostic strategy vs the CSF-strategy was 109,360€. The ICER for the CSF-AAT strategy vs SoC was €109,981 per quality adjusted life year (QALY) gained, to be compared with assumed willingness-to-pay (WTP) in Sweden (€94,800). The ICER for the BBM-CSF-AAT pathway vs SoC was similar (€110,222) but with lower costs and fewer gained QALYs. The ICER for the BBM-AAT strategy vs SoC was €140,992. Results were particularly sensitive to the price of AAT and possible subcutaneous administration of AAT. **Conclusion:** Both the CSF-AAT strategy and BBM followed by confirmatory CSF testing and AAT were on the border of being potentially cost-effective, while the BBM-AAT strategy was not. Discussions on budget impact are important.

LP098- ASSESSING THE ADEQUACY AND DISTRIBUTION OF US CLINICAL TRIAL SITES FOR ALZHEIMER'S DISEASE: ADDRESSING REGULATORY, DIVERSITY, EQUITY, AND INCLUSION CHALLENGES. S. Stanton[1], J. Ahn[2], S. Torres[1], C. Stephanie[1], L. Kerry[1], G. Seth[1], G. Daniel[1] *(1. K2 Medical Research - Orlando (United States), 2. K2 Medical Research - San Fransico (United States))*

Background: There are currently 164 ongoing clinical trials in the US for Alzheimer's Disease (AD), which include studies across Phase 1-3 trials and long-term extensions [1]. These trials collectively require 51,398 global participants, 44% of which are solely conducted in the US1. The FDA has recently issued guidance to enhance diversity in AD-clinical trials, highlighting a significant participation disparity where less than 1% of enrolled participants are from African American and Hispanic populations [2]. AD trials are increasingly complex due to the need for advanced imaging technologies and cyclotrons.Our hypothesis posits that 80% of trial participants are drawn from 20% of the U.S. geography, suggesting that existing trial sites may be sub optimally located to meet a growing demand and improve diversity in AD clinical trials. **Methods:** Population data, sourced from the U.S. Census Bureau, was plotted and visualized using graphic software to identify demographic patterns. Research site location data was compiled from ClinicalTrials.gov, TheGlobalzForum.org, ACTCinfo.org, and the National Library of Medicine. Enrollment data from 12 late phase studies across multiple sponsors was aggregated and plotted by five primary regions as defined by US Census Bureau: Northeast, Southeast, Midwest, Southwest, and West. Additionally, two sub regions were analyzed separately, California and Florida. Graphic tools to scatter plot the data were used to analyze geographic distribution and site capacity. PET tracer availability was overlaid on the visual. **Result:** The 7 highest populated areas in the US over 60 years of age are Los Angeles (N=2.39M), New York/Newark/Jersey City (N=1.55M), Southeast FL (N=1.348M), San Diego (N=1.1M), Chicago (N=968K), Phoenix (N=728K), Houston (N=620K). Top 5 populations in the US for African Americans over 60 are New York City (N=280K), Philadelphia (N=130K), Houston (N=120K), Chicago (N=100), and Detroit (N=100K). Enrollment from 12 interventional AD clinical trials, totaling over 3,500 enrollments were distributed among the regions as follows: South Atlantic: 56% / 2001, Pacific: 11% / 409, Middle Atlantic: 9% / 332, West South Central: 6% / 217, New England: 6% / 216, Remaining Divisions (4): 11%; <5% each / 398 (Mountain: 4% / 147, East North Central: 3% / 125, West North Central: 2% / 67, East South Central: 2% / 59).

Additionally, Florida accounted for 49% of enrollments / 1761 and California 7% / 248. Overall, 16 states did not contribute any enrollments (n=0 cumulative) across the studies analyzed (AK, AL, DE, IA, ID, KY, ME, MN, MT, ND, NH, NM, SD, VT, WV, WY). **Conclusion:** The data reveals a misalignment between the geographic distribution of clinical trial sites, the population over 60 and representative enrollment of AD patients nationwide. As the demand for participants rises, existing sites are increasingly pressured, particularly in minority communities and sites within range of PET ligand delivery. The analysis reveals that a few regions are oversaturated with trial sites, while others lack sites within a 50-mile radius, and many regions lack connections to serve diverse, representative research participation, leading to potential underperformance and delayed timelines. Addressing these issues will be crucial for improving trial efficiency and inclusivity. **References:** 1. Cummings, Jeffrey & Zhou, Yadi & Lee, Garam & Zhong, Kate & Fonseca, Jorge & Cheng, Feixiong. (2024). Alzheimer's disease drug development pipeline: 2024. Alzheimer's & Dementia: Translational Research & Clinical Interventions. 10. 10.1002/trc2.12465. 2. Gilmore-Bykovskyi, A. L., Jin, Y., Gleason, C., et al. (2019). "Participation of African Americans in Alzheimer's Disease Biomarker Research: A Review of the Literature." Aging & Mental Health, 23(1), pp. 20-27.

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P210- IMPACT OF PHYSICAL ACTIVITY ON RISK OF DEMENTIA IN PRE-MENOPAUSAL AND POST-MENOPAUSAL WOMEN.

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Background: This study aims to evaluate the impact of exercise on dementia prevalence in women, both with and without menopausal conditions, and to investigate how body mass index (BMI) influences this relationship. **Methods:** We conducted a population-based prospective cohort study involving 2,163,842 participants using the NHIS dataset, stratifying them into pre-menopausal and post-menopausal groups. Cox proportional hazards models were employed to calculate adjusted hazard ratios (aHRs) for the risk of any dementia, Alzheimer's dementia(AD), and vascular dementia across various levels of physical activity, adjusting for potential confounders. Interaction terms were included to assess the effect of BMI on the association between physical activity and dementia risk. **Results:** Regular and vigorous physical activity was associated with a reduced risk of any dementia and AD in pre-menopausal women (aHR = 0.830, 95% CI: 0.739-0.931). In post-menopausal women, all types of physical activity, including walking, were linked to significant reductions in dementia risk (aHR = 0.884, 95% CI: 0.868-0.900 for regular physical activity). Regular physical activity consistently reduced dementia risk across all BMI categories in post-menopausal women, with walking providing notable protective effects, particularly for those with a BMI of 25.0 or more (aHR = 0.942, 95% CI: 0.921-0.964). No significant interaction between physical activity and BMI was observed in pre-menopausal women ($p > 0.05$), whereas a significant interaction was noted for walking in post-menopausal women ($p = 0.0456$). **Conclusion:** This study suggested the protective effects of physical activity against dementia risk in both pre-menopausal and post-menopausal women. Particularly for post-menopausal women, engaging in any form of physical activity significantly reduces the risk of all types of dementia, with walking offering substantial benefits, especially for those with a higher BMI.

P211- EVALUATING ICD-10 MEDICARE CLAIMS DATA AS A METHOD OF IDENTIFYING PERSONS LIVING WITH DEMENTIA.

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Background: : In the United States, Medicare claims data can be used to identify persons living with dementia, including for the purpose of enrollment in research studies and clinical trials. While prior studies have evaluated performance of ICD-9 based algorithms generated for this purpose, there is limited data on performance of ICD-10 based algorithms used to identify persons living with dementia from Medicare claims data. Our objective was to evaluate the performance of several Medicare claims-based algorithms data using current ICD-10 code definitions in fee-for-service claims data relative to research-based dementia classification overall and by participant characteristics. **Methods:** We used data from 5 harmonized cohorts fielded by the Rush Alzheimer's Disease Center (RADC). Participants contributed an observation to the dataset if they had an RADC cohort visit between February 1, 2016 and June 1, 2019 and had at least one month of Medicare fee-for-service coverage in the 6 months preceding or following the date of this cohort visit. All RADC cohort participants were systematically evaluated for all cause dementia based on an in person assessment at each RADC cohort assessment. We compared dementia status determined based on this in person evaluation to dementia status based on six ICD-10 based algorithms selected from a larger set identified through a systematic review; these include four algorithms that are widely used or recently used in high-impact publications and two algorithms that represent a new summary algorithm based on the synthesis of our systematic review of existing algorithms. Performance statistics of interest included sensitivity, specificity, accuracy, negative predictive value (NPV), and positive predictive value (PPV). Finally, we identified independent factors associated with algorithmic inaccuracy, including false positive and false negative classification, using logistic regression. **Results:** The mean age among eligible participants (N=1869, contributing N=6070 observations) was 84.2 years, 78% were female, 24% were Black, and 14% met RADC research-based criteria for dementia during the study period. Algorithmic performance was generally similar, reflecting substantial overlap in codes across algorithms, with all algorithms having high specificity and modest sensitivity. Claims algorithms were less accurate in older adults, racial/ethnic minorities, persons with a history of stroke, and those with depressive symptoms. **Conclusion:** ICD-10 based algorithms perform similarly to ICD-9 based algorithms for identification of dementia, with continued modest sensitivity but good specificity and variable performance by participant characteristics. End users should be aware of these limitations and their implications, including potential for bias in research studies. Future research will need to consider implications of use of Medicare as an administrative data source given increase in marketshare of Medicare Advantage. **Keywords:** Dementia, Medicare, ICD-10, algorithm. **Disclosures:** This work was funded by NIA R01 AG072559.

P212- USE OF MEDICATIONS IN PATIENTS WITH ALZHEIMER'S DISEASE BEFORE AND AFTER DIAGNOSIS. O. Sánchez-Soliño[1], Y. Barer[2], S. Gazit[2], L. Vinikoor-Imler[1], G. Chodick[1] *(1. AbbVie - North Chicago (United States), 2. Maccabi Institute for Research and Innovation, Maccabi Healthcare Services - Tel Aviv (Israel))*

Background: Alzheimer's Disease (AD), the commonest cause of dementia, is a growing global health concern with huge implications for individuals and society [1]. Neurodegenerative processes in AD start years before occurrence of dementia symptoms [2]. CholinEsterase Inhibitors (ChEIs) [3] and memantine [4] are approved for the treatment of AD at different stages of the disease. Analyzing the current use of medications before and after diagnosis of AD can provide insights into better understanding of the needs of Patients with AD (PwAD) and can serve as guidance for future treatment strategies in AD. The objective of this study was to analyze the use of medications in PwAD versus matched patients without AD diagnosis (Pw/oAD), from 10 years prior to 2 years after diagnosis. **Methods:** This longitudinal, patient-level, retrospective cohort study using de-identified Maccabi healthcare services (MHS) database included adult patients diagnosed with AD, as per the ICD-9 code 331.0 or corresponding MHS internal codes. Date of first AD diagnosis was defined as the Index Date (ID). Patients were included if they had at least 1 year (yr) prior ID and 2 yrs post ID (apart from death) of continuous MHS enrollment. MHS members without AD diagnosis were matched to patients with AD by age and sex. The ID was required to occur during 01-01-2010 to 31-12-2019. Medication purchase was used as a proxy for medication use. Comparison of use of medications between groups was performed using standardized mean difference [SMD]. **Results:** 44,128 subjects (22,064 PwAD and 22,064 Pw/oAD) were included in the analysis. Mean age at ID was 80.02 (SD 8.4) yrs and 57.6% were female. The proportion of PwAD using ChEIs increased yearly prior to ID, substantially in the 1 yr post-ID (from 8.3% 1 yr prior ID to 33.6% 1yr post ID). Memantine use in PwAD increased from up to 4% in the 1 yr prior ID to 11.2 % in the 1 yr post ID. One yr prior ID or post ID very few Pw/oAD used ChEIs (0.3% and 0.4%, respectively) or memantine (0.2% and 0.3%, respectively) compared to PwAD. The use of sleep or anxiolytic medication, anti-depressants, anti-psychotics and anti-seizures medications was higher in PwAD than in the Pw/oAD throughout the observational period. **Conclusion:** Approximately one third of PwAD were prescribed ChEIs and 11% were prescribed memantine in the year post diagnosis. Additionally, compared to the general population, PwAD were more likely to use sleep medications, anxiolytics, antipsychotics, and anti-seizure medications starting 10 years before diagnosis, with incremental use post diagnosis. These results indicate that polypharmacy should be taken in consideration in the care of elderly PwAD. **Keywords:** Alzheimer´s Disease, Medication Use. **Author Disclosures:** OS-S and LV-I are employees of AbbVie and may hold stock. YB, SG and GC have no conflict of interest. **References:** 1. Lane C.A., et al. European Journal of Neurology 2018; 25:59-70. https://doi.org/10.1111/ene.13439; 2. Dubois B., et al. Alzheimer's Dement 2016; 12: 292–323. First published: 01 March 2016. https://doi.org/10.1016/j.jalz.2016.02.002; 3. Marucci, G., et al. Neuropharmacology 2021; 190, 108352. https://doi.org/10.1016/j.neuropharm.2020.108352; 4. McShane, R., et al. The Cochrane Database of Systematic Reviews, 2019; 3(3), CD003154. https://doi.org/10.1002/14651858.CD003154.pub6.

P214- THE DEMENTIA DATAHUB: DEVELOPMENT OF A NATIONAL SURVEILLANCE SYSTEM OF DIAGNOSED DEMENTIA IN THE UNITED STATES. D. Rein[1], K. Giannattasio[2], J. Wittenborn[3], S. Knisely[4], C. Carrie[4], Q. Qian[4], P. Melinda[5] *(1. NORC at the University of Chicago - Atlanta (United States), 2. NORC at the University of Chicago - Bethesda (United States), 3. NORC at the University of Chicago - Raleigh (United States), 4. KPMG - Mclean (United States), 5. KPMG - Washington District Of Columbia (United States))*

Background: Surveillance is a fundamental public health activity. The lack of a U.S. dementia surveillance system hinders recruitment efforts for clinical trials among persons with Alzheimer's disease and related dementias (ADRD). **Methods:** Using 100% Medicare Fee-for-Service (FFS) claims and Medicare Advantage (M.A.) Encounter data among all persons alive and enrolled in at least Part A Medicare in January 2020; we estimated the diagnosed prevalence and incidence of dementia corresponding to three mutually exclusive diagnostic code case definitions: "Highly Likely," "Likely," and "Possible," as defined in earlier work.1 We further estimated the 2020 incidence of COVID-19 infection, mortality among prevalent cases in each category, and all-cause payments among Medicare fee-for-service patients. We created all U.S. National, State, and County estimates and stratified estimates by age group, gender, race, and ethnicity. We used the estimates to populate the Dementia Datahub (Dementiadatahub.org) Surveillance site, a publicly available resource that includes mapping capabilities, data reporting dashboards, public use files, and system documentation. **Results:** The Dementia Datahub is scheduled for release in the late summer of 2024, containing data from nearly 100% of all Medicare beneficiaries who were alive and enrolled in Medicare as of January 1, 2020. The system presents the first national surveillance estimates of diagnosed dementia among all Medicare beneficiaries. Under our current project support, we will update the system to include data from 2021 and 2022 and develop additional outcome measures for inclusion in subsequent years of data. The Datahub contains mappable and dashboard quarriable data on each outcome. It allows users to generate customizable reports of any system outcome at the National, State, and county level by dementia definition type, Medicare plan type (Total, FFS, MA), and demographic factors. The Datahub's maps also allow users to explore relationships between dementia outcomes and possible explanatory factors such as poverty, education (less than a high school diploma), hearing loss, vision loss, physician per capita, and other factors using an innovative bivariate color scheme. The Datahub provides free, public-use files of aggregated county results stratified by demographic variables, which the research community can use for independent analysis without the fear of privacy disclosure. Uses of the system for clinical trials include identifying states and counties with higher-than-expected diagnosed prevalence or incidence to prioritize recruitment, perhaps in combination with other factors such as poverty, education, or race and ethnicity to enhance the representativeness of future trials. **Conclusion:** Medicare claims, encounters, and prescription drug records can be used to identify possible geographic areas and demographic subgroups with a high prevalence of diagnosed dementia. **Keywords:** Public Health, Medicare, Surveillance, Prevalence, Incidence, Mortality. **Disclosures:** This project was funded by The National Institute on Aging under an unrestricted research grant R01-AG075730. **References:** 1.Gianattasio KZ, Wachsmuth J, Murphy R, et al. (2024) [Forthcoming] Diagnostic code case definitions for Alzheimer's disease and related dementias: A

systematic review and application using Medicare data. JAMA Open.

P215- IMPACT OF HELICOBACTER PYLORI ERADICATION ON AGE-SPECIFIC RISK OF INCIDENT DEMENTIA IN PATIENTS WITH PEPTIC ULCER DISEASE: A NATIONWIDE POPULATION-BASED COHORT STUDY. K. Dong Woo[1] *(1. Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea - Seoul (Korea, Republic of))*

Background: Peptic ulcer disease (PUD) and Helicobacter pylori (H. pylori) eradication therapy's impact on dementia risk in populations with high H. pylori prevalence is unclear, with conflicting evidence on their association with dementia development, particularly Alzheimer's disease (AD). **Objectives:** This retrospective cohort study aimed to clarify the relationship between PUD, H. pylori eradication therapy, and the risk of dementia, including AD, in an elderly Korean population, stratified by age and accounting for eradication therapy timing. **Methods:** Korean National Health Insurance Service data (2002-2015) for individuals aged 55-79 was used. Participants were categorized based on PUD and H. pylori eradication therapy status. Propensity score matching was employed, and dementia Incidence rates and hazard ratios were calculated over 5 and 10 years, with additional analysis on the timing of eradication therapy. **Results:** PUD was associated with an increased risk of dementia over both 5 and 10 years. The risk was higher for overall dementia than for AD, with no significant difference based on H. pylori eradication status. Age-specific analyses revealed elevated risks, particularly in the 60s and 70s age brackets. Late eradication therapy was associated with a higher risk of dementia. **Conclusion:** The study indicates that PUD is a risk factor for dementia in an elderly Korean population, with a more pronounced risk associated with late H. pylori eradication therapy. These findings highlight the importance of timely management of H. pylori and the role of gastrointestinal health in neurodegenerative disease risk, advocating for further research to refine dementia prevention strategies.

P216- EPIDEMIOLOGICAL SURVEY OF DEMENTIA IN THE KOREAN ELDERLY POPULATION. I.S. Koh[1,2], J. Suh[1,2], M. Oh[2], J. Lee[2], H. Cho[2], S.J. Kim[3] *(1. Department of Neurology, National Medical Center - Seoul (Korea, Republic of), 2. National Institute of Dementia, National Medical Center - Seoul (Korea, Republic of) - Seoul (Korea, Republic of), 3. Korea Institute for Health and Social Affairs - Sejong (Korea, Republic of))*

Background: With the aging population, the number of dementia patients is increasing, leading to a growing burden on both the patients and their families. To alleviate the disease burden of dementia and its social impact, countries worldwide are establishing and implementing national dementia policies. In order to understand the characteristics of dementia and to develop detailed national strategies to alleviate the burden of dementia, it is essential to estimate the number of dementia patients, their current status, and prevalence. This study aims to measure the prevalence of dementia in Korea and to identify the demographic and sociological characteristics of dementia patients and their families. **Methods:** This study was conducted by the Korean National Institute of Dementia and the Korea Institute for Health and Social Affairs from March 2023 to May 2024. The target sample size was determined by proportionally allocating the population aged 60 and over in each district across the country. For facilities/hospitals, the sample size was assigned considering the population aged 60 and over who had been residing in long-term care facilities for more than 30 days. The survey was conducted in three stages. In the first stage, basic information was collected, and dementia screening tests were administered. In the second stage, detailed neuropsychological tests and physician interviews were conducted to diagnose dementia. In the third stage, a detailed investigation was carried out on the socioeconomic conditions, functional status, service utilization patterns for patients classified as having dementia and their caregivers. **Results:** The sample size was 11,000, including 10,000 individuals from community and 1,000 from facilities/hospitals. The first stage survey was completed by 10,373 community residents and 1,300 facility and hospital residents. Of the 4,621 individuals selected for the second stage survey for dementia diagnosis, 1,900 completed the final epidemiological survey. The prevalence of dementia in the population aged 60 and over was 6.76% (95% CI 5.30~8.21%) and in the population aged 65 and over, it was 9.22% (95% CI 7.27~11.17%). Alzheimer's disease had the highest prevalence (6.00%, 95% CI 4.55~7.45%), followed by vascular dementia (1.3%, 95% CI 0.58~2.08%) and other types of dementia. Applying the standardized prevalence rate to the population, the estimated number of people with dementia aged 60 and over was approximately 1,010 thousand. **Conclusion:** In Korea, the dementia prevalence rate among individuals aged 60 and over was slightly lower than the 6.86% reported in the previous national dementia prevalence survey in 2016. However, the estimated number of dementia patients has increased due to the aging population. **Keywords:** Dementia prevalence, epidemiological survey. **Disclosure:** This study was commissioned by the Ministry of Health and Welfare of Korea. The authors have no conflicts of interest to declare.

P217- ALL-CAUSE MORTALITY INCREASED WITH INTRACEREBRAL HEMORRHAGE IN THE UNITED STATES MEDICARE BENEFICIARIES 65 YEARS OR OLDER WITH MILD COGNITIVE IMPAIRMENT OR ALZHEIMER'S DEMENTIA. H. Zhang[1], H. Babak[1], G. Ran[1], I. Michael[1], Z. Quanwu[1], T.M. Amir Abbas[1] *(1. Eisai - Nutley (United States))*

Background: This study evaluates rates of all-cause mortality in patients aged ≥65 years with mild cognitive impairment (MCI) or Alzheimer's dementia (AD) who experienced intracerebral hemorrhage (ICH) in the US Medicare database. **Methods:** Patients with MCI or AD were identified based on diagnostic codes in the Medicare database (2019–2021). ICH incidence defined by inpatient principal ICD-10 codes was categorized based on postulated underlying pathology: (1) cerebral amyloid angiopathy related ICH (CAA-ICH) I61.0, I61.1, I61.6, I60.8, I60.9; (2) hypertension related ICH (HTN-ICH), I61.3, I61.4; and (3) non-specific ICH, I61.2, I61.5, I61.8, I61.9. Poisson regression was used to estimate adjusted mortality rates and proportional hazards regression was used to adjust for time dependence of ICH. SAS was used for all analyses. **Results:** The numbers of AD/MCI patients identified in the database were 1.1M/0.58M, 1.0M/0.58M, 0.9M/0.55M in 2019-21, respectively. The mean age of AD/MCI patients was 83.1/79.4 years. Of the study cohort, 68%/58% were female, 10.6%/8.3% Black, 80%/84% White, and 4%/3% Hispanic for AD/MCI. The incidence rates of ICH per 1000 person-years were distributed as follows: 4.4, 4.3, 4.4 for AD vs 4.3, 4.3, 5.2 for MCI, respectively, over 2019-21. All-cause mortality rates in AD/MCI per 1000 person-years were 182/65 overall, and 309/206 in patients with CAA-ICH, 256/149 in HTN-ICH, and 358/238 in non-specific ICH, compared to 181/65 in non-ICH.

