The Journal of Prevention of Alzheimer's 13 (2026) 100617

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

18th clinical trials on Alzheimer's disease (CTAD) conference, December 1-4, 2025, San Diego, CA (United States) - Conference proceedings - Oral communications

1. Symposia

S1- Trontinemab's path to Phase III – From proof-of-concept in the ongoing Brainshuttle™ AD study to the pivotal studies TRONTIER 1 and TRONTIER 2 in people with early-stage symptomatic Alzheimer's disease.

L. Kulic[1], C. Mummery[2], C. Lane[3], P. Delmar[1], S. Ahlers[4], C. Hofmann[1], R. Croney[3], S. Salloway[5], R.A. Sperling[6], G.D. Rabinovici[7], H. Zetterberg[8], J.L. Cummings[9], G. Klein[1], J. Smith[3], H. Svoboda[1]

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Presentation 1: Brainshuttle™ AD: New interim results of a randomized, placebo-controlled Phase Ib/IIa proof-of-concept study with trontinemab, a novel anti-amyloid monoclonal bispecific antibody for the treatment of Alzheimer's disease.

Luka Kulic[1], Fabien Alcaraz[1], Gregory Klein[1], Stephen Salloway[2], Carsten Hofmann[1], João A. Abrantes[1], Denise Sickert[1], Jakub Wojtowicz[1], Ruth Croney[3], David Agnew[3], Silke Ahlers[4], Paul Delmar[1], Hanno Svoboda[1], for the Trontinemab Study Group.

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Background: Crossing of the blood–brain barrier (BBB) is a major challenge faced by large molecules like amyloid beta (Aβ)-lowering monoclonal antibodies (mAbs), with only 0.03%–0.2% penetration into brain tissue. Roche's Brainshuttle™ technology harnesses receptor-mediated transcytosis to deliver therapeutic molecules—including mAbs—across the BBB via the brain capillaries. This leads to rapid uptake, substantially increased mAb concentrations, and improved target engagement throughout brain tissue, including deeper brain structures. Trontinemab, a novel bispecific 2 + 1 Brainshuttle™ mAb, combines by recombinant fusion a bivalent Aβ-targeting IgG1 mAb with a monovalent transferrin receptor 1 (TfR-1)-binding moiety (the Brainshuttle™ module) for TfR-1-mediated transport across the BBB. Trontinemab has shown proof of concept for improved brain penetration and amyloid plaque clearance in the ongoing Phase Ib/IIa Brainshuttle™ Alzheimer's disease (AD) study (NCT04639050) evaluating safety, pharmacokinetics, and pharmacodynamics in individuals with mild cognitive impairment or mild-to-moderate AD. The latest safety and biomarker results from the dose-expansion part (Part 2) and emerging data from the ongoing open-label extension part (Part 4) will be presented. **Methods:** In the initial 28-week dose-escalation part (Part 1), 60 participants were randomized to four sequential dose cohorts: 0.2 mg/kg (Cohort 1), 0.6 mg/kg (Cohort 2), 1.8 mg/kg (Cohort 3), and 3.6 mg/kg (Cohort 4). The two higher dose levels (Cohort 3 and Cohort 4) showed favorable PD and safety results in Part 1 and were investigated further in the dose-expansion part (Part 2), with 60 additional participants per cohort and 28 weeks of treatment. Participants in Part 1 and Part 2 were randomized 4:1 (active:placebo). After successful completion of Part 1 and Part 2, participants could transition to an open-label extension (Part 4). **Results:** Recent interim results from 114 participants from the completed Part 1 and Part 2 of Cohort 3, and the completed Part 1 and one-third of Part 2 of Cohort 4, showed dose-dependent amyloid plaque lowering on amyloid positron emission tomography (PET) imaging across active doses, consistent with previous reports (data cut-off: Nov 14, 2024). The latest data showed that over 80% (n = 21/26) of participants with available PET scans reached amyloid clearance below the positivity threshold (≤24 centiloids) after 28 weeks of treatment in the higher 3.6 mg/kg dose level compared with 65% (n = 33/51) in the 1.8 mg/kg dose level. The minimum amyloid reduction in the 3.6 mg/kg dose group was −47 centiloids (mean −96 centiloids), with no amyloid reduction non-responders. Early and pronounced effects on downstream cerebrospinal fluid (CSF) biomarkers (including CSF Aβ42/40, neurogranin, pTau181, and total tau) were observed. Plasma biomarkers (including plasma Aβ42/40, pTau181, and pTau217) showed changes towards normalization. The incidence of amyloid-related imaging abnormalities with edema was below 5%. The most complete amyloid PET, safety, and exploratory biomarker results and first results from the ongoing Part 4 will be presented. **Conclusions:** The totality and consistency of biomarker and safety results from the ongoing Brainshuttle™ AD study support moving forward into the

https://doi.org/10.1016/j.tjpad.2026.100617

Available online 12 June 2026

pivotal phase of clinical development to confirm the efficacy and safety profile of trontinemab in people with AD.

Keywords: Brainshuttle™, trontinemab, safety, biomarkers.
Clinical Trial Registry: NCT04639050; https://clinicaltrials.gov.

Disclosures: LK, FA, GK, CH, JAA, DS, JW, PD, and HS are employees and shareholders of F. Hoffmann-La Roche Ltd. SS has received grants and personal fees from Biogen, Lilly, Roche, Eisai, Novartis, and Novo-Nordisk, and personal fees from Prothena, AbbVie, Acumen, CognitionRX, and Kisbee. RC and DA are employees of Roche Products Ltd, and shareholders of F. Hoffmann-La Roche Ltd. SA is a contractor for F. Hoffmann-La Roche Ltd. and an employee of Excelya Germany GmbH.

Presentation 2: TRONTIER 1 and 2: Rationale and design of two identical Phase III trials to assess the efficacy and safety of trontinemab in early symptomatic Alzheimer's disease.

Catherine Mummery[1], Janice Smith[2], Jeffrey L. Cummings[3], Gil D Rabinovici[4], Stephen Salloway[5], Reisa Sperling[6], Henrik Zetterberg[7], Angeliki Thanasopoulou[8], Christopher Lane[2], Paul Delmar[8], Gregory Klein[8],Carsten Hofmann[8], Luka Kulic[8], for the Trontinemab Study Group.
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Background: Developing potent therapies that clear amyloid plaques below a nominal threshold of approximately 24–30 centiloids on amyloid positron emission tomography (PET) is associated with clinical benefit in the early stages of symptomatic Alzheimer's disease (AD); however, time is required to observe clinical benefit after amyloid clearance. Therefore, it is hypothesized that rapid and deep amyloid plaque clearance may lead to earlier and even increased benefit. Trontinemab is a novel bispecific 2 + 1 Brainshuttle™ Aβ-targeting monoclonal antibody (mAb) specifically engineered for efficient transferrin receptor 1 (TfR-1)-mediated transport across the blood–brain barrier. It combines by recombinant fusion a bivalent Aβ-targeting IgG1 "cargo" mAb with a monovalent TfR1-binding moiety (the so-called Brainshuttle™ module). Trontinemab has demonstrated robust and rapid mean amyloid plaque removal of 107 centiloids after 28 weeks of 3.6 mg/kg treatment in the Phase Ib/IIa Brainshuttle™ AD study (n = 12; NCT04639050), coupled with a low incidence of amyloid-related imaging abnormalities with edema below 5%. Newer interim safety and pharmacodynamic (PD) results from the dose-expansion part (Part 2) and the ongoing open-label extension (Part 4) from the Brainshuttle™ AD study, presented at CTAD 2025 by Kulic et al., have informed the next steps in the clinical development program of trontinemab. The design of the pivotal phase in early symptomatic AD (esAD) will be described. **Methods:** TRONTIER 1 and 2 are two identically designed global, randomized, double-blind, placebo-controlled Phase III studies designed to investigate the efficacy, safety, tolerability, pharmacokinetics (PK), immunogenicity, and PD of trontinemab following intravenous infusion in participants with esAD. Approximately 1600 eligible participants (800 per study; 50–90 years) diagnosed with mild cognitive impairment due to AD or mild AD dementia with confirmed amyloid pathology, Mini-Mental State Examination (MMSE≥22), and Clinical Dementia Rating – Global Score (CDR-GS 0.5 or 1) will be randomized 1:1 to trontinemab or placebo. A pre-screener study, TRAVELLER, based on a brief clinical assessment and a plasma biomarker, will be initiated to enable broad community outreach (presented at CTAD, 2025 by Lane et al.). **Results:** The primary endpoint is the change from baseline on the Clinical Dementia Rating – Sum of Boxes (CDR-SB) at 72 weeks. Secondary and exploratory outcome measures include assessments of cognition, function (including the Alzheimer's Disease Assessment Scale – Cognitive Subscale [ADAS-Cog 13] and the Alzheimer's Disease Cooperative Study – Activities of Daily Living [ADCS-ADL] scale), behavioral symptoms, and quality of life. PD effects of trontinemab will be evaluated using amyloid and tau PET, magnetic resonance imaging, and fluid biomarkers. Additional important objectives include assessment of safety, PK, and immunogenicity throughout the studies. **Conclusion:** The totality and consistency of safety and biomarker results to date, coupled with the emerging evidence from the field on the relationship between amyloid removal and slowing of cognitive decline, support the initiation of the pivotal Phase III TRONTIER 1 and TRONTIER 2 studies to assess whether treatment with trontinemab slows disease progression in people with esAD.

Keywords: Brainshuttle™, trontinemab, TRONTIER, early symptomatic AD.
Clinical Trial Registry: NCT4639050; https://clinicaltrials.gov.

Disclosures: CJM has consulted and/or received honoraria for speaking at events for Biogen, Roche, WAVE, IONIS, Prevail, Lilly, Eisai, Novartis, Neurimmune, and MSD. JS and CL are employees of Roche Products Ltd, and shareholders of F. Hoffmann-La Roche Ltd. JLC has provided consultation to Acadia, Acumen, ALZpath, Annovis, Artery, Axsome, Biogen, Biohaven, Bristol-Myers Squib, Cervomed, Eisai, Fosun, GAP Foundation, Green Valley, Hummingbird Diagnostics. IGC, Janssen, Kinoxis, Lighthouse, Lilly, Lundbeck, LSP/eqt, Merck, MoCA Cognition, Novo Nordisk, NSC Therapeutics, Optoceutics, Otsuka, Praxis, ReMYND, Roche, Scottish Brain Sciences, Signant Health, Simcere, sinaptica, T-Neuro, TrueBinding, and Vaxxinity pharmaceutical, assessment, and investment companies. Dr. Cummings is co-founder of CNS Innovations and Mangrove Therapeutics. JLC is supported by NIGMS grant P20GM109025; NIA R35AG71476; NIA R25AG083721-01; NINDS RO1NS139383; Alzheimer's Disease Drug Discovery Foundation (ADDF); Ted and Maria Quirk Endowment; Joy Chambers-Grundy Endowment. GDR has provided consultation to Eli Lilly, Johnson & Johnson, Merck, Novo Norodisk and Roche. He receives research support as PI/MPI from NIH/NIA P30-AG062422, R35-AG072362, U01-AG057195, U01-AG082350, R56-AG075744; NIH/NINDS R01-NS139383; Alzheimer's Association, American College of Radiology, Genentech, Rainwater Charitable Foundation. He is an associate editor for JAMA and JAMA Neurology. SS has received grants and personal fees from Biogen, Lilly, Roche, Eisai, Novartis, and NovoNordisk, and personal fees from Prothena, AbbVie, Acumen, CognitionRX, and Kisbee. RAS has served as a consultant for AbbVie, AC Immune, Acumen, Alector, Apellis, Biohaven, Bristol Myers Squibb, Genentech, Ionis, Janssen, Merck, Oligomerix, Prothena, Roche, and Vaxxinity over the past 3 years. She has received research funding from Eisai and Eli Lilly for public-private partnership clinical trials and receives research grant funding from the National Institute on Aging/National Institutes of Health, GHR Foundation, and the Alzheimer's Association. Her spouse, K. Johnson, reports consulting fees from Novartis, Merck, and Janssen. 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, Enigma, LabCorp, Merck Sharp & Dohme, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Quanterix, Red Abbey Labs, reMYND, Roche, Samumed, ScandiBio Therapeutics AB, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures sponsored by Alzecure, BioArctic, Biogen, Cellectricon, Fujirebio, LabCorp, Lilly, Novo Nordisk, Oy Medix

Biochemica AB, Roche, and WebMD, is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, and is a shareholder of MicThera (outside submitted work). AT, CH, PD, GK, CH, and LK are employees and shareholders of F. Hoffmann-La Roche Ltd.

Presentation 3: The TRAVELLER master pre-screener protocol: An approach to reduce participant burden and broaden access to clinical trials in Alzheimer's disease.

Christopher Lane[1], Angeliki Thanasopoulou[2], Teresa Gleissl[2], Ross Paterson[1], Christina Rabe[3], Derrek Hibar[3], Alina Bauer[4], Imke Kirste[4], Annunziata Di Domenico[5], Tobias Bittner[2,3], Ruth Croney[1], Janice Smith[1], for Trontinemab Study Group.

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Background: Recruitment into Alzheimer's disease (AD) clinical trials is challenging and often takes much longer than in other therapeutic areas. A major hurdle is identifying potentially eligible individuals who broadly reflect the AD population. Consenting into a complex clinical trial and undergoing comprehensive screening evaluation is burdensome, with many participants found ineligible. Detection of amyloid pathology traditionally relies on positron emission tomography (PET) or cerebral spinal fluid (CSF) biomarkers. Their invasiveness, high cost, and low accessibility limit large-scale implementation in clinical screening. Blood-based biomarker assays are cost-effective, accessible and less invasive, addressing the unmet need for expanded AD screening and identifying patients with cognitive complaints due to AD pathologies. Recently, plasma pTau217 has emerged as a scalable and reliable biomarker to predict the presence of amyloid pathology. Pre-screening approaches using a simple cognitive tool and pTau217 support identifying individuals who may be appropriate for clinical trials, including through community outreach. Roche has developed TRAVELLER for this purpose. The design will be discussed. **Methods:** TRAVELLER is a global, multicenter study designed as a flexible master pre-screening process to assess participants' potential eligibility for Roche interventional AD studies—in the first instance, the Phase III TRONTIER 1 and 2 studies designed to evaluate the safety and efficacy of trontinemab in early stages of symptomatic AD—and determine whether this approach can reach historically understudied populations, supporting their participation. Participants' demographics, social determinants of health (SDOH), and medical and medication histories will be collected, along with blood samples for hematology, serum chemistry, and pTau217 levels. The International Shopping List Test (ISLT) will screen for potential episodic memory impairment. Plasma pTau217 levels will be assessed using the Roche Diagnostics Elecsys® Phospho-Tau (217P) Plasma Immunoassay, initially aiming to exclude those less likely to have amyloid pathology. A biomarker cut-off was selected for the TRONTIER studies with high negative predictive value, defined by amyloid PET or CSF test, as well as sufficient performance for a community and cognitive clinic setting. After excluding individuals with a very low likelihood of meeting eligibility criteria, remaining participants will be recommended for referral to an appropriate Roche interventional AD study for screening and final determination of study eligibility. **Results:** This study aims to determine the biomarker and cognitive status of participants who may be at the early stages or at risk of AD dementia, and their potential eligibility for Roche interventional AD studies using Elecsys® pTau217 plasma assay and ISLT score. Demographic data and SDOH will be summarized. Data will be linked with screening data from associated clinical trials to evaluate this approach. Results will be shared at future conferences. **Conclusions:** Screening out individuals less likely to be eligible for studies early on reduces participant burden and may broaden participant outreach. The study will assess whether a master pre-screening approach facilitates recruitment, including of a more representative population, into AD clinical studies. This coordinated approach aims to reduce participant burden when seeking interventional AD studies compared with typical pre-screening protocols associated with single investigational treatment trials. **Keywords:** Brainshuttle™, trontinemab, prescreening, pTau217.

Disclosures: CL, RP, RC and JS are employees of Roche Products Ltd, and shareholders of F. Hoffmann-La Roche Ltd. AT and TG are employees and shareholders of F. Hoffmann-La Roche Ltd. CR and DH are employees of Genentech Inc., part of F. Hoffmann-La Roche Ltd, and shareholders of F. Hoffmann-La Roche Ltd. AB is an employee of Roche Diagnostics GmbH. AB and IK are employees of Roche Diagnostics GmbH, and shareholders of F. Hoffmann-La Roche Ltd. ADD is an employee of Roche Diagnostics International Ltd. TB is an employee of F. Hoffmann-La Roche Ltd. and Genentech Inc. and a shareholder of F. Hoffmann-La Roche Ltd.

Key takeaway message: This session discusses trontinemab's development journey as a novel Alzheimer's disease treatment, covering emerging Brainshuttle™ AD study results, the rationale and design of the pivotal TRONTIER trials, and a biomarker pre-screening strategy for clinical trials.

S2- The U.S. POINTER Trial: Imaging, neurovascular, and sleep outcomes.

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Presentation 1: U.S. POINTER Trial Outcomes: Results of the Imaging Ancillary Study Theresa M. Harrison[1], Prashanthi Vemuri[2], Charles DeCarli[3], Pauline Maillard[3], Robert A. Koeppe[4], Youngkyoo Jung[3], Danielle J. Harvey[3], Jacinda Taggett[1], Laura Lovato[5], Maria C. Carillo[6], Heather M. Snyder[6], Rachel A. Whitmer[3], Mark Espeland[5], Laura D. Baker[5], Susan M. Landau[1], for the POINTER Imaging and U.S. POINTER Study Groups.

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Background: The U.S. study to PrOtect brain health through lifestyle INTErvention to Reduce risk (U.S. POINTER) was a clinical trial that investigated whether random assignment to two multidomain lifestyle interventions differentially influenced 2-year cognitive trajectories. The self-guided intervention group received information and support through twice yearly group meetings to encourage healthy lifestyle practices. The higher-intensity, structured lifestyle intervention group received frequent coaching and group meetings focused on physical exercise, healthy nutrition, cognitive and social challenge and cardiometabolic risk management. Across 5 U.S. sites, the U.S. POINTER trial enrolled sedentary older adults (N = 2111; 60-79yrs) with a variety of dementia risk factors but without significant cognitive impairment and evaluated cognition at baseline, and at months 6, 12, 18, and 24. The U.S. POINTER Imaging ancillary study aimed to examine the role of brain health in intervention responses. Trial participants from all 5 sites were invited to undergo MRI and Aβ and tau PET imaging to examine whether the interventions (1) influenced neuroimaging biomarkers of Alzheimer's disease (AD) and cerebrovascular (CVD) or 2) resulted in cognitive benefits that were influenced by these biomarkers. **Methods:** U.S. POINTER Imaging enrolled 1052 (50%) of the parent trial participants and carried out longitudinal MRI (baseline, month 12 and month 24) and Aβ and tau PET imaging (baseline, month 24). The primary AD/CVD biomarker measurements included global Aβ in centiloids, measured with 18F-florbetaben PET; tau PET SUVrs in entorhinal cortex and a temporal composite region, measured with 18F-MK6240; hippocampal volumes; tensor-based morphometric change in AD-sensitive cortical regions; and white matter hyperintensity volumes. We examined whether there were differences in longitudinal change in imaging

biomarkers between intervention groups, and whether imaging biomarker changes are associated with intervention-related cognitive change. We also examined whether baseline characteristics of AD/CVD biomarkers influenced intervention-related cognitive responses. Covariates included age, sex, site, scanner and ApoE4 status, and statistical models included linear mixed effects and simultaneous growth curves at a = 0.05. **Results:** 937 U.S. POINTER Imaging participants completed baseline neuroimaging (68.4 ± 5.2 years, 63% female, 32% self-reported under-represented ethnoracial group membership, 31% Aβ+, 30% ApoE4+). Retention through month 24 was 89%. Compared to participants who did not enroll in the imaging substudy, imaging participants were more likely to be male and had higher cardiovascular risk characteristics, but otherwise were comparable. Primary U.S. POINTER Imaging longitudinal findings will be presented, including analyses examining whether lifestyle intervention arm influenced neuroimaging biomarker changes, and whether longitudinal neuroimaging biomarker changes were associated with intervention-related cognitive responses. Finally, we will examine whether any baseline AD/CVD biomarker profiles were predictive of intervention-related cognitive responses. **Conclusions:** The U.S. POINTER Imaging ancillary study results will highlight the biological mechanisms that drive cognitive changes in response to multidomain lifestyle interventions. Furthermore, identification of AD/CVD biomarker profiles that predict maximum cognitive benefit will enable a precision medicine-based approach to lifestyle modification.

Keywords: Non-pharmacological interventions, MRI, PET, amyloid, tau, lifestyle.

Data deposition: ida.loni.usc.edu and uspointer.net.

Clinical Trial Registry: NCT03688126; clinicaltrials.gov.

Disclosures: This work was supported by the National Institute on Aging (R01AG062689) and the Alzheimer's Association (U.S. POINTER-19-611541). SML has received speaking honoraria from Eisai and the Alzheimer's Research Therapeutic Institute (IMPACT AD), has served on the DSMB for the NIH Impact of Intensive Treatment of Systolic Blood Pressure on Brain Perfusion, Amyloid and Tau in Older Adults (IPAT) study, and has consulted for Banner Health. CDC consults for Eisai and Novo Nordisk. MC and HS are full time employees of the Alzheimer's Association, and the spouse of HS works for Abbott Labs in an unrelated field. DH serves as a statistical advisor for PLOS ONE, and has served as a consultant for NervGen Pharma Corp. The other authors have no relevant disclosures.

Presentation 2: POINTER-NV: Results of the U.S. POINTER Neurovascular Ancillary Study,

Tina E. Brinkley[1], Katelyn R. Garcia[1], Iris Leng[1], Charles H. Tegeler[1], John Bennett[1], Laura D. Baker[1], Mark A. Espeland[1], Gary F. Mitchell[2], Aarti Sarwal[3], Jurgen A. Claassen[4], Heather M. Snyder[5], Margie J. Bailey[1], Hossam A. Shaltout[1], for the POINTER-NV and U.S. POINTER Study Groups.

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Background: U.S. POINTER was a 2-year multicenter randomized clinical trial assessing the effects of a self-guided (SG) versus structured (STR) lifestyle intervention on cognitive trajectory in 2111 older adults without cognitive impairment but at risk for Alzheimer's disease and related dementias due to well-established factors. Both multidomain lifestyle interventions promoted physical exercise, a healthy diet, cognitive and social stimulation, and management of cardiometabolic risk factors, but differed in structure, intensity, and accountability. Given the importance of maintaining adequate cerebral blood flow to the brain to preserve cognitive function with aging, the POINTER Neurovascular (POINTER-NV) ancillary study was designed to investigate neurovascular mechanisms that may underlie intervention effects on key brain outcomes. **Methods:** POINTER-NV enrolled 491 parent trial participants to undergo a neurovascular assessment at baseline, month 12, and month 24. Aortic, carotid, and cerebral hemodynamics were measured using complementary non-invasive techniques including ultrasound, tonometry, and continuous blood pressure and heart rate monitoring at rest and during orthostatic and hypercapnic challenges, allowing for a comprehensive assessment of autonomic function, cerebral autoregulation, and vascular structure and function. The primary measures of cerebral autoregulation (i.e., phase shift and gain) were calculated using transfer function analysis based on changes in cerebral blood velocity in response to spontaneous fluctuations in blood pressure. The primary measure of baroreflex sensitivity (i.e., Sequence ALL) was calculated by quantifying sequences of at least three beats in which systolic blood pressure consecutively increases or decreases and is accompanied by changes in the same direction of the R-R interval of subsequent beats. Key secondary measures including autonomic function (heart rate variability and blood pressure variability) and vascular structure and function (carotid-femoral pulse wave velocity, carotid stiffness, carotid intima-media thickness, and cerebral vasomotor reactivity) were also obtained using standard procedures. Parent trial intervention effects will be examined using analysis of covariance with repeated measures based on a two-tailed test with overall a = 0.05. Necessary adjustments for missing baseline data will be made for participants who enrolled at month 12. Covariates will include site, age, sex, and assessment visit. The degree to which intervention-related and longitudinal changes in neurovascular outcomes track with 2-year global and domain-specific cognitive trajectories will be assessed using general linear models. Subgroup analyses will be conducted using interaction tests to explore intervention effects by baseline cognitive function, sex, age, apolipoprotein E4 carrier status, and Framingham Risk Score. **Results:** Neurovascular assessments were obtained for 469 POINTER-NV participants (mean age 68.1 ± 5.3 years, 61.2% female, 33.9% ethnoracial minorities) enrolled at baseline or month 12. Successful neurovascular data collection through month 24 exceeded 90% (n = 429). The intervention effects on cerebral autoregulation, autonomic function, and vascular structure and function will be presented overall and by subgroups of interest. Associations between intervention-related changes in neurovascular and cognitive outcomes will also be presented. **Conclusions:** The results of the POINTER-NV ancillary study will shed light on the role of neurovascular factors in lowering risk for cognitive decline and dementia, which could provide important information to inform future health care policy and programming focused on non-pharmacologic prevention strategies.

Keywords: lifestyle intervention; autonomic function; vascular hemodynamics; cognition.

Clinical Trial Registry: NCT03688126 (https://clinicaltrials.gov).

Disclosures: This work was supported by the National Institute on Aging (R01AG066910) and the Alzheimer's Association (POINTER-19-611541). Heather Snyder is a full-time employee of the Alzheimer's Association. Gary Mitchell is the owner of Cardiovascular Engineering, Inc., and serves as a consultant to and receives grants and honoraria from Novartis, Merck, Bayer, Servier, Philips, and deCODE genetics. All other authors have no conflicts to report.

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MM, Alexander AS, Elbein R, McDonald AM, Salloway S, Wing RR, Antkowiak S, Morris MC, Carrillo MC; U.S. POINTER Study Group. Study design and methods: U.S. study to protect brain health through lifestyle intervention to reduce risk (U.S. POINTER). Alzheimers Dement. 2024 Feb; 20 (2):769-782. https://doi.org/10.1002/alz.13365. Epub 2023 Sep 30. PMID: 37776210; PMCID: PMC10916955.

