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Conference proceedings

SYMPOSIA

S1- DOES THE CURRENT EVIDENCE BASE SUPPORT CONTINUED DOSING WITH LECANEMAB FOR EARLY ALZHEIMER'S DISEASE? M. Irizarry[1], L. Reyderman[1], C. Van Dyck[2] *(1. Eisai Inc. - Nutley (United States), 2. Yale University School of Medicine - New Haven (United States)*

Presentation 1: Mechanistic Rationale for Continued Lecanemab Dosing, M. Irizarry, S. Dhadda, L. Kramer, D. Selkoe

Alzheimer's disease pathophysiology is believed to involve various abnormalities, including those of amyloid beta (Ab) peptide and tau processing, inflammation, oxidative stress, and vascular risk factors. Aβ peptides exist in a dynamic continuum of conformational states from monomeric Aβ, to soluble progressively larger Aβ assemblies that include a range of low molecular weight oligomers to higher molecular weight protofibrils, and finally to insoluble fibrils (plaques). Various lines of evidence support the "amyloid hypothesis" that Aβ plays a central role in the pathogenesis of AD, and several immunotherapies have been developed to interact with this cascade in various different places which may reduce the number of soluble aggregates and insoluble Aβ fibrils deposited in the brain. Lecanemab is a novel humanized immunoglobulin G1 (IgG1) anti-amyloid monoclonal antibody with highest affinity for Aβ protofibrils, a particularly toxic Aβ species. Lecanemab distinguishes itself from other anti-amyloid antibodies in that it selectively targets large soluble protofibrils relative to monomers (greater than 1000-fold over Aβ monomers), with preferential activity over insoluble fibrils (up to 10-fold over fibrils). In the phase 3 Clarity AD study, lecanemab demonstrated a consistent slowing of decline over 18 months in clinical (global, cognitive, functional, and quality of life) outcomes which if used early in the clinical paradigm has shown to slow disease progression for up to 36 months, and reduction in brain amyloid in early Alzheimer's disease. Herein, we will highlight the mechanism-based rationale for continued lecanemab dosing, providing both the current supportive evidence and outstanding questions. Relevant Alzheimer's disease background will be discussed, including the impact of the latest diagnostic criteria. We will share insights on Alzheimer's disease pathophysiology, including how the ongoing/chronic nature of the disease requires continuous therapy. In addition, we will review the latest data on lecanemab mechanism and overview of the mechanistic rationale for development of lecanemab Aβ immunotherapy. The role of tau aggregates, a predictive biomarker for the emergence of neurodegeneration, will be explored. Additional insights on continued dosing based on current knowledge of lecanemab mechanism will be shared. An overview of the mechanistic differences and their implications among anti-amyloid antibodies will be presented. **Keywords:** Clarity AD, lecanemab, mechanism, phase 3 trial. **Disclosure:** M Irizarry is an employee of Eisai.

Presentation 2: Pharmacologic Support for a Maintenance Dosing Regimen with Lecanemab: An Update on the Latest Clinical Pharmacology Data and Modeling, L. Reyderman, B. Willis, N. Penner, A. Charil, S. Dhadda, S. Hersch, M. Irizarry, L. Kramer

Lecanemab is a humanized IgG1 monoclonal antibody binding with high affinity to protofibrils of amyloid-beta (Ab) protein. In 18-month clinical studies, lecanemab has been shown to reduce a complex group of protein interactions associated with early symptomatic Alzheimer's disease (AD) and slow decline on clinical endpoints of cognition and function for up to 36 months to date. In prior research, results from the phase 2 study gap period (no study drug treatment) between the end of the study core and the beginning of retreatment in the open-label extension (OLE) provides evidence regarding the need for continued maintenance therapy beyond 18 months. Clinical pharmacology data can help supplement the clinical and mechanistic data to establish the rationale for ongoing treatment. Herein, we will present how the latest clinical pharmacology data and modeling support continued long-term maintenance lecanemab dosing. Data from the lecanemab phase 2 study (Study 201) and Clarity-AD (Study 301) were pooled, and biomarker, amyloid PET, and CDR-SB scores were used to develop models describing the change in amyloid PET and plasma biomarkers with lecanemab treatment. A model was also developed to show how change in amyloid PET predicts slowing of disease progression. These models were used to explore the change in plasma biomarkers, amyloid PET, and CDR-SB over 4 years, and to evaluate the effect of transitioning to less frequent dosing of lecanemab following 18 to 24 months of initial treatment. Simulations projected that CDR-SB difference between lecanemab and placebo subjects continued increasing over the 4-year simulation period. Low amyloid and less severe disease at baseline were associated with slower disease progression. Continued treatment with lecanemab at less frequent dosing intervals following an initial treatment period was demonstrated to effectively maintain the benefit associated with lecanemab treatment on plasma biomarkers, amyloid PET, and clinical outcomes as compared to the initial dosing regimen. We will offer learnings from these recent analyses into the ability of amyloid reduction to be predictive of slowing Alzheimer's disease progress, the importance of early initiation of treatment, and the utility of continued lecanemab maintenance treatment. **Keywords:** lecanemab, Clarity AD, maintenance, pharmacology. **Disclosure:** L Reyderman is an employee of Eisai.

Presentation 3: Evidence for a Continued Benefit for Long-Term Lecanemab Treatment: A Benefit/Risk Update from Long-Term Efficacy, Safety and Biomarker Data, C. van Dyck, R. Sperling, S. Dhadda, D. Li, S. Hersch, M. Irizarry, L. Kramer

Lecanemab, a humanized IgG1 monoclonal antibody that binds with high affinity to amyloid-beta (Ab) protofibrils, was formally evaluated as a treatment for early Alzheimer's disease in a phase 2 study (Study 201) and the phase 3 Clarity AD study. These trials both included an 18-month, randomized study (core) and an open-label extension (OLE) phase where eligible participants received open-label lecanemab for up to 36 months to date. Clinical (CDR-SB, ADAS-Cog14, and ADCS-MCI-ADL), biomarker (PET, Ab42/40 ratio, and ptau181) and safety outcomes were evaluated. Results demonstrated that lecanemab substantially reduced markers of amyloid and significantly slowed clinical decline on multiple measures of cognition, function, and quality of life in early AD at 18 months and continued for 36 months to date. Lecanemab was associated with amyloid-related imaging abnormalities (ARIA) and infusion reactions, tending to occur early in treatment. Although lecanemab has established a clear benefit/risk benefit for 18 months of treatment, the evidence for continued treatment beyond 18 months has yet to be firmly established. In an effort to evaluate the current evidence base for longer-term dosing, this presentation will summarize the latest clinical and biomarker results from the lecanemab Clarity AD study, including the latest efficacy and safety data out to at least 36 months. We will share details on how lecanemab has demonstrated the ability to slow tau spread in different brain regions of individuals with early Alzheimer's disease and discuss the relevance of these data on continued treatment. Evaluations of clinical and biomarker outcomes by participants considered as having a 'delayed start' (core:placebo followed by OLE:lecanemab) versus those with an 'early start' (core:lecanemab followed by OLE:lecanemab) cohorts will be presented and discussed. Finally, the overall case for the need and benefit of early initiation and continued dosing, considering mechanistic, pharmacology, biomarker and clinical results, will be discussed. **Keywords:** lecanemab, Clarity AD, Phase 3, open-label extension, long-term. **Disclosure:** Christopher van Dyck is a consultant for Roche, Eisai, Cerevel, and Ono and receives research support from Biogen, Eisai, Roche, Genentech, Eli Lilly, Janssen, UCB, Cerevel, and Biohaven

LBS1- THE AHEAD 3-45 STUDY: DESIGN AND RESULTS OF A NOVEL SCREENING PROCESS FOR A PRECLINICAL AD TRIAL. R. Raman[1], P. Aisen[1], R. Sperling[2,3], D. Molina Henry[1] *(1. Alzheimer's Therapeutic Research Institute, University of Southern California - San Diego (United States), 2. Brigham and Women's Hospital, Harvard Medical School - Boston (United States), 3. Massachusetts General Hospital, Harvard Medical School - Boston (United States))*

Presentation 1: The AHEAD 3-45 Study: Adaptation to Challenges

Background: Lecanemab and donanemab have been fully approved by the FDA to treat early symptomatic Alzheimer's disease by removing amyloid from brain, slowing disease progression by about 30%. The AHEAD project evaluates lecanemab treatment of individuals at the pre-symptomatic stage of disease based on the hypothesis that very early intervention will provide greater impact on the disease course. AHEAD, a public-private partnership project of the Alzheimer's Clinical Trials Consortium and Eisai, Inc., consists of two studies sharing sites, screening procedures and study activities. A45 is a large (N≈1000) Phase 3 trial of intravenous lecanemab in amyloid positive (at least 40 centiloids on amyloid PET) clinically normal individuals, with change in the Preclinical Alzheimer's Cognitive Composite-5 (PACC5) as the primary outcome measure. A3 is a smaller (N≈400) Phase 2 trial of a lower-dose regimen of intravenous lecanemab in clinically normal individuals with intermediate amyloid (20-40 centiloids on amyloid PET) for four years with biomarkers (amyloid and tau PET, plasma measures) as key outcomes. The double-blind phase is followed by an extension phase during which all participants receive open-label lecanemab. The enrollment process is nearing its end, with target sample sizes now met for A45 and A3. **Objective:** This presentation provides an overview of the enrollment phase of the study, with a focus on the challenges faced by the AHEAD project and sets the stage for the subsequent talks on pre-randomization data. **Method:** Review of major adjustments to the AHEAD program during its recruitment phase. **Results:** Screening for AHEAD, which requires amyloid PET scanning (with disclosure of eligibility) and tau PET scanning, as well as extensive cognitive, clinical and laboratory assessments, with a very high screen-fail rate (particularly in ethnic- and racial-underrepresented groups), has been a lengthy and burdensome process for study sites and participants. The availability of accurate plasma assays of AD pathology enabled changes that improved the efficiency of screening. The first in-clinic screening visit was abbreviated to focus on plasma testing, minimizing the burden of screen-fails. A pre-screening process, including remote plasma phenotyping, was implemented to further reduce burden on sites and potential participants. These benefits increased as plasma testing, with mass spectroscopy assays of aß ratios and ptau217, became even more accurate. Full approval and coverage of lecanemab therapy for early AD in the United States in 2023 enabled clinical use of lecanemab for symptomatic disease. AHEAD study participants who progressed to symptomatic disease during the double-blind phase could be eligible for clinical treatment. The study team therefore implemented a procedure for accelerated transition to the open-label extension phase based on consecutive global Clinical Dementia Rating scores greater than zero in conjunction with episodic memory impairment assessed on secondary measures, plus clinical assessment of mild cognitive impairment or mild dementia by site clinicians. This strategy aims to offer lecanemab therapy to all study participants who are eligible for clinical treatment. **Conclusion:** The AHEAD project is now completing enrollment into A45 and A3. Effective responses to recruitment and study challenges have been implemented. Results are expected in 2028.

Presentation 2: Screening Plasma Biomarkers, Amyloid and Tau PET Imaging in the AHEAD 3-45 Study

Background: Recent trials with anti-amyloid antibodies at the early symptomatic stages of Alzheimer's disease (AD) demonstrated greater clinical benefit at lower levels of amyloid and tau pathology. The AHEAD 3-45 Study utilizes a shared screening algorithm to enroll two sister trials (A3 and A45) in cognitively unimpaired individuals testing targeted dosing of lecanemab based on screening amyloid PET. We sought to: 1) evaluate the impact of iterative adjustments to the plasma screening algorithm on amyloid PET eligibility, and 2) in the subset of participants amyloid PET eligible for A3 and A45, to assess the cross-sectional inter-relationships of plasma

markers, Amyloid and Tau PET, and cognition to begin to elucidate the "critical windows" for early intervention that could prevent future cognitive decline. **Methods:** Amyloid PET imaging with 18-F-NAV4694 is used to determine eligibility for A3 (20-40 Centiloids (CL)) and A45 (>40CL) trials. Tau PET imaging with 18-F-MK6240 was acquired on amyloid eligible participants. Individualized anatomic regions defined with FreeSurfer MRI were utilized to measure tau PET in medial temporal lobe (MTL) and early neocortical (NEO) composite regions. Plasma screening with C2N mass spectrometry initially utilized an Ab42/40 ratio and later a phosphorylated-tau217/non-phosphorylated tau ratio (p-tau217r). A plasma algorithm including age, APOE, Ab42/40 and p-tau217r was iteratively optimized to determine Amyloid PET eligibility. Baseline Tau PET was obtained on all Amyloid eligible participants. Cognition was assessed with the Preclinical Alzheimer's Cognitive Composite (PACC5). **Results:** Screening for the AHEAD 3-45 Study is continuing in final stages. The Amyloid PET screen-fail rate decreased from >70% prior to plasma screening to ≈50% with Ab42/40 and then down to <30% with increasingly stringent thresholds for p-tau217r. Plasma p-tau217r began to rise prior to 10CL and showed AUC-ROC of .95 prediction of >20CL. The mean/SD amyloid CL for those eligible for A3 (N=348 with both Amyloid and Tau PET data currently available) is 29.3±5.9 CL and for A45 (N=886) is 74.7±25.7. The A3 MTL Tau SUVr is 1.08±0.28 and 1.29±0.41 in A45 (group difference $p<0.001$), and A3 NEO Tau was 1.07±0.16 and 1.21±0.37 in A45 ($p<0.001$). Across A3 and A45 (N=1234), both MTL ($b=-0.72;p<0.001$) and NEO composites ($b=-1.09;p<0.001$) were associated with screening PACC5. Even within the smaller and earlier pathology A3 group, there was a trend level association between MTL Tau and PACC ($b=-.77;p=0.07$). No cross-sectional associations were observed between p-tau217r or Amyloid PET with PACC5 within the restricted range of intermediate-elevated amyloid across A3-A45 eligible participants. **Conclusion:** The introduction of plasma assays, in particular p-tau217r, substantially improved the Amyloid PET screen-fail rate. The early rise in p-tau217r may prove useful in enrolling future even earlier interventional trials aimed at preventing amyloid positivity. Higher levels of MTL and Neocortical tau were observed in the higher amyloid (A45) group. Tau PET showed the strongest contemporaneous relationship with screening cognition but was evident with MTL tau even at lower (A3) levels of amyloid. These findings support Tau PET as a key endpoint, serving as a potential bridging outcome between amyloid and cognition at these very early stages of AD.

Presentation 3: Racial and Ethnic Differences in Plasma P-tau217 Biomarker Eligibility Rates in a Preclinical AD Trial

Background: Participants from racial and ethnic underrepresented groups (RE-URGs) have previously demonstrated disproportionately lower rates of biomarker eligibility in preclinical AD trials, compared to non-Hispanic White (NHW) adults. In the AHEAD 3-45 study, an ongoing preclinical AD program, plasma biomarker screening was performed prior to clinical or cognitive assessments. Differential eligibility of RE-URGs was observed in the first 4905 plasma screened participants using an age and APOE ε4 adjusted Aβ 42/40 algorithm [1]. Given that p-tau217 has been identified as a superior marker of amyloidosis, it has replaced Aβ 42/40 ratio in the plasma screening algorithm as a primary factor. Here we report eligibility rates for the subsequent screened participants incorporating this biomarker test. **Method:** AHEAD participants who underwent plasma screening in North America using the p-Tau217 algorithm were assigned to mutually exclusive groups: Hispanic Black (HB), Hispanic White (HW), Non-Hispanic Asian (NHA), Non-Hispanic Black (NHB) and NHW. We used univariate logistic regression models to evaluate group differences in eligibility rates as determined by an algorithm that includes plasma p-tau217 ratio (phosphorylated p-tau217/non-phosphorylated ptau217 measured by mass spectrometry) adjusted by Aβ 42/40 ratio, age and APOE ε4 status. The algorithm determined likelihood of elevated PET amyloid at the >18 CL amyloid PET cutpoint. **Results:** Among 6449 screened participants included in these analyses, 62 (0.9%) were HB, 877 (13.1%) were HW, 155 (2.3%) were NHA, 512 (7.7%) were NHB, 4843 (72.4%) were NHW. 236 (3.5%) identified as other or unknown race or ethnicity were excluded from these analyses. 1588 (24.6%) of screened participants met plasma eligibility; but eligibility rates significantly differed across groups (0.5% HB, 8.6% HW, 0.5% NHA, 3% NHB and 85.9% NHW; $p<0.001$). Using NHW participants as a reference group, we observed increased odds of plasma ineligibility among racial and ethnic underrepresented groups, HB OR=2.9% [CI 1.4, 6.97]; HW OR=1.6 [95% CI 1.3, 1.9]; NHA OR=2.1 [95% CI 1.4, 3.4]; NHB OR=1.6, [95% CI 1.3, 2.0)]. Plasma-eligibility was greater in individuals who were APOE ε4 carriers across all groups (29.4% vs 4.4% in HB, 41.3% vs 11.4% in HW, 39.4% vs 6.7% in NHA, 38.1% vs 6.7% in NHB, 50.9% vs 12.4% in NHW, carriers vs non carriers, respectively). Overall, 811 (51%) plasma-eligible participants proceeded to PET screening; among these 552 (68%) were PET-eligible. Proportions of plasma-eligible individuals who were also PET-eligible were not statistically different (3 (75%) HB, 48 (63.2%) HW, 3 (50%) NHA, 17 (68%) NHB, 481 (70.4%) NHW; p= 0.4). **Conclusion:** We observed differences among racial and ethnic groups in p-tau217 eligibility consistent with previous reports using plasma Aβ 42/40. Among plasma-eligible participants, we observed similar PET eligibility rates across groups. Our findings support p-tau217 as an accurate blood biomarker in predicting likelihood of PET eligibility and further underscore a single plasma threshold is equally effective at enriching preclinical AD populations across racial and ethnic groups.

LBS2- ONE-YEAR EXPERIENCE ON THE USE OF LECANEMAB IN CLINICAL PRACTICE

Presentation 1: Lecanemab Treatment in Real World Settings in the United States, M. Sabbagh[1], C. Zhao[2], M. Mahendran[3], S. Ryeong Jang[2], F. Laliberté[3], K. Zhang[3], F. Frech[2], K. V. Nair[4] *(1. Department of Neurology Barrow Neurological Institute - Phoenix, Arizona (United States), 2. Eisai Inc. - Nutley, New Jersey (United States), 3. Analysis Group, Inc. - Montréal, Québec (Canada), 4. University of Colorado Anschutz Medical Campus - Aurora, Colorado (United States))*

Background: Lecanemab is the first anti-amyloid monoclonal antibody to receive full approval in the United States for the treatment of early Alzheimer's disease (AD), specifically mild cognitive impairment (MCI) or mild dementia due to AD. Limited real-world data are available on patients receiving lecanemab. This study aims to describe patient demographic and clinical characteristics, diagnostic and utilization patterns in real-world settings. **Methods:** This retrospective observational study used administrative claims data from the Komodo Research Database (1/1/2016–06/30/2024). Patients with ≥1 lecanemab claim between January 6, 2023, and June 30, 2024, and continuous health plan enrollment

or clinical activity≥12 months prior to the first lecanemab administration were included in the study. Continuous clinical activity was defined as consecutive quarters with ≥1 medical or pharmacy claim of any medical/pharmacy utilization. The study observation period per patient was from the first lecanemab administration to the most recent clinical activity or end of health plan enrollment. Descriptive analyses of patient demographics, clinical characteristics, and diagnostic process leading up to lecanemab initiation and treatment patterns post-lecanemab initiation were conducted. Persistence to lecanemab treatment was defined as no interval of >90 days between two consecutive infusions and was evaluated using the Kaplan-Meier method. **Results:** A total of 3,155 patients initiating lecanemab met the inclusion criteria (2,640 from open claims, 515 from closed claims); mean follow-up post initiation was 129.1 days (standard deviation, SD 91.1). Over 90% of these patients initiated lecanemab in or after October 2023. Mean age was 75.0 (SD 6.8) years; 55.8% were female, 84.3% White, 53.7% from the South, and 89.4% Medicare beneficiaries. The vast majority (93.3%) received infusions in urban settings. The most prevalent comorbid conditions were dyslipidemia (54.4%), hypertension (45.7%), sleep disorders (25.2%), joint disorders (24.3%), and dorsalgia (22.3%). According to diagnosis records within 12 months before lecanemab initiation, 60.8% of patients had MCI and 83.8% had AD. Within 30 days prior to index date, 6.0% of patients had an MCI diagnosis and 76.5% had an AD diagnosis. Average time from the earliest observed MCI or AD diagnosis in 2023 or onward to initiating the first lecanemab dose was 4.9 months (SD 4.4). During lecanemab treatment, 3.7% of patients were using anticoagulant medications, and 67.6% were on an acetylcholinesterase inhibitor or memantine. Among each patient with ≥2 lecanemab claims, the average number of lecanemab administrations per month was 1.9 (SD 0.7), with 16.5 (SD 9.2) days apart between consecutive administrations. Time to first MRI post lecanemab initiation was 46.7 days (SD 23.4). Persistence to lecanemab treatment was 85.1% at 4 months of follow-up. Treatment patterns were consistent in the subset of 515 patients with closed data. **Conclusion:** Lecanemab appeared to be utilized in appropriate patient populations within the dosing and monitoring guidelines in the FDA approved label. Access in rural settings and limited use in minorities may require pathways and outreach programs to close these gaps. As clinical practice is rapidly evolving in the AD dementia space, future research may seek to describe how new diagnostics and treatments impact patient outcomes. **Keywords:** lecanemab, anti-amyloid, monoclonal antibody, mild cognitive impairment, Alzheimer's disease. **Disclosures:** This study was funded by Eisai Inc. and Biogen.

Presentation 2: : Lecanemab Use in Clinical Practice at an Academic Medical Center, L. Honig[1], K. Bell[1], W. Gonzalez[1], V. Dimuro[1], J. M. Kim[1], R. Jagannathan[1], J. Noble[1], K. Marder[1], R. Mayeux[1] *(1. Columbia University - New York (United States))*

In the USA, the FDA has approved for Alzheimer's disease three drugs (aducanumab, lecanemab, and donanemab) that have been developed as disease-modifying treatments. Lecanemab has had full traditional FDA approval for 14 months, with full coverage by the Center for Medicare Services. This has resulted in increased use of these anti-amyloid monoclonal antibodies, which in 18-month long clinical trials have demonstrated both biomarker efficacy and slowing of clinical progression of Alzheimer's disease by cognitive and functional measures. Due to the low frequency, but potentially serious side-effects of these drugs, there has been concern that their more widespread use might be accompanied by greater hazards. Here we report real-world clinical experience, in which patients in our academic practice have been prescribed drug, including many who would not have met clinical trial eligibility inclusion criteria. Prescription of the medication has been per package insert, and contingent only upon: diagnosis of AD, early stage disease, amyloid confirmation by CSF or PET, acceptable ARIA-H at baseline MRI, and non-mandatory apolipoprotein-E genotyping. We use a variety of infusion centers and MRI centers, without the uniformity of facilities specified in clinical trials. Patients and their families have had strong interest in anti-amyloid therapy, with apparent good understanding and general acceptance of risks of ARIA-E and ARIA-H. The main barriers associated with use of the drug have been severity of disease, excessive ARIA-H on baseline MRI, caution in apolipoprotein E (APOE) E4 homozygotes, and denied coverage by insurers/payors, other than standard Medicare. We present our center's data on our first 148 patients prescribed lecanemab. Patient average age is 73 ± 9 yr (range 35 - 90); 55% are women; ethnic distribution included 91% white, 6% Hispanic, 3% Asian, and 1% Black. Amyloid confirmation was accomplished by CSF testing alone in 81%, the remainder by PET, and 15% had both CSF and PET performed. APOE testing was accepted by 88% of patients, with distribution of treated patients including 38% non-carriers, 46% E4 heterozygotes, and 15% E4 homozygotes. Patients have had from 1 to 32 infusions each. Adverse event rates have been similar to those in clinical trials with 14% infusion reactions (headache, chills, warmth, and fatigue), mostly but not exclusively after the first one to three infusions. The rate of ARIA–E was 6% (all except one case occurring in first 3 months; one case at 6 months), and a low level of incident ARIA-H. There was a single case of symptomatic ARIA in a APOE4 homozygote, in which there was concomitant severe ARIA-E, and mild ARIA-H, diagnosed promptly by triggered MRI after aphasia developed shortly following 3rd infusion; unfortunately the patient died after developing refractory focal status epilepticus; this was the only death. Overall, there was suspension or discontinuation of therapy in 9% of treated patients (6% due to ARIA, 1% due to persistent infusion reactions, 2% due to disinterest). The aggregate findings at our center suggest that clinical experience with lecanemab may be not dissimilar to that in clinical trials, and that despite a small risk of unavoidable serious adverse events, there is good ease of use, general safety and tolerability.

Presentation 3: Lecanemab Use in Clinical Practice in Japan

LBS3- RESULTS FROM TOGETHER, A DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II STUDY EVALUATING EFFICACY, SAFETY AND TOLERABILITY OF BEPRANEMAB IN PRODROMAL–MILD AD.

M.E. Barton[1], R.J. Bateman[2], W. Byrnes[1], T. Buchanan[3], B. Van Den Steen[3], H. Van Tricht[3], I. Rebollo Mesa[4], T. Arnould[5], K. Taiyari[6], O. Famodimu[7], J. Bloemers[8], R.P. Maguire[3], P. Downey[3], C. Ewen[6], M. Citron[3] *(1. UCB - Raleigh, Nc (United States), 2. Washington University School of Medicine - St Louis, Mo (United States), 3. UCB - Braine-L'alleud (Belgium), 4. UCB - Madrid (Spain), 5. UCB (contracted via Veramed Ltd, Twickenham, UK) - Braine-L'alleud (Belgium), 6. UCB - Slough (United Kingdom), 7. UCB - Oakville, Ontario (Canada), 8. UCB - Breda (Netherlands))*

Presentation 1: Identification and development of bepranemab, an antibody targeting the mid-region of tau

In tauopathies such as Alzheimer's disease (AD) and progressive supranuclear palsy (PSP), it is hypothesised that pathological tau protein physically moves from neuron to neuron, driving pathology and disease progression [1]. However, this has yet to be confirmed in human disease [2]. The tau protein spread hypothesis has attracted the attention of drug developers, as this extracellular target is accessible to therapeutic antibodies designed to neutralise soluble extracellular proteins [3]. We have previously described our approach towards generating such a tau-targeted therapeutic antibody, bepranemab [1,4]. Bepranemab is a recombinant, humanised full-length monoclonal antibody of the immunoglobulin G4 (IgG4) subclass. The IgG4 subclass was chosen because effector function or immune activation is not required for the proposed mechanism of action. In the absence of detailed molecular characterisation of human spreading tau species, bepranemab was originally identified using a quantitative in vitro cell-based assay to screen a number of anti-tau monoclonal antibodies. Bepranemab, which targets amino acids 235–250 – proximal to the microtubule binding region, was identified as having the highest activity against human-brain-derived tau seeds [4]. In contrast, tau-N-terminus targeting antibodies did not work in the assay, suggesting they would be ineffective in the clinic due to failure to block the spreading species [4]. Subsequent to standard preclinical development, the bepranemab first-in-human study was a single-ascending-dose design in healthy participants. Bepranemab demonstrated dose-linear pharmacokinetics (PK), dose dependent reduction of cerebrospinal fluid (CSF)-free tau and no clinically relevant safety findings. A PK study in healthy participants of Japanese descent produced similar outcomes. Based on these data, a Phase I study in people living with PSP was initiated with monthly dosing over 52 weeks. Bepranemab was well tolerated, and no new safety concerns were identified. In this patient group, the bepranemab CSF: serum ratio had a median value of 0.2% at one week after the first administration, and an ~80% reduction in mean levels of bepranemab-targeting free tau species in the CSF was observed. While direct measurement of engagement of the spreading tau species was not possible, the dose-dependent reduction of free CSF tau was predictive of dose administration. These data supported advancing to a large Phase II study in AD. **References:**

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Presentation 2: Results from TOGETHER, a Phase II study of bepranemab in prodromal–mild AD

Background: Preclinical and clinical data to date support the continued investigation of bepranemab for the treatment of tauopathies, including Alzheimer's disease (AD). **Methods:** TOGETHER (AH0003) is a Phase II, global, multicentre, participant- and investigator-blind, placebo controlled, parallel-group study designed to investigate the efficacy, safety and tolerability of bepranemab (two dose levels) – administered intravenously every 4 weeks – versus placebo in participants with prodromal (40% of study population) or mild (60% of study population) AD over an 80-week treatment period, followed by a 48-week open-label extension period, and a 16-week safety follow-up period. The primary objective was to investigate the effect of bepranemab versus placebo on the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB), measured as the change from Baseline to Week 80 in CDR-SB total score. Secondary objectives included investigating: pharmacokinetics (PK); safety and tolerability; the effect of bepranemab on tau burden (change from Baseline to Week 56 and Week 80; assessed by positron emission tomography [PET] imaging using the tau PET tracer Genentech Tau Probe-1) and effect on cognitive and functional measures (change from Baseline in AD Assessment Scale-Cognitive Subscale [ADAS-Cog]14, Amsterdam-Instrumental Activities of Daily Living [A-iADL] and mini-mental state examination [MMSE] at Weeks 56 and 80). Eligible participants met the National Institute of Aging-Alzheimer's Association (NIA-AA) 2018 Stage 3 or 4 definitions of prodromal or mild AD. Participants with prodromal AD were required to have a global CDR score of 0.5 and Clinical Dementia Rating Scale-Memory Box (CDR-MB) score >0.5 at Screening and Baseline; participants with mild AD were required to have a global CDR score of 0.5–1.0 and a CDR-MB score >0.5 at Screening and Baseline. Additional key eligibility criteria included a score <85 for delayed recall domain of the Repeatable Battery for the Assessment of Neurological Status, MMSE score >20 at Screening and the presence of cerebral amyloid beta (Aβ) accumulation by either a positive centrally read amyloid PET scan or positive cerebrospinal fluid pTau181/Aβ1-42 ratio according to NIA-AA 2018. **Results:** Study enrolment met its goals: in total, 466 participants were enrolled across three study arms (high-dose bepranemab, low-dose bepranemab, placebo). The TOGETHER double-blind treatment period study results are expected in September–October 2024. We will present the primary and key secondary data from TOGETHER, including clinical safety, change from Baseline in CDR-SB, ADAS-Cog14, A-iADL, MMSE and tau load as measured by PET imaging. **Conclusions:** TOGETHER is a proof-of-concept study that employs clinical outcome measures, imaging and PK to assess the ability of bepranemab to slow the progression of AD.

Presentation 3: Bepranemab, the tau mid-region hypothesis, and future implications

The data from TOGETHER, a large randomised, double-blind, placebo-controlled study of bepranemab in patients with prodromal or mild Alzheimer's disease (AD), provide an important contribution to the understanding of tau biology in AD. The data will be reviewed to test the hypothesis that targeting the mid-region of tau may achieve biological engagement with anti-tau antibodies and potential impact on the downstream biology, including cognitive and clinical outcomes. The data also provide insights into how tau biology

is altered with anti-tau antibody treatment and the effects on other biological measures. The clinical, cognitive and functional measures, as well as tau-PET imaging and safety data from the TOGETHER study will be critically assessed, and their clinical relevance reviewed in the context of previous anti-tau- and anti-amyloid-directed studies. Finally, the longer-term implications for future research, development and clinical study designs in AD will be reviewed. **Keywords:** Tau, Alzheimer's disease, Phase II clinical trial, bepranemab. **Clinical Trial Resistry:** NCT04867616; https://clinicaltrials.gov/study/NCT04867616. **Disclosures:** MEB, WB, TB, BVDS, HVT, IRM, KT, OF, JB, RPM, PD, CE and MC receive stock and compensation as all full-time employees of UCB. TA is contracted with UCB via Veramed Ltd a contractor of UCB. UCB (contracted via Veramed Ltd, Twickenham, UK), Braine-l'Alleud, Belgium. PD is an inventor of bepranemab. RJB is an employee of Washington University School of Medicine, a C2N Diagnostics Owner and Scientific Advisory Board Member and an owner of stock/shares in C2N Diagnostics. RJB is on the advisory council or committee for Biogen Combination Therapy for AD Advisory Board (unpaid); Roche Gantenerumab Advisory Board (unpaid); UK Dementia Research Institute at UCL Advisory Board; Stanford University Next Generation Translational Proteomics for AD and Related Dementias Advisory Board (unpaid). RJB also reports honoraria from Korean Dementia Association (lecture); American Neurological Association (lecture); Fondazione Prada (lecture); Weill Cornell Medical College (lecture); Harvard University (lecture); University of Pennsylvania (lecture); grants/funds from National Institutes of Health; the National Institute on Aging; Eisai Co., Ltd.; Alzheimer's Association; GHR Foundation; Hoffman La-Roche; Eli Lilly, and an anonymous organisation. His lab receives research funding from the National Institutes of Health; Alzheimer's Association; BrightFocus Foundation; Rainwater Foundation; Association for Frontotemporal Degeneration FTD Biomarkers Initiative; Avid Radiopharmaceuticals; Janssen; Tau Consortium; Novartis; Centene Corporation; Association for Frontotemporal Degeneration; the Cure Alzheimer's Fund; Coins for Alzheimer's Research Trust Fund; The Foundation for Barnes-Jewish Hospital; Good Ventures Foundation; DIAN-TU Pharma Consortium; Tau SILK Consortium (AbbVie, Biogen, Eli Lilly and Company and an anonymous organisation); the NfL Consortium (AbbVie, Biogen, Bristol Meyers Squibb, Hoffman La Roche), and the Tracy Family SILQ Center. Other potential financial relationships for RJB include Washington University w/ RJB as coinventor - Methods for Measuring the Metabolism of CNS Derived Biomolecules In Vivo, US nonprovisional patent application 12/267,974; Washington University w/ RJB as coinventor - Methods for Measuring the Metabolism of neurally Derived Biomolecules in vivo, US nonprovisional patent application 13/005,233; Washington University w/ RJB as coinventor - Plasma based methods for detecting CNS Amyloid Disposition, US nonprovisional patent application 62/492,718; Washington University w/ RJB as coinventor - Plasma based methods for determining A-Beta Amyloidosis, US nonprovisional patent application 16/610,428; Washington University w/RJB as coinventor – Methods of Treating Based on site-specific tau phosphorylation, US nonprovisional patent application 17/015,985; Washington University w/RJB as coinventor – Tau Kinetic Measurements, US nonprovisional patent application 15/515,909. RJB reports non-financial conflicts with Eisai, Janssen, Hoffman La Roche – Receipt of drugs and services, DIAN TU Nex Gen Trial & DIAN-TU Open Label Extension Gantenerumab.

LBS4- CANNABINOID BASED MEDICATIONS FOR NEUROPSYCHIATRIC SYMPTOMS IN ALZHEIMER'S DEMENTIA

Presentation 1: Heterogeneity of treatment response: A post hoc analysis of clinical factors from a randomized placebo-controlled trial of nabilone for agitation in Alzheimer's disease, Oriel J. Feldman[1,2], Myuri Ruthirakuhan[3], Nathan Herrmann[1,3,4], Damien Gallagher[1,3,4], Giovanni Marotta[1,6], Alex Kiss[3], Hui Jue Wang[1,2], Yejin Kang[1,2], Sandra E. Black[3,5], Krista L. Lanctot[1,2,3,4] *(1. Neuropsychopharmacology Research Group, Sunnybrook Health Sciences Centre, Toronto, Ontario (Canada), 2. Department of Pharmacology and Toxicology, University of Toronto (Canada), 3. Hurvitz Brain Sciences Program, Sunnybrook Research Institute (Canada), 4. Department of Psychiatry, Sunnybrook Health Sciences Centre (Canada), 5. Division of Neurology, Sunnybrook Health Sciences Centre (Canada), 6. Division of Geriatric Medicine, Sunnybrook Health Sciences Centre(Canada))*

Background: Agitation is one of the most prevalent neuropsychiatric symptoms (NPS) of Alzheimer's disease (AD). Agitation in AD (AAD) is frequently accompanied by pain, eating changes and other behavioural changes. Currently, agitation is most frequently treated with atypical antipsychotics, which pose significant risk in geriatric populations. Cannabis based medications have recently been explored as they have high potential for addressing agitation and frequent comorbidities simultaneously through neurotransmitter modulation and neuroinflammation reduction [1]; A randomized placebo-controlled crossover trial of nabilone for agitation in Alzheimer's disease (NAB-AAD) found that nabilone was effective in treating agitation with a medium effect size (Cohen's d = 0.52) [2]. We assessed whether clinical factors could be used to predict treatment response to nabilone for agitation. **Methods:** The NAB-AAD data showed no significant treatment order or carry over effects [2], so phases were treated as individual arms for this analysis. Twenty-one clinical factors that were potential predictors, including demographics, other NPS and concomitant medications, were identified a priori. Next, factors were analyzed for their ability to predict response using the major outcome variable of the NAB-AAD trial, the Cohen-Mansfield Agitation Inventory (CMAI). Specifically, univariate analyses and likelihood ratio tests (LRT) were conducted on each factor using NAB-AAD data to estimate individual factor effects on treatment response. Factors showing a difference of at least 8 points on the CMAI between factor levels were included in the subsequent multivariate analysis. Multivariate regression was used to model interactions between treatment and the included factors. Differences in multivariate scores were used to calculate index scores based on identified predictive characteristics for each participant. Index scores for each participant were bootstrapped 1000x to obtain power, and results were grouped into quartiles. **Results:** 35 patients (28 M (80%), mean age [SD] 87.0 [10.2] years, CMAI 67.4 [17.7], standardized Mini-Mental State Exam (sMMSE) 6.6 [6.8]) had complete data for clinical predictors, allowing for 70 cases to be analyzed. Six predictors met criteria for inclusion (difference of -8 points on CMAI) in multivariate modelling, where nabilone was more effective in participants with sMMSE scores > 5 (Δ level estimates = -12.0), higher levels of pain (-15.8), depressive symptoms (-13.4), irritability (-12.2), and appetite and eating changes (-12.5) and not receiving concomitant cholinesterase inhibitors (ChEI) (-8.4). Those in the top two quartiles of predictor scores had large reductions

in agitation (mean [SD] = -24.6 [6.3]; -13.0 [6.3]) compared with the bottom two quartiles (-4.8 [2.7]; 7.2 [4.2]) for nabilone compared with placebo. Reductions for those in the top quartile exceeded the CMAI minimal clinically important difference (17 points) [3]. **Conclusion:** AD patients with pain, irritability, depressive symptoms and appetite changes, and with less cognitive impairment and not on ChEIs, were most likely to benefit from nabilone compared to placebo. These data are consistent with the expected benefits of cannabinoids. If replicated, these predictors may be useful to guide clinicians on who is most likely to benefit from nabilone as an alternative treatment to manage AAD. **Keywords:** nabilone, agitation, cannabinoids, predictors of response. **Disclosures:** This study was supported by the Alzheimer's Drug Discovery Foundation and the Alzheimer Society of Canada. KLL has received grants or contracts from the Canadian Institutes of Health Research, Alzheimer's Drug Discovery Foundation, Weston Brain Institute, Weston Foundation, Alzheimer's Association Part the Cloud and Cerevel Therapeutics. She has received consulting fees from Boehringer Ingelheim, Bristol Meyers Squibb, Eisai Co. Ltd., Exciva, Ironshore Pharmaceuticals, H Lundbeck A/S, Novo Nordisk, Otsuka and Praxis Therapeutics. **References:** 1. Outen et al. Am J Geriatr Psychiatry. 2021. doi:10.1016/j.jagp.2021.01.015; 2. Herrmann et al. The American Journal of Geriatric Psychiatry. 2019. doi:10.1016/j.jagp.2019.05.002; 3. De Mauleon A et al. Alzheimers Dement. 2021;17(10):1687-1697. doi:10.1002/alz.12335.

Presentation 2: The THC-AD Study: The Efficacy and Safety of Dronabinol treatment for Agitation in Alzheimer's Dementia, B. Forester[1], J.-M. Leoutsakos[2], M. Agronin[3], R. Vandrey[2], P. Rosenberg[2] *(1. Tufts Medical Center, Tufts University School of Medicine (USA), 2.Johns Hopkins University (USA); 3. Miami Jewish Health (USA))*

Background: Neuropsychiatric symptoms (NPS) such as agitation, depression, and apathy pose significant burdens to patients with Alzheimer's disease (AD), caregivers, and healthcare systems. Agitation in AD, characterized by behaviors like restlessness and aggression, is particularly distressing. Based on evidence from a case series of treating agitation in AD (Agit-AD) with dronabinol (oral delta-9-tetrahydrocannabinol; THC), we sought to assess its efficacy in clinical trial (THC-AD). **Methods:** The THC-AD trial was a randomized, double-blind, placebo-controlled clinical trial assessing the efficacy and safety of dronabinol (5 mg twice daily) in 80 patients aged 60-95 with severe Agit-AD. Inclusion criteria mandated a diagnosis of AD and clinically significant agitation, while exclusion criteria included serious medical illnesses and the inability to swallow medication. Subjects' pharmacological regimens were stabilized during the trial, and informed consent was obtained from all subjects or their legally authorized representatives. **Results:** A total of 75 subjects were randomized (38 to dronabinol, 37 to placebo), mean age 78.5 (7.5), 65% female and mean baseline MMSE 8.6 (6.8). Concomitant medication use was common (current antidepressant 73%, current antipsychotic 51%). Compared with placebo, dronabinol significantly reduced agitation scores on the Pittsburgh Agitation Scale (change from baseline to Week 3: -.74 (0.31), p<.02) and NPI-C Agitation/Aggression scales (change from baseline to Week 3: -1.31 (0.67), p<.05), compared to those receiving placebo. No significant differences in adverse events or serious adverse events were reported between treatment arms, indicating that dronabinol was well tolerated among participants. **Conclusion:** Agitation is a prevalent symptom impacting the quality of life of individuals with AD and their caregivers. Traditional therapies such as antipsychotic medications have shown limited effectiveness and elevated risk of stroke-like events and mortality, yet emerging data suggests that cannabinoid-based treatments like dronabinol could serve as viable alternatives. Top-line results from the THC-AD trial demonstrated improvements in agitation symptoms in participants receiving dronabinol, without an increase in adverse events. These findings pave the way for further research into cannabinoid therapies for agitation in AD, emphasizing a need for a deeper understanding of treatment response to enhance future clinical applications and trials. **Keywords:** Alzheimer's disease, agitation, dronabinol, cannabinoid therapy. **CT.gov number for THC-AD:** NCT02792257. **Funding source:** National Institute of Aging: R01AG050515. **Disclosures:** BPF Consultant: Rippl Care, Patina Health, CVS Health.

Presentation 3: Cannabidiol for behaviour symptoms in Alzheimer's dementia, L. Velayudhan, M. Dugonjic, S. Pisani, S. Bhattacharyya *(King's College London (UK))*

Background: There are only a limited number of safe and licensed pharmacological treatment options for Behavioural and Psychological Symptoms (BPSD) in Alzheimer's disease (AD). Cannabidiol (CBD) is a promising medicinal candidate with anti-anxiety properties. We aimed to evaluate CBD versus placebo in patients with AD and BPSD. **Methods:** We conducted a single-site, phase 2a, double-blind, randomised controlled trial with oral CBD (n=8) or placebo (n=7) capsules given for 6 weeks, with dose titrated up to 600mg per day. **Results:** CBD was well tolerated, with no serious adverse events or withdrawal. There was a reduction in anxiety and agitation under CBD, but these effects were not significant. Change in anxiety under CBD was significantly correlated with plasma CBD levels at the end of treatment (r=0.83, p=0.020). **Conclusion:** This underscores the need for larger trials to test the efficacy of CBD as a treatment for anxiety and agitation in people with AD. **Key words:** Alzheimer's disease, cannabidiol, behaviour symptoms, anxiety. **Clinical Trials Register:** EudraCT Number-2019-002106-52. **Disclosure:** LV received study drug from Beckley Canopy Therapeutics/Canopy Growth for this study.

Presentation 4: The Use of THC and CBD in the Treatment of Agitated Persons Living with Dementia at the End of Life, O. Brawman-Mintzer[1,2] (on behalf of the LiBBY Study team) *(1. Ralph H. Johnson VA Health Care System and 2. Medical University of South Carolina, Charleston, SC (USA))*

Background: To date, no body of research exists to guide clinicians in the management of agitation in hospice care patients, with or without dementia. In the absence of appropriate evidence-based guidelines, patients are typically treated with a combination of antipsychotics, benzodiazepines, and opiates. Over 73% of patients in inpatient palliative care were shown to use CNS agents [1]. However, these agents cause significant side effects including confusion, constipation, pruritus, and other neurological side effects [2, 3]. Data from a preliminary, double-blind, placebo-controlled, cross-over study in agitated Alzheimer's disease (AD) patients using nabilone, a synthetic derivative of THC and an agonist at cannabinoid receptors CB1 and CB2, showed statistically significant benefits on measures of agitation in this population that is comparable to hospice care-eligible, agitated subjects suffering from AD or other types of dementia (HAD). For the

Life's End Benefits of Cannabidiol and Tetrahydrocannabinol (LiBBY) Study in HAD patients, we chose to use a combination of THC and CBD oils due to enhanced synergistic effects that such combination can provide while maintaining a low side effects profile. **Methods:** We are conducting a 12-week, phase 2, multicenter, randomized, double-blind, parallel-group, placebo-controlled study in HAD patients, with primary outcomes evaluating the efficacy and tolerability of a THC/CBD oral combination at week 2 and week 12. A total daily dose of 8 mg of THC and 400 mg of CBD dissolved in digestible oil is administered 2 times per day with a maximum of 4 mg of THC and 200 mg of CBD per dose. The study will recruit 150 HAD subjects from 15 US sites over a 2-year period. To facilitate recruitment and retention and to monitor long term safety of the THC/CBD combination, completers of the double-blind study have the option to participate in an open-label extension study. **Results:** Four sites are currently enrolling. Nine sites are in a start-up phase. Of those, eight sites have IRB approval, six have executed contracts, three have met personnel requirements, four submitted state licenses, and two sites have submitted DEA applications. Additional site is in feasibility assessment stage. To date, eleven subjects were screened and ten randomized. Three are females and seven males. The mean age is 79.4 years old. At screening the average Functional Assessment Staging Tool (FAST) score is 6.3, and the average Neuropsychiatric Inventory (NPI) Agitation Subscale score is 7.9. Nine caregivers are spouses, two are adult children, and one deemed "other" (one subject has two caregivers). Three subjects reside in nursing homes and seven at home. Eight completed week 2 primary outcome assessments, three are in the open-label phase and one subject passed away. **Conclusion:** This pioneer study fulfills a significant unmet need. The study design and procedures to operationalize a multisite trial using Scheule 1 drug have been challenging. However, a minimal screen failure rate and high adherence to study protocol have been remarkable. The major delay and challenge of the study has been the regulatory process. The presenter will discuss the barriers to the study implementation and the strategies utilized to overcome them. **Keywords:** agitation, hospice care-eligible, dementia, Alzheimer's disease. **Clinical Trial Registry:** 5R01AG068324-03; https://clinicaltrials.gov; ACTC is funded by a Cooperative Agreement from the NIA, NIH, US [U24AG057437]. **Disclosures:** None. **References:** 1. Kwon et al. https://doi.org/10.1016/j.jpainsymman.2017.03.014; 2. Lindqvist et al. https://doi.org/10.1089/jpm.2012.0205; 3. Hodgson et al. https://doi.org/10.1097/AJP.0000000000000018.