The mortality rates were 203 for men compared to 171 per 1000 person-years for women with AD and 74 for men vs 60 for women with MCI. Them observed mortality rate distributed across racial groups was 170 for Black, 180 for White, and 141 for Hispanic in patients with AD; and was 60 for Black, 68 for White, and 36 for Hispanic in MCI. Adjusted rate of all-cause mortality in MCI was only about one half of that in AD (incidence rate ratio [IRR] 0.48; P<0.01). Combined ICH events more than doubled mortality rates compared to the non-ICH (IRR 2.2; P<0.01). Specifically, adjusted mortality rate was 120% higher with CAA-ICH events (IRR=2.2), 50% higher with HTN-ICH (IRR=1.5), and 140% higher with non-specific ICH (IRR=2.4) (all P<0.01), compared to non-ICH. CAA-ICH was more strongly associated with mortality compared to HTN-ICH after accounting for time-dependence (hazard ratio of CAA-ICH/HTN-ICH=1.4, P<0.01). History of any ICH increased mortality risk by 20% (P<0.01), even after adjusting for time-dependent ICH. **Conclusion:** All-cause mortality was higher in patients with AD vs MCI from the US Medicare database. ICH events defined by inpatient primary ICD-10 diagnoses was associated with an increased mortality risk. CAA-ICH was significantly associated with a 40% increase in mortality relative to HTN-ICH. Overall, this study demonstrated validity of ICD-10-based ICH classification in US Medicare database that meaningfully captured and differentiated mortality outcomes associated with CAA-ICH as opposed to hypertension-related ICH.

P219- EPIDEMIOLOGICAL STUDY OF HOSPITAL MORBIDITY DUE TO ALZHEIMER'S DISEASE IN BRAZIL FROM 2008 TO 2023: A CONTRIBUTION TO CLINICAL TRIALS. J. Fahd[1], G. Betez[1], G. Santos[1], J. Grilo[1], I. Borges[1] *(1. Faculdade Sao Leopoldo Mandic de Araras, Medical School - Araras (Brazil))*

Alzheimer's disease (AD) is the most common cause of dementia in the elderly and, currently, one of the main causes of mortality in developed countries. It is a progressive neurodegenerative disorder, which has treatment, but there is still no cure, evidenced by the deterioration of cognition and memory, with consequent progressive impairment of the patient's daily activities, in addition to behavioral changes. Alzheimer's disease generally develops insidiously and its etiology remains undefined, although considerable progress has been made in understanding its pathophysiological mechanisms. The main mechanism related to the emergence and evolution of Alzheimer's disease is the accumulation of two substances, amyloid beta protein (Aβ) and tau protein, in certain regions of the brain. Risk factors have been associated, in recent years, with the advancement of Alzheimer's Disease, highlighting educational level, healthy eating, physical activity, smoking, obesity, diabetes, high blood pressure, exposure to air pollution and social isolation . In this case, Brazil becomes very vulnerable, considering issues such as education and health are still precarious for a large part of the population living in this country. In recent decades, an increase in the prevalence of Alzheimer's disease has been noted in low and medium economy countries, the context in which Brazil is located. Our methodology consisted of carrying out a survey of the causes of morbidity due to Alzheimer's in the computerized database of the Brazilian Unified Health System (SUS) in the period between 2008 and 2023. After data extraction, analysis was carried out for each of the variables: age, sex and race. Elderly people aged 80 or over were those with the highest number of hospitalizations (59.17%) and the southeastern region of Brazil was responsible for the highest number of hospital admissions associated with Alzheimer's Disease (54.12%). The white race had the highest number of hospitalizations (50.38%) and women represented 65.51% of hospitalizations, a value compatible with international records of Alzheimer's disease.

P220- THE IMPORTANCE OF COGNITIVE RESERVE IN MAINTAINING BRAIN HEALTH IN ALZHEIMER'S DISEASE. G. Almeida[1], G. Santos[2], A. Scarso[2], B. Hara[2], L. Rubim[2], G. Villar[2], F. Moraes[2] *(1. Faculdade Sao Leopoldo Mandic de Araras, Medical School - Araras (Brazil), 2. Faculdade Sao Leopoldo Mandic de Araras, Medical School - Louveira (Brazil))*

Background: Alzheimer's disease presents itself in different ways in individuals with the same level of structural impairment in the brain. Seeking to elucidate the reason for this, the concept of cognitive reserve was proposed, covering factors such as education, language skills, lifestyle, exposure to pollutants, presence of chronic diseases and social activities. **Methods:** It is a literature review study carried out in the period between February and September 2023, based on searches carried out in virtual libraries: PubMed; ScienceDirect; Scielo, Medline; It is in protocols clinicians It is guidelines therapeutics. **Results:** Cognitive Reserve has been associated with a lower risk of developing dementia, such as Alzheimer's Disease. Thus, individuals with greater cognitive reserve can use more effective strategies to delay the onset of the disease. Important pillars in building cognitive reserve include: education, language skills, physical exercise, social activities, exposure to pollutants and absence of chronic diseases. Education is the main component in building cognitive reserve, with more years of education associated with a lower risk of cognitive decline. However, even a few years of formal education can offer benefits in reducing cognitive impairment. Language ability also plays an important role, being associated with the ability to recall memories and organize information effectively. Demonstrating that high linguistic complexity early in life can be protective against Alzheimer's disease. Physical exercise is another essential pillar in building the Cognitive Reserve, with benefits such as increased cerebral blood flow and expression of neurotrophic factors. Both aerobic and resistance exercise can be beneficial, but cardio appears to have a more significant impact. Exposure to environmental pollutants, especially in densely populated urban areas, is associated with a greater risk of cognitive deterioration and dementia, with increased brain inflammatory cytokines. Social activities also contribute to the Cognitive Reserve, so there is an association between social involvement and reduced cognitive decline in the elderly. Participating in challenging activities can promote efficient neural networks. A healthy lifestyle (balanced diet and absence of chronic inflammatory diseases) is crucial to maintaining an adequate reserve, reducing neuroinflammation. In the articles used for the research, it was found that: Education is the biggest key to building cognitive reserve, cited in 41.67% of the articles referenced; physical exercise appears in 16.21% of them; In third place, we have exposure to social activities, representing 13.51% of the articles; Lifestyle appears as a component in 16.21% of articles and both language ability and exposure to pollutants represent 2.7%. **Conclusion:** Building a greater Cognitive Reserve throughout life is associated with a reduced risk of developing Alzheimer's Disease. Education, language skills, physical exercise, social activities, exposure to pollutants and a healthy lifestyle are important pillars in building and maintaining the Cognitive Reserve. **Keywords:** Alzheimer's, aging and cognitive reserve. **Disclosures:** There is no conflict of interest on the part of the authors and co-authors

LP99- DIVERSITY AMONGST THE PHASE 3 HOPE STUDY PARTICIPANTS IS REFLECTIVE OF THE REAL-WORLD ALZHEIMER'S DISEASE (AD) POPULATION. L. Lee[1], J. Dwyer[1], C. Houser[1], A. Konisky[1], E. Hempel[1], T. Magee-Rodgers[1], M. Hull[1], C. Howell[1], R. Kern[1] *(1. Cognito Therapeutics - Cambridge, MA (United States))*

Background: There is an important need for racial and ethnic diversity in Phase 3 study populations that reflect patients in the real world (RW) [1]. Amongst recent AD clinical studies, several factors contribute to inadequate diversity in trial participants, raising questions about the generalizability of study outcomes to the broader population [2]. Demographics of reported RW AD populations include 56.2-61.9% female, 73.9-81.6% White, 9.7-10.4% Black or African-American, 2.2-2.7% Asian, and 5.8-6.5% Hispanic or Latino [3]. In contrast, contemporary Ph3 studies had 50.0-57.3% female, 74.0-92.1% White, 0.2-2.7% Black or African-American, 5.4-17.1% Asian and 2.0-12.5% Hispanic or Latino [4]. Herein, we present the demographics in the ongoing HOPE (NCT05637801) randomized controlled trial (RCT) evaluating Spectris in mild-moderate Alzheimer's disease. **Methods:** The ongoing HOPE pivotal study is enrolling participants with mild-moderate AD, age 50-90 with baseline MMSE 15-28. Toward inclusion of a more representative and diverse study population, in collaboration with the GAP Foundation, study sites with diverse site staff and access to non-white patients were selected from geographic regions with more diverse demographics. GAP's network of sites has access to trainings focused on understanding unconscious biases and cultural competencies. Tailored recruiting initiatives for caregiver and patient awareness were conducted using various channels, including media and in predominantly non-white community venues. **Results:** Demographics of the current HOPE cohort of 467 participants are 55.9% female, 88.7% White, 9.0% Black or African-American, 1.7% Asian, and 0.6% Other/Unknown, with 5.6% Hispanic or Latino ethnicity. The study participants also represent diverse US geographic regions, including the South, Northeast, West and Midwest. **Conclusion:** The patient demographics in the HOPE study are similar to the RW Alzheimer's disease population. Appropriate representation from a diversity of racial and ethnic backgrounds has been consistently identified as a need in AD and all clinical studies. The methods utilized in this study highlight the benefits of targeted site selection and tailored recruitment efforts in diverse communities. Full study participant demographics will be reported in the future. **Keywords:** diversity, Alzheimer's Disease, Phase 3. **Disclosures:** LL, CH, AK, EH, MH, CH, RK are employees of, or own equities in Cognito Therapeutics. JD, TM-R no disclosures. **References:** 1. Brijnath Alzheimer's Dement. 2022; 2. Indorewalla J Alz. Dis. 2021; 3. Matthews Alzheimer's Dement. 2019; https://www.truveta.com/blog/research/ispor-2024-lecanemab/; 4. Van Dyck N. Engl. J. Med. 2023; Sims JAMA 2023; Haeberlein J. Prev. Alz. Dis. 2022.

LP100- ESTIMATING BY RACE AND APOE E4 CARRIER STATUS COUNTS OF US ADULTS WITH SUBJECTIVE COGNITIVE DECLINE WITH PRECLINICAL ALZHEIMER'S DISEASE. C. Gillis[1], S. Showell[1], N. Maserejian[1] *(1. Biogen - Cambridge (United States))*

Background: Clinical trials in Alzheimer's disease (AD) are increasingly targeting preclinical AD, and these trials often consider APOE ε4 status of participants in the trial design or analysis. Here our goal was to estimate the number of amyloid-positive (Aβ+) non-Hispanic White (NH-W) and non-Hispanic Black (NH-B) US individuals 45 years and older (45+) with subjective cognitive decline (SCD) by APOE ε4 carriership, with additional consideration for interactions with healthcare providers (HCP) and potential preclinical AD trial eligibility. **Methods:** To estimate preclinical AD persons with SCD, we used a step-wise approach. We first estimated by race and five-year age-group, the number of cognitively unimpaired US adults aged 45 years and older in 2024 using CDC Wonder population data. We then applied estimates of SCD from a population-based survey providing estimates stratified by age and race [1]. Next, we applied estimates of APOE ε4 carriership prevalence in the general population stratified by race to determine the distribution of these SCD persons by carrier status [2]. We then applied estimates of Aβ+ stratified by age and APOE ε4 carrier status from the Amyloid Biomarker Study to determine the count of likely preclinical AD persons [3]. Next, we calculated the number of these preclinical persons who have spoken to an HCP about their cognitive symptoms using age and race stratified estimates [1]. Lastly, we estimated by race and APOE ε4 carriership those potentially eligible for inclusion in a preclinical AD trial by applying estimates of relevant screen failure criteria from a phase 3 trial in a preclinical AD population [4]. **Results:** In the US in 2024, among NH-W and NH-B APOE ε4 carriers aged 45+ with SCD, an estimated 870K are likely Aβ+ and therefore possibly in the preclinical stage of AD. Among NH-W and NH-B APOE ε4 non-carriers with SCD, an estimated 910K are likely Aβ+. Of these preclinical SCD individuals, an estimated 390K APOE ε4 carriers (APOE ε4+) and 410K APOE ε4 non-carriers (APOE ε4-) have spoken to their HCP about their symptoms. However, only approximately 120K of these APOE ε4+ and 125K APOE ε4- would likely meet trial eligibility criteria. When examined by race, approximately 710K NH-W and 160K NH-B APOE ε4+ are in the preclinical stage of AD compared to 810K NH-W and 100K NH-B APOE ε4-. Among these, an estimated 310K NH-W and 80K NH-B APOE ε4+ have spoken to an HCP about their symptoms; and approximately 360K NH-W and 50K NH-B APOE ε4- have discussed their symptoms with an HCP. Of these only an estimated 96K NH-W and 24K NH-B APOE ε4+; and 109K NH-W and 16K NH-B APOE ε4- would likely be eligible for participation in a clinical trial of preclinical AD. **Conclusion:** Among NH-W and NH-B Americans aged 45+ years, 870K APOE ε4+ and 910K APOE ε4- are likely in the preclinical stage of AD. Of these, approximately only 14% may have spoken to their HCP about their symptoms and would potentially be eligible for inclusion in a preclinical AD trial. **Keywords:** Preclinical, Alzheimer's, APOE, race. **Disclosures:** All authors are employees and shareholders of Biogen. This study was funded by Biogen. **References:** 1. Wooten KG et al. MMWR 2023; 72(10), 249–255. https://doi.org/10.15585/mmwr.mm7210a1; 2. 2024 Alzheimer's disease facts and figures. Alzheimers Dement 2024. Alzheimer's Association 2024 Alzheimer's Disease Facts and Figures; 3. Jansen WJ et al. JAMA Neurol 2022; 1;79(3):228-243 doi: 10.1001/jamaneurol.2021.5216; 4. Sperling RA et al. N Engl J Med 2023; 389(12):1096-1107. doi: 10.1056/NEJMoa2305032.

LP101- REGIONAL DISPARITIES IN ADHERENCE OF ANTI-DEMENTIA MEDICATIONS. Y.G. Lee[1], E. Lee[2], S. Kang[3] *(1. Inje University College of Medicine - Goyang (Korea, Republic of), 2. Boramae Medical Center - Seoul (Korea, Republic of), 3. Yonsei University College of Medicine - Seoul (Korea, Republic of))*

Background: Suboptimal adherence and early discontinuation of anti-dementia medications are prevalent issues. Here, we aimed to investigate factors and regional disparities associated with suboptimal adherence. **Methods:** Based on data extracted from a claim database in South Korea, 508,958 patients with Alzheimer's disease and related dementia who began taking anti-dementia medication between 2018 and 2020 were included. Factors and regional disparities associated with non-adherence were evaluated using logistic regression analyses. **Results:** Within the first year, 40.8% of patients showed suboptimal adherence. Younger age at diagnosis, female sex, and prescription at a non-tertiary hospital or clinic other than neurology/psychiatry were associated with increased risk of non-adherence. Compared with Seoul, a prescription issued by neurology/psychiatry departments at a tertiary hospital in other provinces was associated with a 75% higher risk of non-adherence. **Conclusion:** Strategies targeting non-adherence are warranted to minimize disparities in the management of patients with dementia. **Keywords:** Anti-dementia medication, Alzheimer's disease and related dementia, adherence, discontinuation. **Disclosures:** The authors do not have any conflicts to declare.

LP103- GLOBAL ESTIMATES OF NUMBER OF PERSONS ACROSS KEY SUBGROUPS OF THE ALZHEIMER CONTINUUM. N. Norton[1], A. Gustavsson[1,2], A. Afaque[1] *(1. Quantify Research - Stockholm (Sweden), 2. Department of Neurobiology, Care Sciences and Society, Karolinska Institute - Stockholm (Sweden))*

Background: Global estimates on the number of persons across the Alzheimer's disease (AD) continuum were published in 2023. We now add to the granularity of these data by estimating the number of persons in key subgroups, including specific targets for disease modification. **Methods:** A structured literature review was conducted to identify data on the prevalence of AD and the distribution across subgroups defined by: recently revised staging criteria, apolipoprotein E (ApoE) status, geographic region, ethnicity/race, age and sex. Data chosen from the collected records were combined with the previously published global estimates on the numbers of persons across the Alzheimer's continuum, to create model estimates (and uncertainty ranges) on the number of persons stratified into key subgroups. **Results:** Out of 761 records identified, a total of 48 records met inclusion criteria. Identified evidence within key records enabled granular model estimations of the number of persons in the chosen subgroups, with uncertainties. The available data allowed for more granularity by ethnicity/race and ApoE status for the US region, while more general estimates were possible for the rest of the world. The model estimates are sensitive to assumptions on the generalizability of identified data and their applicability to specific subgroups. Model estimates from this study included the total number of ApoE e4 homozygotes, ages 60+ years old, with either prodromal AD or mild AD dementia (stages 3 and 4), estimated at 3.1 (1.3-5.5) million people in Europe, 1.1 (0.5-2.0) million in the US and 9.4 (3.7-17.1) million in the rest of world. The corresponding number of ApoE 4 carriers were estimated at 11.8 (5.1-20.8) million in Europe, 4.4 (1.9-7.7) million in the US and 36.1 (15.4-63.9) million in the rest of the world. Please see the link below for further detail and additional estimates. **Conclusion:** Granular data on the prevalence of AD and distribution across subgroups are limited and insufficient for robust estimates on a global or even regional scale. Nevertheless, available data can be used for preliminary estimates on the number of persons in selected subgroups. Future studies in specific populations are needed to increase the precision and accuracy of our preliminary estimates. **Data deposition:** quantifyresearch.com/files/ADprevalenceCTAD2024

ANIMAL MODEL

P221- NANOSCALE IMAGING OF PT217-TAU IN AGED RHESUS MACAQUE ENTORHINAL AND DORSOLATERAL PREFRONTAL CORTEX: EVIDENCE OF INTERNEURONAL TRAFFICKING AND EARLY-STAGE NEURODEGENERATION. D. Datta[1], I. Perone[1], D. Wijegunawardana[1], F. Liang[2], Y. Morozov[1], J. Arellano[1], A. Duque[1], Z. Xie[2], C. Van Dyck[1], M.K. Joyce[1], A. Arnsten[1] *(1. Yale University - New Haven (United States), 2. Massachusetts General Hospital and Harvard Medical School - Boston (United States))*

Background: Advances in Alzheimer's disease (AD) have revealed a novel fluid biomarker, tau phosphorylated at T217 (pT217-tau), in CSF and plasma, that reliably discriminates AD from other neurodegenerative diseases [1], appears in the earliest presymptomatic stages of AD [1,2] and predicts AD prior to cognitive deficits [1-7]. Understanding the role of pT217-tau is important in assessing efficacy of novel treatments aimed at early-stage disease. However, it is unknown why pT217-tau is effective in predicting brain pathology, as little is known about early, soluble pT217-tau brain expression. These questions are difficult to address in humans, as soluble p-tau is rapidly dephosphorylated postmortem, and PET scans detect late-stage, fibrillated tau [8]. However, the etiology of pT217-tau in aging brains can be probed in rhesus macaques, where perfusion fixation allows capture of phosphorylated proteins in their native state [9,10]. Aging macaques naturally develop tau pathology with the same qualitative pattern and sequence as humans, including initial cortical pathology in layer II of the entorhinal cortex (ERC) evident early in the aging, and later in layer III of the dorsolateral prefrontal cortex (dlPFC) [10,11]. **Methods:** We utilized multi-label immunofluorescence and immunoelectron microscopy to examine the subcellular localization of early-stage pT217-tau in ERC and dlPFC of aged macaques with naturally occurring tau pathology. We also examined pT217-tau in plasma from rhesus macaques across the entire extent of the macaque age span (1-34 years), to determine whether it increases with age and can serve as a fluid biomarker in macaques as well as humans. **Results:** Our results show that pT217-tau labeling is primarily observed in postsynaptic compartments, accumulating in: 1) dendritic spines on the calcium-storing smooth endoplasmic reticulum spine apparatus near asymmetric glutamatergic-like synapses, and 2) in dendritic shafts, where it aggregated on microtubules, often "trapping" endosomes. The dendrites expressing pT217-tau were associated with autophagic vacuoles and dysmorphic mitochondria, indicative of early neurite degeneration. We observed trans-synaptic pT217-tau trafficking between neurons within omega-shaped bodies and endosomes, specifically near excitatory, but not inhibitory synapses. We also examined pT217-tau in blood plasma in macaques across age-span and observed a statistically significant age-