Presentation 3: POINTER-zzz: Results of the U.S. POINTER Sleep Ancillary Study.

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Background: The U.S. Study to Protect Brain Health through Lifestyle Intervention to Reduce Risk (U.S. POINTER) was a Phase 3, multicenter, 2-year, randomized clinical trial assessing the effects of two multidomain lifestyle interventions on cognition in sedentary older adults without cognitive impairment but at risk for Alzheimer's disease and related dementias (ADRD) due to well-established factors. Parent trial participants (N = 2111) at 5 US clinical sites were randomized to the self-guided (SG) or structured (STR) intervention that both promoted physical exercise, healthy nutrition, cognitive and social challenge and cardiometabolic risk management, but differed in structure, intensity, and accountability. POINTER-zzz (R01AG06444) was an ancillary study to assess intervention effects on sleep and associated impact on cognitive response in a large subset of parent trial participants. The high prevalence of sleep disorders in older adults, frequently undiagnosed or untreated and often confounded with changes in brain health, underscores the importance of sleep as a modifiable risk factor for adverse outcomes associated with ADRD. **Methods:** POINTER-zzz targeted enrollment of 780 participants to complete in-home sleep assessments at baseline, month 12 and month 24 using wrist-worn devices for continuous overnight measurement of oxygen desaturation, pulse tonometry, and heart rate with finger pulse oximetry (WatchPAT), followed by 6-day/night measurements of rest-wake activity using actigraphy (GENEActiv). The primary oximetry outcome to quantify sleep-disordered breathing was number of dips per hour in blood oxygen saturation of at least 4% for >10s (4% oxygen desaturation index, ODI), a valid and reliable measure of nocturnal intermittent hypoxemia. The primary actigraphy outcome was sleep fragmentation measured using a probabilistic state transition model to assess minute-to-minute dynamics of sleep activity (kRA). Outcomes were examined using a two-tailed analysis with overall a = 0.05 to test for differences between intervention groups in 4%ODI and sleep fragmentation using analysis of covariance with repeated measures. Covariates included site, age, sex, baseline body mass index, and assessment visit. Degree to which longitudinal and intervention-related changes in 4%ODI and sleep fragmentation track with change in cognitive function will be assessed using general linear models. Intervention effects on sleep by subgroups defined by baseline cognitive function, sex, age, apolipoprotein-e4 genotype, and baseline cardiometabolic health (Framingham Risk Score) will be explored through interactions. Three other ancillary studies to U.S. POINTER provide rich resources for additional analyses given the large number of co-enrolled participants. **Results:** A total of 780 parent trial participants were enrolled in POINTER-zzz (mean age [SD] = 68.7 [5.2], 68.1% female, 36% from minority ethnoracial groups). Sleep assessments were completed in 765 participants at baseline (98%), in 689 participants at month 12 (88%), and in 588 participants at month 24 (75%). The main findings of the sleep ancillary study to U.S. POINTER will be presented, which includes intervention effects on sleep hypoxemia and fragmentation, associations between intervention-related changes in sleep and cognitive trajectory, and the results of subgroup analyses. **Conclusions:** The results of U.S. POINTER's sleep ancillary study could provide important clinically relevant information to inform future health care policy and programming focused on risk reduction and prevention of ADRD.

Keywords: Sleep, cognition, Alzheimer, prevention, risk modification, non-pharmacologic.

Disclosures: POINTER-zzz was funded by NIH/NIA (R01AG06444), and the parent trial was funded by the Alzheimer's Association (POINTER 19-611541). The authors have no conflicts of interest to report.

Key takeaway message: The primary findings from three ancillary studies to the U.S. POINTER trial in older adults at risk for AD/ADRD will be reported describing lifestyle intervention effects on MRI/PET brain imaging, sleep health and neurovascular function.

S3- ALZ-NET: First Look at Real-World Use of Novel Alzheimer's Disease Therapies in the United States.

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Presentation 1: ALZ-NET: An Update on Registry Growth and Collaborations.

Maria C Carrillo.

Chicago on behalf of the ALZ-NET Study Team, IL (United States).

Background: As a provider-enrolled patient registry, ALZ-NET facilitates real-world data (RWD) collection and evidence generation to fill knowledge gaps on long-term health outcomes for individuals evaluated for and treated with novel FDA-approved Alzheimer's and dementia therapies (1). An integrated approach to high-quality data collection from various clinical practices, health records, and a broad patient population is essential to move the field forward. ALZ-NET collects and archives longitudinal patient data, including demographic, medical, neurologic, cognitive, functional, genetic, diagnostic, imaging, biomarker, treatment and safety data. **Methods:** ALZ-NET collects detailed information about practice type, patient population, experience with novel AD therapies, services offered on site, and applicable staff. Data presented here were submitted between August 1, 2022 through May 1, 2025. **Results:** With at least one full active site in 36 states across the US, this presentation will provide the first detailed look at ALZ-NET reach, including geography of sites, and details about sites including their links with other networks in the AD/ADRD research community. As of May 1, 2025, there are 90 active sites, with 71 sites having enrolled 1930 patients. Over 140 sites have registered to participate and are in various stages of the site start-up process. Across all registered sites, 46.6% of patients are being seen in hospital or medical center based settings, and 53.4% are enrolled at office based settings. The ALZ-NET Imaging Network facilitates the clinical pathway between treating clinicians and radiologists, while efficiently collecting diagnostic and safety imaging data about participants; 46 imaging facilities have registered to participate in the Imaging Network (32% hospital outpatient based, 68% independent diagnostic testing facility). A total of 2525 total DICOM studies have been received (2169 MRI; 356 PET), along with 1983 accompanying radiology reports. There are currently five ALZ-NET International partners that share a common goal of aligning and accelerating RWD platform progress globally. ALZ-NET International collaborators share experiences, ideas and outputs to inform infrastructure development, enable innovation and disseminate findings to the field. ALZ-NET is designed to work collaboratively with affiliated studies. Currently, ALZ-NET has two affiliated studies that leverage ALZ-NET infrastructure and data: (1) Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease Following Appropriate Use Recommendations in a Medicare Population: a

Coverage with Evidence Development (CED) Study and (2) LEQEMBI® (lecanemab-irmb) Postmarketing Requirement Study. Access to ALZ-NET data is available for participating sites and the public through the ALZ-NET Data Dashboard and through the Data Access and Use Request process. **Conclusions:** ALZ-NET is a resource for collecting and assessing RWD from communities across the country. Through the collection and archival of a robust multi-modal data set and collaboration with affiliated partners and studies, ALZ-NET is positioned to facilitate research into long-term clinical and safety outcomes in patients receiving novel AD/ADRD therapies.
Clinical Trial Registry: NCT06170268; https://www.clinicaltrials.gov/study/NCT06170268.
Data Deposition: N/A.
Disclosures: MCC is a full-time employee of the Alzheimer's Association. She has a child who is a graduate student at the University of Southern California. Alzheimer's Association disclosures are found at alz.org/transparency.
Reference: 1. https://www.alz-net.org/, last accessed 6/2/2025.

Presentation 2: The ALZ-NET patient population: Demographics, Genetics and Biomarker Testing,
Gil D Rabinovici.
San Francisco on behalf of the ALZ-NET Study Team, CA (United States).

Background: The Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) collects longitudinal clinical, imaging, and safety data for enrolled patients being evaluated for, and treated with, novel FDA-approved Alzheimer's disease therapies and tracks patient long-term health outcomes (effectiveness and safety), associated with the use of these therapies in real-world settings (1). ALZ-NET aims to assess the clinical course of people from a variety of backgrounds and communities in order to achieve representativeness beyond the populations historically enrolled in clinical trials. This first look explores characteristics of the currently enrolled ALZ-NET patient population. **Methods:** Data presented here were submitted between August 1, 2022 - May 1, 2025 during patient registration (enrollment), baseline, and follow up time points. Data tabulation includes participants who were not reported to be taking any treatments and those who have taken at least one dose of a beta-amyloid targeting monoclonal antibody. **Results:** As of May 1, 2025, there were 783 individuals who initiated anti-amyloid treatment prior to ALZ-NET enrollment (n = 575), up to 6 months after enrollment (n = 205) or more than 6 months (n = 3) The median age of the enrolled patient population is 75 (IQR 70-79, range 47-97); 55.9% are female; 82.5% identify as White/European, 3.5% as Hispanic/Latino, 2.2% as Black/African-American, 12.3% as other or unknown ethnicity. Of 205 individuals who initiated anti-amyloid treatment up to 6 months post enrollment in ALZ-NET, 67.3% were at the MCI stage and 31.2% at the mild dementia stage. Baseline data for cognition and function will be presented as part of this talk. APOEe4 data were available on 185 of individuals who initiated anti-amyloid treatment: 30.8% were APOEe4 non-carriers, 56.8% APOEe4 heterozygotes, 9.2% APOEe4 homozygous, 3.2% were not genotyped. Of the population that initiated treatment 0-6 months after enrollment, amyloid status was ascertained by PET in 58.9%, CSF in 30.3% and plasma testing in 20.6%; 20% had more than one biomarker test, while 10.8% did not have any reported biomarker testing. Additional demographic information on education level, insurance type, preferred language and known family history of cognitive issues will also be presented. **Conclusions:** This early look suggests that patients enrolled in ALZ-NET thus far are demographically similar to those enrolled in the clinical trials]. Anti-amyloid treatment was most often initiated at the MCI stage, and amyloid PET was the most commonly used biomarker test. APOEe4 homozygous individuals were slightly underrepresented compared to the clinical trial populations. Future work will assess adherence to FDA prescribing labels and Appropriate Use Recommendations in real-world practice and evaluate the associations between baseline patient characteristics and long-term clinical and safety outcomes in patients treated with novel therapies.
Keywords: Alzheimer's disease, beta-amyloid monoclonal antibodies, treatment, drugs, real world data, clinical care.
Clinical Trial Registry: NCT06170268; https://www.clinicaltrials.gov/study/NCT06170268.
Data Deposition: N/A.
Disclosures: GDR has received research support from NIH, Alzheimer's Association, American College of Radiology, Rainwater Charitable Foundation and Genentech. He has served as a paid consultant to Alector, Avid Radiopharmaceuticals, Bristol Myers Squibb, C2N, Eli Lilly, Johnson & Johnson, Merck, Novo Norodisk, Roche. He has served as a paid speaker for Medscape and Peerview. He is an Associate Editor for JAMA.
Reference: 1. https://www.alz-net.org/, last accessed 5/31/2025.

Presentation 3: Longitudinal assessment of clinical and safety outcomes in participants receiving beta-amyloid targeting monoclonal antibodies: Real world therapy data from ALZ-NET.
Michael S Rafii.
San Diego on behalf of the ALZ-NET Study Team, CA (United States).

Background: The Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) is a voluntary provider-enrolled patient network that collects real-world clinical and imaging data from people evaluated for or treated with new FDA-approved Alzheimer's therapies. Here we present a first look at longitudinal changes for cognition, function, safety and health outcomes in individuals receiving beta-amyloid targeting monoclonal antibody treatment. **Methods:** Data analyzed were submitted between August 1, 2022 - May 1, 2025 during patient registration (enrollment), baseline, and follow up time points. Analysis includes participants who were not reported to be taking any treatments and those who have taken at least one dose of a beta-amyloid targeting monoclonal antibody during 6 months to 1 year from enrollment in ALZ-NET. This first look summarizes data on longitudinal cognition (MMSE/MoCA) (2) and function (FAQ) for participants treatment with anti-amyloid therapies and also provides an initial report of ARIA rates in participants with at least two entry time points of data. **Results:** Among participants who initiated anti-amyloid therapy at or after enrollment and had at least six months of follow-up, 179 received lecanemab and 28 received donanemab. For the MMSE, 126 participants had both baseline and follow-up data. The median change was 0 for the overall group, with an interquartile range (IQR) of −2 to 2, indicating minimal cognitive decline. Participants with mild cognitive impairment (MCI) showed median change of 0, while those with dementia had a median decline of 1 point. For the FAQ, 84 participants had complete data, and the median change was also 0 across all groups, with an IQR of −2 to 3.5. These findings suggest that, over six months, participants generally maintained their cognitive and functional status following therapy initiation. For the 783 patients reported to have taken at least one dose of anti-amyloid treatment (575 pre-enrollment in ALZ-NET, 208 at or post-enrollment), 50 ARIA events (24 ARIA-E events, 26 ARIA-H events) were reported, representing 36 participants. Among those with reported ARIA, characteristics were broadly similar between those who initiated treatment before versus after enrollment. Most ARIA cases were asymptomatic (72.2% pre-enrollment vs. 77.8% post-enrollment), and the majority were mild in radiographic severity (61.1% vs. 77.8%). Only one severe case occurred, in the pre-enrollment group. Most patients who experienced ARIA (E or H) were APOEe4 heterozygotes (66.7% pre-enrollment, 55.6% post-enrollment), followed by homozygotes (22.2% vs. 16.7%) and those with unknown allele status (11.1% vs. 27.8%). Beyond the data reported here, the presentation will include 12-month clinical and safety data from treated patients, and longitudinal clinical outcomes in the untreated group. **Conclusions:** An initial evaluation of outcomes in treated patients enrolled in ALZ-NET found little cognitive change and low rates of ARIA. The majority of ARIA events occurred in APOEe4 carriers (77%), reinforcing the association between APOEe4 genotype

and increased ARIA risk.

Keywords: Alzheimer's disease, beta-amyloid monoclonal antibodies, treatment, drugs, real world data, clinical care.

Clinical Trial Registry: NCT06170268; https://www.clinicaltrials.gov/study/NCT06170268.

Data Deposition: N/A.

Disclosures: MSR has received grants or contracts from Eisai and Eli Lilly, which were paid to his institution. He has received consulting fees from AC Immune and Ionis. He has participated on a Data Safety Monitoring Board or Advisory Board for Alnylam, Alzheon, Aptah Bio, Biohaven, Embic, Helicon, Prescient Imaging, Positrigo and Recall Therapeutics.

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Key takeaway message: ALZ-NET is a resource for collecting and assessing RWD from communities across the country. ALZ-NET is positioned to facilitate research into long-term clinical and safety outcomes in patients receiving novel AD/ADRD therapies.

S4- Top line results from evoke and evoke+: two phase 3 randomized placebo-controlled trials of semaglutide in participants with early-stage symptomatic Alzheimer's disease.

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Background: Alzheimer's disease (AD) is a progressive disease with a high burden on patients and their families, with a need for new treatments at the early disease stage including mild cognitive impairment (MCI) and mild AD dementia. Neuroinflammation has been identified as a key contributor to AD pathobiology (1,2). Based on animal research, preliminary clinical trials in AD, T2D clinical trials and real world evidence, it was hypothesized that the glucagon-like peptide-1 receptor agonist semaglutide would slow AD progression through a multifaceted mechanism of action including modulation of neuroinflammation (3-5). The evoke and evoke + phase 3 trials investigated the long-term efficacy and safety of semaglutide versus placebo in participants with early-stage symptomatic AD. Here, we report the top line results for the primary and key secondary endpoints at 2 years. **Methods:** evoke (NCT04777396) and evoke+ (NCT04777409) were global, randomized (1:1), double-blind, placebo-controlled, parallel-group trials investigating the efficacy and safety of semaglutide versus placebo in participants with early-stage symptomatic AD. Participants were randomized (1:1) to receive semaglutide titrated up to 14 mg orally or placebo for 3 years with a 5-week follow-up period. Dosing was flexible, allowing for extension of dose escalation intervals, dose reduction and treatment pauses. Inclusion criteria were adults aged 55–85 years with MCI as defined by a Clinical Dementia Rating (CDR) global score of 0.5, with a CDR domain score of ≥0.5 in at least one of three activities of daily living (personal care, home and hobbies, and community affairs), or mild AD dementia (CDR global score of 1.0). evoke + also allowed the inclusion of participants with significant small vessel pathology. All patients had confirmed amyloid pathology with positron emission tomography or cerebrospinal fluid (CSF) analysis. The primary objective was to assess superiority of semaglutide over placebo in change in CDR – Sum of Boxes (CDR-SB) score from baseline to week 104. Secondary confirmatory endpoints were change in AD Cooperative Study Activities of Daily Living Scale for MCI (ADCS-ADL-MCI) score from baseline to week 104 and time to progression to dementia (CDR global ≥1) among participants with MCI (CDR global = 0.5) at baseline, assessed up to week 156 in the pooled evoke and evoke + trials. Other endpoints included changes in cognitive assessments (13-item Alzheimer's Disease Assessment Scale – Cognitive Subscale, Alzheimer's Disease Composite Score, Mini-Mental State Examination, Montreal Cognitive Assessment), Neuropsychiatric Inventory, 5-level EQ-5D EuroQol version index score, high sensitivity C-reactive protein (hsCRP), blood and CSF biomarkers, and safety assessments. **Results:** A total of 1855 and 1953 participants were randomized in evoke and evoke+, respectively, to oral semaglutide 14 mg or placebo. At baseline, mean age was 72.2 (standard deviation [SD] 7.1) years and mean CDR-SB score was 3.7 (SD 1.6). In evoke+, 54 participants (2.8%) had significant small vessel pathology. The trials did not meet their primary endpoint. At week 104, the mean changes in CDR-SB score were not significantly different with semaglutide vs placebo (evoke: 2.2 vs 2.2; estimated treatment difference [ETD] based on the treatment policy estimand [95% confidence interval (CI)]: −0.06 [−0.48; 0.36], p = 0.77; evoke+: 2.1 vs 2.0; ETD 0.15 [−0.24; 0.54], p = 0.46). Changes in ADCS-ADL-MCI at week 104 did not show a treatment difference between groups (evoke: −6.6 with semaglutide vs −7.1 with placebo; ETD [95% CI] 0.43 [−1.01; 1.87]; evoke+: −6.5 with semaglutide vs −6.3 with placebo; ETD [95% CI] −0.21 [−1.57; 1.16]). Compared with placebo, semaglutide did not affect time to progression to dementia (hazard ratio [95% CI]: 0.96 [0.86; 1.06] in the pooled analysis). Changes from baseline in other cognitive, neuropsychiatric and quality of life assessments were not different between semaglutide and placebo. Compared with placebo, semaglutide reduced plasma hsCRP (estimated treatment ratio [ETR] [95% CI] in evoke: 0.76 [0.64; 0.90] and in evoke+: 0.71 [0.62; 0.82]) and up to 10% reductions were observed in CSF phosphorylated (p)-tau181 (ETR [95% CI] 0.92 [0.87; 0.97]), p-tau217 (ETR [95% CI] 0.90 [0.81; 0.99]), non-phosphorylated (np)-tau181 (ETR [95% CI] 0.91 [0.84; 1.0]), np-tau-205 (ETR [95% CI] 0.91 [0.83; 0.99]), YKL-40 (ETR [95% CI] 0.93 [0.89; 0.98]), total tau (ETR [95% CI] 0.93 [0.88; 0.98]) and neurogranin (ETR [95% CI] 0.92 [0.87; 0.98]). More adverse events (AEs) were reported with semaglutide; the proportions of participants with serious, severe and AEs with fatal outcome 1.6% and 1.9% for semaglutide and placebo, respectively) were similar between treatment arms. The most common AEs with semaglutide were weight decreased (36.5% vs 7.4% with placebo), decreased appetite (33.1% vs 6.0% with placebo) and nausea (24.3% vs 6.8% with placebo). Weight loss decrease AEs were reported in participants across all BMI categories in both semaglutide and placebo arms (<18.5 kg/m2: 40% and 10.9%; 18.5 to <25 kg/m2: 38.4% and 7.0%; 25 to <30 kg/m2: 37.3% and 6.5%; ≥30 kg/m2: 28.2% and 9.2%, respectively). **Conclusions:** Superiority of oral semaglutide 14 mg once-daily versus placebo was not confirmed on the primary outcome (change in CDR-SB) after 104 weeks. In a CSF subsample, there were significant differences favoring semaglutide on canonical biomarkers along with measures of inflammation and neurodegeneration. The discord between biological and clinical outcomes is not yet understood. Safety and tolerability in participants with early AD were consistent with semaglutide's known mode-of-action and tolerability profile in other populations.

Keywords: Glucagon-like peptide-1 receptor agonist, mild cognitive impairment, neuroinflammation, semaglutide.

Clinical Trial Registry: NCT04777396 (https://clinicaltrials.gov/s

tudy/NCT04777396) and NCT04777409 (https://clinicaltrials.gov/study/NCT04777409).

Funding: Novo Nordisk A/S.

Data deposition: Bona fide researchers may request access to data by submitting a research proposal for approval by Novo Nordisk and an independent review panel. Data sharing requests may be considered after research completion and primary publication, or, if the trial is intended for regulatory submission, after approval of product and product use in both the EU and USA. Individual participant data will be shared in data sets in anonymized format. Information about the data sharing process can be found at novonordisk-trials.com.

Medical writing: Liam Gillies PhD, and Diana Marouco, PhD, of Apollo, OPEN Health Communications, provided medical writing support, which was funded by Novo Nordisk A/S.

Disclosures: JC has provided consultation to Acadia, Actinogen, Acumen, AlphaCognition, ALZpath, Aprinoia, AriBio, Artery, Biogen, Biohaven, BioVie, BioXcel, Bristol-Myers Squib, Cassava, Cerecin, Diadem, Eisai, GAP Foundation, GemVax, Janssen, Jocasta, Karuna, Lighthouse, Lilly, Lundbeck, LSP/eqt, Merck, NervGen, New Amsterdam, Novo Nordisk, Oligomerix, Optoceutics, Ono, Otsuka, Oxford Brain Diagnostics, Prothena, ReMYND, Roche, Sage Therapeutics, Signant Health, Simcere, sinaptica, Suven, TrueBinding, Vaxxinity, and Wren pharmaceutical, assessment, and investment companies. JC is supported by NIGMS grant P20GM109025; NIA grant R35AG71476; NIA R25 AG083721-01; Alzheimer's Disease Drug Discovery Foundation (ADDF); Ted and Maria Quirk Endowment; and Joy Chambers-Grundy Endowment. AA has, in the last 10 years, served as a consultant or received honoraria or support for consulting; participating in independent data safety monitoring boards; providing educational lectures, programs, and materials; and serving on advisory boards for AbbVie, Acadia, Allergan, Alzheimer's Disease International, the Alzheimer's Association, AriBio, Axovant, Axsome, AZTherapies, Biogen, Eisai, Grifols, Harvard Medical School Graduate Continuing Education, JOMDD, Johnson & Johnson, Life Molecular Imaging/Lantheus, Lundbeck, Merck, Michael J Fox Foundation, Novo Nordisk, ONO, Otsuka, Prothena, Qynapse, Roche/Genentech, Sunovion, Suven, Synexus, and Vaxxinity. He receives book royalties from Oxford University Press for a medical book on dementia. He receives institutional research grant/contract funding from National Institute on Aging/National Institutes of Health (NIA/NIH; 1P30AG072980), NIA/NIH U24AG057437, AZ DHS (CTR040636), Foundation for NIH (FNIH), Washington University in St. Louis, and Gates Ventures. His institution receives/received funding for clinical trial grants, contracts, and projects from government, consortia, foundations, and companies, for which he serves/served as a contracted site principal investigator. He has received/receives honoraria from Novo Nordisk for consulting activities, including for service on the evoke (+) program Steering Committee. HHF reports grant support to the University of California San Diego (UCSD) from LuMind Foundation, Annovis (QR Pharma), AC Immune, Biohaven Pharmaceuticals, and National Institute on Aging/National Institutes of Health (U19 AG079444-01, R01 AG061146, R01 AG076634-01, P30 AG062429), Canadian Institutes of Health Research (CNA 137794), Vivoryon Therapeutics, and Allyx Therapeutics. He reports service agreements through UC San Diego for consulting with Arrowhead Pharmaceuticals, Axon Neuroscience, LuMind Foundation, and Biosplice Therapeutics, for being on a DMC and DSMB for Janssen Research & Development LLC, and the Scientific Advisory Board for the Tau Consortium. He serves on the Novo Nordisk evoke (+) steering committee for which he has received/receives consulting fees and travel expenses through a UC San Diego service agreement. He receives personal funds for Detecting and Treating Dementia Serial Number 12/3- 2691 U.S. Patent No. PCT/US2007/07008, Washington DC, U.S. Patent and Trademark Office. He receives philanthropic support for Alzheimer's therapeutic research through the Epstein Family Alzheimer's Research Collaboration. MS has served on the Scientific Advisory Board for Medication and as a consultant for Eisai, Avenir, vTv, Biogen, BioXcel, F. Hoffman LaRoche, Merck, Novo Nordisk, Novartis, Otsuka, Genentech and Bio Vie. She is a member of the Alzheimer Association Medical and Scientific Advisory Group and chair of DSMB: Phase II Trial to Evaluate Safety and Efficacy of GM-CSF/Sargramostim in Alzheimer's Disease (SESAD) sponsor: University of Colorado. WF has been an invited speaker at Biogen MA Inc, Danone, Eisai, WebMD Neurology (Medscape), Novo Nordisk, Springer Healthcare, European Brain Council. All funding is paid to her institution. She is consultant to Oxford Health Policy Forum CIC, Roche, Biogen MA Inc, and Eisai. WF is a member of the steering committee of the Novo Nordisk trials evoke (+). All funding is paid to her institution. She participated in advisory boards of Biogen MA Inc, Roche, and Eli Lilly. All funding is paid to her institution. HZ has served on scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, 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 Cellectricon, Fujirebio, Alzecure, Biogen 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 the submitted work). PS is a full-time employee of EQT Life Sciences (formerly LSP) and Professor Emeritus at Amsterdam University Medical Centers. He is co-chair of the Steering Committee for the phase 3 studies evoke and evoke+ with Novo Nordisk. FKK, PJ, RMA and TL are present or former employees of and shareholders of Novo Nordisk.