ROUNDTABLES

RT1- ADVANCING COMBINATION THERAPY: A ROUNDTABLE DISCUSSION ON KEY CONSIDERATIONS, PERSPECTIVES, AND PROMISING AVENUES FOR THE FUTURE OF ALZHEIMER'S TREATMENTS. Howard Fillit[1], Jeffrey Cummings[2], Suzanne Hendrix[3], Jin Zhou[4], Mark Mintun[5] *(1. Alzheimer's Drug Discovery Foundation - New York (United States), 2. UNLV – Nevada, Las Vegas (United States), 3. Pentara - Salt Lake City (United States), 4. Eisai – Nutley (United States), 5. Eli Lilly and Company)*

There is growing consensus that the future of Alzheimer's clinical trials depends on efficiently advancing combination therapies – following a similar path to cancer and other chronic diseases. Recent findings underscore the importance of a combination approach. While anti-Aβ monoclonal antibody therapies have shown positive Phase 3 results, these therapies, alone, are likely insufficient to arrest disease progression. We now have a better understanding of the diverse, interconnected mechanisms underlying Alzheimer's disease and aging, as well as promising therapeutics in development that target a wider range of these non-amyloid targets. However, combination therapies raise a complex set of questions for investigators, from preclinical research through clinical trial design to regulatory, statistical, and operational considerations. Additionally, these questions will likely become more complex, as a growing number of people have exposure to anti-Aβ monoclonal antibody therapies in the years ahead. In January 2024, the Alzheimer's Drug Discovery Foundation (ADDF) convened a panel of experts from the research, industry, clinical, and regulatory communities to discuss the key considerations that will guide the path forward to combination therapy. A summary of these discussions will be published in a peer-reviewed manuscript prior to CTAD 2024 and serve as a starting point for discussions at the roundtable. During the roundtable, experts will discuss how the Alzheimer's field can best advance combination therapies, including promising avenues and starting points, opportunities for new collaborative models, implementing lessons from other disease areas, and considerations as investigators plan for the future of these trials.

LBRT1- PLASMA P-TAU217 ASSAYS IN CLINICAL PRACTICE: CURRENT USES AND FUTURE CONSIDERATIONS FOR DIAGNOSING ALZHEIMER'S DISEASE. M. Suárez-Calvet[1], J.B. Braunstein[2], R. Beck[3], M. Vandijck[4], M. Carboni[5], R.M. Edelmayer[6], M. Sabbagh[7], J.M. Schott[8], J. Hendrix[3] *(1. Barcelona Beta Brain Research Centre; Hospital del Mar - Barcelona (Spain), 2. C2N Diagnostics - St Louis, Missouri (United States), 3. Eli Lilly and Company - Indianapolis (United States), 4. Fujirebio Europe N.V. - Gent (Belgium), 5. Roche Diagnostics International Ltd. - Rotkreuz (Switzerland), 6. Alzheimer's Association - Chicago, Illinois (United States), 7. Barrow Neurological Institute - Phoenix, Arizona (United States), 8. Dementia Research Centre, UCL, Queen Square Institute of Neurology - London (United Kingdom))*

Introduction: The timely and accurate diagnosis and treatment of Alzheimer's Disease (AD) remains a challenge in primary and secondary care in part due to inconsistent access to diagnostic tests. In recent years plasma P-tau217 has emerged as the leading blood-based biomarker for the detection of AD neuropathologic change. Plasma P-tau217 has high concordance with amyloid positron emission tomography (PET) and cerebrospinal fluid (CSF) biomarker positivity and is elevated in patients with early symptomatic AD (mild cognitive impairment (MCI) and mild dementia). Plasma P-tau217 has potential for use in clinical care to facilitate equitable, accessible, timely, and accurate diagnosis of AD. It also could aid in the identification of individuals who may be appropriate candidates for anti-amyloid immunotherapy. With the high volume of clinical research studies using P-tau217, a variety of P-tau217 tests are either in late-stage development or commercially available for use in clinical practice. Outstanding questions include the current and future state of this diagnostic tool and the standardization, minimum acceptable performance, criteria and guidelines for appropriate use, interpretation in diverse populations and those with clinical comorbidities, and widespread roll-out and access. In this session, validation data and the intended specific context of use in clinical practice for four clinically/commercially available plasma P-tau217 assays from representative diagnostic companies will be presented,

followed by a discussion with influential academic and patient advocacy thought leaders in a moderated panel to discuss current and future obstacles for use of plasma P-tau217 as a diagnostic tool for AD. Due to the large number and evolving list of P-tau217 assays clinically and commercially available, this roundtable will not be able to review all available assays. The PrecivityAD2™ blood test, CertuitAD® assay, Lumipulse® G pTau 217 Plasma assay, and the Elecsys® pTau217 plasma biomarker test will be presented during the session. A brief overview of each assay covered in this session is described below. **PrecivityAD2™:** The PrecivityAD2™ blood test (C2N Diagnostics) is a clinically available multianalyte assay that aids healthcare providers in ruling in or out AD in symptomatic patients. The test is intended for patients aged 55 and older with signs or symptoms of MCI or dementia, who are undergoing evaluation for clinical AD. The test uses high-resolution LC-MS/MS to quantify concentrations of Aβ42 and Aβ40 isoforms as well as phosphorylated and non-phosphorylated tau217 peptides. Two calculated ratios, Ab42/40 and % P-tau217 (P-tau217/nP-tau217), are then combined into a proprietary algorithm, generating a numeric score ranging from 0 to 100 called the Amyloid Probability Score 2 (APS2), which determines whether a patient is positive (APS2 48-100) or negative (APS2 0-47) for the presence of brain amyloid plaques. The PrecivityAD2™ blood test was validated in 583 participants from the PARIS (an IDEAS sub-study) (NCT02420756) and MissionAD studies (NCT02956486 and NCT03036280) using amyloid PET (CL>25) as the reference standard (53% amyloid positivity). All individuals had symptoms of either MCI (82%) or dementia (18%). The test demonstrated an area under the curve (AUC) of 0.94, 88% accuracy, 88% sensitivity, 89% specificity, 90% positive predictive value (PPV), and 87% negative predictive value (NPV) using a single cut-off value. Additionally, a recent, multi-cohort, prospective clinical practice research study (NCT06122415 and NCT06120361) was conducted in 1213 patients with memory concerns presenting to primary or secondary care in Sweden (50% amyloid positivity for the entire patient population). Using a predetermined single cutoff value and CSF analysis (~93% total cohort) or amyloid PET imaging (~7% total cohort) as reference standards, the APS2 test result, delivered 90% diagnostic accuracy in distinguishing patients with and without AD pathology. Additionally, a high concordance with CSF analysis (AUC 0.96-0.97) was observed. Notably, test accuracy using a single cutoff value was equally high across the patients who presented to primary care or secondary care, and was unaffected by frequent complex comorbidities among the study participants, including cardiovascular disease, dyslipdemia, chronic kidney disease, and diabetes. **CertuitAD®:** The Eli Lilly Clinical Diagnostics Laboratory (ELCDL) plasma P-tau217 Assay (P-tau217 Assay) is an immunoassay, using the Quanterix SP-X Imaging and Analysis System™, commercially available for clinical care in the US as CertuitAD®. The assay is intended for use in patients aged 60 years or older who present with cognitive impairment and are being assessed for AD and other causes of cognitive decline. CertuitAD® is intended to be used as part of a comprehensive diagnostic work-up and provides healthcare providers with a qualitative result reported as positive, negative, or indeterminate. A negative test result is consistent with the absence of amyloid plaques in the brain while a positive test result is consistent with the presence of amyloid plaques, as measured by an amyloid PET scan, using a cut-off of <24 Centiloids to define a negative scan. A test result reported as indeterminate indicates that amyloid plaques may or may not be present. CertuitAD® was clinically validated using samples from a large multicenter trial (NCT04437511) screen population, specifically 2071 participants, aged 60 years and older, who presented with cognitive impairment. The trial participants were comprised of 54% females, with 89% of participants self-identifying as White, and 14% identifying as Hispanic or Latino by ethnicity. In this clinical validation population, a positive assay result demonstrated a PPV of 95%, and a negative assay result demonstrated an NPV of 84% as compared to amyloid PET scan. Using a 2 cut-point analysis, validation data indicated sensitivity to be 91% and specificity of 90%, with an indeterminate rate of 18% (note that sensitivity and specificity were calculated without including indeterminate results). **Lumipulse® G pTau 217 Plasma:** The Lumipulse® G pTau 217 Plasma assay (Fujirebio) can be run on the LUMIPULSE G instruments, chemiluminescent enzyme immunoassay platforms that allow fully automated processing of samples in 30 minutes using single analyte, ready-to-use immunoreaction cartridges. The LUMIPULSE G systems demonstrate low variability (allowing single replicate testing), high sensitivity, and reliable dilutional linearity, and are widely available in clinical laboratories around the world. The assay contains a proprietary P-tau217 mAb in the capturing module combined with detection antibodies directed to the mid-domain of tau and is fully optimized for highly specific analyte detection (100 μL of sample volume). The assay is currently available as research use only, with ongoing investigations for potential in vitro diagnostic use. Several studies evaluated the potential clinical use of the assay in patients presenting with signs and symptoms of cognitive decline including subjective cognitive decline, MCI, AD dementia, non-AD dementia, as well as cognitively healthy/normal subjects. These studies highlighted the potential of this assay to predict Aβ-pathology (based on CSF biomarkers and/or Aβ-PET positivity), achieving AUCs above 0.9. In these studies, the implementation of two cut-points results in high PPV (> 90%) and NPV (> 95%), reducing the number of patients that require confirmatory CSF/PET testing. Additional studies are required to further evaluate the performance of the Lumipulse® G pTau 217 Plasma assay alone or in combination with other biomarkers. **Elecsys® pTau217:** In ongoing exploratory clinical research utilizing the NeuroToolKit, Roche Diagnostics systematically identified relevant biomarkers and developed immunoassays for neurological conditions. This rigorous process facilitated the development of the Elecsys® pTau217 assay, intended as a rule-in and rule-out test for amyloid pathology. The Elecsys pTau217 assay is specifically designed to assist in detecting amyloid pathology, a hallmark of Alzheimer's disease, in individuals aged 60 years and older. The assay has undergone comprehensive evaluation across five distinct cohorts that represent a spectrum of disease stages, ranging from cognitively normal individuals to those with mild AD and dementia. These evaluations have demonstrated robust clinical and technical performance across all cohorts. In recognition of its potential, the Elecsys pTau217 assay was awarded breakthrough device designation by the FDA in April 2024. Ongoing efforts aim to validate the assay across a broad population to further establish its clinical utility and reliability.

Oral Communications

OC01- THE EFFECT OF DIFFERENT DONANEMAB DOSING REGIMENS ON ARIA-E AND AMYLOID LOWERING IN ADULTS WITH EARLY SYMPTOMATIC ALZHEIMER'S DISEASE: PRIMARY OUTCOME RESULTS FROM TRAILBLAZER-ALZ 6. H. Wang[1], E.S. Nery[1], P. Ardayfio[1], D. Cheng[1], R. Khanna[1], D. Otero Svaldi[1], P. Hauck[1], S. Shcherbinin[1], D.A. Brooks[1], E.C. Collins[1], M.A. Mintun[1], J.R. Sims[1] *(1. Eli Lilly and Company - Indianapolis (United States))*

Background: Donanemab is a monoclonal antibody specific for an insoluble form of amyloid beta present only in brain amyloid plaques. Donanemab has been approved by the FDA as a treatment to slow the progression of Alzheimer's disease (AD). Amyloid-related imaging abnormalities (ARIA) have been observed with amyloid-targeting therapies, including donanemab. TRAILBLAZER-ALZ 6 (NCT05738486) assessed the impact of different donanemab dosing regimens on the frequency of ARIA-E in relation to amyloid reduction. **Methods:** This was a multicenter, randomized, double-blind, phase 3b study in adults with early symptomatic AD and presence of amyloid pathology. Participants (n=843) were stratified by APOE genotype and baseline amyloid levels and randomly assigned to the standard dosing arm or one of 3 alternative dosing arms in a 1:1:1:1 ratio. The four treatment arms varied in donanemab dosage per infusion and frequency of dosing but the total donanemab exposure by week 16 was the same. Relative risk reduction of ARIA-E by week 24 was analyzed through Bayesian logistic regression models to compare each alternate dosing regimen with the standard dosing approach. Brain amyloid level (as measured by positron emission tomography) and plasma P-tau217 level were also assessed. **Results:** By week 24, the frequency of ARIA-E was 23.7% for the standard dosing arm, and 18.6%, 13.7%, and 18.3% for the 3 alternative dosing arms. The enhanced titration dosing regimen with the lowest ARIA-E (13.7%) had a 41% reduction in the relative risk of ARIA-E compared to the standard dosing arm. The ARIA-E radiographic severity in the enhanced titration arm was significantly less than the standard dosing arm with 4.7%, 9.0%, and 0% of mild, moderate and severe ARIA-E compared to 9.2%, 12.6% and 1.9%, respectively, in the standard dosing arm. The symptomatic ARIA-E frequency was 2.8% in the enhanced titration arm compared to 4.8% in the standard arm. Serious adverse events, discontinuations or treatment-related adverse events in the alternative dosing arms were largely comparable to the standard dosing arm. One participant in the titration arm with an ongoing ARIA-E presented stroke-like symptoms and, after receiving tissue plasminogen activator treatment, subsequently died due to cerebral intraparenchymal hemorrhage. The frequencies of infusion-related reactions in the alternative dosing arms were similar to the standard arm. Participants in all arms had significant amyloid reduction from baseline to 24 weeks with adjusted mean (SE) change of 58.8 (1.8) Centiloids in the standard arm, 56.3 (1.7) in the enhanced titration arm, and 58.7 (1.7), and 51.0 (1.7) Centiloids in the other alternative dosing arms. Plasma P-tau217 reductions at 24 weeks were similar in all dosing arms as well. **Conclusion:** The frequency and severity of ARIA-E at 24 weeks was significantly reduced in the enhanced titration arm and numerically lower in the other two dosing arms compared to the standard arm. Amyloid and plasma P-tau217 reduction was similar in the standard and enhanced titration arm. This study suggests that an enhanced titration approach may limit ARIA risk while maintaining sufficient amyloid reduction.

OC02- FOSGONIMETON FOR THE TREATMENT OF ALZHEIMER'S DISEASE; EFFICACY AND SAFETY RESULTS FROM THE LIFT-AD TRIAL. A. P. Porsteinsson[2], K. J Church[1], J. San Martin[1], M. D Hale[1], L. B Walt[4], S. Daggett[1], H. J. Moebiu[3] *(1. Athira Pharma, Inc., Bothell, WA (United States), 2. Alzheimer's Disease Care, Research and Education Program, University of Rochester School of Medicine and Dentistry, Rochester, NY (United States), 3. moebius-consult GmbH, Baar ZG (Switzerland), 4. SSI Strategy, Parsippany-Troy Hills, New Jersey (United States))*

Background: Alzheimer's disease (AD) is a multifactorial disease characterized by amyloid beta/Tau accumulation, neuroinflammation, loss of neuronal connectivity, and progressive neurodegeneration leading to cognitive and functional decline. Fosgonimeton, an investigational positive modulator of the neurotrophic hepatocyte growth factor (HGF) system, was evaluated in participants with mild-to-moderate AD. **Methods:** In this randomized, placebo-controlled, Phase 2/3 clinical trial (LIFT-AD), eligible participants had Mini Mental State Examination (MMSE) scores of 14 to 24, a Clinical Dementia Rating global score of 1 or 2, and a clinical diagnosis of probable AD dementia. In the primary analysis population, participants not receiving concomitant acetylcholinesterase inhibitor (AChEI) therapy were randomized 1:1 to daily subcutaneous injections of fosgonimeton 40mg or placebo for 26 weeks. The primary end point was the Global Statistical Test (GST), a composite score combining the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog11; range 0-70 with higher scores indicating greater impairment) and Alzheimer's Disease Cooperative Study – Activities of Daily Living, 23-item version (ADCS-ADL23; range 0-78 with lower scores indicating greater impairment) using a mixed model for repeated measures. **Results:** The primary analysis included 287 participants (144 placebo, 143 fosgonimeton 40mg) who had a baseline mean (SD) MMSE score of 19.6 (3.5), ADAS-Cog11 score of 21.5 (7.8), and ADCS-ADL23 score of 62.4 (10.0). Between-group difference in the least-square mean (LSM) change (SE) from baseline to Week 26 was -0.08 (0.10) (p=0.70) in the GST, -0.70 (0.77) (p=0.35) in ADAS-Cog11, and +0.67 (0.92) (p=0.61) in ADCS-ADL23. Changes in plasma biomarkers of AD pathology were directionally in favor of fosgonimeton, with between-group differences in LSM (SE) from baseline to Week 26 of -3.91 (3.46) pg/mL (p=0.26) in neurofilament light chain (NfL), -21.80 (17.16) pg/mL (p=0.21) in glial fibrillary acidic protein (GFAP), -1.63 (1.07) pg/mL (p=0.13) in pTau181, and -0.12 (0.05) pg/mL (p<0.01) in pTau217. Safety analysis evaluated all participants (N=549), including those who received fosgonimeton 70mg dose, which was subsequently discontinued and/or those who had received concomitant AchEI therapy. Fosgonimeton was generally well-tolerated with an acceptable safety profile. Serious treatment-emergent adverse events (TEAEs) were reported in 6.9% of the placebo group, 4.9% of the fosgonimeton 40mg group, and 2.8% of the fosgonimeton 70mg group. More participants in the fosgonimeton group (10.7% fosgonimeton 40mg, 21.5% fosgonimeton 70mg) discontinued from the study due to TEAEs compared with placebo (4.6%). Most of the withdrawals due to TEAEs in the fosgonimeton groups were attributed to injection site reactions (ISRs). ISRs were the most frequently reported TEAEs (14% placebo, 57% fosgonimeton 40mg, 73% fosgonimeton 70mg). Eosinophilia was also reported in 7.3% of participants receiving fosgonimeton compared with none in the placebo group. **Conclusion:** LIFT-AD did not meet the primary or secondary endpoints. Consistent directional improvements

favoring fosgonimeton treatment across clinical and biomarker endpoints suggest that positive modulation of HGF signaling may be beneficial in the treatment of neurodegenerative diseases. **Keywords:** Alzheimer's Disease, fosgonimeton, cognition, function

OC03- IMMUNOMETABOLIC AND VASCULAR MODULATORS FOR COMBINATION THERAPY IN AD: RESULTS OF A PHASE II TRIAL OF INTRANASAL INSULIN AND THE SGLT2 INHIBITOR EMPAGLIFLOZIN.
J. Erichsen[1], T. Register[1], C. Sutphen[1], J.R. Bateman[1], M. Rundle[1], M. Rudolph[1], S. Lockhart[1], S. Craft[1] *(1. Wake Forest School of Medicine - Winston-Salem (United States))*

Background: Metabolic and vascular disorders are powerful risk factors for Alzheimer's disease (AD). Risk-related mechanisms include insulin resistance, inflammation, impaired cerebrovascular function, and b-amyloid (Ab) and tau dysregulation. Accordingly, it has been suggested that medications used to treat metabolic and vascular disorders could be repurposed to serve as therapeutic agents for AD. Such agents have promise for combination therapy with recently approved anti-amyloid monoclonal antibodies. In a phase II clinical trial, we tested the safety and efficacy of two compounds that improve metabolic and vascular function, intranasal insulin (INI) and the sodium glucose co-transporter 2 inhibitor (SGLT2I) empagliflozin (empa) in mild cognitive impairment (MCI) and early AD dementia. Methods: Using a 2x2 factorial, blinded, randomized, placebo-controlled design, participants with MCI or early AD, or amyloid positive controls with memory complaints were assigned to one of four arms: placebo, INI (40 IU q.i.d. regular insulin), empagliflozin (10 mg q.d.), or insulin plus empagliflozin (INI+empagliflozin). Participants received treatment for 4 weeks. Fasting lumbar puncture and blood draw, MRI and cognitive testing were conducted at baseline and after treatment. Safety outcomes included number of treatment-related adverse events. Analyses were conducted comparing insulin-treated (INI and INI+empagliflozin) vs non-insulin treated (placebo and empagliflozin only) for cerebrospinal fluid (CSF) and plasma biomarkers (AD biomarkers measured on Lumipulse platform; inflammatory/immune markers measured on Alamar NULISA platform), diffusion tensor imaging global white matter fractional anisotropy (DTI FA, marker of microstructural health), and cognitive function (Preclinical Alzheimer's Cognitive Composite/PACC5). Mixed model repeated measures were conducted adjusting for age, baseline Mini-Mental State Exam, sex, and APOE-e4 status. **Results:** The insulin-treated group had significantly improved PACC5 scores relative to the non-insulin group ($p<0.05$). Plasma Aβ42 levels increased for the INI group ($p<0.05$). CSF SNAP25, SMOC1, BDNF, and VCAM1 increased significantly after insulin treatment (all p's < 0.05). Levels of more than 50 plasma and CSF innate and adaptive immune/inflammatory markers were moderated following treatment with INI and empa, including known markers such as TREM2, SPP1 and MMP9, as well as novel markers such as PD-L1 and CX3CL1 (ps ranging from 0.00001 to 0.05). Changes in many immune/inflammatory markers were associated with baseline plasma p-tau217 levels. With respect to MRI, DTI FA increased for the insulin-treated group ($p<.05$). Only infrequent, minor adverse events were noted that did not differ between groups. **Conclusion:** INI treatment improved cognition and biomarkers of CNS health, as well as numerous immune/inflammatory biomarkers. Of note, treatment with empa also improved numerous markers of vascular injury and inflammation. These results support the continued investigation of intranasal insulin and empagliflozin combination therapy for AD and suggest these agents may also be useful in combination with anti-amyloid therapies. Further exploration of pathways mediating the changes in CSF and fluid biomarkers should provide insights into mechanisms of action and potential targets for therapy.

OC04- ANTI-TAU THERAPEUTIC ANTIBODY, E2814, REDUCES EARLY AND LATE TAU PATHOLOGY BIOMARKERS IN PATIENTS WITH DIAD.
K. Wildsmith[1], K. Horie[1,2], A. Charil[1], N. Barthelemy[2], D. Verbel[1], A. Reihac-Iaborde[1], B. Gordon[2], P. Boyd[3], R. Bell[1], S. Rawal[1], E. Andreozzi[1], T. Benzinger[2], R. Bateman[2], J. Zhou[1], L. Reyderman[1] *(1. Eisai Inc. - Nutley (United States), 2. Washington University School of Medicine - St Louis (United States), 3. Eisai Europe Ltd. - Hatfield (United Kingdom))*

Background: E2814 targets to delay the clinical progression of Alzheimer's disease by binding to the microtubule biding region (MTBR) of tau, which is required for the seeding and spreading of tau pathology. E2814-G000-103 is an open-label, Ph1b/2 study in Dominantly-Inherited Alzheimer's Disease (DIAD) patients. It was designed to provide safety and pharmacokinetic, data, demonstrate target engagement, and proof-of-mechanism based on tau pathology biomarkers. **Methods:** Study E2814-G000-103 enrolled participants with mild-to-moderate cognitive impairment due to DIAD. Each subject received E2814 IV every 4 weeks escalating from 750mg, 1500mg, 3000mg, to 4500mg (min of 3 doses/dose level). After ascending to 4500mg, patients received 4500 mg for up to 108 weeks. CSF was collected every three months for the first year, and then at week 108. Early (pTau217) and late (MTBR-tau243) tau pathology biomarkers (i.e. T1 and T2 as per the new NIA-AA 2024 criteria), p-tau217 and MTBR-tau243 were measured in CSF by an IP-MS method [1]. Drug interference experiments demonstrated that assay performance was not impacted by the presence of E2814. CSF was also analyzed from healthy subjects in the E2814-G000-001 Ph1 study, to compare pharmacodynamic effects on early and late tau biomarkers in a population without tau pathology. Tau PET (18F-MK-6240) and MRI were acquired at baseline, weeks 60 and 108. Regional Tau SUVR was generated using PMOD. Analyses in DIAN Observational participants will also be evaluated to inform the natural trajectory of these biomarkers. **Results:** Pharmacodynamic effects of E2814 on p-tau217, MTBR-tau243, and Tau PET, were evaluated. E2814 reduced concentrations of p-tau217: -30.4% after 12 weeks (n=7), -48.6% at 36 weeks (n=5), increasing to -57.9% at 108 weeks (n=2). E2814 treatment reduced concentrations of MTBR-tau243 by 50.6% in DIAD participants (n=7) after 12 weeks of treatment. Maximal reduction in MTBR-tau243 levels (-71.6%) was achieved at week 36 (n=4) and was sustained out to 108 weeks (n=2). In healthy volunteers, who lack tau pathology, E2814 has no effect on MTBR-tau243 or p-tau217 after 12 weeks of treatment. Three DIAD patients had tau PET acquired at week 60 and week 108. After 60 weeks of treatment, 1 of 3 patients showed an overall 20% slowing of tau accumulation. At 108 weeks, there was no tau accumulation observed via tau PET in any of the 3 patients. **Conclusion:** E2814 demonstrated effects on both early, CSF pT217, and late, CSF MTBR-tau243 and Tau PET, biomarkers in mild-to-moderate DIAD participants. E2814 has a more robust effect on the tangle-specific biomarker CSF MTBR-tau243. The sustained reduction of CSF MTBR-tau243 may be predictive of the attenuation of tau PET SUVR. No accumulation of tau pathology, as measured by Tau PET, was observed after 60 weeks of treatment. This data supports

further clinical evaluation of E2814. **Keywords:** CSF MTBR-tau243, Tau PET, CSF p-tau217, anti-tau, Dominantly-inherited Alzheimer's disease. **Disclosures:** 1. K Wildsmith, K. Horie, A Charil, D Verbel, A Reihac-Iaborde, B Lalovic, R Bell, J Aluri, S Rawal, E Andreozzi, J Zhou and L Reyderman are employees of Eisai Inc. 2. K. Horie: C2N Diagnostics royalty, N Barthelemy: C2N Receipt of Intellectual Property Rights/ Patent Holder Self, T Benzinger: consultant for Lilly, Biogen, Eisai and J&J; investigator initiated research funded by Siemens; R Bateman: receives research support from NIH, Alzheimer's Association Zenith Grant, American Health Assistance Foundation, Glenn Foundation, Ruth K. Broad Biomedical Research Foundation, Anonymous Foundation, Merck research collaboration. Alzheimer's Association, Association for Frontotemporal Degeneration FTD Biomarkers Initiative, BrightFocusFoundation, Cure Alzheimer's Fund, Foundation for Barnes Jewish Hospital, GHR Foundation, MetLife Foundation, Rainwater Foundation Tau Consortium, Tau SILK Consortium (Abbvie, Biogen, Lilly, Novartis), Centene, The Tracy Family Stable Isotope Labeling Quantitation (SILQ) Center donors Richard Frimel, David & Amy Payne, John & Linda Tracy, Pat and Jane Tracy, Tom & Catherine Tracy, Robert Willman, NfL Consortium (Abbvie, Biogen, Roche, UCL, BMS); co-founded C2N Diagnostics and receives income from C2N Diagnostics for serving on scientific advisory board. Washington University has equity ownership interest in C2N Diagnostics; invited speaker; serves on editorial boards for A&D, Alz Res and Therapy, JPAD; consulting for Roche (unpaid). 3. P Boyd is an employee of Eisai Europe Ltd. **References:** 1. K Horie, et al. Nat Medicine 2023; 29:1954-1963. https://doi.org/10.1038/s41591-023-02443-z.

OC05- RESULTS FROM COG0201: A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, INTERNATIONAL, PHASE 2 STUDY TO EVALUATE THE SAFETY AND EFFICACY OF CT1812 IN ADULTS WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE. M. Woodward[1], E.G.B. Vijverberg[2,3], S.M. Catalano[4], T. Devins[5], V. Di Caro[5], M. Grundman[6], M.E. Hamby[5], J.F. Iaci[5], A.O. Caggiano[5] *(1. Austin Health - Melbourne, Victoria (Australia), 2. Brain Research Center - Amsterdam (Netherlands), 3. Alzheimer Center Amsterdam, Neurology, Amsterdam UMC - Amsterdam (Netherlands), 4. Capsida Therapeutics - Thousand Oaks, California (United States), 5. Cognition Therapeutics, Inc. - Pittsburgh, Pennsylvania & Purchase, New York (United States), 6. Global R&D Partners, LLC - La Jolla, California (United States))*

Background: CT1812 is an experimental oral, small-molecule sigma-2 receptor modulator in development for Alzheimer's disease (AD) and dementia with Lewy bodies. CT1812 displaces Aβ oligomers from receptors on neuronal synapses thereby protecting synapses from their toxic effects. The phase 2 'SHINE' (COG0201) clinical trial assessed safety, tolerability and effects of CT1812 on cognitive function in adults with mild-to-moderate AD. **Methods:** Participants were recruited at appx 40 sites in the United States, Australia, Spain, Netherlands and Czech Republic. Participants with a diagnosis of AD, screening MMSE 18 to 26, and confirmed brain amyloid were randomized equally 1:1:1 to receive placebo or one of two doses (100 or 300mg) of oral CT1812 daily for 6mo. The prespecified efficacy outcome measure is the change in ADAS-Cog11 from baseline for the pooled CT1812 treated group compared to placebo. In addition to a pooled analysis, efficacy comparisons for ADAS-Cog11 will be available for each dose arm. Additional exploratory efficacy outcomes include ADAS-Cog13, NTB, ADCS-CGIC and ADCS-ADL. Core AD biomarkers were assessed in CSF and plasma, along with additional exploratory biomarkers to assess synaptic health and neuroinflammation. **Results:** LPLV was May 29, 2024 and data will be available in July 2024. The study randomized 153 individuals, 40% of whom are men and 60% women. At baseline, participants had a mean age of 73 years, MMSE score of 21, and ADAS-Cog11 score of 19. A more detailed analysis of the data will be presented, including safety, efficacy, CSF and plasma biomarkers, potentially findings from biomarker correlations to cognitive and functional changes, and analyses comparing efficacy in participants stratified by other prespecified criteria. **Conclusion:** Encouraging trends were observed in previous studies of CT1812 (NCT03493282, NCT03522129, NCT04735536) and in an interim analysis of this phase 2 trial (NCT03507790). Complete results from the SHINE trial are expected to provide evidence as to whether CT1812 can modify the disease course in patients with mild-to-moderate AD. In addition, positive findings may support a decision to advance CT1812 to Phase 3. This study was supported by a grant from the NIH (AG058660).

OC06- SCREENING AND BASELINE RESULTS FROM THE DONANEMAB PRECLINICAL ALZHEIMER'S DISEASE TRAILBLAZER-ALZ 3 STUDY. K.C. Holdridge[1], R. Yaari[1], M. Williamson[1], A.M. Wessels[1], S. Shcherbinin[1], V. Kotari[1], N. Hatakeyama[1], P.N. Tariot[2], R. Alexander[2], E.M. Reiman[2], J.B. Langbaum[2], J. Sims[1] *(1. Eli Lilly and Company - Indianapolis (United States), 2. Banner Alzheimer's Institute - Phoenix (United States))*

Background: Amyloid accumulation is an early pathological change in Alzheimer's disease (AD). Clinical trial data suggest greater relative benefit in earlier symptomatic stages of AD for drugs targeting amyloid removal. The TRAILBLAZER-ALZ 3 trial will evaluate the efficacy of donanemab in preclinical AD (individuals with evidence of AD pathology and without cognitive impairment). The present abstract shares study participant screening and baseline characteristics upon enrollment completion. **Methods:** TRAILBLAZER-ALZ 3 (NCT05026866) is a multicenter, randomized, double-blind, placebo-controlled Phase 3 trial in preclinical AD using a decentralized clinical trial (DCT) approach. Inclusion criteria included age 55-80, Modified Telephone Interview for Cognitive Status (TICS-m) score ≥35, and plasma P-tau217 results consistent with the presence of amyloid and early tau pathology. Individuals received donanemab (700 mg intravenously [IV] once every 4 weeks [Q4W] for the first 3 doses, then 1,400 mg IV Q4W for the next 6 doses) or placebo (IV Q4W for 9 doses). Decentralized screening included the use of mobile research units, community screening at health fairs and other community events, and pre-screening through centralized call centers. Participants and study partners received electronic tablets for centralized, remote administration of cognitive and functional scales. The primary endpoint is time to clinical progression as measured by an increase in the Clinical Dementia Rating-global score (CDR-GS) at 2 consecutive visits. The primary efficacy analysis will be conducted when a prespecified minimum number of events is observed. Amyloid- and tau-PET (positron emission tomography) images are being acquired in a subset of participants. **Results:** The trial screened 63,124 participants using plasma P-tau217, enabling randomization of 2,196 participants in the US (n=2,137) and Japan (n=59) with a mean age of 70.2 (SD=5.7) years. Screen failure occurred in 81.2% of participants based on plasma P-tau217 and 5.4% based on TICS-m. P-tau eligibility increased

with age. The majority of randomized participants are female (65.6%), white (93.3%), and APOE ε4 carriers (56.9%). Further racial and ethnic distribution includes Black/African American (2.6%), Asian (3.5%), and Hispanic/Latino (8.2%) participants. The median baseline TICS-m (score range 0-50) and Montreal Cognitive Assessment (MoCA, score range 0-30) scores for a subgroup of participants with a baseline CDR-GS = 0 (CDR0) were 40 and 25, respectively, and 39 and 23, respectively, for participants with baseline CDR-GS = 0.5 (CDR0.5). Participants in the PET sub-study had an average amyloid plaque level of 63.15 Centiloids (SD=44.96) in the CDR0 subgroup (n=229) and 70.65 Centiloids (SD=43.25) in the CDR0.5 subgroup (n=177). The average tau-PET AD signature-weighted neocortical volume of interest was 1.04 SUVr (SD=0.09) and 1.10 SUVr (SD=0.17) in the CDR0 (n=173) and CDR0.5 (n=137) subgroups, respectively. Among randomized participants who received ≥1 blinded treatment infusions (n=1,697), 1,099 individuals were in the CDR0 subgroup and 594 were in the CDR0.5 subgroup. **Conclusion:** Enrolling a preclinical AD study using a blood-based biomarker and a DCT approach is feasible. This cohort represents an earlier clinical and pathological stage compared with prior studies in early symptomatic AD, despite enrolling CDR0.5 participants. The study is ongoing. **Keywords:** Clinical trials, amyloid-targeting therapy, preclinical Alzheimer's disease, donanemab. **Disclosures:** Karen C Holdridge, Roy Yaari, Melissa Williamson, Alette Wessels, Sergey Shcherbinin, Vikas Kotari, Naohisa Hatakeyama, and John Sims are full-time employees and minor shareholders of Eli Lilly and Company. Pierre Tariot, Jessica Langbaum, Robert Alexander, and Eric Reiman are employees of Banner Health. Banner Alzheimer's Institute's receives funding from Eli Lilly and Company for its collaborative partnership on TRAILBLAZER-ALZ 3. Robert Alexander reports consulting income from Alkermes, Boehringer- Ingelheim, Biohaven, Cardiff University Medicines Discovery Unit, Immunobrain, Lundbeck, Novartis, Novo Nordisk, Reunion Neuro, T3D Therapeutics, and Vigil Neuro. Jessica Langbaum reports consulting in income from Biogen and Denovo Biopharma. Eric Reiman is a co-founder and advisor of ALZpath and a compensated scientific advisor to Alzheon, Denali, Cognition Therapeutics, Enigma, Retromer Therapeutics, and Vaxxinity. Pierre Tariot reports consulting income from AC Immune, Acadia, Athira, Biogen, BioXcel, Bristol Myers Squibb, Cognition Therapeutics, Corium, Cortexyme, CuraSen, Eisai, Genentech, Immunobrain, Janssen, Lundbeck, MapLight, Merck & Co., Novartis, Novo Nordisk, Otsuka & Astex, Roche, Syneos, and T3D Therapeutics.

OC07- EFFICACY, CARDIOVASCULAR SAFETY AND ADVERSE EVENTS ASSOCIATED WITH ESCITALOPRAM IN ALZHEIMER'S DEMENTIA: RESULTS FROM THE S-CITAD TRIAL. H. Okhravi[1], M. Parulekar[2], S. Baksh[3], E. Clark[4], I. Zahinoor[5], D.M. Shade[3], C.G. Lyketsos[6,7], A.P. Porsteinsson[4] *(1. Goldrich Neurohealth Institute, Eastern Virginia Medical School - Norfolk (United States), 2. Hackensack Meridian School of Medicine, Division of Geriatrics - Hackensack (United States), 3. Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health - Baltimore (United States), 4. Department of Psychiatry, University of Rochester School of Medicine and Dentistry - Rochester (United States), 5. University of Calgary - Calgary (Canada), 6. Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine - Baltimore (United States), 7. Johns Hopkins Bayview Medical Center - Baltimore (United States))*

Background: Escitalopram is commonly used to treat neuropsychiatric symptoms (NPS) in Alzheimer's dementia (AD). While Citalopram, containing both R- and S-enantiomers, has shown effectiveness in treating agitation in AD (AAD), it carries cognitive and cardiac risks primarily linked to its R-enantiomer1. Escitalopram, comprising only the S-enantiomer, may present a safer profile2. The primary objective of the S-CitAD RCT was to examine the cardiovascular safety and adverse events associated with escitalopram, alongside its efficacy, for treating AAD in patients unresponsive to a structured psychosocial intervention (PSI). **Methods:** S-CitAD is an NIH-funded, multicenter, community-based, phase 3, double-masked randomized placebo-controlled trial. Assessments were conducted at enrollment, baseline, and then weeks 3, 6, 9, and 12. Participants were adults with AD, a telephone Mini-Mental State Examination Telephone score from 3 to 20, and clinically significant agitation/aggression as assessed by the Neuropsychiatric Inventory with either frequency being "Very frequently", or frequency being "Frequently" and severity being "Moderate" or "Marked". Following three weeks of PSI alone, participants not showing response were randomized (1:1) to receive escitalopram at a target dose of 15mg/day or placebo for 12 weeks while continuing PSI. Participants who responded to three weeks of PSI alone continued to receive the intervention and were monitored on usual care through week 12. The primary outcome was the proportion of participants with clinically significant improvement in agitation from baseline on the modified Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change (mADCS-CGIC). Secondary outcomes included adverse events, cardiovascular safety (particularly the QTcB interval from ECGs), balance and gait stability, and other NPS domains assessed by the Neuropsychiatric Inventory–Clinician Rating (NPI-C) and the Alzheimer's Disease Cooperative Study Activities of Daily Living Scale (ADCS-ADL). **Results:** A total of 187 participants were enrolled, with 173 randomized to either escitalopram or placebo for 12 weeks while continuing PSI. Here, we briefly present efficacy results and detailed findings on the cardiovascular safety profile, adverse events, and the risk of falls associated with escitalopram. In the S-CitAD study, escitalopram does not appear to be effective for treating agitation in AD and is associated with similar cardiac conduction delays as citalopram. More falls and diarrhea were seen in the escitalopram group compared to placebo. Consequently, clinicians may need to be cautious in recommending escitalopram as a safe and effective alternative to citalopram for this condition. **Conclusion:** Given the widespread use of escitalopram for NPS in dementia, the outcomes of the S-CitAD study has significant implications for clinical care, highlighting the drug's safety and tolerability. The results also elucidate escitalopram's impact on managing symptoms and daily living activities in individuals with mild-to-moderate AD, thus informing future clinical guidelines and treatment strategies for AAD. **Keywords:** Alzheimer's Disease, agitation, escitalopram, Cardiovascular safety. **Clinical Trial Registry:** NCT03108846. **Funder:** National Institutes of Health/National Institute on Aging; R01AG052510. **Disclosures:** Hamid R Okhravi. **Research Support:** Bill Gates Foundation and USC Schaffer's Institute, American College of Radiology, Biogen Pharmaceuticals, Eisai Pharmaceuticals, NIH/NIA, Alzheimer's Association, Optina Diagnostics, Commonwealth Health Research Board (CHRB); Advisory Board, Biogen Pharmaceuticals, Optina Diagnostics; Dr. Parulekar has no personal financial relationships to disclose; Dr. Baksh received funding from the NIH, the American Lung Association, the State of Maryland, and the Department of

Defense (Defense Health Agency); Dr. Clark has no personal financial relationships to disclose; Dr. Ismail has served as an advisor/consultant to CADTH, Eisai, Lilly, Lundbeck/Otsuka, Novo Nordisk, and Roche; Dr. Shade has received funding from the NIH, the American Lung Association, the State of Maryland, and the Department of Defense (Defense Health Agency); Dr. Lyketsos has received research funding from the NIH, the Alzheimer Association, NFL Benefits, Functional Neuromodulation Ltd, Bright Focus Foundation and private donors. He has served as paid consultant or advisor for Astra-Zeneca, Glaxo-Smith Kline, Eisai, Novartis, Forest, Supernus, Adlyfe, Takeda, Wyeth, Lundbeck, Merz, Lilly, Pfizer, Genentech, Elan, NFL Players Association, NFL Benefits Office, Zinfandel, BMS, AbbVie, Janssen, Orion, Servier, Astellas, SVB Leerink, Roche, Avanir, Karuna, Maplight, Axsome, GIA, GW Research Limited, Merck, EXCIVA GmbH, Otsuka, IntraCellular Therapies, Medesis, BMS; Dr. Porsteinsson reports personal fees from Acadia Pharmaceuticals, Athira, Biogen, BMS, Cognitive Research Corp, Eisai, IQVIA, Lundbeck, Novartis, ONO Pharmaceuticals, WCG, WebMD, and Xenon; grants to his institution from Alector, Athira, Biogen, Cassava, Eisai, Eli Lilly, Genentech/Roche, Vaccinex, NIA, NIMH, and DOD. He is a member of the Scientific Advisory Board of Alzheon, Athira, and Cognition Therapeutics. **References:** Ho T, Pollock BG, Mulsant BH, Schantz O, Devanand DP, Mintzer JE, Porsteinsson AP, Schneider LS, Weintraub D, Yesavage J, Drye LT, Munro CA, Shade DM, Lyketsos C, Bies R. R- and S-citalopram concentrations have differential effects on neuropsychiatric scores in elders with dementia and agitation. Br J Clin Pharmacol. 2016 Sep;82(3):784–792. Published online 2016 Jun 20. doi: 10.1111/bcp.12997. PMCID: PMC6445501. PMID: 27145364. Leonard B, Taylor D. Escitalopram—translating molecular properties into clinical benefit: reviewing the evidence in major depression. J Psychopharmacol. 2010 Aug;24(8):1143–1152. Published online 2010 Aug. doi: 10.1177/0269881109349835. PMCID: PMC2923415. PMID: 20147575.