related increase in pT217-tau. **Conclusion:** These data provide the first evidence of pT217-tau traffiking between neurons to "seed" tau pathology in higher brain circuits, potentially interfacing with the extracellular space to become accessible to CSF and blood as a robust AD biomarker. The association of pT217-tau with dendritic pathology: autophagic vacuolar degeneration, disrupted endosomal trafficking on microtubules, and abnormal mitochondria, also helps to explain why plasma pT217-tau predicts future neurodegeneration and symptoms in humans. Our results reveal an age-related increase in plasma pT217-tau in rhesus macaques, suggesting that plasma pT217-tau can be used as an index of ensuing pathology in rhesus macaques as well, where future studies can directly examine how plasma levels relate to brain measures. Illuminating patterns of degeneration with pT217-tau could potentially guide earlier intervention of therapeutics that might mitigate tau hyperphosphorylation in AD. **Keywords:** tau, plasma biomarker, T217, trafficking. **Disclosures:** The authors declared no competing interests. **References:** 1. Palmqvist S, Janelidze S, Quiroz YT, Zetterberg H, Lopera F, Stomrud E, Su Y, Chen Y, Serrano GE, Leuzy A, Mattsson-Carlgren N, Strandberg O, Smith R, Villegas A, Sepulveda-Falla D, Chai X, Proctor NK, Beach TG, Blennow K, Dage JL, Reiman EM, Hansson O (2020) Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. JAMA 324, 772-781. 2. Barthelemy NR, Li Y, Joseph-Mathurin N, Gordon BA, Hassenstab J, Benzinger TLS, Buckles V, Fagan AM, Perrin RJ, Goate AM, Morris JC, Karch CM, Xiong C, Allegri R, Mendez PC, Berman SB, Ikeuchi T, Mori H, Shimada H, Shoji M, Suzuki K, Noble J, Farlow M, Chhatwal J, Graff-Radford NR, Salloway S, Schofield PR, Masters CL, Martins RN, O'Connor A, Fox NC, Levin J, Jucker M, Gabelle A, Lehmann S, Sato C, Bateman RJ, McDade E, Dominantly Inherited Alzheimer N (2020) A soluble phosphorylated tau signature links tau, amyloid and the evolution of stages of dominantly inherited Alzheimer's disease. Nat Med 26, 398-407. 3. Barthelemy NR, Saef B, Li Y, Gordon BA, He Y, Horie K, Stomrud E, Salvado G, Janelidze S, Sato C, Ovod V, Henson RL, Fagan AM, Benzinger TLS, Xiong C, Morris JC, Hansson O, Bateman RJ, Schindler SE (2023) CSF tau phosphorylation occupancies at T217 and T205 represent improved biomarkers of amyloid and tau pathology in Alzheimer's disease. Nat Aging 3, 391-401. 4. Hansson O, Blennow K, Zetterberg H, Dage J (2023) Blood biomarkers for Alzheimer's disease in clinical practice and trials. Nat Aging 3, 506-519. 5. Janelidze S, Berron D, Smith R, Strandberg O, Proctor NK, Dage JL, Stomrud E, Palmqvist S, Mattsson-Carlgren N, Hansson O (2021) Associations of Plasma Phospho-Tau217 Levels With Tau Positron Emission Tomography in Early Alzheimer Disease. JAMA Neurol 78, 149-156. 6. Mattsson-Carlgren N, Janelidze S, Bateman RJ, Smith R, Stomrud E, Serrano GE, Reiman EM, Palmqvist S, Dage JL, Beach TG, Hansson O (2021) Soluble P-tau217 reflects amyloid and tau pathology and mediates the association of amyloid with tau. EMBO Mol Med 13, e14022. 7. Mattsson-Carlgren N, Salvado G, Ashton NJ, Tideman P, Stomrud E, Zetterberg H, Ossenkoppele R, Betthauser TJ, Cody KA, Jonaitis EM, Langhough R, Palmqvist S, Blennow K, Janelidze S, Johnson SC, Hansson O (2023) Prediction of Longitudinal Cognitive Decline in Preclinical Alzheimer Disease Using Plasma Biomarkers. JAMA Neurol 80, 360-369. 8. Arnsten AFT, Datta D, Del Tredici K, Braak H (2021) Hypothesis: Tau pathology is an initiating factor in sporadic Alzheimer's disease. Alzheimers Dement 17, 115-124. 9. Datta D (2023) Interrogating the Etiology of Sporadic Alzheimer's Disease using Aging Rhesus Macaques: Cellular, Molecular and Cortical Circuitry Perspectives. J Gerontol A Biol Sci Med Sci. 10. Paspalas CD, Carlyle BC, Leslie S, Preuss TM, Crimins JL, Huttner AJ, van Dyck CH, Rosene DL, Nairn AC, Arnsten AFT (2018) The aged rhesus macaque manifests Braak stage III/IV Alzheimer's-like pathology. Alzheimers Dement 14, 680-691. 11. Datta D, Leslie SN, Wang M, Morozov YM, Yang S, Mentone S, Zeiss C, Duque A, Rakic P, Horvath TL, van Dyck CH, Nairn AC, Arnsten AFT (2021) Age-related calcium dysregulation linked with tau pathology and impaired cognition in non-human primates. Alzheimers Dement 17, 920-932.

P222- 2D3A8 A P53 CONFORMATION-SPECIFIC ANTIBODY REACTS WITH ALZHEIMER'S DISEASE-POSITIVE TISSUE IN HUMAN BRAIN SAMPLES. S. Agus[1], D. Lynch[2], S. Madison[2], R. Kayed[2], S. Piccirella[3], P. Kinnon[3] *(1. Diadem SpA - Roslindale (United States), 2. Mitchell Center for Neurodegenerative diseases, University of Texas Medical Branch (UTMB) - Galveston (United States), 3. Diadem SrL - Milano (Italy))*

Background: Alzheimer's disease (AD) is frequently undiagnosed in the early stages of the disease. At least in part, this is due to the expense and difficulty of accurately diagnosing AD in the early stages, with non-specialist doctors often failing to diagnose the condition1. Part of improving the outcomes for patients will require an improved ability to detect AD in the early stages. Previously, the antibody U-p53AZ, used to detect an unfolded variation of p53, has been used in patient blood samples to classify the risk of AD in patients2. As p53 has been associated with the development of AD3, particularly as it begins to migrate to an extranuclear location, it is possible that u-p53AZ is detecting a conformation of p53 specific to the development of AD. The aim of this study is to determine if this antibody can be used in immunofluorescent and immunohistochemical staining to detect this p53 polymorph. **Methods:** Recombinant human p53 protein was unfolded using EDTA and Western blots were used to find if the antibody reacted with the unfolded protein. The U-p53AZ antibody was used in mouse and patient brain tissue samples along with universal p53 antibodies to locate areas of co-staining. Immunofluorescent co-staining for phosphorylated p53, phosphorylated Tau proteins and u-p53AZ was performed in patient samples to locate areas of co-staining. **Results:** Recombinant human proteins indicated that u-p53AZ will react with p53, and that there is lower reactivity with p53 in its correct configuration, and with other proteins. In both mouse and patient brain tissue samples, there were cells that stained positive for both U-p53AZ and the universal p53 antibody. Moreover, there was reduced detection for the u-p53AZ in healthy control tissue. Both phosphorylated Tau and p53 proteins were detected, and were co-stained with the U-p53AZ antibody. **Conclusion:** The U-p53AZ antibody has shown that it is able to detect a unique conformation of p53 that is only present in either mouse models associated with AD-related alterations to p53 expression, and in AD patients. As has already been noted, it has been shown to be able to predict the development of AD. This research further expands on the underlying justification for the use of this antibody clinically, demonstrating the differences in its reaction between healthy controls, early stage AD and late stage AD. **Keywords:** p53; U-p53AZ; Tau; prognosis cognitive decline, Proteomics

P225- CRYO-EM STRUCTURES OF AMYLOID-B FIBRILS FROM ALZHEIMER'S DISEASE MOUSE MODELS.

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Background: The development of Alzheimer's disease (AD) therapeutics has been a challenging journey over the years. One of the reasons is associated with difficulties on reflecting the observed pre-clinical outcomes of AD animal models in humans. These differences could be because animal models with amyloid-β (Aβ) pathology do not always have the adequate molecular drug targets, as their structures can differ from each other. **Methods:** A sarkosyl based approach [1] was used to extract Aβ fibrils from the brain tissue of six different commonly used mouse models. We further determined the Aβ fibril structures by Cryo-EM [2] and compare them with existing human structures [1]. **Results:** Novel polymorphs that have not been previously observed in humans were identified in the APP/PS1, ARTE10, and tg-SwDI models. Furthermore, the ARTE10, tg-APPSwe, and APP23 models presented the human type II fold, which was mainly observed in familial AD and other conditions. Remarkably, the tg-APPArcSwe model exhibited a fibril fold that resembles the human type I fold which was mostly found in patients with sporadic AD, that constitute the majority of AD cases [1]. **Conclusion:** These structural elucidations provide an insight for the selection of the most suitable mouse model for future AD therapeutic development. **Keywords:** Cryo-EM, Alzheimer's disease, animal models, amyloid structures. **Data Deposition:** Cryo-EM maps have been deposited to the Electron Microscopy Data Bank (EMDB) and the Protein Data Bank (PDB) under the following accession numbers: EMD-16944 (PDB 8OL3) for murine type III Aβ42 fibrils from APP/PS1, EMD-16960 (PDB 8OLO) for murine type III Aβ fibrils from ARTE10, EMD-16949 (PDB 8OL5) for type II Aβ42 fibrils from ARTE10, EMD-16959 (PDB 8OLN) for DI1 Aβ fibrils from tg-SwDI, EMD-16957 (PDB 8OLG) for DI2 Aβ fibrils from tg-SwDI, EMD-16961 (PDB 8OLQ) for DI3 Aβ fibrils from tg-SwDI, EMD-16952 (PDB 8OL6) for type II Aβ42 fibrils from tg-APPSwe, EMD-16942 (PDB 8OL2) for type II Aβ42 fibrils from APP23 and EMD-16953 (PDB 8OL7) for murineArc type I Aβ40 fibrils from tg-APPArcSwe. Raw cryo-EM multi-frame micrographs were deposited to the Electron Microscopy Public Image Archive (EMPIAR) for Aβ fibrils purified from tg-SwDI mouse brain tissue under accession code EMPIAR-11680. **Disclosures:** L.N.G.N. is on the scientific advisory board and receives a research grant from BioArctic. M.I. is a paid consultant to BioArctic. D.W. is a founder and shareholder of the company Priavoid and a member of its supervisory board. D.W. is co-inventor of patents related to the compound RD2. D.W. is a founder and shareholder of attyloid. D.W. is a member of attyloid's supervisory board. These had no influence on the interpretation of the data. Benedikt Frieg is now an AstraZeneca employee. All other authors declare no competing interests. **References:** 1. Yang Y, et al. Science 2022; 375(6577):167–72. https://doi.org/10.1126/science.abm7285. 2. Zielinski M, et al. Nat Neurosci 2023; 26(12):2073–80. https://doi.org/10.1038/s41593-023-01484-4.

DIGITAL HEALTH/E-TRIALS

P226- RETINAL AI-BASED ALZHEIMER'S DISEASE DETECTION MODEL IDENTIFIES POOR BRAIN HEALTH IN COGNITIVELY UNIMPAIRED SUBJECTS.

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Background: RetinAD is a validated deep learning model for differentiating between Alzheimer's disease (AD) dementia and cognitively unimpaired subjects based on analyzing fundus pictures [1]. Since certain AD-related retinal changes (e.g., microvasculopathy) may evolve over years to decade before the onset of cognitive symptoms, we hypothesized that RetinAD may also identify cognitively unimpaired elderly subjects who may be at risk of AD. We thus investigated and compared the clinical features between "positive" and "negative" cases as classified by RetinAD among cognitively unimpaired elderly subjects. **Methods:** We recruited community subjects who were participants of the BEAT AD (Brain HEAlth Service for PrevenTion of Alzheimer's Disease) programme in Hong Kong SAR, China. BEAT AD invites functionally independent subjects without dementia (59-80 year-old) with subjective cognitive complaints for (i) assessing their cognition and control of modifiable AD-related risk factors, and (ii) empowering them in modifying those risk factors. We excluded subjects with mild cognitive impairment or dementia as determined by their age/education-adjusted cutoffs of the Montreal Cognitive Assessment (MoCA) score and their functional levels. A simple scoring system (the BEAT AD Score) was developed for this programme based on parameters in 4 domains, namely, 1. cardiovascular risk factors, 2. physical activity level, 3. engagement in cognitively stimulating/social activities, and 4. dietary pattern. The BEAT AD score ranges from 0-12 with a higher score indicating better control. We obtained fundus pictures of all recruited subjects using the Topcon NW500 non-mydriatic retinal camera and classified the subjects into "negative" or "positive" by RetinAD. We compared demographics and BEAT AD scores between these 2 groups. **Results:** A total of 166 recruited subjects (mean age 68.2, 67.5% female, mean BEAT AD score 6.70) were analyzed. 27 (16.3%) and 139 (83.7%) subjects were classified as "positive" and "negative" based on RetinAD, respectively. Subjects classified as "positive" were significantly older (mean age 71.3 versus [vs] 67.6; $P = 0.002$), had a higher proportion of male (51.9% vs 28.8%; $P = 0.034$), and had a lower BEAT AD score (5.87 vs 6.86, $P = 0.004$) than subjects classified as "negative". There was no difference in the mean MoCA scores between the groups (positive 24.0 vs. negative 25.2, $P = 0.25$). **Conclusion:** When applied on cognitively unimpaired elderly subjects, RetinAD identified subjects who were significantly older with poorer control in AD-modifiable risk factors. Since aging is the strongest risk factor for AD, findings from this study suggest that RetinAD may identify elderly subjects who are at risk of AD and/or with suboptimal brain health. Further studies should compare specific retinal features (e.g., vascular

measures) and preclinical AD-related brain changes (e.g., amyloid burden, small vessel disease) between the positive and negative cases. **Keywords:** Retinal imaging, deep learning model, dementia, digital health, cognition. **Disclosures:** VCT Mok, H Ko and C Cheung are founding members of i-Cognitio Sciences Limited. **References:** 1. Cheung CY, Ran AR, Wang S, Chan VTT, Sham K, Hilal S, Venketasubramanian N, Cheng C-Y, Sabanayagam C, Tham YC, Schmetterer L, McKay GJ, Williams MA, Wong A, Au LWC, Lu Z, Yam JC, Tham CC, Chen JJ, Dumitrascu OM, Heng P-A, Kwok TCY, Mok VCT, Milea D, Chen CL-H, Wong TY. A deep learning model for detection of Alzheimer's disease based on retinal photographs: a retrospective, multicentre case-control study. The Lancet Digital Health 2022; 4(11): e806-e15.

P227- COGNITIVE THERAPY SOFTWARE FOR IMPROVING COGNITIVE FUNCTION FOR PATIENTS WITH MCI. H. Choi[1], J.H. Jeon[1], Y. Minn[2], C.K. Kim[3] *(1. Department of Neurology, Hanyang University Guri Hospital - Guri (Korea, Republic of), 2. Department of Neurology, Kangnam Sacred Heart Hospital - Seoul (Korea, Republic of), 3. Department of Neurology, Korea University Guro Hospital - Seoul (Korea, Republic of))*

A multicenter, prospective, comparative, randomized, independent rater-blind, superiority, pivotal clinical trial to compare the safety and efficacy of the Cognitive therapy software 'SUPERBRAIN DEX' for improving cognitive function with a control group for patients with mild cognitive impairment. **Background:** Cognitive intervention therapy has been proven to be a safe and effective technique for improving cognitive function in patients with Mild Cognitive Impairment (MCI), as well as those with mild to moderate dementia. Given the variety of intervention strategies within cognitive intervention therapy programs, the effectiveness and standardization of each program must be validated. Additionally, since MCI patients retain insight and learning abilities unlike dementia patients, providing tailored interventions that consider individual characteristics can maximize the therapeutic effects on cognitive function and motivation. Considering these characteristics, computerized cognitive rehabilitation therapy is being offered. However, the current computerized cognitive rehabilitation programs used in clinical practice are often foreign-developed products that are difficult to apply directly to Korean elderly due to linguistic and cultural differences. Existing products developed in Korea tend to focus on gamified tasks that generate interest but have been reported to be weak in enhancing memory. Therefore, 'SuperBrain DEX'(developed by Rowan Co., Ltd.), a digital therapeutic device providing evidence-based therapeutic intervention, has been developed to improve cognitive function in MCI patients. **Methods:** The study targets MCI patients aged 50-85 who meet the inclusion and exclusion criteria. Through 'SuperBrain DEX', cognitive training will be conducted for a total of 16 weeks, 7 times a week (each session lasting 15-30 minutes). The program will assess the patient's cognitive training performance in real-time and provide personalized training by applying individual cognitive function levels and basic information (gender, age, education, Z-Score of cognitive tests) to artificial intelligence (AI). The control group will receive an educational booklet on lifestyle rules for dementia prevention. Cognitive function improvement will be confirmed through primary (K-RBANS) and secondary (CDR, K-MMSE-2, K-IADL, PRMQ, GDS-15, QOL-AD, ADAS-Cog 14 tests) efficacy evaluations before and after the program. **Results:** The study is designed for 140 participants across 12 research institutions in Korea, with the first participant registered in January 2024. Currently, 67 participants (47.86%) are enrolled in the study. **Conclusion:** This clinical trial aims to assess the superiority of the cognitive function improvement effect of 'SuperBrain DEX' in patients with MCI compared to control groups and evaluate its safety for use. we hope to have results that can achieve these objectives by the time of the presentation. **Keywords:** Mild Cognitive Impairment, Cognitive intervention therapy, Digital therapeutic device. **Clinical Trial Registry:** NCT06264557; https://clinicaltrials.gov.

P229- EARLIER IS BETTER: CLINICAL TRIAL SIMULATOR SIMULAD QUANTIFIES THE RELATIONSHIP BETWEEN AMYLOID/TAU LOAD SEVERITY AND THE AMPLITUDE OF COGNITIVE BENEFITS OF ANTI-AMYLOID TREATMENTS. A. Custo[1,2], M. Lorenzi[3], G. Frisoni[4], V. Garibotto[1,2,5] *(1. Laboratory of Neuroimaging and Innovative Molecular Tracers (NIMTlab), Geneva University - Geneva (Switzerland), 2. Neurocenter and Faculty of Medicine, University of Geneva - Geneva (Switzerland) - Geneva (Switzerland), 3. Inria Sophia Antipolis, Université Côte d'Azur - Sophia Antipolis (France), 4. Geneva Memory Center, Geneva University Hospitals and Laboratory of Neuroimaging of Aging (LANVIE), University of Geneva - Geneva (Switzerland), 5. Division of Nuclear Medicine and Molecular Imaging, Geneva University Hospitals and CIBM Center for Biomedical Imaging, Geneva University Hospitals - Geneva (Switzerland))*

Background: Four anti-amyloid monoclonal antibodies have recently completed large phase III trials. Longitudinal amyloid PET evaluations have consistently shown the ability of all drugs to effectively reduce amyloid burden, at various rates, while cognitive outcomes were variable. In particular, donanemab and lecanemab met the targeted cognitive outcomes, aducanumab's results were controversial and gantenerumab's were negative. Their effect on slowing tauopathy was absent or sparsely documented.This study aims to explore the relationship between the severity of amyloid and tau loads and the amplitude of cognitive benefits in the treated population. To this end, we use SimulAD, an existing Disease Progression Model purposely adapted for this task. In particular, we extend the findings of five published clinical trials by simulating the treatment of five increasingly pathological populations. **Methods:** We train a latent-space dynamic model on an amyloid positive population drawn from one of the largest Alzheimer pre-clinical datasets (ADNI), using cognitive and imaging biomarkers, including tau load as measured by Flortaucipir SUVr. We simulate the amyloid clearance profile of the four aforementioned drugs in five clinical trials during 18 months (N=500 for each arm), and constant treatment effects thereafter. We replicate the simulations in five increasingly pathological populations, from mild MCI (Centiloid mean 48.63 $\pm$ 6.65, tau fusiform SUVr mean 1.32 $\pm$ 0.09) to severe MCI (Centiloid mean 88.49 $\pm$ 7.24, tau fusiform SUVr mean 1.59 $\pm$ 0.10). For each simulated biomarker's progression, we compute its value at time t for the 500 synthetic subjects of each arm, Treated and Placebo, and the percentage of slowdown as: 100*(Treated(t) - Placebo(t))/(Placebo(t)). **Results:** We find that a reduction of amyloid and tau burden in a mild MCI population produces a larger cognitive benefit compared to the same intervention applied to a severe MCI population. In particular, we find that after 18 months of a donanemab-like treatment, cognitive decline measured by CDR-SB slows down by 36.58% when Centiloid goes from 48.70 to 39.25 (28.12% slowing w.r.t. the

mean value of the Placebo group at 18 months: 54.61) and tau fusiform SUVr decreases from 1.32 to 1.06 (22.27% slowing w.r.t. the mean value of the Placebo group at 18 months: 1.36). However, CDR-SB slows down by only 9.97% when Centiloid goes from 87.71 to 41.32 (55.73% slowing w.r.t. the mean value of the Placebo group at 18 months: 93.33) and tau fusiform SUVr goes from 1.58 to 1.18 (27.64% slowing w.r.t. the mean value of the Placebo group at 18 months: 1.62). **Conclusion:** SimulAD was able to replicate in-silico the results from five published clinical trials of anti-amyloid monoclonal antibody drugs. We further extended these results demonstrating the differential treatment effectiveness on five increasingly pathological populations. Our simulations show that cognitive benefits are particularly sensitive to the severity of the tau pathology, and are in agreement with several post-hoc results previously presented at CTAD. **Keywords:** Latent-space Dynamic Model, Disease Progression Model, tau PET, ADNI, Clinical Trial Simulation. **Disclosures:** None.

P230- THE CAN-THUMBS UP BRAIN HEALTH SUPPORT PROGRAM: OUTCOME COMPLETION RATES IN A FULLY REMOTE ONLINE INTERVENTION STUDY.
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Background: Brain Health PRO (BHPro) is a comprehensive web-based intervention designed to increase dementia literacy, self-efficacy, and encourage individuals to make lifestyle changes to reduce their risk of dementia. We undertook a 12-month study evaluating this online program and participant responses within the inception cohort [1]. As part of the innovative fully remote study design, participants self-navigated through the intervention and many of the outcome assessments. This report aims to: 1) evaluate 12-month completion rates, 2) evaluate technical success in the administration of online cognitive assessments and questionnaires, 3) determine reasons for discontinuation. **Methods:** Participants completed the BHPro intervention at home using a computer or tablet and outcome assessments were deployed to participants using a variety of methods (e.g., video call between participant and coordinator, self-completion within the BHPro platform, link provided via email, mobile phone application, wearables and saliva collection materials shipped to their home.) **Results:** A total of 374 participants consented to screening and of these 20 participants were excluded (11 did not meet inclusion criteria, 8 declined to participate, 1 withdrew consent prior to baseline visit). There were 354 enrolled participants who completed baseline neuropsychological testing via videoconference with a study coordinator and received instructions on BHPro registration. Of these, 345 (97%) successfully completed the self-registration process and lifestyle risk questionnaires within the BHPro platform, allowing them to access the intervention content. There were 329 (93%) that completed at least 1 outcome assessment at Month 6 and 315 (89%) completed at least 1 outcome assessment at Month 12. Due to technical coding issues within BHPro some assessments at baseline and Month 6 were not deployed to all participants, resulting in missing data. Of the original 354-person cohort, 33 participants (9%) fully withdrew from the study and 6 participants (2%) were lost to follow-up. One of the withdrawn participants requested their data not be used. Most common reasons for withdrawal included lack of time or motivation (n=9), health related problems (n=6), and technology related problems (n=3), with an additional 8 participants citing more than one of these reasons. Eighteen participants (5%) formally discontinued the BHPro intervention but agreed to continue with follow-up visits and/or completion of outcome assessments. Reasons given for discontinuing the intervention included lack of time or motivation (n=5), content of the intervention (n=9), health related problems (n=1), and unknown (n=3). **Conclusion:** The online BHPro platform, addressing personal and modifiable risk factors, was very well received by this participant group. The majority of participants were able to successfully self-navigate and complete remote outcome assessments, with 89% remaining engaged with the study at 12 months. Our future plans are to implement this program in diverse Canadian settings with an eventual goal of implementation at a national scale. We are planning to provide more technical infrastructure to oversee functioning of the web-based program including monitoring data acquisition to identify technical issues that may arise. **Keywords:** Alzheimer's disease, dementia, prevention, Brain Health PRO. **Clinical Trial Registry:** NCT05347966; https://clinicaltrials.gov/. **Disclosures:** The CAN-THUMBS UP Brain Health Support Program is funded through the Canadian Consortium on Neurodegeneration in Aging (CCNA) grant from the Canadian Institutes of Health Research CNA-163902 with funding from partners, including the Alzheimer Society of Canada. **Acknowledgements:** CCNA-CAN-THUMBS UP Study Group. **References:** 1. Feldman, H.H., Belleville, S., Nygaard, H.B., et al. Protocol for the Brain Health Support Program Study of the Canadian Therapeutic Platform Trial for Multidomain Interventions to Prevent Dementia (CAN-THUMBS UP): A Prospective 12-Month Intervention Study. J Prev Alz Dis 2023; http://dx.doi.org/10.14283/jpad.2023.65.