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S5- Advancing the Science of Recruitment for Preclinical Alzheimer's Disease Clinical Trials.

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Presentation 1: Impact of upcoming FDA enrollment requirements on recruitment for Alzheimer's disease clinical trials.

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Background: The regulatory framework for recruiting participants into Alzheimer's disease clinical trials continues to evolve. Recent legislation (P.L. 117-328, §§ 3601-2) requires sponsors of certain drug and device trials to develop plans that specify enrollment goals for clinically relevant populations, provide a rationale for those goals, and outline how the sponsor intends to meet them. In 2024, the Food and Drug Administration (FDA) published draft guidance, and while the content of the final guidance is not yet certain, the requirement to submit these plans is expected to take effect in December 2025. **Discussion:** Some trials, including AHEAD and TRAILBLAZER-ALZ 3, are already incorporating recruitment strategies directionally aligned with anticipated FDA requirements. Once in effect, the new requirements may improve representation of clinically relevant populations by requiring sponsors to identify measures to help achieve specified enrollment goals. They may also increase utilization of innovative approaches—including decentralized trials, focused data collection, and artificial intelligence tools for selecting trial sites—that may improve representation and, in some cases, reduce study costs. However, the ultimate impact remains uncertain, with important details about the program not yet specified. The benefits and costs will depend on resolution of questions such as how the

FDA will evaluate plan submissions, when plan issues might delay trials, and how the agency will address trials that fail to implement their plans or meet enrollment goals. Once the program takes effect, sponsors will need to quickly implement, and the field will need to evaluate the impact.

Keywords: Clinical trials, regulatory requirements, recruitment, representation.

Disclosures: The author declared no competing interests.

Presentation 2: Recruitment and screening in TRAILBLAZER-ALZ 3: A decentralized study of donanemab in preclinical Alzheimer's disease.

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Background: Inclusive clinical trials are important so the findings can be generalizable to real-world Alzheimer's disease (AD) populations. Increasing representation has been a growing U.S. regulatory focus for decades. Early guidance called for reporting on sex and race with demographic results, and later for expanding the participation of women and underrepresented groups (1). The study design and execution of the TRAILBLAZER-ALZ 3 (NCT05026866) trial of donanemab in preclinical AD included elements aimed to increase participation across racial and ethnic groups and underserved geographies. **Methods:** Multiple advocacy groups were consulted to share the perspectives of potential participants and inform the study design. Participant-facing roles included individuals representative of the participant populations with whom they would interact. All participant-facing study materials were reviewed to ensure health literacy and cultural competence, including representative imagery. Census demographic mapping was used to identify previously underserved regions, including community-based research sites. Mobile research units further allowed community screening in these underserved areas. To help decrease the burden on randomized participants, decentralized study activities, such as community-based delivery capabilities, were implemented. Screening and randomization results were analyzed to evaluate the effectiveness of these efforts and to identify further improvements. **Results:** Sites expanded to include 79% of continental US states compared with 60% in a previous Phase 3 preclinical AD study. Over 9000 individuals who identified as a race other than White and over 7000 individuals who identified as Hispanic were screened in TRAILBLAZER-ALZ 3. Distribution across racial and ethnic groups was greater in the screening population than in those randomized. Screen failure by biomarker differed by race and ethnicity. Further investigation of these differences identified opportunities to refine study design and delivery in subsequent trials to help expand representation. Ideas for enhancements include allowing options for assessment location (in person or remote); consenting participants to the full study at the beginning of screening rather than using a separate screening consent; initiation of vendor programs to help transition participants from screening through randomization; and sub-studies for additional participants from underrepresented groups. **Conclusions:** Decentralization and other screening efforts in TRAILBLAZER-ALZ 3 resulted in broader representation in the screening population. However, enrolling clinical trial populations representative of the general population with AD remains a challenge. Future efforts may include focusing on further understanding differences in clinical and pathophysiologic profiles across populations, including sub-studies for underrepresented groups, and retention of eligible candidates through to randomization and study completion.

Keywords: Clinical trials, donanemab, recruitment, diversity.
Clinical Trial Registry: NCT05026866; https://clinicaltrials.gov.

Disclosures: Karen C Holdridge, Roy Yaari, Melissa Williamson, Alette Wessels, Dawn East, Tony Pearson, and John Sims are full-time employees and minor shareholders of Eli Lilly and Company.

References: 1. Kulkarni D. The Evolution of US FDA Diversity Requirements in Clinical Research. DIA Global Forum; 2023. https://globalforum.diaglobal.org/issue/december-2023/#fdadiversity.

Presentation 3: Building a scalable and efficient recruitment funnel for preclinical Alzheimer's disease: The AHEAD 3–45 model,

Rema Raman[1], Doris P. Molina-Henry[1], Oliver Langford[1], Andy Liu[1], Shobha Dhadda[2], Michael Irizarry[2], Michael C. Donohue[1], Robert A. Rissman[1], Crystal Glover[3], Keith A. Johnson[4,5], Paul Aisen[1], Reisa A. Sperling[4,5], Joshua D. Grill[3], On Behalf of the AHEAD 3-45 Study Team[6]
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4. Massachusetts General Hospital, Harvard Medical School, Boston, MA (United States), 5. Brigham and Women's Hospital, Boston, MA (United States), 6. AHEAD 3-45 (https://www.aheadstudy.org/learn-more/) (United States).

Background: Recruiting individuals into preclinical Alzheimer's disease (AD) trials from demographically and geographically heterogeneous communities is resource-intensive, requiring large-scale screening efforts to identify individuals who meet threshold levels for brain amyloid positivity. The AHEAD 3-45 Study, a global preclinical AD trial, implemented an adaptive, multi-stage recruitment strategy for North American (NA) sites. **Methods:** The AHEAD study recruitment strategy integrated (a) centralized/local outreach with remote risk identification, (b) site-level prescreening, and (c) plasma biomarker enrichment to optimize amyloid PET screening. Efforts focused on enrolling individuals from racially and ethnically underrepresented groups, those with a high school education or less, residents of rural communities, and individuals from low socio-economic backgrounds, with a goal of 30% of the screened and 15% of the randomized sample. Individuals first completed an online pre-screener to assess basic eligibility. Those preliminarily eligible were referred to their closest study sites for further prescreening. Following consent, plasma biomarker assays were conducted to enrich for amyloid-positive individuals before cognitive/clinical testing and then amyloid PET imaging. Recruitment metrics were tracked at each stage of the recruitment funnel, overall and across sociodemographic groups. **Results:** North America (NA) screening ran from May 2020 to October 2024. Central outreach efforts generated 989,765 study website views from 492,418 unique visitors. A total of 74,094 online pre-screeners were completed; ~60% met preliminary criteria and were referred to study sites. Successful prescreening strategies included remote plasma collection via community phlebotomy centers (1) and population-targeted outreach efforts. These central and site prescreening efforts led to 16,814 NA participants completing in-person screening visits. Upon referral to study, recruitment efforts aimed to reduce site and participant burden by incorporating blood plasma-based screening. Previous work (2) demonstrated that plasma testing achieved an AUC ~0.92. Use of this model significantly enriched for amyloid PET eligibility, decreasing amyloid PET screen failure rates from 70% pre-plasma screening to under 40% post-plasma screening. A total of 3695 PET scans were completed. NA randomizations met and exceeded targets by 19% (374 for A3 and 981 for A45). The study surpassed inclusive recruitment goals; 42.7% of the screened sample and 30.2% (A3) and 26.4% (A45) of the randomized sample included individuals who self-identified as belonging to at least one population of focus. Additional successful strategies included plasma algorithm development and refinement and strong site engagement. The return of amyloid PET results and optional APOE ε4 disclosure further supported recruitment. **Conclusions:** The AHEAD Study's multi-tiered, adaptive, plasma biomarker informed recruitment model successfully broadened demographic reach and inclusivity, improved amyloid PET screening efficiency, and reduced participant and site burden by requiring fewer participant screening activities or visits. These results offer a scalable framework for future preclinical AD trials.

Keywords: Clinical trials, recruitment, screening, inclusivity.

Clinical Trial Registry: NCT04468659; https://clinicaltrials.gov.
Disclosures: RR has received grant funding from the National Institute on Aging, Eisai (public-private partnership trial funding), Alzheimer's Association, and the American Heart Association.
References: 1. Walter S et al. J Prev Alzheimers Dis. 2024; 11 (5):1435-1444. https://doi.org/10.14283/jpad.2024.101. 2. Rissman RA et al. Alzheimers Dement. 2024 Feb; 20 (2):1214-1224. https://doi.org/10.1002/alz.13542.
Key takeaway message: Innovative recruitment strategies—driven by evolving regulatory guidance, decentralized models, and biomarker-based approaches—are expanding representation and efficiency in preclinical Alzheimer's trials, offering scalable solutions to meet inclusive enrollment goals across diverse populations.

LBS1- The Global Neurodegeneration Proteomics Consortium: additional insights into ApoE, cellular aging clocks from the V1 Harmonized Dataset, and what's coming in V2.

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Presentation 1: Proteomic signatures of the APOE ε4 and APOE ε2 genetic variants and Alzheimer's disease.

Lina Lu[1], Alexa Pichet Binette[1,2], Ines Hristovska[1], Shorena Janelidze[1], Bart Smets[3], Irene Cumplido Mayoral[1], Aparna Vasanthakumar[4], Britney Milkovich[4], The Global Neurodegeneration Proteomics Consortium (GNPC), Rik Ossenkoppele[1,5,6], Varsha Krish[7], Farhad Imam[7], Sebastian Palmqvist[1,9], Jacob Vogel[9], Erik Stomrud[1,9], Oskar Hansson[1], Niklas Mattsson-Carlgrenn[1,9]
1. Lund University, Lund (Swede), 2. Université de Montréal, Montréal, QC (Canada), 3. Johnson & Johnson company, Beerse (Belgium), 4. Abbvie, North Chicago, IL ((United States), 5. Vrije Universiteit Amsterdam, Amsterdam (Netherlands), 6. Amsterdam UMC location VUmc, Amsterdam (Netherlands), 7. Gates Ventures, Seattle, WA (United States), 8. SciLifeLab, Lund University, Lund (Sweden), 9. Skåne University Hospital, Malmö (Sweden).

Background: The APOE locus is the strongest genetic factor for Alzheimer's disease (AD), with ε4 (APOE4) increasing and ε2 (APOE2) decreasing risk, yet the molecular programs reflecting these divergent effects remain unclear. Here, we conducted a large-scale, multi-cohort proteomic analysis across plasma and cerebrospinal fluid (CSF), integrating five independent datasets (a total of 10,000 individuals) including the Global Neurodegeneration Proteomics Consortium (GNPC), BioFINDER-2, the Alzheimer's Disease Neuroimaging Initiative (ADNI), UK Biobank (UKBB), and the Parkinson's Progression Markers Initiative (PPMI) and two affinity-based platforms (SomaLogic, OLINK). **Methods:** Using GNPC (plasma SomaLogic, N = 4045), we mapped a comprehensive APOE-protein network and applied mediation modeling to classify genotype-related signals as upstream mediators, downstream consequences, or APOE-specific changes. We then leveraged CSF beta-amyloid (Aβ) biomarker data from BioFINDER-2 (plasma SomaLogic, N = 1421) to improve temporal resolution and isolate early, Aβ-independent proteomic programs. **Results:** Proteomic alterations linked to APOE2 and APOE4 were largely detectable in preclinical stages, even before detectable Aβ pathology, and remained relatively stable across aging and disease stages. In APOE2 carriers, most dysregulated proteins were involved in DNA repair, mitochondrial metabolism, proteostasis, and anti-inflammatory regulation, acting mainly as upstream mediators with limited remodeling by pathological cascades; only a minority showed pathology-related reprogramming, consistent with systemic resilience. In APOE4 carriers, a small subset of proteins enriched in cell-cycle and oligodendrocyte precursor cells (OPCs) may help explain its association with AD risk, whereas a broader set linked to vascular remodeling, immune activation, and proteostasis loss underwent pronounced downstream pathology-driven remodeling, reflecting a shift from genotype-related to pathology-driven regulation. Comparative analyses identified three key contributors reflecting divergent AD risk: allele-specific mediators supported by genetic or transcriptomic evidence (e.g., SPC25 for APOE4, APOB and SNAP23 for APOE2), oppositely regulated "switch-node" proteins (e.g., VPS29, PHGDH), and a broader set of concordantly regulated proteins showing ε4-dominant effects (e.g., S100A13, TBCA, ARL2). Cross-platform comparisons (UKB plasma OLINK, N = 4,820, and BF2 CSF OLINK, N = 1475) revealed matrix- and assay-specific heterogeneity, underscoring challenges in reproducibility. **Conclusions:** Collectively, these findings suggest that asymmetric molecular architectures, rather than mirror-image regulation, underlie the divergent AD risks of APOE2 and APOE4, highlighting upstream pathways and genetically supported mediators as promising biomarkers and potential targets for allele-tailored interventions in AD.
Keywords: Proteomics, Alzheimer, APOE, APOE2, APOE4.
Data Deposition: https://discover.alzheimersdata.org/catalogue/datasets/e2f3536b-d97b-4303-89bd-6864200807a4.
Disclosures: NMC has received consultancy/speaker fees from Biogen, BioArctic, Eli Lilly, Novo Nordisk, Merck and Owkin. **Reference:** https://pubmed.ncbi.nlm.nih.gov/40799961/

Presentation 2: Plasma Proteomics Identifies Early-Life Differences in APOE e4/e4 Individuals Related to Key AD Biological Pathwaysμ.

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Background: The APOE e4 genotype is the strongest genetic risk factor for late-onset Alzheimer's disease (LOAD). How APOE e4 influences biological pathways potentially related to LOAD over the lifespan is unknown. **Methods:** We analyzed the plasma proteomes of 413 APOE e4/e4 carriers and compared plasma protein levels to those of 2764 APOE e3/e3 carriers who have neutral risk for AD in the GNPC harmonized dataset. We restricted the analysis to only e4/e4 individuals who were either cognitively unimpaired or on the AD spectrum, and e3/e3 controls. Because APOE e4 homozygosity has been shown to cause onset of AD symptoms at a mean age of 65.6 with variance in the estimated year of onset (EYO) comparable to individuals who carry autosomal dominantly inherited AD mutations (1), we modeled the longitudinal changes of 7334 plasma proteins from cross-sectional proteomic data to understand the biological pathways that are altered by e4 homozygosity over time. **Results:** We observed 881 plasma protein isoforms that were different in e4/e4 individuals compared to e3/e3 individuals at any point between EYO –46 and + 25 (i.e., age 20 to 90). Although the number of proteins that were increased in e4/e4 carriers was similar, more proteins were decreased early in life in e4/e4 carriers. Biological pathway analysis by multiple techniques showed constitutive changes in lipoproteins in e4/e4 carriers, as expected, and constitutive changes in proteins involved in mitochondrial, energy metabolism, microtubule, steroid, and retinol pathways, with a notable overall decrease in energy metabolism. Pathways that were altered in e4/e4 carriers from age 20 and evolved over time included RNA processing, GLP-1, proteostasis, synaptic, adaptive and innate immunity, and Wnt signaling. Innate immune/complement pathways were altered approximately 20 years before symptom onset. Hemostasis, angiogenesis, insulin growth factor binding, and extracellular matrix pathways were strongly altered during and after symptom onset. **Conclusions:** Plasma proteomics demonstrates biological pathway changes in APOE e4 homozygotes in early adulthood that are also altered in LOAD. Alterations in these pathways likely predispose e4/e4 individuals to develop multiple different AD endophenotypes such as synaptic loss, brain metabolic

failure, neurofibrillary tangle formation, and loss of vascular integrity. Targeting these pathways for therapeutic intervention in e4/e4 individuals early in life will likely be the most effective approach to decrease risk for LOAD in this population.

Keywords: Proteomics, APOE e4, Alzheimer's disease.

Data Deposition: https://discover.alzheimersdata.org/catalogue/datasets/e2f3536b-d97b-4303-89bd-6864200807a4.

Disclosures: We declare no competing interests. This work was supported by R01AG089497.

Reference: 1. Fortea, J. et al., Publisher Correction: APOE4 homozygosity represents a distinct genetic form of Alzheimer's disease. Nat Med, 2024. 30 (7): p. 2093. https://doi.org/10.1038/s4159.

Presentation 3: Cellular Aging Signatures in the Plasma Proteome Record Aging and Neurodegeneration.

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Background: Molecular studies of aging across various organisms, including humans, indicate that aging is asynchronous. Cells and organs age at different rates, potentially influencing overall organismal aging and disease susceptibility. **Methods:** To explore this variation, we analyzed the expression of ~7000 plasma proteins in 14,281 individuals from the Global Neurodegeneration Proteomics Consortium (GNPC). Our analysis identified clusters of proteins that change in concert with age and are preferentially expressed in specific cell types. Leveraging these data, we developed machine learning models to estimate the biological age of 43 distinct cell types including those of neuronal, immune, glial, endocrine, epithelial, musculoskeletal, and mesenchymal origin. We identified disease-specific cellular aging signatures and demonstrated the generalizability of our findings across multiple external cohorts including the 1946 British Birth Cohort (UK1946) and the UK Biobank (UKB). **Results:** Our results demonstrate that biologically healthy individuals possess diverse and individualized aging profiles: 24.36% show accelerated aging in a single cell type, while 1.46% experience widespread acceleration across 10 or more cell types. Notably, we identified temporal patterns of cell-specific aging, with intestinal goblet cells exhibiting early-onset aging (<60 years), and neuronal and glial cell types—including Schwann cells and excitatory neurons—showing marked aging acceleration in late life (>85 years). Moreover, we identified coordinated shifts in aging acceleration across multiple cell types. In individuals with neurodegenerative diseases, we discovered that biologically older cell types are uniquely associated with disease status. Specifically, amyotrophic lateral sclerosis (ALS, n = 245) is significantly associated with aged skeletal myocytes and cardiomyocytes; notably, in the UK Biobank, skeletal myocyte age predicted ALS risk with more than a 12-fold difference between the oldest and youngest age groups. Meanwhile, Alzheimer's disease (AD, n = 2761) showed accelerated aging across a wide range of cell types, most prominently oligodendrocyte precursor cells, pancreatic endocrine cells, inhibitory neurons, and proximal enterocytes, underscoring the systemic nature of the disease. **Conclusions:** Our findings reveal cellular underpinnings of neurodegenerative disease risk, providing granular insights into the role of heterogeneous aging in human health.

Keywords: Aging clock, large-scale proteomics, cell type, neurodegenerative disease, Alzheimer's disease, amyotrophic lateral sclerosis, machine learning. **Data availability:** GNPC data is available upon request to qualified researchers through a standard protocol (https://www.neuroproteome.org/harmonized-data-set-hds).

Disclosures: T.W.-C. is a co-founder and scientific advisor of Alkahest Inc., Teal Rise, Vero Biosciences and has received equity stakes in these companies. T.W.-C. and D.Y.D. are inventors on a patent application based on the research findings presented here. **Reference:** Cellular Aging Signatures in the Plasma Proteome Record Aging and Neurodegeneration. In revision.

Key takeaway message: Members of the Global Neurodegeneration Proteomics Consortium share three multi-cohort analyses revealing APOE ε4/ε2 molecular signatures, early-life proteomic changes in ε4 homozygotes, and diverse cellular aging profiles, highlighting biomarkers and therapeutic targets for intervention.

LBS2- Lecanemab Subcutaneous Formulation for Treatment Initiation in Early Alzheimer's Disease: Optimizing Patient Care with a Potential New Option.

S. Cohen[1], L. Reyderman[2], M. Irizarry[2], N. Penner[2], S. Rawal[2], J. Aluri[2], D. Li[2], M. Gee[3], T. Doherty[3], A. Patten[3], E. Andreozzi[2], S. Hersch[2], S. Dhadda[2], L. Kramer[2]

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2. Eisai Inc - Nutley (United States), 3. Eisai Limited (United States).

Presentation 1: Rationale and Early Development of Subcutaneous Lecanemab, Larisa Reyderman, Michael Irizarry, Natasha Penner, Sumit Rawal, Jagadeesh Aluri, David Li, Steven Hersch, Shobha Dhadda, Lynn D. Kramer *(Eisai Inc., Nutley, NJ (United States)*.

Background: Lecanemab is a humanized IgG1 monoclonal antibody that is distinct from other anti-amyloid antibodies in its preferential targeting of large soluble protofibrils over monomers and insoluble fibrils. In the phase 3 Clarity AD study, intravenous (IV) lecanemab demonstrated a consistent slowing of decline in clinical (global, cognitive, functional, and quality of life) outcomes and reduction in brain amyloid in individuals with early Alzheimer's disease (AD). A subcutaneous (SC) autoinjector formulation of lecanemab is being developed to improve patient convenience. A maintenance dose of 360 mg SC injection using an autoinjector was recently approved by the FDA and a 500 mg SC dose has been submitted to the FDA for treatment initiation. In this presentation, an update on the clinical development of SC lecanemab will be provided, focusing on the comparability of the IV 10 mg/kg biweekly and SC 500 mg weekly administration. **Methods:** The subcutaneous SC development program evaluated a range of doses and delivery methods (e.g. vial/syringe and autoinjector) to establish the SC doses for initiation and maintenance with comparable exposure to IV dosing for amyloid removal, efficacy, and ARIA-E. The 4 SC substudies within the Clarity AD phase 3 study evaluated 1) 720 mg SC by vial to establish that safety and efficacy are exposure-related, 2) 720 mg SC by vial and autoinjector to evaluate the safety and pharmacokinetics of SC lecanemab, 3) 360 mg by autoinjector to confirm pharmacokinetics for maintenance dosing, and 4) 500 mg by autoinjector to establish the SC dose with bioequivalence to the 10 mg/kg IV biweekly dose for treatment initiation. Exposure-response modeling was conducted to characterize relationships between lecanemab exposure and efficacy, amyloid PET, as well as incidence of ARIA-E. **Results:** Across the SC studies, 613 subjects were treated. The initial phase 1 study found the absolute bioavailability of SC vial lecanemab was 49.7% (90% CI: 43.5, 56.8). In Clarity AD SC substudy, lecanemab bioavailability for 500 mg SC autoinjector and 720 mg SC autoinjector was 77.5%. Steady-state exposure (AUCss, 2 weeks) of lecanemab is bioequivalent between 500 mg SC autoinjector weekly and lecanemab IV 10 mg/kg biweekly. IV data and data from lecanemab naïve patients who initiated 720 mg SC vial demonstrated that amyloid reduction was defined by lecanemab exposure and was independent of the route of administration (IV and SC). Exposure-response modeling demonstrated similar efficacy with bioequivalent exposures. The incidence of ARIA-E was correlated with lecanemab serum concentrations and modeling accurately predicted ARIA-E rate for each APOE4 genotype following SC and IV dosing. The ARIA-E incidence following a 500 mg SC autoinjector dose is predicted to be similar to that of 10mg/kg biweekly IV lecanemab for initiation. **Conclusions:** The 500 mg SC autoinjector is bioequivalent to 10 mg/kg IV biweekly for efficacy, amyloid clearance and ARIA-E. The SC option is

being developed for treatment initiation to improve patient convenience, access, and safety.

Presentation 2: Safety Profile of a Subcutaneous Lecanemab Formulation, Michael Irizarry[1], Larisa Reyderman[1], Steven Hersch[1], Michelle Gee[2], Thomas Doherty[2], Natasha Penner[1], Anna Patten[2], Shobha Dhadda[1], Lynn D. Kramer[1]
1. Eisai Inc., Nutley, NJ (United States), 2. Eisai Limited, Hatfield (United Kingdom).

Background: In two randomized controlled trials, lecanemab, a novel anti-amyloid protofibril antibody, has demonstrated reduction in brain amyloid and a consistent slowing of decline in clinical outcomes for up to 48 months in early Alzheimer's disease (AD). A maintenance dose of weekly 360 mg subcutaneous (SC) injection using an autoinjector was recently approved by the FDA. In addition, a weekly 500 mg SC dose that is bioequivalent to 10 mg/kg intravenous (IV) biweekly has been submitted to the FDA for treatment initiation. Amyloid reduction, efficacy, and safety (ARIA-E incidence) are explained by lecanemab exposure and are independent of route of administration (intravenous [IV] or SC). A SC lecanemab formulation has better safety profile, with lower rates of systemic administration reactions. This presentation will provide an update on the clinical safety results for the lecanemab 500 mg SC autoinjector. **Methods:** Clarity AD is a phase 3, double-blind, placebo-controlled study of 18-month treatment duration with an ongoing open-label extension (OLE) in patients with early AD. The 4 SC substudies within the Clarity AD phase 3 study all evaluated safety, including frequency and severity of adverse events. Although a subset of participants in a previous SC substudy (720 mg) were lecanemab naïve, all subjects treated with 500 mg SC autoinjector had previously received lecanemab. Validated anti-drug antibodies (ADA) and neutralizing antibody assays were performed using a tiered approach. **Results:** In the Clarity AD phase 3 study, lecanemab SC has a safety and tolerability profile consistent with what was reported for IV lecanemab, except for systemic injection related reactions that occurred at a lower rate (<2%) and severity with SC, compared to the rate (~26%) and severity of infusion-related reactions with IV lecanemab. In the 500 mg SC autoinjector substudy (mean duration: 3 months), seven participants (2.9%) experienced ARIA-H on 500 mg SC lecanemab. There were no systemic injection-related reactions, ARIA-E, intracerebral hemorrhages, or hypersensitivity reactions reported in participants receiving 500 mg SC lecanemab. Injection site reactions were infrequent and mostly of mild or moderate severity. All doses of IV and SC including lecanemab 500 mg SC weekly dosing had a low-risk for immunogenicity, with a benign ADA profile. **Conclusions:** SC lecanemab has a safety and tolerability profile that compares favorably to the approved 10mg/kg biweekly IV dose, but with low rate of systemic injection reaction relative to IV infusion-related reactions. Given that the majority of ARIA E generally occurs early in treatment (<6 months) in newly treated subjects, a low incidence of ARIA-E in these subjects was expected. Taken together with previous data in naïve patients that showed ARIA-E is exposure related and IV and SC formulations have equivalent exposures for treatment initiation, similar ARIA-E rates for weekly 500 mg SC and biweekly IV are expected. SC lecanemab has low-risk for immunogenicity. Autoinjector administration provides greater patient convenience with the opportunity for in-home administration by patient or care partner. Lecanemab 500 mg SC is being used as the backbone anti-amyloid therapy for the add-on study of the anti-tau antibody etalanetug in early AD.