OC08- DIFFERENCES IN AMYLOID PET RESULTS AND SOCIAL DETERMINANTS OF HEALTH BY RACE/ETHNICITY: RESULTS FROM NEW IDEAS. G. Rabinovici[1], P. Dilworth-Anderson[2], L. Hanna[3], J. Steingrimsson[3], I. Gareen[3], E. Glavin[4], B. Hillner[5], A. March[4], B. Siegel[6], C. Weber[7], C. Windon[1], R. Whitmer[8], C. Gatsonis[3], M. Carrillo[7], C. Wilkins[9] *(1. University of California San Francisco - San Francisco (United States), 2. University of North Carolina - Chapel Hill (United States), 3. Brown University - Providence (United States), 4. American College of Radiology - Reston (United States), 5. Virginia Commonwealth University - Richmond (United States), 6. Washington University - St. Louis (United States), 7. Alzheimer's Association - Chicago (United States), 8. University of California Davis - Sacramento (United States), 9. Vanderbilt University - Nashville (United States))*

Background: The New Imaging Dementia-Evidence for Amyloid Scanning study (New IDEAS) evaluated the clinical utility of amyloid PET in a racially and ethnically diverse cohort of Medicare beneficiaries. Here we present preliminary results of a secondary, post-hoc analysis evaluating associations between self-identified race/ethnicity and (1) amyloid PET results; (2) clinical features and social determinants of health (SDOH). **Methods:** New IDEAS recruited Medicare beneficiaries with MCI/dementia at 151 dementia clinics between December 2020 - March 2024. Multifaceted, community-engaged and culturally-tailored strategies were implemented to enhance the diversity of the cohort. Based on self-identified race/ethnicity, patients were grouped into 1 of 3 cohorts: Black/African-American (BAA), Latino/Hispanic (LAT), or not BAA or LAT (NBL, all other racial/ethnic identities). Patients underwent PET using an FDA-approved amyloid radiopharmaceutical at 107 imaging facilities. PET scans were interpreted locally by imaging specialists as positive/negative for cortical amyloid. The primary endpoint of this analysis evaluated the association between ethnoracial cohort and amyloid PET positivity using logistic regression. Secondary endpoints evaluated the associations between SDOH and ethnoracial cohort using univariate logistic regression (categorical variables) or t-tests (continuous variables). In all analyses, pair-wise comparisons were conducted separately for BAA vs. NBL and LAT vs. NBL. There was no correction for multiplicity. **Results:** Out of 6,057 registered participants, 4,898 (80.9%) were included in the analysis based on availability of pre-PET data and amyloid PET results. 1,040 (21.2%) self-identified as BAA, 891 (18.2%) as LAT, and 2,967 (60.6%) as NBL (of which 90.9% identified as White). Median age was 75 (IQR 70-80, range: 35-98), 55.4% were female, 63.4% presented with MCI/36.6% with dementia, 25.6% were enrolled in a Medicare Advantage (MA) plan and 65.2% had positive amyloid PET. **Primary analysis:** Rates of amyloid PET+ were BAA 60.4%, LAT 60.7%, NBL 68.2%. Compared to NBL, BAA (OR 0.71, 95% CI: 0.61-0.82) and LAT (OR 0.72, 95% CI: 0.62-0.84) were less likely to be amyloid-PET+. **Secondary analysis:** Mean age-at onset-of cognitive symptoms was slightly lower in BAA (71.4±7.9) than in NBL (72.4±6.7, p=0.0005), but similar in LAT (71.9±8.0, p=0.0984). BAA (64.2%) and LAT (62.1%) had a higher proportion of females than NBL (50.3%; both p<0.0001). Proportions of patients who did not complete high school were higher in BAA (7.7%) and LAT (27.6%) than NBL (3.2%, both p<0.0001). Compared to NBL, BAA and LAT were more likely to present at dementia vs. MCI stage (ORs: BAA 2.0, 95% CI: 1.7-2.3; LAT 1.8, 95% CI: 1.5-2.0), had lower MMSE scores at presentation (BAA mean 22.1, LAT 22.0, NBL 24.7, both p<0.0001) and were more likely to be enrolled in MA vs. Medicare fee-for service (OR: BAA 2.8, 95% CI: 2.4-3.3; LAT 2.2, 95% CI: 1.9-2.6). **Conclusion:** In a large, real-world study of specialty dementia care, we found significant disparities in rates of amyloid-PET positivity, clinical stage and SDOH based on self-identified race/ethnicity. These disparities must be addressed to ensure equitable access to dementia care and emerging therapeutics for AD and related disorders. **Keywords:** Amyloid PET, social determinants of health, diversity. **Clinical Trial Registry:** NCT04426539. **Disclosures:** New IDEAS was funded by the Alzheimer's Association, American College of Radiology, Avid Radiopharmaceuticals, GE Healthcare and Life Molecular Imaging.

OC09- FIRST RESULTS FROM THE REAL AD STUDY: VALIDATION OF A REALISTIC SCREENING APPROACH FOR EARLY ALZHEIMER'S DISEASE. K. Blennow[1,2], S. Kern[1,2], I. Bosch[2], H. Zetterberg[1,2,3,4], M. Schöll[1,2,3] *(1. University of Gothenburg - Gothenburg (Sweden), 2. Västra Götaland Region - Gothenburg (Sweden), 3. University College London - London (United Kingdom), 4. University of Wisconsin-Madison - Madison (United States))*

Background: Early detection of AD with its protracted preclinical phase is crucial for disease-modifying treatments to be successful. While established PET- and CSF-derived biomarkers enable reliable and early diagnostics, those modalities are only available in specialized care. In Sweden, most AD diagnoses (between 50-80%, depending on regional healthcare providers) are made in primary care based on a

clinical assessment, a routine blood panel, and a brain CT to exclude potential non-degenerative causes of cognitive impairment, i.e., without access to disease-specific biomarkers. Recent developments such as remotely administered cognitive tests to detect early cognitive impairment and blood-based biomarkers (BBMs) for early AD pathophysiology offer novel, truly scalable and cost-effective ways to screen for cognitive and biomarker changes that indicate preclinical AD. REAL AD aims to validate their diagnostic and prognostic performance for early AD detection in a realistic population-based screening setting fully embedded in an existing large-scale healthcare infrastructure to facilitate concrete implementation. **Methods:** We aim to recruit a representative population sample of at least N=3,000 (up to N=10,000) 50-80-year-olds without dementia diagnosis in the Swedish Västra Götaland Region (VGR) to be examined for early, potentially preclinical AD using remote cognitive testing and BBM analyses. Using a fully digitalized approach, offered in the four most-spoken languages in VGR, participants enroll through the study website (www.realad.se) to reach an individual study platform which guides through all subsequent steps. After screening and filling out questionnaires on demographic and lifestyle factors, as well as subjective cognitive performance and the Quick Dementia Rating System (QDRS) (Step 1), participants are asked to test their cognition at home using either an app (neotiv) or a website-based test battery (Cognitron) for three months (Step 2). Therein, they are asked to visit any of the 111 public VGR primary care units to donate blood samples (Step 3), which are sent to the Neurochemistry Laboratory of the University of Gothenburg for analysis of relevant BBMs and to University College London for genetic analyses. Steps 2 and 3 are repeated after 18 months, Step 2 again after 27 and 36 months. A validation study using established PET, MRI and CSF biomarkers assessed on two occasions (baseline and 24 months) together with a full clinical assessment will be performed in a stratified sub-sample of N=440 participants to retroactively validate the diagnostic and prognostic performance of the remote cognitive testing and BBM screening approach. **Results:** To date, six weeks after study launch, N=3,900 individuals have registered for REAL AD, whereof N=3,300 (Age 63.7 ± 7.7 y, 69% females) have passed screening and signed the informed consent. N=2,635 participants have finalized Step 1; of these, 80% were cognitively normal, 19% had MCI, and 1% mild dementia according to their total QDRS score. Seven percent were born outside Sweden, 17% had parents born outside Sweden, 66% had attended higher education, and 60% reported a family history of dementia. Detailed Step 1 and Step 2 results, as well as first findings from Step 3, pending available data, will be presented at CTAD. **Conclusion:** REAL AD has the potential to concretely inform the implementation of novel biomarker modalities in Swedish primary care in order to improve the care and prognosis of AD patients. **Keywords:** Early AD detection, screening, biomarkers, primary care. **Disclosures:** REAL AD is supported by the Swedish Research Council,), the European Union's Horizon Europe research and innovation program under grant agreement no 101132933 (AD-RIDDLE) and 101112145 (PROMINENT), the Swedish state under the agreement between the Swedish government and the County Councils, the ALF-agreement (ALFGBG-813971 and ALFGBG-965326), the Swedish Alzheimer Foundation (AF-994900), the Sahlgrenska Academy at the University of Gothenburg, and the Västra Götaland Region R&D (VGFOUREG-995510) and Innovation platform. The principal investigators report non-academic support (to the institution) for REAL AD by Alzpath, Bioarctic, NovoNordisk and Roche.

OC11- BIOMARKERS OF NEURODEGENERATION AND SYNAPTIC DYSFUNCTION DIFFERENTIATE COGNITIVELY UNIMPAIRED INDIVIDUALS WITH HIGH LEVELS OF ALZHEIMER'S DISEASE (AD) NEUROPATHOLOGY FROM INDIVIDUALS WITH AD DEMENTIA.

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Background: Alzheimer's disease (AD) neuropathology is commonly associated with neurodegeneration and subsequent cognitive decline. However, approximately one third of individuals accumulate significant AD neuropathology without developing cognitive impairment [1-3]. These individuals (mismatches) show lower levels of neurodegeneration and focal hypertrophy that may explain cognitive maintenance. Recently, biomarkers of synaptic dysfunction and neuroinflammation have been implicated in early AD-related cognitive decline [4]. We examined the role of global atrophy, hippocampal volume, neuroinflammation, neurodegeneration, and synaptic dysfunction in differentiating AD/mild cognitive impairment (MCI) individuals from cognitively unimpaired individuals with (mismatches) and without (controls) substantial amyloid and tau accumulation. **Methods:** We analyzed a cohort (N=506) from the Wisconsin Registry for Alzheimer's Prevention and the Alzheimer's Disease Research Center who underwent positron emission tomography (PET) scans with both MK6240 and Pittsburgh compound B (PiB) tracers, and cognitive assessment within one year. We differentiated cognitively unimpaired individuals without amyloid and tau accumulation (controls, n=422) from those with amyloid accumulation (global PiB>1.19) and PET-derived Braak stage III-VI (mismatches, n=38). AD/MCI individuals (n=46) were defined as cognitively impaired with Braak stage III-VI and amyloid accumulation. We used mixed models with a random effect for individual to compare magnetic resonance imaging-derived global atrophy and hippocampal volumes between AD/MCI vs. mismatches and controls. CSF biomarkers were measured using the Roche NeuroToolKit, a panel of robust prototype immunoassays, in a subsample (N=226; control n=188, mismatch n=17, AD/MCI n=21). We compared markers of neuroinflammation (chitinase-3-like protein [YKL-40] and glial fibrillary acidic protein [GFAP]), neurodegeneration (total tau and neurofilament light [NfL]), and synaptic dysfunction (synaptosomal associated protein 25 [SNAP-25], alpha synuclein [α-syn], neurogranin [Ng], and neuronal pentraxin II [NPTX2]) between groups. Models were adjusted for age, APOE-ε4 carriage, and sex. CSF models were additionally adjusted for days between lumbar puncture and MK6240 scan, and atrophy models were adjusted for intracranial volume (mL). Skewed dependent variables were logged. **Results:** The cohort was aged 66.8 years (mean), had 36.5% APOE-ε4 carriage, and was 68.3% female. In mixed models, mismatches demonstrated significantly lower global atrophy (β=-0.046[0.017]; p=.007) and higher hippocampal volume (β=734.95[174.55]; p=.000) than AD/MCI individuals, as did controls (β=-0.019[0.006]; p=.002; β=850.25[143.47]; p=.000). Neuroinflammatory biomarkers YKL-40 and GFAP did not differentiate mismatches from AD/MCI individuals. However, neurodegeneration biomarkers total tau (β=-0.23[0.089]; p=.011)

and NfL (β=-0.32[0.096]; p=.001) were significantly lower in mismatches versus AD/MCI individuals. Presynaptic proteins SNAP-25 (β=-0.018[0.094]; p=.049) and α-syn (β=-0.25[0.125]; p=.048) differentiated mismatches (and controls) from AD/MCI individuals. Although correlated strongly with SNAP-25 (r=0.89) and α-syn (r=0.81), Ng did not differentiate mismatches from AD/MCI individuals. NPTX2 was uninformative in differentiating all groups. **Conclusion:** Mismatches exhibited lower global atrophy and higher hippocampal volume than AD/MCI individuals, consistent with their lower levels of neurodegenerative CSF biomarkers. Our finding that synaptic dysfunction biomarkers (SNAP-25 and α-syn) differentiated mismatches and controls from AD/MCI individuals suggests a role of presynaptic processes in protecting against neurodegeneration and contributing to cognitive maintenance. The results are also consistent with evidence from autopsy studies suggesting that accumulation of mistargeted hyperphosphorylated tau within the synaptic compartment contributes to neurodegeneration and associated cognitive decline. **Keywords:** Cognitive maintenance, CSF biomarkers, presynaptic proteins, neurodegeneration. **Disclosures:** C Q-R is a full-time employee of Roche Diagnostics International Ltd, Rotkreuz, Switzerland. GK is a full-time employee of Roche Diagnostics GmbH, Penzberg, Germany.The work herein was generously supported by National Institute on Aging Awards 1U19AG078109-01, P30 AG062715, and RF1 AG027161; and by the Clinical and Translational Science Award (CTSA) program, through the NIH National Center for Advancing Translational Sciences (NCATS), grant UL1TR002373. The content is solely the responsibility of the authors. **References:** 1. Perez-Nievas BG, et al. Brain 2013;136(8):2510-26. https://doi.org/10.1093/brain/awt171; 2. Merluzzi AP, et al. Neurology 2018;91(5):e436-43. https://doi.org/10.1212/WNL.0000000000005901; 3. Gomez-Isla T, Frosch MP. Nature Reviews Neurology. 2022;18(6):323-32. 10.1038/s41582-022-00642-9; 4. Van Hulle C, et al. Alzheimer's & Dementia. 2021;17(3):431-45. https://doi.org/10.1002/alz.12204.

OC12- STUDY DESIGN AND SCREENING EXPERIENCE FROM THE PHASE 2 AUTONOMY TRIAL OF ANTI-P-TAU MONOCLONCAL ANTIBODY POSDINEMAB FOR EARLY ALZHEIMER'S DISEASE. D. Henley[1,2], J. Bogert[3], Z.S. Saad[4], G. Triana-Baltzer[4], T. Wang[4], H.C. Kolb[4], M. Fedgchin[1] *(1. Janssen Research & Development, LLC - Titusville, New Jersey (United States), 2. Indiana University School of Medicine, Psychiatry - Indianapolis, Indiana (United States), 3. Janssen Research & Development, LLC - Bridgewater, New Jersey (United States), 4. Janssen Research & Development, LLC - La Jolla, California (United States))*

Background: Autonomy, an ongoing, phase 2, global, double-blind, placebo-controlled, randomized, parallel-group common-close study assesses whether the anti-tau monoclonal antibody posdinemab (mid-domain epitope, requiring phosphorylated amino acid 217) will slow clinical decline in participants with early symptomatic (prodromal/mild dementia) Alzheimer's disease (early AD). **Methods:** Adults (55-80 years) with early AD were eligible upon meeting clinical and plasma p217+tau criteria followed by intermediate levels of tau burden on tau PET (18FMK6240). Participants receive posdinemab (low or high dose) or placebo IV, every 4 weeks. The primary outcome is change from baseline in the modified integrated Alzheimer's Disease Rating Scale (iADRS) Total Score at Week 104 (complete ADAS Cog13 plus ADCS-ADL MCI). Secondary outcomes include change from baseline on ADAS Cog13, RBANS, ADCS-ADL MCI, CDR-SB, and tau PET. This presentation discusses the Autonomy study design including unique aspects, correlations between screening biomarkers and clinical scores and preliminary screening/baseline characteristics of the population enrolled. **Results:** 115 global sites screened 2670 participants and the overall screen failure rate was 80.4%. 522 of 523 participants randomized received at least one dose of blinded treatment. Mean age of the population is 71.4 (SD 5.86) years, 52.3% are female, 78.4% white, and 11.1% Hispanic. Prodromal AD accounts for 56.4% of the clinical diagnoses and 58% of the population was taking acetylcholinesterase inhibitors/memantine at baseline. 58.6% of the screened population screen failed by not meeting plasma p217+tau criteria and of the remaining 41.4%, 31.4% were not in the intermediate tau PET range (15.2% were tau PET negative, 16.2% had widespread tau). Within the intermediate tau PET range, 44.7% were in the low and 55.3% in the high tau strata. All 522 participants had screening CDR global score 0.5; 90.8% were still 0.5 at baseline. The mean baseline (standard deviation [SD]) iADRS score was 101.8 (11.8), ADAS Cog 13 was 25.18 (7.98), ADCS ADL MCI was 41.91 (6.27), RBANS was 71.56 (13.26), RBANS DMI was 57.36 (16.60) and CDR-SB was 2.89 (1.15). Baseline tau PET SUVr correlated with baseline ADAS Cog13 score in various regions of interest (ROI) (rs=0.35 - 0.38, p<0.01) and the strongest correlation with tau PET was baseline RBANS immediate memory domain score with the total cortex ROI (rs = 0.41, p<0.01). Other clinical scales and tau PET ROIs will be presented. **Conclusion:** Lessons learned from the Autonomy screening experience are informative for the field, largely based on being the first trial employing a plasma biomarker as a prescreen to minimize the number of tau PET scans required to enroll the target patient population. Baseline tau PET SUVr correlated with clinical outcomes in multiple ROIs including all of cortex with the greatest correlations with immediate memory, language, and delayed memory RBANS domains. **Keywords:** Alzheimer's disease, phase 2 trial, posdinemab, screening experience, study design. **Disclosures:** All authors are or were employees or contractors of Janssen Pharmaceuticals and may hold stock or stock options in Johnson & Johnson.

OC13- PERFORMANCE OF PLASMA P-TAU217 IN AN AFRICAN AMERICAN COHORT: FINDINGS FROM THE AFRICAN AMERICANS FIGHTING ALZHEIMER'S IN MIDLIFE STUDY. G. Ennis[1], D. Norton[1], F. Carter[1], D. Gooding[1], A. Gee[2], T. Smith[1], H. Salazar[1], R. Wilson[1], R. Langhough[1], M. Zuelsdorff[1], S. Bouges[1], S. Asthana[1], S. Johnson[1], H. Zetterberg[1], C. Gleason[1] *(1. University of Wisconsin-Madison - Madison (United States), 2. Nehemiah Center for Urban Leadership Development - Madison (United States))*

Background: Biomarker tests should be validated in groups underrepresented in research to facilitate successful screening into clinical trials for Alzheimer's disease (AD). Blood-based phosphorylated tau217 (p-tau217) has emerged as a leading screening biomarker due to its close association with AD pathology detected by positron emission tomography (PET). The performance of p-tau217, however, is less well-understood in non-Hispanic Black adults, who in the US have a high prevalence of AD dementia [1] and comorbid conditions (e.g., kidney disease) found to influence p-tau217 levels in samples comprised predominantly of White adults [2]. In adults self-identifying as non-Hispanic Black enrolled in the African Americans Fighting Alzheimer's in Midlife study, we investigated associations between comorbidities

and p-tau217 and examined relationships of p-tau217 to AD PET biomarkers, genetic risk (APOE4), and cognitive status. **Methods:** Plasma stored on n=233 participants (Meanage= 64.44 years, SD=9.29, n=190[81.5%] cognitively-unimpaired) was assayed for p-tau217 (Simoa®,ALZPath,Inc.) for cross-sectional study. Subsamples had amyloid (PiB-index, n=63) and tau (meta-temporal-ROI, n=69) PET (n=55 had both). Amyloid (A) and tau (T) positivity status was determined separately for p-tau217 [3] and PET [4] using published thresholds. Comorbidities (assessment method) included: impaired kidney function (estimated glomerular filtration rate [eGFR], n=139), hypertension (SBP and DBP, n=231), obesity (BMI, n=232), self-reported diabetes (n=220), and cardiovascular disease (CVD: report of MI, stroke, or congestive heart failure, n=222). Kruskal-Wallis and Spearman correlation tested unadjusted associations between comorbidities and continuous p-tau217. Regression tested associations with log-transformed-p-tau217 adjusting for age and sex. Comorbidities significantly related to p-tau217 were tested as predictors of log-transformed-AD-PET-biomarkers. Kruskal-Wallis tested whether p-tau217 varied across A/T PET statuses, APOE4 allele count (n=192), and cognitive statuses (n=232), and whether amyloid or tau PET differed across p-tau217 statuses. **Results:** P-tau217 status proportions were: 11.2% A+/T+, 7.7% A+/T-, 81.1% A-/T-; and PET A/T status proportions were: 14.5% A+/T+, 3.6% A-/T+, 10.9% A+/T-, 70.9% A-/T-. Lower eGFR (eGFR<60: 13.7%) and CVD history (10.4%) were significantly associated with higher p-tau217 (unadjusted and models adjusted for age and sex). Stage 2 hypertension (SBP≥140mmHg or DBP≥90mmHg; 11.3%) demonstrated significantly higher p-tau217 than normal BP but was not significant when controlling age and sex. Diabetes and obesity were not significantly related to p-tau217. eGFR and CVD were not significantly related to log-transformed amyloid and tau PET. P-tau 217 levels were significantly higher in: 1) PET A+/T+ versus A-/T-, 2) APOE4 homozygotes (4.7%) versus heterozygotes (37.5%) and non-carriers (57.8%), and 3) MCI (9.5%) versus cognitively-unimpaired and impaired-other (7.3%). P-tau217 A+/T+ versus A-/T- status had significantly higher amyloid and tau PET. **Conclusion:** In this group of predominantly cognitively-unimpaired non-Hispanic Black adults, probable kidney disease and CVD were associated with higher p-tau217 but not amyloid and tau PET. Results suggest that comorbidities may interfere with accurate interpretation of p-tau217. In a smaller subsample, p-tau217 aligned with AD PET biomarkers, largely consistent with prior investigation [3]. Research assessing larger samples of adults with comorbidities from diverse racial/ethnic groups is needed. The p-tau217/non-phosphorylated-tau-217 ratio, which may be less influenced by kidney disease [5], should be investigated as an alternative to p-tau217. **Keywords:** P-tau217, comorbidities, African Americans. **Disclosures:** DG: R01-AG054059; RL: NIA (R01-AG027161; R01-AG021155; R01-AG0540590); MZ: NIA (R03-AG063303); SA: NIA (P30-AG062715); SJ: NIA (R01-AG027161; R01-AG021155; P30-AG062715); HZ: Swedish Research Council (2022-01018 and 2019-02397), European Union's Horizon Europe Research and innovation programme (grant agreement 101053962), Swedish State Support for Clinical Research (ALFGBG-71320), Alzheimer Drug Discovery Foundation (201809-2016862), AD Strategic Fund, and Alzheimer's Association (ADSF-21-831376-C, ADSF-21-831381-C, and ADSF-21-831377-C), Bluefield Project, Olav Thon Foundation, Erling-Persson Family Foundation, Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden (FO2022-0270), European Union's Horizon 2020 research and innovation programme (Marie Skłodowska-Curie grant agreement 860197, MIRIADE), European Union Joint Programme–Neurodegenerative Disease Research (JPND2021-00694), National Institute for Health and Care Research University College London Hospitals Biomedical Research Centre, and UK Dementia Research Institute at UCL (UKDRI-1003); CG: NIA (R01-AG054059; P30-AG062715). **References:** 1. Rajan et al. Alzheimers Dement 2021; 17(12):1966-1975. doi: 10.1002/alz.12362; 2. Mielke et al. Nat Med 2022; 28: 1398-1405. doi: 10.1038/s41591-022-01822-2; 3. Ashton et al. JAMA Neurol 2024; 81(3):255-263. doi:10.1001/jamaneurol.2023.5319; 4. Cody et al. Brain 2024; Apr 26:awae116. doi: 10.1093/brain/awae116; 5. Janelidze et al. JAMA Neurol 2023; 80(5):516-522. doi:10.1001/jamaneurol.2023.0199

OC14- EARLY INCREASE OF THE SYNAPTIC BLOOD MARKER B-SYNUCLEIN IN ASYMPTOMATIC INDIVIDUALS WITH AUTOSOMAL DOMINANT ALZHEIMER´S DISEASE.

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Background: Synaptic degeneration is a major hallmark of Alzheimer´s disease (AD) and the pathological correlate of memory impairment. Monitoring of synaptic changes in AD patients is therefore of importance for diagnosis, prognosis and assessing disease progression but also to track beneficial effects on synaptic loss in clinical trials. The protein β-synuclein is a promising and easily accessible blood marker to track synaptic degeneration in AD but changes in preclinical AD are unclear. The Dominantly Inherited Alzheimer Network (DIAN) observational study is a worldwide multicenter initiative to longitudinally study dominantly inherited AD and provides the unique opportunity to study blood β-synuclein levels in very early (asymptomatic) AD and assess the timing

and relation of β-synuclein changes to other pathological alterations. **Methods:** We used immunoprecipitation mass spectrometry (IP-MS) for the quantification of β-synuclein in serum samples of 178 participants of the DIAN study including 69 cognitively unimpaired mutation non-carriers (NC), 78 cognitively unimpaired AD mutation carriers (asymptomatic AD, aMC) and 31 symptomatic MC (sMC). Changes of β-synuclein serum levels were compared and correlated with cerebrospinal fluid (CSF) biomarkers (Aβ42/40, tTau, pTau variants), amyloid deposition ([11C]-Pittsburgh Compound B - positron emission tomography (PiB-PET)), brain atrophy (magnetic resonance imaging (MRI)) and metabolism ([18F]-fluorodeoxyglucose - PET (FDG-PET)), axonal degeneration (serum NfL) and cognitve impairment (MMSE, Clinical Dementia Rating sum-of-boxes (CDR-SB), DIAN cognitive composite). Longitudinal trajectories were estimated using the expected years to symptom onset (EYO). **Results:** Blood β-synuclein levels were already higher in asymptomatic autosomal dominant AD (ADAD) mutation carriers (median 7.29pg/mL, interquartile range (IQR) 5.89-8.59) compared with non-carriers (5.25pg/mL, IQR 4.63-6.66) and highest in sMC (14.4pg/mL, IQR 11.7-18.4). Longitudinal trajectories based on the EYO indicated that serum β-synuclein start to rise 11 years before symptom onset and preceding the rise of serum NfL levels, brain atrophy and hypometabolism and cognitive decline. β-synuclein levels were more strongly correlated to amyloid plaque load (r=0.46) than to hippocampal volume (r=-0.38) and cortical metabolism (r=-0.34) supporting the closer temporal association with amyloid deposition. Furthermore, β-synuclein was associated with cognitive impairment (MMSE: r=-0.41, CDR-SB: r=0.55) and gradually increased with declining cognition. **Conclusion:** Our data rank synaptic degeneration as one of the earliest events in the ADAD pathophysiological cascade as it is close to the start of amyloid deposition. It supports the use of blood β-synuclein to track synaptic changes in preclinical AD and as a surrogate marker for cognitive impairment which might be used in early diagnosis and to support patient selection and monitoring of treatment effects in clinical trials of putative AD-modifying therapies. **Keywords:** β-synuclein, blood biomarker, synaptic degeneration, autosomal dominant Alzheimer´s disease, asymptomatic mutation carriers, preclinical Alzheimer´s disease. **Disclosures:** The study was supported by the Cure Alzheimer´s Fund (granted to PO and MO). Patrick Oeckl received research support from the Alzheimer Forschung Initiative e.V. (20059CB), ALS Association/ALS Finding A Cure (24-SGP-691, 23-PPG-674-2)), Charcot Foundation (D.7090), DZNE Innovation-to-Application (I2A_call7_Oeckl, I2A_call9_Oeckl) and consulting fees from LifeArc and Fundamental Pharma. Markus Otto received research support from German Federal Ministry of Education and Research (FTLDc 01GI1007A), the EU Joint Programme-Neurodegenerative Diseases networks Genfi-Prox (01ED2008A), the EU (MOODMARKER 01EW2008), the German Research Foundation/DFG (SFB1279), the foundation of the state Baden-Württemberg (D.3830), Boehringer Ingelheim Ulm University BioCenter (D.5009), and the Thierry Latran Foundation. Markus Otto and Patrick Oeckl are co-inventors of a patent application for using β-synuclein measurement in blood (EP4014048A1, US2022283184A1). Johannes Levin reports speaker fees from Bayer Vital, Biogen, EISAI, TEVA, Esteve, Zambon and Roche, consulting fees from Axon Neuroscience, EISAI and Biogen, author fees from Thieme medical publishers and W. Kohlhammer GmbH medical publishers and is inventor in a patent "Oral Phenylbutyrate for Treatment of Human 4-Repeat Tauopathies" (EP 23 156 122.6) filed by LMU Munich. In addition, he reports compensation for serving as chief medical officer for MODAG GmbH, is beneficiary of the phantom share program of MODAG GmbH and is inventor in a patent "Pharmaceutical Composition and Methods of Use" (EP 22 159 408.8) filed by MODAG GmbH, all activities outside the submitted work. JLlG's research is supported by NIH-NIA (K01AG073526), the Alzheimer's Association (AARFD-21-851415, SG-20-690363), the Michael J. Fox Foundation (MJFF-020770), the Foundation for Barnes-Jewish Hospital and the McDonnell Academy. FL has grants and Support from NIA, NIH, RED-LAT, LATAM-Fingers, Large PD, Roche, Biogen, Tau Consortium, Alzheimer Association and Viewmind. All other authors declare no competing interests. Data collection and sharing for this project was supported by The Dominantly Inherited Alzheimer Network (DIAN, U19AG032438) funded by the National Institute on Aging (NIA), the Alzheimer's Association (SG-20-690363-DIAN), the German Center for Neurodegenerative Diseases (DZNE), Raul Carrea Institute for Neurological Research (FLENI), Partial support by the Research and Development Grants for Dementia from Japan Agency for Medical Research and Development (AMED), the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), Korea Dementia Research Center (KDRC), funded by the Ministry of Health & Welfare and Ministry of Science and ICT, Republic of Korea (HI21C0066), and Spanish Institute of Health Carlos III (ISCIII).

OC15- ADVANCING PATIENT OUTCOMES WITH REAL-WORLD EVIDENCE. A. Hartry[1], H. Butzkueven[2,3], R. Perneczky[4], C. Ritchie[5] *(1. Eli Lilly and Company - Indianapolis (United States), 2. MSBase Foundation - Melbourne (Australia), 3. Monash University - Melbourne (Australia), 4. Ludwig-Maximilians-Universität Munich - Munich (Germany), 5. University of St. Andrews - St. Andrews (United Kingdom))*

Background: Real-world evidence (RWE) in Alzheimer's disease (AD) is needed to understand effectiveness, safety, and appropriate use of disease-modifying therapies. In addition, RWE supports regulatory and clinical decision making by providing key insights into disease progression, treatment access, quality of care, and other important epidemiological questions. Here we describe the value of registries and real-world studies in generating the RWE needed to optimize treatment and improve patient outcomes in early symptomatic AD. **Methods:** There are several ongoing and upcoming large-scale efforts to support RWE generation for AD therapies. These methods include pragmatic studies, site-based studies with extensive physician interaction, site-based studies and platforms utilizing batch processing of electronic medical records (EMRs), and patient-based studies with bespoke acquisition of EMR data and potential for primary data collected by a central rater. These methods also include linkage with prescription claims data. Patient registries are valuable approaches to real-world data collection that can support research on the safety, efficacy, and outcomes for AD therapies. **Results:** Rigorously collected and scrupulously analyzed data from real-world studies and data platforms can answer important questions regarding treatment patterns, long-term outcomes, patient-centered impact, and occurrence and management of risks. These findings give a more comprehensive understanding of the benefits, risks, and costs of therapies, help translate clinical research to routine practice, inform changes to labels, and support reimbursement decisions. RWE can build upon findings from randomized controlled trials, as registries and real-world studies typically collect outcomes over longer periods of time

and from less restricted, more diverse populations. **Conclusion:** Real-world data is an important source of clinical evidence in AD and a key component to making data-driven decisions to improve healthcare systems and delivery. Robust RWE will be increasingly important for monitoring patient outcomes and evaluating disease progression with new and emerging AD therapies. **Disclosures:** Ann Hartry is an employee and shareholder of Eli Lilly and Company. Helmut Butzkueven's institution has received compensation for advisory boards or lecture fees from Novartis, Biogen, Merck, UCB Pharma and Roche. His institutions receive research funding from Novartis, Biogen, Merck, Roche, the NHMRC of Australia, The Medical Research Future Fund (Australia), Monash Partners, the Trish MS Foundation, The Pennycook Foundation, and MS Australia. He receives personal compensation as the Managing Director of the MSBase Foundation. Robert Perneczky has received honoraria for advisory boards and speaker engagements from Roche, EISAI, Eli Lilly, Biogen, Janssen-Cilag, Astra Zeneca, Schwabe, Grifols, Novo Nordisk, Tabuk, GSK and Bristol Myer Squibb. Craig Ritchie is the CEO, Founder, and majority shareholder of Scottish Brain Sciences. He has received consulting feeds from Biogen, Eisai, MSD, Actinogen, Roche, and Eli Lilly. He has received payment or honoraria from Eisai and Roche.

OC16- LONGITUDINAL TRAJECTORIES OF PLASMA P-TAU217 IN EARLY ALZHEIMER'S DISEASE: IMPLICATIONS FOR USE IN CLINICAL TRIALS.

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Background: Several cross-sectional studies have demonstrated the efficacy of plasma p-tau217 in identifying early Alzheimer's disease (AD) pathology. However, it is possible that longitudinal change in plasma p-tau217 concentration may be an even earlier indicator of AD pathology onset and progression than single measures. In this study, we aim to investigate if longitudinal measurements of plasma p-tau217 can be used to differentiate cognitively stable individuals from progressors in predementia AD. **Method:** CSF and plasma p-tau217 concentrations were measured on the Simoa HD-X platform with the University of Gothenburg (UGOT) p-tau217 assay. Using Linear Mixed Models, we assessed longitudinal trajectories of plasma and CSF p-tau217 in 746 participants from the Norwegian Dementia Disease Initiation cohort (1230 observations up to 8.48 years, [Myears=3.26, SDyears=1.56]). Participants were classified as either cognitively normal (CN) or mild cognitive impairment (MCI) with normal or abnormal cerebrospinal fluid (CSF) Aβ42/40 ratio (A) at baseline [CN A-, n=229; MCI A-, n=216; CN A+, n=93; MCI A+, n=208]. Biomarker change according to clinical progression within a subset (n=295) of the A+ cases (426 observations up to 7.09 years, [Myears=2.85, SDyears=1.29]) was also assessed, including cases remaining stable CN (n=76) and stable MCI (n=161) or progressing from CN to MCI (n=12) or from MCI to dementia (n=42). **Results:** Plasma and CSF p-tau217 levels were similar in CN A- and MCI A- at baseline (Plasma: β=-0.03; CSF: β=0.07, both n.s.), but higher in CN A+ (Plasma: β=0.81; CSF: β=1.37, both p<.001) and MCI A+ (Plasma: β=1.22; CSF: β=1.72, both p<.001). In plasma, only CN A+ (β=0.09, p<.01) and MCI A+ (β=0.06, p<.05) showed increase over time. In CSF, p-tau217 also increased in CN A- (β=0.09, p<.001) and MCI A- (β=0.13, p<.001), but steeper increases were observed for CN A+ (β=0.16, p<.001) and MCI A+ (β=0.17, p<.001). Within the A+ group, both plasma and CSF p-tau217 levels were higher at baseline for stable MCI cases (Plasma: β=0.46; CSF: β=0.48, both p<.001) and MCI cases progressing to dementia (Plasma: β=0.79; CSF: β=0.69, both p<.001) as compared to stable CN cases. Over time, a more rapid increase in both plasma and CSF p-tau217 were found for cases progressing from CN to MCI (Plasma: β=0.26, p<.01; CSF: β=0.30, p<.001) and MCI to dementia (Plasma: β=0.26, p<.01; CSF: β=0.34, p<.001) than for stable CN (Plasma: β=0.09, p<.05; CSF: β=0.18, p<.001) or stable MCI (Plasma: β=0.08, p<.05; CSF: β=0.23, p<.001). **Conclusion:** Baseline CSF and plasma p-tau217 differentiate preclinical and prodromal cases, and increases over time are associated with clinical progression in predementia AD. Performing repeated measurements of this marker in blood could be an easily accessible way to distinguish individuals that will remain cognitive stable from those who will present cognitive deterioration, this will be essential to prioritize access to disease modifying therapies. Moreover, monitoring plasma p-tau217 levels over time could provide valuable insights into disease progression and therapeutic efficacy. **Keywords:** Blood biomarkers; prognostic; clinical utility; therapy efficacy. **Disclosures:** 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). BEK has served as a consultant for Biogen and advisory board for Eisai. TF has served as a consultant and at the advisory boards for Biogen, Eisai, Novo Nordisk, Eli Lilly and Roche. RES has served on an advisory board for Eisai.

OC17- PRECISION NEUROSCIENCE: RATIONALE AND DESIGN FOR THE RETAIN PHASE 2B STUDY WITH A TAU ACTIVE IMMUNOTHERAPY IN PRECLINICAL ALZHEIMER'S DISEASE. L. Steukers[1], I. Kezic[1], C. Bleys[1], L. Li[2], C. Theunis[1], A. Beckers[1], G. Triana-Baltzer[3], T. Thornton-Wells[4], Z.S. Saad[3], D. Henley[2], F. Elwood[4], M.C. López López[5] *(1. Johnson & Johnson - Beerse (Belgium), 2. Johnson & Johnson - Titusville (United States), 3. Johnson & Johnson - La Jolla (United States), 4. Johnson & Johnson - Cambridge (United States), 5. Johnson & Johnson - Allschwil (Switzerland))*

Background: Preclinical AD, A+T+ specifically, is associated with near-term (ie, 3-5 years) cognitive decline in cognitively unimpaired individuals and is, therefore, of high clinical relevance.1 The sequential emergence of tau pathology across interconnected brain regions supports the hypothesis that tau pathology spreads in a "prion-like" fashion across connected neurons.2-5 The identification of extracellular pathological phosphorylated tau (pTau) and its ability to spread across the brain provides opportunities to target pTau with antibodies. A promising therapeutic approach is to prevent or halt pTau spreading, and consequently the formation of new neurofibrillary tangles and progression of AD. The newly launched Phase 2b REτAIN study is the first clinical trial in Preclinical AD with a tau targeting active immunotherapy (JNJ-64042056) to assess efficacy, safety and immunogenicity. JNJ-64042056 is designed to stimulate the immune system to produce antibodies against pTau which can block the spread of pTau aggregates between brain regions. The following work will present the rationale and study design for REτAIN. **Methods:** REτAIN initiated prescreening in April 2024 and will compare treatment with JNJ-64042056 to placebo over 48 months in 498 people with Preclinical AD. To identify this population, a plasma p217+tau assay is being used to prescreen cognitively unimpaired individuals for evidence suggestive of elevated brain amyloid and tau burden.6 The presence of pathologic pTau as an eligibility criterion will be confirmed using tau PET (T+ status). The primary efficacy endpoint is change from baseline in PACC-5 at 48 months. In addition, a key secondary objective is to assess the effect of JNJ-64042056 on the propagation of tau pathology, as measured by tau PET. Planned secondary endpoints include the CDR-GS (time-to-event), CDR-SB, MBI-C, ADCS-ADL-PI, volumetric MRI, and CSF/plasma biomarkers. Eligible participants will be randomized in a 1:1 ratio to JNJ-64042056 or placebo. The randomization will be balanced and stratified by geographical region and baseline tau burden. A sample size of 174 completers per group achieves 90% power to detect a group difference of 0.88 in change from baseline on PACC-5, assuming 2-sided alpha of 0.05 and SD of 2.53 (which translates to 40% slowing of cognitive decline compared to placebo). **Results:** This study aims to provide proof-of-concept that JNJ-64042056 slows the spread of pTau and delays the onset of clinical symptoms of AD in Preclinical AD. The ease of administration (e.g., intramuscular injection) and low-burden dosing regimen (e.g., Q6M) make JNJ-64042056 a convenient candidate for large scale intervention in people with the asymptomatic stage of the disease. We will discuss the impact of the two-step biomarker precision strategy on the screening funnel including the 3.5-fold expected reduction in the number of screening PET scans, challenges with the establishment of a suitable disclosure process, and the impact of the availability of anti-amyloid mAbs on retention. **Conclusion:** The REτAIN study is the first interventional, double blind, clinical trial using an anti-tau treatment in Sporadic Preclinical AD. Design considerations and challenges will be discussed. It is expected that early interception of AD will have a significant impact on the societal burden associated with AD. **Keywords:** Preclinical AD, active immunotherapy, clinical trial, anti-tau, tau seeding. **Disclosures:** LS, IK, CB, LL, CT, GTB, ZSZ, DH, FE and CLL are employees of Johnson & Johnson. AB is a paid consultant for Johnson & Johnson. **References:** 1) Ossenkoppele R, Binette AP, Groot C, et al. Amyloid and Tau PET positive cognitively unimpaired individuals are at high risk for future cognitive decline. Nat Med. 2022;28(11):2381-2387. 2) Calafate S, Buist A, Miskiewicz K et al. Synaptic Contacts Enhance Cell-to-Cell Tau Pathology Propagation, Cell Reports. 2015;11(8):1176-1183. 3) de Calignon A, Polydoro M, Suárez-Calvet M, et al. Propagation of tau pathology in a model of early Alzheimer's disease. Neuron. 2012;73(4):685-697. 4) Franzmeier N, Dewenter A, Frontzkowski L, et al. Patient-centered connectivity-based prediction of tau pathology spread in Alzheimer's disease. Sci Adv. 2020;27:6(48):eabd1327. 5) Meisl G, Hidari E, Allinson K, et al. In vivo rate-determining steps of tau seed accumulation in Alzheimer's disease. Sci Adv. 2021;7(44):eabh1448. 6) Doré V, Doecke J, Saad Z, et al. Plasma p217+tau versus NAV4694 amyloid and MK6240 tau PET across the Alzheimer's continuum. Alzheimers Dement (Amst) 2022;14(1):e12307.

OC18- BLOOD BIOMARKERS TO DETECT ALZHEIMER'S DISEASE IN CLINICAL PRACTICE – A CROSS-SECTIONAL STUDY IN PRIMARY AND SECONDARY CARE. S. Palmqvist[1], P. Tideman[1], N. Mattsson-Carlgren[1], R. Smith[1], R. Ossenkoppele[1], S. Schindler[2], M. Monane[3], T. West[3], K. Blennow[4], P. Verghese[3], J. Braunstein[3], S. Janelidze[1], E. Stomrud[1], G. Salvadó[1], O. Hansson[1] *(1. Lund University - Malmo (Sweden), 2. Washington University School of Medicine - Saint Louis (United States), 3. C2N Diagnostics - Saint Louis (United States), 4. Gothenburg University - Gothenburg (Sweden))*

Background: An accurate blood test for Alzheimer's disease (AD) could streamline the diagnostic work-up and treatment of AD. We therefore aimed to prospectively evaluate a clinically available AD blood test in primary and secondary care, using predefined biomarker cutoffs and plasma analyses. **Methods:** We evaluated the diagnostic accuracy of plasma %p-tau217 combined with plasma Aβ42/40 (Amyloid Probability Score-2; APS2) measured by mass spectrometry in 1,213 symptomatic patients. The main outcome was AD pathology determined by abnormal cerebrospinal fluid Aβ42/40 and p-tau217. Secondary outcome was clinical AD. Blood biomarker cutoffs established in an independent cohort were applied to primary (n=307) and secondary care (n=300) cohorts comprised of patients undergoing cognitive evaluation (plasma samples analyzed in one single batch per study). The blood test was then evaluated prospectively in primary (n=208) and secondary (n=398) care (plasma analyzed bi-weekly). **Results:** The mean age was 74.2 years, 48% were women, 23% had subjective cognitive decline, 44% mild cognitive impairment, and 33% dementia. 50% had AD pathology in primary and secondary care. When samples were analyzed in a single batch in primary care, the AUC for APS2 was 0.97 (95%CI 0.95–0.99), PPV 91% (95%CI 87–96%), and NPV 92% (95%CI 87–96%); in secondary care, the AUC was 0.96 (95%CI 0.94–0.98), PPV 88% (95%CI 83–93%), and NPV 87% (95%CI 82–93%). When samples were analyzed prospectively (bi-weekly) in primary care, the AUC was 0.96 (95%CI 0.94–0.98), PPV 88% (95%CI 81–94%), and NPV 90% (95%CI 84–96%); in secondary care, the AUC was 0.97 (95%CI 0.95–0.98), PPV 91% (95%CI 87–95%), and NPV 91% (95%CI 87–95%). Primary care physicians identified clinical AD correctly in 61% of

patients (95%CI 53–69%) after clinical examination, cognitive testing, and a CT scan versus 91% (95%CI 86–96%) for APS2 (p<0.001). Dementia specialists had an accuracy of 73% (95%CI 68–79%) versus 91% (95%CI 85–95%) for APS2 (p<0.001). In the whole population, the accuracy of APS2 (90%, 95%CI 88–92%]) was not significantly different from %p-tau217 (90% 95%CI 88–91%]). **Conclusion:** Mass spectrometry-based APS2 and %p-tau217 had high accuracy for identifying AD among individuals with cognitive symptoms in primary and secondary care using predefined cutoffs. At CTAD we will also include results from prospective assessments using different p-tau217 immunoassay tests (Fujirebio, Janssen and Lilly) in both primary and secondary care. Future studies should evaluate whether such blood tests influence clinical care. **Key words:** Blood biomarkers, p-tau217, primary care, secondary care. **Clinical trial registry:** NCT06120361, NCT06122415. Conflicts of interest: 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 Alzpath, BioArctic, Biogen, Bristol Meyer Squibb, Eisai, Eli Lilly, Fujirebio, Merck, Novartis, Novo Nordisk, Roche, Sanofi and Siemens.