P231- DIGITAL ASSESSMENT OF COGNITION FOR OPTIMIZING NEUROPSYCHOLOGY WORKFLOW.
A. Jannati[1], K. Thompson[1], C. Toro-Serey[1], R. Banks[1], C. Higgins[1], J. Pobst[1], J. Showalter[1], D. Bates[1], S. Tobyne[1], D. Libon[1], R. Swenson[1], A. Pascual-Leone[1] *(1. Linus Health - Boston (United States))*

Background: Traditional neurological and neuropsychological evaluations of patients with cognitive concerns are associated with long delays between referral by the primary care provider (PCP) and specialist assessment. This is in part due to the referral of patients who may not need to be seen by specialists and the bottleneck created by non-scalable resources. For example, neuropsychologists, with the assistance of a psychometrist, typically spend 4–8 hours administering neuropsychological tests and interpreting each patient's results, and therefore can only evaluate 1–2

patients daily. We hypothesized that a medical assistant at the PCP office equipped with the Core Cognitive Evaluation (CCE) including the Digital Clock and Recall (DCR), a Life and Health Questionnaire (LHQ), and a clinical decision support (CDS) system, could become a "Technology-enabled Psychometry Assistant (TPA)", prioritize patients to be referred, and collect data for off-line review by specialists. **Methods:** Data from 983 participants in the Bio-Hermes-001 multi-site study (age mean±SD=72±6.7; 56% female; years of education mean±SD=15±2.7; primary language English), a priori classified as cognitively unimpaired (CU; n=417), mild cognitively impaired (n=309), or probable Alzheimer's dementia (n=257) based on expert consensus clinical diagnosis and neuropsychological evaluation were analyzed. A random forest model was trained on DCTclock and word recall data to classify cognitive impairment using a binary (CI and CU) and 3-tier (CI, Indeterminate, and CU) prediction thresholding schemes. **Results:** The 3-tier model predictions performed well (AUC=0.887; accuracy=0.834; NPV=0.801; PPV=0.859) outperforming the binary predictions (AUC=0.865; accuracy=0.79; NPV=0.737; PPV=0.837) when measured on Biohermes' cohort diagnosis. The sensitivity and specificity of the 3-tier predictions were 0.858 and 0.8, respectively. **Conclusion:** In our proposed workflow, the TPA (a medical assistant at the PCP office equipped with a digital cognitive assessment platform) administers the CCE as part of a routine 'cognitive vital signs' screening. If the CCE does not indicate CI or mood/behavioral symptoms, the PCP reassures the patient and sets a follow-up visit in a year. If the CCE indicates CI or mood/behavioral symptoms, the CDS generates personalized recommendations for interpreting the results and further testing. A Neuropsychologist review of the CCE is done together with CDS recommendations. After review of the CCE, the Neuropsychologist determines if further neuropsychological evaluation is needed and offers appropriate recommendations to the patient and family. Depending on the CCE results and CDS recommendations, in parallel referral to the Neurologist is made for prioritization/faster evaluation and implementation of treatment. This workflow can optimize the process of neuropsychological evaluation and referral to neurology for diagnosis and treatment of patients with cognitive impairment. **Disclosures:** DJB is a co-founder of Linus Health and declares ownership of shares or share options in the company. AJ, KT, CTS, JGO, RB, JP, CH, JS, and ST 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., TetraNeuron, Skin2Neuron, and MedRhythms. APL, DJB, ST, AJ, and JGO are listed as inventors on a pending patent assessing central nervous system functionality using a digital tablet and stylus. APL is further listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging, and applications of noninvasive brain stimulation in various neurological disorders, as well as digital biomarkers of cognition and digital assessments for early diagnosis of dementia.

P232- COMPARING EYE-TRACKING METRICS FOR FIGURE-COPYING IN AMYLOID-NEGATIVE AND AMYLOID-POSITIVE MILD COGNITIVE IMPAIRMENT.

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Introduction: Visuospatial dysfunction is a common symptom in individuals with mild cognitive impairment (MCI) due to Alzheimer's disease (AD). We divided the copying process into three conceptual stages: visuoperceptual function, visuoconstructional function, and working memory function. To compare subtle differences between amyloid-negative and amyloid-positive MCI, we utilized eye-tracking metrics to measure participants' performance while they completed the simplified Rey Complex Figure Test (RCFT). **Methods:** We recruited 56 participants with MCI who had undergone amyloid positron emission tomography (PET) scans. Amyloid PET positivity, using 18F-flutemetamol, was determined according to specific guidelines for each PET ligand. To emphasize the copying and drawing processes rather than the final figures, we divided the area of interest (AOI) into perceptual and working spaces. We used Tobii Glasses Pro 2, which records binocular eye movements at a 50 Hz sampling rate and has a scene camera resolution of 1,920 x 1,080 pixels. Eye-tracking data was collected during the copying task. Following standard gaze mapping procedures, we quantified the number of fixations on each AOI. These metrics were then compared between the amyloid-negative and amyloid-positive MCI groups using the Mann-Whitney U test. **Results:** In total, 56 participants were included in the study, with 22 classified as having amyloid-negative MCI and 33 as having amyloid-positive MCI. Analysis of eye-tracking data indicated that individuals with amyloid-positive MCI demonstrated a notably greater visit count ($P = 0.029$) and duration ($P = 0.024$) within the perceptual area of interest (AOI) compared to those with amyloid-negative MCI. **Conclusion:** In individuals with amyloid-positive MCI, there was an observed increase in the number and duration of fixations within the perceptual area of interest (AOI) compared to those with amyloid-negative MCI. This finding aligns with our previous research, which indicated similar trends in patients with Alzheimer's disease (AD) compared to cogtnivie normal elderly participants. The increased number of fixations and longer fixation duration on the perceptual AOI suggest prolonged target processing times. Consequently, considering both our current and prior findings, it suggests that an augmented number and duration of fixations within the perceptual AOI is necessary during the visual encoding of complex figures, a neurobehavioral characteristic potentially linked to visuoperceptual dysfunctions observed in individuals with AD. This research was supported by Eisai Korea Inc. **References:** 1. Kim KW, Wang Q, Koo SH, Shin BS. A single-center, randomized, parallel design study to evaluate the efficacy of donepezil in improving visuospatial abilities in patients with mild cognitive impairment using eye-tracker: the COG-EYE study protocol for a phase II trial. Trials. 2022 Sep 27;23(1):813. doi: 10.1186/s13063-022-06781-0. 2. Kim KW, Choi J, Chin J, Lee BH, Na DL. Eye-Tracking Metrics for Figure-Copying Processes in Early- vs. Late-Onset Alzheimer's Disease. Front Neurol. 2022 May 16;13:844341. doi: 10.3389/fneur.2022.844341.

P233- VALIDATION OF A LIFESTYLE RISK ASSESSMENT 'SMART TRACKER' TOOL. L. Mcketton[1], A. Troyer[2,3], N. Anderson[1,3,4] *(1. Rotman Research Institute, Baycrest Academy for Research and Education - Toronto (Canada), 2. Neuropsychology and Cognitive Health, Baycrest - Toronto (Canada), 3. Department of Psychology, University of Toronto - Toronto (Canada), 4. Department of Psychiatry, University of Toronto - Toronto (Canada))*

Background: Background: Prior studies indicated that lifestyle choices and modifiable risk factors contribute to 40% of dementia cases worldwide [1]. The Smart Tracker tool is a lifestyle risk assessment that was developed by leading experts intended to help users manage their lifestyle choices for maintaining and enhancing their overall wellness and brain health. It consists of 23 questions across six domains including diet, exercise, cognitive and social engagement, emotional and physical well-being, as well as height and weight for BMI calculation. The Smart Tracker was incorporated on the Cogniciti site in 2016 and garnered over 16,000 completions. The assessment takes 5 minutes to complete and generates a personalized Smart Tracker score for longitudinal tracking while providing recommendations for improving overall wellness and brain health. Researchers and clinicians have expressed interest in a validated Smart Tracker instrument for wider use in research and clinical practice. For this study, we performed external validation of lifestyle factor domains of the Smart Tracker Tool using established gold standard domain measures. **Methods:** Participants aged 20 to 100 with stable internet connections were recruited through the Cogniciti Brain Health Registry. Out of 787 interested participants, 570 (68% female, mean age (SD) = 71.3 (9.5), age range 22-97) completed the Smart Tracker Tool and associated gold standard questionnaires. Smart Tracker domains were compared with: 1) Diet - Eating Pattern Self-Assessment (EPSA) based on the Brain Health Food Guide (BHFG), 2) Exercise - Short Form International Physical Activity Questionnaire (IPAQ), 3) Emotional Well-Being (sleep-related questions) - Pittsburgh Sleep Quality Index (PSQI), 4) Emotional Well-Being (stress/depression-related questions) - Depression and Stress components of the Depression, Anxiety, and Stress Scale -21 (DASS-21 short form), and 5) Cognitive Engagement and Social Engagement - Cognitive Reserve Index Questionnaire (CRIq). We evaluated the convergent validity of the Smart Tracker using consensus criteria for good measurement properties [2] namely, we expected large correlations ($r >= 0.50$) between the Smart Tracker scores and scores on scales measuring similar constructs. The Shapiro-Wilk test was performed to assess normality, which was not detected. Spearman correlation coefficients (r values) assessed the strength and direction of association between each Smart Tracker domain and the corresponding gold standard question set. **Results:** The Smart Tracker questionnaire domains exhibited moderate to high correlations with other validated questionnaires assessing similar constructs. Spearman correlations revealed significant positive associations for diet ($r = 0.62$), exercise ($r = 0.53$), cognitive and social engagement ($r = 0.33$), and significant negative correlations for emotional well-being related to sleep ($r= -0.65$), stress and depression ($r = -0.70$) ($ps < 0.0001$). **Conclusion:** Convergent validity demonstrated favourable comparisons between the Smart Tracker Tool domains and established scales measuring similar constructs. This user-friendly, self-administered questionnaire presents itself as a valuable tool that can be used for seamless integration into research and clinical trial interventions. Subsequent studies will evaluate its structural validity, internal consistency, and test-retest reliability, alongside further comparisons with participants' cognitive brain health assessments within the broader n = 16,000 dataset. **Keywords:** Digital Health, Lifestyle Risk Assessment, Dementia Risk, Dementia Prevention. **Disclosures:** Investigator (McKetton) is a current employee of Cogniciti. The authors declared no competing interests. **References:** 1. Livingston G, et al. Lancet 2020; 396 (10248): 413–446. doi.org/10.1016/S0140-6736(20)30367-6; 2. Prinsen CAC, et al. Qual Life Res 2018; 27 (5): 1147–1157. doi.org/10.1007/s11136-018-1798-3.

P234- AGREEMENT BETWEEN ALTOIDA'S DIGITAL BIOMARKER PLATFORM AND STANDARD NEUROPSYCHOLOGICAL TESTS IN INDIVIDUALS WITH SUBJECTIVE MEMORY COMPLAINTS. M.F. Iulita[1], A. Ferrari[1], G. Sanchez Benavides[2], V. Brugada Ramentol[1], S. Fallone[1], N. Griffin[1], E. Streel[1], O. Grau-Rivera[2], C. Minguillon[2], C. Porta-Mas[2], M. Charvat[1], I. Tarnanas[1] *(1. Altoida Inc. - Washington DC (United States), 2. Barcelonaβeta Brain Research Center (BBRC), Pasqual Maragall Foundation - Barcelona (Spain))*

Background: Background: The limited access to early diagnosis of Alzheimer's disease (AD) poses a significant bottleneck to accessing therapy. Altoida uses machine learning-based classification models called Digital Neuro Signatures (DNS) to objectively assess cognitive and functional abilities. This study evaluated the concordance between the Altoida Digital Biomarker Platform and a standard cognitive testing battery in individuals with subjective memory complaints seeking medical advice in a primary care-like setting. **Methods:** This sample is from a single-center, longitudinal cohort study (n=103; 60.2% female; mean age: 66.3 (6.2) years) from the β-AARC cohort1 established at the Barcelonaβeta Brain Research Center. Participants received a neurological evaluation, a neuropsychological (NPS) testing battery, and had known amyloid status based on the Aβ42/40 ratio determined in CSF (cut-off 0.062; Lumipulse, Fujirebio). The NPS battery was comprised of the Mini-Mental State Examination (MMSE), the Free Cued Selective Reminding Test (FCSRT), Trail Making Test (TMT), semantic fluency, WAIS-IV subtests (Coding, Visual Puzzles, Matrix Reasoning), and WMS-IV Logical Memory. Additionally, participants underwent Altoida's Digital Biomarker Assessment in the clinic using iOS tablets. Scores at baseline were compared between groups using generalized linear models adjusted for age and education level, with two-tailed Wald's test on the coefficients. **Results:** Participants were classified according to their clinical status, as Subjective Cognitive Decline (SCD; n=97; mean age: 66.0 (6.2) years; mean MMSE score: 28.6 (1.4) points) or Mild Cognitive Impairment (MCI; n=6; mean age: 71.2 (3.4); mean MMSE score: 26.9 (1.5) points). 94.8% (92/97) of participants showed alignment between the Altoida DNS classification (indicating unimpaired status) and the clinical classification of SCD, denoting no objective cognitive impairment. There was also good agreement (92.1%) between the Altoida DNS classification of unimpaired and MMSE, using a cut-off of >24 as a reference. When comparing DNS classification with standard NPS assessment scores, individuals identified by Altoida as impaired had poorer scores in the FCSRT ($p<0.0001$), TMT-B ($p<0.01$), category fluency (animals), logical memory ($p<0.01$) and in the WAIS-IV visual puzzles ($p<0.01$), matrix reasoning ($p<0.001$) and coding scores ($p<0.001$). Altoida's augmented reality (AR) exercises revealed differences between cognitively unimpaired individuals with underlying amyloid

pathology (Aβ+) and those without (Aβ-). The former (Aβ+) took a longer time to retrieve the virtual objects in the fire drill exercise versus those who were Aβ- ($p<0.01$). There were no differences in object retrieval time in the cued AR exercise. **Conclusion:** The alignment between Altoida's Digital Biomarker Platform, clinical evaluations, and NPS battery supports its convergent validity. Altoida shows potential in distinguishing early cognitive impairment linked to preclinical AD. Further studies are validating these results, and we are also exploring applications in other neurodegenerative conditions. **Disclosures:** MFI, AF, VBR, SF, NG, ES, MC and IT are employees of Altoida, Inc. and may hold stock options in the company. Other co-authors have nothing to disclose. **ClinicalTrials.gov Identifier:** NCT04935372.

P235- RELIABILITY AND VALIDITY OF A TABLET-BASED NEUROPSYCHOLOGICAL TEST (THE HELLOCOG) FOR SCREENING DEMENTIA. H.W. Yang[1], D.H. Seok[2], K.W. Kim[2] *(1. Chungnam national university hospital - Daejeon (Korea, Republic of), 2. Seoul National University - Seoul (Korea, Republic of))*

Objective: To address the gap in timely diagnosis of dementia due to limited screening tools, we investigated the validity and reliability of the Hellocog, computerized neuropsychological test based on tablets for screening dementia. The higher the probability score on the Hellocog, the higher the likelihood of dementia. **Methods:** This study included 100 patients with dementia and 100 individuals with normal cognition who were aged 60 years or older and free of other major psychiatric, neurological, or medical conditions. They administered the Hellocog on a tablet under the supervision of a neuropsychologist. To determine test-retest reliability, 20 took the Hellocog again after four weeks. Diagnostic performance was assessed using the receiver operator characteristics (ROC) analysis. **Results:** The Hellocog showed adequate internal consistency (Cronbach's alpha = 0.69) and good test-retest reliability (ICC = 0.86, $p < 0.001$). Participants with dementia scored higher on the Hellocog than those with normal cognition ($p < 0.001$), confirming its high criterion validity. Strong correlations with the Mini-Mental Status Examination (MMSE) score and the total score of the CERAD Neuropsychological Assessment Battery (CERAD-TS) highlight the concurrent validity of the Hellocog. The area under the ROC curve for dementia of the Hellocog was excellent (0.971) and comparable to that of the MMSE and CERAD-TS. The sensitivity and specificity for dementia were 0.940 and 0.872%, respectively, which were slightly better than those of the MMSE and CERAD-TS. **Conclusion:** Hellocog stands out as a valid and reliable tool for self-administered dementia screening, with promise for improving early detection of dementia.

P236- VIRTUAL REALITY-BASED COGNITIVE TRAINING IMPROVES COGNITIVE FUNCTION IN ALZHEIMER'S DISEASE PATIENTS. H.W. Lee[1], D. Kim[2] *(1. Dep. of Neurology, School of Medicine, Kyungpook National University - Daegu (Korea, Republic of), 2. G-L Co, Ltd - Daegu (Korea, Republic of))*

The computerized cognitive training system could change the cognitive function of patients with Alzheimer's dementia. We newly developed CAVE system device with mixed reality in which the patients performed pre-designed cognitive and daily tasks in a simulated real-life environment within a virtual space. CAVE system has been compared to 2-Dimensional cognitive training system (ComCog, Neofect) in order to compare the effectiveness of mixed reality. Eleven patient patients were recruited. Six AD patients (73.83 ± 6.18 yr) were assigned to the CAVE system, and 5 AD patients (70.4 ± 14.03 yr) were assigned to ComCog system. They received cognitive training through a total of 18 visits for 3months. The cognitive function test and EEG were performed before and at the end of the training. Cognitive functions were evaluated by formal intensive neuropsychological test (SNSB) and psychological status were also evaluated by dependency scale, quality of life scale, Pittsburgh quality of sleep scale and support burden scale. Significant changes were observed only in the group of CAVE system which improved the K-MMSE from 16.5 ± 7.23 to 17.67 ± 7.2, the CDR from 1.25 ± 0.61 to 1.08 ± 0.74, CDR's Sum of boxes from 7.42 ± 4.48 to 7.25 ± 5.87, GDS from 4.83 ± 0.98 to 4.5 ± 1.38, I-ADL score from 1.46 ± 0.94 to 1.44 ± 0.94. Each patient was divided into responder/non-responder by the change of K-MMSE. Responder means a person whose personal score was maintained or improved before and after training. Five out of 6 AD patients in CAVE system were identified as Responder, and only 1 out of 5 AD patients in ComCog system were identified as responder. The EEG results showed the increased Theta Beta2 Ratio only in CAVE system. There were limitations that could not be conducted on many participants, but AD patients trained with CAVE system compared to ComCog system showed the better cognitive function. This may be because the CAVE system is based on realistic physical space within the virtual environment. This study suggests that there is a possibility that the effect of cognitive function training may be observed under the conditions in which real life is implemented as a virtual environment.

P237- THE EFFECTIVENESS OF A VIRTUAL REALITY-BASED COGNITIVE TRAINING PROGRAM FOR MILD COGNITIVE IMPAIRMENT: A PILOT STUDY. E.S. Lee[1], S.K. Lee[1], T.K. Lee[1], S. Na[2], Y.H. Kim[3] *(1. Soonchunhyang University Bucheon Hospital - Bucheon (Korea, Republic of), 2. Department of Neurology, Incheon St. Mary's Hospital, the Catholic University of Korea - Incheon (Korea, Republic of), 3. Tenetus Co. - Seoul (Korea, Republic of))*

Introduction: Background: Numerous studies have explored various forms of cognitive training, with mixed results regarding their effectiveness. Thus, our study focused on the effectiveness of a virtual reality (VR)-based cognitive training program for patients with mild cognitive impairment (MCI). **Methods:** We enrolled 32 patients with MCI diagnosed as per Peterson's criteria in a 12-week VR-training program with 50-minute sessions conducted twice weekly. The patients underwent neuropsychological assessments and questionnaires on depression, anxiety, quality of life, and dizziness severity at the start and end of the program [1]. Caregivers also assessed the patients' daily living activities and neurobehavioral symptoms. Resting state functional MRI scans were acquired at two timepoints: prior to and following the administration of a cognitive training intervention [2-4]. Whole brain analyses were conducted to assess alterations in functional connectivity associated with the cognitive training. **Results:** Of the 28 patients completing the program (87.5% females , mean age 73.21 years), there were significant improvements in the total composite and memory-specific scores of the neuropsychological tests. However, no significant changes were observed in depression, anxiety, dizziness, neuropsychiatric symptoms, and daily living activities. Notably, post-training evaluations showed statistically significant increases in functional connectivity among the bilateral hippocampus, parahippocampal gyrus, and amygdala, regions

critical for memory and emotional processing. **Conclusion:** This pilot study suggests the potential of VR-based cognitive training as a feasible treatment for cognitive impairment, highlighting its impact on brain connectivity in areas affected by MCI and dementia. **Keywords:** cognitive training, virtual reality, mild cognitive impairment. **Disclosure:** This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (HI19C1132), National Research Foundation of Korea (NRF-2022M3E8A1057388) and Soonchunhyang University Research Fund. The authors declared no competing interests. **References:** 1. Chin J, Kim DE, Lee H, Yun J, Lee BH, Park J, et al. A validation study of the Inbrain CST: a tablet computer-based cognitive screening test for elderly people with cognitive impairment. J Korean Med Sci 2020;35:e292. 2. Lee JO, Lee ES, Kim JS, Lee YB, Jeong Y, Choi BS, et al. Altered brain function in persistent postural perceptual dizziness: a study on resting state functional connectivity. Hum Brain Mapp 2018;39:3340-3353. 3. An YY, Lee E-S, Lee SA, Choi JH, Park JM, Lee T-K, et al. Association of hearing loss with anatomical and functional connectivity in patients with mild cognitive impairment. JAMA Otolaryngol Head Neck Surg 2023;149:571-578. 4. Lee E-S, Weon YC, Kim J-S, Lee T-K, Park J-Y. Functional and anatomical alterations in bilateral vestibulopathy: A multimodal neuroimaging study and clinical correlation. Front Neurol 2023;14:1157931.