Presentation 3: Potential Benefits of a Subcutaneous Formulation of Lecanemab.
Sharon Cohen[1], Erica Andreozzi[2], Steven Hersch[2], Michelle Gee[3], Michael Irizarry[2], Lynn D. Kramer[2]
1. Toronto Memory Program, Toronto, ON (Canada), 2. Eisai Inc. Nutley, NJ (United States), 3. Eisai Limited, Hatfield (United Kingdom).

Background: Lecanemab treatment has demonstrated substantially reduced markers of amyloid and significantly slowed clinical decline on multiple measures of cognition, function, and quality of life in individuals with early Alzheimer's disease (AD) at 18 months and with increasing magnitude of benefit demonstrated out to 48 months. Lecanemab was associated with ARIA and infusion reactions, tending to occur early in treatment. A subcutaneous (SC) administration of lecanemab was approved for maintenance therapy and is in development for initiation dosing to improve patient and caregiver convenience as well as to reduce healthcare resource utilization relative to intravenous administration. In this presentation, the potential benefits and place in therapy for a SC formulation of lecanemab will be highlighted. **Methods:** The results of the SC lecanemab clinical program in context of the current early AD treatment paradigm utilizing the available data, expert consensus treatment guidelines, and available AD literature will be highlighted. Results of the human factors validation study which evaluated whether the new lecanemab autoinjector can be safely and effectively used under the expected use environments by 110 trained and untrained participants (patients, caregivers, and healthcare providers) will be presented. In addition, we will present results from a recent device acceptability study that evaluated autoinjector ease of use and satisfaction/convenience as rated by patients, caregivers, and healthcare providers. **Results:** The newly developed lecanemab autoinjector offers an additional administration option with a weekly dosing schedule while enabling easier administration, increased access to the medication, and reduced burden. Overall, human factors study revealed that 94.5% and 82.7% of participants successfully administered the maintenance dose (1 injection) and the initiation dose (2 injections), respectively. Most user errors were (1) not using the 2nd autoinjector for administration or (2) study artifacts. Training increased the likelihood of administering a full SC dose (2 injections) for caregivers (94.1% trained vs. 73.3% untrained) and patients (90.6% trained vs. 74.2% untrained even with a 1-week ±2-day decay period between training and dose administration). Training was most impactful for lower MMSE patients (93.3% trained vs. 53.3% untrained). In the device acceptability study, most participants (≥96%) found the autoinjector very or extremely easy to use with or without any help. Results for satisfaction/convenience and confidence using the autoinjector were similar. SC lecanemab may have a prominent place in therapy for individuals with early AD. This formulation has the potential for substantial benefit for patients, caregivers, and healthcare providers. Survey data from patients who used the lecanemab SC autoinjector will be presented. **Conclusions:** Lecanemab is the first available SC antibody treatment for AD, which is now approved in the United States as a maintenance therapy (360 mg) and under development for treatment initiation (500 mg). The SC formulation of lecanemab may provide improved access, compliance, convenience, and patient safety (low rate of system injection reactions), and a diminished burden on patients, caregivers, and HCPs, with lower overall costs to healthcare systems. The lecanemab autoinjector can be used safely and effectively by appropriate patients, care partners, and health care providers, with high levels of satisfaction and confidence.

Disclsoures: Sharon Cohen is a consultant (no personal fees) for Alnylam, Alzheon, Biogen, Cognivue, Cogstate, Eisai, GSK, INmune Bio, J&J, Lilly, Novo Nordisk, RetiSpec, and Roche; Dr Cohen has received research grants (paid to institution) from AbbVie, Acumen, Alnylam, Alzheon, Biogen, BMS, Eisai, GSK, INmune Bio, Janssen, Lilly, Merck, Novo Nordisk, RetiSpec, Roche, and UCB Biopharma. All other authors are employees of Eisai.
Keywords: Early Alzheimer's disease, subcutaneous formulation, anti-amyloid therapies, mechanism, clinical pharmacology, biomarkers, lecanemab.

Key takeaway message: The lecanemab 500 mg subcutaneous formulation has the potential to become an expanded option for treatment initiation of patients with early Alzheimer's disease, with results showing comparable efficacy and safety to the IV formulation.

2. Roundtables

RT1- Charting the Path Forward for Combination Therapy in Alzheimer's Disease: Challenges, Considerations, and Collaborative Solutions.

H. Fillit[1], J. Cummings[2], D. Gallagher[3], S. Schindler[4]
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Presentation 1: Add-On Combination Therapy with Monoclonal Antibodies: Implications for Drug Development.

Presentation 2: Considerations in the Development and Use of Biomarkers for Combination Therapy in Alzheimer's Disease.

As the field of Alzheimer's disease (AD) therapeutics evolves, there is growing consensus that combination therapy will be necessary to maximize therapeutic benefit across the disease continuum. However, the development of combination therapies introduces complex questions and decisions for trial sponsors, ranging from clinical trial design and biomarker strategies to regulatory and operational considerations. Building upon a recent Journal of Prevention of Alzheimer's Disease (JPAD) Special Edition on this topic, this timely symposium features three expert presentations followed by a roundtable discussion focused on advancing combination therapy trials for AD. Given the multifactorial nature of AD pathophysiology, optimizing treatment response will require add-on therapies to the currently available anti-amyloid monoclonal antibody treatments for early AD. Yet, clinical experience with add-on therapies in this context remains limited. Well-defined strategies are needed both for enrolling patients already receiving available anti-amyloid agents into trials and for evaluating the safety and efficacy of add-on treatments. To initiate this dialogue, the first presentation outlines these and other critical considerations and offers recommendations for study sponsors planning future add-on trials. The second presentation examines the critical role of biomarkers in supporting combination therapy. Personalized treatment strategies for AD will likely involve combinations of therapeutic agents targeting multiple pathological processes. The success of these trials will depend heavily on biomarker-driven patient stratification and outcome assessment. This presentation outlines key considerations for biomarker selection, tailored to the mechanism of action, co-pathologies, and operational feasibility, and proposes immediate steps in biomarker development needed to prepare for future combination trials. The third presentation offers a regulatory perspective on the design and execution of combination therapy trials. To facilitate timely market access for effective combination therapies, it is essential for the field to engage with existing regulatory guidance and to interpret how regulatory frameworks support or challenge combination drug development. Early and proactive communication with regulatory authorities, along with the use of consistent, regulatory-aligned language, will be critical to advancing these efforts. This presentation offers practical insights on how trial sponsors can engage with regulators, strategically collect data, and align development plans with regulatory expectations to help streamline approval pathways and accelerate clinical development. The symposium will conclude with a roundtable discussion, providing the opportunity to address key considerations and questions raised in the presentations and share forward-looking perspectives on the future of combination therapies. Given the field's expanding understanding of AD biology, emerging therapeutic targets, and advancements in biomarkers, now is the time for coordinated, innovative, and proactive efforts to address the complexities of combination therapy development.

Keywords: Combination therapy, biomarker, clinical trials, drug development.

Key takeaway message: Given the field's expanding understanding of AD biology, emerging therapeutic targets, and advancements in biomarkers, now is the time for coordinated, innovative, and proactive efforts to address the complexities of combination therapy development.

3. Oral communications

3.1. Clinical trials: methodology

OC09- INSIGHTS INTO CLINICAL TRIAL RECRUITMENT: AN ANALYSIS OF PRESCREENING DATA FROM THE AHEAD STUDY.

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Background: Recruiting participants into clinical trials is challenging and can have a significant influence over the study completion timelines. Clinical trial sites commonly use prescreening questionnaires (prior to consent) to identify participants who are most likely to qualify for the trial at the screening visit, though these prescreening methods are rarely standardized or collected centrally. To develop evidence-based recruitment methods, it is important to better characterize individuals who have been prescreened at study sites and understand the underlying reasons many potential participants do not proceed to screening visit consent. The Alzheimer's Clinical Trials Consortium (ACTC) launched a study entitled A Data Driven Approach to Recruitment (DART), with the primary goal being to better understand the prescreening pipelines at study sites by centrally capturing a subset of participant-level prescreening data. The DART study was implemented for the AHEAD study, which consists of two sister trials in the preclinical Alzheimer's disease population (1). **Methods:** The AHEAD study is ongoing and aims to evaluate the safety and efficacy of lecanemab (BAN2401, Eisai Inc.) in cognitively unimpaired adults who have evidence of amyloid on PET imaging. Enrollment completed in October 2024. DART captured a subset of prescreening data, including age (collected in years but here categorized as age group-55-64; 65-80), sex (Male; Female), race (White, Black or African American, Asian, Native American/Alaskan Native; Hawaiian or other Pacific Islander; Other), ethnicity (Not Hispanic or Latino/a (NH); Hispanic or Latino/a), recruitment source (National Campaign; Social Media; Referral; Registry; Local Campaign; Website), prescreen eligibility (Eligible; Ineligible), and if ineligible, reason for prescreen-fail (Medical Inclusion/Exclusion; Non-medical Inclusion/Exclusion; No Longer Interested; Lost to Follow-up; Other). We examined differences in recruitment source, eligibility to pre-screen, and reason for prescreen-fail across age groups, sex, race and ethnicity. Fisher's Exact Tests were used for comparisons, and unadjusted p-values of 0.05 were considered statistically significant. **Results:** Thirty-six US-based AHEAD 3-45 study sites participated in DART from August 2021 through October 2024. The analyses included prescreening data from 11,337 participants, with a range of 17-1625 participants prescreened data entered per site. The sample was primarily female (65.4%) and of White race (73.8%), with 34% of participants at the young age group (55-64 years), and 66% of participants in the older age group (65-80 years). Overall, there were statistically significant

differences in recruitment sources by race, ethnicity, sex, and age group. The most common recruitment source overall was the AHEAD study website (42.9%). Local campaigns recruited the most participants who identified as Black or African American (60.7%), and Hispanic or Latino/a (33.8%). Recruitment sources were similar across men and women. Participants in the older age group were most often recruited through local campaigns (33.0%) and study website (34.5%), while the highest observed source of participants in the younger age group was the AHEAD study website (47.2%). Prescreen eligibility rates were similar across groups based on race and sex. Participants who identified themselves as Hispanic or Latino/a were less likely to be eligible following the prescreen (30.5%) compared to non-Hispanic or Latino/a participants (40.5%). In the older age group, 43.4% of participants were eligible at prescreen, compared to 35.2% of younger participants. Apparent differences in reasons for prescreen-fail were observed across demographic groups. Black or African American participants were more likely to be lost to follow-up (35.6%) as compared to the other racial groups. Black or African American and Asian participants had slightly higher ineligibility rates due to non-medical criteria (22.1% and 24.3%, respectively), compared to White participants (17.2%). Hispanic or Latino/a participants were more likely to be excluded based on a non-medical criterion (24.3% vs. 18.5%), while Non-Hispanic or Latino/a participants were more likely to be excluded due to a medical criterion (18.1% vs. 12.2%). Compared to the younger age group (age 55-64), older participants were more often ineligible due to medical criteria (24.1% vs. 13.7%), no longer being interested in the study (29.8% vs. 19.6%), or lost to follow-up (26.8% vs. 21.6%), whereas younger participants were more likely to be ineligible based on non-medical criterion (36.1% vs. 7.8%). **Conclusions:** These results support the use of central study websites in the recruitment process for multi-center clinical trials, while also demonstrating that the addition of local efforts are key to recruiting a more inclusive study cohort. Observed differences in reasons for prescreen-fail among demographic subgroups may suggest opportunities for revised study design and screening protocols, and removal of specific barriers to participation, as ways of increasing the representativeness of trial cohorts. **Keywords:** Clinical trial, recruitment, prescreening.

Disclosures: DRK has received research support from the National Institute on Aging and the Foundation for Neurologic Diseases. SW, KE: has received research support from the National Institute on Aging and Eisai (public-private partnership trial funding). JDG reports grant funding from NIA, BrightFocus Foundation, Alzheimer's Association, Eli Lilly, Genentech, Biogen, and Eisai. He reports travel provided by the Alzheimer's Association and provides paid editorial service to Alzheimer's & Dementia. GJM has received research support from the National Institutes of Health (NIH), the Alzheimer's Association, the American Heart Association, Gates Ventures, Eli Lilly, and Eisai. DMH has received grant support from the Alzheimer's Association, American Heart Association, NIH, NIA and Eisai. PA has research grants from NIH, the Alzheimer's Association, Lilly and Eisai, and consults with Merck, Roche, Genentech, Abbvie, Biogen, ImmunoBrain Checkpoint, AltPep, Bristol Myers Squibb and Neurimmune. RS has served as a consultant for AbbVie, AC Immune, Acumen, Alector, Apellis, Biohaven, Bristol Myers Squibb, Genentech, Ionis, Janssen, Oligomerix, Prothena, Roche, and Vaxxinity over the past 3 years. She has received research funding from Eisai and Eli Lilly for public-private partnership clinical trials and receives research grant funding from the National Institute on Aging/National Institutes of Health, GHR Foundation, and the Alzheimer's Association. Her spouse, K. Johnson, reports consulting fees from Novartis, Merck, and Janssen. RR has received grant funding from the National Institute on Aging, Eisai (public-private partnership trial funding), Alzheimer's Association, and the American Heart Association.

Reference: Rafi M et al. Alzheimer's and Dementia 2023; 19 (4): 1227-1233. https://doi.org/10.1002/alz.12748.

Key takeaway message: Our collection and analysis of prescreening data highlights differences in reasons for prescreen-fail across demographic subgroups and provides insights for study design, screening protocols, and removal of barriers to improve representation in multicenter clinical trials.

OC38- STRATEGIES FOR INCREASED REPRESENTATION IN TRIALS FROM THE NIA HEALTH AND AGING BRAIN STUDY.

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HABS-HD was intentionally designed to identify the earliest indicators of Alzheimer's disease (AD) and its related dementias across diverse racial and ethnic group by assessing AD related biomarkers in blood and CSF using highly sensitive proteomics-based techniques including the Luminex (n = 1141) and Single Molecule Array (SIMOA) platforms (n = 4462). The comprehensive effort within HABS-HD to identify blood biomarkers and their link to AD progression across diverse populations will be highlighted during this presentation. Specifically, it will 1) discuss the presence of selected blood biomarkers including Aβ42/42, total tau, NfL, ptau181, ptau217, and GFAP in certain groups; 2) examine the differences observed in blood biomarkers when participants are categorized by cognitive diagnosis and race/ethnicity; 3) describe the relationship observed between blood and neuroimaging biomarkers and 4) its application to predict amyloid and tau PET positivity in specific representative groups. Blood extracellular vesicles (EVs), small membrane-bound vesicles released by most cells and carry bioactive molecules, are currently being explored as novel AD biomarkers within HABS-HD. Blood measures of Aβ42/40, total tau, and NfL from neuronally-derived EVs (NEVs) will also be presented (n = 792). By extensively examining key blood biomarkers and their relationship to AD progression across diverse populations, this work enhances the broad applicability of our findings. Furthermore, this work marks a crucial step for HABS-HD in developing a population-specific, informed precision medicine approach that will lead to more targeted and effective interventions for all.

Key takeaway message: Strategies used by HABS-HD for recruiting minorities can be applied to trials to increase representation.

OC43- CONSIDERATIONS FOR PHASE 2 TRIALS OF AN AB VACCINE, AV-1959R, FOR SECONDARY PREVENTION OF ALZHEIMER'S DISEASE.

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Background: The AV-1959R vaccine was developed on a novel multiepitope platform designed to induce robust immune responses across diverse populations. It targets the N-terminal B cell epitope of pathological amyloid (Aβ1-11). A phase 1 first-in-human trial in 16 volunteers aged 40 to 60, used intramuscular injections with adjuvanted AV-1959R at doses of 100 μg, 300 μg, or placebo given at baseline, 4, and 14 weeks, followed by an 8-week observation period. This vaccine was observed to be safe and highly immunogenic, inducing a high magnitude of antibody responses in 100% of vaccinated individuals, suggesting its strong potential for at-risk populations. Based on these phase 1 outcomes (c.f., description of phase 1 in companion presentation: Agadjanyan et al.) we have planned a phase 2 study to extend assessments of safety, tolerability, and immunogenicity, and explore potential surrogate efficacy and clinical endpoints. Such a trial must be flexibly designed to allow for adaptations as greater knowledge is gained and for changes in the diagnostic and regulatory landscape. **Methods:** The randomized, controlled trial will evaluate safety primarily and then assess antibody titers of the adjuvanted AV-1959. Participants randomized to the vaccine or placebo vaccine will have an initial baseline injection followed by a booster at 4 weeks and a second booster at 48 weeks. The follow-up

period includes analysis of continuing safety and immune responses at 96 weeks. **Eligibility:** men and women, 65 to 80, with preclinical Alzheimer's supported by a positive amyloid PET or positive plasma pTau217/Aβ42 ratio. **Intervention:** AV-1959R, 300 μg, i.m. or adjuvant at baseline, week 4 and week 48. Randomization: stratified by age bracket to account for potentially differential age-related baseline characteristics and clinical course, and blocked by site to achieve an overall allocation ratio 4:1. **Sample size:** Based on phase 1 outcomes, 100+ participants will clearly show differential immune response and level of endogenous amyloid-targeting antibodies, providing a firm basis for assessing safety. **Recruitment:** Duration of about 10-12 months, 4 to 6 clinical sites, expected rate of 10 per month. **Primary Objectives:** Safety and tolerability of the adjuvanted AV-1959R. **Secondary Objectives:** Cellular and humoral immune responses. **Humoral immunity:** Plasma immunoglobulin isotypes (IgM, total IgG) and IgG subclasses (IgG1, IgG2, IgG3, IgG4). Plasma cytokine profiles. Cellular immunity (PBMC-based): Phenotyping of activated T cells. T cell proliferation assays. Cytokine polarization analysis (e.g., Th1, Th2, Th17 responses). Exploratory Objectives (plasma and molecular biomarkers): Aβ42, Aβ40, Aβ42/40 ratio, pTau217, pTau181, pTau231, Neurofilament light chain, glial fibrillary acidic protein (GFAP); Amyloid PET. **Immune Response Profiling:** PBMCs at baseline, week 4, week 48, and week 96. Average gene expression in non-activated and antigen-activated PBMC will provide insights into the overall transcriptome of different populations of T and B lymphocytes. Additionally, we can analyze the TCR of T cells and the BCR of B cells specific to our MultiTEP platform-based AV-1959R Aβ vaccine. **Results:** We expect a 10–12-month recruitment period that will allow all participants to be followed for 96 weeks and about half to have been followed for and additional 48 weeks (approximately) under a common close design. This flexible phase 2 design allows for adaptation of sample size, length of follow-up, repeated testing and safety assessment, a common close outcome, or an add-on sequential design component, any of which would increase the potential to detect important changes. **Conclusions:** We developed a MultiTEP, platform-based, Aβ vaccine to avoid the autoreactive T-cell infiltration of brain that occurred with the earlier AN-1792. Adjuvanted AV-1959R was safe, highly immunogenic, and induced very high titers of antibodies that recognized amyloid protofibrils and fibrils in all vaccinated individuals in phase 1. These characteristics make AV-1959R an appropriate candidate for secondary prevention for individuals with preclinical AD, by persistently inhibiting amyloid aggregation, potentially delaying tau pathology, and illness progression.

Key takeaway message: Adjuvanted AV-1959R was safe, highly immunogenic, and induced very high titers of antibodies that recognized amyloid protofibrils and fibrils. These characteristics make AV-1959R an appropriate candidate for secondary prevention through persistent inhibition of amyloid aggregation, potentially delaying tau pathology, and illness progression.

LB26- PHASE 1B/2A, 12-MONTH, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE SAFETY/TOLERABILITY AND PRELIMINARY EVIDENCE OF EFFICACY OF A TAU ANTI-SENSE OLIGONUCLEOTIDE IN PATIENTS WITH TAUOPATHIES.

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Background: Tauopathies are a heterogeneous group of neurodegenerative diseases characterized by abnormal accumulation of the microtubule-associated protein tau in the brain. These conditions are devastating, relentlessly progressive, and currently untreatable, leading to profound impairments in cognition, movement, and behavior that severely diminish quality of life and strain caregivers and health systems. 1 Tau aggregates disrupt neuronal function, trigger neuroinflammation, and ultimately cause neuronal death. Although tauopathy is most widely recognized in Alzheimer's disease, a number of tauopathies exist in which tau pathology is the central defining feature. These include progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and frontotemporal lobar degeneration (FTLD) associated with pathogenic variants in the MAPT gene. 2 The lack of disease-modifying treatments underscores the urgent need for innovative clinical trial designs that can efficiently test tau-directed interventions across syndromes, while accounting for heterogeneity in clinical course, pathology, and biomarker expression. **Methods:** The primary objective of this study is to evaluate the safety and tolerability of 12 months of a tau-directed ASO in a multi-disease basket trial enrolling patients with PSP, CBD, and MAPT variant–associated FTLD. The secondary objective is to assess target engagement through measurement of tau levels in cerebrospinal fluid (CSF) and plasma, as well as in vivo tau burden using tau PET imaging in a planned sub-study. Exploratory objectives include evaluating clinical efficacy through standardized clinical rating scales, functional measures, digital assessments, and longitudinal imaging and fluid biomarkers. The study will enroll N = 36 participants who meet consensus diagnostic criteria for PSP or CBD (the latter AD-biomarker negative), or who are confirmed carriers of pathogenic MAPT variants. Participants will be randomized 2:1 to active drug or placebo. The study drug will be delivered intrathecally every six months, after which all participants will be eligible to enroll in a 12-month open-label extension, providing critical longer-term safety and biomarker data. The trial will be conducted across 7–10 academic and specialty centers with expertise in PSP, CBD, and genetic FTD. **Results:** This is the first application of a within-syndrome basket approach in corticobasal syndrome (CBS) and the first multi-disease basket study of a tau-directed ASO across three distinct tauopathies. By enrolling patients with PSP, CBD, and MAPT mutations under a single protocol, the study establishes a framework for precision medicine trials in rare neurodegenerative diseases. Anticipated results include safety/tolerability, target engagement, and clinical trajectories. Together, these outcomes will build the foundation for larger efficacy-focused studies, while clarifying whether different tauopathies respond similarly or differentially to tau reduction strategies. **Conclusions:** A stratified "basket trial" design is a viable mechanism to enroll tauopathies to test a tau-directed ASO in three distinct tauopathies within a unified trial design.

Key takeaway message: This first-in-field basket trial of a tau-directed antisense oligonucleotide across PSP, CBD, and MAPT variant carriers will assess safety, target engagement, and exploratory efficacy, establishing a scalable framework for precision medicine in tauopathies.

3.2. Clinical trials: results

OC06- IMPACT OF A 10-YEAR MULTIDOMAIN LIFESTYLE INTERVENTION ON LONG-TERM RISKS FOR COGNITIVE IMPAIRMENT: THE LOOK AHEAD PROGRAMS WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE.

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Background: Obesity and type 2 diabetes in midlife increase risks for mild cognitive impairment and dementia. Whether a multidomain lifestyle intervention targeting weight loss, physical activity, nutrition counseling, and metabolic risk factor monitoring reduces these risks is unknown. **Methods:** Look AHEAD was a 10-year randomized controlled clinical trial to assess the impact of multidomain intensive lifestyle intervention (ILI) relative to a comparator of diabetes support and education (DSE) on health outcomes (1). Adults 45-76 years old with

established type 2 diabetes and overweight or obesity enrolled in the trial. On average, those assigned to ILI successfully maintained weight loss and increased physical activity during intervention delivery relative to DSE (2). For participants scoring below age- and education specific cutpoints on a standardized cognitive screener and completing a full neuropsychological assessment, a central panel of experts adjudicated no impairment, mild cognitive impairment (MCI) and probable dementia (PDM) using standardized criteria. Illness-death models (controlling for competing risks) were fitted to model the hazard ratio (HR) between ILI and DSE arms for 1) composite cognitive impairment (CCI: MCI or PDM) with adjustment for deaths occurring prior to and following CCI (3,4). The consistency of hazard ratios across prespecified subgroups was examined using tests of interactions. Censoring was at the last cognitive assessment. **Results:** Analyses between groups ($N = 4908$) were based on an average (standard deviation) of up to 16.5 ± 5.6 years of follow-up. This included 588 participants with adjudicated CCI who continued to be followed and 242 participants with adjudicated CCI who subsequently died. An additional 1452 participants who died without an adjudicated CCI and 2624 who were censored due to lost follow-up also contributed to the illness-death model analysis. At Look AHEAD enrollment these participants averaged 59.9 ± 6.8 years of age, 6.7 ± 6.4 years of diabetes duration, and 35.9 ± 5.9 kg/m2 body mass index (BMI). CCI incidence was greater ($p < 0.0001$) among individuals who were older, male, heavier, APOE-e4 carriers, and who had a history of cardiovascular disease and longer durations of diabetes. The risk of CCI did not differ between ILI and DSE: HR = 0.96 [95% confidence interval 0.83,1.11]. Baseline BMI significantly modified the effect of intervention (ILI vs. DSE) on cognitive impairment risk (interaction $p = 0.01$) such that participants in the intervention group who had overweight at baseline (BMI 25–29 kg/m^2) had a relatively lower risk of CCI HR = 0.63 [0.43,0.91], while those with obesity levels of BMI 30–39 kg/m^2 and >40 kg/m2 did not with HR = 0.97 [0.81,1.16] and HR = 1.38 [0.97,1.98] respectively. Incidence rates did not differ between intervention groups across subgroups based on sex, history of cardiovascular disease, duration of diabetes, and APOE-e4 carriage (all interaction $p > 0.40$). **Conclusions:** The 10-year Look AHEAD multidomain ILI did not reduce risks for cognitive impairment overall, however it may have markedly reduced risks among individuals with overweight (but not obesity) at baseline.