OC19- CLINICAL PROGRESSION ON CDR-SB: RESIDENCE TIME AT EACH LEVEL IN THE DIAN AND ADNI COHORTS. G. Wang[1], Y. Li[1], E. Mcdade[1], J. Morris[1], L. Schneider[2] *(1. School of Medicine, Washington University in St Louis - St Louis (United States), 2. Keck School of Medicine, University of Southern California, Los Angeles - Los Angeles (United States))*

Background: CDR-SB© is a common primary outcome used in pivotal or phase 3 trials of early Alzheimer disease. It serves as an FDA-approved composite rating for MCI and mild dementia in trials that would otherwise require co-primary outcomes. Although the CDR-SB drug-placebo differences are statistically significant in recent AD trials, their effect sizes are small ranging from mean +0.03, to -0.39, -0.45, and -0.70, leading to substantial controversy over their clinical importance. It is crucial to understand how the difference in CDR-SB can be interpreted in a clinically meaningful manner by clinicians, patients, and researchers. To establish a standardized way of evaluating the delay in disease progression, we estimated the residence time at each stepwise (0.5 units) CDR-SB level before progression to a higher level across the entire spectrum of natural disease progression for untreated participants. We propose to use the residence time (i.e., time-to-0.5-unit progression) as a potential measure of clinically important change. **Methods:** We analyzed 214 participants from the Dominantly Inherited AD Network (DIAN) observational study and 406 participants from the ADNI observational study for individuals with sporadic AD. We employed a disease progression model to estimate the disease progression trajectory of CDR-SB, which was then used to estimate the residence time at each CDR-SB level across the entire natural disease progression spectrum. **Results:** The estimated residence time at each 0.5-unit CDR-SB level of progression is similar in the DIAN and sporadic AD cohorts. From 0.5 to 1, 1 to 1.5, 1.5 to 2, 2 to 2.5, 2.5 to 3, 3 to 3.5, 3.5 to 4, 4 to 4.5, 4.5 to 5, 5 to 5.5, 5.5 to 6, and 6 to 6.5, they are: 2.09, 1.17, 0.82, 0.63, 0.51, 0.43, 0.37, 0.33, 0.29, 0.26, 0.24, and 0.22 years, respectively, for DIAN; and 2.25, 1.35, 0.97, 0.76, 0.62, 0.53, 0.46, 0.41, 0.36, 0.33, 0.30, and 0.28 years for sporadic AD. Using these residence times, we estimate that untreated participants would experience a decline from a baseline CDR-SB value of 3.22 to 6.26 (reflecting a 3.09-point decline observed in the Clarity AD lecanemab trial from baseline to the OLE) over 2.3 years. In contrast, continuous treatment with lecanemab would extend this progression to 3 years, resulting in a delay in disease progression of 0.7 years. The residence time for higher CDR-SB levels (≥7) and the delay in disease progression for participants treated with other anti-amyloid treatments will be reported. **Conclusion:** In early AD, low CDR-SB scores indicate that patients on average do not change over 1 to 2 years and thus a 0.5 decrease is clinically notable. When CDR-SB scores are somewhat higher, around 2.5, time at that level is much briefer, about 0.5 to 0.6 years, and a two-level decrease, or 1.0 point, might be considered minimally clinically important. Estimating the residence time at each CDR-SB level provides clinically meaningful insight into disease progression course and treatment effects over extended periods and in long-term clinical trials. **COI:** Guoqiao Wang, PhD, is the biostatistics core co-leader for the DIAN-TU. He discloses serving on the DSMB for Eli Lilly and Company, Amydis Corporate, and Abata Therapeutics, as well as working as a statistical consultant for Alector, Inc. and Pharmapace, Inc. He also serves as DSMB member for another five studies funded by NIH.

OC20- INITIAL RESULTS FROM REMOTE SPEECH-BASED SCREENING IN THE FIRST 900 DIGITALLY RECRUITED PARTICIPANTS IN ADNI-4. C. Skirrow[1], J. Weston[1], M.J. Miller[2,3], R.L. Nosheny[2,4], B. Albala[5,6], M.W. Weiner[2,3,4], E. Fristed[1] *(1. Novoic Ltd - London (United Kingdom), 2. Northern California Institute for Research and Education (NCIRE) - San Francisco (United States), 3. Department of Veterans Affairs Medical Center - San Francisco (United States), 4. University of California, San Francisco - San Francisco (United States), 5. University of California Irvine - Irvine (United States), 6. Research Service, Veterans Administration Long Beach Healthcare System - Long Beach (United States))*

Background: The Alzheimer's Disease Neuroimaging Initiative-4 (ADNI-4) aims to recruit 20,000 participants into a digital remotely assessed cohort, whilst enhancing access and participation for historically underrepresented populations (URPs). Subsamples will progress to more in-depth blood biomarker (N=4,000) and subsequently in-clinic evaluations (N=500). Storyteller, a remote web-based story recall test battery, is the sole objective measure of cognitive impairment currently utilised in ADNI4's digital recruitment and remote assessment campaign. **Methods:** ADNI-4's remote digital cohort are recruited using a culturally informed digital marketing strategy. Demographic information, self-reported diagnosis (Mild Cognitive Impairment (MCI), Alzheimer's Disease (AD), or dementia), and a measure of subjective cognitive/functional decline (Measurement of Everyday Cognition, ECog-12), are collected via the online study portal. Participants also complete Storyteller, a speech-based cognitive assessment battery based on story recall tasks. The generalised matching algorithm (G-Match) evaluates proportional recall of stories, scored from 0-100, with a higher score representing better test performance. The current study evaluates the association between G-match scores and demographic background, self-reported diagnosis, and subjective/functional decline on the ECog-12. **Results:** As of May 28, 2024, 1739 individuals were enrolled in the digital cohort and 903 (52%) completed Storyteller and provided a valid score (mean age 67.02 ± 7.51 years, 77% female, average 16.1 years education). Among them, 109 (12%) self-reported a diagnosis of MCI, AD, or dementia (mean age 70.4 ± 7.62 years).

The sample was demographically diverse, with 35.5% being URP participants (including 24% Black or African American, 7% Latino/a and 2% or less for Asian, Pacific Islander, Native American or Mixed race). Participants accessed and completed Storyteller assessments across multiple common personal devices and browsers. Regression analyses evaluating G-match scores in relation to participant demographics (age, sex, years of education), showed a subtle but significant age-related decline (β=-0.15, p=0.03), higher scores for more educated participants (β=1.95, p<0.0001) and higher scores in females (β=4.35, p=0.0005). G-Match scores were higher for participants without a self-reported diagnosis (mean 57.6 ± 15.00) compared to those with a self-reported diagnosis (mean 42.7 ± 19.11, t=7.84, p<0.001), and predicted self-reported diagnosis: Area Under Receiver Operator Curve (AUROC)= 0.73. There was a weak but highly significant correlation between G-match scores and the ECog-12 (rho=-0.26, p<0.0001). **Conclusion:** At this time, 903 participants from ADNI-4's remote digital cohort have been assessed using Storyteller. More data is anticipated at the time of presentation. A diverse sample, including participants with self-reported MCI, AD, or dementia, were able to complete the test remotely and unsupervised. Subtle decrements in test performance were seen with increasing age, with better performance in female participants and those with more years in education, in line with prior research in similar cognitive tasks. Test scores were lower in participants with self-reported diagnosis and agreed modestly with self-reported subjective decline, supporting the validity of Storyteller. As ADNI-4 further progresses, more in-clinic evaluations of participants from the remote digital sample will be available, enabling a fuller assessment of Storyteller's effectiveness in efficiently prioritizing cognitively impaired older adults for clinical research in a remote, unsupervised setting. **Keywords:** Alzheimer's Disease, Pre-screening, Speech-based testing, ADNI-4. **Clinical Trial Registry:** NCT05617014; https://clinicaltrials.gov. **Disclosures:** EF, JW and CS are employed by and/or option- or shareholders of Novoic. MJM reports no disclosures. BA's only relevant disclosure is ADNI4 grant support. RLN reports grants to institution from NIH, California Department of Health, and Genentech, Inc. MW serves on Editorial Boards for Alzheimer's & Dementia, MRI and TMRI. He has served on Advisory Boards for Acumen Pharmaceutical, ADNI, Alzheon, Inc., Biogen, Brain Health Registry, Cerecin, Dolby Family Ventures, Eli Lilly, Merck Sharp & Dohme Corp., National Institute on Aging (NIA), Nestle/Nestec, PCORI/PPRN, Roche, University of Southern California (USC), NervGen. He has provided consulting to Baird Equity Capital, BioClinica, Cerecin, Inc., Cytox, Dolby Family Ventures, Duke University, Eisai, FUJIFILM-Toyama Chemical (Japan), Garfield Weston, Genentech, Guidepoint Global, Indiana University, Japanese Organization for Medical Device Development, Inc. (JOMDD), Medscape, Nestle/Nestec, NIH, Peerview Internal Medicine, Roche, T3D Therapeutics, University of Southern California (USC), and Vida Ventures. He has acted as a speaker/lecturer to The Buck Institute for Research on Aging, China Association for Alzheimer's Disease (CAAD), Japan Society for Dementia Research, and Korean Dementia Society. He holds stock options with Alzheon, Inc., Alzeca, and Anven. The following entities have provided funding for academic travel: University of Southern California (USC), NervGen, ASFNR, and CTAD Congress.

OC21- VALIDATING SPEECH-BASED BIOMARKERS FOR MEASURING DISEASE PROGRESSION IN AD: A HEAD-TO-HEAD COMPARISON OF THREE BIOMARKER DEVELOPMENT STRATEGIES.

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Background: Changes in the structure and use of language are established clinical characteristics of Alzheimer's disease (AD). Natural Language Processing (NLP) tools allow for more objective measurement of language complexity and production, spurring interest in the development and validation of speech biomarkers for tracking clinical change over time. Our objective was to evaluate multiple biomarker development strategies using recordings from two Phase 2 placebo controlled clinical trials. **Methods:** Recordings of the Clinical Dementia Rating (CDR) interview were analyzed for 232 English speaking participants enrolled in 2 Phase 2 trials of semorinemab. [MCI and mild AD (Tauriel; NCT03289143) and mild to moderate AD (Lauriet; NCT03828747)]. For the Lauriet trial, only placebo arm data was used, as the primary analysis showed a treatment effect as measured by ADAS-Cog11. An NLP speech analysis pipeline was used to extract acoustic and linguistic features from patients' responses to the "recent experience" prompt. Data were split ~60/40 into training (n=139) and test (n=93) sets for development and validation. Composites were simple linear combinations of standardized and sign matched features. We tested 3 different feature selection strategies: 1) features from our previously published speech biomarker (Robin et al., 2023) (9 features), 2) features which showed a significant effect of change over time at p<0.001 (12 features), and 3) features with greater clinical interpretability (e.g., linguistic vs. signal processing features), a significant effect of time (p<0.05), and an ICC>0.5, excluding those with marked skewness (skewness>2) and high intercorrelation (r>0.8) (18 features). Composite performance was evaluated by comparing correlations with clinical endpoints, ICC values (screening vs. baseline comparison), overlap of longitudinal trajectories, and effect sizes in training and test sets. **Results:** No significant differences were observed for mean clinical endpoint scores or longitudinal trajectories between training and test sets. Within the test set, all 3 composites showed significant change over time (β=0.49-0.61, all p's<0.001) with effect sizes of baseline to endpoint scores (Cohen's D) ranging from 0.47-0.59. Screening vs. baseline ICC values were adequate, ranging from 0.67 to 0.8. All 3 composites were significantly correlated (with similar magnitude) with clinical endpoints at baseline. Change score correlations were more variable; all composite change scores were significantly correlated with change scores for the ADAS-Cog11 and ADCS-ADL. Only one was significantly correlated with the CDR-SB and none were associated with the MMSE. When comparing longitudinal trajectories, training and test trajectories were overlapping for all 3 composites, indicating good generalizability. **Conclusion:** We demonstrated that speech characteristics can be combined into meaningful indices of disease progression across the spectrum of MCI to moderate AD. The best performing composite was our previously published Tauriel derived biomarker. It had the highest effect size for change (0.59), ICC (0.80) and was the simplest, most explainable measure (including only 9 features) and showed strong replication in this novel dataset. These data highlight the potential utility of a speech-based biomarker as a supplementary measure in AD clinical trials. Future work on clinical interpretation and patient relevance of these language changes is ongoing.

OC22- ELIGIBILITY FOR ANTI-AMYLOID TREATMENT IN REAL WORLD MEMORY CLINIC POPULATIONS. A. Matton[1,2], M. Daniilidou[1,2], A. Hall[1,3], U. Öhlund-Wistbacka[1,4], U. Ekman[1], A. Rennie[1], L. Jönsson[1], G. Hagman[4], A. Solomon[1,3], A. Rosenberg[1,3], M. Kivipelto[1,4] *(1. Karolinska Institutet - Stockholm (Sweden), 2. FINGERS Brain Health Institute - Stockholm (Sweden), 3. University of Eastern Finland - Kuopio (Finland), 4. Karolinska University Hospital - Stockholm (Sweden))*

Background: Determining anti-amyloid treatment eligibility in patients at memory clinics will become an essential task as new treatment options enter the market. Anti-Aβ monoclonal antibodies have been shown to reduce amyloid burden in the brain and slow the rate of clinical decline in patients with early Alzheimer's disease (AD). Appropriate Use Recommendations (AUR) became available to assist the implementation of the treatment in clinical practice [1]. As this is an emerging new field, more information is needed to assess their generalizability in real world clinical practice. The aim of this study was to apply the AUR in broader memory clinic populations to assess the real-world applicability of the workup. **Methods:** We included 2126 patients from 7 memory clinics across Stockholm region in Sweden, who had their first diagnostic visit between 2015-2022 with available clinical and imaging data [2]. A sub-sample (N=918; 43% of the population) had performed lumbar puncture and measures of CSF biomarkers (Aβ42, p-tau181, t-tau, NfL). ATN classification was based on CSF Aβ42 (A) CSF p-tau181 (T) and medial temporal lobe atrophy (MTA; N). Laboratory cutoffs were applied for the CSF markers. Eligibility for anti-amyloid treatment was determined by operationalization of the published AUR for Lecanemab. **Results:** Mean age of the total cohort was 77.1 years (SD 6.6), 50.4% were women. 24.2% had dementia, 61.8% MCI, 13.7% subjective cognitive decline and 0.4 % other diagnosis. Mean MMSE was 27.0 (SD 2.4). Pathologic MTA and Fazekas scores were observed for 49% and 32% of the total cohort respectively. Among those with available CSF biomarkers, 34.3% had abnormal Aβ42, 32.5% abnormal p-tau, 50.4% abnormal t-tau and 20.6% abnormal NfL. ATN profiles were the following: A–T–N– 26.1%; A–T–N+ 18.5%; A+T–N+ 11.8%; A–T+N– 10.7%; A+T–N– 9.6%; A–T+N+ 9.3%; A+T+N– 7.0%; A+T+N+ 7.1%. When applying the inclusion and exclusion criteria based on our operationalization of the recommendations, 86 individuals (9.6 % of the CSF cohort, 4.1% of the total patient sample) were potentially eligible for anti-amyloid treatment. Of these patients, 64% had MCI and 36% had mild AD dementia. **Conclusion:** Using the current diagnostic workup around 10% of the patients with available CSF data were identified as eligible to anti-amyloid treatment. The results, deriving from real-world memory clinic settings, are in line with previous reports from highly specialized university memory clinics [3,4]. The relatively limited proportion of patients identified as eligible is mainly due to a lack of AD-specific CSF biomarker positivity, highlighting the need for further developing interventions with different mechanisms of actions and combination treatments using a precision medicine approach. **Keywords:** Alzheimer's disease, anti-amyloid treatment, Lecanemab, eligibility. Disclosures: The project is part of a scientific collaboration with, and funding from IHI project Prominent/ BioArctic. **References:** 1. Cummings et al. J Prev Alzheimer Dis. 2023; 10:362–377. https://doi.org/10.14283/jpad.2023.30. 2. Ekman et al. BMC Geriatr. 2020 Mar 6;20(1):93. https://doi.org/10.1186/s12877-020-1478-3. 3. Rosenberg et al. Neurology. 2022 Nov 8;99(19):e2102-e2113. https://doi.org/10.1212/WNL.0000000000201043. 4. Pittock et al. Neurology. 2023 Nov 7;101(19):e1837-e1849. https://doi.org/10.1212/WNL.0000000000207770.

OC23- TRANSCRANIAL MAGNETIC STIMULATION (TMS) FOR MCI: TRIALS USING ADVANCED STIMULATION AND PRECISION APPROACHES. J. Taylor[1], Y.H. Chou[2], A. Benitez[3] *(1. Stanford University - Palo Alto (United States), 2. University of Arizona - Tucson (United States), 3. Medical University of South Carolina - Charleston (United States))*

Background: Repetitive transcranial magnetic stimulation (rTMS) and innovations in its delivery – specifically accelerated intermittent theta burst (iTBS) – uniquely position this transdiagnostic treatment for rapid translation to clinic to improve symptoms of Mild Cognitive Impairment (MCI). The goals of this talk are (a) to present a series of phased trials to provide an evidence base for MCI as an indication for iTBS, and (b) to highlight related studies of how variations in stimulation site may improve the precision of cognitive remediation in MCI. **Methods:** A phase I open-label trial of iTBS was conducted with individuals with MCI due to AD. A MagVenture R30 MagPro TMS System with Cool-B65 figure-8 coil delivered 50 Hz iTBS triplet bursts at an intensity of 120% resting motor threshold over 3 treatment days with 8 stimulation sessions per day, resulting in 14,400 pulses to the left dorsolateral prefrontal cortex (left dlPFC targeted at F3 EEG coordinate with neuronavigation guidance). Endpoints were safety (i.e. no neuroradiological, neurocognitive, or severe/serious adverse events), retention (i.e. >80%), tolerability (i.e. rapid resolution of common effects), and acceptability one week post-treatment. **Results:** Of the 24 participants enrolled, 22 initiated and 1 discontinued treatment (i.e. 95.5% retention). There were no post-treatment changes in neuroradiological and neurocognitive outcomes, and there were no severe or serious adverse events. Expected side effects of headache and pain at stimulation site were reported by some and were rated as having resolved after stimulation. Participants reported little desire to quit and high motivation to complete treatment. This sample was euthymic with no changes in depression symptoms. Target engagement was demonstrated by a large improvement (d=0.98) in fluid cognition. Improved fluid cognition correlated with increased functional connectivity of the left dlPFC regions of interest (belonging to the frontoparietal [FPN], default mode [DMN], and ventral attention [VAT] networks) and increased network-level segregation of FPN, DMN, and VAT. Change in fluid cognition was not correlated with change in functional connectivity in negative controls (i.e. primary visual cortex, somato-motor network). **Conclusion:** Based on these promising results in euthymic individuals, a double-blind, randomized sham-controlled, parallel group, dose-ranging phase II trial is now underway which builds on the transdiagnostic quality of iTBS. This phase II trial of iTBS to the left dlPFC aims to establish separate dose-response curves for depression and cognition in MCI due to AD and/or cerebral small vessel disease with co-morbid major depressive disorder. We also seek to evaluate dose-response curves for functional connectivity among cognitive networks. Related MCI trials seek to expand iTBS and rTMS delivery beyond the left dlPFC, specifically to the parietal lobe which is implicated in early AD pathophysiology. First, a sham-controlled RCT found significant improvements in spatial and associative memory following left parietal iTBS, with precision guidance using diffusion MRI-derived structural connectivity of the parietal-hippocampal network. Second, a phase II RCT found significant improvements in immediate and delayed recall following lateral

parietal rTMS, with supportive changes in plasma-derived brain derived neurotrophic factor. In conclusion, iTBS/rTMS research robustly demonstrates the viability of this treatment for MCI. **Keywords:** Transcranial magnetic stimulation, depression, Mild Cognitive Impairment, prefrontal cortex, parietal. **Clinical Trial Registry:** NCT04503096 and NCT05992831 (PI: Benitez); NCT03331796 (PI: Taylor); NCT03962959 (PI: Chou). **Disclosures:** NCT04503096 was funded by the National Center of Neuromodulation for Rehabilitation (P2CHD086844) and NCT05992831 is funded by the National Institute on Aging (R01AG081237); both were also supported by the New Vision Research Foundation. NCT03331796 was funded by the National Institute on Aging (R01AG055526) and by the Tinklenberg family endowment to Stanford University. NCT03962959 is funded by the National Institute on Aging (R01AG062543).

OC24- RESULTS OF A 52-WEEK PHASE II TRIAL OF REPETITIVE TMS OF THE DEFAULT MODE NETWORK IN MILD TO MODERATE ALZHEIMER'S DISEASE. E. Casula[1], S. Bonni[1], M. Maiella[1], M. Assogna[1], E. Santarnecchi[2], A. Martorana[3], G. Koch[3] *(1. Santa Lucia Foundation IRCCS - Rome (Italy), 2. Massachusetts General Hospital - Boston (United States), 3. University of Rome Tor Vergata - Rome (Italy))*

Background: Repetitive transcranial magnetic stimulation (rTMS) of the default mode network (DMN) is emerging as a new non-invasive therapeutic approach in treating Alzheimer's disease (AD). AD patients primarily show alterations of the precuneus (PC) which is an important functional area of the DMN. We performed a randomized, double-blind, sham-controlled, phase II, 52-week trial to determine the safety and efficacy of treatment with personalized rTMS applied over the PC in patients with mild-to-moderate AD. **Methods:** Forty-eight patients with mild-to-moderate AD were consented for the trial. Eighteen patients were recruited de-novo and 30 patients accepted to extend treatment duration up to 52 weeks after completion of a 24-week trial (NCT03778151) with the same experimental design. The trial included an initial 2-week intensive course where rTMS (or sham) was applied over the PC daily (5 times per week, Monday to Friday), followed by a 50-week maintenance phase in which the same stimulation was applied once weekly. Each rTMS session consisted of forty, 2-second trains delivered at 20 Hz. Personalization of rTMS treatment was established using single-pulse TMS in combination with electroencephalography (TMS-EEG) based on the evaluation of transcranial evoked potentials (TEPs). The primary outcome measure was the change from baseline to week 52 of the Clinical Dementia Rating Scale–Sum of Boxes. Secondary outcomes included score changes in the Alzheimer's Disease Assessment Scale– Cognitive Subscale (ADAS-Cog)11, Mini Mental State Examination (MMSE), Alzheimer's Disease Cooperative Study–Activities of Daily Living scale (ADCS-ADL) and Neuropsychiatric Inventory (NPI). Changes in cortical activity and connectivity were monitored by TMS-EEG. **Results:** Among 48 patients randomized (mean age 72.8 years; 56% women), 32 (68%) completed the study. The procedure was safe and well tolerated with very few minor adverse events reported. Repetitive TMS of the PC (PC-rTMS) had a significant effect on the primary outcome measure. The estimated mean change in CDR-SB after 52 weeks was 1.36 for PC-rTMS (95% confidence interval (CI) [0.68, 2.04]) and 2.45 for sham-rTMS group (95%CI [1.85, 3.05]). There were also significant effects for the secondary outcomes ADAS-Cog11, ADCS-ADL and NPI scores. TMS-EEG also showed an increase of functional connectivity within the DMN in patients treated with rTMS but not in the sham group. **Conclusion:** Fifty-two weeks of personalized neuromodulation of the DMN may slow down the impairment of cognitive functions, activities of daily living and behavioral disturbances in patients with mild-to-moderate AD. **Keywords:** default mode network, neural plasticity, connectivity, P2 clinical trial. **Clinical Trial Registry:** NCT05454540; https://clinicaltrials.gov/. **Disclosures:** 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.

OC25- TARGETTAU-1: A PHASE 2 TRIAL DESIGNED TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF THE ANTI-MTBR TAU MONOCLONAL ANTIBODY, BMS-986446, IN PATIENTS WITH EARLY ALZHEIMER'S DISEASE. O. Hansson[1], A. Kahl[2], G. Abelian[2], M. Donovan[2], M. Ahuja[2], D. Watson[3], R. Ossenkoppele[4], T. Iwatsubo[5], C. Van Dyck[6] *(1. Clinical Memory Research Unit, Department of Clinical Sciences, Lund University, Malmö, Sweden, and Memory Clinic, Skåne University Hospital, Malmö, Sweden - Malmö (Sweden), 2. Bristol Myers Squibb, Princeton, New Jersey, USA - Princeton (United States), 3. Alzheimer's Research and Treatment Center, Wellington, Florida, USA - Wellington (United States), 4. Clinical Memory Research Unit, Department of Clinical Sciences, Lund University, Malmö, Sweden, and Memory Clinic, Skåne University Hospital, Malmö, Sweden; Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc, Amsterdam, The Netherlands; Amsterdam Neurosc - Malmö (Sweden), 5. Department of Neuropathology, Graduate School of Medicine, University of Tokyo, and the National Center of Neurology and Psychiatry, Tokyo, Japan - Tokyo (Japan), 6. Alzheimer's Disease Research Unit, Yale School of Medicine, New Haven, Connecticut, USA - New Haven (United States))*

Background: Alzheimer's disease (AD) is the leading cause of cognitive impairment and dementia worldwide and is rising in prevalence, morbidity, and mortality. Limited treatment options underscore a significant unmet need. A pathologic hallmark of AD is the accumulation of intracellular neurofibrillary tangles containing aggregates of microtubule-associated protein tau. The microtubule binding region (MTBR) of tau is involved in neuronal uptake of neurotoxic tau species and aggregation of higher-order tau species. Furthermore, MTBR tau concentration in cerebrospinal fluid correlates with clinical progression of AD. BMS-986446 (formerly PRX005), a novel humanized immunoglobulin class G1 kappa monoclonal antibody that binds to MTBR tau, is being developed as a potential therapeutic for early AD. In vitro studies demonstrated that BMS-986446 and its murine parent antibody 3D6 equivalently inhibit aggregated tau uptake into neurons, inhibit tau-induced neurotoxicity, and promote aggregated tau uptake into phagocytic cells preventing further cell-to-cell tau transmission. The phase 2 TargetTau-1 study (NCT06268886) will assess efficacy, safety, and tolerability of BMS-986446 in individuals with early symptomatic AD. **Methods:** TargetTau-1 is a randomized, double-blind, placebo-controlled trial enrolling adults aged 50–80 years diagnosed with mild cognitive impairment or mild AD dementia. Inclusion criteria include objective impairment in episodic memory, a Mini Mental State Examination (MMSE) score of 22–30, and evidence of

AD pathology confirmed by positive plasma biomarkers and tau positron emission topography (PET) imaging. Exclusion criteria include diagnosis of a non-AD neurological condition that could contribute to cognitive impairment, psychiatric diagnosis or symptoms that could interfere with the study, and any significant findings on brain magnetic resonance imaging (MRI) at screening. The 76-week double-blind treatment period is followed by a planned optional 96-week open-label extension. The primary endpoint is mean change from baseline in the Clinical Dementia Rating Sum of Boxes score at week 76. Secondary endpoints include mean change from baseline at week 76 in brain tau deposition as evidenced on PET-computed tomography, integrated Alzheimer's Disease Rating Scale score, Alzheimer's Disease Assessment Scale-Cognitive Subscale, MMSE score, and Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living Scale score. Key assessments will include cognitive evaluations, tau PET, MRI, and plasma and serum AD biomarkers. Incidence of adverse events (AEs), AEs of special interest, serious AEs, and AEs leading to treatment discontinuation will be monitored. **Results:** The TargetTau-1 trial began enrollment on March 20, 2024. Approximately 475 participants across 14 countries in North America, Europe, and Asia-Pacific regions will be randomized 4:3:3 to receive placebo, BMS-986446 high dose or BMS-986446 low dose. **Conclusion:** The phase 2 TargetTau-1 study will assess the efficacy, safety, and tolerability of BMS-986446, an anti-MTBR tau monoclonal antibody, in patients with early symptomatic AD. **Keywords:** Alzheimer's disease, tau proteins, neurofibrillary tangles, clinical trial protocol. **Clinical Trial Registry:** NCT06268886. **Data Deposition:** Study is ongoing. **Disclosures:** 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 Alzpath, BioArctic, Biogen, Bristol Myers Squibb, Eisai, Eli Lilly, Fujirebio, Merck, Novartis, Novo Nordisk, Roche, Sanofi, and Siemens. AK, GA, MD, and MA: employees and/or shareholders of Bristol Myers Squibb. DW: paid advisor/consultant at AbbVie, Bristol Myers Squibb, Eisai, and F. Hoffmann-La Roche. RO: has received research funding/support from Avid Radiopharmaceuticals, Janssen Research & Development, Roche, Quanterix, and Optina Diagnostics, has given lectures in symposia sponsored by GE Healthcare, is an advisory board member for Asceneuron, and a steering committee member for Bristol Myers Squibb. All the aforementioned has been paid to the institutions. TI: advisor/consultant for Eisai, Eli Lilly, Biogen, Roche/Chugai. CvD: advisor/consultant for Bristol Myers Squibb, Cerevel, Eisai, Ono Pharmaceuticals, and Roche Pharmaceuticals; Yale University and Dr. van Dyck receive grant support from Biogen Idec, Cerevel, Eisai, Eli Lilly, Genentech, Janssen Pharmaceuticals, Roche Pharmaceuticals, and UCB. **Acknowledgments:** This study was sponsored by Bristol Myers Squibb. Writing and editorial assistance was provided by Emilie Croisier, PhD, and Traci Stuve, MA, of Peloton Advantage, LLC, an OPEN Health company, funded by Bristol Myers Squibb.

OC26- A MULTI-STAGE APPROACH TO SCREEN AMYLOID STATUS USING PLASMA P-TAU217 PRIOR TO CONFIRMATORY IMAGING APPLIED TO THE BIO-HERMES TRIAL.

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Background: Effective and efficient screening of patients for abnormal amyloid status is highly desirable for patient enrolment in Alzheimer's Disease (AD) clinical trials and identifying patients suitable for treatment with new anti-AB immunotherapies. Here we evaluate a multi-stage screening approach [1] to determine amyloid status utilising plasma biomarkers for initial screening and secondary confirmatory assessment, using data from the Bio-Hermes trial[2]. In this approach we assess the potential savings of confirmatory amyloid screening, by AB-PET or CSF, needed to effectively identify patients as amyloid positive given an initial plasma assay. **Methods:** We employed gradient-boosted tree models to evaluate various feature combinations for predicting amyloid status, as defined by AB-PET visual reads. For each feature combination we computed AUCs and estimated the probability thresholds corresponding to 95% sensitivity and 95% specificity to classify patients as AB- and AB+ respectively. Participants who did not reach these thresholds would be referred for follow-up screening (e.g. AB-PET or AB-CSF) to enable robust classification as AB+/AB-. **Results:** A total of 842 participants (n=316 AB+) were selected from the Bio-Hermes dataset with complete data across plasma biomarkers, age, sex, APOE-e4 status and AB-PET visual read. When using pTau217 as the sole predictor we observe an AUC=0.89 (95% CI=[0.87-0.91]). This increased to AUC=0.91 (95% CI=[0.89-0.92]) when including age, sex and APOE e4 status as predictors. When additionally including pTau181 and AB40 and AB42 as features AUC=0.92 (95% CI=[0.91-0.94]). When applying the 95% thresholds for the best AUC model, the mean positive predictive value (ppv) was 88% (stdev=3.4%) and the negative predictive value (npv) was 96% (stdev=1.8%) with 25% (CI=[18%-35%]) of samples requiring confirmatory follow-up screening with CSF or Amyloid PET. Using pTau217 as the sole predictor reported reduced sensitivity, 38% (CI=[28%-53%]) of test samples requiring confirmatory screening, but comparable accuracy (ppv=87%, npv=94%). To assess potential population biases between participants identifying as White non-Hispanic (n_total=620;n_AB+=243), Black non-Hispanic (n_total=97;n_AB+=25), and Hispanic (n_total=93;n_AB+=33), we trained models on the White population using nested cross validation and compared model performance for AB+/- predictions between the intra-population validation set and other populations using Fisher's exact test on the confusion matrices. The lower bound of 95% confidence intervals for the odds ratio did not exceed 1 for any comparison when using a 95% sensitivity/specificity threshold. **Conclusion:** Plasma pTau217 provides an accurate biomarker for AB status prediction, which when used as part of a staged screening workflow can significantly reduce the number confirmatory PET scans needed improving efficiency, reducing patient burden and cost associated with screening in AD clinical trials. The additional inclusions of APOE-e4 status, and other plasma biomarkers can further increase the accuracy and sensitivity of this approach. Operationalisation the proposed workflow within a software platform would enable cost effective, low burden screening and eligibility assessment for patients in AD clinical trials and clinical treatment paths. We show a

threshold-based screening approach may help mitigate biases in population grouping, however further assessment is required to assess potential biases in diverse screening schemas. **Keywords:** Clinical Trials, Plasma Biomarkers, Screening and Eligibility. **References:** 1 - Mohs, R.C, et al. Alzheimer's & Dementia 2024; https://doi.org/10.1002/alz.13722; 2 - Brum, W.S, et al. Nature Aging 2023, 3(9), pp.1079-1090. https://doi.org/10.1038/s43587-023-00471-5.

OC27- RESULTS OF SIGNAL-AD, A RANDOMIZED, PHASE 1B/2 TRIAL TO EVALUATE SAFETY AND EFFICACY OF PEPINEMAB, ANTI-SEMA4D ANTIBODY BELIEVED TO BLOCK REACTIVE ASTROGLIOSIS, IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT (MCI) DUE TO AD. E. Evans[1], A. Porsteinsson[2], T. Fisher[1], M. Boise[1], A. Foster[1], J. Leonard[1], V. Mishra[1], C. Mallow[1], E. Siemers[1], R. Turner[3], J. Huffaker[4], M. Zauderer[1] *(1. Vaccinex - Rochester (United States), 2. University of Rochester - Rochester (United States), 3. Georgetown University - Washington, DC (United States), 4. Neuropsychiatric Research Center of Southwest Florida - Stuart (United States))*

Background: The earliest recognized biomarker of AD is deposition of Aβ amyloid that leads to formation of plaques and may, over time, trigger or at least be followed by gliosis/neuroinflammation and formation of neurofibrillary tangles. These sequelae are accompanied by neurodegenerative changes including neuronal and synaptic loss. We have previously reported that semaphorin 4D (SEMA4D), the major ligand of plexin B1/B2 receptors expressed on astrocytes, is upregulated in diseased or damaged neurons during progression of AD and Huntington's disease (HD). Receptor mediated signaling triggers astrocyte reactivity, leading to loss of homeostatic support functions, including downregulation of glutamate and glucose transporters that, respectively, recycle the excitatory transmitter and support energy metabolism. In parallel, morphogenic and functional changes lead to gain of inflammatory processes by reactive astrocytes (1). Pepinemab, humanized, high affinity, SEMA4D blocking antibody, demonstrated evidence of clinical benefit and was well tolerated in a completed Phase 2 study in patients with early manifest HD, particularly those with evidence of cognitive impairment (MoCA score 18-25) (2). These data showed that pepinemab prevented metabolic decline in glucose uptake (FDG-PET) and significantly reduced levels of plasma GFAP, biomarkers associated with astrocyte reactivity. Importantly, pepinemab slowed cognitive decline by 36% (p=0.007) as determined by the HD Cognitive Assessment Battery composite score (2). Given the many physiological parallels between glial activation and inflammatory processes in AD and HD, results from the SIGNAL-HD trial suggest that preventing astrocyte activation and reducing brain inflammation with pepinemab could be an attractive alternative or complement to anti-Aβ antibodies as treatment for AD. **Methods:** The randomized, double-blind, SIGNAL-AD trial was designed to evaluate safety and efficacy of pepinemab treatment in people with MCI or mild dementia due to AD (NCT04381468). 50 individuals (MMSE 17-26, CDR-GS 0.5-1) with amyloid positive status, determined by PET scan or CSF markers, were randomized 1:1 and treated for 12 months with pepinemab (40 mg/kg) or placebo by IV infusion, Q4W. The primary objective of the study was safety and tolerability, and a key efficacy objective was evaluation of brain metabolic activity using FDG-PET. Additional prespecified secondary and exploratory assessments include fluid biomarkers including plasma GFAP and pTau-217, multiplex proteomics in CSF to evaluate neuroinflammatory responses, as well as cognitive measures (CDR-SB, iADRS, ADAS-Cog13) and subgroup analyses. **Results:** A statistically significant positive effect of pepinemab treatment was observed for FDG-PET SUVR in Medial Temporal Cortex, a brain region previously reported to undergo early changes in metabolic activity and atrophy in patients with MCI. This was supported by positive trends of change in multiple additional brain regions by FDG-PET, plasma biomarkers, and cognitive measures in this population. Similar treatment effects were not observed for patients with mild dementia. **Conclusion:** Despite relatively small group sizes, a statistically significant increase in metabolic activity in Medial Temporal Cortex and associated positive trends for plasma biomarkers and cognitive measures were observed for subjects with MCI. The results suggest that pepinemab treatment is safe and effective in people with MCI due to AD but may not overcome aggravating changes in disease pathology that occur during subsequent progression to dementia. **Keywords:** SEMA4D, Plexin B1/B2, astrocyte, neuroinflammation. **Clinical Trial Registry:** NCT04381468; https://clinicaltrials.gov. **Disclosures:** E. Evans and M Zauderer are full-time employees, stockholders, and officers of Vaccinex., T. Fisher, J. Leonard, M. Boise, A. Foster, V. Mishra, C. Mallow are full-time employees and stockholders of Vaccinex. Vaccinex received funding support from Alzheimer's Association and Alzheimer's Drug Discovery Foundation. E. Seimers is a full time employee of Acumen, has consulting agreements with Vaccinex, Athira Pharma, Inc., Biogen, Cogstate, Hoffman La-Roche Ltd., Takeda, and stockholder of Acumen and Eli Lilly. R. Turner, W. Bond, J. Huffaker, Porsteinsson A have no disclosures.

OC28- DESIGN AND RATIONALE OF CAPPRICORN-1, A PHASE 2 STUDY OF MIVELSIRAN IN PATIENTS WITH CEREBRAL AMYLOID ANGIOPATHY. J.M. Lee[1], E.S. Van Etten[2], M.J.P. Van Osch[2], C.J.M. Klijn[3], A. Sostelly[4], S. Goteti[4], F. Sepehrband[5], A. Avbersek[5], R.W. Deering[4], N.S. Parikh[4], S.M. Greenberg[6] *(1. Washington University School of Medicine - St. Louis (United States), 2. Leiden University Medical Center - Leiden (Netherlands), 3. Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Centre - Nijmegen (Netherlands), 4. Alnylam Pharmaceuticals, Inc. - Cambridge (United States), 5. Regeneron Pharmaceuticals, Inc. - Tarrytown (United States), 6. Harvard Medical School, Massachusetts General Hospital - Boston (United States))*

Background: Cerebral amyloid angiopathy (CAA) is a progressive disease characterized by pathologic deposition of amyloid-beta (Aβ) in cerebral blood vessels, resulting in intracerebral hemorrhage (ICH), cognitive impairment, and/or transient focal neurological episodes. Most commonly, CAA occurs in older adults without a known genetic cause (sporadic CAA); however, a rare, inherited form of CAA is associated with a variant in the amyloid precursor protein (APP) gene and has an aggressive course with an earlier age of onset (Dutch-type CAA). There are no disease-modifying therapies for patients with CAA and few potential treatments in clinical development. Additionally, CAA is often comorbid with Alzheimer's disease (AD), and patients with imaging features consistent with CAA (e.g., microhemorrhage, superficial siderosis) are often ineligible to receive antibody-based therapies for AD. Mivelsiran (ALN-APP) is an investigational, intrathecally administered RNA interference therapeutic designed to reduce production of APP, the precursor to Aβ.

Treatment with single doses of mivelsiran demonstrates robust reductions in cerebrospinal fluid levels of soluble APP peptides as well as Aβ40 and Aβ42 in an ongoing Phase 1 study of patients with early-onset AD. Here, we describe the design of cAPPricorn-1 (NCT06393712), a Phase 2 study evaluating the efficacy, safety, tolerability, and pharmacodynamics of mivelsiran in patients with CAA. **Methods:** Eligible patients include those with sporadic CAA (aged ≥50 years with probable CAA per Boston Criteria Version 2.0) or Dutch-type CAA (aged ≥30 years with a known E693Q APP variant). Key exclusion criteria include clinical history of ICH <90 days prior to randomization and significant cognitive impairment. Patients are randomized 1:1 to receive intrathecal mivelsiran or placebo over a 24-month double-blind period and an optional 18-month open-label extension period. The overall enrollment target is approximately 200 patients. The primary endpoint is the annualized rate of new lobar cerebral microbleeds determined by blinded, centrally-adjudicated magnetic resonance imaging. A novel global rank endpoint that encompasses clinical and radiographic features of new cerebral hemorrhagic events will be analyzed as a secondary endpoint. Additional secondary endpoints include changes in vascular reactivity, white matter hyperintensities, CAA total small vessel disease severity score, pharmacodynamic activity as measured by soluble APP in cerebrospinal fluid, and frequency of adverse events. The primary endpoint of the study is with respect to the sporadic CAA cohort; the Dutch-type CAA cohort will be analyzed descriptively. Enrollment begins in 2024, and trial sites are in North America, Europe, and Australia. **Discussion:** CAA causes significant morbidity and mortality, and no disease-modifying treatment exists. Despite recent therapeutic progress in AD, there are few potential treatments in development for CAA. The global Phase 2 cAPPricorn-1 clinical study will evaluate the impact of treatment with mivelsiran, employing a novel RNA interference therapeutic approach to reduce APP production and downstream Aβ species in patients with CAA. **Acknowledgements:** The authors would like to thank Bret Bostwick and Eric Smith for their contributions to the cAPPricorn-1 study inception and design. We would also like to acknowledge Joseph Chiarappa for his contributions to endpoint design. **Keywords:** cerebral amyloid angiopathy, mivelsiran, RNA interference, amyloid precursor protein. **Disclosures:** JML and ESvE are steering committee members for a clinical study for Alnylam Pharmaceuticals Inc. MJPvO reports payments to his institution as part of the TRACK consortium and grants for the Leducq Consortium and Dutch Research Council, is a non-paid steering committee member for a clinical study for Alnylam Pharmaceuticals Inc., has received research support to his institution form Philips; he is also the President of the Neurofluids study group of the ISMRM. CJMK has received grants from the Promising Care funding scheme of the National Health Care Institute and ZonMw, Penumbra Inc., and the Dutch Heart Foundation, payments to her institution for her part on an advisory committee for Alnylam Pharmaceuticals, Inc., for the ENRICH-AF and ELAPSE studies, and as a participant in a consensus panel meeting organized by EMCREG-International through an unrestricted educational grant from AstraZeneca (also an unpaid participant in ESO ICH committees). AS, SG, RWD, and NSP are employees of and shareholders in Alnylam Pharmaceuticals, Inc. AA is an employee of and shareholder in Regeneron Pharmaceuticals, Inc. FS is an employee of and shareholder in Regeneron Pharmaceuticals, Inc. and is a co-inventor on the patent, "Mapping brain perivascular spaces." SMG reports payments to his institution by Alnylam Pharmaceuticals, Inc.

OC29- USE OF PLASMA P-TAU217 TO IDENTIFY AB-POSITIVE COGNITIVELY UNIMPAIRED PARTICIPANTS FOR CLINICAL TRIALS: A MULTICOHORT STUDY.

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Background: Clinical trials for Alzheimer's disease (AD) are increasingly focusing on preclinical stages of the disease. Hence, it is imperative to investigate scalable and non-invasive approaches to facilitate the inclusion of cognitively unimpaired (CU) participants with amyloid-β (Aβ) pathology. Here, we aimed to test the accuracy of plasma phosphor-tau217 (p-tau217), as stand-alone test or in combination with cerebrospinal fluid (CSF) biomarkers, for identification of Aβ-positive CU participants. **Methods:** We included 2,551 CU participants from ten independent cohorts worldwide with available plasma p-tau217 and Aβ-PET, of which 1,595 participants also had CSF biomarkers. Aβ-PET was used as reference standard (Centiloid threshold >12). We derived the plasma p-tau217 thresholds, maximizing sensitivity at specificity 95% and 97.5%, in part of the cohort (30%) and tested them in the remaining sample (70%). In the subsample with CSF biomarkers, we investigated whether the diagnostic accuracy improved when adding CSF biomarkers in those that were plasma p-tau217 positive. Number of participants and costs needed to include 100 Aβ-positive CUs in a trial for each approach was calculated assuming a cost ratio of 1:4:16 for plasma:CSF:Aβ-PET. **Results:** Aβ-PET positivity rate was 27% in the total sample. Plasma p-tau217 exhibited PPVs ranging between 79-86% with 13-17% of the participants being positive on the plasma test. The PPVs increased to

94-96% when adding CSF biomarkers in a second step to the participants that were plasma p-tau217 positive, with 82-86% of the plasma p-tau217 positive cases also being positive on the CSF biomarkers. Simulating recruitment of Aβ positive CU individuals to a preclinical AD trial, using plasma p-tau217 as a confirmatory test reduced the overall cost for biomarker testing with 81-86% saved compared to performing Aβ-PET in all cases. When adding CSF biomarkers to plasma p-tau217 positive individuals, the reduced cost was still high (73-77%). **Conclusion:** Plasma p-tau217 might be used alone to identify individuals for preclinical AD trials where it is sufficient that ~80% of the recruited population is Aβ-positive (as shown here with Aβ-PET). Adding CSF as a second step in plasma p-tau217 positive people increases the Aβ positivity to ~95% in the recruited population. Selecting participants using plasma p-tau217 alone, or followed by a CSF measure, would significantly facilitate the recruitment process and reduce costs and participant burden in preclinical AD trials. **Keywords:** Trial participant selection; Plasma biomarkers; Preclinical Alzheimer's disease. **Disclosures:** JT has served as a paid consultant for Neurotorium and Alzheon. PRN has served at scientific advisory boards and/or as a consultant for Roche, Novo Nordisk, Eisai, and Cerveau radiopharmaceuticals. 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. S.E.S. has served on scientific advisory boards for Eisai and Novo Nordisk. She has received speaker fees from Eli Lilly. R.O. has received research support from Avid Radiopharmaceuticals, Janssen Research & Development, Roche, Quanterix and Optina Diagnostics. He has given lectures in symposia sponsored by GE Healthcare and serves on advisory boards for Asceneuron and Bristol Myers Squibb. 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.

OC30- PREVENTE4: A DOUBLE-BLIND PLACEBO-CONTROLLED CLINICAL TRIAL TESTING HIGH DOSE DHA IN APOE4 CARRIERS BEFORE THE ONSET OF DEMENTIA.