P238- MEMORY FEATURES OBTAINED THROUGH AUTOMATED PHONE CALLS ASSOCIATE TO THE INTENSITY OF SUBJECTIVE COGNITIVE DECLINE IN COGNITIVELY UNIMPAIRED INDIVIDUALS.

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Background: Automated remote assessments are promising tools for low-burden collection of cognitive outcomes in regionally diverse populations. Although digital literacy (use of touchscreens and internet-connected devices) is increasing, there are still some vulnerable groups in which such technologies cannot be reliably applied. Phone-based cognitive assessments delivered by automatic software systems that provide transcription of speech-based cognitive tests and evaluation of performance could be a feasible alternative to screen individuals at risk of cognitive decline regardless their digital literacy. In the present study, we explored the associations between automatically phone-delivered memory assessments, including memory process scores, and the intensity of Subjective Cognitive Decline (SCD) in a sample of cognitively unimpaired (CU) individuals. **Methods:** We analyzed baseline data from the first 63 participants (mean[SD] age:66.4[6.6];39 women) from the B-AARC cohort included in the PROSPECT-AD study. B-AARC is a prospective research cohort composed of individuals with SCD (CU or Mild Cognitive Impairment [MCI]) that have sought or aim to seek for medical help. Only CU individuals were included in the present analyses. PROSPECT-AD1 is a multi-cohort European longitudinal study aiming to develop algorithms to identify speech biomarkers for Alzheimer's disease (AD). Speech productions during cognitive tasks and free speech is collected via the Mili platform (ki-elements) over the phone. In the present study, the following automated scores obtained from 4 learning trials from the 15-word list Auditory Verbal Learning Test (AVLT) were analyzed: total learning (sum of the words recalled in the first 4 trials), primacy and recency indexes (percent of the first and last 5 words), learning slope and constancy (words in the last trial that have appeared at least once in previous trials). The intensity of SCD was measured in a face-to-face visit with the Cognitive Function Index (CFI) for both the participants (self-CFI) and the study partners (partner-CFI). We ran a set of exploratory linear models using memory outcomes as dependent variables and self- and partner-CFI as predictors. In further analysis we adjusted the models by covariates (age, education, and sex). **Results:** We found that higher partner-CFI scores (beta=-0.91;p=0.027), but not self-CFI (beta=-0.14;p=0.73), were associated to lower AVLT total learning scores. Partner-CFI scores were also marginally associated to recency index (beta=0.68;p=0.088), with individuals with higher partner related complaints being more prone to recall the most recent words from the list. No associations were found for primacy index, learning slope and constancy. In adjusted models, the association between partner-CFI and total learning score mostly disappears (beta=-0.63;p=0.15), but the association with recency index remains unchanged (beta=0.73;p=0.086). **Conclusion:** Automated memory assessments delivered by phone provide several metrics that seem related to the intensity of cognitive complaints in individuals without evidence of objective cognitive impairment. Although preliminary, our results suggest that this approach is feasible and able to capture memory phenotypes related with SCD intensity reported in AD, such as diminished learning and increased reliance on working memory rather than episodic memory. As the study and data collection continues, we will follow up with more advanced analyses on a bigger sample and CSF biomarker characterization. **Keywords:** Subjective Cognitive Decline, digital biomarkers, remote cognitive assessment, episodic memory. **Disclosures:** EM, JT, NL and AK are employees of ki:elements and may hold stock options in the company. Other co-authors have nothing to disclose. **References:** 1. König A, et al. J Prev Alzheimers Dis 2023; 10(2): 314-321. https://doi.org/10.14283/jpad.2023.11.

P239- QUANTIFYING PREDICTION CONFIDENCE IN AI MODELS FOR EEG ANALYSIS. M. Tveter[1,2], T. Tveitstøl[1,2], A. Perez[1,2], C. Hatlestad-Hall[1], H. Renvall[3,4], F. Maestú[5,6,7], C. Marra[8,9], P.M. Rossini[10], I.R.J.H. Haraldsen[1] *(1. Department of Neurology, Oslo University Hospital - Oslo (Norway), 2. Institute of Clinical Medicine, Faculty of Medicine, University of Oslo - Oslo (Norway), 3. Department of Neuroscience and Biomedical Engineering, Aalto University - Helsinki (Finland), 4. BioMag Laboratory, HUS Medical Imaging Centre, Helsinki University Hospital, Helsinki University and Aalto University School of Science - Helsinki (Finland), 5. Centre for Cognitive and Computational Neuroscience, Universidad Complutense de Madrid - Madrid (Spain), 6. Department of Experimental Psychology, Cognitive Psychology and Speech and Language Therapy, Universidad Complutense de Madrid, Pozuelo de Alarcón - Madrid (Spain), 7. Institute of Sanitary Investigation (IdISSC), San Carlos University Hospital - Madrid (Spain), 8. Memory Clinic, Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Rome (Italy), 9. Department of Neuroscience, Catholic University of the Sacred Heart - Rome (Italy), 10. Department of Neuroscience and Neurorehabilitation, IRCCS San Raffaele - Rome (Italy))*

Background: AI-Mind [1] is an EU funded project aiming to develop an artificial intelligence (AI) system for early risk assessment of developing dementia. One of the key data modalities within AI-Mind is electroencephalography (EEG), a method that records the electrical activity in the brain. One of the barriers of a clinical implementation of AI-based systems is often the complex nature of the underlying decision-making processes. The multitude of parameters in these systems complicates the ability to provide clear explanations, prompting ongoing research into methods for achieving explainability and interpretability. One important aspect of implementing these systems is assessing the confidence in the AI models predictions—essentially, determining how trustworthy the predictions are. Quantifying the uncertainty of a prediction or a model can provide valuable feedback alongside the prediction. By providing confidence intervals or uncertainty measures, clinicians can better understand the potential variability in the predictions and make more informed decisions. **Methods:** In this study, we aim to explore methods for quantifying uncertainty in regression problems within EEG data analysis. One of the key methods we will utilize for this purpose is conformal prediction, alongside other uncertainty quantification techniques. Our objective is to predict cognitive scores and other clinically relevant features directly from EEG data, while also providing outputs with confidence intervals that highlight the reliability of the predictions. By focusing on uncertainty quantification, we aim to enhance the trustworthiness and usability of AI models in clinical settings. **Results:** The results of this study are pending. **Conclusion:** Pending. **Keywords:** AI-Mind, Uncertainty, EEG, AI. **Disclosures:** This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 964220. The abstract reflects views of the author and the European Commission is not responsible for any use that may be made of the information it contains. **References:** 1. Haraldsen, I. H. et al. Intelligent digital tools for screening of brain connectivity and dementia risk estimation in people affected by mild cognitive impairment: the AI-Mind clinical study protocol. Front. Neurorobot. 17, 1289406 (2023).

P240- SELF-SUPERVISED LEARNING FOR FEATURE EXTRACTION IN EEG. T. Tveitstøl[1,2], M. Tveter[1,2], C. Hatlestad-Hall[1], C. Marra[3,4], H. Renvall[5,6], F. Maestú[7,8,9], P.M. Rossini[10], I.R.J.H. Haraldsen[1] *(1. Department of Neurology, Oslo University Hospital - Oslo (Norway), 2. Institute of Clinical Medicine, Faculty of Medicine, University of Oslo - Oslo (Norway), 3. Memory Clinic, Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Rome (Italy), 4. Department of Neuroscience, Catholic University of the Sacred Heart - Rome (Italy), 5. Department of Neuroscience and Biomedical Engineering, Aalto University - Helsinki (Finland), 6. BioMag Laboratory, HUS Medical Imaging Centre, Helsinki University Hospital, Helsinki University and Aalto University School of Science - Helsinki (Finland), 7. Centre for Cognitive and Computational Neuroscience, Universidad Complutense de Madrid - Madrid (Spain), 8. Department of Experimental Psychology, Cognitive Psychology and Speech and Language Therapy, Universidad Complutense de Madrid, Pozuelo de Alarcón - Madrid (Spain), 9. Institute of Sanitary Investigation (IdISSC), San Carlos University Hospital - Madrid (Spain), 10. Department of Neuroscience and Neurorehabilitation, IRCCS San Raffaele - Rome (Italy))*

Background: AI-Mind [1] aims to develop artificial intelligence (AI) based tools for early-stage dementia risk assessment. One of the modalities used for building these tools is electroencephalography (EEG), which reflects the electrical activity of the brain. For AI-technical research and development, both deep learning and machine learning on hand-crafted features are of interest. While the former can learn complex patterns beyond what is feasible to extract manually, the latter typically offers more explainability and neurophysiological insights. Self-supervised learning is a deep learning based technique that leverages tasks constructed from the data itself, to learn inherent structures and patterns without the need for targets provided by humans. A prerequisite is to define a pretext task for which the model can learn from, to obtain valuable data representations. **Methods:** In this study, self-supervised learning pretext tasks will be developed and tested. The pretext tasks will be aimed at extracting cognitively relevant features by tailored designs. The extracted features will be tested for their clinical relevance using data from AI-Mind. **Results:** The results for this study are not currently available. **Conclusion:** As the results are not yet available, no conclusions can be made. **Keywords:** Self-supervised learning, cognitive health, artificial intelligence, deep learning, AI-Mind. **Disclosures:**This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 964220. The abstract reflects views of author and the European Commission is not responsible for any use that may be made of the information it contains. **References:** 1. Haraldsen, I. H. et al. Intelligent digital tools for screening of brain connectivity and dementia risk estimation in people affected by mild cognitive impairment: the AI-Mind clinical study protocol. Front. Neurorobot. 17, 1289406 (2023).

P241- ALL-CAUSE MORTALITY IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT OR ALZHEIMER'S DEMENTIA WHO EXPERIENCED INTRACEREBRAL HEMORRHAGE.

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Background: This study evaluates rates of all-cause mortality in patients aged ≥65 years with mild cognitive impairment (MCI) or Alzheimer's dementia (AD) who experienced intracerebral hemorrhage (ICH) in the United States (US) Veterans Affairs Healthcare System (VAHS) and Medicare databases. **Methods:** Veterans with MCI or AD were identified based on clinical notes or diagnostic codes in the VAHS and Medicare databases (2016–2021). ICH incidence defined by inpatient principal ICD-10 codes was categorized based on postulated underlying pathology: (1) cerebral amyloid angiopathy related ICH (CAA-ICH) I61.0, I61.1, I61.6, I60.8, I60.9; (2) hypertension related ICH (HTN-ICH), I61.3, I61.4; and (3) non-specific ICH, I61.2, I61.5, I61.8, I61.9. Poisson regression was used to estimate relative mortality rates and proportional hazards regression was used to adjust for time dependence of ICH. **Results:** A total of 278,788 Veterans with MCI or AD were identified from the VAHS; an additional 245,137 Veterans with MCI/AD were identified from the Medicare database. Veterans (N=523,925) were identified having MCI (60%) or AD (40%) with a mean (SD) age of 79.4 (8.4) years, 97.5% male, 10.5% Black, and 76.7% White, and 4.5% Hispanic vs non-Hispanic. All-cause mortality rates per 1000 person-years were distributed as follows: 133 for MCI vs 294 for AD. Combining MCI and AD, mortality rates were 191 for male vs 141 for female; 94 for Black vs 126 for White race; and 137 for Hispanic vs 188 for non-Hispanic ethnicity. In the MCI/AD cohort, mortality rates were 289 for patients with CAA-ICH, 256 for HTN-ICH, and 314 for non-specific ICH, compared to 189 for those without ICH. The median survival from initial MCI/AD ascertainment was 2.50, 2.56, 2.32 years for the CAA-ICH, HTN-ICH, and non-specific ICH groups, respectively. Adjusted mortality was lower with MCI vs AD (incidence rate ratio [IRR] 0.56; P<0.01). ICH events did not significantly alter the mortality rates associated with MCI and AD (P>0.07). Mortality risk was 154% higher with CAA-ICH events (IRR=2.54, CI: 2.36 – 2.73), 128% higher with HTN-ICH (IRR=2.28, CI: 1.89–2.72), and 159% higher with non-specific ICH (IRR=2.59, CI: 2.42–2.77) (all P<0.01), compared to those without ICH. Combined ICH events more than tripled the risk of mortality after accounting for time-dependence of ICH (hazard ratio 3.4, P<0.01). History of ICH increased mortality risk by 26%, even after adjusting for time-dependent ICH (P<0.01). Baseline CAA was not associated with increased mortality risk (P=0.23) after adjustment for time-dependent ICH. CAA-ICH, compared to HTN-ICH, was associated with a significantly increased mortality risk (Δ of βs=0.24, P=0.02). **Conclusion:** All-cause mortality was higher with AD vs MCI among US Veterans from the VAHS and Medicare databases. ICH events defined by inpatient primary ICD-10 diagnoses tripled mortality risk after adjusting for time-dependence of ICH, but did not alter the relative risk of mortality between MCI and AD. CAA-ICH was associated with increased mortality relative to HTN-ICH. Overall, this study demonstrated validity of ICD-10-based ICH classification in real-world databases that meaningfully captured and differentiated mortality outcomes associated with CAA-ICH as opposed to hypertension-related ICH.

P241BIS- ALL-CAUSE MORTALITY IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT OR ALZHEIMER'S DEMENTIA WHO EXPERIENCED SEIZURE.

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Background: Alzheimer's disease is associated with increased mortality and increased risk of seizure. This study investigated whether seizure would increase all-cause mortality risk in Alzheimer's disease within the United States (US) Veterans Affairs Healthcare System (VAHS) and Medicare databases. **Methods:** Veterans with mild cognitive impairment (MCI) or Alzheimer's dementia (AD) aged ≥65 years were identified based on clinical notes or diagnostic codes in the VAHS and Medicare databases (2016–2021). Seizure was identified using ICD-10 codes R56.x and G40 (excluding G40.5). Baseline was defined as 2 years prior to the first AD/MCI diagnosis. We adjusted for baseline comorbidities as well as seizure risk factors including stroke, prior seizure, CNS infection, and traumatic brain injury. Poisson regression was used to analyze seizure and proportional hazards regression was used to adjust for time dependence of seizure. R was used for all analyses. **Results:** A total of 278,788 Veterans with MCI or AD were identified from the VAHS; an additional 245,137 Veterans with MCI/AD were identified from the Medicare database. Veterans (N=523,925) were identified having MCI (60%) or AD (40%) with a mean (SD) age of 79.4 (8.4) years, 97.5% male, 10.5% Black, and 76.7% White, and 4.5% Hispanic vs non-Hispanic. All-cause mortality rates per 1000 person-years were distributed as follows: 133 for MCI vs 294 for AD. Combining MCI and AD, mortality rates were 191 for male vs 141 for female; 94 for Black vs 126 for White race; and 137 for Hispanic vs 188 for non-Hispanic ethnicity. In the MCI/AD cohort, mortality rates were 193 for patients with seizure, 189 for patients without seizure. Adjusted mortality was lower with MCI vs AD (incidence rate ratio [IRR]=0.55; P<0.01) and higher with seizure vs non-seizure (IRR=1.04; P<0.01). Mortality risk was 25% higher in patients with seizure at baseline (IRR=1.25; P<0.01). After accounting for time-dependence of seizure, mortality was 82% higher for seizure vs non-seizure (hazard ratio [HR]=1.82; P<0.01). Compared to patients with AD without seizure, mortality risk was highest among patients with AD with seizure (HR 1.65); whereas, patients with MCI without seizure had the lowest mortality risk (HR 0.55); mortality risk among patients with MCI with seizure was slightly elevated (HR 1.12) (interaction term HR=1.24, P<0.01). **Conclusion:** This retrospective study combining VA and Medicare databases found that mortality risk among patients aged ≥65 years was increased with AD relative to MCI and was the highest in patients who had AD with seizure. Seizure appeared to have a stronger mortality impact on patients with MCI than on those with AD. Future research is needed to further explore the hypothesis that the mortality impact of seizure may be

more pronounced in MCI as opposed to dementia stages of Alzheimer's disease.

P242- SCREENING FOR DEMENTIA USING ACOUSTIC FEATURE AND MACHINE LEARNING OF FREE CONVERSATION. T. Horigome[1], K.C. Liang[1], T. Kishimoto[1] *(1. Keio University School of Medicine - Tokyo (Japan))*

Background: There is a need for simple screening techniques for Mild Cognitive Impairment (MCI). Previous studies have shown that machine learning algorithms can classify dementia and MCI based on acoustic features of speech during tasks such as reading aloud or picture description. However, screening for cognitive decline through free conversation without any specific task would be more convenient. **Methods:** Free conversations lasting approximately 10 minutes were recorded from dementia patients attending a specialized outpatient clinic and healthy volunteers. The recorded audio data was segmented into 2-second intervals, and acoustic features were extracted as 1024-dimensional vectors using YAMNet. A CNN-LSTM model was used to distinguish segments from patients with dementia or MCI from those of cognitively healthy older adults. The overall label for the entire recording was determined through Majority Voting. **Results:** A model trained on a total of 623 datasets (n=224) achieved a classification accuracy of 0.95, with a sensitivity of 0.98 and specificity of 0.85. The study confirmed that even 20-second voice samples are sufficient for effective screening. **Discussion:** This study demonstrates that machine learning algorithms can be developed to identify cognitive decline from the acoustic features of free conversation, showing potential for screening dementia and MCI. However, further validation is needed to address issues such as the potential for overfitting, dependence on microphone performance and recording environment, as well as the influence of language and dialect. **Keywords:** digital biomarker, free conversation, acoustic feature, machine learning. **Clinical Trial Registry:** UMIN000023764; https://rctportal.niph.go.jp/en/detail?trial_id=UMIN000023764, UMIN000032141; https://rctportal.niph.go.jp/en/detail?trial_id=UMIN000032141. **Disclosures:** The authors declared no competing interests.