Keywords: Multidomain lifestyle intervention, type 2 diabetes, cognitive impairment.

Clinical Trial Registry: NCT00017953.

Data Deposition: NIDDK Central Repository (https://repository.niddk.nih.gov/home).

Disclosures: The Look AHEAD was funded by grants and cooperative agreements from NIDDK and NIA. MAE receives research funding from the Alzheimer's Association. The authors have no other relevant conflicts to disclose.

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Key takeaway message: A 10-year multidomain lifestyle intervention may markedly reduce risks for composite mild cognitive impairment and dementia among adults with type 2 diabetes and overweight, but not obesity.

OC07- OUTCOMES FROM THE BETTERBRAINS TRIAL, A MULTI-DOMAIN, PERSON-CENTERED, DEMENTIA RISK FACTOR MANAGEMENT RANDOMISED CONTROLLED TRIAL TO PREVENT COGNITIVE DECLINE.

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Background: Many risk factors for dementia are well understood and can be modified. However, many barriers limit the application of modification strategies. One major limitation is adherence. While there is no consensus on the optimal level of participation in lifestyle interventions, a threshold of 66% completion of prescribed interventions has been suggested due to its widespread application in studies, and its suitability for behavioural interventions. Using this definition, adherence to all multi-domain interventions has been low (e.g., 19% in FINGER, 50% in MAPT, and 34% in Maintain Your Brain) (1,2). As dementia risk factors, physical capabilities, and interests vary substantially between adults, adherence may be improved by interventions targeted to individuals, rather than the general prescriptive approach used in previous trials. The BetterBrains trial aimed to test the hypothesis that a person-centered dementia risk factor management program could optimize adherence and prevent cognitive decline in community-dwelling, middle-aged adults with a family history of dementia. **Methods:** This is a prospective, blinded endpoint, 24-month randomized control trial to test the effectiveness of BetterBrains, an online, person-centered, risk factor management intervention to prevent cognitive decline. Computer-generated allocation was conducted using permuted blocks of variable sizes after the baseline assessment. The intervention arm received standard health education, telehealth-based person-centered goal setting, motivational interviewing, and follow-up support, health care provider communication and community linkage for management of known modifiable dementia risk factors (3). The control arm received standard health education only. The primary outcome is superior cognition at 24-months post-baseline, defined as the absence of decline (rate of change over 24-mths that is less than 0.5 SD) on one or more of the following tests, (a) Cogstate Detection, (b) One Card Learning, (c) One Back tests, and the (d) Cognitive Function Instrument total score. **Results:** Between August 2021 and July 2023, 1830 participants enrolled, 1384 completed risk factor assessment (76%), 1061 completed baseline assessment (58%), and 1053 were randomised (57%). Randomised participants were aged 59.7 (±6.8) years, 83% women, 90% highly educated (>12 years of education), 93% White, and 100% reported a first- or second-degree family history of dementia. 27% (n = 285) resided in regional or rural Australia. Participants were randomised to intervention (n = 526) or control (n = 527). At final visit, 2.9% (n = 15) of the sample had discontinued from intervention, 89% (n = 469) had adhered to the intervention (minimum 4 out of 6 telehealth calls), with 88% (n = 463) reporting that they have achieved at least one goal. Final participant, final visit will be completed on 30 June 2025. Database lock will occur in July 2025. Primary and secondary outcomes of this trial will be reported in exclusivity in December 2025 at CTAD. We will report on the efficacy and feasibility of the BetterBrains intervention in preventing cognitive decline. **Conclusions:** This randomized controlled trial will test the hypothesis that an online, personalized intervention program (BetterBrains) can prevent cognitive decline. By leveraging existing community services and using a risk factor management pathway that tailors the intervention to each participant, we demonstrate that the BetterBrains methodology can increase likelihood for engagement and long-term adherence in at-risk individuals.

Clinical Trial Registry: ACTRN 12621000458831.

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multidomain interventions for dementia prevention: Data from the FINGER and MAPT trials. Alzheimer's and Dementia 2019; 15:729-741. 2. Brodaty H, Chau T, Heffernan M et al. An online multidomain lifestyle intervention to prevent cognitive decline in at-risk older adults: A randomised controlled trial. Nature Medicine 2025; 31:565-573. 3. Lim YY, Ayton D, Perin S et al. An Online, Person-Centered, Risk Factor Management Program to Prevent Cognitive Decline: Protocol for A Prospective Behavior-Modification Blinded Endpoint Randomized Controlled Trial. J Alzheimers Dis 2021; 83:1603-1622.

Key takeaway message: This trial shows that a personalized, telehealth-delivered intervention (BetterBrains) can achieve high adherence in at-risk adults. Primary and secondary outcomes will be reported at CTAD.

OC08- QUANTIFYING TAU KNOCKDOWN IN INDIVIDUALS WITH ALZHEIMER'S DISEASE RECEIVING INTRATHECAL TAU MAPT ANTISENSE OLIGONUCLEOTIDE NIO752 USING STABLE ISOTOPE LABELLING KINETICS (SILK) – INTERIM ANALYSIS OF A PHASE 1B RANDOMISED, DOUBLE-BLINDED, PLACEBO-CONTROLLED, MULTICENTRE TRIAL.

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Background: Tau deposition is associated with clinical disease progression and cognitive impairment in Alzheimer's disease (1,2), making it a promising therapeutic target in symptomatic AD (3,4). Increased tau production is observed in the presence of amyloid pathology (5). To address tau overproduction, a promising therapeutic approach is to block tau translation using mRNA therapy. Antisense oligonucleotides (ASO) are single-stranded oligodeoxynucleotides that can alter RNA and reduce protein expression (6). They have demonstrated impact on disease progression in other neurodegenerative disease such as Spinal Muscle Atrophy (7). A major problem in targeting translation of an intracellular protein like tau, is that it is difficult to quantify the amount of tau knockdown achieved in human brain tissue. There is likely to be a mismatch between the large repositories of intracellular tau and tau released into the extracellular space and cerebrospinal fluid (CSF) compartment (8). Furthermore, the turnover of tau in CSF is long (half-life 23 days) (5) with no way of distinguishing 'old' tau from newly translated tau. One way to overcome this is to use stable isotope labelling kinetics (SILK) to accurately quantify the rate of new tau translation. This addresses a major knowledge gap in the field of tau therapies, providing a more direct readout of tau target engagement. This will allow for more accurate dose selection for later phase trials and avoid overshooting which may have important safety implications. **Methods:** Phase 1B, randomised, double-blinded, placebo-controlled, trial of NIO752 in participants with mild-moderate sporadic ($n = 5$) and autosomal dominant AD (ADAD) ($n = 5$), assigned to receive NIO752 or placebo in ratio of 3:2 in both cohorts. Key inclusion criteria include CDR <2. Participants receive an intrathecal (IT) injection of NIO752 or placebo on Day 0 followed by an intravenous infusion of 13C6 Leucine stable isotope between 24 and 72 hours post IT injection. CSF and plasma are collected on days 0, 23, 60, 85, 123. All participants receive open label NIO752 IT injection on Day 123 with another overnight stay for safety monitoring. Stable isotope enrichment of free leucine is quantitated in plasma using gas chromatography-mass spectrometry (GC-MS) from samples collected at serial timepoints during isotopic infusion. Isotopic enrichment of tau is quantified using immunoprecipitation mass spectrometry. Tau synthesis and clearance is modeled using tau tracer to tracee ratio adjusted for plasma leucine enrichment. **Results:** Five participants are recruited to date with 5 more expected to be recruited by Q1 2026. Interim analysis providing safety data and showing the rate of tau synthesis on Day 23 will be presented. We will provide data on CSF tau characterisation and phosphorylation profile in response to NIO752. **Conclusions:** We present interim analysis of safety data and tau SILK data from a phase 1B randomised, double-blinded, placebo-controlled, multicentre trial of tau MAPT ASO therapy in individuals with sporadic AD and ADAD. Our study aims to optimize tau MAPT ASO dose and demonstrate the feasibility of using SILK to quantify tau production rates in early phase AD trials.

Keywords: Alzheimer's Disease, AD, Tau, MAPT, Antisense Oligonucleotide, ASO, Stable Isotope Labelling Kinetics, SILK, phase 1b, trial.

Clinical Trial Registry: NCT06372821; https://clinicaltrials.gov/study/NCT06372821?term=nio-silk&rank=1.

Disclosures: RJB and CS may receive income based on technology (''Tau kinetics measurements'') licensed by Washington University to C2N Diagnostics. CM has provided consultancy to Alector, Biogen, Eisai, Ionis, Lilly, MSD, Neurimmune, Novartis, Prevail, Roche/Genentech, Wave. She is an advisor to the Drug Delivery Foundation. She has received honoraria for teaching and education from Biogen, Eisai and Lilly, and received academic funding award from Biogen. She is supported by the NIHR UCLH Biomedical Research Centre. NG has participated, or is currently participating, in clinical trials of anti-dementia drugs sponsored by Bristol Myers Squibb, Eli Lilly and Avid Radiopharmaceuticals, Janssen Immunotherapy, Novartis, Pfizer, and Wyeth, as well as the Study of Nasal Insulin to Fight Forgetfulness (SNIFF) and the Anti-Amyloid Treatment in Asymptomatic Alzheimer Disease (A4) trial. She receives research support from the Tau Consortium and the Association for Frontotemporal Dementia and is funded by the NIH. She consults for BCBSA. NG has participated, or is currently participating, in clinical trials of anti-dementia drugs sponsored by Bristol Myers Squibb, Eli Lilly and Avid Radiopharmaceuticals, Janssen Immunotherapy, Novartis, Pfizer, and Wyeth, as well as the Study of Nasal Insulin to Fight Forgetfulness (SNIFF) and the Anti-Amyloid Treatment in Asymptomatic Alzheimer Disease (A4) trial. She receives research support from the Tau Consortium and the Association for Frontotemporal Dementia and is funded by the NIH. She consults for BCBSA. EMM has received research support from the National Institutes of Health, the National Institute on Aging, Alzheimer's Association, GHR Foundation, an anonymous organization, Knight Family, and the DIAN-TU Pharma Consortium (Biogen, Eisai, Eli Lilly and Company/Avid Radiopharmaceuticals, F. Hoffman-La Roche/Genentech, and Janssen). He is a co-inventor of the "Methods of diagnosing AD with phosphorylation changes" technology licensed by Washington University to C2N Diagnostics. Washington University also holds 5% equity in C2N. Through these relationships, Washington University and EMM are entitled to receive royalties from the license agreement with C2N. He is co-author of the Alzheimer Association's 2024 Alzheimer's disease updated diagnostic criteria. He has received travel support from the Alzheimer's Association for work related to the development of the document. He has served as a consultant, a member of advisory boards, or a DSMB member for Eli Lilly, Alector, Alzamend, Sanofi, AstraZeneca, Hoffman La-Roche, and Merck. RJB has received research support from the National Institutes of Health, Alzhemier's Association, GHR Foundation, an anonymous organization, DIAN-TU Pharma Consortium (AbbVie, Biogen, Bristol Myers Squibb, Eisai, Eli Lilly and Company, F Hoffman-La Roche/Genentech, Ionis, Janssen, Prothena), the Tau SILK Consortium (AbbVie, Biogen, Eli Lilly and Company, Novartis), and the NfL consortium (AbbVie, Biogen, F. Hoffman-La Roche, and Bristol Myers Squibb). He has also received funding from Eisai, Eli Lilly and Company, Avid Radiopharmaceuticals, Janssen, and F. Hoffmann-La Roche. He has received in-kind support from

Cogstate, Cerveau, and Signant Health. RJB co-founded C2N Diagnostics, which offers the PrecivityAD2 blood test. Washington University and RJB have equity ownership interest in C2N Diagnostics and receive income based on technology (stable isotope labelling kinetics, blood plasma assay, and methods of diagnosing AD with phosphorylation changes) and receives income from C2N Diagnostics for serving on the scientific advisory board. He has served as an unpaid member of advisory boards for Roche and Biogen. RWP has received honoraria from GE Healthcare for academic talks and co-leads the Neurofilament light consortium which receives funding from Abbvie, Biogen, Bristol Myers Squibb and Roche.

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Key takeaway message: We present interim tau SILK data from a phase 1B trial aiming to optimize tau MAPT ASO dosing and demonstrate SILK's feasibility to quantify tau production rates in early-stage clinical studies.

OC10- RESULTS FROM THE OPEN-LABEL EXTENSION PERIOD OF TOGETHER, A PHASE II STUDY EVALUATING EFFICACY, SAFETY AND TOLERABILITY OF BEPRANEMAB IN PRODROMAL–MILD ALZHEIMER'S DISEASE.

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Background: Tau is a key neuropathological hallmark of Alzheimer's disease (AD). Bepranemab, an IgG4 monoclonal antibody, targets a mid-region epitope of human tau (amino acids 235–250), proximal to the microtubule binding region. The Phase II TOGETHER study investigated the efficacy, safety and tolerability of intravenous bepranemab (45/90 mg/kg or placebo every 4 weeks for 76 weeks of double-blind treatment) in prodromal-to-mild AD, with the primary analysis timepoint at Week 80. Results from the double-blind treatment period showed that bepranemab was well tolerated and resulted in a reduction in the rate of tau accumulation, as assessed by positron emission tomography (PET). This was associated with a reduction in the rate of cognitive decline (14-item AD Assessment Scale-Cognitive Subscale [ADAS-Cog14]), but not with functional change (Clinical Dementia Rating Scale-Sum of Boxes [CDR-SB]). The open-label extension (OLE) period of TOGETHER aimed to assess the long-term safety and tolerability of bepranemab. **Methods:** TOGETHER was a global, multicenter, participant- and investigator-blind, placebo-controlled, parallel-group study. Following completion of the 80-week double-blind treatment period, participants were eligible to enter the 48-week OLE period and receive bepranemab (45/90 mg/kg, intravenously every 4 weeks) for a further 44 weeks, followed by a safety follow-up period, 20 weeks after the last infusion of bepranemab. Participants who received bepranemab during the double-blind treatment period continued on the same blinded dose. Participants randomized to placebo during the double-blind treatment period were re-randomized 1:1 to 45 or 90 mg/kg bepranemab. The main focus of the OLE period was to assess safety over time, and key exploratory endpoints included: safety; change from Baseline to the end of the study in the CDR-SB, ADAS-Cog14 and Mini-Mental State Examination total scores; and change in tau pathology, measured by PET. Some endpoints were analyzed from the Baseline of the double-blind treatment period and all endpoints were analyzed from the Baseline of the OLE period. **Results:** In total, 466 participants were randomized into the double-blind treatment period of the TOGETHER study, of which 391 completed and entered the OLE period. At Week 124, 346 participants had completed the last dosing visit. In the double-blind treatment period, bepranemab reduced cognitive decline (21–25% reduction in ADAS-Cog14 total score versus placebo), and slowed tau accumulation in the whole cortical gray and Jack temporal meta-regions (33–58% versus placebo) with nominal significance. Results from the OLE period of TOGETHER will be presented, including final disposition data, an overview of the long-term safety of bepranemab, and exploratory clinical endpoints. **Conclusions:** Results from the TOGETHER OLE will provide further information about the long-term safety and efficacy of bepranemab.

Keywords: Alzheimer's disease, tau, monoclonal antibody, open-label extension.

Clinical Trial Registry: NCT04867616; https://clinicaltrials.gov/study/NCT04867616.

Disclosures: WB, IRM, TB, BVDS, HVT, KT, OF, JB, SS, UM, RPM and CE declare current or previous employment by UCB. IRM, TB, BVDS, HVT, KT, JB, SS, UM, RPM and CE declare ownership of UCB stock/shares. TB and CE declare a patent application pending for bepranemab to protect results in Alzheimer's disease and progressive supranuclear palsy. This research was funded by UCB.

Key takeaway message: Results from the TOGETHER open-label extension will provide further information about the long-term safety and efficacy of bepranemab.

OC21- DONANEMAB IN EARLY SYMPTOMATIC ALZHEIMER'S DISEASE: ADDITIONAL INSIGHTS FROM THE TRAILBLAZER-ALZ 2 LONG-TERM EXTENSION.

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Background: TRAILBLAZER-ALZ 2 (NCT04437511) is a multicenter, randomized, double-blind, placebo-controlled (PC) Phase 3 trial designed to assess the efficacy and safety of donanemab in participants with early symptomatic Alzheimer's disease. At 76 weeks, donanemab treatment significantly slowed clinical progression in the PC period. Participants who completed this period were eligible to continue into the participant- and investigator-blinded long-term extension (LTE) period, lasting an additional 78 weeks. **Methods:** Delayed start participants (those initially randomized to placebo in the PC period) began treatment with donanemab in the LTE. Both early start participants (those initially randomized to donanemab in the PC period) and delayed start participants were switched to placebo if treatment completion criteria were met based on amyloid level during any treatment period. All analyses are exploratory and not controlled for multiplicity. **Results:** The final analysis is pending completion. The results will be updated by the late-breaking abstract deadline. **Conclusions:** Conclusions are pending completion of the final analysis. **Keywords:** Alzheimer's

disease, donanemab, clinical trials, amyloid-targeting therapies.
Clinical Trial Registry: NCT04437511; https://clinicaltrials.gov.
Disclosures: JRS is an employee and minor shareholder of Eli Lilly and Company.
Key takeaway message: Pending completion of the final analysis.

OC22- A FIRST-IN-HUMAN DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTIPLE ASCENDING DOSE PHASE 1 STUDY EVALUATING THE SAFETY AND PHARMACOKINETICS OF PRX005/BMS-986446, A NOVEL ANTI-MTBR TAU MONOCLONAL ANTIBODY, IN HEALTHY ADULTS AND PATIENTS WITH ALZHEIMER'S DISEASE.

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Background: Alzheimer's disease (AD) is the leading cause of cognitive impairment and dementia worldwide, with rising prevalence and mortality highlighting the need for new, transformative treatment options. Amyloid plaques and neurofibrillary tangles composed of intracellular misfolded tau protein are the neuropathologic hallmarks of AD. Of the two, the accumulation of tau tangles correlates more robustly with progressive cognitive decline (1). Tau pathology is believed to progress via cell-to-cell transmission (2). PRX005/BMS-986446, a humanized immunoglobulin G1 (IgG1) kappa monoclonal antibody, targets the microtubule-binding region of tau (MTBR-tau), a key region in tau aggregate formation, and is designed to prevent cell-to-cell tau transmission and delay cognitive decline in AD. To characterize the safety/tolerability, pharmacokinetics, and immunogenicity of intravenously administered PRX005/BMS-986446, a single-ascending dose (SAD) and multiple-ascending dose (MAD) study in healthy adults and patients with AD was conducted. SAD data were previously reported; PRX005/BMS-986446 was safe and well tolerated and plasma exposure increased dose-proportionally in healthy participants (3). Presented here are results from the MAD portion of the first-in-human phase 1 clinical trial. **Methods:** The MAD population was divided into 2 cohorts: healthy participants and patients with biologically defined early AD. All participants were aged 55–85 years. Participants in both cohorts were randomly assigned 3:1 to intravenously infused PRX005/BMS-986446 or placebo (administered on days 1, 29, and 57) followed by pharmacokinetic and safety assessments up to day 113. Cerebrospinal fluid (CSF) was collected in patients with AD either on days 30 and 58 (subgroup A) or days 58 and 85 (subgroup B). Key safety endpoints included treatment-emergent adverse events (TEAEs), serious TEAEs, and treatment-related TEAEs. **Results:** Multiple doses of PRX005/BMS-986446 were generally safe and well tolerated in healthy participants and in those with AD. There were no deaths, serious TEAEs, severe TEAEs, or treatment-related TEAEs leading to discontinuation. No confirmed positive anti-drug antibodies were observed in any participant receiving PRX005/BMS-986446. Time of the maximum measured concentration (Tmax) was similar in healthy participants and those with AD (ranging from 1.0 to 3.1 hours). Systemic exposures (maximum observed concentration [Cmax] and area under plasma concentration-time curve [AUC]) were lower in patients with AD than in healthy participants; no substantial accumulation was observed after the third dose on day 57 in either cohort. Terminal elimination half-life (T1/2) was similar between healthy participants (mean = 349 hours) and patients with AD (mean = 350 hours). Mean CSF/plasma ratios ranged from 0.002 to 0.010 across all sampling time points, with considerable interindividual and intergroup variabilities. **Conclusions:** In this first-in-human MAD study in healthy participants and patients with early AD, PRX005/BMS-986446 was safe and well tolerated. Observed CSF concentrations indicate adequate distribution to the central nervous system for targeting of MTBR-tau. These results support further clinical development of PRX005/BMS-986446, including in an ongoing phase 2 trial.
Keywords: Anti-tau, Alzheimer's disease, microtubule-binding region.
Disclosures: DW is an employee of CenExelCNS. BC, PD, DM, and CS are employees of Prothena. FM and JL were employees of Prothena at the time the study was conducted. MT, MC, ADS, NC, NH, and IG are employees and/or shareholders of Bristol Myers Squibb.
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Key takeaway message: This first-in-human MAD phase 1 study demonstrated that novel anti-MTBR tau monoclonal antibody PRX005/BMS-986446 was safe and well tolerated in patients with Alzheimer's disease, with peripheral and central pharmacokinetic results supporting further clinical development.

OC23- FIRST-IN-HUMAN STUDY OF ADEL-Y01, A MONOCLONAL ANTIBODY TARGETING ACETYLATED TAU (ACK280) IN THE MTBR: SAFETY AND PHARMACOKINETICS IN HEALTHY ADULTS AND EARLY ALZHEIMER'S DISEASEE.

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Background: Despite intensive efforts to develop tau-targeting immunotherapies for Alzheimer's disease (AD), antibodies directed against the N-terminal or C-terminal regions of tau have failed to demonstrate clinical efficacy. These failures have highlighted the need to target domains more directly involved in pathological tau aggregation and propagation. The microtubule-binding region (MTBR), particularly the hexapeptide motif VQIINK (residues 275–280), plays a critical role in tau fibrillization and prion-like seeding. Within this motif, acetylation at lysine 280 (acK280) is a pathologically relevant post-translational modification that enhances aggregation propensity and impairs tau clearance. ADEL-Y01 is a first-in-class humanized IgG1 monoclonal antibody specifically targeting acK280 in the MTBR, designed to intercept tau seeding and propagation. By neutralizing acetylated, seed-competent tau and promoting its clearance, ADEL-Y01 offers a mechanistically distinct and potentially disease-modifying approach compared to previous tau immunotherapies. **Methods:** This randomized, double-blind, placebo-controlled Phase 1 trial consists of two parts. The phase 1a, single ascending dose (SAD) part evaluates five IV dose levels (2.5, 7.5, 20, 50 and 100 mg/kg) in healthy adults, with each cohort comprising 6 active and 2 placebo participants (n = 8). The phase 1b, multiple ascending dose (MAD)part enrolls patients with mild cognitive impairment due to AD or mild AD into three cohorts. Safety, pharmacokinetics (PK), cerebrospinal fluid (CSF) penetration, and exploratory biomarker analyses are assessed. **Results:** Dosing has been completed in all Phase 1a (SAD) cohorts, with no serious or dose-limiting toxicities observed. Pharmacokinetic profiles showed dose-proportional increases in serum exposure, and central nervous system (CNS) penetration was confirmed by measurable ADEL-Y01 concentrations in the CSF. The phase 1b (MAD) part is currently ongoing. **Conclusions:** ADEL-Y01 demonstrated favorable preliminary safety, tolerability, predictable PK, and confirmed CNS penetration in healthy volunteers. As a first-in-class monoclonal antibody specifically targeting acK280-MTBR tau, ADEL-Y01 represents a novel approach to disrupt the pathological cascade of tau seeding and propagation. The ongoing MAD evaluation may propose potential disease-modifying effects, positioning ADEL-Y01 as a promising therapeutic candidate for AD and potentially other tauopathies.

Keywords: Phase 1, Alzheimer's disease, tau, antibody.
Clinical Trial Registry: NCT06247345; https://clinicaltrials.gov/study/NCT06247345.
Disclosures: This work was supported by a grant (HU23C0296) from the Korea Dementia Research Center (KDRC), funded by the Ministry of Health and Welfare, Republic of Korea.
Key takeaway message: ADEL-Y01, a first-in-class anti-acK280 tau antibody, showed favorable safety, PK, and CNS penetration in Phase 1a, offering a novel disease-modifying approach to target tau seeding in Alzheimer's disease.

OC25- RESULTS OF A PHASE 1, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF ASCENDING SINGLE IV DOSES OF VY7523, A TAU-TARGETING THERAPEUTIC, IN HEALTHY ADULT PARTICIPANTS.