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Lower blood omega-3 level is correlated with worse cognitive function in several observational cohorts, particularly among APOE ε4 carriers. Yet the effect of omega-3 supplementation on cognitive outcomes in randomized clinical trials of non-demented individuals is inconsistent. Using 11C docosahexaenoic acid (DHA) PET scans, we previously reported an increased brain uptake of plasma-derived DHA before the onset of dementia in younger APOE ε4 carriers compared to non-carriers. Since plasma DHA levels are largely determined by dietary intake, this finding implies vulnerability of APOE ε4 carriers to a low DHA diet. It is not known whether DHA supplementation in APOE ε4 carriers with limited DHA consumption and dementia risk factors can delay or slow down disease progression when started before the onset of clinical dementia. PreventE4 (NCT03613844) is a single-site, double-blind, randomized, placebo-controlled trial in cognitively unimpaired individuals with limited seafood consumption (< 200 mg per day DHA intake) and dementia risk factors. Its objectives are to determine (1) whether carrying the APOE ε4 allele is associated with lower delivery of DHA to the brain; and (2) whether high dose DHA supplementation affects brain imaging biomarkers of AD and cognitive function. 365 cognitively unimpaired individuals aged 55 to 80 (mean age 65) were randomized to 2 grams of DHA per day or identically appearing placebo for 2 years. Half the participants were asked to complete lumbar punctures at baseline and 6-month visits to obtain cerebrospinal fluid (CSF). Forty-two percent of participants randomized to treatment were males, 39% identified as Latino; 13% had <12 years of education; 39% had a BMI >30 kg/m2, 52% had hypertension, 69% had hyperlipidemia, and 69% exercised < 3 days/week. By design, 50% of the individuals randomized to treatment were APOE ε4 carriers. The baseline MMSE score was 29 mean (SD 1.6, range 23-30), WMS logical memory II, delayed recall score was 11 (SD 3.1, range 3-18), with education years at 14 (SD 4, range 1-24). The trial was completed in May of 2024. The primary trial outcome measure is the change in CSF DHA levels after the intervention (n=181, at 6 months). Secondary trial outcomes include functional and structural connectivity change using resting-state functional MRI (n=365, at 2 years). Exploratory outcomes include the Repeatable Battery of the Assessment of Neuropsychological Status (RBANS) (n=365, at 2 years). Primary outcomes will be presented during CTAD 2024. PreventE4 will clarify whether high dose DHA supplementation has a role in preventing or slowing disease progression in persons with an increased risk of dementia and limited baseline omega-3 consumption. The authors have no conflict of interest to declare.

OC31- THE ALZHEIMER'S TAU PLATFORM (ATP) AND PROGRESSIVE SUPRANUCLEAR PASLY TRIAL PLATFORM (PTP): A COMBINATION AMYLOID AND TAU THERAPY TRIAL FOR EARLY AD, AND A TAU MONOTHERAPY TRIAL FOR MILD-MODERATE PSP.

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Background: Therapies that directly target tau can potentially produce substantial clinical benefit in tauopathies, such as AD and PSP, because the accumulation of insoluble tau protein is strongly correlated with the disease progression. Tau biology, including tau genetics, aggregate structure and cellular vulnerability, differ in each tauopathy. Most nonclinical models incorporate non-AD tau adding to the complexity of interpreting anti-tau therapeutic effects in clinical trials. Which tau therapies are likely to be efficacious, whether or not to combine them with anti-amyloid therapies in AD, and which individuals are most likely to benefit are important unresolved questions that would require many parallel design trials to answer. Platform (umbrella) trials test multiple therapies

in the same trial, allowing for substantial savings in time, cost and participant burden. **Method:** Both trials are NIH-funded Phase 2 clinical trial platforms that will be conducted in collaboration with the ACTC in partnership with industry and philanthropic groups. ATP's goal is to investigate the effects of tau therapies on the biological hallmarks of AD including insoluble and soluble tau species, amyloid and other biomarkers of neurodegeneration. ATP will initially evaluate two tau therapies alone or in combination with an anti-amyloid therapy. 750 participants with late preclinical or early prodromal AD (CDR 0 or 0.5) will be randomized to either of two tau drug regimens (three arms per regimen) for two years of blinded treatment, followed by an optional open label extension (OLE). At least 20% of participants will be from URGs. The primary endpoint is 18F MK6240 tau PET, with key secondary endpoints including plasma P-tau and MTBR243-tau, amyloid PET and clinical assessments (CDR-SB, PACC5). Inclusion criteria are based on plasma P-tau217, clinical status and regional 18F MK6240. PTP will evaluate 440 participants with mild-moderate PSP-Richardson's Syndrome. Inclusion criteria are based on clinical criteria and a vMRI diagnostic tool. Individuals will be randomized to one of three drug regimens (two arms per regimen) for twelve months of blinded treatment followed by an optional 12 month OLE. The primary endpoint is a modified version of the PSP Rating Scale, with key secondary endpoints including the Corticobasal Functional Scale, the PSP cognitive composite and vMRI measures. **Results:** Two tau therapies and an anti-amyloid therapy have been chosen for inclusion in ATP and startup is underway. The final design, choice of therapies and design as well as plans for inclusion of additional tau therapies after the trial begins and other details will be presented. For PTP, one tau therapy and one non-tau therapy, with a third therapy from either category, are currently being selected. Further details of the design and startup process will be presented. **Conclusion:** The ATP is a two tau drug regimen, six arm platform trial that will support efficient development of tau and combination therapies for early, sporadic AD. PTP is a three drug regimen, six arm platform trial for mild-moderate PSP. We hypothesize that simultaneous investigation of multiple tau therapies in two different tauopathies may more rapidly identify the optimal tau therapeutic strategies for human disease. **Keywords:** Tau therapies, combination therapies, sporadic Alzheimer's disease, Progressive Supranuclear Palsy, platform trial. **Disclosures:** Adam Boxer has served as a paid consultant to AGTC, Alchemab, Alector, Amylyx, Arkuda, Arrowhead, Arvinas, Aviado, Eli Lilly, Muna, Oligomerix, Oscotec, Pfizer, Switch, Transposon and UnlearnAI. His institution received research support from Biogen and Eisai for serving as a site investigator for clinical trials, as well as from Regeneron. He has received research support from the National Institutes on Aging: NIH U19AG063911, R01AG078457, R01AG073482, R56AG075744, R01AG038791, RF1AG077557, P01AG019724, R01AG071756, U24AG057437; Rainwater Charitable Foundation, Bluefield Project to Cure FTD, GHR Foundation, Alzheimer's Association, Association for Frontotemporal Degeneration, Gates Ventures, Alzheimer's Drug Discovery Foundation.

OC32- AN EVALUATION OF THE IMPACT OF A MULTI-ANALYTE BLOOD BIOMARKER TEST FOR EVALUATING COGNITIVE IMPAIRMENT: RESULTS OF THE QUIP II CLINICAL UTILITY STUDY. J. Braunstein[1], D. Maraganore[2], R. Carlile[3], K. Johnson[4], D. Merrill[5], D. Gitelman[6], K. Sharlin[7], L. Vandevrede[8], K. George[9], J. Wang[10], T. West[1], P. Verghese[1], L. Jacobs[1], M. Monane[1] *(1. C2N Diagnostics, LLC - St Louis (United States), 2. Tulane University - New Orleans (United States), 3. Palmetto Primary Care Physicians - Summerville (United States), 4. Duke University - Durham (United States), 5. Pacific Brain Health Center - Santa Monica (United States), 6. Advocate Lutheran General Hospital - Park Ridge (United States), 7. Sharlin Health and Neurology - Ozark (United States), 8. University of California - San Francisco (United States), 9. JWM Neurology - Indianapolis (United States), 10. Stat4ward - Pittsburgh (United States))*

Background: There is an unmet need for accurate, accessible, acceptable, and equitable tools to aid in the assessment of Alzheimer's disease (AD) pathology, highlighted by recent availability of anti-amyloid, disease-modifying therapies. Blood biomarkers (BBMs) may offer advantages over positron emission tomography (PET) scans and cerebrospinal fluid (CSF) analysis for such assessment. The PrecivityAD2™ blood test (C2N Diagnostics, LLC, St. Louis, MO) uses liquid chromatography-tandem mass spectrometry for quantification of amyloid beta 42 (Aβ42) and Aβ40 peptide concentrations as well as phosphorylated and non-phosphorylated tau peptide concentrations at amino acid threonine, position 217 (p-tau217 and np-tau217) in plasma. A statistical algorithm combines the Aβ42/Aβ40 ratio and the p-tau217/np-tau217 ratio (%p-tau217) measurements to generate the likelihood of brain amyloid plaques. The BBM test's clinical validity has previously been demonstrated (88% sensitivity and 89% specificity). In this study, we sought to determine the BBM test's effect on clinical decision-making. **Methods:** The Quality Improvement PrecivityAD2 (QUIP II) Clinician Survey (NCT06025877) is a prospective, single cohort, outpatient study among patients 55 years and older presenting with signs or symptoms of mild cognitive impairment or dementia. The objective of the QUIP II Study was the assessment of clinical utility, including patient selection and score interpretation by clinicians, of the BBM and its result, the Amyloid Probability Score 2 (APS2). The APS2 is reported on a scale of 0-100: Negative (APS2 0-47) and Positive (APS2 48-100) results represent low and high likelihood for the presence of brain amyloid plaques by amyloid PET scan, respectively. After receiving the BBM test results, clinicians completed surveys on clinical decision-making and management strategies for each patient. Collected data included patient demographics and APS2 result as well as clinician AD diagnostic certainty, planned drug therapy, and additional brain amyloid evaluation pre- and post-blood BBM testing. **Results:** A total of 193 surveys from 8 sites and 12 memory specialists were submitted between November 2023 and May 2024. Patients had a median age of 74, 54% were female, and 30% were under-represented Black, Hispanic, and Asian minorities. Concordance with intended use of the test was 98% (190/193). The mean APS2 was 52 (range 1-100), and 51% (n=98) of patients had Negative results. From pre- to post-BBM testing, clinician-reported AD probability decreased from 54% to 11% among Negative result patients ($p<0.0001$) and increased from 65% to 93% among Positive result patients ($p<0.0001$). The composite primary endpoint, defined as a change in AD diagnostic certainty, drug therapy, or additional brain amyloid evaluation pre- and post- BBM testing, was 79% ($p < 0.0001$ versus a pre-specified threshold of 20% clinically meaningful

change). Clinician orders for anti-AD medication and additional brain amyloid testing significantly decreased among Negative result patients ($p<0.0001$). **Conclusion:** We believe the memory specialists' use of the PrecivityAD2™ blood test led to clinically meaningful changes in decision-making around AD diagnostic certainty, drug therapy management, and additional amyloid evaluation among patients evaluated for cognitive impairment. This blood biomarker test can help memory specialists guide patients to current and emerging anti-AD therapies as well as to rule out AD to allow for other diagnostic considerations. **Keywords:** Alzheimer's disease, blood biomarker, clinical utility, clinical decision-making. **Clinical Trial Registry:** NCT06025877; https://clinicaltrials.gov/study/NCT06025877. **Disclosures:** Darren Gitelman has received consulting/advisory fees from AbbVie, Biogen, Eisai,, Lilly, Alzheimer's Association. He has received clinical trial support from Biogen, Cassava, Eisai, Lilly, National Institute of Aging, and Davos Alzheimer's Collaborative. Kim Johnson has received consulting fees from the University of Southern California. She has received research support from Eisai. Kenneth Sharlin has received research support from Biogen, Lilly, Bristol Myers Squibb, and Ari Bio. Lawren VandeVrede has received research support from Biogen, the National Institute of Aging, and the Alzheimer's Association. Joel Braunstein, Leslie Jacobs, Mark Monane, Philip Verghese, and Tim West are consultants and employees of C2N Diagnostics, LLC and have received consulting fees, salary, and/or stock compensation from C2N Diagnostics, LLC. Jimin Wang is an employee of Stat4Ward and has received consulting fees from C2N Diagnostics, LLC. Matt Carlile, Kristi George, Demetrius Maraganore, and David Merrill have no competing interests.

OC33- THE ROLE OF TRIALS IN HEALTH-ECONOMIC EVALUATION OF ANTI-AMYLOID TREATMENT FOR EARLY ALZHEIMER'S DISEASE. R. Handels[1], A. Wimo[2], B. Winblad[2], L. Jönsson[2] *(1. Maastricht University - Maastricht (Netherlands), 2. Karolinska Institutet - Stockholm (Sweden))*

Introduction: Health-economic evidence is crucial for decisions on reimbursing anti-amyloid treatment for early Alzheimer's Disease (AD). Recent phase 3 trials showed significant effects on symptoms over an 18-month follow-up period, leading to regulatory approvals of lecanemab in the United States, Japan and China. Current trial designs do not allow direct assessment of cost-effectiveness of anti-amyloid therapies. A large part of the clinical benefit can be expected to be incurred beyond the period of observation, and trials do not capture effects on resource utilization and care costs, as shown in our previous review [1]. Health-economic simulation models implement trial efficacy evidence, extrapolate over a lifetime period and estimate the associated impact on health-economic outcomes. This modelling relies on key assumptions regarding the sustainability or waning of the treatment effect, as well as how disease progression interacts with mortality. In addition, health-economic outcomes are possibly driven by the design of the diagnostic workup, treatment management method, treatment efficacy in (genetic) subgroups. We present results from a health-economic evaluation of anti-amyloid treatment based on phase 3 trial efficacy evidence and discuss how to overcome limitations in underlying trial data. **Methods:** We developed an open-source economic model [2] to simulate the lifetime health-economic effects of lecanemab anti-amyloid treatment on reducing disease progression in people with early AD, and its corresponding impact on quality-adjusted life years and care costs in a U.S. setting. The model is available in different formats and can freely be accessed at https://github.com/ronhandels/ipecad. The model was populated with data from the registrational trials of lecanemab. **Results:** Anti-amyloid treatment at the current US list price ($26,500) resulted in mean per-person lifetime quality-adjusted life year (QALY) gains (0.35) and care costs savings ($3,095) at additional diagnostic and drug costs ($113,381). Incremental cost-effectiveness ratio (ICER) was $292,650 per QALY gained. Assuming sustained effect and waning improved ICER ($161,696/QALY) and even more when assuming no waning ($85,306/QALY). ApoE4 noncarrier genetic subgroup improved ICER ($213,014/QALY) and ApoE4 carrier had worse ICER ($354,677/QALY). Blood-based markers can be positions as a screening test only forwarding persons with abnormal amyloid for a follow-up (cerebrospinal fluid (CSF) test or PET scan). This resulted in less required expensive CSF/PET test to identify persons eligible for treatment. However, part of the population was incorrectly labelled as normal amyloid, missing the opportunity to generate the effect of anti-amyloid treatment. A future subcutaneous injection formulation has the potential to reduce treatment administration costs, which contributed a large part of the costs. **Discussion:** Our cost-effectiveness estimates for anti-amyloid treatment in early AD may exceed common willingness-to-pay thresholds in the U.S. However, cost-effectiveness estimates improved with the use of blood-based markers and subcutaneous administration. Anti-amyloid treatment is potentially cost-effective in specific subgroups. These results strongly rely on assumptions on extrapolating effects beyond current trial follow-up period. We recommend setting up a registry system to obtain real-world long-term follow-up data on patient-relevant effectiveness outcomes. Such data can be analyzed for optimal subgroups and for the effect of different treatment stopping rules. In addition, real-world evidence collection could be supported by "pay-for-performance" in which payers incur treatment costs proportional to the treatment benefit within an individual. **Conflict of interest statement:** No specific funding was received for this work. RH received outside this study consulting fees in the past 3 years from Lilly Nederland (2023), iMTA (2023), and Biogen (2021) (paid to institution); is member of IPECAD and member of ISPOR special interest group open-source models (un-paid).

OC34- A ULTRA-FAST MRI PROTOCOL TO AID DIAGNOSIS AND TREATMENT OF ALZHEIMER'S DISEASE. M. Rosa-Grilo[1], H.R. Chughtai[2,3], D. Thomas[1,4], C.R.S. Belder[1], M. Beament[1], N. Magill[5], M. Mazher[2], E. Lim[6,7], D. Mallon[7], H.R. Jäger[7], G.J.M. Parker[2,8,9], D.C. Alexander[2], N. Fox[1], C. Mummery[1], F. Barkhof[1,10] *(1. Dementia Research Centre, UCL Queen Square Institute of Neurology - London (United Kingdom), 2. Centre for Medical Image Computing, Medical Physics & Biomedical Engineering, UCL - London (United Kingdom), 3. Advanced Research Computing Centre, UCL - London (United Kingdom), 4. Department of Brain Repair and Rehabilitation, UCL Queen Square Institute of Neurology - London (United Kingdom), 5. Department of Medical Statistics, London School of Hygiene and Tropical Medicine - London (United Kingdom), 6. Department of Imaging, Imperial College Healthcare NHS Trust - London (United Kingdom), 7. Lysholm Department of Neuroradiology, National Hospital for Neurology and Neurosurger - London (United Kingdom), 8. NMR Research Unit, Queen Square MS Centre, Department of Neuroinflammation, UCL Queen Square Institute of Neurology - London (United Kingdom), 9. Bioxydyn Limited - Manchester (United Kingdom), 10. Department of Radiology and Nuclear Medicine, Amsterdam UMC - Amsterdam (Netherlands))*

Background: In clinical practice and Alzheimer's disease (AD) trials, structural brain imaging is critical for diagnosis, treatment eligibility and safety monitoring [1,2]. However, access to MRI is often limited due to lengthy acquisition times, which reduce availability, challenge patient cooperation, and increase costs. To address these limitations, we developed a fast-imaging protocol using advanced parallel imaging (wave-CAIPI) [3]. We hypothesised that the variability introduced by the scan type (standard-of-care clinical vs. fast) would be no greater than the variability among individual neuroradiologists interpreting clinical scans, suggesting non-inferiority of the fast scan. **Methods:** We recruited individuals aged 50–90 years from a cognitive outpatient service who underwent routine MRI as part of their clinical assessment. Participants completed both clinical and fast protocols in the same session, with acquisition times of 17:39 and 6:29 minutes, respectively. Each protocol included T1-weighted, T2-weighted, FLAIR, and SWI sequences. Three neuroradiologists, blinded to clinical data (except age) and type of protocol, independently assessed the scans. Fleiss' kappa coefficients and bootstrapped 95% confidence intervals (CIs) were used to estimate inter-rater reliability for each protocol and pooled intra-rater reliability between scan type. We present the exponentiated bootstrapped log ratios comparing pooled intra-rater reliability between scans to inter-rater reliability for clinical scans and their 95% CIs. **Results:** Of 92 individuals recruited, 2 were excluded due to incomplete imaging. Among the remaining 90 (46% female, median age 62 years, IQR 57–67), 37 had no neurodegenerative or structural brain disease, while 19 were diagnosed clinically with AD. For the most likely diagnoses (normal, AD, other causes) on the clinical scan, the inter-rater reliability coefficients were 0.65 (95% CI: 0.52–0.77) for a "normal" scan, 0.42 (0.28–0.58) for AD, and 0.60 (0.46–0.73) for other diagnoses. For fast scans, the respective values were 0.61 (0.47–0.74), 0.38 (0.23–0.54), and 0.55 (0.41–0.68). Pooled intra-rater agreements between scan types were 0.80 (0.72–0.87), 0.72 (0.62–0.81), and 0.84 (0.76–0.90), with ratios for the three groups of diagnoses being 1.23 (1.01–1.57), 1.72 (1.21–2.63), and 1.38 (1.11–1.85). For visual rating scales (medial temporal lobe atrophy, Koedam, Fazekas), microhaemorrhage counts, and radiological eligibility for disease-modifying treatments similar results were observed. For the latter, the respective coefficients were, in the same order, 0.76 (0.58–0.90) for the clinical scan, 0.80 (0.62–0.93) for the rapid scan, and 0.94 (0.86–0.99) for the intra-rater coefficient between scan types. The respective ratio was 1.24 (1.03–1.62). All ratios and corresponding 95% CI did not include one, indicating that the reliability between the two types of scans was greater (and statistically different) than the inter-rater reliability for the clinical scan. **Conclusion:** Our findings suggest the variability introduced by the fast scan is smaller than the variability between neuroradiologists reporting clinical scans, providing evidence supporting non-inferiority of the fast protocol. Accelerated MRI sequences enable shorter protocols while maintaining diagnostic quality. The potential cost savings, greater scanner access and reduced patient burden are highly relevant for anti-amyloid immunotherapies. **Keywords:** fast imaging, MRI, Alzheimer's disease, wave-CAIPI. **Disclosures:** This research was funded by the Alzheimer's Society Heather Corrie Impact Fund (grant number 577 [AS-PG-21-045]). **References:** 1. Harper L, Barkhof F, Scheltens P, Schott JM, Fox NC. An algorithmic approach to structural imaging in dementia. J Neurol Neurosurg Psychiatry. 2014;85(6):692-698. doi:10.1136/jnnp-2013-306285; 2. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA. July 2023. doi:10.1001/jama.2023.13239; 3. Bilgic B, Gagoski BA, Cauley SF, et al. Wave-CAIPI for highly accelerated 3D imaging. Magn Reson Med. 2015;73(6):2152-2162. doi:10.1002/mrm.25347.

OC35- ANTI-AMYLOID ANTIBODY PREFERENCE FOR VASCULAR AB AGGREGATES DOES NOT EXPLAIN ARIA RATES. E. Francis[1], L. Meunier[1], K. Anderson[1], L. Hennessey[1], B. Miller[1], A. Lemere[1], J. Selkoe[1], M. Stern[1] *(1. Brigham and Women's Hospital - Boston (United States))*

Background: Lecanemab, donanemab, and aducanumab all bind to aggregates of Aβ and all clear amyloid PET in clinical trials, but they cause amyloid related imaging abnormality (ARIA) at different rates. Aducanumab causes approximately three-fold more ARIA than lecanemab. Because ARIA may represent blood-brain barrier breakdown, and because cerebral amyloid angiopathy (CAA) is a risk factor for ARIA, we hypothesized that the rank-order of antibody affinity for vascular (CAA) amyloid over parenchymal (plaque) amyloid would be the same rank-order of ARIA rates: aducanumab > donanemab > lecanemab. **Methods:** We developed a new immunoprecipitation-ELISA method for measuring antibody binding affinity to Aβ40-rich aggregates from leptomeninges, likely principally CAA, and to Aβ42-rich aggregates from grey matter, likely principally plaque. We synthesized aducanumab-, donanemab-, and lecanemab-like antibodies based on their patented amino acid sequences (termed adu-L, don-L, and lec-L, respectively). Antibody titration curves generated a KD for each antibody to these two populations of Aβ, and the ratio, termed "MP KD ratio" is a measure of relative preference for CAA over plaque, with higher MP KD ratio indicating less preference for CAA over plaque. The plateau, or Bmax, of the titration curves is a measure of the total accessible Aβ, and thus the "MP Bmax ratio" Is a measure of the relative availability of an antibody to bind CAA over plaque aggregates. We used one-way repeated measures ANOVA to compare the raw KDs and Bmaxs, as well as their ratios, across aqueous homogenates from occipital lobes of eighteen AD cases. **Results:** There was no difference between the three antibodies in preference for vascular Aβ measured by log(MP KD ratio) ($P = 0.53$). The 95% confidence interval for the difference in log(MP KD ratio) between lec-L and adu-L had an upper bound of 0.261, implying a maximum difference

in preference for vascular Aβ of 1.8-fold. Don-L had lower raw affinity (higher KD) and less total available Aβ (lower Bmax) than adu-L and lec-L for both vascular and parenchymal aggregates. Don-L had slightly less available vascular Aβ than parenchymal Aβ (lower MP Bmax ratio) compared to adu-L and lec-L (P = 0.039 and 0.030, respectively). **Conclusion:** Within the limitations of measuring in vitro binding activity of commercial-like antibodies to aqueously extracted Aβ from human postmortem brain tissue, antibody preference for meningeal Aβ40-rich aggregates over parenchymal Aβ42-rich aggregates cannot explain differences in ARIA rates. Other factors, such as ability to activate immune responses, may be more important determinants of ARIA. **Keywords:** amyloid; Aβ; donanemab; lecanemab; aducanumab; immunotherapy; Alzheimer disease; ARIA. **Disclosures:** DJS is a director and consultant to Prothena Biosciences. CAL is a consultant to Acumen Pharmaceuticals and Eli Lilly. The other authors declare no conflicts of interest.

OC36- ARTIFICIAL INTELLIGENCE-ENABLED SAFETY MONITORING IN ALZHEIMER'S DISEASE CLINICAL TRIALS. G. Jimenez-Maggiora[1], M. Donohue[1], M. Rafii[1], R. Raman[1], P. Aisen[1] *(1. Keck School of Medicine of USC - San Diego (United States))*

Background: Investigators conducting clinical trials have an ethical, scientific, and regulatory obligation to protect the safety of trial participants. Traditionally, safety monitoring includes manual review and coding of adverse event data by expert clinicians. Our study explores the use of natural language processing (NLP) and artificial intelligence (AI) methods to streamline and standardize clinician coding of adverse event data in Alzheimer's disease (AD) clinical trials. **Methods:** Our quantitative retrospective study aimed to develop a gold standard AD adverse event data set, evaluate the predictive performance of NLP-based models to classify adverse events, and determine whether automated coding is more efficient, accurate, reliable, and consistent than clinician coding. We collected demographic and adverse event data from eight completed clinical trials in participants (n=1920) with symptomatic AD conducted between 2005 and 2020 [1, 2]. Original expert clinician-confirmed codes were used for all model performance comparisons. F1 score was used as the primary model selection metric. Final classifier performance was evaluated using predictive accuracy. Clinician effort was measured in time to code, review, and confirm coded adverse events. **Results:** In a sample of 1000 adverse events, AI-based AE coding achieved higher accuracy (~20% increase in accuracy) and was more cost-effective (~80% cost reduction) than traditional clinician coding. **Conclusion:** Our study results demonstrate how approaches that effectively combine AI and human expertise can improve the efficiency and quality of adverse event coding and clinical trial safety monitoring. **Keywords:** Artificial Intelligence, Alzheimer's Disease, Clinical Trial, Safety, Adverse Event, Medical Coding, Classification. **Disclosures:** The authors report no relevant disclosures. **References:** 1. University of California, San Diego Alzheimer's Disease Cooperative Study (ADCS) (National Institute on Aging Grant Number U01AG010483). https://www.adcs.org; 2. University of Southern California's Alzheimer's Therapeutic Institute (ATRI). https://atri.usc.edu.

OC37- FIRST-IN-HUMAN AV-1980R/A TAU VACCINE FOR ALZHEIMER'S PREVENTION (IND 29644). L. Schneider[1], A. Ghochikyan[2], R. Alexander[3], D. Tosun-Turgut[4], M. Agadjanyan[2] *(1. Keck School of Medicine, University of Southern California - Los Angeles (United States), 2. Institute for Molecular Medicine - Huntington Beach (United States), 3. Banner Alzheimer's Institute - Phoenix (United States), 4. University of California, San Francisco - San Francisco (United States))*

Background: Amyloid-β aggregates precede cortical tau accumulation and inflammation that drive neurodegeneration. AV-1980R/A is a recombinant protein-based adjuvanted tau vaccine composed of tau2-18 peptide fused to a platform of multiple foreign Th epitopes that are recognized by various human immune response genes (MHC class II). It generates robust cellular immune responses to foreign T helper (Th) epitopes avoiding activation of potentially harmful autoreactive CD4+ T cells and induces high titers of a potentially potent antibody specific to the Phosphatase Activating Domain (PAD) of pathological tau. (The PAD region becomes exposed in aggregated pathological tau and appears to inhibit anterograde fast axonal transport and polymerization of tau). AV-1980R/A vaccination should induce anti-PAD antibodies that will bind to pathological tau – not native tau – and inhibit its accumulation. **Methods:** This first-to-human phase 1 study is a multicenter, double-blind, randomized, placebo-controlled, cohort trial to determine the safety and tolerability of AV-1980R/A in 20 μg, 60 μg, and 180 μg IM dosing cohorts of up to 16 participants each (4 on placebo). Participants are 65–80 years with preclinical AD requiring a PrecivityAD2 Amyloid Probability Score 2 > 54 and absence of cognitive impairment as evidenced by CDR-g = 0, MMSE > 25, and WMS-R LM II > 6. They will be immunized at weeks 0, 4, 12, and 36 and have a follow-up 20-weeks post last immunization. **Results:** The primary objective is to evaluate the safety and tolerability of AV-1980R/A. Secondary objectives are to evaluate its immunogenicity by assessing humoral immune responses in plasma (anti-tau antibodies); T helper (Th) cell response specific to the multi-epitope vaccine platform; and possible activation of autoreactive (specific to Tau2-18 peptide) Th cell responses. Exploratory objectives evaluate changes in AD-related brain and plasma biomarkers including Aβ42, Aβ40, Aβ42/40, p-tau217, p-tau181, p-tau231, t-tau, NfL, GFAP, and tau MK-6240 PET tracer retention; and evaluate immune response profile by plasma IgM and IgG isotypes, IgG1, IgG2, IgG3, IgG4, cytokine profile, and other measures. **Conclusion:** Passive immunotherapy may be impractical because of the need for frequent administration. The primary goal with the vaccine is to induce a sufficient level of antibodies in older people often with age-related impaired T helper (Th) cell immune responses. Safe and immunogenic tau vaccines could be initiated in cognitively unimpaired participants with preclinical AD as preventive treatment. **Keywords:** phase 1 trial, tau vaccine, AV-1980R/A, prevention. **Disclosures:** NIH: P30 AG066530 (ADRC), R01 AG052510 (S-citalopram), R01 AG053267 (DIAN-TU), R01 AG054434 (APOE and DHA), R01 AG062687 (phenserine/exosomes), R01 AG051346 (NoMAD), R01 AG055444 (Banner API), P01 AG02350 (vascular), R01 AG063826 (allopregnanolone), R01 AG074983 (Aβ vaccine), others; State of California CADC 15-10291; Alzheimer's Association (allopregnanolone). Contracts or grants from Eli Lilly, Roche/Genentech, Eisai, Biogen. Grants from Washington University, St. Louis/NIA DIAN-TU, UCSD ADCS, USC ATRI. Consulting: ImmunoBrain Checkpoint Ltd, BioVie, AC Immune, Athira, Avid/Lilly, BMS, Lighthouse (Cortexyme), Linus Health Merck, Muna Ltd, Neurim Ltd, Otsuka/Lundbeck, Roche/

Genentech, Pharmatrophix (Stanford), Novo Nordisk, Vivli.org. •The Lancet Commission on Dementia Prevention and Care. The Della Martin Foundation.

OC38- DIFFERENTIAL ROLES OF ALZHEIMER'S DISEASE PLASMA BIOMARKERS IN STEPWISE BIOMARKER-GUIDED DIAGNOSTICS: HEAD-TO-HEAD COMPARISON AMONG AN ASIAN POPULATION. H. Jang[1], D. Shin[2], H. Yoo[2], H. Zetterberg[3,4,5,6], K. Blennow[3,7,8,9], F. Gonzalez-Ortiz[3,4], N.J. Ashton[3,10,11,12], T.A. Day[13], E.H. Lee[2], J. Yun[14], D.L. Na[2], H.J. Kim[2,15,16,17], S.H. Kang[18], J.P. Kim[2], S.W. Seo[2,15,16,17] *(1. Department of Neurology, Seoul National University Hospital, Seoul National 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. Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg - Gothenburg (Sweden), 4. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, - Gothenburg (Sweden), 5. Department of Neurodegenerative Disease, UCL Institute of Neurology - London (United Kingdom), 6. UK Dementia Research Institute at UCL - London (United Kingdom), 7. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, - Gothenburg (Sweden) - Gothenburg (Sweden), 8. Paris Brain Institute, ICM, Pitié-Salpêtrière Hospital, Sorbonne University - Paris (France), 9. Neurodegenerative Disorder Research Center, Division of Life Sciences and Medicine, and Department of Neurology, Institute on Aging and Brain Disorders, University of Science and Technology of China and First Affiliated Hospital of USTC - Hefei (China), 10. King's College London, Institute of Psychiatry, Psychology and Neuroscience, Maurice Wohl Clinical Neuroscience Institute - London (United Kingdom), 11. NIHR Biomedical Research Centre for Mental Health and Biomedical Research Unit for Dementia at South London and Maudsley NHS Foundation - London (United Kingdom), 12. Centre for Age-Related Medicine, Stavanger University Hospital - Stavanger (Norway), 13. Eli Lilly and Company - Indianapolis (United States), 14. Department of Neurology, Soonchunhyang University Bucheon Hospital - Gyeonggi-Do (Korea, Republic of), 15. Alzheimer's Disease Convergence Research Center, Samsung Medical Center, - Seoul (Korea, Republic of), 16. Department of Health Sciences and Technology, SAIHST, Sungkyunkwan University - Seoul (Korea, Republic of), 17. Neuroscience Center, Samsung Medical Center - Seoul (Korea, Republic of), 18. Department of Neurology, Korea University Guro Hospital, Korea University College of Medicine - Seoul (Korea, Republic of))*

Background: A stepwise strategy utilizing plasma biomarkers is needed for efficient biomarker-guided diagnostics in the field of Alzheimer's disease (AD). We aimed to investigate the differential roles of AD plasma biomarkers in stepwise biomarker-guided diagnostics by comparing multiple plasma biomarkers analyzed by different analytical methods. **Methods:** In this multicenter study, 2984 patients (666 cognitively unimpaired [CU], 2032 AD cognitively impaired [ADCI], 190 subcortical vascular cognitively impaired [SVCI], and 96 with frontotemporal dementia [FTD]) were recruited from 25 hospitals. All participants underwent blood sampling for measurements of plasma β-amyloid (Aβ) 42/40, phosphorylated tau (p-tau) 181, p-tau217 (ALZpath), p-tau217 (MSD), p-tau231, glial fibrillary protein (GFAP), and neurofilament light chain (NfL) levels and Aβ positron emission tomography (PET); 160 participants also underwent tau PET. **Results:** Non-specific AD biomarkers, especially NfL levels, screened CI groups from CU groups, regardless of type of CI group (AUC 0.71-0.94). Both p-tau217 (ALZpath) and p-tau217 (MSD) were the best discriminators for Aβ PET (+) (AUC 0.88-0.95) across all diagnostic groups and tau PET (+) (AUC 0.90-0.91) in ADCI group. Furthermore, all p-tau variants, GFAP, and NfL were more specifically associated with tau PET uptake than Aβ PET uptake in the ADCI group. Plasma p-tau217 (ALZpath) showed the best performance in distinguishing Aβ PET (-) non-AD dementias from Aβ PET (+) ADCI (AUC 0.94-0.95). All plasma biomarkers were predictive of cognitive decline in ADCI, whereas p-tau217 (ALZpath) and GFAP were predictive of cognitive decline in the CU group (all $p<0.05$). **Conclusion:** Our findings suggest differential roles for each plasma biomarker in stepwise biomarker-guided diagnostics. **Keywords:** Plasma biomarkers; Neurofilament light chain; Phosphorylated tau. **Disclosures:** The authors declared no competing interests.

Late Breaking Communications

LB01- DONANEMAB: APPROPRIATE USE RECOMMENDATIONS. G. Rabinovici[1], S. Salloway[2], S. Schindler[3], P. Aisen[4], L. Apostolova[5], A. Atri[6], S. Greenberg[7], S. Hendrix[8], R. Petersen[9], M. Weiner[1], D. Selkoe[7], J. Cummings[10] *(1. UCSF - San Francisco, CA (United States), 2. Brown - Providence, RI (United States), 3. Washington University - St. Louis, MO (United States), 4. USC - San Diego, CA (United States), 5. Indiana University - Indianapolis, IN (United States), 6. Banner Health - Phoenix, AZ (United States), 7. Harvard - Boston, MA (United States), 8. Pentara - Millcreek, UT (United States), 9. Mayo Clinic - Rochester, MN (United States), 10. UNLV - Las Vegas, NV (United States))*

Background: Donanemab (Kisunla ®) is an IgG1 monoclonal antibody directed at the N-terminally truncated, pyroglutamate-modified form of amyloid-β present on mature plaques. In July 2024 the U.S. FDA approved donanemab for the treatment of early-stage clinical Alzheimer's disease (AD). TRAILBLZAER-ALZ (Phase 2) and TRAILBLAZER ALZ2 (Phase 3) trials that led to approval of donanemab included innovative aspects (e.g., tau PET for eligibility, amyloid-PET based stopping criteria) that may be challenging to replicate in clinical practice. The Appropriate Use Recommendations (AUR) were developed to guide the implementation of donanemab in real-world practice, prioritizing safety considerations and opportunity for effectiveness. **Methods:** The AUR were developed by the AD and Related Disorders Therapeutic Workgroup and invited experts. Workgroup members reviewed donanemab clinical trial data, FDA prescribing information, and other relevant literature. AUR criteria were developed by consensus, integrating all available data and expert opinion. **Results:** Potential candidates for donanemab include persons meeting clinical criteria for MCI or mild dementia due to AD (Clinical Stages 3-4; MMSE 20-30), and showing biomarker support for amyloid pathology by PET or CSF. Tau PET is not required for eligibility, though, if available, can be considered to individualize estimates of likely clinical response. High-performing blood-based biomarkers may, in the near future, be sufficient to inform treatment eligibility. Apolipoprotein E genotyping is required prior to treatment, in order to ensure patients are adequately informed about their risk for ARIA. A pre-treatment MRI should be obtained ≤ 1 year before initiating treatment, and patients showing severe white matter disease or evidence of significant cerebral amyloid angiopathy (e.g., > 4 microbleeds, macrohemorrhage > 1 cm) should be excluded.

While patients taking anticoagulants were not at increased risk for ARIA in the TRAILBLAZER trials, the data are limited, and the AUR conservatively advise against donanemab treatment for patients on anticoagulants, especially given the high morbidity and mortality associated with intracerebral macro-hemorrhages. Ultimately, the decision to treat with donanemab should be reached via a person-centric shared decision-making process, also considering additional patient-specific factors and resource availability in the prescribing practice and health system. Donanemab is administered 700 mg IV every 4 weeks (Q4Wk) for the first 3 doses, followed by 1400 mg IV Q4WK. Surveillance MRI should be performed prior to the 2nd, 3rd and 4th infusions, and at any time that symptoms suspicious for ARIA occur. ARIA management and treatment continuation depend on ARIA clinical and radiographic severity. Thrombolytics are contra-indicated while on active therapy, while mechanical thrombectomy without use of thrombolytics is likely to be safe. Clinicians may consider discontinuing therapy if a follow-up amyloid PET (typically obtained 12-18 months after starting treatment) is negative. **Conclusion:** The AUR provide a framework for patient selection and implementation of donanemab therapy in real-world practice. Individualized clinical judgment and shared decision-making are paramount in determining whether donanemab therapy is appropriate for any individual patient. These guidelines are likely to evolve as we accumulate more real-world data and clinical experience with novel AD biomarkers and therapies. **Disclosures:** Dr. Rabinovici has received research support from Avid Radiopharmaceuticals, Eli Lilly, Genentech, GE Healthcare and Life Molecular Imaging. He has served as a paid scientific advisor for Alector, Avid Radiopharmaceuticals, C2N, Eli Lilly, GE Healthcare, Johnson & Johnson, Merck, Novo Nordisk, Roche. He is an Associate Editor for JAMA Neurology. Dr. Salloway receives research support for clinical trials from Janssen, Lilly, Eisai, Genentech, Roche, Biogen. He has provided consultation to Eisai, Biogen, Lilly, Roche, Genentech, Bolden, Novo Nordisk, Prothena, Acumen, Labcorp, Alector, Corium, Kisbee, AbbVie. Dr. Schindler has served on advisory boards and/or as a speaker for Eisai, Eli Lilly, Novo Nordisk. Dr. Aisen has research grants from Eli Lilly and Eisai, and consults with Merck, Roche, Genentech, Abbvie, Biogen, ImmunoBrain Checkpoint, AltPep, Alector, Arrowhead and Neurimmune. Dr. Apostolova has received grant support from Avid Radiopharmaceuticals, Life Molecular Imaging, Roche Diagnostics, Eli Lilly. She has consulted for Biogen, Two Labs, IQVIA, Genentech, Siemens, Corium, Eli Lilly, GE Healhcare, Eisai, Roche Diagnostics, Alnylam, Otsuka. Dr. Atri over the last 15 years, has received honoraria or support for consulting; participating in independent data safety monitoring boards; providing educational lectures, programs, and materials; or serving on advisory boards for AbbVie, Acadia, Allergan, AriBio, Axovant, AZ Therapies, Biogen, Eisai, Forest, Grifols, JOMDD, Life Molecular, Lundbeck, Merck, Novo Nordisk, ONO, Prothena, Qynapse, Roche, Genentech, Sunovion, Suven, Synexus, and Vaxxinity. He has served as a consultant to Biogen, Eisai, Prothena and Roche/Genentech and has served as a site-PI (institutional contract) for clinical trials sponsored by Biogen, Eisai, and Lilly. He served as project arm leader for DIAN-TU gantenerumab OLE study (WUSTL with Roche/Genentech). He currently serves as site PI for the USC/ATRI/ACTC & Eisai AHEAD 3-45 study, DIAN-TU ART study (lecanemab DIAD Amyloid Plaque Reduction and Prevention study), and Biogen BIIB080 Celia Study. At his previous institution. He served as site PI for the Biogen EMERGE study. He receives royalties from Oxford University Press. Dr. Greenberg has consulted for Eli Lilly. Dr. Hendrix is owner of Pentara, and consults with dozens of companies in the Alzheimer's space, including Eli Lilly. Dr. Petersen has served as a consultant for Roche, Genentech, Eli Lilly, Eisai, Nestle, Novo Norodisk. He receives royalties from Oxford University Press and UpToDate. Dr. Weiner received research support for research from the following funding sources: Siemens, Biogen, Johnson & Johnson, GE. He has served on Advisory Boards for Acumen Pharmaceutical, Alzheon, Inc., Amsterdam UMC; MIRIADE, Cerecin, Merck Sharp & Dohme Corp., NC Registry for Brain Health, and REGEnLIFE. He also serves on the USC ACTC grant which receives funding from Eisai. He has provided consulting to Boxer Capital, LLC, Cerecin, Inc., Clario, Dementia Society of Japan, Dolby Family Ventures, Eisai, Guidepoint, Health and Wellness Partners, LCN Consulting, MEDA Corp., Merck Sharp & Dohme Corp., NC Registry for Brain Health, Prova Education, T3D Therapeutics, University of Southern California (USC), and WebMD. He has acted as a speaker/lecturer for China Association for Alzheimer's Disease (CAAD) and Taipei Medical University, as well as a speaker/lecturer with academic travel funding provided by: AD/PD Congress, Amsterdam UMC, Cleveland Clinic, CTAD Congress, Foundation of Learning; Health Society (Japan), Kenes, U. Penn, U. Toulouse, Japan Society for Dementia Research, Korean Dementia Society, Merck Sharp & Dohme Corp., National Center for Geriatrics and Gerontology (NCGG; Japan), University of Southern California (USC). He holds stock options with Alzeca, Alzheon, Inc., ALZPath, Inc., and Anven. Dr. Weiner serves on Editorial Boards for Alzheimer's & Dementia, and the Journal for Prevention of Alzheimer's Disease (JPAD). Dr. Selkoe is a director of Prothena Biosciences and an ad hoc consultant and speaker for Eisai. SES has served on advisory boards or as a speaker for Eisai, Eli Lilly, and Novo Nordisk. Dr. Cummings 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, Eli 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.