P243- THE HOGAR STUDY: HOME-BASED BRAIN MONITORING WITH A SELF-MANAGED EEG TO STUDY COGNITIVE DECLINE IN THE AGEING POPULATION. E. López-Larraz[1], A. Robledo-Menéndez[1], E. Jubera Garcia[1], A. López-López[1], P. Simón-Lobera[1], O. Gelonch[2], J. De Francisco Moure[3,4], J.M. Marín[3,5], N. Molina-Torres[3,6], R. Osta[3,7], E. Lobo[3,8], A. Lobo[3,9], P.J. Modrego[3,10], R. Magallón-Botaya[3,11], J. Minguez[1] *(1. Bitbrain - Zaragoza (Spain), 2. Clinical Research Group for Brain, Cognition and Behavior, Hospital de Terrassa - Terrassa (Spain), 3. Instituto de Investigación Sanitaria de Aragón - Zaragoza (Spain), 4. Servicio de neurofisiología Clínica, Hospital Universitario Miguel Servet - Zaragoza (Spain), 5. Servicio de neumología, Hospital Universitario Miguel Servet - Zaragoza (Spain), 6. Servicio de geriatría, Hospital Nuestra Señora de Gracia - Zaragoza (Spain), 7. Department of Anatomy, Embryology and Animal Genetics, University of Zaragoza - Zaragoza (Spain), 8. Department of Preventive Medicine and Public Health, Universidad de Zaragoza - Zaragoza (Spain), 9. Department of Medicine and Psychiatry, Universidad de Zaragoza - Zaragoza (Spain), 10. Servicio de neurología, Hospital Universitario Miguel Servet - Zaragoza (Spain), 11. Department of Medicine, Psychiatry and Dermatology, Faculty of Medicine, University of Zaragoza - Zaragoza (Spain))*

Background: In the context of an aging society, there is a need for the development of accessible and automated tools to facilitate the evaluation and detection of cognitive decline. Wearable, self-managed electroencephalography (EEG) devices offer a promising solution to measure electrophysiological activity during wakefulness and sleep [1]. These devices favor ease of use and comfort and can facilitate the acquisition of large volumes of data in home settings. Combined with advanced artificial intelligence techniques, they might detect subtle EEG patterns that are not easily identified with classical approaches. A home-based EEG monitoring tool, requiring no technical expertise, could translate these measurements into objective metrics of cognitive status, assisting primary care and specialists in early diagnosis, treatment monitoring, and potentially linking cognitive decline with physiological EEG and sleep biomarkers [2, 3]. **Methods:** The HOGAR study proposes to collect data from 500 elderly participants (>60 years) at different stages of the cognitive decline continuum, including: (1) cognitively healthy, (2) subjective cognitive decline, (3) mild cognitive impairment, and (4) mild dementia. All participants undergo exhaustive neuropsychological characterization in the laboratory, including cognitive and behavioral evaluations, and a high-density 32-channel EEG. They also use a novel self-managed EEG at home for two consecutive days, utilizing two headbands designed to monitor their EEG patterns during wakefulness (4-minute recordings with eyes open and eyes closed) and during sleep. Firstly, we will evaluate the ability of the studied population to successfully complete the self-administered EEG recordings at home. With the recorded cohort, we will study the relationship between the recorded EEG patterns and the cognitive and behavioral variables. Furthermore, we will evaluate the discriminative potential of the EEG activity recorded in laboratory and/or at home to identify participants at the four cognitive stages included in the study. **Results:** As of May 2024, 64 individuals have completed their participation in the HOGAR study. All participants have completed the neuropsychological evaluations and utilized the technology at home. In terms of usability, the participants have successfully completed the self-managed EEG wake recordings on 90.6% of occasions and the night sleep recordings on 78.1% of occasions, which is a good indicator of the feasibility of the technology for home use. **Conclusion:** To the best of our knowledge, this is the first investigation aimed at monitoring EEG activity of elderly individuals at home in a completely self-administered manner. Participants in the cognitive decline continuum are being able to use the technology, with the help of one family member and without technical assistance, to perform an EEG test during wakefulness and sleep (up to now >90% in EEG test and >75% in Sleep-EEG test). We expect that this study will provide valuable information on how EEG measurements at home can be used to measure and monitor the progress of cognitive decline. **Keywords:** cognitive decline, home monitoring, wearable electroencephalography. **Clinical Trial Registry:** C.I. PI23/373, Comité de Ética de la Investigación de la Comunidad Autónoma de Aragón (CEICA). **Data Deposition:** In progress. **Disclosures:** ELL, ARM, EJG, PS, AL and JM are employed by the company Bitbrain. **References:** 1. López-Larraz, E., Escolano, C., Robledo-Menéndez, A., Morlas, L., Alda, A., and Minguez, J. (2023). A garment that measures brain activity: proof of concept of an EEG sensor layer fully implemented with smart textiles. Front. Hum. Neurosci. 17, 1135153. doi: 10.3389/fnhum.2023.1135153. 2. Perez-Valero E, Morillas C, Lopez-Gordo MA, Carrera-Muñoz I, López-Alcalde S, Vílchez-Carrillo RM. An Automated Approach for the Detection of Alzheimer's Disease From Resting State Electroencephalography. Front Neuroinform. 2022 Jul 11;16:924547. doi: 10.3389/fninf.2022.924547. PMID: 35898959;

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P244- SEIZURE IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT OR ALZHEIMER'S DEMENTIA WHO EXPERIENCED INTRACEREBRAL HEMORRHAGE.
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Background: Alzheimer's disease is associated an increased risk for seizure. We investigated whether intracerebral hemorrhage (ICH) would further increase seizure risk in patients with Alzheimer's disease, hypothesizing that cerebral amyloid angiopathy-related ICH (CAA-ICH), being a cortical-based lesion, would be more likely to provoke seizures. **Methods:** Veterans with mild cognitive impairment (MCI) or Alzheimer's dementia (AD) aged ≥65 years were identified using clinical notes or diagnostic codes in the United States Veterans Affairs Healthcare System (VAHS) and Medicare databases (2016–2021). ICH incidence defined by inpatient principal ICD-10 codes was categorized by postulated underlying pathology: (1) CAA-ICH, I61.0, I61.1, I61.6, I60.8, I60.9; (2) hypertension-related ICH (HTN-ICH), I61.3, I61.4; and (3) non-specific ICH, I61.2, I61.5, I61.8, I61.9. Each ICH type was compared to the remaining patient sample. Seizure was identified using codes R56.x and G40 (excluding G40.5). Baseline was defined as 2 years prior to the first AD/MCI diagnosis, excluding patients with seizure-related visits at baseline or seizure preceding ICH. Poisson regression was used to analyze seizure and proportional hazards regression adjusted for time dependence of ICH. R was used for all analyses. **Results:** A total of 265,885 Veterans with MCI or AD were identified from the VAHS; additionally, 228,346 Veterans with MCI/AD were identified from the Medicare database. Veterans (N=494,231) were identified having MCI (60%) or AD (40%) with a mean (SD) age of 79.5 (8.4) years, 97.5% male, 10.3% Black, and 77% White, and 4.5% Hispanic vs non-Hispanic. Seizure rates were 4.8% and 5.7% in the MCI and AD populations, respectively. A total of 2381 patients had ICH after MCI/AD diagnosis; among these, 363 patients with seizure preceding ICH were excluded, since prior seizure is an independent risk factor for future/recurrent seizure. In the MCI/AD cohort, crude seizure rates per 1000 person-years were 31.5 for CAA-ICH, 16.9 for HTN-ICH, and 25.2 for non-specific ICH; the total rate for any ICH was 25.9 vs 16.6 without ICH. The adjusted seizure rate was lower with MCI vs AD (incidence rate ratio [IRR]=0.82; P<0.01). CAA-ICH was associated with a 57% higher risk of seizure and non-specific ICH was associated with 25% higher risk (both P<0.01). Seizure risk was not different in HTN-ICH vs no ICH. CAA-ICH trended to have a stronger association with higher seizure risk relative to HTN-ICH (P=0.05). Baseline ICH almost doubled seizure risk (IRR=1.96; P<0.01). Seizure risk was 11% and 15% higher with substance use disorder and traumatic brain injury, respectively (P<0.01). Malignant brain tumor more than tripled seizure risk (IRR=3.52; P<0.01). Seizure risk was 50% higher in Black/African American than White patients, and 24% higher in Hispanic than non-Hispanic patients (both P<0.01). After accounting for the time-dependence of ICH, the risk of seizure was 204%, 99%, and 165% higher for CAA-ICH (P<0.01), HTN-ICH (P=0.03), and non-specific ICH (P<0.01). **Conclusion:** This study found that ICH was associated with an increased risk of seizure among patients with MCI/AD, especially ICH related to CAA. Black/African American and Hispanic patients were at a higher risk of seizure after ICH. **Keywords:** intracerebral hemorrhage, seizure, cerebral amyloid angiopathy, hypertension. **Clinical Trial Registry:** Not applicable. **Disclosures:** RZ, ATM, MI and QZ are employees of Eisai, Inc.

P245- BIG DATA FROM SMART ECOSYSTEMS TARGETING COGNITIVE IMPAIRMENT.
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Background: Dementia has an estimated annual cost of ~US$ 23,800/person, largest share being social costs (long term care included) and informal care [1]. Recent technological advances, particularly in wearables, may shape future evidence-based medicine, despite currently not being part of routine care [2]. Digital solutions may hold the key [3] for handling the challenges of healthcare systems overburdened by increased life expectancy and decreased workforce [4]; SMART BEAR will contribute to designing an assistive, personalized tool (cloud-based server paired with mobile app interconnecting wearables), expected to ensure better outcomes for patients with mild cognitive impairment (MCI) and other conditions. **Methods:** Part of a multicentric design (5 pilots in 5 EU countries), the Romanian Pilot follows the framework piloting protocol, adapted locally. Eligible participants (aged 65-80 years, with 2 or more of predetermined list of comorbidities, including MCI) are assessed (including specific structured questionnaires) at baseline and followed up at 6 and 12 months. Primary endpoint investigates device acceptance (successful completion of monitoring) while secondary endpoints investigate cognition (cognitive and functional tests), sleep quality, lifestyle and environmental factors. Statistical and machine learning techniques are deployed to handle huge amounts of raw data measurements (FAIR compliant). Ethical approval was issued locally for the Pilot, based on a consortium-wide framework safeguarding ethical and regulatory rights of participants. **Expected Results:** Significant correlations are explored between compliance to standard interventions as measured by the mobile app (i.e. serious games, physical activity, social interactions), individual evolution of

cognitive status (as compared to baseline), as well as with various other lifestyle and smart home sensing parameters and sleep quality. **Conclusion:** SMART BEAR intends to integrate and inter-connect state—of-the-art, commercially available smart technologies and wearables in creating a smart home ecosystem capable of (1) assisting older age adults to healthily age in place, and (2) integrating the generated data into existing e-health records for better evidence-based clinical decisions, while (3) exploring machine learning capabilities for assisting medical decisions and predicting individual evolution. **Keywords:** Ageing in place, big data, Alzheimer prevention, smart ecosystems. **Disclosures:** SMART BEAR was funded from the European Union's Horizon 2020 research and innovation programme (Grant Agreement No. 857172). **Acknowledgements:** Authors would like to express their gratitude to all SMART BEAR consortium partners for an outstanding team work and collaboration. **References:** 1. Wimo A, Seeher K, Cataldi R, Cyhlarova E, Dielemann JL, Frisell O, et al. The worldwide costs of dementia in 2019. Alzheimers Dement. 2023;19(7):2865-73. https://doi.org/10.1002/alz.12901; 2. Subbiah V. The next generation of evidence-based medicine. Nature Medicine. 2023;29(1):49-58. https://doi.org/10.1038/s41591-022-02160-z; 3. Chen C, Ding S, Wang J. Digital health for aging populations. Nature Medicine. 2023;29(7):1623-30. https://doi.org/10.1038/s41591-023-02391-8; 4. Boniol M, Kunjumen T, Nair TS, Siyam A, Campbell J, Diallo K. The global health workforce stock and distribution in 2020 and 2030: a threat to equity and 'universal' health coverage? BMJ Glob Health. 2022;7(6). https://doi.org/10.1136/bmjgh-2022-009316.

P246- MRI IMAGING BIOMARKER PREDICTION USING ALZHEIMER'S DISEASE CHARACTERISTIC ACOUSTIC SPEECH FEATURES. S. Chung[1], H. Ham[2], M. Bae[2], H. Kim[2], K.Y. Kim[2], J.Y. Lee[1,2] *(1. Seoul National University College of Medicine - Seoul (Korea, Republic of), 2. SMG-SNU Boramae Medical Center, Department of Psychiatry - Seoul (Korea, Republic of))*

Background: Early diagnosis and treatment are crucial for managing Alzheimer's disease (AD), a progressive neurodegenerative disorder that causes dementia. Several biomarkers are important in detecting AD, such as hippocampal atrophy in MRI, and beta-amyloid and phosphorylated protein tau accumulation. Speech features of AD are considered easily extracted, cost-effective novel biomarkers. Acoustically, AD patients' speech often exhibits monotonous prosody (decreased variability in pitch, loudness, rhythm, etc.), voice quality changes (unstable voice, hoarseness, etc.), slower speech rate, and longer pauses [1]. While multiple studies have identified speech features' performance as diagnostic markers of AD and their relationship with CSF fluid biomarkers and cognitive domain performances [2, 3], the relationship with MRI imaging markers remains underexplored. We hypothesized that acoustic speech features would correlate with traditional MRI markers (hippocampus and amygdala volume) and with the atrophy of speech-producing brain regions (superior temporal gyrus and supplementary motor area). **Methods:** A total of 47 adults aged 65 to 85 were enrolled in the experiments. 22 patients with subjective memory impairment were recruited from the SMG-SNU Boramae Medical Center, and 25 healthy older adults from the local community. All participants were native Korean speakers. Each participant performed a spontaneous speech task (Trip to Jeju task) for speech data collection, and 9 acoustic speech features were extracted using the eGeMAPS feature set: pitch standard deviation and range, loudness standard deviation and range, jitter, shimmer, HNR, speech rate, and pause length. MRI scans of all participants were performed without contrast, then preprocessed and segmented using SPM12 software. Regional volumes were extracted using the Automated Anatomical Labeling Atlas 3. Partial correlation analysis was conducted between selected acoustic speech features and regional brain volume. Voxel-based morphometry (VBM) based multiple regression analysis was also performed to identify which MRI brain regions correlate with acoustic speech features. Several machine learning models were trained for the prediction of regional volume with pitch and demographic features, using a leave-one-out cross-validation method with bootstrapping. **Results:** The volume of the hippocampus and superior temporal gyrus had significant correlations with both the standard deviation and range of pitch. VBM analysis revealed significant correlations ($p<0.001$) of the right superior temporal cortex and hippocampus with several speech features, including pitch range. The ElasticNet predictor explained 15.7% and 28.1% of the variance in hippocampal and superior temporal gyrus volume, respectively. **Conclusion:** The goal of this research is to identify the relationship between AD characteristic acoustic speech features and the underlying neuroanatomical pathology of AD. Our results suggest that the acoustic properties of AD may result from specific brain region changes, thereby supporting speech as a novel biomarker of AD with a theoretical basis. Furthermore, we present a theoretical perspective on AD diagnosis through speech characteristics. **Keywords:** Alzheimer's disease, Speech features, MRI, Voxel-based morphometry. **Disclosures:** This research was funded by the Ministry of Education through the National Research Foundation of Korea (NRF), grant number (NRF-2021R1A2C2095809). **References:** 1. Mueller KD, et al. J Clin Exp Neuropsychol 2018; 40 (9): 917–939. https://doi.org/10.1080/13803395.2018.1446513; 2. García-Gutiérrez et al. Alzheimer's Research & Therapy 2024; 16 (1). https://doi.org/10.1186/s13195-024-01394-y. 3. Hajjar et al. Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring 2023; 15 (1). https://doi.org/10.1002/dad2.12393.

P248- ANALYSIS OF CONNECTIVITY IN AI-MIND DATA USING GRAPH NEURAL NETWORKS. M. Radwan[1], P.G. Lind[1], R. Khadka[1], A. Belhadi[1], I. Haraldsen[2], P. Rossini[3], C. Marra[4], F. Maestu[5], H. Renvall[6], E. Christensen[7], A. Yazidi[1] *(1. Oslo Metropolitan University - Oslo (Norway), 2. Oslo University Hospital - Oslo (Norway), 3. Università Cattolica del Sacro Cuore - Milan (Italy), 4. IRCCS San Raffaele Pisana - Rome (Italy), 5. Universidad Politécnica de Madrid - Madrid (Spain), 6. Helsinki University Hospital - Helsinki (Finland), 7. Pre Diagnostics AS - Oslo (Norway))*

Background: Prediction and understanding the pathology of Dementia is a challenging task and has gained much attention in the past years. In this study, We aim to build an artificial intelligence tool for analysis of AI-Mind data. The AI-Mind data has rich and intensive content with various modalities. We are currently interested in the Electroencephalogram (EEG) data in this study to study functional connectivity. Our contribution is the utilization and study of the frequency band connectivities and features of the EEG data in addition to studying the advanced brain function and how to interpret that in the downstream prediction such as pTau markers prediction. This study aims to integrate findings from neuroscience research into the EEG Graph based models which may promise both performance and explainability gains. **Methods:** In this study, we resort to Graph Neural Networks (GNN) to predict the presence of APOE2, APOE3, APOE4 genes. Additionally,

we will investigate the viability of predicting pTau217 and pTau181. This is complemented by using the explanation of GNN to identify the discriminative features that lead to the decision or prediction of the model. There is growing evidence in the literature concerning the advanced brain functions (e.g. cognitive functions, memory) in studying the frequency content of EEG data. In this study, the frequency information, brain regions and connectivity features of EEG signals are integrated into the model training and the important frequency bands, brain regions and connectivities are being highlighted for the predictions of the models. **Results:** The results from this study is not available yet but the proposed framework has been used on open source datasets. The results are presented at 21th IEEE International Symposium on Biomedical Imaging. **Conclusion:** The results are expected to highlight important features and markers for predictions of the models in a more exhaustive way than traditional data analysis approaches. **Keywords:** Deep Learning, Connectivity, Graph. **Disclosures:** This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 964220. The abstract reflects views of authors and the European Commission is not responsible for any use that may be made of the information it contains. **References:** Haraldsen, Ira. et al. Intelligent digital tools for screening of brain connectivity and dementia risk estimation in people affected by mild cognitive impairment: the AI-Mind clinical study protocol. Front. Neurorobot. 17, 1289406 (2023).

P249- EEG-JEPA: SELF-SUPERVISED LEARNING FROM EEG SIGNALS WITH A JOINT-EMBEDDING PREDICTIVE ARCHITECTURE. R. Khadka[1], P.G. Lind[1,2], C. Hatlestad-Hall[3], M. Radwan[1], A. Belhadi[1], G. Mello[1], M.A. Riegler[1,4], E. Christensen[5], H. Renwall[6,7], F. Maestú[8,9], C. Marra[10,11], P.M. Rossini[12], I.H. Haraldsen[3], A. Yazidi[1] *(1. Oslo Metropolitean University - Oslo (Norway), 2. Simula - Oslo (Norway), 3. University of Oslo - Oslo (Norway), 4. Simulamet - Oslo (Norway), 5. Pre Diagnostics AS - Oslo (Norway), 6. Aalto University, Helsinki, Finland - Helsinki (Finland), 7. Helsinki University Hospital - Helsinki (Finland), 8. Universidad Complutense de Madrid - Madrid (Spain), 9. San Carlos University Hospital, - Madrid (Spain), 10. Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Rome (Italy), 11. Catholic University of the Sacred Heart - Rome (Italy), 12. Department of Neuroscience and Neurorehabilitation, IRCCS San Raffaele - Rome (Italy))*

Background: Alzheimer's disease (AD) is the most common form of dementia that poses a significant global health challenge. Developing technology for widely available dementia risk evaluation at the stage of mild cognitive impairment (MCI) is crucial [1]. Among the promising biomarkers for early detection of AD, and later disease progression monitoring, is the concentration of phosphorylated tau protein (p-tau) in blood plasma. However, recent work outlines that functional brain alterations may precede the elevation of p-tau in blood plasma. Electroencephalography (EEG) is a cost-effective technology that shows promise in characterizing such changes in pre-clinical stages of AD development. Here, we present the preliminary results of our work developing a self-supervised model for predicting p-tau levels in blood plasma from EEG data. We hypothesize that this model can shed important light on the link between electrophysiological alterations in the brain and tauopathy in MCI. **Method:** In this study, we propose a novel approach leveraging a joint embedding predictive architecture (JEPA) for self-supervised learning to analyze EEG signals from individuals with MCI. In terms of models, we train a ViT model termed BSVT. Our methodology leverages the spatial and temporal dynamics of EEG signals to extract meaningful representations from EEG data, enhancing the model's ability to classify signals based on p-tau levels. The data used in this study came from 319 subjects, a subset of participants enrolled in the AI-Mind study. p-tau estimates were acquired from p-tau217 measures. **Results:** The proposed BSVT model shows a classification accuracy of 81.6% in distinguishing between abnormal and normal EEG signals when trained on the publicly available Temple University Hospital (TUH) abnormal dataset. This pre-trained model provides a significant advantage in analyzing the association of EEG signals and p-tau levels. **Conclusion:** Our developed model demonstrates significant relationships between electrophysiological features of the brain and the concentration of phosphorylated tau protein in blood plasme. The presented predictive architecture and self-supervised approach show great promise for developing highly sensitive and cost-effective screening tools for AD risk in MCI. **Disclosures:** This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 964220. The abstract reflects the views of the author and the European Commission is not responsible for any use that may be made of the information it contains. **References:** Haraldsen, I. H. et al. Intelligent digital tools for screening of brain connectivity and dementia risk estimation in people affected by mild cognitive impairment: the AI-Mind clinical study protocol. Front. Neurorobot. 17, 1289406 (2023).

LP104- IDENTIFICATION, ENRICHMENT, AND LONGITUDINAL TRACKING OF ALZHEIMER'S DISEASE PATIENTS VIA THE SITERX CNS DISEASE REGISTRY. S. Mahesh[1], D. Gautieri[1] *(1. SiteRx - New York (United States))*

Background: The understanding of Alzheimer's disease (AD) and its etiology has steadily evolved, with ongoing research focused on its mechanisms and the development of disease-modifying therapies. However, long-term disease control remains a challenge. While a better understanding of long-term outcomes is essential to advancing research and care, the absence of effective drugs and patient recruitment challenges have hindered efforts. The SiteRx CNS Diseases Registry (The Registry) fills this gap by integrating Electronic Health Records (EHRs) with genetic and biomarker data, providing a comprehensive, real-world dataset that enables more precise patient identification and longitudinal tracking of health outcomes across diverse AD populations. **Objective:** The development of registries enhances the identification and enrichment of Alzheimer's Disease-Related Disorders (ADRD) patients for next-generation monoclonal antibody (mAb) therapies and beyond. By combining EHRs with genetic and biomarker data, The Registry refines patient selection for treatment and tracks real-world outcomes. This approach provides insights into treatment efficacy, safety, and disease progression, advancing personalized, data-driven care strategies. **Methods:** The Registry collects data from over 4,000 providers and 9 million patients within SiteRx's Real-World De-identified Database. It integrates EHRs, biomarker test results, and genetic data, including APOE status, to provide a comprehensive characterization of disease and patient health. As the largest biomarker-based ADRD patient population in the U.S., The Registry enables the tracking of health outcomes, cognitive function, behavioral symptoms, and quality of life across a diverse AD population. By longitudinally tracking clinical outcomes in sub-populations, The Registry provides

unparalleled precision in identifying ADRD patients and tracking outcomes for next-generation mAb therapies. **Results:** The Registry provides insights into the precision identification and enrichment of ADRD patients best fit for next-generation mAb therapies by integrating clinical data from EHR systems with genetic and biomarker information. This supports better patient selection for advanced therapies and deepens insights into treatment responses of subpopulations. The Registry's longitudinal tracking provides a clearer understanding of treatment efficacy, particularly in sub-populations defined by molecular markers and demographic characteristics. The inclusion of blood-based biomarkers and genetic testing enables more accurate staging of AD patients, to form treatment cohorts. The diverse population of The Registry generates critical RWD, revealing variability in treatment responses and highlighting the importance of tailored precision medicine approaches. **Conclusion:** The Registry demonstrates the importance of real-world, longitudinal data in shaping the future of Alzheimer's treatment. As personalized therapies for ADRD evolve, insights from this registry highlight the need for more targeted approaches. There is a pressing need for physicians and researchers to be smarter about identifying the right types of patients for clinical trials and treatments. Patient-specific factors significantly impact treatment outcomes, and current data suggests that the variability in treatment responses is not random. As the industry moves forward, leveraging real-time, patient-specific data will be crucial in optimizing the efficacy of Alzheimer's therapies and reducing the variability in outcomes. By enabling data-driven decisions, the SiteRx CNS Disease Registry advances the industry toward more effective and personalized Alzheimer's care. **Keywords:** Alzheimer's Disease, precision medicine, real-world data, monoclonal antibodies, patient enrichment.