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Background: Accumulation and seeding of pathological tau in Alzheimer's disease (AD) is believed to propagate preferentially through brain regions that are synaptically and functionally connected. The pattern of tau protein spread in AD correlates with the development and progression of cognitive symptoms and functional decline. VY7523 (formerly VY-TAU01) is a humanized immunoglobulin gamma 4 (IgG4) monoclonal antibody that targets a specific epitope on the C-terminal region of tau. VY7523 is hypothesized to inhibit the extra-cellular spread of pathological tau and, thereby, potentially prevent AD progression. **Objectives:** This first-in-human study assessed the safety, tolerability and pharmacokinetics (PK) of 6 single intravenous (IV) ascending doses of VY7523 in healthy adult participants. **Methods:** 48 healthy participants aged 18-75 years were planned to receive VY7523 or placebo administered once intravenously. Each of the 6 sequential dose-level cohorts included 2 sentinel participants randomized in a 1:1 ratio to VY7523 or placebo, followed by 6 participants randomized in a 5:1 ratio, treatment-to-placebo, after at least 48 hours and safety review of the sentinel cohort. After dosing, participants underwent clinical, electrocardiographic and laboratory assessments over up to 12 weeks for Cohorts 1 to 3 and up to 16 weeks for Cohorts 4 to 6 to evaluate incidence of treatment emergent adverse events (TEAEs), serum anti-VY7523 antibodies, serum and cerebrospinal fluid (CSF) VY7523 concentrations. **Results:** 48 heathy participants (age range 21-75 years, mean 45.4 years, SD = 14.1; n = 21 women) were enrolled and received VY7523 or placebo. VY7523 was well tolerated across all 6 ascending dose cohorts. There were no infusion related reactions or serious adverse events reported. No clinically significant changes in vital signs, physical exam, routine laboratory tests, or electrocardiogram. Mild-to-moderate adverse events were uncommon and similar between treatment and placebo groups. Serum concentrations increased in a dose proportional manner and observed half-life supports monthly dosing. The CSF-to-serum ratio was 0.3%, consistent with the range of other monoclonal antibodies approved for the treatment of AD. **Conclusions:** A single IV dose of VY7523 was well-tolerated and showed dose proportional PK supporting continuation of its development in the ongoing multiple ascending dose (MAD) study in participants affected by AD (NCT06874621). Topline safety, PK and immunogenicity data will be presented.
Keywords: Alzheimer's disease, tau, first-in-human clinical trial, pharmacokinetics.
Clinical Trial Registry: NCT06874621, https://clinicaltrials.gov.
Disclosures: 1. Voyager Therapeutics employees and shareholders. 2. Voyager Therapeutics contractors.
Key takeaway message: VY7523 was safe and well tolerated in healthy adults across all single ascending dose levels, showed dose-proportional pharmacokinetics, and achieved expected CSF penetration, supporting ongoing development in Alzheimer's disease.

OC30- INTERIM ANALYSIS OF POST-MARKETING OBSERVATIONAL STUDY OF LECANEMAB IN JAPAN.

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Background: In the global phase 3 clinical trial (1), the most commonly reported adverse events with lecanemab were infusion-related reactions and Amyloid-related imaging abnormalities (ARIA). The aim of the study is to evaluate the occurrence of these adverse events in real-world settings in Japan. **Methods:** An all-case surveillance study was initiated in Japan when lecanemab was launched in December 2023. Patients with early Alzheimer's disease (mild cognitive impairment or mild dementia due to Alzheimer's disease) who are administered lecanemab are being observed for up to three years. Adverse events of ARIA and infusion-related reactions are collected. **Results:** As of the data cutoff date of January 5, 2024, a total of 5125 patients were enrolled from 549 medical institutions. The interim analysis included 491 patients who had received lecanemab up to 28 weeks. The median age (min-max) was 75.0 years (49-92), 65.4% were female, 59.5% were mild cognitive impairment. Mean (standard deviation) body weight was 53.2 kg (10.2 kg). Mean baseline Clinical Dementia Rating-Sum of Boxes score was 2.43 ± 1.37 (n = 338). Amyloid positivity was determined by positron emission tomography in 53.6% (n = 263) of patients, by measurement of Aβ1-42 in cerebrospinal fluid in 44.2% (n = 217) of patients and both of them in 0.4% (n = 2) of patients. Mean duration of treatment with lecanemab was 27.1 weeks. Adverse events of ARIA occurred in 3.9% of patients, with all cases being asymptomatic. ARIA with edema or effusions (ARIA-E) were reported in 1.2% of patients. For ARIA-H, cerebral microhemorrhages were reported in 2.9% of patients and superficial siderosis in 0.2% of patients. No intracerebral hemorrhage $\geq$ 1 cm occurred. No serious adverse events were reported for either ARIA-E or ARIA-H. The severity of ARIA-E was mild or moderate based on magnetic resonance imaging, whereas all ARIA-H cases were mild. Adverse events of infusion-related reactions were reported in 17.5% of patients. **Conclusions:** In an interim analysis of patients with a mean duration of treatment of 27.1 weeks, the rate of ARIA-E and ARIA-H were 1.2% and 3.1%, respectively. **Keywords:** Lecanemab, amyloid-related imaging abnormalities, infusion-related reactions, post-marketing study.
Clinical Trial Registry: NCT06322667; https://clinicaltrials.gov/.
Disclosures: AI has received honoraria as a medical advisor for this study. YS, KK, AE, WK, KS and MI are employees of Eisai Co., Ltd.
Reference: 1. van Dyck CH et al. N Engl J Med. 2023; 388 (1):9-21. https://doi.org/10.1056/NEJMoa2212948.

OC31- COMPLETION OF A PHASE 2 TRIAL EVALUATING SAFETY AND EFFICACY OF THE SYNAPTIC REGENERATIVE SMALL MOLECULE SPG302 IN PARTICIPANTS WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE.

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Background: Alzheimer's disease (AD) is at its core a synaptopathy characterized by an early and progressive loss of glutamatergic synapses that essentially uncouples limbic and cortical circuits involved in memory and cognition. The well-established role of synapse loss in AD etiology, combined with observations that aged individuals with normal

synaptic density demonstrate cognitive resilience in the face of AD-like molecular pathology, prompt the hypothesis that synaptic regeneration presents a viable approach to slowing or even reversing memory and cognitive symptoms. SPG302 is a novel, rapid-acting synaptogenic small molecule developed by Spinogenix that triggers the formation of new axospinous glutamatergic synapses. In a NIH supported a mouse model of AD [1; 1R43 AG058278-01A1], once-daily treatment with SPG302 for 1 month rapidly reversed large deficits in synaptic density in the hippocampus and performance on hippocampal dependent tasks. Completed Phase 1 trials in healthy volunteers established that once-daily SPG302 is safe and well tolerated, and that doses well below the NOAEL achieve plasma exposures associated with efficacy in preclinical models. These findings supported advancement of SPG302 to clinical evaluation. Described herein are the results from a Phase 2 study evaluating the safety and efficacy of SPG302 in participants with mild-to-moderate AD. Efficacy outcomes presented include mini-mental status exam (MMSE), Clinic Dementia Rating Scale – Sum of Boxes (CDR-SB), integrated Alzheimer's Disease Rating Scale (iADRS), and neurophysiological outcomes (e.g. resting state EEG). **Methods:** A Phase 2, multicenter study (NCT06427668) was initiated in Australia to assess the safety, tolerability, pharmacokinetics, pharmacodynamics and clinical efficacy of SPG302 in 24 participants with mild-to-moderate AD (MMSE scores range 16-26). Participants were enrolled into one of two cohorts, and randomized (2:1) to placebo or to active at 300 mg or 150 mg. Here we present the data of both cohorts. The initial 28d is double blinded placebo controlled followed by an open label extension for 24 weeks of active treatment. Safety, cognitive testing, and neurophysiological assessments were conducted every four weeks. AD participants completing the open label extension have the option to enroll in a second open label period for an additional 28 weeks of treatment (NCT06833281). **Results:** SPG302 was safe and well tolerated with no treatment-related adverse events (AE) or serious AE, and with plasma pharmacokinetic exposure profiles similar to those observed in healthy volunteers in Phase 1 testing. To date the 300 mg cohort ($n = 10$ or 12) has shown improvements in MMSE observed at 24 weeks of 2.20 ± 0.8 (mean $\pm$ SEM) points increase over baseline. Improvements for cohort 1 at 300 mg were also observed in the CDR-SB at 24 weeks showed average improvement of 1.3 points. Changes in MMSE and CDR-SB correlated. The iADRS, a composite measure of cognition and activities of daily living, exhibited stability overall, with a subset of 10 cohort 1 participants at 16 weeks showed no apparent change 1.69 ± 2.2 mean$\pm$SEM points over baseline). These complete data for cohort 1 and the comparative data for cohort 2 at 150 mg will be presented. Additionally target engagement assessed by EEG assessment at rest and also under analysis at the time of submission, will be presented. **Conclusions:** Once-daily treatment with the novel synaptogenic small molecule, SPG302, shows early signs of improvement in multiple measures of cognition and overall function in mild to moderate AD participants, and is safe and well tolerated.

Key takeaway message: Alzheimer's participants treated with the synaptic regenerative small molecule SPG302 demonstrated signs of improvement as measured by MMSE, CDR sum of boxes and other key endpoints.

OC34- THE MULTITEP-BASED VACCINE, AV-1959R, SAFELY ELICITS HIGH CONCENTRATIONS OF ANTIBODIES SPECIFIC TO AB42 PROTOFIBRILS/FIBRILS/PLAQUES IN VACCINATED HEALTHY VOLUNTEERS.

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Background: The amyloid cascade hypothesis posits that the formation of amyloid-β (Aβ) oligomers is a critical initiating event in Alzheimer's pathogenesis, triggering downstream pathological processes, including tau aggregation, neuroinflammation, oxidative stress, synaptic dysfunction, and neuronal loss. These neurodegenerative changes underlie the progressive cognitive decline observed in Alzheimer's disease (AD). Substantial evidence suggests that Aβ accumulation begins decades before the onset of clinical symptoms, including memory impairment and personality changes. Among current therapeutic strategies, immunotherapy targeting Aβ has emerged as one of the most promising approaches for disease modification in AD. Recently, the FDA approved mAbs, Leqembi and Kisunla, have demonstrated efficacy in reducing Aβ plaque burden, attenuating the progression of tau pathology, and modestly slowing cognitive decline. These mAbs approved for early AD patients pose several challenges that limit their use as preventive interventions. These include safety, such as ARIA-E and ARIA-H, the need for frequent intravenous administration at high antibody doses, and substantial treatment costs. These limitations underscore the need for a prophylactic, active immunization approach that can induce therapeutically effective levels of anti-Aβ antibodies in cognitively unimpaired individuals while minimizing safety risks. To address this need, we have developed the MultiTEP platform, a novel vaccine technology that incorporates 12 promiscuous foreign T helper (Th) cell epitopes, designed to overcome MHC class II polymorphism and induce robust immune responses across diverse populations. Using this platform, we developed AV-1959R, a MultiTEP-based Aβ vaccine specifically targeting the N-terminal Aβ1-11 epitope. A first-in-human clinical trial was conducted by Nuravax & Arvax companies to evaluate the safety, tolerability, and immunogenicity of adjuvanted AV-1959R developed by the Institute for Molecular Medicine (IMM) in healthy adult volunteers. **Methods:** The Phase 1 single-center, double-blind, randomized, placebo-controlled clinical trial enrolled 16 healthy adult volunteers aged 40 to 60 years. Participants were randomized in a 3:1 ratio to receive intramuscular injections of AV-1959R at doses of either 100 μg or 300 μg or placebo, formulated with Advax-CpG55.2 adjuvant. Immunizations were administered at Weeks 0, 4, and 14, followed by an 8-week observation period after the final dose. The primary outcome measure was the incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs). Secondary outcomes included evaluating clinically significant changes in electrocardiograms (ECGs), vital signs, blood chemistry, and humoral immune responses specific to Aβ and the MultiTEP platform. Antibody responses against Aβ42 protofibrils and fibrils were assessed using a validated ELISA protocol with standard curves generated with aducanumab and lecanemab as reference antibodies. Additionally, antibody titers specific to pyroglutamated Aβ peptides were measured using donanemab as a reference. **Results:** As anticipated from preclinical studies in wild-type mice, AD mouse models, and non-human primates, the MultiTEP platform-based, adjuvanted AV-1959R vaccine was found to be safe and highly immunogenic in healthy volunteers aged 40 to 60 years. Immunization with either 100 μg or 300 μg of AV-1959R, followed by a single booster dose, induced robust antibody responses in all vaccinated participants. Specifically, 100% of participants developed high titers of anti-Aβ antibodies in both the 100 μg and 300 μg dose groups, with an average geometric mean endpoint titer (GMT) of 1:41380 and 1:62201 against Aβ42 protofibrils and fibrils, respectively. Antibody concentrations, calculated using standard curves generated with aducanumab and lecanemab as references, were also high, at 18 μg/mL and 8.3 μg/mL, respectively. Isotyping revealed that the majority of antibodies were of the IgG1 and IgG3 types. Immunohistochemical analysis demonstrated that these antibodies selectively bound to pathologic Aβ plaques in brain sections from AD patients but not in those from non-AD controls, confirming their disease-relevant specificity. Notably, a second booster immunization administered 10 weeks after the first boost did not significantly increase anti-Aβ42 titers, suggesting that the timing was suboptimal. The data indicated that this response after the second boost may reflect the rapid clearance of the AV-1959R vaccine from the immune system by pre-existing anti-Aβ antibodies. Unfortunately, this

study did not investigate regulatory T cells, which can suppress further antibody production following frequent immunizations. To our knowledge, AV-1959R is the only Aβ-targeting vaccine that has induced such a high magnitude of antibody responses in 100% of vaccinated individuals, highlighting its strong potential as primary and/or secondary preventive immunotherapy for at-risk aging populations. **Conclusions:** The exceptional immunogenicity of the adjuvanted AV-1959R vaccine is attributed to the proprietary MultiTEP platform that was designed with several key objectives: (i) to overcome immunological self-tolerance to amyloid-β; (ii) to activate both naïve and pre-existing memory $CD4^+$ T helper cells primed by prior infections or routine vaccinations; (iii) to avoid induction of autoreactive T cells targeting endogenous molecules implicated in AD pathology; and (iv) to provide broad immunological coverage across the highly polymorphic human MHC class II gene repertoire. Following our long-standing research strategy, we submitted IND 30496 to advance AV-1959R into a Phase 2 clinical trial for AD prevention. This secondary preventive trial study will enroll cognitively unimpaired individuals at elevated risk for AD, as determined by blood-based biomarkers. The trial will assess whether AV-1959R can delay the onset of clinical symptoms by inhibiting pathological amyloid and tau accumulation in the brains of cognitively unimpaired individuals with Aβ-positive status.

Key takeaway message: Safety and immunogenicity data from the AV-1959R Phase 1 suggest that this MultiTEP platform-based vaccine is an ideal candidate for primary and secondary preventive therapy for Alzheimer's disease.

OC40- LONG-TERM NICOTINE TREATMENT OF MILD COGNITIVE IMPAIRMENT: THE MIND TRIAL.

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Background: Cognitive decline in neurodegeneration is related to loss of cholinergic neurons as well as a decline in nicotinic receptor number in Alzheimer's disease (AD). Nonspecific cholinergic enhancement via acetylcholinesterase inhibition has modest benefits in patients with AD and mild cognitive impairment (MCI). Treatment directly targeting nicotinic cholinergic receptors may be an additional option. Cognitive decline in AD has been linked to a decrease in the availability of nicotinic acetylcholine receptors and receptor subunits and electrophysiological and animal studies show that nicotinic agonist treatment can increase cholinergic signaling, suggesting that nicotinic treatment may have similar effects in humans, particularly in those cognitive domains commonly affected by neurodegenerative disorders. Cognitive improvement is one of the best-established therapeutic effects of nicotinic stimulation. Nicotine improves performance on attentionally and cognitively demanding vigilance tasks and response inhibition performance, suggesting that nicotine may act to optimize attention/response mechanisms as well as enhancing working memory. We have shown proof of concept in a 6-month multicenter trial (1) that transdermal nicotine provides significant improvement in attention, episodic memory, and global ratings of functioning with minimal side effects in MCI. The MIND trial (Memory Improvement with Nicotine Dosing) is a larger and longer (2-year) trial to determine whether long-term transdermal nicotine treatment results in persistence of cognitive improvement and attenuation of cognitive decline in patients with MCI. **Methods:** At 39 sites, MCI participants were randomized 1:1 to either transdermal nicotine, beginning at 3.5 mg/day, increasing to 21 mg/day or matching placebo over 5 weeks. The original sample size was planned to be 300 but was increased to 342 to account for participant attrition. Participants were assessed at 0, 3, 6, 12, 18, and 24 months, with a subset undergoing MRI scans at 0, 12, and 24 months, and CSF collection at 0 and 24 months. Participants were allowed concomitant anticholinesterase or disease modifying therapies if initiated after baseline. Primary cognitive outcomes included the International Shopping List Test- Total Immediate Recall (ISLT-TIR) score. Key secondary outcome is the MCI-CGIC. Secondary cognitive outcomes include the Cogstate battery. Secondary clinical measures include behavioral/functional scales and the CDR-SOB. An optional MRI and CSF sub-study was designed to examine AD-associated structural, biochemical, and functional effects of nicotine therapy. Biomarker data was collected to examine AD biomarkers but was not required for study enrollment. Plasma was also collected for nicotine levels and calculation of indices of nicotine metabolism. **Results:** 692 participants were screened and 348 were randomized including 151 females (43%) and 197 males (57%). Mean age was 73.7 ± 7 (55-90), education 15.9 ± 2.9 (4-30) years. Mean MMSE was 27.1 ± 2 (19-30) and CDR Global was 0.5. Randomization of populations of special interest was 7.2% (Black/African-American 6.3%, Asian 2%, Hispanic/Latino 3%). Treatment and/or study discontinuations were higher than expected at 43%. Adverse events and study withdrawal due to other reasons were the most common reasons for discontinuation. There are anticipated to be 196 completers. Baseline imaging included 67 MRI scans and 32 lumbar punctures. Safety data indicate that treatment was generally well tolerated. The most frequent adverse events for treatment discontinuation included dizziness, insomnia, and nausea. No serious adverse events were definitively or probably tied to study participation or investigational product. No drug withdrawal symptoms were reported following treatment cessation. The trial is scheduled to conclude in September, 2025. Efficacy results on the primary and secondary outcomes will be presented along with secondary analyses on nicotine plasma levels and biomarker/genetic influences on study outcomes. **Conclusions:** If the hypotheses are validated, this would support a novel, broadly available, and inexpensive repurposed cognitive intervention for MCI/early AD and could provide early treatment to improve symptoms, attenuate progression of cognitive impairment, and possibly augment treatment with disease modifying agents that interact with Aβ, tau or other mechanisms. The unexpectedly high treatment discontinuation rate may reflect the length of the trial, adverse events with dose titration, pandemic related issues, and the emergent availability of disease modifying therapies during the trial.

References:

1. Newhouse P, Kellar K, Aisen P et al.: Nicotine treatment of mild cognitive impairment: a 6-month double-blind pilot clinical trial. Neurology 2012; 78:91-101.

Key takeaway message: A positive trial would support a novel, broadly available, and inexpensive repurposed novel cholinergic intervention for MCI and lead to combination trials with disease modifying agents that interact with Aβ, tau or other mechanisms.

LB13- BENEFIT CONTINUES TO ACCUMULATE WHEN TREATMENT IS CONTINUED BEYOND PLAQUE CLEARANCE- ESTIMATING ACCUMULATED OR MAINTAINED TREATMENT BENEFIT IN THE CLARITY AD AND TRAILBLAZER-ALZ2 TRIALS.

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Background: Two monoclonal antibodies (mAbs) targeting amyloid-b have received traditional FDA approval and have been shown to slow disease progression in early Alzheimer's disease (lecanemab which targets both toxic soluble Ab species and insoluble plaques, and donanemab which targets only insoluble plaques). These antibodies have a disease-modifying effect, meaning the benefits persist even after treatment is stopped. As such, in randomized, placebo-controlled trials of disease-modifying therapies the active and placebo groups may continue

to diverge even after treatment ends. This divergence can be misinterpreted as a continued accumulation of benefit when it may actually be due to the previously treated group simply maintaining the disease at a milder state, and thus having a different rate of progression. Understanding these two different effects—the continued accumulation of benefit due to ongoing treatment versus the maintenance of a milder disease state after stopping treatment—is crucial for making informed clinical decisions around stopping or continuing therapy after plaque clearance. **Methods:** Using publicly available data from the CLARITY AD and TRAILBLAZER-ALZ 2 trials, we aimed to distinguish between the accumulating continuous-treatment benefit with ongoing therapy and the maintained post-treatment benefit after stopping therapy at plaque clearance, respectively. Comparing only those that cleared plaque early (at 12 months and switched to placebo from month 12-18) in the TRAILBLAZER-ALZ 2 trial to the full placebo population may be an inappropriate comparison. Therefore, we created an appropriate placebo comparison for the early completers in the TRAILBLAZER-ALZ 2 trial by considering the characteristics of those participants who reached plaque negativity by 12 months and simulated a more appropriate matching placebo group with similar characteristics. To account for difference of severity between subjects who were treated for 12 months and those on placebo, we mapped the trajectory of the simulated placebo arm at the same point in time and disease stage as the group receiving active treatment, thus allowing us to calculate % slowing between 12 and 18 months. For early completers, donanemab treatment was stopped based on amyloid clearance at 12 months and clinical assessments were continued to 18 months. This completers comparison highlights the treatment benefit of maintaining a milder disease state when treatment has stopped. To study the effect of continuing treatment, we mapped the progression of the full CLARITY-AD placebo group to those taking lecanemab between 12 and 18 months (participants in this trial remained on lecanemab for the duration of the study) and calculated the percent slowing. **Results:** In our analysis of the TRAILBLAZER-ALZ 2 completers, when compared to the simulated placebo group, and with the adjusted placebo trajectory, the percent slowing was approximately 17% for the 6 months after stopping therapy at plaque clearance (month-12 to month-18). In the CLARITY AD study, when comparing the full active and placebo populations over the last 6 months of continued treatment (month-12 to month-18) in the double-blind phase, using the adjusted placebo trajectory, the percent slowing was approximately 29%. **Conclusions:** Our findings suggest that while discontinuing mAb treatment after 12 months would still show a persistent benefit (17% with donanemab for 6 months post-treatment period) due to maintained benefit, continuing treatment beyond 12 months with lecanemab results in additional accumulation of benefit, leading to an overall 29% slowing of disease progression. This highlights the importance of including an appropriately matched placebo comparator for TRAILBLAZER studies when evaluating long-term benefits, and provides support that continued treatment with lecanemab is superior to stopping treatment with donanemab.

Key takeaway message: Continuous anti-amyloid monoclonal antibody therapy provides superior clinical benefit compared with discontinuing treatment once amyloid plaque clearance is achieved.

LB20- PERFORMANCE OF BLOOD-BASED SCREENING ALGORITHM FOR PREDICTING AD PATHOLOGY AND BASELINE CHARACTERISTICS OF PARTICIPANTS IN A PHASE 2 TRIAL OF ETALANETUG AND CONCURRENT LECANEMAB.

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Background: E2814-G000-202 is the first trial of the anti-MTBR tau antibody etalanetug in sporadic AD, concurrently administered with lecanemab. This trial utilized a blood-biomarker approach to confirm amyloid status without requiring PET imaging during screening. Etalanetug's unique mechanism of action suggests potential to prevent tau spread and accumulation in early AD. Therefore, this trial aimed to enrol amyloid-positive participants with tau levels likely to progress over the 18 months of study duration. The screening approach utilized a predictive algorithm of amyloid PET Centiloid (CL) based on blood biomarkers (ptau217 ratio and Ab42:40), as established in prior research (1,2). This analysis evaluates the effectiveness of this novel screening strategy in a clinical trial setting and presents the baseline characteristics of the enrolled population for this clinical trial. **Method:** A total of 678 participants were screened using PrecivityAD2, which served as the first tier of inclusion by predicting amyloid pathology levels. Only individuals with predicted CL values meeting the 50 CL threshold were eligible to proceed to further screening. This threshold was selected based on its strong association with tau pathology in the medial temporal lobe, with an area under the receiver operating characteristic curve (AUROC) greater than 0.8 (2). Model predictions were generated using continuous inputs of p-tau217 ratio, Ab42/40 ratio, age and sex. Observed baseline CL values were compared with predicted values. Performance metrics such as the positive predictive (PPV) were calculated by dichotomising predictions around the 50 CL threshold to assess classification accuracy. The first tier of screening involved the blood biomarker-based predictions. The second tier included clinical assessments, ECG and safety laboratory tests. The third tier consisted of an MRI scan. Baseline assessments include PET imaging, CSF biomarkers, and clinical scales. Descriptive statistics were used to characterize the participants across all baseline measures. The full baseline cohort included a total of 105 participants who were randomised after meeting 3 tiers of inclusion criteria. All enrolled participants underwent amyloid and tau PET imaging at baseline after passing all 3 tiers of screening, however there were no PET imaging scans for inclusion into the study. **Results:** Consistent with the prior analysis (1) our predictive algorithm demonstrated a PPV of 86.4% for identifying participants with observed amyloid PET CL values greater than 50 with all subjects confirmed amyloid positive by APS2 scores and 5 subjects falling below the CL threshold for amyloid positivity. Baseline characteristics showed APOE e4 homozygotes at 18%. The cohort comprised of 79% MCI participants and 21% with a clinical diagnosis of mild AD with a higher proportion of females (65%) compared to males. The racial composition included 76% Caucasian, 19% Asian and 2% African American or Black. In addition, 21% identified as Hispanic or Latino. Cognitive and functional assessments were consistent with the diagnostic profile, with mean scores of 2.8 (SD 1.03) on CDR-SB and 25.0 (SD 2.87) on the MMSE. The mean baseline CL value was 91 (39.3 [min −7, max 191]) (tau PET data is currently being analyzed and will be presented). Whilst the screen fail rate was slightly higher (87% vs ~80% in prior studies utilizing PET-based inclusion) the total number of subjects requiring PET scans to fully enrol the study was significantly reduced. **Conclusions:** These results demonstrate that blood-based biomarkers alone are effective in identifying participants with desired AD pathology in clinical trials. The performance of the predictive algorithm to select subjects with amyloid burden of 50CL aligns with prior work when setting a higher threshold for participants level of amyloid burden. The majority of selected subjects have amyloid pathology levels that are predictive of tau accumulation likely to progress over the 18-month study period. The baseline demographics and clinical characteristics confirm that the enrolled population is in the early stages of AD, with balanced representation across ethnicity, gender and ApoE4 status. **Keywords:** Etalanetug, Tau pathology, amyloid PET, Blood-based biomarkers, Predictive modelling, Combination Therapy.