LB02- LATEST INTERIM RESULTS FROM THE BRAINSHUTTLETM AD STUDY, A PHASE IB/IIA STUDY OF TRONTINEMAB IN PEOPLE WITH ALZHEIMER'S DISEASE. L. Kulic[1], F. Alcaraz[1], G. Klein[1], C. Hofmann[1], S. Yilmaz[1], J.A. Abrante[1], D. Sickert[1], M. Marchesi[1], J. Wojtowicz[1], R. Croney[1], D. Agnew[1], S. Ahlers[2], P. Delmar[1], H. Svoboda[3], I. Wiesel[1] *(1. F. Hoffmann-La Roche Ltd. - Basel (Switzerland), 2. Excelya Germany GmbH - Freiburg (Germany), 3. F. Hoffmann-La Roche Ltd. - Penzberg (Germany))*

Background: Trontinemab is a novel amyloid targeting Brainshuttle™ antibody specifically engineered for efficient Transferrin receptor 1 (TfR1) mediated transport across the blood–brain barrier. It is currently under evaluation in the Phase Ib/IIa Brainshuttle ™ AD study (NCT04639050). **Objectives:** Brainshuttle™ AD is a randomized, double blind, placebo-controlled study designed to investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of trontinemab following intravenous (IV) infusion in participants aged 50 to 85 years with prodromal or mild to moderate AD, who are amyloid positive based on amyloid positron emission

tomography (PET).The study consists of four parts: Part 1 (dose escalation), Part 2 (dose expansion), Part 3 (PK/PD relationship) and Part 4 (open-label extension). **Methods:** The initial Part 1 of the Brainshuttle™ AD study uses a staggered parallel group design, with participants recruited in four initial dose cohorts: 0.2 mg/kg, 0.6 mg/kg, 1.8 mg/kg, and 3.6 mg/kg. Following review of emerging data, dose levels tested in Part 1 may be expanded further in Part 2 to establish a more robust safety and PK/PD profile in a larger number of study participants (+60 participants per expanded cohort). **Results:** Previous interim analyses from Part 1 revealed dose-dependent amyloid plaque lowering across all active dose groups.An analysis based on a snapshot date in October 2023 revealed a very rapid amyloid PET reduction of 91 Centiloids (CL) versus baseline (BL) after 12 weeks of treatment in cohort 4, at 3.6 mg/kg trontinemab (n=8 participants on active treatment). This exceeded a reduction of 62 CL versus BL observed in cohort 3, at 1.8mg/kg, after 12 weeks (n=11 on active treatment). 63% of participants at 3.6 mg/kg reached amyloid levels below the positivity threshold defined as ≤24 CL, compared to 36% at 1.8 mg/kg. No new cases of amyloid-related imaging abnormalities with edema/ effusions (ARIA-E) or amyloid-related imaging abnormalities with hemorrhages (ARIA-H) were reported. At CTAD 2024, the latest results from the most recent data cut, including 28-week data from cohort 4 Part 1 as well as relevant insights and results from the ongoing Part 2 of the Brainshuttle™ AD study, will be presented. **Conclusion:** The recent interim results suggest that rapid and robust amyloid plaque clearance may be achieved with low ARIA incidences. The overall favorable safety and PD interim results support further investigation of trontinemab as a promising novel amyloid targeting therapy for AD. **Disclosures:** LK is a full-time employee and owns stock in F. Hoffmann-La Roche Ltd. FA is a full-time employee and owns stock in F. Hoffmann-La Roche Ltd. GK is a full-time employee and owns stock in F. Hoffmann-La Roche Ltd. CH is a full-time employee and owns stock in F. Hoffmann-La Roche Ltd. SY is a full-time employee and does not own stock in F. Hoffmann-La Roche Ltd. JAA is a full-time employee and owns stock in F. Hoffmann-La Roche Ltd. DS is a full-time employee and owns stock in F. Hoffmann-La Roche Ltd. MM is a full-time employee and owns stock in F. Hoffmann-La Roche Ltd. JW is a full-time employee and owns stock in F. Hoffmann-La Roche Ltd. RC is a full-time employee and owns stock options in F. Hoffmann-La Roche Ltd. DA is a full-time employee of and owns stock in F. Hoffmann-La Roche Ltd. PD is a full-time employee and owns stock in F. Hoffmann-La Roche Ltd. HS is a full-time employee of Roche Diagnostics GmbH and owns stocks in F. Hoffmann-La Roche Ltd. IW is a full-time employee of and owns stock in F. Hoffmann-La Roche Ltd.

LB03- DIAGNOSTIC PERFORMANCE OF CAPILLARY PTAU217 IN ALZHEIMER'S DISEASE: THE DROP-AD PROJECT. H. Huber[1], L. Montoliu-Gaya[1], W.S. Brum[1], J. Vávra[1], Y. Yakoub[1], S. Kern[1], H. Weninger[1], B. Borroni[2], A. Corbett[3], O. Hansson[4], X. Morató[5], H. Zetterberg[1], K. Blennow[1], N.J. Ashton[1] *(1. University of Gothenburg - Gothenburg (Sweden), 2. University of Brescia - Brescia (Italy), 3. University of Exeter - Exeter (United Kingdom), 4. University of Lund - Lund (Sweden), 5. Ace Alzheimer Center Barcelona - Barcelona (Spain))*

Background: Phosphorylated tau at Thr 217 (pTau217) has emerged as the most effective blood test to identify Alzheimer disease (AD) pathology, showing higher accuracy than other blood biomarkers. Increased and simplified access to this biomarker could be crucial for early diagnosis, proper patient management and prompt initiation of disease-modifying treatments. The DROP-AD project aims to streamline blood sample collection for clinical care and research by introducing an alternative method that addresses the challenges of traditional blood collection. Here, we investigated the diagnostic performance of finger-prick collection to accurately measure pTau217. **Methods:** In this prospective study, n=203 participants with or without cognitive impairment (mean [SD] age, 71.8 [8.6] years; 115 females [59.2%]) from five participating European centers provided paired venous EDTA plasma and dried plasma from on-site finger-prick collection (DPScapillary; Noviplex®; Capitainer Plasma®). In a sub-cohort, a second finger-prick sample was self-collected by the participants without supervision. Capillary cards were shipped to Gothenburg, Sweden, without temperature control or cooling, extracted by a custom protocol and measured by the ALZPath pTau217 Simoa assay. Cerebrospinal fluid (CSF) biomarkers were available in 151 individuals. Participants were defined as amyloid positive by an abnormal plasma pTau217 (ALZpath) (≥ 0.42 pg/mL), CSF Aβ42/40 (<0.063) or CSF Aβ42/pTau181 (<11.94) test result. Cognitive testing (MMSE and/ or CDRglobal) was available for all participants. Statistical analysis included Spearman correlations, linear models, receiver operating characteristic (ROC) area under the curve (AUC), and analyses focusing on diagnostic properties of cut-offs. **Results:** A high association between capillary and venous samples was found throughout the entire study group (n = 203, rs = 0.779, CI 95% 0.719-0.828; P < 0.001). Head-to-head comparison of self-collected samples with samples collected by the study personnel showed no significant difference (n = 45, 0.03 pg/mL vs. 0.03 pg/mL, P = 0.97), highlighting the reproducibility of both the collection method and laboratory processing. We tested the potential of capillary pTau217 to detect abnormal venous pTau217 plasma values (≥ 0.42 pg/mL1), achieving a discriminative accuracy of 0.921 (95% CI, 0.887-0.956). A capillary cutoff of 0.017 pg/mL, with 90% specificity for abnormal plasma pTau217, led to a PPV of 0.915 (95% CI 0.841-0.956) and an NPV of 0.714 (95% CI 0.624-0.790). Capillary pTau217 had a discriminative accuracy of 0.844 (95% CI, 0.778-0.908) to detect abnormal CSF Aβ42/40 (n=148), which was lower than for venous plasma (0.955; 95% CI, 0.925-0.984). Plasma and capillary pTau217 had a discriminative accuracy of 0.982 (95% CI, 0.967-0.997) and 0.884 (95% CI, 0.829-0.934) to detect abnormal CSF Aβ42/pTau181 (n=151), respectively. Finally, finger-prick pTau217 reflected cognitive performance (CDRglobal [n=177], r = 0.3270, P < 0.0001; MMSE [n=175], r = -0.3482, P < 0.0001) highly comparable to plasma (CDRglobal [n=214], r = 0.3168, P < 0.0001; MMSE [n=216], r = -0.3735, P < 0.0001). **Conclusion:** This study demonstrates the capability of detecting and accurately identifying pTau217 protein levels from finger-prick collection. The findings of this pilot project suggest that this simple, self-executable, temperature-independent, and reliable method could identify individuals of high risk of AD pathology. **References:** 1Ashton, NJ (2024), 10.1001/jamaneurol.2023.5319. **Disclosures:** O.H. has acquired research support (for the institution) from ADx, Avid Radiopharmaceuticals, Biogen, C2N Diagnostics, Eli Lilly, Eisai, Fujirebio, GE Healthcare, Pfizer and Roche and served as consultant/speaker for AC Immune, Alzpath, BioArctic, Biogen, Bristol Meyer Squibb, Cerveau, Eisai, Fujirebio, Genentech, Merck, Novartis, Novo Nordisk, Roche and Siemens. K.B. has served as consultant/ speaker/ advisory board for Abbvie, AriBio, ALZpath, BioArctic, AC Immune, Biogen, Eisai, Lilly, Julius Clinical, Novartis, Ono Pharma, Prothena, Roche,

Siemens and is co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. 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, Triplet Therapeutics, and Wave and is co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. B.B. has served as advisory board for AviadoBio, UCB, Lilly/Prevail, Denali, Alexion. N.J.A. has served as consultant/ speaker for Alamar Biosciences, Biogen, Eli-Lilly, and Quanterix.

LB04- SAFETY AND PRELIMINARY EFFICACY OF AAV GENE THERAPY (LX1001) IN PATIENTS WITH APOE4 HOMOZYGOTE ALZHEIMER'S DISEASE – INTERIM DATA FROM A PHASE 1/2, OPEN-LABEL, 52-WEEK, MULTICENTER STUDY. K. Johnson[1], M. Kaplitt[2], S. Kaminsky[2], G. Amato[3], N. Selvan[3], R. Khanna[3], S. See Tai[3], R. Crystal[2] *(1. Duke University - Durham (United States), 2. Cornell Medical College - New York (United States), 3. Lexeo Therapeutics - New York (United States))*

Background: Alzheimer's disease (AD) is associated with a strong genetic risk resulting from polymorphisms of the apolipoprotein E (APOE) allele with APOE4 homozygotes having a 14.5-fold greater risk of developing late-onset AD compared with APOE3 homozygotes, the most common genotype. APOE2/E4 heterozygotes have a ~2.6-fold greater risk of developing AD compared with APOE3 homozygotes, suggesting a potential protective effect of the presence of APOE2. LX1001 is an adeno-associated viral vector (AAV) investigational gene therapy (AAVrh.10hAPOE2) designed to deliver the protective APOE2 gene into the central nervous system (CNS) of APOE4 homozygous AD patients, to convert the APOE4 homozygous profile to an APOE2/E4 profile, thereby possibly halting or slowing disease progression mediated by the APOE4 allele. **Methods:** This is an ongoing first-in-human, Phase 1/2, open label, dose-finding study (NCT03634007) evaluating the safety and tolerability of LX1001 in four ascending single-dose cohorts: 1.4E10, 4.4E10 and 1.4E11 gc/ml CSF, and a fixed dose cohort of 1.4E14 gc, administered into the cerebrospinal fluid (CSF) at the craniocervical junction, with 3 to 5 participants per cohort. Participants receive prednisone for 8 weeks following dosing. Enrollment criteria include APOE4 homozygous status, age ≥ 50 years, positive amyloid PET, CSF biomarkers consistent with AD, and mild cognitive impairment (MCI) or mild to moderate dementia due to AD. Following the one-time dose, the CSF APOE2/E4 profile in addition to other CSF and imaging AD biomarkers are assessed at regular intervals over 12 months. After completing this 1-year study, participants may enroll into a long-term follow-up study for an additional 4 years. **Results:** Fifteen participants have been dosed across 4 dose cohorts: cohort (C) 1 n=5, C2 n=4, C3 n=3, C4 n=3; mean age ±SD of 65.3 ±6.4 years, 80% female, 50% MCI, 14% mild and 36% moderate dementia due to AD. Twelve months of data are available for C1-C3 and 6 months for C4. To date, treatment with LX1001 was generally safe and well-tolerated. No events of ARIA have been observed. Transient CSF pleocytosis (>5cells/ul), predominantly lymphocytic, was observed in 12 participants, with no significant associated adverse events. Post-treatment, APOE2 was expressed in the CSF in all participants, with a dose-and time-dependent increase in APOE2:E4 expression. Interim results to date do not show a directional trend in CSF Aβ42/40 or amyloid PET. However, the data demonstrated a decrease in CSF T-Tau and P-Tau181 in 9 of 13 participants, with a decrease also observed for CSF P-Tau217 and 231. Tau PET evaluated in C3 and C4 demonstrated a decrease in global uptake in 5 of the 6 participants. **Conclusion:** LX1001 is the first investigational gene therapy to specifically address the unmet need for APOE4 homozygotes, a well-recognized genetic risk for late-onset AD. Interim data suggest LX1001 is generally safe and well tolerated and results in a dose- and time-dependent effect on APOE2 expression. A decrease in several CSF AD tau biomarkers and changes on Tau PET suggest a treatment effect of LX1001 on tau, a critical component in the pathobiology of AD. **Keywords:** APOE, gene therapy, Phase 1/2, LX1001. **Disclosures:** KGJ is the primary investigator of LX1001 at Duke University; MK is the primary investigator at Weill Cornell; SK has equity in Lexeo Therapeutics; GA, NS, RK and SST are employees of Lexeo Therapeutics; RGC has equity and is founder and chief scientific adviser to Lexeo Therapeutics.

LB05- COGNITIVE AND BEHAVIORAL OUTCOMES IN PATIENTS WITH DEMENTIA WITH LEWY BODIES TREATED WITH NILOTINIB. F. Pagan[1], Y. Torres-Yaghi[1], M. Hebron[1], B. Wilmarth[1], R.S. Turner[1], C. Moussa[1] *(1. Georgetown - Washington (United States))*

Background: We evaluated the safety, tolerability and efficacy of a potential disease-modifying treatment for individuals with dementia with Lewy bodies (DLB). **Methods:** We conducted a single-center, phase 2, randomized, double-blind, placebo-controlled study. 43 participants were randomized 1:1 into nilotinib, 200mg, or matching placebo groups. Study drug was taken orally once daily for 6 months followed by one-month wash-out. We hypothesized that nilotinib is safe and can improve cognitive and/or behavioral features in DLB. **Results:** Of the forty-three (43) individuals enrolled, fourteen (14) were women (33%), age (mean±SD) was 73±8.5 years. Nilotinib was safe and well-tolerated and more adverse events were noted in the placebo (74) vs nilotinib (37) groups (95% CI, 0.98 to 2.32, p=.054). The number of falls were reduced in the nilotinib (six) compared to placebo (21) group (95% CI, 1.30 to 10.12, p=0.006). ADAS-cognition 14 scores improved by 2.8pts (ADAS-Cog14; 95% CI, 0 to 6.34, p=0.037) in nilotinib versus placebo. Psychiatric features, irritability and cognitive fluctuations were worse in placebo compared to nilotinib. No differences were observed in MDS-UPDRS part II and III, but part I (cognition) improved (0.9 pts, 95% CI, 0 to - 2, p=0.044) in nilotinib compared to placebo. Other cognitive and functional scores, including MoCA (1.5pts, 95% CI, 95% CI, 0 to - 3, p=0.061) and ADCS-ADL, (-3.3 pts, 95% CI, -5 to - 1, p=0.084) trended towards an improvement. CSF HVA as a marker of dopamine level was increased (98.53nM, 5% CI, 27.81 to 169.3, p=0.004). The CSF ratio of pTau181/Aβ42 was reduced (Fig. 3E, -0.13nM, 5% CI, -0.27 to 0.01, p=0.034). **Conclusion:** Nilotinib has shown favorable safety and efficacy in patients with LBD supporting a multi-center phase 3 trial for individuals with DLB or advanced Parkinson's disease with dementia.

LB06- LECANEMAB FOR THE TREATMENT OF MILD COGNITIVE IMPAIRMENT AND MILD DEMENTIA DUE TO ALZHEIMER'S DISEASE IN ADULTS THAT ARE APOLIPOPROTEIN E E4 (APOE E4) HETEROZYGOTES OR NON-CARRIERS. R. Perry[1], C. Kipps[2], R. Mcmurray[3], S. Dhadda[4], M. Kanekiyo[4], M. Irizarry[4], L. Kramer[4] *(1. Imperial College London - London (United Kingdom), 2. University Hospital Southampton NHS Foundation Trust - Southampton (United Kingdom), 3. Eisai Europe Ltd - Hatfield (United Kingdom), 4. Eisai Inc. - Nutley (United States))*

Background: In the United Kingdom (UK), it is estimated that 982,000 people are living with dementia, and Alzheimer's disease (AD) is the cause in 60-70% of people with dementia. Lecanemab, an amyloid beta-directed antibody, was recently approved in Great Britain for the treatment of mild cognitive impairment (MCI) and mild dementia due to AD in adult patients that are apolipoprotein E ε4 (ApoE ε4) heterozygotes or non-carriers. Lecanemab reduces neuronal damage and cognitive impairment by selectively binding to Aβ aggregate species, with preferential activity for toxic Aβ protofibrils as well as fibrils (a major component of Aβ plaques). Herein, we present the data from the subgroup of Clarity AD patients who were ApoE ε4 heterozygotes or non-carriers, upon which the UK approval was based. **Methods:** Clarity AD was a phase 3, 18-month treatment (Core study), multicenter, double-blind, placebo-controlled, study in patients with early AD (MCI or mild dementia due to AD, with confirmed presence of amyloid pathology). Eligible patients were randomized 1:1 across 2 treatment groups (placebo and lecanemab 10 mg/kg biweekly). The primary endpoint was the change from baseline at 18 months in the global cognitive and functional scale, CDR-SB. Key secondary endpoints included change from baseline at 18 months in amyloid positron emission tomography (PET), Alzheimer's Disease Assessment Scale-Cognitive Subscale 14 (ADAS-Cog14) and Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL,). Amyloid imaging related abnormalities (ARIA) occurrence was monitored throughout the study by central reading of magnetic resonance imaging. Results were evaluated in the subgroup of Clarity AD patients who were ApoE ε4 heterozygotes or non-carriers. **Results:** 1,795 patients with early AD were enrolled in Clarity AD, of which 1,521 were ApoE ε4 heterozygotes or non-carriers. Of the total number of patients randomized, 31% were non-carriers, 53% were heterozygotes, and 16% were homozygotes. Lecanemab reduced clinical decline on CDR-SB by 33% at 18 months compared to placebo in the ApoE ε4 heterozygotes or non-carriers subgroup. The adjusted least-squares mean change from baseline at 18 months was 1.15 with lecanemab and 1.73 with placebo (difference: -0.58; 95% confidence interval [CI]: -0.81 to -0.34; P<0.00001). Secondary endpoint results were consistent with the primary endpoint. The ADAS-Cog14 score was 4.2 in the lecanemab group and 5.8 in the placebo group (difference: -1.6; 95% CI: -2.6 to 0.7; P=0.00052). The adjusted mean changes from baseline at 18 months in the ADCS-MCI-ADL score was -3.5 in the lecanemab group and -5.7 in the placebo group (difference:2.2; 95% CI:1.3 to 3.1; P<0.00001). In addition, the mean change in amyloid PET from baseline relative to placebo was statistically significant for lecanemab at 18 months (P<0.00001). In the analysis subgroup, the most common adverse reactions for lecanemab were infusion-related reaction (26%), ARIA-H (13%), fall (11%), headache (11%), and ARIA-E (9%). **Conclusion:** In the early AD subgroup of Clarity AD patients who were ApoE ε4 heterozygotes or non-carriers, lecanemab resulted in less decline on measures of cognitive function than placebo and reduced markers of amyloid at 18 months. **Keywords:** Lecanemab, Early Alzheimer's Disease. **Disclosures:** RP has been a consultant for Biogen, Eisai, Eli Lilly, Hoffman-LaRoche, and Merck Sharp and Dohm. CP has nothing to disclose. RM, SD, MK, MI, and LK are employees of Eisai.

LB06 BIS- THE GLOBAL NEURODEGENERATION PROTEOMICS CONSORTIUM - BIOMARKER AND DRUG TARGET DISCOVERYACROSS >40,000 BIOSAMPLES FOR AD, PD, ALS, FTD, AND AGING. F. Imam[1], M. Bringmann[2], V. Krish[1] *(1. Gates Ventures - Seattle, WA (United States), 2. Johnson&Johnson - Spring House, PA (United States))*

Background: Limited understanding of biological mechanisms behind the onset and progression of Neurodegenerative Disorders has been a burden for the discovery of novel biomarkers and treatments. Large, harmonized, patient-derived datasets will be key in unraveling the complex biology leading to neurodegeneration. The Global Neurodegeneration Proteomics Consortium (GNPC) is a major biomarker discovery effort to unite and expand the available proteomic data for thousands of patient samples from leading dementia cohorts from around the world and comprises, to our knowledge, the largest discovery proteomics dataset to date. **Method:** The GNPC has brought together over 40,000 samples from over 20 different international cohorts to create and collaborate on a fully anonymized Harmonized Dataset (HDS). The HDS spans multiple neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and frontotemporal dementia (FTD). Secure access to GNPC data is facilitated through the Alzheimer's Disease Data Initiative's online platform, the AD Workbench. De-identified datasets submitted by each participating cohort were harmonized and further anonymized by professional data vendors. After one year of intra-consortium analysis, the HDS will be accessible by the broader research community as a shared, global resource. **Result:** The first version of the Harmonized Dataset (HDS) includes over 40,000 unique samples on theSomaScan 5k and/or 7k proteomics array platform. All samples are accompanied by >40 phenotypic indicators including demographic, cognitive data, clinical scores, and disease-specific genotype. Central hosting of de-identified and harmonized data within the secure cloud environment provides the necessary data security, access to scalable compute resources, and facilitates collaboration between participants in diverse geographies and regulatory environments. **Conclusion:** With over 300,000,000 unique protein measures, the GNPC represents the largest protein biomarker discovery effort for neurodegenerative diseases to date. Initial research underway is organized via several core workstreams, including cross-sectional and longitudinal profiling, proteogenomic mapping, multivariate prediction, and combinatorial analysis across a single disease area.

LB07- PLASMA P-TAU217 AND RELATED CSF PROTEOMIC MARKERS OF PATHOLOGICAL PROGRESSION ARE SLOWED BY P75NTR MODULATION: A PHASE 2A TRIAL OF LM11A31 IN ALZHEIMER'S DISEASE. H.R.C. Shanks[1], K. Pandey[2], M. Bangs[3], V. Venkatesh[4], M.R. Meyer[4], M. Windisch[5], N.T. Seyfried[2,3], S.M. Massa[6,7], F.M. Longo[8], T.W. Schmitz[1] *(1. Western University - London (Canada), 2. Emtherapro Inc. - Atlanta (United States), 3. Emory University - Atlanta (United States), 4. C2N Diagnostics - St. Louis (United States), 5. NeuroScios Gmbh - St. Radegund (Austria), 6. San Francisco Veterans Affairs Health Care System - San Francisco (United States), 7. University of California, San Francisco - San Francisco (United States), 8. PharmatrophiX - Menlo Park (United States))*

Background: LM11A-31 is a first-in-class small molecule modulator of the p75 neurotrophin receptor, a key degenerative signaling receptor which contributes to amyloid beta (Aβ) and pathological phosphorylated tau (p-tau)-induced neuronal dysfunction and degeneration, as well as microglial reactivity. In a recent Phase 2a safety and exploratory trial of participants with mild to moderate Alzheimer's disease (AD), LM11A-31 slowed longitudinal progression of grey matter volume loss, glucose hypometabolism, and cerebrospinal fluid (CSF) biomarkers of synaptic degeneration and glial activation compared to placebo [1]. This presentation will provide an update on the effects of LM11A-31 on a novel set of exploratory biomarkers collected and analyzed at a later stage of the Phase 2a trial, which include plasma p-tau217 and CSF proteomic network modules derived from mass spectrometry. Moreover, we will describe how these plasma and CSF proteomic biomarkers relate with ELISA-based CSF biomarkers, neuroimaging, and cognitive data which were previously reported [1]. **Methods:** Data were collected as part of a randomized, double-blinded, placebo-controlled 26-week Phase 2a safety and exploratory endpoint trial of LM11A-31. Participants with mild to moderate AD dementia (n=241) were treated twice daily with placebo, 200mg of LM11A-31 or 400mg of LM11A-31. Exploratory endpoints included plasma p-tau217 as measured by liquid chromatography-mass spectrometry (LC-MS/MS; C2N, St. Louis) and CSF proteomic modules as measured by tandem mass tag-based mass spectrometry (TMT-MS; Emtherapro, Atlanta) [2]. Additionally, relationships with CSF AD (Aβ40, Aβ42, p-tau181, t-tau), synaptic (SNAP25, SYT1, neurogranin), and glial markers (sTREM2, YKL40), as well as neuroimaging (structural MRI, FDG PET) and cognitive test data (MMSE, ADAS-Cog13, NTB) as reported in [1] were evaluated. **Results:** Treatment with LM11A-31 over the 26-week trial period significantly attenuated longitudinal increases in plasma p-tau217 relative to placebo. Of the 10 preserved modules from a consensus AD CSF proteomic network, LM11A-31 treatment reduced the levels of AD-relevant modules associated with ubiquitination and glycolysis, which included tau and neurogranin. Notably, plasma p-tau217 levels showed significant correlations at baseline with degenerative measures, including sMRI, FDG-PET and CSF synaptic biomarkers. Moreover, plasma p-tau217 correlated with CSF markers of glial activation, as well as with the CSF ubiquitination and glycolysis proteomic modules, and with cognitive test scores. These correlations remained present at the 26-week follow-up, highlighting the stability of these relationships. **Conclusion:** Overall, 26-week treatment with LM11A-31 slows progression of AD biomarkers, as measured by plasma p-tau217 and CSF proteomic modules, in addition to previously demonstrated sMRI, FDG-PET and CSF synaptic and glial biomarkers. The relevance of plasma p-tau217 and the CSF proteomic modules to AD clinical status is highlighted by significant correlations with cognitive function. **Keywords:** phase 2a, plasma, CSF. **Clinical trial registry:** EU Clinical Trials 2015-005263-16; ClinicalTrials.gov NCT03069014. **Disclosures:** NTS is co-founder and board member of Emtherapro. KP is an employee of Emtherapro. VV and MRM are employees of C2N diagnostics. MW is the vice president for research and development of NeuroScios. FML has equity interest, is a board member, and has a consulting relationship with PharmatrophiX, a company developing LM11A-31. FML and SMM are listed as inventors of LM11A-31 and hence entitled to royalties and related payments. The trial was funded by the National Institute on Aging (NIA AD pilot trial 1R01AG051596) and PharmatrophiX (Menlo Park, California). **References:** Shanks HRC et al. Nat Med 2024; 30(6): 1761-1770. doi:10.1038/s41591-024-02977-w; Modeste ES et al. Mol Neurodegener 2023; 18(1):48. doi:10.1186/s13024-023-00638-z.

LB08- BRIDGING THE GAP: PARAHIPPOCAMPAL TAU-PET IMPROVES DETECTION OF THE TRANSITION FROM AGE-RELATED TAUOPATHY TO ALZHEIMER'S DISEASE. E.G. Thibault[1], M.E. Farrell[2], J.F. Fu[3], J.S. Sanchez[1], B.C. Healy[2,4], B.J. Hanseeuw[1,5], H.I.L. Jacobs[3], J.C. Price[3], J.A. Becker[1], R.A. Sperling[2,6], K.A. Johnson[1,6] *(1. Department of Radiology, Massachusetts General Hospital - Boston (United States), 2. Department of Neurology, Massachusetts General Hospital - Boston (United States), 3. Department of Radiology, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital - Boston (United States), 4. Biostatistics Center, Massachusetts General Hospital - Boston (United States), 5. Department of Neurology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain - Bruxelles (Belgium), 6. Center for Alzheimer Research and Treatment, Department of Neurology, Brigham and Women's Hospital - Boston (United States))*

Background: Growing evidence suggests that preventing initial tau spread from the medial temporal lobe (MTL) into the temporal neocortex (NEO) may be a critical intervention point in Alzheimer's prevention and treatment. The nearly universal nature of age-related increase in MTL-tau complicate its use as a screening tool to identify those on the cusp of increasing NEO-tauopathy for clinical trials. While much research has focused on the entorhinal cortex (ERC) as the origin of cortical tau, the parahippocampal gyrus (PH) may be a more effective biomarker for those close to transitioning to NEO-tau proliferation given its role as an anatomical, functional, and cytoarchitectural bridge between ERC and NEO. We aim to evaluate PH-tau as an indicator of the transition between amyloid-independent MTL-tau and AD-related NEO tau spread in the presence of amyloid. **Methods:** Longitudinal [18F] Flortaucipir (FTP)-PET data from 260 cognitively unimpaired older adults from the Harvard Aging Brain Study (HABS) were used to evaluate ERC, PH, and amygdala (AM) tau as predictors of future NEO-tau proliferation. [11C]Pittsburgh Compound B (PiB)-PET positivity was determined at FTP-baseline. We assessed whether baseline PH FTP-SUVR mediates the relationship between baseline ERC FTP-SUVR and NEO FTP-SUVR slopes in the presence of amyloid. Next, using Gaussian mixture model-derived thresholds, we determined tau+/- for each ROI. Survival analyses were used to estimate time to NEO+ by baseline PiB-group*tau-ROI (ERC/PH/AM). Separate power analyses were conducted within three potential target groups (PiB+, PiB+/ERC+, PiB+/PH+) to determine the sample size needed to detect a 30% treatment effect on NEO-tau over 3 years with 80% power. **Results:** We found

that the association between baseline ERC FTP-SUVR and NEO FTP-SUVR slope was fully mediated by baseline PH FTP-SUVR and moderated by the presence of amyloid (β=0.020, p<.001). ERC FTP-SUVR was associated with PH FTP-SUVR in both PiB+ (r=0.72, p<0.001) and PiB- (r=0.61, p<0.001) groups. However, the relationship between PH FTP-SUVR and increasing NEO FTP-SUVR slope occurs only in PiB+ individuals (r=0.52, p<0.001; PiB- r=-0.16, p=0.06). Median time to NEO+ was shortest in baseline PH+/PiB+ individuals (2.4 years). Longer durations were needed for ERC+/PiB+ (5.0 years) and AM+/PiB+ (4.8 years) groups to reach NEO+. None of the PH+/PiB- individuals progressed to NEO+ over a median follow-up of 6.0 years. Combined PH+/PiB+ predicted which individuals would convert to NEO+ within 3 years with 83% sensitivity and 99.6% specificity, compared to 67% sensitivity and 96.5% specificity using ERC+/PiB+, and 17% sensitivity and 98.7% specificity using AM+/PiB+. Power analyses indicated that targeting PH+/PiB+ individuals would require the smallest sample size (n=234) to detect a 30% reduction in NEO-tau over 3 years, reducing the sample size needed by 302% relative to PiB+ only (n=708) and 220% relative to ERC+/PiB+ (n=514). **Conclusion:** Our findings support that PH-tau may serve as a bridge between age-related MTL-tauopathy and AD-related NEO-tauopathy. As a result, using PH-tau in combination with amyloid status may serve as an effective tool for clinical trials seeking to select individuals on the cusp of NEO-tau proliferation to test preventative treatments in preclinical participants. **Keywords:** tau-PET, PiB-PET, amyloid, tau, preclinical, longitudinal. **Disclosures:** M.E.F., E.G.T., J.S.S, J.A.B., J.F.F, J.C.P., and H.I.L.J. have no disclosures. B.J.H. has served as a paid consultant for Biogen, Eisai, and Roche. B.C.H. has received research support from Analysis Group, Celgene, Bristol-Myers Squibb, Verily Life Sciences, Merck-Serono, Novartis and Genzyme. R.A.S. has served as a paid consultant for Abbvie, AC Immune, Acumen, Alector, Biohaven, Genentech, Janssen, Ionis, Prothena, and Roche. She has received research support as an investigator for Eli Lilly, and Eisai public private partnership clinical trials. K.A.J. has served as paid consultant for Janssen, Merck, Prothena, and Novartis. He has served as a site coinvestigator for Lilly, Eisai, Janssen, Cerveau, and Biogen. These relationships are not related to the content in the manuscript.

LB09- PHASE IIB/III TRIAL OF BLARCAMESINE IN EARLY ALZHEIMER DISEASE DEMONSTRATES PRE-SPECIFIED CLINICAL EFFICACY THROUGH UPSTREAM SIGMAR1 ACTIVATION. M. Sabbagh[1], J.C. Lopez-Talavera[2], K. Jin[2], W. Chezem[2], M. Christopher[2] *(1. Barrow Neurological Institute - Phoenix (United States), 2. Anavex - New York (United States))*

Background: Blarcamesine, an orally bioavailable small molecule activator of the Sigma-1 receptor (SIGMAR1), offers a novel treatment for early Alzheimer disease (AD) through restoration of cell homeostasis including autophagy enhancement with full regulatory submission in Europe (EMA) expected in Q4 2024. In the recent ANAVEX2-73-AD-004 randomized, double-blind, placebo-controlled, 48-week phase IIb/III trial, blarcamesine significantly improved clinical efficacy over placebo for the ADAS-Cog13 and CDR-SB. New data will be presented at CTAD24 on the prespecified SIGMAR1 gene variant subgroup analysis. In order to confirm the blarcamesine-specific MoA through SIGMAR1 activation in AD, clinical efficacy endpoints were analyzed based on pre-specified genetic SIGMAR1 variants [wild-type (WT) genotype and rs1800866 genotype (RS variant)]1 for all participants. **Methods:** In the ANAVEX2-73-AD-004 trial, 508 participants with confirmed diagnosis of early AD were randomized between the prespecified blarcamesine (n = 338) in medium dose group 30 mg or in high dose group 50 mg or placebo (n = 170) oral capsules once daily for 48 weeks. Pre-specified genetic variant analysis was performed for primary endpoint ADAS-Cog13 and key secondary endpoint CDR-SB. Pre-specified subgroup analysis was performed by comparing non-carriers (WT SIGMAR1) to RS variant carriers. Whole blood samples were collected from all participants and used for genotyping of sequencing variants. All clinical endpoints were analyzed using mixed model for repeated measures (MMRM). **Results:** Participants with the SIGMAR1 wild-type (WT) gene, i.e., without the mutated SIGMAR1 rs1800866 variant treated with blarcamesine compared to the full ITT population experienced a greater clinical benefit for both ADAS-Cog13 (slowed clinical progression by 49.8% vs. 36.3%) and CDR-SB (slowed clinical progression by 33.7% vs. 27.6%), consistent with the MoA of SIGMAR1 activation. For ADAS-Cog13, SIGMAR1 WT participants in the blarcamesine group vs. placebo group demonstrated a difference of -2.317 (95%CI -4.182 to -0.453), resulting in 49.8% less decline at Week 48, P = 0.015; for RS variant participants the difference from placebo was -1.593 (95%CI -4.174, 0.989), P = 0.2254. For SIGMAR1 WT participants, the CDR-SB blarcamesine group vs. placebo difference was -0.601 (95%CI -1.070 to -0.133), resulting in 33.7% less decline at Week 48, P = 0.012; for RS variant participants the CDR-SB treatment difference for blarcamesine vs. placebo at week 48 was -0.230 (95%CI -0.826, 0.367), P = 0.4485. **Conclusion:** The prespecified SIGMAR1 gene variant subgroup analysis confirmed beneficial clinical effect of blarcamesine group through upstream SIGMAR1 activation - participants without the mutated SIGMAR1 rs1800866 variant experienced an even greater significant clinical benefit with slowed clinical progression by 49.8% at 48 weeks on the prespecified primary cognitive endpoint ADAS-Cog13. Conversely, participants with at least one copy of the rs1800866 variant had a weaker response to blarcamesine on average, supporting SIGMAR1 activation as a primary mechanism of action (MoA) for blarcamesine's effects in AD patients. This suggests that SIGMAR1 gene variant analyses could be an effective tool for confirming precision medicine MoA of blarcamesine in early AD. Oral once daily blarcamesine could represent a novel treatment in early AD and be complementary or alterative to anti-beta amyloid drugs. **References:** Hampel H, Williams C, Etcheto A, Goodsaid F, Parmentier F, Sallantin J, et al. A precision medicine framework using artificial intelligence for the identification and confirmation of genomic biomarkers of response to an Alzheimer's disease therapy: Analysis of the blarcamesine (ANAVEX2-73) Phase 2a clinical study. Alzheimer's & Dementia. 2020; 6(1).

LB10- DISCREPANCIES BETWEEN CSF AND PET DETERMINATIONS OF ELEVATED BRAIN AMYLOID AND THEIR PROGNOSTIC SIGNIFICANCE. D. Knopman[1], S. Weigand[1], H. Wiste[1], J. Graff-Radford[1], N. Graff-Radford[1], R. Petersen[1], C. Jack[1], M. Machulda[1], J. Fields[1], V. Ramanan[1], H. Botha[1], S. Mccarter[1], D. Jones[1], B. Neth[1], G. Day[1], A. Algeciras-Schimnich[1], J. Bornhorst[1], V. Lowe[1], D. Johnson[1], B. Boeve[1] *(1. Mayo Clinic - Rochester MN (United States))*

Background: Cerebrospinal fluid (CSF) assays to detect elevated brain amyloid-beta-peptide (Aβ) are highly concordant with amyloid positron emission tomography (PET). When CSF and PET measurements of amyloid-related pathology are discordant, especially when CSF measures are abnormal

and PET not abnormal, therapeutic decision-making becomes uncertain. **Methods:** Using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), we examined baseline characteristics and longitudinal clinical outcomes in persons who had undergone CSF (p-tau/Aβ42 ratios) and PET (global centiloid values) measurements for estimating brain Aβ burden. Persons were grouped according to diagnostic status: cognitively unimpaired (CU) (n=507), mild cognitive impairment (MCI) (n=587) or dementia (n=194) and normal/abnormal CSF/PET determination using standard cutpoints. Longitudinal clinical outcomes included performance on the Rey Auditory Verbal Learning Test (AVLT) learning phase and the Clinical Dementia Rating Scale® sum of box scores (CDRsb). **Results:** Both discordant groups for brain Aβ status (CSF+/PET- and CSF-/PET+) were small, in the ~5% range in CU and MCI. There were too few discordant cases among persons with dementia to conduct longitudinal analyses. Focusing on the MCI CSF+/PET- group, as the one relevant to therapeutic decision-making at present, this group had similar baseline AVLT test performance and CDRsb compared to the CSF−/PET- group and had less abnormal CSF values compared to the CSF+/PET+ group. Longitudinally, the MCI CSF+/PET- group did not show decline on either the AVLT or CDRsb over a median 4 years in contrast to the CSF+/PET+ group that exhibited decline on both measures. Examination of individual participants in the MCI CSF+/PET- group suggested heterogeneity in outcomes, however. **Conclusion:** In contrast to the decline observed in the MCI group with the CSF+/PET+ pattern, persons with MCI with the CSF+/PET- brain Aβ pattern did not exhibit group-wise decline, raising questions about the justification for treatment with an anti-amyloid monoclonal antibody without additional evidence for the likelihood of disease progression. **Acknowledgements:** *Data used in preparation of this abstract were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). 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. **Keywords:** Alzheimer's disease, Amyloid PET imaging, CSF Amyloid biomarkers, mild cognitive impairment, longitudinal outcomes. **Disclosures:** Dr. Lowe receives research support from GE Healthcare, Siemens Molecular Imaging, AVID Radiopharmaceuticals.

LB11- ALTITUDE-AD: USE OF A VALIDATED P-TAU217 ASSAY TO SCREEN POTENTIAL PARTICIPANTS IN AN ONGOING RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 2 STUDY OF SABIRNETUG FOR PARTICIPANTS WITH EARLY ALZHEIMER'S DISEASE.

T. Feaster[1], K. Sundell[1], M. Hyland[1], G. Sethuraman[1], V. Skljarevski[1], J. Kaplow[1], R.A. Dean[1], J. Jerecic[1], E. Siemers[1] *(1. Acumen Pharmaceuticals, Inc - Newton, Massachusetts (United States))*

Background: Many Alzheimer's disease (AD) clinical trials screen and exclude a substantial number of potential participants who do not meet study criteria relating to amyloid pathology consistent with AD. In the Phase 1 INTERCEPT-AD study of sabirnetug (ACU193), 75% of the individuals screened did not meet entry criteria; 60% of people undergoing an amyloid positron emission tomography (PET) scan with florbetapir had a negative result based on visual read.Plasma concentrations of the biomarker p-tau217 are highly predictive for AD [1]. Therefore, an initial assessment of patients using a p-tau217 cut-point would be expected to enrich the population of potential study participants with those who are likely to show amyloid burden by amyloid PET or cerebrospinal fluid (CSF) Ab42/40 ratio that is sufficient for inclusion in a study. Likewise, the plasma p-tau217 assessment may identify individuals likely to be ineligible for the study based on amyloid PET or CSF results, thus sparing them the radiation exposure of amyloid PET or the invasive lumbar puncture (LP) needed to collect CSF. **Methods:** ALTITUDE-AD (NCT06335173) is an 80-week, global, randomized, double-blind, placebo-controlled, multi-site Phase 2 study of sabirnetug (ACU193) in individuals with early AD and evidence of amyloid pathology. Screening occurs in two parts. Blood drawn in the first part is tested using the Fujirebio plasma p-tau217 assay, a Lumipulse platform-based, research-use-only assay that has been analytically and clinically validated as a Lab-Developed Test in a manner consistent with Clinical Laboratory Improvement Amendment regulations. Individuals with p-tau217 concentrations ≥0.15 pg/mL are eligible for the second screening part, when a confirmatory test of amyloid pathology is performed using either amyloid PET or a CSF Aβ42/40 ratio cutoff. The p-tau217 cut-point of ≥0.15 pg/mL was designed for enrichment purposes in this study of early AD and was not intended as a diagnostic cut-point. **Results:** Among participants screened to date, 46% had p-tau217 plasma concentrations ≥0.15 pg/mL and were eligible for a confirmatory test of amyloid pathology. Of participants who underwent amyloid PET imaging, 75% met the amyloid burden inclusion criterion. Of participants who underwent LP for CSF testing of Aβ42/40 ratio, 56% met the amyloid burden inclusion criteria. The difference observed between patients screened with PET and LP is likely an artifact of the small number of patients screened by LP rather than a true difference between the screening methods. Overall, 74% of participants with p-tau217 ≥0.15 pg/mL met study amyloid burden eligibility requirements. **Conclusion:** More than half of potential study participants were excluded from the study because of a plasma p-tau217 test result <0.15 pg/mL. Participants who proceeded to amyloid PET or CSF Aβ42/40 were enriched for meeting amyloid-based inclusion criteria. Thus, the p-tau217 enrichment strategy appears to be performing as intended, reducing unnecessary amyloid PET scans or LP procedures for potential clinical trial participants compared to our previous study, which did not use plasma p-tau217 screening. **Keywords:** p-tau217, amyloid PET imaging, clinical trials, sabirnetug, ACU193. **Clinical Trial Registry:** NCT06335173 www.clinicaltrials.gov. **Disclosures:** All authors are employees of or consultants for Acumen Pharmaceuticals, Inc. **References:** 1. Ashton NJ, et al. JAMA Neurol. 2024;81(3):255–263. doi:10.1001/jamaneurol.2023.5319.

LB12- A PHASE 1 CLINICAL TRIAL OF BDNF GENE THERAPY IN ALZHEIMER'S DISEASE AND MCI.

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Background: We performed a Phase 1 clinical trial of AAV2-BDNF gene therapy in patients with early stage Alzheimer's disease and Mild Cognitive Impairment (MCI). In preclinical studies, BDNF gene delivery to the entorhinal cortex prevents neuronal death, activates neuronal function, restores synapses and improves learning and memory. These effects are observed in APP transgenic mice, aged rats, perforant path-lesioned

rats, aged rhesus monkeys and perforant path-lesioned rhesus monkeys (Nature Medicine 2009; 15:331). Cellular and molecular benefits are observed in both the entorhinal cortex and the hippocampus. In addition to its anti-apoptotic and neuronal activating effects, BDNF reduces Tau phosphorylation in cultured neurons. Following extensive pre-clinical safety studies we advanced this program to a first-in-human clinical trial in 2023. **Methods:** 6 subjects with a diagnosis of AD with MMSE 22-28 will be enrolled, followed by 6 subjects with a diagnosis of MCI. BDNF gene delivery consists of MRI-guided infusions of adeno-associated virus serotype 2 (AAV2) vectors expressing full length human BDNF into the entorhinal cortex. Subjects undergo baseline cognitive assessment, CSF sampling and PET scans (FDG, amyloid, Tau imaging). Followup vists occur at 1, 3, 6, 12, 18 and 24 months. The primary outcome measure is safety, together with cognitive outcome measures including the Rey Auditory Verbal Learning Task (RAVLT) and the Benson complex figure test, as well as standard neuropsychological tests. **Results:** As of this date, four subjects have safely undergone the gene delivery procedure. Eight more subjects remain to be treated. The first two subjects received unilateral (right entorhinal cortex) gene delivery, and the subsequent subjects are treated bilaterally. Two vector dose groups are being examined. The first patient was treated in April 2023. One year followup PET scan data are available for the first subject who underwent BDNF gene therapy. The right, treated entorhinal cortex exhibited an increase in FDG PET uptake; the contralateral, left entorhinal cortex exhibited a decline in FDG PET uptake. Other cortical regions that were not targeted with BDNF also exhibited declines in FDG PET activity. Subject enrollment and treatment are ongoing. BDNF gene therapy has the potential to slow neuronal degeneration, activate the functional state of remaining neurons, and restore synaptic markers. Results to date support its safety and the possibility, in a single unilaterally treated subject, that it is activating neuronal metabolic activity. Analyses are ongoing. Supported by the NIH (R01AG071656), the Alzheimer's Association (PTC-17-439955) and the Shiley Family Foundation.