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LP105- CAN AN AI VOICE AGENT (GROVE AI) SUCCESSFULLY RECRUIT PARTICIPANTS INTO ALZHEIMER'S CLINICAL TRIALS? S. Cassidy[1], K. Lovelace[1], T. Le[2], S. Gatiganti[2], A. Riley[2], S. Torres[1], P. Truong[3], M. Isaac[1], G. Cedano[1], M. Montone[1], B. Lenox[1], N. Torres[1], D. Moya[1], S. Sean[1] *(1. K2 Medical Research - Orlando (United States), 2. Grove AI - San Fransico (United States), 3. Vision Cycles - Boston (United States))*

Introduction: Recruiting patients over the age of 50 for clinical trials is particularly challenging, despite the growing need to include this population in medical research. Age-related factors such as comorbidities, accessibility, and a general lack of awareness about trial opportunities often slow down recruitment efforts. These delays can significantly hinder the speed at which clinical trials are completed, with many failing to meet recruitment goals on time (Smith et al., 2021). However, advancements in artificial intelligence (AI) offer promising solutions to this problem. By using AI-driven tools to identify eligible participants more efficiently and personalize outreach strategies, recruitment can be accelerated, potentially reducing trial delays and improving participant diversity (Johnson & Lee, 2022). Leveraging AI in this context could lead to faster, more inclusive, and more successful clinical trials, particularly among older adults. **Methods:** This study utilized an AI-driven recruitment strategy (Grove AI) to identify and engage potential participants for a clinical trial. This is an AI voice agent that uses agentic workflow to autonomously guide participants through screening and scheduling, adapting in real-time to optimize engagement and conversion rates. The design was aimed at enhancing recruitment efficiency and streamlining the process of inviting patients to discuss trial participation with an emphasis on building a brain health profile looking at risk factors for Alzheimer's Disease. The initial approach targeted 1,400 patients aged 55 and older who had previously expressed interest in clinical trials, selected from a pre-existing database. The AI recruitment tool was deployed to process and analyze these patient profiles, focusing on age and prior interest in clinical research. This design aimed to streamline the recruitment process and improve the effectiveness of engaging eligible patients to discuss their participation in the trial. The strategy went beyond traditional methods, incorporating AI-driven phone calls alongside a multi-channel engagement approach. During the phone call conducted by the AI voice agent, participants were guided through a pre-screening questionnaire to assess their eligibility, and those who qualified were promptly scheduled for an on-site visit at the clinic where their brain health profiles would be assessed. To sustain engagement, reduce drop-off rates, and improve the overall patient experience, follow-up texts, emails, reminder notifications, and scheduled callbacks were seamlessly integrated into the process. Patients were also given the option to connect with a live representative if they preferred. This comprehensive approach enhanced recruitment efficiency and ensured a smoother, more seamless participation process for the clinical trial. **Results:** Over a span of less than six days, 1,460 unique contacts were completed, resulting in 4,600 bi-directional interactions with the AI Agent. These interactions included 436 inbound calls and 4,170 outbound calls. As a result, 173 participants (12%) had in-clinic visits scheduled. Of the total participants, 147 (12%) selected Spanish as their preferred language, while 1,313 (88%) chose English. Among the Spanish-speaking participants, 21 (14%) were scheduled for an in-clinic visit. Overall, the agent handled 3,300 minutes of calling, sent 4,970 text messages, and 1,200 emails. As of September 9, 2024, of the 173 participants initially scheduled, 52 (30%) were seen and evaluated during the 5-day span between the first call and clinic visit. Out of these, 28 (16%) participants completed pre-screening visits, and 22 (13%) successfully scheduled a screening visit. The clinic will continue to analyze data as more patients are seen. In addition, the AI agent has been deployed to engage 1,000 patients aged 50–85 who are concerned about Alzheimer's disease. The results from this cohort will be completed by October 1, 2024, and will be presented at the upcoming conference. **Conclusion:** The AI-driven recruitment strategy demonstrated superior performance in engaging and enrolling participants, particularly among the 50+ age group. By efficiently managing over 4,600 bi-directional interactions and scheduling 173 enrollment visits in less than six days, the AI Agent significantly accelerated the recruitment process. The ability to automate calls, personalize outreach, and navigate language preferences in real-time highlights the potential of AI as a transformative tool in clinical trial recruitment. Notably, 54% of those scheduled for pre-screening visits completed the process, and 79% proceeded to schedule a screening visit, further underscoring the effectiveness of AI in facilitating engagement. As AI technology continues to evolve, it holds the potential to replace traditional human-led telemarketing and recruitment calls. AI-driven voice systems are becoming increasingly sophisticated, allowing for natural, conversational interactions that can mimic human communication (Brown & Smith, 2023). These advancements suggest that AI will not only complement but may soon replace human tele-calls, creating scalable, efficient, and cost-effective solutions for patient recruitment in clinical trials and beyond. By automating routine

tasks, clinical research professionals will be able to focus on higher-impact activities, ensuring they can devote more time to providing personalized care and best serving the needs of patients. **References:** Smith, J. L., Williams, P. R., & Evans, M. T. (2021). Barriers to patient recruitment in clinical trials for older adults: A growing challenge. Clinical Research in Aging, 30(1), 45-56. Johnson, R. B., & Lee, C. M. (2022). Artificial intelligence in clinical trial recruitment: Transforming the speed of patient enrollment. Journal of Medical Technology and AI, 15(3), 80-90.

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LP106- DIFFERENTIAL DIAGNOSIS OF ALZHEIMER'S DISEASE AND FRONTOTEMPORAL DEMENTIA USING MULTIMODAL DEEP LEARNING. G. Guarnier[1,2], J. Reinelt[1], E.N. Molloy[1], P.G. Mihai[1], P. Einaliyan[1], S. Valk[3,4,5], A. Modestino[1], M. Ugolini[1], A. Dabas[1,6], R. Agombar[1], K. Mueller[3,7], W. Qiong[3], A. Babayan[2], M. Castellaro[8], A. Villringer[3,9], K. Thierbach[1,3], M.L. Schroeter[3,9] *(1. AICURA medical GmbH - Berlin (Germany), 2. Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig (Germany), 3. Max Planck Institute for Human Cognitive and Brain Sciences - Leipzig (Germany), 4. Institute of Neuroscience and Medicine, Brain & Behaviour (INM-7), - Jülich (Germany), 5. Institute of Systems Neuroscience, Medical Faculty, Heinrich Heine University Düsseldorf - Düsseldorf (Germany), 6. Max Planck Institute for Human Cognitive and Brain Sciences - Leipzig, (Germany), 7. Department of Neurology, Charles University in Prague, First Faculty of Medicine and General University Hospital in Prague - Prague (Czech Republic), 8. Department of Information Engineering, University of Padua - Padua (Italy), 9. Clinic for Cognitive Neurology, University Hospital Leipzig - Leipzig (Germany))*

Background: Differential diagnosis of dementia subtypes is error-prone and requires extensive expertise. AI-based clinical decision support systems (CDSS) could disentangle distinct neuropathologies with similar clinical presentation. Despite this, CDSS struggle with real-world clinical data, which are often incomplete and of high dimensionality. Here, we evaluated TelDem, a multimodal AI system using real-world clinical data to classify cognitively impaired patients. This advanced AI system is versatile and can be adapted for various clinical applications beyond diagnostics. **Methods:** We utilized data from the ADNI (n=1,487), AIBL (n=713), and FTLDNI (n=296) datasets, comprised of healthy volunteers (n=1,606), and patients with Alzheimer's Disease (n=751), non-fluent variant PPA (n=40), semantic variant PPA (n=39), and behavioral variant FTD (n=77). We partitioned data into training and validation sets (80/20) balancing missing data between sets. We applied a multimodal transformer-based neural network architecture, trained using cognitive/behavioral assessments, T1-weighted MRI scans, and demographics. We subsequently conducted an interpretability analysis with dimensionality compression (t-SNE) and attention-based metrics. **Results:** Results show ~10% superior accuracy with multiclass compared to single-modality classifiers, with the TelDem system successfully discriminating between groups. Furthermore, t-SNE visualizations showed a reliance on subtype specific features. Attention-based metrics suggest a focus on critical clinical indicators including lower cognitive scores, highlighting TelDem's ability to use relevant features for heightened diagnostic precision. **Conclusion:** TelDem represents a significant advancement in CDSS-based differential dementia diagnosis. We show that TelDem can evaluate the diagnostic importance of individual input parameters by analyzing the parameter-dependent improvement of the task-specific classification accuracy. TelDem, therefore, can improve clinical workflows, advance clinical research, and facilitate patient selection for clinical trials. The flexible integration of both public and proprietary multimodal datasets allows for the AI system to be rapidly adapted for other clinical and research purposes, such as optimizing clinical trial design, patient stratification, and supporting various stages of clinical drug development. **Keywords:** Differential dementia diagnosis, Multimodal Deep Learning, Diagnostic tools, Computerized decision support systems. **Disclosures:** The authors declared no competing interests.

LP107- XPRESSO: A DIGITAL COGNITIVE SELF-EVALUATION FOR POPULATION SCREENING. W. Huijbers[1], J. Gruber[1], H. Wischmann[2], M. Gillies[1], Z. Nasreddine[1] *(1. MoCA Cognition - Montreal (Canada), 2. Charité – Universitätsmedizin Berlin - Berlin (Germany))*

Background: XpressO is an online self-screening tool developed by MoCA Cognition. It provides a brief cognitive evaluation to help determine whether users should follow-up with primary care physician or memory clinic. Online cognitive tests can assist in recruitment for clinical trials and help alleviate the burden on primary care or memory clinics. XpressO is self-administered using a computer, tablet, or smartphone and involves a visual memory and a logical task. The test was launched in early 2024. Between January and August, over 9,000 unique users self-enrolled, and more than 24,000 tests were recorded. All users agreed that their anonymized data could be used for product development and research purposes. Here, we evaluate the test results from online users at baseline, i.e., when performing their initial test. **Methods:** We used a logistic regression model, previously established in a clinical cohort, to estimate a logistic regression score (Klil-Drori et al., 2024). This "XpressO score" reflects the probability that users will score above 25 on the Montreal Cognitive Assessment (MoCA), the threshold between cognitively normal and mild cognitive impairment (MCI). As an external reference, we contrasted the results with the prevalence of MCI in the US population between ages 60 and 85, as reported by Petersen et al (2018). For the online users, demographics including age, sex, and education were self-reported. In a subset of users (n=500), we gathered additional information using an online user-feedback questionnaire. **Results:** We evaluated the baseline results of 9,185 users, with a mean age of 56.2 (SD 15.8, 60.6% female. The mean XpressO score was 72.6 (SD 23.7): 12.2% had a low XpressO score (<= 42), indicating an increased risk for MCI; 21.7 % had an intermediate XpressO score, and 66.1% had a high XpressO score (>= 72), indicating normal cognition. The relative proportion of low XpressO scores increases with age, in-line with the prevalence of MCI. The user-questionnaire indicated that 60% of users worry about their cognitive health and 45% reported that they would discuss the result with their healthcare provider. **Conclusion:** These results demonstrate that the XpressO score is associated with age-related cognitive decline. The proportion of users with a low XpressO score slightly exceeds the previously reported prevalence of MCI. Along with user feedback, the results suggest that our online population is enriched with individuals who are concerned about their cognitive health and may be experiencing age-related cognitive decline. Collectively, these findings provide evidence for the relevance of the XpressO test for identifying individuals at an increased risk of MCI and support its use

for cognitive pre-screening in also primary care or clinical trials. **Keywords:** online pre-screening, cognition, recruitment, MoCA. **Disclosures:** The study and the authors WH, JG, MG, and ZN were funded by MoCA Test Inc. **References:** Klil-Drori, S., Bodenstein, K. C., Sun, S., Kojok, L., Gruber, J., Ghantous, Y., Cummings, J., & Nasreddine, Z. (2024). Montreal Cognitive Assessment (MoCA) XpressO: Validation of a digital self-administered cognitive prescreening tool. Journal of the American Geriatrics Society, 72(8), 2516–2522. Petersen RC, Lopez O, Armstrong MJ, Getchius TSD, Ganguli M, Gloss D, Gronseth GS, Marson D, Pringsheim T, Day GS, Sager M, Stevens J, Rae-Grant A. Neurology. 2018 Jan 16;90(3):126-135.

LP108- PRESCRIBING REMOTE DIGITAL SELF-TESTING FOR SUSPECTED MILD COGNITIVE IMPAIRMENT: RESULTS OF THE RE.COGNI.ZE STUDY ON FEASIBILITY AND ACCEPTANCE WITH THE NEOTIVCARE APP. E. Düzel[1,2], C. Bartels[3], D. Czesnik[4], T. Duning[5], A. Lüschow[6], G. Nelles[7], G. Reifschneider[8], M. Schöttler[9], B.H. Schott[3], M. Griebe[10] *(1. Deutsche Zentrum für Neurodegenerative Erkrankungen (DZNE) - Magdeburg (Germany), 2. Institut für Kognitive Neurologie und Demenzforschung, Otto von Guericke Universität - Magdeburg (Germany), 3. Klinik für Psychiatrie und Psychotherapie, Universitätsmedizin Göttingen (Germany), 4. Gemeinschaftspraxis für Neurologie - Göttingen (Germany), 5. Klinik für Neurologie - Klinikum Bremen-Ost (Germany), 6. MVZ Campus Benjamin Franklin - Charité Berlin (Germany), 7. Neuromed-Campus - Köln (Germany), 8. NeuroCentrum Odenwald - Erbach (Germany), 9. Roche Pharma AG - Grenzach-Wyhlen (Germany), 10. Neurologische Klinik, Medizinische Fakultät Mannheim, Universität Heidelberg - Heidelberg (Germany))*

Background: The timely diagnosis of mild cognitive impairment (MCI) in Alzheimer's disease is challenging in routine care due to the complexity and time burden of required cognitive assessments. New unsupervised digital remote self-assessment tools could address this challenge. **Objectives:** To assess the feasibility, added value and satisfaction of remote digital self-assessment for mild cognitive impairment in primary and specialized routine care with a digital app certified as a medical device (neotivCare). **Method:** The multicentric healthcare study «re.cogni.ze» evaluated the usability, adherence and acceptance of remote digital self-assessment (neotivCare, installed on patient's own smartphone) over a period of 22 months with 27 office-based specialist physicians (neurologists and psychiatrists), specialists physicians and neuropsychologists in 3 memory clinics and 13 GPs in Germany. re.cogni.ze is the largest completed evaluation to date for remote digital self-assessment of cognition in suspected MCI. neotivCare uses three different clinically and psychometrically validated tests of episodic memory. Each test is repeated once a week, four times in total, leading to an assessment period of 12 weeks. neotivCare calculates a composite score combining results from the three test types and produces a findings letter that patients can discuss with their physician. **Results:** 765 persons with subjectively perceived memory problems were recommended neotivCare by their doctors. 574 patients (75%) followed the recommendation (mean age 67 - SD 10; 50.2% female). 573 (93%) used the app and of these 496 patients (93%) completed the assessment and discussed the results using the in-app generated findings letter with their doctor. 368 patients also completed a separate (independent from the app) survey about usability, worries, experienced added value etc. 40% of the patients with a composite score fell below the prevalidated cut-off for MCI while 60% performed within norm. Specialists reported a higher satisfaction with the app compared to standard paper-pencil tests (5.2 versus 4.4 on a 7point Likert scale). There was no such difference for GPs. 71% of all doctors found that the app easy to use. 80% saw an added value in using the app and would use the app again. 71.5% of the patients thought that the app was easy to use. 67.6% reported an added value over paper pencil tests. Using the app reduced experienced worries in 52% of the patients and left worries unchanged in 27%. The patients rated the duration of the app-use and the self-testing at home favourably (both 8.5 scores on a Likert scale 0 -10). **Conclusion:** The results of the re.cog.nize study show that remote digital self-assessment in routine care is feasible and is well accepted by health care providers and patients. The high adherence rates indicate that a timely assessment of MCI is possible with this type of digital technology.

LP109- PILOT PROGRAM OF DIGITAL COGNITIVE TESTING BY PRIMARY CARE CLINICIANS IN A LARGE HEALTH SYSTEM. D. Gitelman[1,2,3], J. Mishos[1], M. Malone[4,5] *(1. Advocate Health - Downers Grove (United States), 2. Rosalind Franklin University of Medicine and Science - Chicago (United States), 3. Northwestern University - Chicago (United States), 4. Aurora Health Care - Milwaukee (United States), 5. University of Wisconsin School of Medicine & Public Health - Madison (United States))*

Background: Primary Care Clinicians (PCPs) are at the front lines of healthcare for a majority of older adults and are often the first clinicians seen by those developing neurocognitive disorders (NCDs). Studies suggest that nearly two-thirds of patients eventually diagnosed with NCD's were initially misdiagnosed or experienced a delay in diagnosis. Barriers to care include limitations in PCP time and expertise and in operational resources. Minority populations may be particularly impacted due to a greater risk of NCD's and healthcare access. The developing consensus in the field is that an early NCD diagnosis is important for defining prognosis, enabling advanced care planning, enhancing patient safety and allowing access to newer disease modifying therapies. The Medicare Annual Wellness Visit (AWV) provides an opportunity for cognitive assessment and early diagnosis; however, many PCPs opt to either state the patient appears normal to observation during the visit, or use tests (e.g., minicog) that are rapid but insensitive to early cognitive change. We implemented digital cognitive testing during AWV's to demonstrate the feasibility of improving the rate of cognitive testing in Primary Care Clinics serving an older population. **Methods:** The project was formulated as a quality improvement initiative as part of the Davos Alzheimer's Collaborative Health System Preparedness early detection grant and was exempt from IRB review. Physicians and advanced practice clinicians were recruited initially through service line leadership, and later by word-of-mouth. Fifty percent of clinic sites were in medically underserved or rural areas. We used the BrainCheck digital testing tool. The tool has shown 86% sensitivity and 83% specificity for differentiating mild cognitive impairment vs. healthy individuals and 88% sensitivity and 94% specificity for differentiating dementia vs. healthy. Clinic staff were trained to administer the tests. Testing typically takes 10-15 min and provides immediate results. A more recent screening version takes only 3 minutes. **Results:** Between August 2022 and March 2024, BrainCheck was deployed to 63 providers.

A total of 1044 standard assessments and 294 screens were performed. Forty-two percent of the standard assessments were identified as likely abnormal, and an additional 20% as possibly abnormal. Twenty-four percent of the screens were abnormal. Analyses are ongoing to understand the care pathways of the tested patients, which will be reported during the conference. Implementation of the tool required ongoing training of clinicians and their staff for interpreting the results and administering the tests, respectively. IT provided support for aspects of the implementation, but integration with the electronic medical record (EMR) is still pending. **Conclusion:** Use of a digital cognitive tool identified a high percentage of patients with possible cognitive impairment. Many of these patients come from medically underserved communities and would have been missed by standard AWV cognitive assessment practices. Analyses are ongoing to determine the care that these patients received. The digital tool was well received by PCPs, but came with a number of challenges including acceptance by staff, need for extensive training, financial sustainability and EMR integration. Lessons learned from the pilot study and future plans will be discussed.

LP110- DEFINING CLINICAL CONTEXTS OF USE AND PERFORMANCE STANDARDS FOR DIGITAL COGNITIVE ASSESSMENTS: RECOMMENDATIONS FROM THE GLOBAL CEO INITIATIVE ON ALZHEIMER'S DISEASE. L. Thompson[1], A.M. Barrett[2], S. Fittipaldi[3,4], B. Gaster[5], D. Hammers[6], C. Butler[7] *(1. Brown University - Providence (United States), 2. University of Massachusetts Chan Medical School - Massachusetts (United States), 3. Universidad Adolfo Ibáñez - Santiago (Chile), 4. University of California San Francisco - San Francisco (United States), 5. University of Washington - Seattle (United States), 6. Indiana University School of Medicine - Indianapolis (United States), 7. Imperial College London - London (United Kingdom))*

Background: Early detection of cognitive impairment due to Alzheimer's disease and related dementias (ADRD) is challenging due to limited time- and cost-effective cognitive assessment tools sensitive to subtle cognitive change. This can result in delayed diagnosis and treatment, and missed opportunities for older adults to participate in clinical trials targeting early-stage disease. Recently-updated AD diagnostic criteria and use guidelines for blood-based biomarkers highlight the importance of early and sensitive cognitive screening to guide further workup and treatment considerations. Existing paper-based screening assessments have many limitations, including low sensitivity to early-stage cognitive impairment, long completion times, subjective scoring, and need for specialized training. Many also contain socioeconomic and cultural biases. Digital cognitive assessments (DCAs) have the potential to overcome these limitations and meet the growing need for early detection in clinical practice and enrollment in ADRD clinical trials. **Methods:** The Global CEO Initiative on Alzheimer's Disease (CEOi) convened a multidisciplinary workgroup led by clinicians and researchers with expertise in neuropsychology, biometrics, and early detection of ADRD. Using literature reviews, weekly discussions, and monthly progress meetings with stakeholders, the workgroup has defined contexts of use and developed recommendations for DCA test characteristics and performance to address cognitive assessment needs in primary and specialty care settings. The recommendations support the development of high-performing DCAs, which will: A) guide their incorporation into clinical workflows and health systems, and B) inform recruitment and screening plans for future decentralized ADRD clinical trials. These objectives serve a secondary goal of reducing barriers to brain health assessment and enrollment in clinical research across diverse populations. **Results:** The DCA Workgroup identified three clinic-based, health-care initiated contexts of use for DCAs: 1) detection of possible cognitive impairment in the absence of a recognized concern, 2) confirmation of a diagnosis of either mild cognitive impairment or a dementia syndrome in the presence of a cognitive concern, and 3) evaluation of neurodegenerative etiology once cognitive impairment has been confirmed, including assessing for AD if relevant. Reference standards (e.g., neuropsychological evaluation) for validation and target DCA sensitivities and specificities set for each context were based on a comparative review of existing non-digital measures in the literature to optimize acceptable context outcomes. Opportunities and limitations for remote context of DCA use are described toward future tailored guideline development. Key DCA characteristics considered and defined for each context of use include, but are not limited to, test duration, linguistic and culturally applicability, accessibility, diagnostic accuracy, and psychometric integrity (reliability and validity). **Conclusion:** Given limitations of traditional cognitive screening, integrating highly performing DCAs into clinical care and research protocols may enable more timely and accurate diagnosis, better care and treatment, and improved efficiency and inclusivity. CEOi's DCA Workgroup defined acceptable performance and test characteristics for unique contexts of use to serve as a benchmark for both clinical and research applications. With ongoing multi-stakeholder collaboration and expert-driven consensus, we can achieve the full potential of DCAs to revolutionize the diagnosis and monitoring of cognitive impairment.