Clinical Trial Registry: NCT06602258 Study Details | A Study of E2814 With Concurrent Lecanemab Treatment in Participants With Early Alzheimer's Disease | ClinicalTrials.gov.

Disclosures: All authors are employees of Eisai.

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Dhadda S, Irizarry MC. Plasma pTau217 predicts continuous brain amyloid levels in preclinical and early Alzheimer's disease. Alzheimers Dement. 2024 Aug; 20 (8):5617-5628. 2. Doherty et al. (2025) ADPD Presentation. Clinical trial design for concurrent anti-amyloid and anti-tau antibody therapy for sporadic Alzheimer's Disease.
Key takeaway message: Screening for clinical trials using only blood based biomarkers for AD pathology confirmation, without PET scans for inclusion, is feasible and successful within this phase 2 cohort. As the first trial in early AD of Etalanetug and Lecanemab, the baseline characteristics show a cohort aligned clinically and pathologically at this stage of the disease.

LB25- PHASE 1B/2A DATA FROM SORT-IN-2: SORTILIN INHIBITION WITH VES001 IN GRN MUTATION CARRIERS WAS WELL-TOLERATED AND ELEVATED PLASMA AND CSF PROGRANULIN.

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Background: Progranulin (PGRN) deficiency is associated with several neurodegenerative diseases, including frontotemporal dementia (FTD) where around 10% of cases are caused by mutations in the progranulin gene (GRN) known as FTD-GRN (1). FTD-GRN patients have reduced PGRN levels relative to healthy controls and these reduced levels are associated with distinct and overlapping pathological processes, including gliosis, complement activation, TDP-43 accumulation, and neurodegeneration (2). Sortilin controls PGRN levels and is a key part in the sortilin-P75NTR apoptotic signalling complex3. Vesper Bio has developed novel small molecule sortilin inhibitors for oral administration and is investigating the therapeutic potential of these in different neurodegenerative diseases. VES001 is currently in clinical development for FTD-GRN. The phase 1a study in healthy volunteers was successfully completed in Q3 2024 (NCT06226064), and the phase 1b/2a study in GRN mutation carriers will be completed during Q4 2025 (NCT06705192). The aim for VES001 treatment is to normalize PGRN levels in both plasma and CSF. **Methods:** VES001 has previously been tested in healthy volunteers in single ascending dose (SAD) and multiple ascending dose (MAD) paradigms, measuring PGRN concentrations in plasma and CSF. In phase 1b/2a, VES001 was tested at two dose levels in GRN mutation carriers. Levels of PGRN in plasma and cerebrospinal fluid (CSF) were measured using the MesoScale Discovery (MSD) platform. **Results:** The Phase 1a study showed dose-dependent elevation of plasma and CSF progranulin levels in healthy volunteers with SAD and MAD treatment paradigms of VES001 whereas no change was seen in placebo groups. The Phase 1b/2a study was successfully completed and the aim of normalizing plasma and CSF PGRN levels in GRN mutation carriers was met. A total of 6 asymptomatic GRN carriers (mean age 46.8 (SD 9.5) years, 33.3% were female, dosing period for 84 days and follow-up post last dosing was 28 days) were included in the study that demonstrated a significant dose-dependent elevation of plasma and CSF progranulin levels compared to baseline. No serious adverse events and few adverse events were associated with treatment. **Conclusions:** Sortilin inhibition with the novel oral small molecule, VES001, increases PGRN in plasma and CSF and holds promise as a novel therapeutic approach to increase PGRN and attenuate neuroinflammation and neurodegeneration in people with FTD-GRN.
Keywords: Sortilin, progranulin, clinical trials, frontotemporal dementia, FTD-GRN, NCT06705192.
Clinical Trial Registry: NCT06705192.
Disclosures: The authors MFK and AN have patents and financial equity in Vesper Bio.
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Key takeaway message: Oral treatment of VES001 successfully increases plasma and CSF progranulin levels in FTD-GRN mutation carriers.

LB29- IMPACT OF BCG IMMUNOTHERAPY ON PLASMA P-TAU217 IN PATIENTS WITH TYPE 1 DIABETES AT RISK OF ALZHEIMER'S DISEASE: A FIVE-YEAR, PHASE II, RANDOMIZED, CONTROLLED TRIAL.

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Background: In epidemiologic studies of nearly 8000 elderly patients, treatment with high-dose bacillus Calmette-Guérin (BCG) immunotherapy for bladder cancer, the standard treatment against bladder cancer since the 1970s, was associated with a reduced risk of developing Alzheimer's disease. In a Phase I clinical trial conducted at our institution with one-year of follow up, two doses of the BCG vaccine were shown to be safe in elderly patients with and without Alzheimer's disease. Patients vaccinated with BCG in this trial showed central nervous system (CNS) responsiveness, including greater clearance of amyloid protein from the brain, but only in the non-Alzheimer's group, which had a reduction in the cerebrospinal fluid (CSF)-to-blood ratio of amyloid protein. BCG may work through multiple mechanisms to prevent dementia or Alzheimer's disease. One mechanism may be by correcting an impairment in the nerve cells' ability to take up sugar for energy. Without energy from sugar metabolism, nerve cells cannot survive. BCG has been shown to convert select cell types to accelerated aerobic glycolysis. A second mechanism may the BCG-triggered removal of tau protein or amyloid protein from the brain into peripheral blood. BCG activates the proteasome that could facilitate protein processing, and may lead to greater amyloid clearance, as seen in the Phase I trial. Other mechanisms may include BCG's ability to induce an anti-inflammatory response through the induction of regulatory T cells (Treg) and the well-reported ability of BCG to provide broad-based infectious disease protection, as some forms of Alzheimer's disease may be initiated by infections that trigger long-term activation of the immune system. Patients with type 1 diabetes (T1D) have a higher risk of dementia, including Alzheimer's disease, compared to the non-diabetic population. Here we present data from a Phase II clinical trial in adults with T1D on the effect of BCG immunotherapy on the blood-based biomarker for Alzheimer's disease, plasma phosphorylated tau217 (p-tau217). **Methods:** This five-year, Phase II, double-blinded, randomized, controlled clinical trial at our institution comprised 150 diabetic adults, including those with latent autoimmune diabetes in adults (LADA), a form of T1D, who were vaccinated with BCG six times over the course of the trial. Mean subject age at enrollment was 45.8 years (BCG-treated) and 46.9 years (placebo). The primary outcome of the trial related to blood sugar control, but an exploratory outcome was CNS markers for diabetes complications. Clinically meaningful prevention of dementia or Alzheimer's disease was one of the monitored outcomes, and was assessed via p-tau217 assay performed by a CLIA certified clinical laboratory on serum stored at 80°C, obtained at 6 month intervals for 5 years and assayed at the same time to prevent assay drift at study end. **Results:** At the start of the clinical trial, none of the subjects had cognitive impairments nor clinical Alzheimer's disease. BCG was safe and well tolerated with no serious side effects. Older patients who received 6 doses of BCG had a statically significant decline in p-tau217 over the 5 years of monitoring ($p = 0.003$). In contrast, patients in the placebo arm had a non-statistical increase of p-tau217 over 5 years. The percentage difference between BCG-treated patients and placebo control was statistically significant when evaluating percent change from baseline ($p = 0.003$). The p-

tau217 trend was still pointed downward at study end for the BCG treated cohort. **Conclusions:** This data set from a Phase II randomized clinical trial in adults with T1D show that the p-tau217 biomarker is statically lowered after administration of multi-dose BCG compared to self at baseline, in contrast to a placebo group that exhibited gradual elevations in p-tau217 over the 5-year study period. The final p-Tau217 levels were also statistically significantly different in the treated and untreated groups. These findings suggest that multi-dose BCG may represent a safe and affordable immunotherapy for patients at risk of Alzheimer's disease. Like other clinical trials evaluating the off-target effects of the BCG vaccine, the time course of protection is best studied over 5 years, as BCG de-methylates genes on select pathways in a gradual way, reprogramming of the immune system and possibly directly affecting cells of the CNS. Prevention trials in at risk populations are needed to confirm and expand this data set. Further study of these subjects from Year 5 to Year 8 will provide insight into the durability of protection from CNS disease.

Keywords: BCG immunotherapy, regulatory T cells (Tregs), neuroinflammation, Phase II randomized clinical trial, diabetes, p-tau217.
Disclosures: This work was sponsored by the Cure Diabetes Now Fund. All authors on this study have no conflict of interest. Denise L. Faustman's research funding for this project is from non-profit support and support from the public. She receives no industrial grant support. Dr. Faustman is a full-time employee of MGH and Harvard Medical School and all technology is fully owned by her employer. She receives the BCG drug supply through a licensing agreement with Japan Laboratories. Dr Faustman and her laboratory do not receive grant support from the drug supplier, they do not dictate trial design nor control outcome reporting. Dr Faustman does not receiving consulting income from Japan Laboratories.

Key takeaway message: In adults with T1D, a population at risk of developing Alzheimer's disease, treatment with multi-dose BCG immunotherapy statically significantly lowered p-tau217 over 5 years of a Phase II randomized clinical trial.

LB31- RESULTS OF THE PHASE 2B TRIAL OF NEFLAMAPIMOD IN DEMENTIA WITH LEWY BODIES.

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Background: Degeneration of basal forebrain cholinergic neurons is a hallmark of dementia with Lewy bodies (DLB). In advanced disease, hippocampal atrophy and Alzheimer's disease (AD) co-pathology are often also present. Neflamapimod, an oral inhibitor of p38α kinase, targets molecular mechanisms implicated in cholinergic degeneration. In preclinical models, the drug rescued basal forebrain cholinergic neuronal loss. Phase 2a clinical testing produced promising results, particularly in patients without AD pathology, as determined by low plasma ptau181 levels. Building on these findings, the phase 2b RewinD-LB trial evaluated neflamapimod in DLB and demonstrated meaningful effects on clinical progression during the first 16 weeks of the neflamapimod-only Extension (Gomperts et al., AD/PD2025; Honig et al., AAIC2025). Here we present the full clinical results and discuss the potential of neflamapimod as a disease-modifying therapy for DLB. **Methods:** 159 participants meeting consensus diagnostic criteria for DLB. The trial consisted of a 16-week randomized, placebo-controlled period, followed by a 32-week neflamapimod-only Extension. To enrich for patients without AD co-pathology, only individuals with plasma ptau181 < 27.2 pg/mL (Quanterix® ptau181 v2.1) were randomized. Two batches of the drug product were used: NFMD/A, which did not achieve target plasma exposure, and NFMD/B, which did. Only NFMD/A was used during the placebo-controlled phase, while NFMD/B was introduced during the Extension as NFMD/A supply was exhausted. In the first 16 weeks of the Extension, 94 participants received ≥ 8 weeks of NFMD/B and 55 received only NFMD/A (most subsequently transitioned to NFMD/B). Treatment effects were evaluated in several ways: Placebo-controlled comparison: NFMD/A vs. placebo during the randomized period. Extension batch comparison: NFMD/B vs. NFMD/A during the first 16 weeks of the Extension. Within-participant comparison: Participants who received placebo initially and then NFMD/B during the 1st 16 weeks of the Extension. Time-to-progression analysis: Given variable lengths of treatment, Kaplan-Meier estimates of time to $\geq$1.5-point increase in Clinical Dementia Rating–Sum of Boxes (CDR-SB) utilized to analyze the full dataset, including 32 weeks of the Extension. Outcomes were analyzed both in the full study population and in a "low ptau181 subset" (screening plasma ptau181 < 21 pg/mL). This threshold, recently validated in a large ($N = 1298$) multicenter study, indicates a low probability of AD pathology in both AD and non-AD dementias. All analyses followed a prespecified Statistical Analysis Plan (SAP). An SAP addendum, finalized in February 2025—post-hoc to the placebo-controlled results but before Extension data became available—added planned comparisons by drug batch (NFMD/B vs. NFMD/A) and sensitivity analyses using the $<$21 pg/mL cutoff. **Results:** Placebo-controlled phase: On the primary endpoint (change in CDR-SB at 16 weeks), no overall difference was seen between NFMD/A and placebo. However, in the low ptau181 subset, there was a favorable trend toward NFMD/A (difference -0.53, $p = 0.10$, linear mixed-effects model). Extension (first 16 weeks): NFMD/B demonstrated significant benefit vs. NFMD/A on CDR-SB (difference -0.57, $p = 0.007$ in all participants; -0.58, $p = 0.024$ in the low ptau181 subset). Superiority of NFMD/B was also observed on the ADCS-Clinical Global Impression of Change (ADCS-CGIC), Dementia-Cognitive Fluctuations Scale, ISLT-Recognition, and UPDRS-Motor Part III (latter two significant in the low ptau181 subset only). Within-participant comparisons: Participants who transitioned from placebo to NFMD/B showed significant improvement on change in CDR-SB over 16 weeks when they received NFMD/B relative to change seen during the 16 weeks they were receiving placebo (difference $= -1.11$; $p = 0.005$ in the low ptau181 subset; nonsignificant in the full cohort) and on ADCS-CGIC while they were on NFDMD/B relative to when on placebo ($p = 0.004$ in the low ptau181 subset; $p = 0.06$ in the full cohort). No benefit of NFMD/A vs. placebo was observed in these within-participant comparisons. Time-to-progression: NFMD/B reduced the risk of clinically meaningful progression ($\geq$1.5-point CDR-SB increase) by 54% ($p = 0.003$) compared with NFMD/A and 50% compared with placebo. In the low ptau181 subset, NFMD/B reduced risk by 67% vs. NFMD/A ($p = 0.0002$) and 75% vs. placebo. Although the magnitude of benefit observed in this relatively short trial may appear striking, the results align with both the biology of DLB and the known mechanism of action of neflamapimod. The drug targets the basal forebrain cholinergic system, which plays a central role in DLB symptomatology. Patients without AD co-pathology (as indicated by low plasma ptau181) are more likely to show pronounced treatment effects, since hippocampal atrophy and other AD-related changes—less responsive to therapy directed towards cholinergic neurons—are not driving disease progression. The Extension data also clarify the initially inconclusive results from the placebo-controlled phase, i.e., absence of efficacy in NFMD/A reflected inadequate plasma exposure, not lack of drug activity. By contrast, NFMD/B, which achieved target exposure, consistently showed benefit across primary, secondary, and exploratory endpoints. **Conclusions:** While the initial results did not meet the primary objective, neflamapimod, when achieving appropriate plasma concentrations during the Extension, slowed clinical progression in patients with DLB. Benefits were most pronounced in individuals without AD co-pathology (indicated by low plasma ptau181 levels). These findings replicate and extend prior phase 2a results, supporting proof-of-concept for neflamapimod as a disease-modifying therapy for DLB.

Moreover, the results are consistent with preclinical data demonstrating the capacity of neflamapimod to protect basal forebrain cholinergic neurons, offering a biologically coherent rationale for the observed clinical effects.
Key takeaway message: Neflamapimod, when achieving target plasma concentrations, durably slows clinical progression in patients with DLB, most prominently in individuals without AD co-pathology (assessed by plasma ptau181), supporting proof-of-concept for neflamapimod as a disease-modifying therapy for DLB.

LB5- CLINICAL, SAFETY, AND BIOMARKER OUTCOMES FROM A POSTTREATMENT OBSERVATIONAL EXTENSION OF THE PHASE 2 PROSPECT-ALZ STUDY OF CEPEROGNASTAT IN EARLY SYMPTOMATIC ALZHEIMER'S DISEASE.
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Background: Ceperognastat—an orally available O-linked N-acetyl glucosaminidase inhibitor—failed to show clinical benefit for early symptomatic Alzheimer's disease (AD) in the phase 2 PROSPECT-ALZ study (NCT05063539). While the low-dose (0.75 mg) treatment group had a similar effect as that of placebo, greater treatment-related clinical decline was observed in the high-dose (3 mg) treatment group. Weight loss occurred in both treatment groups. These findings were in contrast to evidence showing a favorable impact of ceperognastat treatment on tau pathology, inflammation, and brain volume as measured by volumetric magnetic resonance imaging (MRI). An optional, posttreatment observational extension was added to assess long-term clinical, safety, and biomarker outcomes. **Methods:** All participants randomized in the PROSPECT-ALZ trial were invited to participate in a posttreatment observational extension study beginning an average of 26 weeks after participants' last treatment exposure. The extension included 2 visits, approximately 12 weeks apart. Measured endpoints included clinical (integrated Alzheimer's Disease Rating Scale [iADRS] and Clinical Dementia Rating Scale–Sum of Boxes [CDR-SB] scores), safety (adverse events [AEs] and body weight), and biomarker outcomes (phosphorylated tau [P-tau]217, glial fibrillary acidic protein [GFAP], and neurofilament light chain [NfL] levels, and brain volume). Descriptive statistics including means (standard deviations [SDs]) and percentages are reported. Posttreatment outcomes were evaluated using a mixed model for repeated measures, comparing least-squares (LS) means change differences from the double-blind baseline between ceperognastat treatment groups and placebo. **Results:** Overall, 122 study participants were enrolled in the extension period (ceperognastat 0.75 mg, n = 42; ceperognastat 3 mg, n = 38; placebo, n = 42). The extension had a mean (SD) duration of 261.9 (50.5) days. Baseline characteristics of participants who continued into the extension were similar to those of the overall study population, including mean (SD) age (73.0 [5.3] years), years of education (14.4 [2.8] years), and Mini-Mental State Examination scores (24.9 [2.5]), as well as the percentage of females (64.8%) and apolipoprotein E ε4 carriers (65.6%). During posttreatment observation, participants in all 3 study groups showed continued cognitive and functional decline. In the ceperognastat 0.75-mg group, LS means change differences in cognitive and functional scores on the iADRS (4.19 [95% confidence interval [CI], −2.81 to 11.19]) and CDR-SB (−0.36 [95% CI, −1.67 to 0.95]) were similar to those seen with placebo at the end of the extension. In the ceperognastat 3-mg group, cognitive decline generally slowed, compared to the on-treatment period, but remained numerically worse as compared to placebo at the end of the extension. Within the 3-mg group at the end of the extension, iADRS scores showed a numerically greater change from baseline than placebo (23.7%), with an LS means change difference of −4.30 (95% CI, −11.57 to 2.98), while CDR-SB scores showed a greater total change from baseline than placebo (58.9%), with an LS means change difference of 1.75 (95% CI, 0.40 to 3.10). In both ceperognastat treatment groups, whole brain volume on MRI was similar to that shown with placebo by the end of the extension (LS means change difference [95% CI]: ceperognastat 0.75 mg, 6.00 [−0.54 to 12.54]; ceperognastat 3 mg, 2.60 [−4.24 to 9.43]). No significant difference was observed between either treatment group and placebo at the end of the extension for P-tau217 (LS means change difference [95% CI]: ceperognastat 0.75 mg, 0.03 [−0.03 to 0.09]; ceperognastat 3 mg, 0.04 [−0.03 to 0.10]), GFAP (LS means change difference [95% CI]: ceperognastat 0.75 mg, 0.01 [−0.04 to 0.07]; ceperognastat 3 mg, −0.01 [−0.07 to 0.04]), or NfL levels (LS means change difference [95% CI]: ceperognastat 0.75 mg, −0.05 [−0.11 to 0.01]; ceperognastat 3 mg, −0.04 [−0.10 to 0.02]). The dose-proportional weight loss observed with ceperognastat across the double-blind treatment period generally recovered and was comparable with weight levels seen in the placebo group by the end of the extension (LS means change difference [95% CI]: ceperognastat 0.75 mg, −1.27 [−3.57 to 1.02]; ceperognastat 3 mg, 2.23 [−0.14 to 4.60]). No considerable differences were observed in the number of AEs reported across study groups after treatment discontinuation. **Conclusions:** As seen in the double-blind period, clinical measures for the ceperognastat high-dose group (3 mg) remained worse than those seen with placebo at the end of the extension period. However, the rate of decline slowed after treatment ended. Volumetric MRI and fluid biomarker effects observed during treatment in both ceperognastat groups were similar to those seen with placebo by the end of the extension. These findings suggest a lack of sustained efficacy or clinically meaningful disease-modifying effect from at least 76 weeks of treatment with ceperognastat. Furthermore, the observation of slowed brain volume loss during the treatment period was unlikely to represent slowing of AD-related neurodegeneration. Treatment-related weight loss was recovered by the end of the extension, and no meaningful differences in the number of AEs between groups was seen. This study emphasizes the importance of clinical outcomes in assessing treatment efficacy and the challenges of interpreting AD-related biomarker outcomes in clinical trials. Although ceperognastat did not show clinical benefits, the development of tau-targeting therapeutics remains critically important in the continued efforts to treat and prevent AD.
Keywords: Ceperognastat, OGA inhibitor, phase 2 trial results, posttreatment observations.
Clinical Trial Registry: NCT05063539; https://clinicaltrials.gov.
Disclosures: All authors are employees and shareholders of Eli Lilly and Company.
Key takeaway message: The phase 2 PROSPECT-ALZ study of ceperognastat in early symptomatic Alzheimer's disease did not demonstrate clinical benefit. Posttreatment observation showed no evidence of enduring adverse effects or sustained disease modification.

LB9- NEUROPATHOLOGICAL INSIGHTS INTO THE EFFECTS OF ADUCANUMAB ON PATIENTS WITH ALZHEIMER'S DISEASE.
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Background: Fluid and imaging biomarker data show that anti-amyloid (Aβ) antibodies promote the clearance of Aβ from the brains of patients with Alzheimer's disease (AD). We examined postmortem brain tissue of individuals who participated in aducanumab clinical trials and investigated the drug's effects on Aβ pathology and other AD phenotypes. **Methods:** The medial temporal lobe of six aducanumab clinical trial

participants – who had extensive exposure to aducanumab and happened to die between 7 weeks and 5 years after their last antibody infusion – was compared to that of nine untreated AD patients matched for age, sex, APOE genotype, and Braak neurofibrillary tangle stage, to determine how aducanumab impacts the AD pathobiology. **Results:** Patients treated with aducanumab displayed a robust reduction in Aβ burden throughout the medial temporal lobe, with plaque numbers increasing approximately 2.5 years after drug withdrawal. Importantly, in aducanumab-treated patients, Aβ was associated with non-arterial microvessels, suggesting a redistribution of Aβ from the neuropil compared to untreated AD patients. Neuritic phospho-tau decreased in parallel with Aβ plaque clearance, but the density of PHF-1+ and AT8+ neurofibrillary tangles remained unchanged relative to the average untreated AD donor. Measures of microglial and astroglial reactivity were also comparable to those in untreated AD controls. **Conclusions:** These findings confirm aducanumab's potent ability to target and remove brain Aβ and support the idea that plaques gradually redeposit post-treatment. The selective reduction of neuritic, but not neurofibrillary phospho-tau implies that Aβ-targeted antibodies such as aducanumab alleviate plaque-associated dystrophy but may not address established tangles. Overall, this study provides crucial insights into the long-term outcomes of anti-Aβ immunotherapy in AD.

Keywords: Immunotherapy, aducanumab, autopsy, neuropathology.

Disclosures: SS is a consultant for Amylyx, Alnylam, Biogen, Bolden, Eisai, Eli Lilly, Genentech, NovoNordisk, Ono, Prothena, and Roche. CB serves on the scientific advisory board for NovoNordisk. DG was the Chief Medical Officer for AriBio from 2023 to 2024. TB is a former employee and shareholder of Biogen. EDP is an employee and shareholder of Biogen. BTH serves on a scientific advisory board or is a consultant for AbbVie, Alexion, Ambagon, Aprinoia Therapeutics, Arbor Bio, Arvinas, Avrobio, AstraZenica, Biogen, Bioinsights, BMS, Cell Signaling, Cure Alz Fund, CurieBio, Dewpoint, Eisai, Etiome, Latus, Merck, Novartis, Paragon, Pfizer, Sanofi, Sofinnova, SV Health, Takeda, TD Cowen, Vigil, Violet, Voyager, WaveBreak; his laboratory is supported by research grants from the National Institutes of Health, Cure Alzheimer's Fund, Tau Consortium, and the JPB Foundation – and sponsored research agreement from Abbvie and Sanofi; he has a collaborative project with Biogen and Neurimmune.

Key takeaway message: This postmortem neuropathological assessment of individuals who received aducanumab offers important insights into the enduring impact of anti-Aβ immunotherapy on the AD brain.

3.3. Clinical trials: imaging

OC12- BRAIN VOLUME CHANGES WITH GANTENERUMAB: RELATIONSHIP WITH AMYLOID REMOVAL.