LB13- PLASMA PTAU217 ALONE IS NOT ENOUGH FOR STAGING ALZHEIMER'S DISEASE. J.D. Doecke[1], E.C. Stage[2], C.J. Fowler[3], V. Dore[4], N. Boehm[2], C. Kleinert[2], A. Feizpour[5], L. Ward[6,7,8], J. Mejan-Fripp[1], C.L. Masters[3], C. Rowe[5], A.W. Bannon[2] *(1. Australian E-Health Research Centre, CSIRO - Herston (Australia), 2. Abbvie Inc - North Chicago (United States), 3. The Florey Institute of Neuroscience and Mental Health - Parkville (Australia), 4. Australian E-Health Research Centre, CSIRO - Melbourne (Australia), 5. Department of Molecular Imaging & Therapy, Austin Health - Melbourne (Australia), 6. Australian Imaging, Biomarkers and Lifestyle Study of Ageing (AIBL) - Parkville (Australia), 7. Australian Dementia Network (ADNeT) - Parkville (Australia), 8. Faculty of Medicine, Dentistry and Health Sciences - Parkville (Australia))*

Background: Plasma pTau217 has been shown to demonstrate equal performance to CSF biomarkers for the prediction of Amyloid beta (Aβ) in both symptomatic and pre-symptomatic populations. Recently the Global CEO Initiative on Alzheimer's Disease (AD) provided feedback on the use of blood biomarkers (BBM's) either as triaging tests for Aβ positivity prior to confirmatory PET/CSF tests, or as confirmatory tests given performance equivalent to CSF tests (sensitivity & specificity ~90%1). Whilst such high performing plasma tests provide confirmatory information on Aβ positivity, further information is desperately needed to discern optimal markers across disease stage. In response to this unmet need, the current study investigated the potential of both central nervous system (CNS) and inflammatory BBM's to predict Aβ (A) and tau (T) stage. **Methods:** From the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of ageing, 387 participants with Amyloid PET, Tau PET and blood-based measures for pTau217 (ALZpath & Lumipulse) and the Alamar Biosciences NULISASeqTM platform (120 CNS & 250 Inflammatory proteins) were assessed. Disease stage was investigated using two methods, 1) AT staging using A+ as a centiloid value >25 and T+ as a meta-temporal SUVR >1.24 (A-T- (N=120) vs A+T- (N=72), A-T- vs A+T+ (N=175), A+T- vs A+T+), and 2) PET-based Braak staging using stages 0-III vs IV-VI. Multivariate (LASSO) modelling (using only Alamar panel BBM's) was used to investigate the performance of a panel of BBM's to predict disease stage as compared with pTau217 alone. Performance was captured using Area Under the Curve (AUC) with 95% Confidence Intervals (95%CI). **Results:** For the early stage A-T- vs A+T-, the multivariate model (pTau217, pTau231, Aβ42, GFAP, BMP7, TGFB1, Aβ4240, KITLG and VSNL1, age, gender, APOEε4; AUC: 0.981 [0.97 – 0.99]) had a significantly higher AUC than that from pTau217 (ALZpath: 0.908 [0.87 - 0.95]; Lumipulse: 0.863 [0.81 – 0.92], $p<0.001$). For the later stage comparison (A-T- vs A+T+), the multivariate model (pTau217, Aβ42, KITLG, GFAP, MMP1, CSF3R, age, gender, APOEε4) showed complete separation between groups (AUC: 1 [1 – 1]) which was significantly better than pTau217 (ALZpath: 0.986 [0.98 – 1]; Lumipulse: 0.978 [0.96 – 0.99], $p<0.01$). Amongst A+ participants, the multivariate model (pTau217, FAPB3, NPTXR, ACHE, VSNL1, IL10, age, gender, APOEε4; 0.938 [0.91 – 0.97]) was not significantly higher than pTau217 for Lumipulse (0.902 [0.86 – 0.94], $p=0.086$), however it was significantly higher than pTau217 for ALZpath (0.828 [0.77 – 0.89], $p=0.002$) at separating T status. For Braak stage 0-III vs IV-VI, the AUC value for the multivariate model (pTau217, Aβ42, ACHE, FLT3LG, FABP3, CNTN2, NPTXR, IFNA2, SCNA, age, gender, APOEε4; AUC: 0.967 [0.96 – 0.98]) performed similarly to the Lumipulse pTau217 (0.960 [0.94 – 0.98], $p=0.64$), however it was higher than that for ALZpath (0.929 [0.90 – 0.96], $p=0.02$). **Conclusion:** Utility of extra BBM's in addition to pTau217 provides more information about each participant during the A+T- and A+T+ stages compared with A-T-. ALZpath pTau217 performed better when predicting A+, whilst Lumipulse performed better when predicting T+, which was further supported using Braak stage. Such information will be useful to ascertain during trial candidate selection, especially for pre-clinical AD. **Keywords:** Disease stage, pTau217, Alamar, PET Ab, PET Tau, Braak stage, Inflammatory BBM. **Disclosures:** ES and AB are both employees and stockholders of AbbVie Inc. **References:** 1Schindler SE, Galasko D, Pereira AC, et al. 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.

LB14- NOT ALL PLASMA TAU BIOMARKERS ARE EQUALLY ASSOCIATED WITH TAU TANGLES AND AFFECTED BY CO-PATHOLOGIES. L. Montoliu-Gaya[1], E. Valeriano-Lorenzo[2], N.J. Ashton[1], A. Rábano[2], H. Zetterberg[1], J. Gobom[1], K. Blennow[1], P. Sánchez-Juan[2] *(1. University of Gothenburg - Mölndal (Sweden), 2. Alzheimer's Centre Reina Sofia-CIEN Foundation-ISCIII - Madrid (Spain))*

Background: Blood biomarkers, particularly phosphorylated tau (p-tau), are becoming crucial not only for diagnosing Alzheimer's disease (AD) but also as tools for screening and

monitoring AD treatments. To interpret these biomarkers accurately, we need a clear understanding of how they change in relation to AD brain pathology and how they are influenced by brain co-pathologies and comorbidities. Plasma-to-autopsy studies are essential to address these questions, with the most valuable studies being those where the interval between plasma collection and brain examination is the shortest. **Methods:** Plasma samples, along with clinical and neuropathological data, were collected from 102 brain donors participating in the VACS cohort. The average time from blood draw to death was 141.5±142.5 days. Plasma concentrations of six phosphorylated tau (p-tau181, p-tau199, p-tau202, p-tau205, p-tau217, and p-tau231) and two non-phosphorylated tau peptides (195-209, 212-221) were measured using a targeted mass spectrometry method1. The ratios of p-tau199/195-209, p-tau205/195-209, and p-tau217/212-221 were also included in the analysis. Donors were grouped into three categories based on the neuropathological examination: AD (intermediate or high AD neuropathological change [ADNC]), AD+ (AD pathology with concurrent other pathologies such as Lewy body disease or vascular disease), and non-AD (presence of other pathologies outweighing AD, or no high ADNC). **Results:** The plasma p-tau217 ratio was the best-performing biomarker for distinguishing AD from non-AD (AUC=0.97), AD+ from non-AD (AUC=0.95), and combined AD/AD+ from non-AD cases (AUC=0.92). This was followed by the p-tau205 ratio (AUC for AD vs non-AD=0.85; AD+ vs non-AD=0.87; combined AD/AD+ vs non-AD=0.87) and p-tau217 (AUC for AD vs non-AD=0.88; AD+ vs non-AD=0.83; combined AD/AD+ vs non-AD=0.84). Most plasma tau species showed a significant positive correlation with neurofibrillary tangle counts in the temporal and frontal cortices. However, in the parietal cortex, only p-tau217 (ϱ=0.38, P<0.001), p-tau205 (ϱ=0.25, P<0.001), the p-tau217 ratio (ϱ=0.36, P<0.001), and the p-tau205 ratio (ϱ=0.22, P=0.039) showed significant associations. Interestingly, plasma p-tau199 did not correlate with neurofibrillary tangle counts in any brain region, and the p-tau199 ratio showed a negative association in the temporal cortex (ϱ=-0.22, P=0.039). Additionally, Lewy body pathology was negatively associated with non-phosphorylated tau 195-209 (β=-0.37; P=0.036) and the six phosphorylated tau species, but not with any of the ratios (p-tau217 ratio, p-tau205 ratio, or p-tau199 ratio). Partial correlations between plasma tau concentrations and creatinine levels, an indicator of kidney dysfunction, were significant for all tau biomarkers except for the p-tau217, p-tau205, and p-tau199 ratios. Finally, multiple linear regression analysis showed that non-phosphorylated tau 195-209 (β=-1.61; P=0.038) and p-tau199 (β=-11.6; P=0.042) were stronger predictors of survival time. **Conclusion:** Plasma tau biomarkers, particularly p-tau217, either alone or as a ratio, are accurate biomarkers for detecting AD, even in the presence of co-existing brain pathologies. However, plasma tau biomarkers vary in their associations with tau neurofibrillary tangle counts across different brain regions. In addition, while plasma tau biomarkers are correlated with Lewy body pathology and kidney dysfunction, these effects are diminished when using the corresponding ratios. Plasma p-tau199 and non-phosphorylated tau may be more reliable biomarkers for prediction of survival time. **References:** 1. Montoliu-Gaya, L., et al. Mass spectrometric simultaneous quantification of tau species in plasma shows differential associations with amyloid and tau pathologies. Nat Aging (2023). **Keywords:** blood, tau phosphorylation, mass spectrometry, neuropathological examination. **Disclosures:** The presenting author declares no conflict of interest.

LB15- STUDY DESIGN FOR TRAILRUNNER-ALZ 3: A DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 3 CLINICAL TRIAL INVESTIGATING SUBCUTANEOUS REMTERNETUG IN EARLY ALZHEIMER'S DISEASE.

K. Biglan[1], E. Rizvi[1], T. Wang[1], M. Hufford[1], M. Lidogoster[1], C. Dickson[1], S. Warner[1], I. Gueorguieva[1], Y. Vandenburg[1], M. Dabora[1] *(1. Eli Lilly and Company - Indianapolis (United States))*

Background: The initial period in which individuals have Alzheimer's disease (AD) pathology prior to the onset of dementia is known as early AD. According to recent guidelines for diagnosis of AD, early AD corresponds to AD Stages 1 through 3, encompassing preclinical AD and mild cognitive impairment due to AD [1-3]. Emerging data in the field suggest that amyloid-targeting therapies may have greater benefit when started earlier in the disease continuum [4,5]. Remternetug is an IgG1 monoclonal antibody directed at deposited brain amyloid plaques that has demonstrated robust dose-dependent amyloid plaque removal in AD. The TRAILRUNNER-ALZ 3 study will evaluate the efficacy and safety of remternetug in participants with early AD. **Methods:** TRAILRUNNER-ALZ 3 is a multicenter, randomized, double-blind, placebo-controlled, parallel group, event-driven Phase 3 study of the effect of subcutaneous remternetug versus placebo in participants with early AD. The primary endpoint is time to clinical progression, defined as an increase from baseline in Clinical Dementia Rating score. Secondary outcome measures include assessments of cognition, behavior and function, descriptive safety, pharmacokinetics, and immunogenicity. This study will implement multiple decentralized elements including cognitive outcome measures assessed by a remote central rater. The study will take a hybrid approach to decentralization by allowing both onsite and remote visits. **Results:** The study is sponsored by Eli Lilly and Company and is being conducted at multiple sites globally. Enrollment is anticipated to open in October 2024. **Conclusion:** The TRAILRUNNER-ALZ 3 study provides the opportunity to assess whether treatment with remternetug delays clinical cognitive and/or functional progression in participants with early AD. Initiating treatment in an earlier population is anticipated to result in a more favorable benefit-risk profile than observed in clinical trials studying more advanced populations. **Keywords:** Alzheimer's disease, cognition, disease progression, remternetug. **Data Deposition:** not applicable. **Disclosures:** K. Biglan, E. Rizvi, T. Wang, M. Hufford, M. Lidogoster, C. Dickson, S. Warner, I. Gueorguieva, Y. Vandenburg and M. Dabora are employees and shareholders of: Eli Lilly and Company. This study is sponsored by Eli Lilly and Company. **References:** 1. Jack CR Jr, et al. Alzheimers Dement. 2024;1-27. https://doi.org/10.1002/alz.13859; 2. Dubois B, et al. Lancet Neurol. 2021;20:484-496. https://doi.org/10.1016/S1474-4422(21)00066-1; 3. Food Drug Administration Center for Drugs Evaluation Research (2024). Early Alzheimer's Disease: Developing Drugs for Treatment Guidance for Industry (FDA Maryland). https://www.fda.gov/media/110903/download; 4. Sims JR, et al. JAMA. 2023;330:512–527. https://doi.org/10.1001/jama.2023.13239; 5. Raket LL, et al. Presented at AAIC; July 28-August 1, 2024; Philadelphia, USA; Session 2-4-FRS-D - Clinical trial analysis strategies, Presentation 2.

LB16- THE ANATOMY OF TAU PET ASSOCIATIONS WITH BIOMARKERS AND COGNITIVE DECLINE IN THE A4 STUDY. J. Sanchez[1], M. Properzi[1], A. Schultz[1], E. Thibault[1], M. Farrell[1], A. Becker[1], B. Hanseeuw[1], P. Aisen[2], R. Raman[2], M. Donohue[2], R. Sperling[1], K. Johnson[1] *(1. Massachusetts General Hospital / Harvard Medical School - Boston (United States), 2. University of Southern California - Los Angeles (United States))*

Background: Emerging evidence suggests that patients in the earliest stages of dementia with elevated amyloid-β (Aβ) and limited tau pathology may benefit most from Alzhiemer's disease (AD)-modifying treatments. Identifying which biomarkers are most predictive of or associated with cognitive decline could enhance trial design and eventually clinical decision-making. This study uses data from the A4 trial and LEARN sub-study to evaluate baseline and longitudinal biomarkers associated with cognitive decline in individuals who were cognitively unimpaired at baseline. In particular, we aimed to explore the specific anatomic progression of tauopathy in A4 study participants, including early tau deposition in medial temporal lobe (MTL) regions, and to elucidate the anatomic-temporal relationship with cognitive decline. **Methods:** The A4 study enrolled cognitively unimpaired participants aged 65-85 with elevated Aβ confirmed by Florbetapir PET. Participants who were otherwise eligible for A4 but low-Aβ were referred to the LEARN sub-study. Participants underwent serial cognitive testing and biomarker assessments, including a sub-sample with tau PET and plasma P-tau217. For the present analysis, we included 203 participants from A4 (placebo group, not treated with solanezumab) and 55 from LEARN who had tau PET data; 221 (85%) had serial tau PET. The mean+/-S.D. follow-up time was 3.6+/-1.8 years. Aβ (Florbetapir) and tau (Flortaucipir) PET were acquired using standard imaging protocols and quantified as standardized uptake value ratios (SUVr). We assessed tau PET SUVr in Freesurfer ROIs including MTL, temporal, parietal and frontal neocortex, as well as vertex-wise across the cortical surface. Annualized rates of change in cognitive and biomarker measures were quantified using linear mixed effects models. Relationships between baseline and change in biomarkers and cognitive outcomes (PACC) were assessed using Pearson correlations. Unique and shared variance among predictors was quantified with hierarchical modeling and variance decomposition. **Results:** Inferior temporal (IT) tau PET change was found to be the most closely-associated biomarker of cognitive decline (r=-0.66, p<0.0001). Whole-brain tau PET analysis confirmed this relationship to be anatomically specific to temporal neocortex. In combined models, plasma P-tau217 change (r vs. PACC change = -0.37, p<0.0001), but not Florbetapir PET change (p=0.7), explained additional unique variance in cognitive decline. Regarding predictors of IT tau PET increase, baseline MTL tau PET (rhinal cortex, r=0.42), IT tau PET (r=0.40), and plasma P-tau217 (r=0.45) performed similarly when adjusting for baseline Aβ. Whole brain analysis showed strongest effects of baseline medial temporal lobe tau predicting IT tau increase. Baseline MTL tau PET and plasma P-tau217 explained unique variance in inferior temporal tau PET progression. **Conclusion:** Consistent with the known anatomical progression of AD tau pathology, inferior temporal tau PET signal was the most closely associated biomarker of cognitive decline, while medial temporal tau PET was the strongest predictor of tau PET change. P-tau217 was also associated with and predictive of cognitive decline and it captured unique variance in cognitive decline in combined models with tau PET. These findings highlight anatomic specificity of tau PET biomarkers in predicting and tracking biomarker and cognitive outcomes in AD and could inform the design of future clinical trials. **Keywords:** imaging, tau PET, plasma P-tau, cognitive decline.

LB18- AI-DERIVED PROGNOSTIC COVARIATES ENHANCE THE PRECISION OF LECANEMAB EFFICACY ASSESSMENTS AND OPTIMIZE ALZHEIMER'S DISEASE CLINICAL TRIALS. V. Devanarayan[1], Y. Ye[1], L. Zhu[1], L. Tian[2], L. Kramer[1], M. Irizarry[1], S. Dhadda[1] *(1. Eisai Inc. - Nutley (United States), 2. Stanford University - Stanford (United States))*

Background: Heterogeneity in patient progression rates negatively affects our ability to evaluate treatment effects in Alzheimer's disease (AD) clinical trials. To reduce this variability, AD prognostic covariates (APCs) that capture this heterogeneity can be employed (Kahan et al., 2014; Zhang & Ma, 2019; FDA guidance, 2023). AI-based models leveraging external control data can generate high-quality APCs by predicting clinical progression from screening data (Schuler et al., 2021). This study evaluates the impact of incorporating model-predicted progression from an individual's baseline characteristics as a covariate in assessing lecanemab, an IgG1 monoclonal antibody targeting soluble aggregated amyloid-beta, across pivotal and confirmatory trials, and examines its broader implications for AD clinical trials. **Methods:** Clinical progression was measured by changes in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score over time. AI-based models from prior Elenbecestat trials (Devanarayan et al., 2024) were applied to screening data to predict progression and generate baseline APCs. Two versions of APC were used: APC.v1 (cognitive and demographic data) and APC.v2 (adding structural MRI features). The treatment effect was measured as the difference in CDR-SB decline with lecanemab 10 mg/kg biweekly versus placebo. Time saved due to delayed progression (TSDP) was also calculated (Wang et al., 2024). A mixed-effects model for repeated measures (MMRM) was employed, including baseline covariates such as medications, cognitive function, ApoE4 status, and study site. The precision of treatment effect estimates from the MMRM with versus without APCs was investigated in the phase-II trial and confirmed in the phase-III trial. Additional simulations were performed to assess impacts on sample size and statistical power. **Results:** In the phase II trial, APC.v1 and APC.v2 explained 21% and 29% of the variance (R^2) in predicting 18-month CDR-SB changes in placebo participants. Adding these APCs to the MMRM reduced the variance of the lecanemab 10 mg/kg biweekly effect by 12.2% (APC.v1) and 16.8% (APC.v2). The treatment effect estimate changed from -0.4 (95% CI: -0.9 to 0.11, p=0.125) without APCs, to -0.57 (95CI: -1.04 to -0.09, p=0.019) with APC.v1, and -0.54 (95%CI: -1 to -0.08, p=0.023) with APC.v2. These findings were confirmed in the phase III trial, where APC.v1 and APC.v2 achieved 15% and 24% R^2, reducing treatment effect variance by 11.1% and 19.1%, respectively. The treatment effect estimate changed from -0.45 (95%CI: -0.67 to -0.23, p=5.32e-05) without APCs to -0.51 (95%CI: -0.71 to -0.3, p=1.52e-06) with APC.v1 and -0.5 (95%CI: -0.69 to -0.3, p=7.28e-07) with APC.v2. TSDP estimates shifted from 5.3 to 5.93 and 5.92 months respectively, with up to 33% variance reduction. These APCs showed broad applicability to other endpoints such as ADAS-Cog-14 and ADCS-MCI-ADL. Simulations showed that incorporating these APCs into MMRM increased power from 80% to 88% and reduced the sample size by up to 25% to detect a 30% slowing in decline in future trials. **Conclusion:** Incorporating AI-derived APCs enhances

treatment effect precision, increases power, and reduces required sample sizes in Alzheimer's trials. This is especially impactful for smaller phase Ib and II studies. Integrating fluid biomarkers could further enhance efficiency. **Keywords:** machine learning, Alzheimer's disease progression, disease heterogeneity, sample size optimization, covariate adjustment, imaging, biomarker integration, clinical trial methodology. **Clinical Trial Registry:** NCT01767311; NCT03887455; https://clinicaltrials.gov. **Disclosures:** All authors, except Lu Tian, are employees of Eisai, Inc. **References:** Kahan BC, Jairath V, Doré CJ, Morris TP. The risks and rewards of covariate adjustment in randomized trials: an assessment of 12 outcomes from 8 studies. Trials. 2014 Apr 23;15:139. doi: 10.1186/1745-6215-15-139. PMID: 24755011; PMCID: PMC4022337. Zhang Z, Ma S. Machine learning methods for leveraging baseline covariate information to improve the efficiency of clinical trials. Stat Med. 2019 May 10;38(10):1703-1714. Doi: 10.1002/sim.8054. Epub 2018 Nov 25. PMID: 30474289. U. S. Food and Drug Administration. Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products. 2023 Schuler A, Walsh D, Hall D, Walsh J, Fisher C; Critical Path for Alzheimer's Disease; Alzheimer's Disease Neuroimaging Initiative; Alzheimer's Disease Cooperative Study. Increasing the efficiency of randomized trial estimates via linear adjustment for a prognostic score. Int J Biostat. 2021 Dec 22;18(2):329-356. Devanarayan V, Ye Y, Charil A, Andreozzi E, Sachdev P, Llano DA, Tian L, Zhu L, Hampel H, Kramer L, Dhadda S, Irizarry M; Alzheimer's Disease Neuroimaging Initiative (ADNI). Predicting clinical progression trajectories of early Alzheimer's disease patients. Alzheimers Dement. 2024 Mar;20(3):1725-1738. doi: 10.1002/alz.13565. Epub 2023 Dec 13. Wang G, Cutter G,Oxtoby NP, et al. Statistical considerations when estimating time-saving treatment effects in Alzheimer's disease clinical trials.Alzheimer's Dement. 2024;20:5421–5433. https://doi.org/10.1002/alz.14035.

LB19- COMPARISON OF ONE-STEP AND TWO-STEP WORKFLOWS FOR DETERMINING PHOSPHORYLATED TAU 217 CUT-OFF POINTS FOR AMYLOID POSITIVITY IN DIFFERENT SUBGROUPS. J. Ahn[1], E.H. Lee[2], H. Yoo[3], B. Park[4], H. Zetterberg[5,6,7,8], K. Blennow[5,6,9,10], F. Gonazalez-Ortiz[5,11], N.J. Ashton[5,12,13,14], K. Kim[4,15,16], S.W. Seo[1,2,16,17] *(1. Alzheimer's Disease Convergence Research Center, Samsung Medical Center - 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, Republic of Korea - Seoul (Korea, Republic of), 4. Biomedical Statistics Center, Research Institute for Future Medicine, Samsung Medical Center - Seoul (Korea, Republic of), 5. Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg - Goteborg (Sweden), 6. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital - Goteborg (Sweden), 7. Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square - London (United Kingdom), 8. UK Dementia Research Institute at UCL, Queen Square - London (United Kingdom), 9. Paris Brain Institute, ICM, Pitié-Salpêtrière Hospital, Sorbonne University, 47, boulevard de l'Hôpital - Paris (France), 10. Neurodegenerative Disorder Research Center, Division of Life Sciences and Medicine, and Department of Neurology, Institute on Aging and Brain Disorders, University of Science and Technology of China and First Affiliated Hospital of USTC Hefei - Hefei (China), 11. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, - Goteborg (Sweden), 12. King's College London, Institute of Psychiatry, Psychology and Neuroscience, Maurice Wohl Clinical Neuroscience Institute, De Crespigny Park - London (United Kingdom), 13. NIHR Biomedical Research Centre for Mental Health and Biomedical Research Unit for Dementia at South London and Maudsley NHS Foundation, De Crespigny Park, Denmark Hill - London (United Kingdom), 14. Centre for Age-Related Medicine - Stavanger (Norway), 15. Department of Data Convergence and Future Medicine, Sungkyunkwan University School of Medicine - Seoul (Korea, Republic of), 16. Department of Digital Health, Samsung Advanced Institute for Health Sciences & Technology (SAIHST), Sungkyunkwan University - Seoul (Korea, Republic of), 17. Department of Health Sciences and Technology, Samsung Advanced Institute for Health Sciences & Technology (SAIHST), Sungkyunkwan University - Seoul (Korea, Republic of))*

Background: The importance of cost-effective screening for Alzheimer's disease (AD) is growing with the introduction of disease-modifying therapies. P-tau217, a promising plasma biomarker for brain amyloid pathology, requires comprehensive discussion on the approaches to its use and interpretation. In this study, we aimed to compare single or two cut-off workflows of phosphorylated tau217 for amyloid positivity, as well as to examine these workflows across different subgroups based on age or diagnosis. **Methods:** We recruited 2,699 participants including cognitively unimpaired (CU, n=665), mild cognitive impairment (MCI, n=1431), and dementia of Alzheimer's type (DAT, n=603) from Korea-Registries to Overcome and Accelerate Dementia research. Plasma p-tau217 levels were measured using the commercial ALZpath p-tau217 single-molecule array assays and Meso Scale Discovery (MSD) Eli Lilly immunoassay. Optimal p-tau217 cut-off points were determined using two methods: a single cut-off based on Youden's index, and a two-step procedure. The two-step process included a first step with p-tau217 stratifying patients into low, intermediate, or high amyloid-β risk with 95% sensitivity and specificity, and a second step applying

Youden's index to the intermediate group, adjusting p-tau217, age, and APOE ε4 carrier. The resulting cut-offs were assessed for balanced accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). We also determined diagnosis- and age-specific cut-off points in the subsets of CU, MCI, DAT, under 65 years (< 65), 65 to 79 years (65~79), and over 80 years (≥ 80). **Results:** For the ALZpath p-tau217, using two cut-off points in all participants showed slightly higher balanced accuracy (90.8%) than a single cut-off (90.2%). In CU group, diagnostic group-specific two cut-off points showed higher balanced accuracy (89.0%) than the total population-based single cut-off point (85.3%). In MCI group, two cut-off points showed higher balanced accuracy (diagnostic group-specific cut-off: 90.6%; total population-based cut-off: 90.5%) than single cut-off points (diagnostic group-specific cut-off: 88.8%; total population-based cut-off: 88.7%). However, in DAT group, the total population-based single cut-off point showed higher balanced accuracy (89.0%) than other conditions. Among the age groups, < 65 group showed higher balanced accuracy with age-specific single cut-off point (95.5%) compared to the total population-based single cut-off point (95.1%). In 65~79 and ≥ 80 groups, total population-based two cut-off points showed higher balanced accuracy (65~79: 90.1%; ≥ 80: 88.4%) than age-specific single cut-off points (65~79: 89.7%; ≥ 80: 86.6%). The MSD p-tau217 findings were generally comparable to ALZpath p-tau217 findings. Overall, subgroup-specific single cut-off points showed comparable or higher balanced accuracy and other parameters compared to total population-based or two cut-off points approaches, only except in CU group, where diagnostic group-based two cut-off points showed higher balanced accuracy (83.0%) than other conditions. **Conclusion:** This study compared p-tau217 cut-off points for amyloid positivity using one- and two-step workflows across various subgroups based on age and diagnosis. Given that the appropriate workflow for determining cut-off points depends on the clinical context and research goals, this study provides valuable insights to support practical decisions in utilizing plasma p-tau217 by offering comprehensive information on cut-off determination workflows and results in different subgroups. **Keywords:** Plasma biomarkers; Phosphorylated tau 217; Cut-off points; Diagnostic performance; Subgroup analysis. **Disclosures:** The authors declare that they have no conflicts of interest to disclose.

LB21- THE ROLE OF PTAU217 IN INTEGRATED AMYLOID AND TAU STAGING: IMPLICATIONS FOR COGNITIVE TRAJECTORIES IN ALZHEIMER'S DISEASE. D. Shin[1], H. Jang[2], K. Kim[1], H. Yoo[1], H. Zetterberg[3,4,5,6], K. Blennow[3,4,7,8], F. Gonzalez-Ortiz[3,4], N.J. Ashton[4,9,10,11], T.A. Day[12], E.H. Lee[1], J. Yun[13], D.L. Na[14], H.J. Kim[14,15,16,17], S.H. Kang[18], K.W. Kim[19], S.E. Kim[20], Y.J. Kim[21], Y. Kim[22], J. Kim[23], C.H. Kim[24] *(1. Departments of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine - Seoul (Korea, Republic of), 2. Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine - Seoul (Korea, Republic of), 3. Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg - Gothenburg (Sweden), 4. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital - Gothenburg (Sweden), 5. Department of Neurodegenerative Disease, UCL Institute of Neurology - London (United Kingdom), 6. UK Dementia Research Institute at UCL - London (United Kingdom), 7. Paris Brain Institute, ICM, Pitié-Salpêtrière Hospital, Sorbonne University - Paris (France), 8. Neurodegenerative Disorder Research Center, Division of Life Sciences and Medicine, and Department of Neurology, Institute on Aging and Brain Disorders, University of Science and Technology of China and First Affiliated Hospital of USTC - Hefei (China), 9. King's College London, Institute of Psychiatry, Psychology and Neuroscience, Maurice Wohl Clinical Neuroscience Institute - London (United Kingdom), 10. NIHR Biomedical Research Centre for Mental Health and Biomedical Research Unit for Dementia at South London and Maudsley NHS Foundation - London (United Kingdom), 11. Centre for Age-Related Medicine, Stavanger University Hospital - Stravanger (Norway), 12. Eli Lilly and Company, Lilly Corporate Center - Indianapolis (United States), 13. Department of Neurology, Soonchunhyang University Bucheon Hospital - Gyeonggi-Do` (Korea, Republic of), 14. Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine - Seoul (Korea, Republic of), 15. Alzheimer's Disease Convergence Research Center, Samsung Medical Center - Seoul (Korea, Republic of), 16. Department of Health Sciences and Technology, SAIHST, Sungkyunkwan University - Seoul (Korea, Republic of), 17. Neuroscience Center, Samsung Medical Center - Seoul (Korea, Republic of), 18. Department of Neurology, Korea University Guro Hospital, Korea University College of Medicine - Seoul (Korea, Republic of), 19. Department of Neurology, Jeonbuk National University Medical School and Hospital - Jeonju (Korea, Republic of), 20. Department of Neurology, Inje University College of Medicine, Haeundae Paik Hospital - Busan (Korea, Republic of), 21. Department of Neurology, Kangdong Sacred Heart Hospital, Hallym University College of Medicine - Seoul (Korea, Republic of), 22. Department of Neurology, Kangwon National University Hospital, Kangwon National University School of Medicine - Chuncheon (Korea, Republic of), 23. Department of Neurology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine - Hwaseong (Korea, Republic of), 24. Department of Neurology, Hallym University Sacred Heart Hospital, Hallym University - Anyang (Korea, Republic of)))*

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by accumulation of amyloid-beta (Aβ) and tau. Recent advancements in positron emission tomography (PET) have enabled the quantification of Aβ and tau uptake, facilitating the differentiation of multiple disease stages based on their regional distribution. The recently developed pTau217 has shown strong correlations with both Aβ and tau uptake. This study aims to investigate the effectiveness of pTau217 in distinguishing integrated Aβ and tau PET stages (A/T stages) and whether it can effectively

differentiate between multiple stages of Aβ PET (Global/Striatum) and tau PET (Medial Temporal/Neocortex). Lastly, we will evaluate if the cut-points of pTau217 accurately reflect cognitive trajectories. **Methods:** A total of 2,923 participants underwent blood sampling for plasma pTau217, measured using the ALZpath p-tau217 assay kit. A subgroup of 160 participants also underwent tau PET imaging. Aβ uptake was quantified using a regional direct comparison centiloid (rdcCL) method. For binary PET staging, Aβ uptake was assessed at the global region-of-interest (ROI) with a threshold of rdcCL 25.5, while tau uptake was evaluated at the medial temporal ROI with a threshold of 1.38 SUVR. For multiple PET staging, Aβ uptake was measured at global (G) and striatum (Str) ROIs, and tau uptake at medial temporal lobe (MTL) and neocortex (NEO) regions, with respective thresholds of rdcCL 25.5, rdcCL 36.8 for Aβ PET, and 1.31 SUVR, 1.43 SUVR for tau PET. **Results:** pTau217 demonstrated excellent accuracy in discriminating Aβ PET-positive (Aβ (+)) cases, with an area under the curve (AUC) of 0.93-0.95, and very good to excellent accuracy for tau PET-positive (tau (+)) cases, with an AUC of 0.88-0.90. The cut-point for pTau217 was higher for tau PET (+) at 0.84 compared to 0.50 for Aβ (+). These cut-points were associated with significant declines in Mini-Mental State Examination (MMSE) scores. In Aβ PET multi-staging, pTau217 effectively differentiated between Aβ PET G(+) Str(-) and G(-) Str(-), achieving an AUC of 0.80-0.85. The cut-point for G(+) Str(+) was higher at 0.69 compared to 0.36 for G(+) Str(-). In tau PET multi-staging, pTau217 effectively discriminated between tau PET MTL(+) NEO(+) and MTL(+) NEO(-) with an AUC of 0.83-0.84, but had lower accuracy (AUC 0.62-0.68) for distinguishing MTL(+) NEO(-) from MTL(-) NEO(-). The cut-point for MTL(+) NEO(+) was 0.40 for MTL(+) and 0.89 for NEO(+), both associated with significant declines in MMSE scores. Taken together pTau217 cutpoints followed this order: were: G(+) < Str(+) = MTL(+) < NEO(+). Among the pTau217 quadruple staging groups, G(+) Str(+)NEO(+) stage showed the most significant MMSE decline, while G(+)Str(+)NEO(-) was more similar to G(+)Str(-)NEO(-) in terms of MMSE decline. **Conclusion:** In conclusion, this study demonstrates that pTau217 effectively distinguishes integrated A/T stages and their cut-points of pTau217 accurately predicts cognitive trajectories, highlighting its potential utility as a biomarker for monitoring AD progression. However, in multi-staging categories, particularly for tau PET, the AUC values are notably lower, suggesting that while pTau217 is a useful tool, its effectiveness may vary across different stages of the disease. **Keywords:** Plasma biomarkes; Phosphorylated tau. **Disclosures:** The authors declared no competing interests.

LB22- TIMING OF CHANGES IN ALZHEIMER'S DISEASE PLASMA BIOMARKERS USING AMYLOID AND TAU PET CLOCKS. M. Milà-Alomà[1], D. Tosun[1], S.E. Schindler[2], Y. Li[2], K.K. Petersen[2], L.M. Shaw[3], J.L. Dage[4,5], Z.S. Saad[6], D.L. Raunig[7], L. Du-Cuny[8], C.E. Rubel[9], J. Coomaraswamy[7], E.G. Rosenbaugh[1], A.W. Bannon[11], W.Z. Potter [12] *(1. University of California San Francisco - San Francisco (United States), 2. Washington University School of Medicine - St. Louis (United States), 3. Perelman School of Medicine, University of Pennsylvania - Philadelphia (United States), 4. Department of Neurology, Indiana University School of Medicine - Indianapolis (United States), 5. Stark Neurosciences Research Institute - Indianapolis (United States), 6. Johnson and Johnson Innovative Medicine - San Diego (United States), 7. Takeda Pharmaceutical Company Ltd. - Cambridge (United States), 8. AbbVie - Rheinland-Pfalz (United States), 9. Biogen - Cambridge (United States), 10. Foundation for the National Institutes of Health - North Bethesda (United States), 11. AbbVie - North Chicago (United States), 12. Highly qualified expert - Philadelphia (United States))*

Background: Plasma biomarkers are increasingly being used in cognitively impaired patients for clinical diagnosis of Alzheimer disease (AD) as well as for identifying cognitively unimpaired individuals with AD pathology for clinical prevention trials. This study examined the trajectories and timings of change in key AD plasma biomarkers, along with established AD biomarkers, using disease progression timelines based on amyloid and tau PET in ADNI participants. **Methods:** The age at amyloid and tau onset (i.e., age at a positive PET scan: Amyloid [18F] florbetapir PET SUVR>0.78 or tau [18F] flortaucipir PET SUVR>1.41) was estimated in all ADNI participants with at least one positive amyloid (n=704) or tau (n=276) PET scan. They also had at least one measure of CSF p-tau181/Ab42, cortical thickness, or cognition (CDR-SB and MMSE). N=197 participants with amyloid onset and n=85 with tau onset had longitudinal plasma measures of Ab42/Ab40, p-tau181, p-tau217, GFAP and NfL from several platforms (C2N Diagnostics PrecivityAD2, Fujirebio Diagnostics Lumipulse, ALZpath Quanterix, Janssen LucentAD Quanterix, NeuroToolKit [Roche Diagnostics International Ltd] and Quanterix Neurology 4-Plex). Tau onset age was used to predict age at symptom onset using data from 17 participants who progressed from cognitively unimpaired (CU) to impaired (CI) during the study duration (Adj R2 = 0.76). Estimated years from amyloid, tau and symptom onset were calculated as the age at each outcome measure minus the estimated amyloid, tau or symptom onset age. Generalized additive mixed models (GAMMs) were used to model biomarker trajectories across the estimated timelines and the earliest time point of biomarker abnormality when compared to a reference group of amyloid-negative CU individuals was identified. In addition, time periods of significant rate of change in biomarkers as a function of each estimated timeline were determined. **Results:** All modeled plasma biomarkers except NfL became abnormal (significantly different from the reference group) prior to amyloid and tau onset. Plasma Ab42/Ab40 was the earliest to reach abnormal levels in the amyloid and clinical timelines (up to -7.3 years prior to amyloid onset or -17.3 prior to symptom onset), followed by CSF p-tau181/Ab42, amyloid PET, p-tau217, p-tau181, tau PET, cognitive and neurodegeneration outcomes. In the tau timeline, GFAP, Ab42/Ab40 and p-tau181 were the earliest to change (-11.5 years, -9.5 and -9.0 years prior to tau onset, respectively). Across the three timelines, Ab42/Ab40 and GFAP showed an early increase and their rate of change reached a plateau, while

p-tau181 and particularly p-tau217 measures showed a steady increase throughout the course of AD progression. Results were generally consistent across plasma assays, with the greatest variability found in Ab42/Ab40 measures. **Conclusion:** Plasma Ab42/Ab40 and GFAP are the earliest to become abnormal in individuals with an estimated amyloid or tau onset age. However, their rate of change over estimated AD progression timelines is limited, suggesting their primary utility may lie in identifying individuals at high risk of progression rather than tracking disease stage. In contrast, p-tau217 measures change monotonically throughout disease progression, reinforcing their potential as biomarkers for staging. **Keywords:** amyloid time, tau time, plasma biomarkers, estimated years from symptom onset. **Disclosures:** M.M.A receives funding from the Alzheimer's Association (AARF-23-1141384). K.P., B.S., D.T., and E.G.R. declared no competing interests. S.E.S. has served on advisory boards and received speaking fees from Eisai and Eli Lilly. She has analyzed data from C2N Diagnostics that was provided to Washington University at no cost. S.E. Schindler has not directly received any research or personal compensation from C2N Diagnostics or any other diagnostics companies. Y.L. is the co-inventor of the technology "Novel Tau isoforms to predict onset of symptoms and dementia in Alzheimer's disease" which is in the process of licensing by C2N. L.M.S. receives funding from the NIA for ADNI4 and from NIA for the University of Pennsylvania ADRC P30 for the Biomarker Core. J.L.D. is an inventor on patents or patent applications of Eli Lilly and Company relating to the assays, methods, reagents and / or compositions of matter for P-tau assays and Aβ targeting therapeutics. J.L.D. has served as a consultant or on advisory boards for Eisai, Abbvie, Genotix Biotechnologies Inc, Gates Ventures, Karuna Therapeutics, AlzPath Inc., Cognito Therapeutics, Inc., and received research support from ADx Neurosciences, Fujirebio, AlzPath Inc., Roche Diagnostics and Eli Lilly and Company in the past two years. J.L.D. has received speaker fees from Eli Lilly and Company. J.L.D. is a founder and advisor for Monument Biosciences. J.L.D. has stock or stock options in Eli Lilly and Company, Genotix Biotechnologies, AlzPath Inc. and Monument Biosciences. Z.S. is employed by Johnson & Johnson Innovative Medicine and may receive salary and stock for his employment. D.L.R. and J.C. receive salary and company stock as compensation for their employment with Takeda Pharmaceutical Company Limited. L.D.C. is employed by AbbVie Deutschland GmbH & Co. C.E.R. is an employee of and may own stock in Biogen. A.W.B. receives salary and company stock as compensation for his employment with AbbVie Inc. W.Z.P. was previously employed by the National Institute of Mental Health, and he is a stockholder in Merck & Co., Inc. Currently residing in Philadelphia, PA, W.Z.P. serves as a consultant for Karuna, Neurocrine, Neumarker, Vaaji and receives grant support from the NIA along with stock options from Praxis Bioresearch.

LB23- EFFECTS OF INITIAL MEDIAL TEMPORAL LOBE TAUOPATHY AND AMYLOID-BETA ON THE TIMELINE TO CATAUSTROPHE. M.E. Farrell[1], E.G. Thibault[1], G. Del Carmen Montenegro[1], J.F. Fu[1], J.C. Price[1], B.J. Hanseeuw[1], J.R. Sims[2], R. Yaari[2], S. Shcherbinin[2], K.C. Holdridge[2], R. Raman[3], M.C. Donohue[3], P. Aisen[3], R.A. Sperling[1], K.A. Johnson[1] *(1. Massachusetts General Hospital, Harvard Medical School - Boston (United States), 2. Eli Lilly and Company - Indianapolis (United States), 3. Keck School of Medicine, University of Southern California - Los Angeles (United States)*

Background: Tau pathology accumulates slowly in the medial temporal lobe (MTL) throughout the lifespan, becoming nearly ubiquitous in older adults. The accelerated proliferation of MTL-tau and its spread into the neocortex in the presence of amyloid-beta (Aβ) is thought to be a critical event in Alzheimer's disease (AD) pathogenesis, known as 'caTAUstrophe'. Optimized targeting of those near caTAUstrophe is crucial for AD prevention trials, but standard PET methods were designed for later disease stages and may be suboptimal during preclinical AD. We recently demonstrated that how far Aβ has spread (spatial extent) was more sensitive than traditional global Aβ level in early disease stages and more strongly linked to tau proliferation. Additionally, the amount of age-related MTL tauopathy is likely an important but overlooked factor in determining the timeline to caTAUstrophe. **Objective:** To evaluate whether the accelerated proliferation of MTL-tau and its spread into the temporal neocortex differ as a function of both the initial level of MTL tauopathy and how far Aβ has spread. **Methods:** 246 cognitively unimpaired older adults (ageyears=71.2±4.7, 61% female, educationyears=16.1±2.8) from the placebo arm of the A4 trial (n=191) and the LEARN study (n=55) with a baseline Aβ-PET scan (florbetapir) and 1-4 tau-PET scans (flortaucipir) over up to 5.5 years were included. Baseline Aβ was quantified using neocortical spatial extent (EXT; %florbetapir+) and classified into 3 groups: Aβ- (EXT<7%), Aβ+ (spreading Aβ, 7%<=EXT>=95%), Aβ++(widespread Aβ; EXT>95%). Tau SUVR was computed in two composites: MTL (entorhinal, parahippocampal, amygdala) and neocortical temporal (TEMP; inferior temporal, middle temporal, fusiform). Baseline MTL-tau high/low status was dichotomized using the mean of the lower gaussian distribution from its fitted gaussian mixture model. This yielded 6 baseline Aβ/MTL-tau groups: Aβ-/MTlow, Aβ-/MThigh, Aβ+/MTlow, Aβ+/MThigh, Aβ++/MTlow, Aβ++/MThigh. Linear mixed effects models assessed change over time in MTL and TEMP-tau by baseline Aβ/MTL group, covarying for baseline age, sex and education and including random participant intercept and slope. **Results:** In Aβ- individuals, MTL-tau increased slowly over time and did not differ by baseline MTL-tau (slopeAβ-/MT_low=0.009, slopeAβ-/MT_high=0.008, time*Aβ-MThigh β(SE)= -.001(0.006), p=0.73). TEMP-tau did not change (slopeAβ-/MT_low=0.002, slopeAβ-/MT_high=0.003). Tau proliferation diverged once Aβ was detected. In MTlow participants, it was not until Aβ was widespread that MTL-tau change exceeded the slow pre-Aβ rate of MTL-tau proliferation (time*Aβ++/MTlow β(SE)=0.010(.005), p=.049) and that TEMP-tau increased (β(SE)=0.017(008), p=.030). In MThigh participants, tau proliferation increased with the first signs of spreading Aβ in the Aβ+/MThigh group, with MTL-tau change exceeding the slow pre-Aβ rate (β(SE)=0.013(004), p<.001) and TEMP-tau change becoming significant (β(SE)=0.024(.005), p<.001). Tau increased further in the Aβ++/MThigh group for both MTL (β(SE)=0.021(004), p<.001) and TEMP (β(SE)=0.036(006), p<.001). **Conclusion:** We observed that the timeline to caTAUstrophe differed based on the level of existing MTL-tau, with rapid tau proliferation at the first signs of Aβ when high but delayed tau proliferation until after Aβ was widespread when low. These results may have important implications for prevention trials, as they suggest the optimal Aβ window for treatment to prevent caTAUstrophe may differ based on initial MTL-tau burden. **Disclosures:** M.E.F., E.G.T., G.D.C.M., J.F.F, and J.C.P have no disclosures. B.J.H. has served as a paid consultant for Biogen, Eisai, and Roche. J.R.S, R.Y., S.S., and K.C.H. are employees of Eli Lilly. R.R. has received research support from Eisai. R.A.S. has served as a paid consultant for Abbvie, AC Immune, Acumen, Alector, Biohaven, Genentech, Janssen, Ionis, Prothena, and Roche. She

has received research support as an investigator for Eli Lilly, and Eisai public private partnership clinical trials. K.A.J. has served as paid consultant for Janssen, Merck, Prothena, and Novartis. He has served as a site coinvestigator for Lilly, Eisai, Janssen, Cerveau, and Biogen. These relationships did not influence the content in the manuscript.