LP111- REAL-WORLD CARE OF ALZHEIMER'S DISEASE PATIENTS (N=2,153) IN GERMANY: INSIGHTS FROM REGISTRY OF THE NEUROLOGISTS NETWORK NEUROTRANSDATA (NTD) USING THE PHYSICIAN/PATIENT PLATFORM (DESTINY). A. Bergmann[1], S. Braune[1], O. Fasold[1], H. Dikow[1], N. Tavakoli[1] *(1. NeuroTransData GmbH, NTD Study Group, Neuburg an der Donau - Neuburg An Der Donau (Germany))*

Background: NeuroTransData (NTD) is a network of neurologists and psychiatrists in Germany, focusing on optimizing treatment protocols and improving patient outcomes through data-driven approaches and advanced analytics. Data acquisition is standardized via the web-based physician-patient interface platform DESTINY (DatabasE-assisted Therapy decision support sYstem), incorporating an integrated clinical registry. The objective of the study is to assess the current patient journey and treatment landscape in patients with Alzheimer's disease. **Methods:** This is a retrospective analysis of real-world data of patients with Alzheimer's dementia (SDAT) of the NTD dementia disease registry captured during clinical visits in NTD offices in Germany between September 1998 and August 2024. Patients were categorized by Mini-Mental State Examination (MMSE) scores into (MCI, MMSE $\geq$ 26), (16 $\leq$ MMSE $<$ 26), and (MMSE $<$ 16). The analysis focused on the frequency of neuropsychological assessments, the use of imaging modalities, biomarker evaluations, and medication prescriptions. **Study Population:** A total of 2,153 patients with confirmed diagnoses of ICD F00 (Alzheimer's dementia) or G30 (Alzheimer's disease) were included, with an average age of 83.2 years, ranging from 44 to 100. Of the patients, 57% were female (1,226) and 43%

male (927). Mean follow-up time was 2.7 years, ranging from 0.1 to 26.3 years. **Results:** The following results demonstrate the current frequency and density of information captured in the NTD registry. At this stage, we cannot differentiate between missing data and lack of documentation. **MMSE Score Distribution:** 13.75% (296) patients showed MMSE<16, 57.45% (1237) MMST>=16, MMST<26 and 16.76% (361) MMST>=26. **Medication History:** 22.7% (489) were treated with Donepezil, 21.74% (468) with Memantine, 1.9% (41) with Galantamine, 0.84% (18) Rivastigmine: and 0.3% (6) with Gingko. Documentation in 52.16% showed no specific medication for SDAT. **Imaging Diagnostics:** 24.4% (525) patients underwent cranial MRI, 24.1% (519) cranial CT, and 10.7% (230) received nuclear medicine scans. **Biomarker:** 12.1% (261) patients underwent biomarker analysis through Cerebrospinal Fluid (CSF) testing. **Neuropsychological Testing:** 75.8% (1631) of patients were tested employing MMSE test, 38.8% (835) were assessed with DemTect, and 0.6% (12) completed CERAD. All numbers refer to the time of diagnosis. **Conclusion:** The NTD dementia registry provides a tried and tested, web-based data capturing platform to enable in-time standardized documentation of cognitive assessments, biomarkers, imaging data, and clinical course information [1]. This real-world data capturing framework with established data quality protocols [2] enables reliable retrospective and prospective analyses, thereby underpinning the registry's role as a critical resource for advancing dementia research clinically and socioeconomically. The registry supports risk stratification for novel therapies, like amyloid antibody treatments, by managing risks and tracking amyloid-related imaging abnormalities (ARIA). It also facilitates cognitive monitoring, capturing early cognitive impairment dynamics, such as subjective cognitive impairment (SCI). Additionally, it integrates blood and nasal biomarker results and, with AI-driven tools, enables speech and passive digital biomarker analysis. This holistic approach aids evidence-based identification of clinically relevant cognitive impairment. **Keywords:** DESTINY, Dementia, Personalized Medicine, Real-World Evidence, Digital Health, Alzheimer. **Disclosures:** Dr. med. Arnfin Bergmann has received consulting fees from advisory board/speaker/other activities for NeuroTransData. Prof. Dr. med Stefan Braune has received honoraria for clinical services from the Kassenärztliche Vereinigung Bayern und private health insurances, for clinical studies and lecturing from Novartis, Merck, Roche and Sanofi. He received honoraria for consulting from NeuroTransData and as board member. Dr. med. Oliver Fasold has received honoraria for clinical services from the Kassenärztliche Vereinigung Berlin and private health insurances, for clinical studies and lecturing from Novartis, Merck, GAIA, Biogen, Roche and Sanofi. He received honoraria for consulting from NeuroTransData and as board member. Heidi Dikow, Niloofar Tavakoli, and NTD Study Group declare that they have no conflicts of interest to disclose. **References:** 1. Bergmann, A., Stangel, M., Weih, M., van Hövell, P., Braune, S., Köchling, M., & Roßnagel, F. (2021). Development of registry data to create interactive doctor-patient platforms for personalized patient care, taking the example of the DESTINY system. Frontiers in Digital Health, 3, Article 633427. https://doi.org/10.3389/fdgth.2021.633427. 2. Wehrle, K., Tozzi, V., Braune, S., Roßnagel, F., Dikow, H., Paddock, S., Bergmann, A., & van Hövell, P. (2022). Implementation of a data control framework to ensure confidentiality, integrity, and availability of high-quality real-world data (RWD) in the NeuroTransData (NTD) registry. JAMIA Open, 5(1), Article ooac017. https://doi.org/10.1093/jamiaopen/ooac017.

CLINICAL TRIALS EARLY CAREER INVESTIGATOR SHOWCASE

P250- THE RISK FACTORS AFFECTING CDR-SOB CHANGES IN AMYLOID-BETA NEGATIVE INDIVIDUALS WITH MILD COGNITIVE IMPAIRMENT AND SUBJECTIVE MEMORY IMPAIRMENT.

H. Lee[1] *(1. Pusan National Univalsity Hospital - Busan (Korea, Republic of))*

Background: The factors influencing conversion to Alzheimer's disease (AD) among patients with amyloid-β positive mild cognitive impairment(MCI) have been studied. For example, age, sex, education level, apolipoprotein E gene(APOE), Aβ deposition, white matter hyperintensities(WMH), hippocampal volume, neuropsychological assessment etc. However, there are few study results in the Aβ negative individual groups. In this study, we investigate which factors affect the prognosis in Aβ negative non-demented individuals. **Methods:** This is a longitudinal study of 82 Aβ negative non-demented individuals. We evaluated prognosis based on Clinical dementia rating scale-sum of boxes (CDR-SOB) changes. All participants underwent Seoul Verbal Learning Test for memory function, Clinical Dementia Rating(CDR) scale and CDR-SOB, APOE genotyping, and brain MRI. To determine Aβ deposition status, each participant underwent amyloid PET scans using 18F-florbetaben. The association of factors with CDR-SOB changes was examined using multiple linear regression analysis. **Results:** In participants, age($p=0.032$), memory function($p=0.009$), amyloid loading level($p=0.043$), and WMH($p=0.000$) were found to affect CDR-SOB changes. **Conclusion:** Our study showed that age, memory function, amyloid loading level and WMH affect the pregression to dementia in Aβ negative non-demented individual group. This suggests that even in the Aβ negative group, the level of amyloid loading is important. **Keywords:** Aβ, MCI, SMI, CDR-SOB. **Data Deposition:** The data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. **Disclosures:** The authors have no potential conflicts of interest to disclose.

P251- ASSOCIATION OF ALZHEIMER'S DISEASE BIOMARKERS AND EMOTIONAL STATES: ANALYSIS OF INDIVIDUALS WITH AND WITHOUT PRECLINICAL ALZHEIMER'S DISEASE IN THE A4 TRIAL.

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Background: Loneliness has been identified as a predictor for cognitive decline, and its presence doubles the risk of Alzheimer's disease (AD) dementia, suggesting its role as either a prodromal symptom or a behavioral response to the underlying biological changes of AD [1, 2]. However, there has been limited efforts to characterize other emotional states that may serve as modifiable risk factors of AD. The Geriatric Depression Scale (GDS) is a self-report measure of depression in older adults that includes individual questions that may reflect different emotional states such as life satisfaction, happiness, or helplessness [3]. This study aims to elucidate the relationship between positive and negative emotional states with biomarkers of early stages of AD. The Asymptomatic Anti-Amyloid Aging (A4) study represented a large, multinational clinical trial of secondary prevention of AD dementia in

individuals with preclinical AD [4]. The A4 preliminary data represents one of the largest, most richly characterized datasets of older adults and therefore offers a unique opportunity to identify the relationships between emotional states and neuropathological hallmarks of AD. **Methods:** A series of cross-sectional reverse regression analyses was performed to explore the association between GDS questions and imaging data in the A4 preliminary dataset. Each of 8 GDS questions was treated as the outcome variable: life satisfaction, feeling of emptiness, boredom, happiness, social isolation, subjective memory loss, worthlessness, and hopelessness. Covariates included sex, age, education, APOE status, and three sets of predictors: MRI brain volumes (left hippocampus, right hippocampus, left entorhinal, right entorhinal), mean 18F-flortaucipir tau PET levels within the same regions, and mean 18F-florbetapir amyloid PET levels. **Results:** A total of 4486 (2646 female) participants completed the GDS questions and amyloid PET scans and were therefore included in the analysis. All participants were 65 to 85 years of age. Of these participants, 1323 (29%) were amyloid positive. In addition, 1221 person received a volumetric MRI scan, and 445 individuals completed a tau PET scan. In this analysis, life satisfaction was significantly associated with mesial temporal tau burden ($p = 0.028$). However, the associations between life satisfaction and tau levels in specific brain regions varied in magnitude and direction: left hippocampus – $\beta = 0.34$, $p = 0.045$; right hippocampus – $\beta = 0.44$, $p = 0.01$; left entorhinal cortex – $\beta = -0.041$, $p = 0.73$; right entorhinal cortex – $\beta = 0.18$, $p = 0.091$. Additionally, feelings of worthlessness were significantly associated with the mesial temporal volumes on MRI ($p = 0.017$), and this relationship was particularly driven by the left hippocampus ($\beta = -0.041$, $p = 0.015$). No significant associations were found between other GDS questions and chosen regions. **Conclusion:** Life satisfaction was associated with increased tau levels in the left hippocampus and right entorhinal cortex and decreased levels in the right hippocampus and left entorhinal cortex. Worthlessness may be associated with a decrease in mesial temporal volumes, particularly the left hippocampus. Emotional states that are associated with the neurobiological changes of AD will be targeted as disease-modifying factors for a planned psychosocial intervention clinical trial to prevent accelerated progression of cognitive decline. **Keywords:** A4 clinical trial, Alzheimer's disease, preclinical, biomarkers, emotional states. **Disclosures:** I.S.S. has received funding for clinical trials research from Eli Lilly, Eisai, Biogen, Janssen, Novartis, Alector, AbbVie, Genentech/Roche, Cortexyme, UCB Biopharma, and Alzheon. **References:** 1. Donovan, N. J. et al (2017). Loneliness, depression and cognitive function in older US adults. International journal of geriatric psychiatry, 32(5), 564-573. 2. Donovan, N. J. et al (2016). Association of higher cortical amyloid burden with loneliness in cognitively normal older adults. JAMA psychiatry, 73(12), 1230-1237. 3. Herrmann, N. et al (1996). A validation study of the Geriatric Depression Scale short form. International Journal of Geriatric Psychiatry, 11(5), 457-460. 4. Sperling, R. A. et al (2023). Trial of solanezumab in preclinical Alzheimer's disease. New England Journal of Medicine, 389(12), 1096-1107.

P252- CHANGES IN COGNITIVE AND NEURAL MARKERS OF ALZHEIMER'S DISEASE IN RESPONSE TO AEROBIC AND NON-AEROBIC EXERCISE AMONG COGNITIVELY HEALTHY OLDER AFRICAN AMERICANS: THE ROLE OF BODY COMPOSITION, GENETICS, AND SEX. B. Fausto[1] *(1. Rutgers–The State University of New Jersey - Newark, NJ (United States))*

Older African Americans bear a disproportionate burden of both (1) Alzheimer's disease (AD) and (2) obesity–a risk factor for AD–as compared to non-Hispanic white older adults. The most common way to measure obesity is body mass index (BMI), which can be classified as underweight, normal, overweight, and obese. Encouragingly, our previous exercise intervention studies show that individuals in the obese range experience greater cognitive benefits from exercise. However, emerging evidence suggests the abdominal obesity subtype is particularly detrimental to health, a body composition characteristic that BMI fails to capture. Further, body morphology differs by race/ethnicity and sex, and AD genetic risk may further influence its impact on brain health. Waist-to-hip ratio (WHR) is one alternative measure that captures abdominal obesity. Our cross-sectional pilot data show that the WHR abdominal obesity group had significantly poorer cognitive performance, while there were no BMI group differences in cognition. As such, measures of abdominal obesity, like WHR, may be superior to BMI as a marker of cognitive health in older African Americans. Building on these cross-sectional findings, the relationship between baseline and exercise-related changes in body composition (e.g., abdominal adiposity) and brain health changes in older African Americans remains unclear. Whether these effects are further influenced by genetic risk factors aside from APOE-ε4 is heretofore unknown. ABCA7 rs115550680 and rs3764650 are two such recently identified AD genetic risk factors implicated in AD among African Americans. Here, we propose to recruit 90 cognitively healthy older African American participants, ages ≥60. Participants will be randomized to one of two six-month interventions: (1) Cardio-Dance Fitness, an aerobic exercise program, and (2) Strength, Flexibility & Balance, a low-intensity, non-aerobic exercise program. All participants will complete—at baseline and post-intervention—a body composition protocol (anthropometry [BMI and WHR measurement] and whole-body dual x-ray absorptiometry [DEXA]); cognitive testing; and a neuroimaging session. Participants will also undergo genotyping for AD genetic risk factors. These innovative methods will enable us to address: Aim 1) Investigate the relationships between baseline and changes in anthropometry/absorptiometry on intervention-related cognitive changes; Aim 2) Examine the relationships between baseline and changes in anthropometry/absorptiometry on intervention-related neuroimaging changes; and Aim 3) Explore the moderating roles of sex and genetic risk variants of APOE-ε4 and ABCA7 in Aims 1 and 2. Impact: More nuanced measures of body composition may facilitate identification of individuals at-risk for AD within sex-specific and racially, ethnically, and/or genetically diverse populations who may benefit the most from exercise interventions.

P253- ASSOCIATION BETWEEN COGNITIVE PERFORMANCE AND EMOTIONAL STATES: ANALYSIS FROM THE A4 TRIAL. J. Kelbert[1], I.S.K.Y.L. Kouser[2], I. Luo[2], C. Young[2], Z. He[2], I. Skylar-Scott[1] *(1. University of Arizona - Phoenix (United States), 2. Stanford University - Palo Alto (United States))*

Background: The presence of feelings of loneliness increases the risk of Alzheimer's disease (AD) dementia and predicts cognitive decline, which suggests that loneliness is either a behavioral response to the neuropathological changes seen in AD or a prodromal symptom of AD [1, 2]. The degree to which additional emotional states may represent modifiable risk factors of AD needs to be investigated. The A4 trial represented a large, international clinical study of solanezumab in cognitively unimpaired individuals with amyloid positivity [3]. The A4 preliminary dataset comprises an extensive, richly characterized body of data of older individuals, and this study aims to identify the relationships between emotional states and hippocampally-dependent cognitive performance. **Methods:** The 8 Geriatric Depression Scale (GDS) questions of interest focused on life satisfaction, feeling of emptiness, boredom, happiness, social isolation, subjective memory loss, worthlessness, and hopelessness.4 Participants underwent detailed neuropsychological tests of memory, processing speed, working memory, attention, and cognitive screening. These tests included One-Card Learning (OCL), Face Name Associative Memory Exam (FNAME), Free Cued and Selective Reminding Test (FCSR15), Wechsler Memory Scale-Revised Logical Memory Delated Recall (LMDR), Detection (DET), Digit Symbol Substitution Test (DSST), One-Back Test (ONB), Identification (IDN), and Mini-Mental State Examination (MMSE). FNAME and the Cogstate Battery (IDN, DET, ONB, and OCL) are both part of the Computerized Cognitive Assessment (C3). We performed a principal components analysis (PCA) on these neuropsychological measures and created a global cognitive composite using the first principal component. If significant Spearman correlations ($p<0.05$) were identified between neuropsychological tests and GDS questions, multiple linear regressions were performed with covariates gender, age, education, and APOE status. **Results:** A total of 1204 participants completed testing (ages 65 to 85). A test of attention (IDN) was highly associated with a test of processing speed (DET, rho=0.55), and both IDN and DET were negatively associated with all other measures. The global cognition score was at least moderately correlated with all measures (all positive correlations with rho=0.25 or greater; all negative correlations with rho=-0.34 or lower), making it a good composite of overall cognitive performance. After linear regression analysis, there was a positive association between subjective memory loss and global cognition as well as a test of processing speed (DET; β=0.19, p=0.01 and β=0.019, p=0.02, respectively), and there was a negative association with visual memory (FNAME, β=-0.04, p=0.01). Self-report of happiness was positively associated with a test of processing speed (DSST, β=0.29, p=0.02). Greater feelings of emptiness were associated with worse performance on a test of working memory (ONB, β=-0.086, p=0.03). **Conclusion:** In a large and deeply characterized cohort, higher subjective memory loss was associated with lower visual memory scores, higher levels of happiness were associated with greater processing speed, and higher feelings of emptiness was associated with worse working memory. The associations between subjective memory loss and both global cognition and processing speed require further investigation. Emotional states that are associated with performance on cognitive testing of AD will be targeted in a future clinical trial involving psychosocial interventions in preclinical AD to slow cognitive decline. **Keywords:** A4 clinical trial, Alzheimer's disease, preclinical, cognition, cognitive domains, neuropsychological tests, emotional states. **Disclosures:** I.S.S. has received funding for clinical trials research from Eli Lilly, Eisai, Biogen, Janssen, Novartis, Alector, AbbVie, Genentech/Roche, Cortexyme, UCB Biopharma, and Alzheon. **References:** 1. Donovan, N. J. et al (2017). Loneliness, depression and cognitive function in older US adults. International journal of geriatric psychiatry, 32(5), 564-573. 2. Donovan, N. J. et al (2016). Association of higher cortical amyloid burden with loneliness in cognitively normal older adults. JAMA psychiatry, 73(12), 1230-1237. 3. Herrmann, N. et al (1996). A validation study of the Geriatric Depression Scale short form. International Journal of Geriatric Psychiatry, 11(5), 457-460. 3. Sperling, R. A. et al (2023). Trial of solanezumab in preclinical Alzheimer's disease. New England Journal of Medicine, 389(12), 1096-1107.

LP112- DISCREPANCIES IN DEMENTIA SELF-AWARENESS: CORRELATIONS WITH WELL-BEING ACROSS DAILY CHALLENGES. H. Horie[1], F. Nakai[1], T. Kishimoto[1], M. Mimura[1], T. Horigome[1] *(1. Keio University Hospital - Tokyo (Japan))*

Background: Dementia self-awareness plays a crucial role in patient autonomy and decision-making capacity. Lack of self-awareness may undermine these abilities, leading to reduced autonomy. Conversely, heightened self-awareness has been associated with increased depression and lower quality of life (QOL) in dementia patients. This study focuses on examining how self-awareness correlate with measures of well-being, across various daily challenges faced by dementia patients. **Methods:** A total of 67 dementia patients (mean age, 79.9±5.3; 62.7% female, dementia (61.2%, n=41), mild cognitive impairment (MCI) (35.8%, n=24), and subjective cognitive impairment (SCI) (3.0%, n=2)) were enrolled from two specialized outpatient clinics in Japan. Self-awareness was assessed by examining the discrepancy between patient and caregiver reports using a comprehensive questionnaire covering 25 daily challenges, including mobility, eating, shopping, and housing (categorized as self-care, task management and sensory discomfort). The sum of discrepancies was defined as a measure of self-awareness. Demographic and clinical characteristics, including cognitive function (MMSE, MoCA-J, CDR), behavioral and psychological symptoms (NPI), depression (GDS), apathy (Apathy Scale), life satisfaction (SWLS), positive emotions (SPANE), general health status (EQ-5D-5L), and sleep quality (PSQI) were analyzed. **Results:** Patients with lower self-awareness, as indicated by a greater discrepancy between patient and caregiver reports, were more likely to be female and showed poorer performance on orientation tasks, including time and space orientation on the MMSE ($r = -0.26$, $p = 0.036$), memory on the CDR ($r = 0.25$, $p = 0.038$), and orientation on the MoCA-J ($r = -0.26$, $p = 0.037$). They also exhibited higher severity ($r = 0.34$, $p = 0.006$) and burden ($r = 0.37$, $p = 0.002$) scores on the NPI. Moreover, there was a significant inverse correlation between self-awareness and the overall GDS score ($r = -0.32$, $p = 0.009$), indicating that patients with lower self-awareness were less likely to report depressive symptoms. This was particularly evident in GDS items 6 and 8, where they were less likely to report feelings of future uncertainty or helplessness. These patients were also less likely to experience apathy, as reflected in their responses to Apathy Scale items

13 and 14, and were more likely to express life satisfaction and positive emotions, as indicated by positive responses on the SWLS (items 1 and 2) and SPANE (items 5, 7, 10, and 12). When examining the correlation between the discrepancy scores and well-being measures such as SWLS and SPANE, no significant overall correlations were found. However, significant correlations emerged within specific categories of daily challenges. These findings suggest that while the overall relationship between self-awareness and well-being is weak, certain domains can reveal more pronounced correlations. **Conclusion:** Although no significant overall correlation was observed between lower self-awareness and well-being in dementia patients, sub-analysis revealed significant correlations within specific daily challenges. These findings suggest that certain aspects of daily life are more closely tied to well-being, depending on the level of self-awareness. Larger studies are needed to confirm and explore these relationships, which could inform more personalized care approaches. **Keywords:** dementia, self-awareness, anosognosia, well-being, QOL, quality of life. **Clinical Trial Registry:** UMIN000048358 https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000055112 **Disclosures:** The authors declare no conflicts of interest.