LB24- UPDATING DIAGNOSTIC CRITERIA FOR ALZHEIMER'S DISEASE: RECOMMENDATIONS OF THE INTERNATIONAL WORKING GROUP (IWG). H. Feldman[1], N. Villain[2], G. Frisoni[3], A. Moscoso[4], B. Dubois[2] *(1. Department of Neurosciences, University of California San Diego - San Diego (United States), 2. Sorbonne Université, INSERM U1127, CNRS 7225, Institut du Cerveau - Paris (France), 3. UniGE - Geneva (Switzerland), 4. Wallenberg Centre for Molecular and Translational Medicine, University of Gothenburg, Sweden - Gothenburg (Sweden))*

Background: There has been a movement to define Alzheimer's disease (AD) as a purely biological entity based on evolving and accessible AD biomarkers. This position has been furthered by the recent revisions to the Alzheimer Association (AA) criteria [1] While sharing the overarching goal of fostering effective treatments including prevention of symptoms and dementia, there are important considerations to still address including the readiness of this framework, its context of use, and foreseeable adoption in clinical settings. The International Working Group (IWG) will present its updated 2024 recommendations which offer an alternative definitional view of AD as a clinical biological construct which focus on "at risk" states including "asymptomatic at risk" and "presymptomatic". **Methods:** Evidence review of PubMed July 1, 2020 to September 1, 2024 including search terms biomarker or amyloid or tau or neurodegeneration or preclinical or CSF or PET or Plasma and Alzheimer's disease. Collaborative writing led by the authors and interacting with 41 IWG contributors. **Recommendations:** The IWG contextualizes the AA biomarkers Core 1 (Abeta related proteinopathy and T1 phosphorylated and secreted AD tau) and Core 2 (T2 AD tau proteinopathy) as being risk factors for the clinical expression of AD. While in agreement that Core 1 and Core 2 biomarkers reflect the presence of the pathology/pathophysiology of AD, the IWG is recommending that these biomarkers require a clinical context for their diagnostic application. Where biomarkers are undertaken in people who are asymptomatic or cognitively normal IWG recommends that the communication be focused on their interpretation as risk factors for disease and not for AD diagnosis (aka clinical-biological disease). This is more akin to the example of hypercholesterolemia as a risk factor for cardiac disease. More specifically in a clinical context the IWG recommends the alternative view of a) "asymptomatic at risk" for Core 1, reflecting that this is an increased risk state for progressing to AD dementia and that there is an absence of clear knowledge of when or whether symptoms will develop, b) "presymptomatic" where the aggregate predictive data indicates that the risk of developing dementia approaches that of a penetrant autosomal dominant mutation. This latter designation can be expected to be increasingly applied with better understanding of the combination of some of the biomarkers, resilience factors and the expression rates of symptoms and dementia. These distinctions are particularly important as AD remains a much-feared diagnosis with potential for significant negative consequences with its disclosure in those who might not progress to express symptoms in their lifetime. **Conclusion:** This alternative view of the IWG, may be useful across settings of care and may help clinicians who are facing a context where biomarkers particularly blood based are widely available and reach clinical use despite not being recommended by AA. While the differences in nosology may be seen by some as semantic, their impact to those "at risk" or "affected by disease" could be very different. Further studies of these frameworks are warranted. **Keywords:** Alzheimer's disease, diagnosis, asymptomatic at risk, presymptomatic. **Disclosures:** None directly related to this presentation. He reports grant funding to UCSD from Allyx Therapeutics, Biohaven Pharmaceuticals, Vivoryon, and LuMind Foundation; service agreements with UCSD for consulting activities with LuMind, Axon Neuroscience, Novo Nordisk, Arrowhead Pharmaceuticals, Roche/Genentech Pharmaceuticals (DMC/DSMB), Tau Consortium (SAB), Janssen Research & Development (DSMB), Biosplice Therapeutics; support for travel, Royal Society of Canada, Translating Research in Elder Care (TREC), Association for Frontotemporal Dementia (AFTD), and Rainwater Charitable Foundation; and a philanthropic donation for the Epstein Family Alzheimer Research Collaboration. For these activities, no personal funds have been received with all payments to UC San Diego. A. Moscoso reports no disclosures. **References:** [1] Jack CR et al Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alz & Dementia 2024 DOI: 10.1002/alz.13859.

LB25- PLASMA BIOMARKER DATA INDICATES CLINICAL ACTIVITY OF NEFLAMAPIMOD IN DEMENTIA WITH LEWY BODIES (DLB) IS MEDIATED THROUGH EFFECTS ON THE BASAL FOREBRAIN CHOLINERGIC SYSTEM. J. Alam[1], C. Teunissen[2] *(1. CervoMed Inc. - Boston (United States), 2. Amsterdam UMC, location Vrije Universiteit - Amsterdam (Netherlands))*

Background: Degeneration of cholinergic neurons in the basal forebrain is a hallmark of dementia with Lewy bodies (DLB). As the disease advances, in association with developing biomarker evidence of amyloid and/or tau pathology, patients also develop medial temporal lobe atrophy (MTA). Neflamapimod, which in preclinical studies rescues basal forebrain cholinergic neuronal loss, in a phase 2a ("AscenD-LB") clinical study in DLB demonstrated positive effects on multiple clinical endpoints associated with cholinergic function; with the clinical effects most prominent in patients without elevation in plasma ptau181 (i.e., early-stage DLB). Recently, plasma glial-fibrillary-acidic-protein (GFAP) has emerged as a potential biomarker of the neurodegenerative disease process in DLB, both in early-stage DLB (e.g. GFAP is elevated in prodromal DLB when cholinergic degeneration is predominant), as well as a biomarker of disease progression in patients with advanced DLB (i.e. after MTA is present). Herein, we report on the effects of neflamapimod on plasma GFAP in AscenD-LB and correlate the results to emerging understanding of DLB pathogenesis. **Methods:** GFAP and ptau181 levels (pg/mL) in stored plasma samples from AscenD-LB were measured using Simoa® platform. Overall design of AscenD-LB and results have been published. Early-stage vs. advanced DLB was defined prospectively as a pre-treatment plasma ptau181 $<$ or $\geq$ 2.2 pg/mL, respectively. This a cut-off is based on literature to identify both amyloid and tau pathology in patients with AD, and levels above the cutoff have been associated with positive temporal lobe tau PET signal in patients with DLB. **Results:** Baseline GFAP levels, which were elevated compared to historical controls, were highly correlated to baseline CDR-SB scores ($r=0.52$, $p<0.0001$). In addition, at baseline, GFAP was higher ($p=0.02$, mean 282 vs. 215) in

advanced DLB (n=29) versus that in early-stage DLB (n=28). At the end of treatment (week 16), in early-stage DLB patients, a significant reduction (p=0.04) in GFAP levels was seen with neflamapimod (n=15, change from baseline -10.6±6.4) compared to placebo (n=13, change from baseline +14.1±10.2), while no placebo-neflamapimod differences were seen in advanced DLB. Further, in neflamapimod-treated participants with early-stage DLB there was a significant correlation (r=0.54, p=0.036) between the effects on GFAP and clinical outcomes. Specifically, in these participants, increased GFAP was associated with worsening CDR-SB, while reduction in GFAP was associated with improvement on CDR-SB; a correlation not seen in placebo-recipients with early-stage DLB (r=0.33, p=NS). **Conclusion:** The selective effect of a cholinergic degeneration directed therapeutic such as neflamapimod on GFAP in early-stage DLB further supports that basal forebrain cholinergic degeneration is the primary driver of disease in patients with DLB who have not progressed to the point of having MTA. Conversely, the results affirm neflamapimod having the intended pharmacological effect on the basal forebrain cholinergic system and the clinical activity being mediated by these effects. **Keywords:** Dementia with Lewy bodies, plasma biomarkers, cholinergic degeneration. **Disclosures:** JA is CEO of CervoMed Inc, a publicly traded company that is developing neflamapimod as a treatment for **References:** Jiang et al, Nature Communications, 2022, DOI: 10.1038/s41467-022-32944-3; Alam et al, Neurology, 2023, DOI: 10.1212/WNL.0000000000207755; Prins, et al, JPAD, 2024, DOI: 10.14283/jpad.2024.36; Kentarci et al, Brain Communications, 2022, DOI: 10.1093/braincomms/fcac013; Diaz-Galvan et al, Alzheimers Dement, 2024, DOI: 10.1002/alz.13653.

LB26- SEX MODERATES RELATIONSHIPS BETWEEN P-TAU217 AND LONGITUDINAL TAU-PET: 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.A.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: Multiple neuroimaging studies using positron emission tomography (PET) show that women exhibit higher levels of insoluble tau aggregates relative to age-matched men, particularly in the context of high amyloid-β (Aβ). Whether higher tau aggregation in women is due to sex differences in upstream soluble phosphorylated tau (p-tau) levels is unclear. As the efficacy of new AD treatments is influenced by tau levels, we examined sex differences in soluble p-tau217 concentrations (using electrochemiluminescence immunoassay) and investigated how this difference was associated with tau-PET outcomes. **Methods:** Participants were 1303 clinically normal individuals (mean age 71.8; 767 women [59%], 647 APOEε4-carriers [55%]) with baseline p-tau217 and Aβ-PET from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4; N=1010) trial and the companion Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN; N=293) study. 376 participants also underwent baseline and longitudinal 18F-Flortaucipir (FTP) tau-PET (mean age 72.1; 213 women [57%]). Seven frontal, temporal and parietal brain regions previously demonstrating sex differences were selected as tau-PET outcomes (rostral middle frontal gyri, fusiform gyrus, inferior temporal and parietal gyri, the superior parietal lobule, precuneus and lateral occipital cortex). The average tau-PET follow-up time was 3.4 years (SD=1.6 years, range=1.3-7.1 years). At baseline, sex differences (and sex × Aβ-PET interaction) on baseline p-tau217 levels were investigated using simple linear models. Longitudinally, random-effects models estimated sex × baseline p-tau217 interactions on each tau region, including participant-specific intercepts and slopes. All models covaried baseline age, years of education and APOE4 carrier status. βs were standardized and P values were FDR corrected (7 comparisons for each tau region). **Results:** Women exhibited elevated p-tau217 concentrations relative to men, particularly at higher levels of global Aβ (β=-0.16, P=0.008). Sex moderated associations between p-tau217 and inferior temporal (β=-0.36, P=0.007), inferior parietal (β=-0.34, P=0.008) and superior parietal (β=-0.24, P=0.045) tau-PET at baseline, such that women had higher levels of tau pathology relative to men in the setting of elevated p-tau217 concentrations. Over time, sex also moderated the effect of p-tau217 on tau accumulation in the middle frontal gyri (β=-0.09, P=0.007), inferior parietal gyri (β=-0.09, P=0.021), superior parietal lobule (β=-0.08, P=0.022) and precuneus (β=-0.10, P=0.018), such that women with elevated baseline p-tau217 exhibited faster rates of regional tau aggregation relative to men with elevated baseline p-tau217. **Conclusion:** In the A4 and LEARN studies, amyloid-associated soluble p-tau levels were elevated in women compared to men. The association between elevated p-tau and greater tau aggregation was more apparent in women. These findings suggest that sex differences in tau-related processes occur upstream of tau aggregation and proliferation, which may have considerable implications for therapeutic interventions and interpretations of trial outcomes by sex. **Keywords:** Sex differences, ptau217, tau-PET, Longitudinal. **Disclosures:** RAS 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. RAR 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.

LB27- PERFORMANCE OF THE LILLY SPX P-TAU217 BLOOD-BASED IMMUNOASSAY (LDT) IN CLINICAL VALIDATION COHORT SUBPOPULATIONS. M.E. Hodsdon[1], S.C. Burnham[1], A. Morris[1], M.J. Pontecorvo[1], R.C. Beck[1] *(1. Eli Lilly and Company - Indianapolis (United States))*

Background: Blood-based biomarkers are more accessible and scalable than positron emission tomography (PET) or cerebrospinal fluid tests, offering great potential to aid in the diagnosis of Alzheimer's disease (AD).1 The objective of this study was to evaluate the performance of a plasma P tau217 immunoassay for identifying amyloid PET-detectable AD pathology in subgroups of clinical validation cohort subjects stratified by sex, age (<75 vs. ≥75 years), race (white vs. non-white), ethnicity (Hispanic/Latino vs. non-Hispanic/Latino), and apolipoprotein E (APOE) ε4 carrier status. **Methods:** Plasma samples were acquired from subjects screened in the donanemab Phase 3 trial (NCT04437511). Plasma P-tau217 concentration was analyzed using a chemiluminescent immunoassay on the Quanterix SP-X platform. Receiver Operating Characteristic (ROC) analysis against amyloid (Aβ) PET status was used to establish 2 assay cut-points to define positive, negative, and indeterminate values, as previously

described.2 Aβ+ by PET was defined as ≥24.1 Centiloids. Performance characteristics of the assay, including sensitivity, specificity, positive predictive value, and negative predictive value were calculated within subgroups (sex, age, race, ethnicity, APOE ε4 carrier status). **Results:** Overall, plasma samples from 2071 subjects were included, of which 53.3% were female, 55.2% were <75 years of age, 88.8% were white, 16.3% were Hispanic/Latino ethnicity, and 50.7% were APOE ε4 carriers. The overall percentage of Aβ+ subjects was 65.3%; 85.3% of APOE ε4 carriers and 37.1% of subjects with Hispanic/Latino ethnicity were Aβ+. Mean (standard deviation) Mini Mental State Examination score was 24.8 (2.5) in the overall population, and was similar across subgroups. The area under the ROC curve for P-tau217 to identify Aβ+ was 0.915 in the overall population. Stratification of subjects into high, low, and indeterminate groups resulted in accuracy of 91.0% for the overall population. Similar accuracy was observed for cohort subgroups, albeit with a slightly lower value for the Hispanic/Latino (86.8%) subgroup. Positive and negative predictive values of 95.0% and 83.8% were observed in the overall population; the corresponding values for the subgroups were: 95.5% and 82.4%, females; 94.4% and 85.2%, males; 94.3% and 85.0%, <75 years; 95.6% and 80.9%, ≥75 years; 95.1% and 83.4%, white; 94.3% and 85.5%, non-white; 87.2% and 86.7%, Hispanic/Latino; 95.6% and 82.3%, non-Hispanic/Latino; and 97.1% and 64.9%, APOE ε4 carriers; 90.9% and 89.8%, non-APOE ε4 carriers. The percentage of subjects in the indeterminate group was 18.4% overall (59.7% were Aβ+) and for subgroups was: 17.7% (54.9%), females; 19.1% (64.7%), males; 18.2% (53.4%), <75 years; 18.6% (67.4%), ≥75 years; 19.0% (60.4%), white; 13.9% (50.0%), non-white; 21.1% (36.6%), Hispanic/Latino; 17.8% (64.2%), non-Hispanic/Latino; and 17.7% (80.0%), APOE ε4 carriers; 19.2% (40.5%), non-APOE ε4 carriers. **Conclusion:** High concordance of plasma P-tau217 concentration with amyloid PET for identification of amyloid pathology was observed across subgroups by sex, age, race, ethnicity, and APOE ε4 carrier status. Positive and negative predictive values appeared to vary within the ethnicity and APOE status subgroups, consistent with observed variations in Aβ+ prevalence in these subgroups. These data support the potential clinical utility of the Lilly plasma P tau217 assay in multiple subpopulations to aid in the diagnosis of AD. **Keywords:** Alzheimer's disease, amyloid, P-tau217, positron emission tomography. **Clinical Trial Registry:** NCT04437511; https://clinicaltrials.gov. **Data Deposition:** not applicable. **Disclosures:** M. E. Hodsdon, S. C. Burnham, A. Morris, M. J. Pontecorvo, and R. C. Beck are employees and shareholders of: Eli Lilly and Company. This study is sponsored by Eli Lilly and Company. **References:** 1. Schindler SE, et al. Nat Rev Neurol. 2024;20:426-439. https://doi:10.1038/s41582-024-00977-5; 2. Hodsdon ME, et al. Presented at AAIC; July 28-August 1, 2024; Philadelphia, USA; P#95087.

LB28- TIMING AND DURATION OF ADVERSE EVENTS DURING 24 WEEKS OF BREXPIPRAZOLE TREATMENT IN PATIENTS WITH AGITATION ASSOCIATED WITH DEMENTIA DUE TO ALZHEIMER'S DISEASE: RESULTS FROM A RANDOMIZED TRIAL AND AN EXTENSION TRIAL. A.P. Porsteinsson[1], M. Brubaker[2], S.R. Chumki[2], A.M. Palma[2], D. Wang[3], Z. Zhang[2], P. Such[4], C.B. Montano[5] *(1. University of Rochester Alzheimer's Disease Care, Research and Education Program (AD-CARE) - Rochester (United States), 2. Otsuka Pharmaceutical Development & Commercialization Inc. - Princeton (United States), 3. Lundbeck LLC - Deerfield (United States), 4. H. Lundbeck A/S - Copenhagen (Denmark), 5Connecticut Clinical Research - Cromwell (United States))*

Background: Brexpiprazole is approved in a number of countries for the treatment of agitation associated with dementia due to Alzheimer's disease. Elderly patients with dementia may be particularly vulnerable to antipsychotic adverse events, which may offset advantages of treatment. Furthermore, because of safety concerns in this population, it is suggested that antipsychotics are used at the lowest effective dose, and with caution over treatment duration. It is therefore vitally important to study antipsychotic safety over the long term. This post hoc analysis of clinical trial data aimed to evaluate the timing and duration of treatment-emergent adverse events (TEAEs) throughout up to 24 weeks of brexpiprazole treatment. **Methods:** Data were included from a Phase 3, 12-week, randomized, double-blind, placebo-controlled trial of brexpiprazole in patients aged 55–90 years with agitation associated with dementia due to Alzheimer's disease (ClinicalTrials.gov identifier: NCT03548584 [Trial 213]) and a 12-week extension trial (NCT03594123 [Trial 182]). In the randomized trial, patients were randomized 2:1 to brexpiprazole (2 or 3 mg/day; titration: Days 1–7, 0.5 mg/day; Days 8–14, 1 mg/day; Days 15–28, 2 mg/day; Day 29 onwards, assigned dose) or placebo. The extension trial enrolled patients who had completed 12 weeks of treatment with brexpiprazole or placebo in the randomized trial; all patients received brexpiprazole (2 or 3 mg/day). In this post hoc analysis, data were analyzed for the subgroup of patients who were treated with brexpiprazole in the randomized trial and also continued into the extension trial. Data from the two trials were combined to obtain data for up to 24 weeks of treatment with brexpiprazole 2 or 3 mg/day (FDA-approved dose). Incidence of TEAEs was determined over the full 24 weeks, and over each 2-week interval. Time-to-event analyses were performed to first occurrence of any TEAE, and are presented using descriptive statistics and Kaplan–Meier methodology. For TEAEs with reported end dates, duration was also determined (which may be biased towards events with shorter duration). **Results:** The analyzed sample comprised 163 patients who received brexpiprazole in the randomized trial and were also treated with brexpiprazole in the extension trial. Across the full 24-week treatment period, TEAEs were reported by 79/163 (48.5%) patients. The incidence of all TEAEs in 2-week intervals was 2.5–12.9% during the first 12 weeks and 1.3–8.9% in the second 12 weeks. Median (interquartile range [IQR]) time to first TEAE was 7.4 (3–12) weeks. Median (IQR) duration of all TEAEs was 3 (1–8) days. Kaplan–Meier curves indicated that, among patients who had not already experienced a TEAE in the randomized trial, TEAEs were rare throughout the extension trial. **Conclusion:** The incidence of TEAEs remained low over 24 weeks in patients with agitation associated with dementia due to Alzheimer's disease treated with brexpiprazole, indicating that longer-

term treatment with brexpiprazole was not associated with increased risk of TEAEs. This post hoc analysis was restricted to patients who enrolled in the extension trial, which may have resulted in a sample better able to tolerate brexpiprazole. **Keywords:** agitation; brexpiprazole; Alzheimer's disease; safety. **Disclosures:** Anton P. Porsteinsson has received personal fees from Acadia Pharmaceuticals, Athira, BMS, Cognitive Research Corp, IQVIA, Lundbeck, Novartis, ONO Pharmaceuticals, Otsuka, WCG, WebMD, and Xenon, and grants to institution from Athira, Biogen, Cassava, Eisai, Eli Lilly, Genentech/Roche, Vaccinex, NIA, NIMH, and DOD. He is a member of the Scientific Advisory Board of Alzheon, Athira, and Cognition Therapeutics. Malaak Brubaker, Sanjeda R. Chumki, Anton M. Palma and Zhen Zhang are full-time employees of Otsuka Pharmaceutical Development & Commercialization Inc. (Princeton, NJ, USA). David Wang is a full-time employee of Lundbeck LLC (Deerfield, IL, USA). Pedro Such is a full-time employee of H. Lundbeck A/S (Valby, Denmark). C. Brendan Montano has received consulting fees from AbbVie, Acadia, Alkermes, Arbor, Eisai, Neos, Novo Nordisk, Otsuka, Sunovion, Supernus, and Takeda, and has received payment/honoraria from AbbVie, Arbor, Eisai, Otsuka, and Takeda. This work was supported by Otsuka Pharmaceutical Development & Commercialization Inc. (Princeton, NJ, USA) and H. Lundbeck A/S (Valby, Denmark). Writing support was provided by Chris Watling, PhD, and Liz Kelly, BSc, of Cambridge (a division of Prime, Knutsford, UK), funded by Otsuka Pharmaceutical Development & Commercialization Inc. and H. Lundbeck A/S.

LB29- THE USE OF PLASMA BIOMARKERS FOR THE PREDICTION OF AMYLOID POSITIVITY. F.I. De Simone[1], L. Buitrago[1], N. Benina[1], R.R. Radwan[1], D. Hawkin[2], A. Moghekar[3], M. Albert[3], O. Hansson[4,5], E. Stomrud[4,5], P. Sachdev[6], D. Dickson[1] *(1. Fujirebio Diagnostics, Inc. - Malvern, Pa (United States), 2. Scottsdale Scientific LLC - Austin, TX (United States), 3. Department of Neurology, Johns Hopkins School of Medicine - Baltimore, MD (United States), 4. Clinical Memory Research Unit, Department of Clinical Sciences Malmö, Lund University - Lund (Sweden), 5. Memory Clinic, Skane University Hospital - Malmö (Sweden), 6. Eisai Inc. - Nutley, NJ (United States))*

Background: Plasma biomarkers for amyloid pathology prediction have the potential to revolutionize the diagnostic work-up of Alzheimer's dementia (AD) in clinical practice, offering significant advantages over CSF biomarkers and PET1,2,3,4,5,6. In the early stages of amyloid accumulation, the combination of plasma Aβ proteins with plasma pTau217 has been shown to be more sensitive than pTau217 alone for detecting AD7. This study evaluated plasma biomarkers' ability (alone or in combination) to predict amyloid positivity determined by PET and/or CSF. **Methods:** This study assessed the performance of plasma pTau217, plasma β-Amyloid1-42/β-Amyloid1-40, and plasma pTau217/β-Amyloid1-42 ratios by evaluating the PET and/or CSF-positive predictive value (indicated as Predictive Value, PV) and frequency of results (FR) of the tested samples. The goal was to assess the potential use of these biomarkers as a rule-out method (confirming 95% negative predictive value (NPV)) and a triage method (confirming 85% positive predictive value (PPV) and 95% NPV)8. NPV was calculated first for specificity determination, followed by PPV for sensitivity determination using the indicated biomarker configurations as candidate methods against an available comparator (FDA-cleared amyloid tracer and/or FDA-cleared CSF biomarker ratios). In this exercise, we also evaluated the impact on Likelihood Ratios (Positive and Negative PLR/NLR) to capture all possibilities (pre-test/post-test, disease/disease-free) to eliminate the impact of AD prevalence on the dataset. Based on screening for an amyloid negativity rate of 60% and a standard error of ≤ 0.15, a sample size of 208 human biobanked K2EDTA plasma from pharmaceutical and observational studies was used. The potential impact of ApoE4 status (prototyping), age, and sex were also evaluated. All plasma testing was performed on a LUMIPULSE G1200 System. **Results:** In this study (prevalence of amyloid pathology ~ 55%), the use of plasma β-Amyloid1-42/β-Amyloid1-40 ratio met the high NPV criteria (NPV ≥ 95%), while it did not meet the target PPV of ≥ 85%. Plasma pTau217 alone, on the other hand, achieved PPV=92.4% and FR of 35.0% but achieved NPV=91.8%. Furthermore, a significant percentage of the population (35.1%) fell between the two groups. Plasma pTau217/β-Amyloid1-42 ratio not only achieved both targets of high PPV and NPV (94.6% and 95.7%, respectively) but identified a smaller percentage of subjects within the "indeterminate" group (20.2%) and achieved the target PLR of 14. Furthermore, including age, sex, and/or ApoE4 status did not impact the performance of the plasma biomarkers evaluated in this study. **Conclusion:** In this study, the plasma pTau 217/β-Amyloid 1-42 ratio showed better performance in identifying patients that would be classified as likely positive or unlikely to have amyloid pathology based on amyloid PET/CSF results, compared to plasma pTau217 alone and the plasma β-Amyloid1-42/β-Amyloid1-40 ratio. Furthermore, the plasma pTau 217/β-Amyloid 1-42 ratio significantly reduced the number of subjects in the indeterminate zone compared to plasma pTau217 alone. These results highlight the high performance of the pTau 217/β-Amyloid 1-42 Plasma Ratio in predicting amyloid positivity. **Keywords:** Lumipulse G1200 System, pTau217/β-Amyloid 1-42 Plasma Ratio, Blood-based Biomarkers, Amyloid positivity prediction. **Disclosures:** Francesca I. De Simone, Luna Buitrago, Natalya Benina, Rachel R. Radwan, and Diana Dickson are employed by Fujirebio Diagnostics Inc.; Douglas Hawkin is a statistical consultant for Fujirebio Diagnostics Inc.; Abhay Moghekar receives research support from Fujirebio Diagnostics, Inc.; Marilyn Albert has nothing to disclose; Marilyn Albert has nothing to disclose; Sara Ho has nothing to disclose; 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; Pallavi Sachdev is an employee of Eisai. **References:** Hansson O. Biomarkers for neurodegenerative diseases. Nat Med. 2021 Jun;27(6):954-963. doi: 10.1038/s41591-021-01382-x. Epub 2021 Jun 3. PMID: 34083813. 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LB30- AMYLOID MODIFIES THE ASSOCIATION BETWEEN LATE-LIFE BMI AND LONGITUDINAL COGNITION IN COGNITIVELY UNIMPAIRED INDIVIDUALS. W.Y.W. Yau[1,2], R. Raman[3], S. Wang[3], N. Aggarwal[4], A. Brickman[5], J. Chhatwal[1,2,6], P. Cogswell[7], J. Graff-Radford[7], J. Pillai[7], P. Vemuri[7], M. Rafii[3], P. Aisen[3], R. Sperling[1,2,6], T. A4 And Learn Study Teams[8] *(1. Massachusetts General Hospital - Boston (United States), 2. Harvard Medical School - Boston (United States), 3. University of Southern California - San Diego (United States), 4. Rush University Medical Center - Chicago (United States), 5. Columbia University - New York (United States), 6. Brigham and Women's Hospital - Boston (United States), 7. Mayo Clinic - Rochester (United States), 8. Alzheimer Clinical Trials Consortium - Https://www.actcinfo.org/a4-Study-Team-Lists/)*

Background: While there is growing consensus that midlife obesity is associated with increased risk of Alzheimer's disease (AD), the relationship between late-life obesity and AD risk is less clear. Prior studies demonstrated both detrimental and protective effects of elevated late-life BMI on cognitive decline. Given the growing interest in combination AD prevention trials targeting both amyloid and vascular risk factors in older individuals, it is essential to establish a clear understanding of how late-life BMI and amyloid burden may interact to influence cognitive decline. **Methods:** We leveraged longitudinal data from the A4 and LEARN studies. Detailed methodology has been previously described. Briefly, individuals aged 65-85 who were cognitively unimpaired at baseline underwent amyloid PET imaging (18F-Florbetapir) using whole cerebellum as reference. Those with elevated baseline amyloid burden were included in A4 and were randomized to receive Solanezumab (N=564) or Placebo (N=583). Individuals without elevated amyloid were included in LEARN (N=521) and were followed using the same protocol. Cognition was assessed longitudinally using the Preclinical Alzheimer Cognitive Composite (PACC) score over 4.1±1.5 years. Combining A4 and LEARN participants, we examined for interactive effects between baseline BMI and amyloid burden on cross-sectional (linear regression) and longitudinal (natural cubic spline model) PACC scores, adjusting for age, sex, education, APOE4 carrier status, cognitive test version, and study/treatment assignment. **Results:** We included 1668 participants across A4 and LEARN (baseline age 71.5±4.7, 59.9% female, amyloid burden 47±40 Centiloid, BMI 28±5). At baseline, higher BMI was associated with lower PACC scores (β=-0.03 [-0.05 to -0.003], p=0.02), after adjusting for amyloid and other covariates. There was no BMI*Amyloid interaction on baseline PACC (p=0.54). Longitudinally, we identified a significant interaction between baseline BMI and amyloid burden on longitudinal PACC performance (p<0.001). To better understand the direction of this interaction, we visualized predicted PACC trajectories across representative levels of BMI (mean±1SD) and amyloid burden (25th, 50th and 75th percentiles), respectively. When baseline amyloid burden was low (13 Centiloid), lower/normal BMI was associated with a more favorable PACC trajectory. By contrast, when baseline amyloid was elevated at moderate (42 Centiloid) and especially at high (74 Centiloid) levels, lower/normal BMI was associated with more rapid cognitive decline over time. **Conclusion:** In a large group of cognitively unimpaired older adults from A4 and LEARN, we found that lower BMI was associated with better baseline cognition regardless of amyloid burden. By contrast, the relationship between BMI and longitudinal cognitive trajectories was modified by baseline amyloid burden. When there were low levels of baseline amyloid, lower/normal BMI was associated with more favorable cognitive trajectories, suggesting obesity may be a negative risk factor in these individuals. However, when there was substantially elevated baseline amyloid, lower/normal BMI was associated with accelerated cognitive decline, which potentially reflect increased physiological vulnerability to underlying AD pathology. Taking the current findings in context of existing literature, our results suggest that targeting obesity as a prevention strategy for late-life cognitive decline may be best implemented in older individuals with minimal to very early amyloid accumulations, or in younger individuals prior to late-life. **Keywords:** Preclinical Alzheimer's disease, Obesity, Amyloid, Cognitive decline. **Clinical Trial Registry:** NCT02008357; https://clinicaltrials.gov. **Data Deposition:** https://www.a4studydata.org. **Disclosures:** Dr. Yau has received research support from the National Institutes of Health (NIH). Dr. Raman has received research support from the NIH, the Alzheimer's Association, American Heart Association, and Eisai (public-private partnership). Shunran Wang has received research support from the NIH and Eisai (public-private partnership). Dr. Aggarwal has received research support from the NIH. Dr. Brickman has received personal fees from Cognition Therapeutics, Cognito Therapeutics, and IQVIA outside the submitted work; in addition, Dr Brickman had a patent issued (9867566) and has a patent pending (20230298170),

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LB31- RETINAL HYPERSPECTRAL IMAGING AND BLOOD-BASED BIOMARKERS DEMONSTRATE COMPARABLE PERFORMANCE FOR PREDICTING BRAIN AB PATHOLOGY: A HEAD-TO-HEAD COMPARISON FROM THE BIO-HERMES-001 STUDY. S. Grapentine[1], A. Hazan[1], E. Shaked[1], J. Giordano[1], C. Bornbaum[1], D. Beauregard[2] *(1. RetiSpec - Toronto (Canada), 2. Global Alzheimer's Platform Foundation - Washington, Dc (United States))*

Background: Given the biological parallels between the retina and brain, retinal hyperspectral imaging (rHSI) offers a promising solution to the increasing demand for non-invasive, scalable diagnostic tools for the detection of Alzheimer's disease (AD) markers. Building on our previous work demonstrating the feasibility of combining rHSI with an artificial intelligence (AI)-based model to predict Aβ-PET status in unblinded and blinded data, we evaluate the predictive accuracy of RetiSpec's AI-based rHSI model across Cognitively Normal (CN), Mild Cognitive Impairment (MCI) and Probable AD cohorts. To contextualize the predictive performance of the retina-based AI-model against alternative diagnostic methods, it was compared to the performance of emerging blood-based markers (BBM)s on the same participant group. **Methods:** This analysis was a substudy of the Bio-Hermes-001 prospective cohort study. A total of 360 participants, aged 60-85 were enrolled across 6 sites (20% participants from underrepresented groups) and were stratified into 3 cohorts: Cognitively Normal (CN), Mild Cognitive Impairment (MCI) and Probable AD, as described in Bio-Hermes-001 study. The primary outcome was the AI-model's performance in predicting Aβ-PET status across cohorts, assessed through receiver operator characteristic (ROC) curve analysis with an area under the curve (AUC) performance threshold ≥0.7, using Aβ-PET status as the comparator. Additionally, the predictive performance was evaluated relative to 4 emerging BBMs, using 2 versions of most tests: pTau181, pTau217, Aβ42/Aβ40 ratio, and an Alzheimer's Probability Score (APS). Sample size for BBM analysis was limited to participants with results from all tests for comparison. **Results:** N=271 participants with sufficient image quality were evaluated. The retina-based AI-model exceeded predictive performance threshold in all cohorts, with the strongest accuracy in MCI (AUC=0.83, n=74), followed by CN (AUC=0.75, n=135), and Probable AD (AUC=0.74, n=62). Of these, n=187 (86%) were able to be evaluated by all 8 tests, primarily due to insufficient target protein levels for detection by certain BBMs. The retina-based AI-model exceeded the performance threshold, achieving an AUC of 0.76, performing comparably to BBM AUCs in predicting Aβ-PET status. BBMs achieved AUCs of 0.80 and 0.79 for pTau181 tests, 0.86 and 0.76 for pTau217 tests, 0.78 and 0.80 for Aβ42/Aβ40 test and 0.84 for the APS test. The retina-based AI model's sensitivity of 0.74 and specificity of 0.65 were in line with BBMs sensitivity (range=0.74-0.85; median AUC=0.795) and specificity (range=0.65-0.72; median AUC=0.68). The retina-based AI-model's positive predictive value and negative predictive value were also within the ranges observed for the BBMs, further demonstrating its similar performance to emerging BBMs. **Conclusion:** The AI-based rHSI model successfully predicted Aβ-PET status across cohorts, particularly in the MCI disease stage, with performance comparable to emerging BBMs. This demonstrates its potential as a scalable test to inform AD diagnosis and provide real-time, non-invasive decision support at the point-of-care, enabling more efficient access to treatment. **Keywords:** Alzheimer's disease, Amyloid burden, Artificial Intelligence, AI, retinal imaging, biomarker, diagnostics, screening. **Clinical Trial Registry:** NCT04733989. **Disclosures:** Co-authors employed by RetiSpec either hold equity ownership or company options. **Acknowledgements:** We wish to thank the many participants and care partners who generously shared their time with us throughout this study.

LB32- PARTICIPANTS ENROLLED IN THE REWIND-LB CLINICAL TRIAL: A LARGE COHORT OF PATIENTS WITH DEMENTIA WITH LEWY BODIES (DLB) WITHOUT TEMPORAL LOBE NEURODEGENERATION, AS DEFINED BY ABSENCE OF ELEVATION IN PLASMA PTAU181. S. Gomperts[1], J.P. Taylor[2], P. Maruff[3], A. Amanda[4], B. Kelly[4], J. John[4], G. James[5] *(1. Massachusetts General Hospital - Charlestown (United States), 2. Newcastle University - Newcastle Upon Tyne (United Kingdom), 3. Cosgstate Ltd - London (United Kingdom), 4. CervoMed - Boston (United States), 5. U. of Miami Miller School of Medicine - Boca Raton (United States))*

Background: The RewinD-LB phase 2b clinical study is evaluating the investigational drug neflamapimod (oral p38¤ kinase inhibitor that targets basal forebrain cholinergic degeneration; Jiang, 2022) in patients with DLB. It is designed to confirm the findings from a phase 2a study of neflamapimod that demonstrated positive effects on multiple clinical endpoints measuring cognition and/or function (Prins, 2024) and most prominently in patients without evidence of tau-related temporal lobe neurodegeneration, as assessed by plasma levels of the neurodegeneration biomarker ptau181. Plasma ptau181in DLB is correlated with cognitive decline (Abdelnour, 2024) and is a marker of temporal-lobe tau pathology with elevated ptau181 in DLB being associated with positive temporal lobe tau PET signal in one report (Diaz-Galvan, 2024), elevated CSF ptau181/Ab42 ratio in another (Abdelnour, 2024) and CSF A+/T+ status in a third (Vrillon, 2024); consistent with AD co-pathology in DLB being associated with medial temporal lobe atrophy. Herein, we report on the baseline disease characteristics of the patients enrolled in RewinD-LB, which, along with requirement of meeting consensus diagnostic criteria, was selected based on absence of elevation in plasma

ptau181. **Methods:** RewindD-LB is a randomized, 16-week, double-blind, placebo-controlled clinical trial, with 32-week open label extension being conducted in 43 investigational sites (32 USA, 8 UK, 3 Netherlands). 159 patients with DLB by consensus clinical criteria, global CDR=0.5 or 1.0 and plasma ptau181 at screening <2.4 pg/mL (equivalent to 27.2 pg/mL in version 2.0 of the assay); randomized 1:1 to neflamapimod 40mg or matching placebo, stratified by background therapy (none, acetylcholinesterase inhibitor (AChEI), or memantine). The primary endpoint is change in CDR-SB; secondary endpoints: the timed up and go (TUG) test, cognition measured using the Cogstate cognitive test battery, and the ADCS-CGIC. **Results:** 335 individuals screened; 159 participants randomized between August 2023 and June 2024. Of the patients undergoing ptau181 testing, 66.7% (94 of 142) of CDR=0.5 patients and 75.2% (103 of 137) of CDR=1.0 patients were deemed eligible by the plasma ptau181 criterion. Baseline characteristics of the sample were males 85%, age (mean (SD) =71.4(6.1), clinical disease severity (CDR-SB) = 4.4(2.0), MMSE=23.3(4.4), movement (TUG=14.2(15.1) seconds) psychiatric symptoms (NPI-10=11.5(13.8). prevalence of core clinical features: fluctuations=73%, visual hallucinations=57%, REM sleep disorder=78%, parkinsonism=87%; 75% were receiving AChEI therapy (of which 15% were also receiving memantine) and 3% were receiving memantine without AChEI. The magnitude of cognitive impairment in the group (i.e. mean deficit z-score relative age-adjusted norm on the Cogstate tests) was -0.77 for a composite attention score, -2.34 for working memory (One Back-Accuracy), -2.34 for visual learning (One Card Learning Test). -2.56 for verbal learning (ISLT-Immediate) and -1.66 for verbal memory (ISLT-Delayed). **Conclusion:** Approximately 70% of patients with very mild or mild dementia with Lewy bodies recruited to the RewinD-LB clinical trial did not have temporal lobe neurodegeneration, as defined by absence of elevation in plasma ptau181. Despite this, and treatment with AChEI, the clinical disease burden is substantial in such patients. The combination (limited neurodegeneration, accessible, sufficient clinical signal) makes DLB without elevated plasma ptau181 an attractive patient population for drug development. **Keywords:** DLB, neflamapimod, plasma phosphorylated tau. **Disclosures:** SNG has acted as consultant for EIP Pharma. PM is an employee of Cogstate Ltd. JA, KB, AG and JC are employees of CervoMed Inc, the company developing neflamapimod and the parent company of the study sponsor (EIP Pharma). Primary funding source: US National Institutes of Aging (NIA) Grant #R01AG080536. **References:** Jiang et al, Nature Communications, 2022, DOI: 10.1038/s41467-022-32944-3; Alam et al, Neurology, 2023, DOI: 10.1212/WNL.0000000000207755; Prins, et al, JPAD, 2024, DOI: 10.14283/jpad.2024.36; Vrillon et al, Alz Res & Ther, DOI. 10.1186/s13195-024-01502-y; Abdelnour et al, Annals Neurol, 2024, DOI: 10.1002/ana.27003; Diaz-Galvan et al, Alzheimers Dement, 2024, DOI: 10.1002/alz.13653.

LB33- VARIATIONS IN INCIDENCE, PROGRESSION, AND RISK FACTORS ACROSS MILD COGNITIVE IMPAIRMENT (MCI) SUBTYPES. C.Y. Wu[1], K. Duff[2], C. Guerrero[2], S. Gothard[2], R. Croff[2], H. Dodge[1], J. Kaye[2] *(1. Massachusetts General Hospital/ Harvard Medical School - Charlestown (United States), 2. Oregon Health & Science University - Portland (United States))*

Background: Mild cognitive impairment (MCI) is a heterogeneous condition with multiple subtypes, possible underlying disease mechanisms, and outcomes. Despite this heterogeneity, much research treats MCI as a single entity, which hinders our understanding of subtype-specific risk factors and incidence and weakens the development of personalized treatments. Here, we leveraged data from a self-driven nationwide brain health program to characterize MCI subtypes and profile associated risk factors for their incidence. **Methods:** AARP Staying Sharp, launched in 2018, is a non-diagnostic, voluntary online program aimed at promoting a healthy lifestyle through cognitive assessments, brain games, educational videos, and articles. Upon enrollment, participants completed a survey assessing six pillars of health (engage your brain, eat right, exercise, restorative sleep, be social, and manage stress) and a self-administered cognitive battery (which they could repeat every 90 days). A cognitively unimpaired sample of adults aged 55 and older at enrollment who completed at least two cognitive tests were identified. The first incidence of MCI was categorized as: 1) single-domain amnestic MCI (aMCI: only memory impaired), 2) multi-domain amnestic MCI (maMCI: memory plus at least one other domain impaired), 3) single-domain non-amnestic MCI (naMCI: only one non-memory domain impaired), or 4) multi-domain non-amnestic MCI (mnaMCI: multiple non-memory domains impaired). Delayed entry Cox proportional hazards models with right-censored events and age as timescale were used to assess the association between each lifestyle factor and time to MCI subtype, adjusting for sex, education, race, employment status, and marital status. Multiple hypothesis testing was addressed using Bonferroni correction of p-values. **Results:** Among Staying Sharp registrants (n=179,016; 68.5±6.9 years old; 34.2% male; 7.4% African American), 89% completed cognitive testing only once. Among those who underwent repeated testing, 54% (11,144) remained cognitively unimpaired (CU), while 13% (2,709) progressed to aMCI, 7% (1,358) to maMCI, 20% (4,175) to naMCI, and 6% (1,157) to mnaMCI. The average time to onset or censoring was 1.09 (SD=0.89) years for CU and 0.98-1.07 (SDs=0.84-0.89) years for MCI subtypes. African Americans had an 84% to 109% higher hazard of developing multi-domain MCIs compared to Caucasians [Hazard Ratios (HRs): 1.84-2.09]. Males had a 14-39% higher hazard of developing amnestic MCIs [HRs: 1.14-1.39], where females had a 23-44% higher hazard of developing non-amnestic MCIs [HRs: 1.23-1.44]. Frequent cognitive stimulating activities [HRs: 0.78-0.91], efficient sleep latency [HRs: 0.86-0.94], and regular exercise habits [HRs: 0.92-0.95] were linked to reduced hazards of all MCI subtypes, with larger effect sizes observed for multi-domain MCIs. In contrast, only the Mediterranean diet and active community engagement were associated with a lower hazard of single-domain MCIs [HRs: 0.93-0.96], but not for multi-domain MCIs. **Conclusion:** In this large online cohort, nearly half developed cognitive impairments suggestive of a MCI subtype. Demographic factors (e.g., race, sex) and lifestyle choices (e.g., diet, sleep, community engagement) influenced the incidence of the MCI subtype in this cohort. As such, tailoring intervention strategies to each MCI subtype is critical for effectively delaying the progression of Alzheimer's disease and related dementias. **Keywords:** disease heterogeneity; personalized medicine; Alzheimer disease and related dementias. **Disclosures:** The authors declared no competing interests.

LB34- DIAGNOSTIC ACCURACY AND ADDED VALUE OF [18F]APN-1607 PET IN THE CLINICAL WORKUP OF PATIENTS WITH COGNITIVE SYMPTOMS. Y.U. Jin-Tai[1], W. Jun[2] *(1. Huashan Hospital, Fudan University - Shanghai (China), 2. Daping Hospital, Third Military Medical University - Chongqing (China))*

Background: The novel positron emission tomography (PET) tracer [18F]APN-1607 allows in vivo detection of tau pathology and exhibits disease-specific spatial pattern. We aimed to evaluate the diagnostic accuracy and added value of [18F]APN-1607 PET to a standard clinical workup in participants with cognitive symptoms. **Methods:** In this real-world cohort study, 1476 participants with congitive complaints who underwent a standard diagnostic workup, including medical history, clinical examination, neuropsychological assessments, routine blood tests, structural magnetic resonance imaging of brain and [18F] APN-1607 tau PET scan, were consecutively recruited at the tertiary memory clinics in Shanghai, China, from Jan 2019 through July 2024. Clinicians reported the diagnosis, diagnostic confidence and treatement plan before and after the tau PET reads, respectively. The primary outcomes were the diagnostic accuracy of tau PET pattern by visual read for tauopathies, and changes in diagnosis, diagnostic confidence and medication between the pre- and post-PET reads. The secondary outcome was associations of variable factors with changes in diagnosis and diagnostic confidence. **Results:** A total of 1476 participants with a mean age at onset of 62.1 (SD, 9.6) years (775 female) were included. Based on disease-specific spatial pattern, [18F] APN-1607 PET exhibited the overall accuracy of 97.2%, 95.3%, 94.7% and 97.7%, respectively, for separating Alzheimer's disease (AD), frontotemporal dementia (FTD), progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) from others. The tau PET results led to a change in diagnoses in 318 participants (21.5%), an increase of diagnostic confidence from 67.7% (SD, 9.8) to 80.7% (SD, 12.5), and a change in medication in 405 participants (27.4%). Cognitive impairment at the MCI and dementia level, co-existing motor systems and a lower baseline diagnostic confidence (<70%) were associated with the changes of diagnosis and diagnostic confidence. **Conclusion:** [18F]APN-1607 tau PET has high accuracy in separating cognitive disorders, and exhibits added value on the routine clinical workup in patients with cognitive symptoms. The added value is more pronounced in MCI or dementia participants with lower diagnostic confidence and without co-existing motor symptoms, suggesting the application of [18F]APN-1607 tau PET in appropriate patients in memory clinics. **Keywords:** Alzheimer's disease, [18F]APN-1607 tau PET, accuracy, diagnosis, diagnostic confidence, treatment. **Disclosures:** The authors declared no competing interests.