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Background: Gantenerumab is a monoclonal antibody that targets aggregated forms of amyloid-beta (Aβ). Although the gantenerumab program was terminated due to the benefit-risk observed in the early Alzheimer's disease population not supporting further development, the Phase III GRADUATE I (NCT03444870) and GRADUATE II (NCT03443973) trials showed that gantenerumab treatment led to substantial amyloid plaque removal. These trials also revealed greater brain volume loss in treated participants compared to placebo, a phenomenon consistently observed in recent anti-Aβ immunotherapy trials and hypothesized to be related to the extent of amyloid removal (Belder et al., 2024). The analysis presented herein aimed to investigate the relationship between amyloid removal and regional brain volume changes in participants treated with gantenerumab. **Methods:** Participants in the GRADUATE studies underwent MRI at screening, week 48, week 104, and week 116. A subset also received amyloid PET with either 18F-florbetaben or 18F-flutemetamol at screening, week 52, week 104, and week 116. Baseline T1-w MR images were segmented using Freesurfer 6.0, and regional volume changes from baseline were calculated using the Tensor-Based Morphometry technique as implemented in SPM12. Regional amyloid changes from baseline were computed using centiloid conversion equations applied to amyloid PET SUVR images. A mixed model for repeated measures was used to estimate the volumetric mean percentage change from baseline. Two separate analyses were performed to test whether the greater volume change observed with gantenerumab was related to the amount of amyloid removal: Between-region correlation analysis: for each brain region, the difference in mean change from baseline between gantenerumab and placebo was calculated for both volume and amyloid load, and a Spearman correlation coefficient was computed across regions. For this analysis, regions were grouped as five bilateral cortical lobes (frontal, parietal, temporal, cingulate, and occipital), four bilateral subcortical nuclei (caudate, putamen, pallidum, and thalamus), and the cerebellum. Between-subject correlation analysis: Spearman correlation coefficients between volume change and centiloid change from baseline were calculated within each individual region obtained from Freesurfer. This analysis was restricted to participants in the gantenerumab arm who had longitudinal amyloid PET data. Due to the exploratory nature of this analysis, multiplicity adjustments were not applied to the tests. **Results:** A total of 1268 participants were included in these analyses (N placebo/gantenerumab = 660/608; age placebo/gantenerumab = 71 ± 7/71±8years; female % placebo/gantenerumab = 56/59), of which 170 had amyloid PET at both screening and at the end of the study (N placebo/gantenerumab = 82/88; age placebo/gantenerumab = 72 ± 8/71±8years; female % placebo/gantenerumab = 51/50). By study end, participants treated with gantenerumab had numerically greater volume changes compared to placebo in all cortical and subcortical regions assessed, ranging from (difference in adjusted mean percentage changes from baseline ±SE) $-0.64 \pm 0.14\%$, $p < 0.0001$ in the parietal cortex to $-0.14 \pm 0.08\%$, $p = 0.057$ in the pallidum. Notably, in the cerebellum, the opposite result was observed ($0.23 \pm 0.06\%$, $p = 0.0002$). Between-region correlation analysis revealed that the regional amount of volume change relative to placebo strongly correlated with the regional amount of amyloid removed (rho = 0.89, $p = 0.0006$ including cerebellum; rho = 0.76, $p = 0.017$ excluding cerebellum), indicating that regions with greater amyloid clearance exhibited greater relative volume changes. Between-subject correlation analysis revealed a dual pattern that varied between regions typically affected by tau pathology (e.g., inferior temporal cortex, inferior parietal cortex, and precuneus) and those that are not (e.g., sensorimotor cortex, thalamus, and caudate). In regions with typically low or no tau pathology, greater amyloid removal was associated with greater volume change (e.g., sensorimotor cortex rho = 0.35, $p = 0.0009$; thalamus rho = 0.38, $p = 0.0002$; caudate rho = 0.26, $p = 0.014$). In regions typically affected by tau, greater amyloid removal was paradoxically associated with less volume change (e.g., inferior parietal cortex rho = −0.34, $p = 0.001$; inferior temporal cortex rho = −0.27, $p = 0.012$; precuneus rho = −0.25, $p = 0.021$). We further explored the effect of baseline tau on volume change and amyloid removal in these regions in a subset of treated participants with baseline 18F-GTP1 tau PET (N = 38). In this subset, higher regional baseline tau SUVR strongly predicted greater volume change (inferior parietal cortex rho = −0.75, $p < 0.0001$; inferior temporal cortex rho = −0.85, $p < 0.0001$; precuneus rho = −0.74, $p < 0.0001$), while at the same time it was also positively associated with reduced amyloid removal (inferior parietal cortex rho = 0.43, $p = 0.007$; inferior temporal cortex rho = 0.42, $p = 0.008$; precuneus rho = 0.50, $p = 0.002$),

suggesting that tau pathology may limit amyloid clearance. **Conclusions:** In this study, we found that brain regions with greater amyloid removal exhibited greater volume change compared to regions with less amyloid removal. Interpretation of the between-subject correlation analysis was complicated by interactions with tau pathology. In regions commonly affected by tau, baseline tau burden was the primary driver of volume changes, and the effect of amyloid removal on these changes was relatively limited. Unexpectedly, higher baseline tau appeared to reduce the amyloid removal capacity of gantenerumab, resulting in an apparent association between minimal amyloid removal and substantial volume change in these areas. Although the mechanisms underlying this tau-mediated interference remain unclear, in regions such as the thalamus, caudate, and sensorimotor cortex - where tau is typically very low - volume changes correlated positively with the degree of amyloid removed. Taken together, these findings demonstrated a clear association between gantenerumab-induced brain volume changes and amyloid plaque clearance and raise interesting questions about what may modify regional amyloid removal.

Keywords: GRADUATE I & II, gantenerumab, volume change, amyloid clearance.

Author disclosures: Matteo Tonietto and Gregory Klein are full-time employees and own stock in F. Hoffmann-La Roche Ltd. Erica Silvestri is an external consultant of F. Hoffmann-La Roche Ltd. Christopher Belder has nothing to disclose. Frederik Barkhof has served on Steering committees or Data Safety Monitoring Boards for Biogen, Merck, Eisai and Prothena. He has served in advisory boards for Combinostics, Scottish Brain Sciences, and Alzheimer Europe. He has provided consultancy services for Roche, Celltrion, Rewind Therapeutics, Merck, and Bracco. He has research agreements with ADDI, Merck, Biogen, GE Healthcare, and Roche. He is co-founder and shareholder of Queen Square Analytics LTD. Nick Fox has provided consultancy services or served on advisory boards for Abbvie, Biogen, Eisai, Eli Lilly, Ionis, and Roche. Janice Smith is a full-time employee of Roche Products Ltd and owns stock in F. Hoffmann-La Roche Ltd.

References: Belder et al., Lancet Neurol 2024; 23: 1025–34. https://doi.org/10.1016/S1474-4422(24)00335-1. Clinical Trial Registry: NCT03444870, NCT03443973; https://clinicaltrials.gov.

Key takeaway message: Volume changes observed with gantenerumab treatment were strongly linked to amyloid plaque removal in the GRADUATE phase III trials, with regions exhibiting greater amyloid clearance experiencing more pronounced volume changes compared to placebo.

OC13- HEAD-TO-HEAD COMPARISON OF SWI AND T2*-WEIGHTED GRADIENT ECHO MRI SEQUENCES TO DETECT ARIA-H IN THE TRAILBLAZER-ALZ 6 TRIAL OF DONANEMAB.

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Background: Amyloid-related imaging abnormalities (ARIA) are a class-related safety risk associated with the removal of amyloid with amyloid targeting therapies (ATTs). TRAILBLAZER-ALZ 6 (NCT05738486), a randomized, double-blind phase 3b study, assessed the impact of different donanemab dosing regimens on ARIA frequencies in participants with early symptomatic Alzheimer's disease. In this study, a more gradual titration of donanemab dosing was associated with a significant reduction in ARIA-E risk while demonstrating comparable pharmacokinetics/pharmacodynamics as those observed with standard dosing regimen. ARIA-edema/effusions (ARIA-E) and ARIA-hemorrhages/hemosiderin deposits (ARIA-H) are identified radiographically using magnetic resonance imaging (MRI). ARIA-H has traditionally been assessed in clinical practice and clinical trials (for eligibility determination as well as monitoring) using T2*-weighted (T2*W) gradient-recalled echo (GRE) MRI sequences. However, another GRE sequence, susceptibility-weighted imaging (SWI), is also used in the clinic and has shown more sensitivity to hemorrhagic lesions due to enhanced contrast. How eligibility and detection of ARIA-H determined by GRE translates to SWI has not been well studied. Furthermore, the presence of cortical superficial siderosis and greater number of microhemorrhages at baseline has been shown to increase risk for treatment-emergent ARIA-E. Whether superior sensitivity of SWI enhances this association has not been assessed. This exploratory analysis compares T2*W GRE versus SWI in (1) sensitivity to detect ARIA-H (including microhemorrhages and cortical superficial siderosis) and (2) the association of baseline ARIA-H measures with treatment emergent ARIA-E by 76 weeks in donanemab-treated participants enrolled in TRAILBLAZER-ALZ 6. **Methods:** Key study exclusion criteria based on screening MRI were ARIA-E, >4 cerebral microhemorrhages, >1 area of cortical superficial siderosis (CSS), and any macrohemorrhages on centrally-read screening MRI using standard T2*W GRE. Our exploratory analyses included ARIA-H presence and radiographic severity determined via visual read of microhemorrhage counts and number of focal areas of superficial siderosis from MRI performed using T2*W GRE (standard sequence) and SWI (advanced sequence) from enrolled individuals before the first infusion and at Weeks 4, 12, 24, 52, and at unscheduled visits through 76 weeks. T2*W GRE-based ARIA-H criteria were applied to all scans. Sequences were compared in terms of ARIA-H eligibility criteria at baseline. In a post-hoc analysis, presence and radiographic severity of treatment-emergent ARIA-H by 76 weeks were compared (alpha = 0.05, McNemar's and Bowker's tests). Additionally, to test for associations between baseline ARIA-H measures and treatment emergent ARIA-E by 76 weeks, multivariate logistic regression was conducted for each MRI endpoint with presence of ARIA-E as the dependent variable. Independent variables included the MRI endpoint and the number of Apolipoprotein E (APOE) ε4 alleles. **Results:** Baseline analyses included N = 840 participants who were scanned using both T2*W GRE and SWI prior to the first infusion. After applying T2*W GRE-based inclusion criteria to the baseline SWI scans of enrolled participants, 38 (4.5%) exceeded eligibility thresholds on SWI. Longitudinal analyses included N = 837 participants with baseline and at least one pair of post-baseline T2*W GRE and SWI scans. The number of participants with ARIA-H by week 76, as detected by T2*W GRE versus SWI, was similar (228 GRE, 243 SWI); however, the radiographic severity of ARIA-H (defined according to number of treatment emergent microhemorrhages or areas of superficial siderosis) was significantly greater when assessed using SWI relative to T2*W GRE ($p < 0.001$). By 76 weeks, there were 162 treatment-emergent ARIA-E events across all dosing arms, only 1 of which occurred after the week 52 visit. Baseline cortical superficial siderosis was associated with occurrence of ARIA-E through 76 weeks both on T2*W GRE ($p < 0.001$) and SWI ($p < 0.01$), but only baseline microhemorrhage counts from SWI (1 vs 0: $p < 0.05$, 2+ vs 0: $p < 0.05$) were significantly associated with ARIA-E. **Conclusions:** Results from this study support improved sensitivity to ARIA-H measures in SWI relative to T2*W GRE. The impact of baseline superficial siderosis and microhemorrhage counts on treatment eligibility, as well as the frequency of treatment emergent ARIA-H, were similar using T2*W GRE and SWI sequences. However, ARIA-H radiographic severity was greater on SWI. The additional sensitivity of SWI to microhemorrhages may provide improved associations with ARIA-E in clinical trial settings and ancillary information to support T2*W GRE findings, but further analyses are needed to harmonize safety assessments using SWI and T2*W GRE sequences.

Disclosures: All authors involved in this study are employees and minor shareholders of Eli Lilly and Company. Additionally, the study was funded by Eli Lilly and Company.
Keywords: SWI, T2*W GRE, ARIA, Donanemab.

Key takeaway message: The presence of ARIA-H is similar between SWI and T2*W GRE, but more analyses are needed to harmonize safety assessments using SWI and T2*W GRE sequences.

OC36- BIOMARKERS OF COGNITIVE PERFORMANCE IN ALZHEIMER'S DISEASE IN ADULTS WITH DOWN SYNDROME.

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Background: Clinical trials are increasingly focusing on earlier clinicopathological stages of Alzheimer's disease (AD). During the preclinical stage, it is crucial to accurately stage AD and predict timelines of cognitive decline to identify participants who are most likely to benefit from an intervention trial. Adults with DS will almost certainly develop AD pathology and cognitive decline due to the triplication of the amyloid precursor protein gene on chromosome 21. In the present study, we assess the time course and relationship between AD pathology, neurodegenerative changes, and cognitive performance in an observational longitudinal cohort study of adults with DS (Alzheimer's Biomarker Consortium – Down Syndrome (ABC-DS) to establish the temporal relationship between PET, MRI and plasma measures of AD pathology and neurodegeneration, and how these changes relate to cognition allowing for improved planning of intervention trials in adults with DS. We specifically focus on the basal forebrain (BF) and hippocampus, structures critical for normal cognitive function and among the earliest affected by AD, exploring the hypothesis that degeneration of these regions may serve as predictors of early cognitive decline. **Methods:** Participants are 402 adults with DS, 42.8 years old (range 25-72), and 43.8% females with up to 5 visits (18-month intervals) from the ABC-DS study. Data includes cognitive testing, biofluid analysis, MRI, amyloid- and tau-PET. For analysis, MRIs were parcellated using FreeSurfer 7.2, calculating cortical, cerebellar, hippocampal, and BF volumes, all normalized to total intracranial volume. Global amyloid accumulation was calculated from [11C]-PiB and [18F]-FBP PET scans using the standard centiloid pipeline. Tau accumulation from [18F]-FTP scans in composite Braak-defined regions was calculated using PetSurfer in subject space after motion correction, using a cerebellar gray matter reference region. Linear mixed-effects models (LMEMs) assessed the relationship between age and variables of interest, with false discovery rate (FDR) corrections. Davies tests were performed to establish whether a segmented model better represented the variable-age relationship. Relationships between AD-related pathology and markers of neurodegeneration (PET imaging, plasma neurofilament light (NfL), and plasma total tau) and volumetric changes on MRI, as well as relationships between MRI-changes and cognitive performance, including the modified cued recall test (mCRT) and Down Syndrome Mental State Exam (DSMSE), were assessed using LMEMs. All models were corrected for age and sex and included a random subjects term. Cognitive models were also adjusted for premorbid intellectual impairment. An AT(N)-based path analysis was performed using the cross-sectional baseline data. All variables were transformed to z-scores. A simple model from age to amyloid accumulation (A), to tau accumulation in Braak regions 1 and 2 composite (T), to decreasing volume in the basal forebrain and hippocampus (N), to total recall on the mCRT was compared to a more complex model including additional direct effects. All statistical analyses were performed in R v.4.5.0. **Results:** Amyloid accumulation (marginal R2: 0.464), tau accumulation in all Braak-defined regions (1-2: 0.327; 3-4: 0.288; 5-6: 0.205), BF (0.190), hippocampal (0.410), occipital lobe (0.117), and cerebellar volumes (0.174), DSMSE total (0.351) and non-memory scores (0.330), mCRT total (0.273) and free recall (0.274), and plasma NfL (0.220), all displayed a significant association with age after FDR correction, plasma total tau did not (0.056). Except for cerebellar volume and plasma NfL, all displayed a significant change in slope. Amyloid accumulation was found to start earliest (at 36.4 years), followed by tau accumulation in Braak regions 1 and 2 composite, and decline in total recall on mCRT at 37.8 and 37.5 years, respectively. hippocampal, BF, and occipital lobe volumes started to decline at 40.0, 41.6, and 41.9 years, respectively, while tau accumulation in Braak regions 3 and 4 composite, 5 and 6 composite, and decline in DSMSE total score occurred at 48.5, 47.8, and 47.7 years, respectively. Plasma NfL was found to be the best predictor of BF and hippocampal atrophy. BF and hippocampal atrophy predicted decreased mCRT total recall, while hippocampal atrophy also predicted decreased mCRT free recall. The path analysis revealed the predicted associations following the AT(N) framework, while the BF association with mCRT total recall was mediated by hippocampal atrophy. However, a model that included direct effects between amyloid accumulation, hippocampal volume, and mCRT total recall, and direct effects between tau accumulation in Braak regions 1 and 2 composite and mCRT total recall, provided an improved fit. **Conclusions:** BF and hippocampal volume loss, two regions that exhibit the earliest changes in AD, occur shortly after the onset of cognitive decline as measured by mCRT. BF and hippocampal atrophy show associations with NfL (marginal R2: 0.216 and 0.453, respectively), suggesting that these are good measures of neurodegeneration within the AT(N) framework. Path analysis indicates direct relationships between amyloid and tau accumulation and mCRT total recall, not mediated through BF or hippocampal atrophy. These data suggest that while BF and hippocampal atrophy are good measures of neurodegenerative changes and predictors of cognitive performance, brain volumetry may not be sensitive enough to the earliest neuropathological changes leading to cognitive deficits. Future studies are needed to understand whether novel techniques for assessing neurotransmitter systems, such as cholinergic PET imaging, accurately measure early neurodegenerative changes and could serve as biomarkers for AD-related cognitive decline in future clinical studies. **Keywords:** Down syndrome, cognition, cholinergic, hippocampus.

Disclosures: Dr. Rafii reports personal fees from AC Immune, Alzheon, Aptah Bio, Biohaven, Keystone Bio, Positrigo, Ionis, grants from Eisai and Lilly, outside the submitted work. The remaining authors report no disclosures.

Key takeaway message: Decreased hippocampal and basal forebrain volumes are associated with measures of neurodegeneration and cognitive decline during Alzheimer's disease progression in Down syndrome. However, MRI volumetric analysis appears insensitive to the earliest neurodegenerative and cognitive changes.

OC44- TAU POSITRON EMISSION TOMOGRAPHY HARMONIZATION USING THE CENTAUR APPROACH: GENERAL CONVERSION EQUATIONS AND EXTERNAL VALIDATION.

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Background: Tau PET imaging is a powerful tool for the in vivo

quantification of tau neurofibrillary tangle pathology in Alzheimer's disease (AD), with growing importance in clinical trial design, staging, and outcome evaluation. However, variability in tracer properties, acquisition protocols, and image processing pipelines poses major challenges for comparing results across studies, especially across clinical trials that use different tau PET tracers. To address this issue, the Critical Path for Alzheimer's Disease (CPAD) Consortium developed the CenTauR approach, a standardized framework designed to harmonize tau PET quantitative metrics. Here, we provide a comprehensive description of the core components of the CenTauR harmonization method, outline the step-by-step process for converting tau PET data into CenTauR units for end users, and present an external validation of the method using independent datasets. **Methods:** We define the core components of the CenTauR harmonization approach: the 'Standard Method' for SUVR quantification and the Joint Propagation Model (JPM) for between-tracer harmonization. The 'Standard Method' establishes a consistent framework for tau PET quantification by applying consistent preprocessing and analysis steps, including standardized tau-PET acquisition windows. SUVR is quantified using a dedicated pipeline within five predefined 'Standard CenTauR' ROIs, designed to support both global measures of tau burden as well as region-specific staging approaches. The full pipeline will be made available through the Global Alzheimer's Association Interactive Network (GAAIN) [https://www.gaain.org/centaur-project]. To perform between-tracer harmonization, we used the Joint Propagation Model (JPM). Unlike traditional approaches that rely on a single reference tracer, the JPM leverages data from head-to-head, anchor point, and test-retest cohorts to model tracer relationships within a unified statistical framework. This method enhances conversion accuracy, eliminates reliance on a reference tracer, and maintains ease of use by providing simple linear conversion equations for end users. External validation of the JPM-based conversion equations was conducted using three matched cohorts with tau PET scans acquired using different radiotracers: [^{18}F]flortaucipir (ADNI (1), A05 (2,3), SCAN (4), [^{18}F]MK-6240 (CPAS5, SCAN4), and [^{18}F]PI-2620 (HABS-HD (6), LMU (7), SCAN (4). Participants were matched 1:1 based on age, clinical diagnosis, and Aβ status. CenTauR value distributions and tau positivity rates were then compared across tracers to assess across-tracer consistency. **Results:** General CenTauR conversion equations were derived by processing tau PET data from five radiotracers—[^{18}F]flortaucipir, [^{18}F]MK-6240, [^{18}F]PI-2620, [^{18}F]RO948, and [^{18}F]GTP-1—using the Standard Method across multiple datasets: head-to-head ($n = 118$), anchor point ($n = 368$), and test-retest ($n = 65$). The resulting SUVR values were entered into the JPM to generate tracer-specific linear transformations to the CenTauR scale. Based on the previous general conversion equations, the CenTauR framework supports two computation pathways to harmonize tau PET data across tracers: Level-1 CenTauR computation involves direct processing of tau PET scans using the 'Standard Method' and applying the Joint Propagation Model (JPM)-derived linear conversion equations to generate CenTauR values. This approach is supported by publicly available code and reference datasets for validation. Level-2 CenTauR computation allows harmonization of tau PET data obtained using non-standard methods (e.g., alternative acquisition windows, metrics, or ROIs). With this approach, users must derive linear conversion equations between the non-standard metric and SUVR measured using the 'Standard Method'. Once the non-standard metric is transformed, the resulting standard SUVR values can be converted into CenTauRs using the general JPM equations. External validation of Level-1 CenTauR computation in a total of 2028 matched individuals scanned with tau-PET (676 per radiotracer) demonstrated strong consistency across tracers in both CenTauR value distributions and tau positivity rates. Differences in median CenTauR values were minimal (<10 CenTauR units), and across-tracer variation in positivity frequencies remained lower than 10%. This result held true for both binary positivity and topography-based staging definitions. **Conclusions:** This study formally introduces the CenTauR approach, a standardized framework for harmonizing tau PET quantification across radiotracers and analysis pipelines that provides a common unit of measurement for tau PET results across trials. The framework supports both direct computation using a standardized pipeline (Level-1) and transformation of site-specific metrics into CenTauR units (Level-2), with public tools available to facilitate implementation. External validation across matched cohorts scanned with different tracers showed high consistency in CenTauR distributions and tau positivity rates, supporting the method's robustness. Together, these findings demonstrate the feasibility and utility of the CenTauR approach for multi-tracer harmonization in clinical trials.

Keywords: Alzheimer's disease, CPAD, CenTauR, Centiloid, C-Path; Imaging, PET, [18F]Flortaucipir, [18F]GTP1, [18F]MK-6240, [18F]PI-2620, [18F]RO948, head-t-head, standardization, tau.

Disclosures: Alexis Moscoso is a consultant to the Critical Path for Alzheimer's Disease (CPAD). Antoine Leuzy is a consultant to CPAD and to Enigma Biomedical Group. Nadine Tatton and Yashmin Karten reported that their organization (Critical Path Institute) received research funding via membership fees paid by members of the CPAD Consortium outside the submitted work. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement by, FDA/HHS or the U.S. Government. Lars Lau Raketi s full-time employees of Eli Lilly. Victor L. Villemagne has received research grants from NHMRC (GNT2001320), the Aging Mind Foundation (DAF2255207), and NIH 2P01AG025204-16) and is and has been a consultant or paid speaker at sponsored conference sessions for Eli Lilly, Life Molecular Imaging, Ace Barcelona, BRI Japan, and AC Immune. Gregory Klein and Matteo Tonietto are full-time employees of Hoffmann-La Roche Ltd. Emily Olafson is a full-time employees of Genentech, Inc. Ziad Saad is a full-time employees of Janssen. Hartmuth C. Kolb is a consultant to Enigma Biomedical Group. Christopher C Rowe has received research grants from the National Health and Medical Research Council, Enigma Australia, Biogen, Eisai and AbbVie. He is on the scientific advisory board for Enigma/Meilleur Technologies and has consulted for Prothena, Eisai, Roche and Biogen Australia. 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 and/or speaker fees from AC Immune, ALZpath, BioArctic, Biogen, Bristol Meyers Squibb, Cerveau, Eisai, Eli Lilly, Fujirebio, Merck, Novartis, Novo Nordisk, Roche, Sanofi and Siemens. The other authors report no competing interests.

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Key takeaway message: The CenTauR framework enables standardized harmonization of tau PET data across tracers and pipelines, facilitating consistent quantification, staging, and interpretation of tau pathology in Alzheimer's disease clinical trials and research studies.

3.4. Clinical trials: biomarkers including plasma

OC03- BIOLOGICAL STAGING OF ALZHEIMER'S DISEASE USING BLOOD-BASED BIOMARKERS.

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Background: Biological staging of Alzheimer's disease (AD) can enhance patient stratification, aiding diagnosis, prognosis, and the selection of individuals for targeted clinical trials. Current biological staging approaches often rely on β-amyloid and tau PET imaging, which limits scalability. In a recent study (Salvadó et al. Nature Aging, 2024), we created an effective disease staging model using several cerebrospinal fluid (CSF) biomarkers from a single sample. To enhance scalability, we now aimed to develop and validate a blood-based biological staging model using just two high-performing plasma biomarkers. **Methods:** We included 739 participants from the BioFINDER-2 cohort, representing the full biological AD continuum. All individuals had available plasma %p-tau217 and MTBR-tau243 levels (reflecting the microtubule-binding region containing epitope 243, Horie and Salvadó et al. Nature Medicine, 2025), which both reflect different aspects of tau metabolism. Logistic regression models were used to define optimal thresholds for both biomarkers to mimic the PET-based staging model defined by the Alzheimer's Association revised criteria (i.e., A-T-, A + T-, A + TMTL+, A + TMOD+ and A + THIGH++). We compared the performance of this dual-biomarker model to a model based solely on plasma %p-tau217 using the same approach. Associations with PET and other AD-related biomarkers were assessed both cross-sectionally and longitudinally. Validation was conducted in an independent imaging cohort (BioFINDER-pilot, n = 108, independent individuals) and a neuropathological cohort (Knight ADRC, n = 78). **Results:** The plasma-based staging model using %p-tau217 and MTBR-tau243 accurately reflected the PET-based stages (C-index = 0.91). This model also outperformed the model based on %p-tau217 alone (ΔC-index = 0.02, $p < 0.001$) and demonstrated greater stability (ΔFleiss's $\kappa = 0.04$, $p < 0.001$). Higher plasma-based stages were associated with worse clinical outcomes and biomarker profiles. The abnormality in other AD-biomarkers followed the expected stereotypical sequence with amyloid-PET becoming abnormal first (stage 1), followed by tau-PET in different regions (medial temporal lobe: stage 2, neotemporal: stage 3, Braak V-VI: stage 4), and neurodegeneration and cognition (stage 4). In longitudinal analyses, rate of change of amyloid-PET followed the expected inverted-U shape while tau-PET rates of change increased until the late stages. Using the same thresholds in the validation cohorts, the model showed strong agreement with PET-based stages (C-index = 0.97) and also with the classification of presence of AD pathology at autopsy based on the Alzheimer's disease neuropathologic change scale (ADNC: C-index = 0.85). **Conclusions:** Our findings support the use of a blood-based biological staging model as a scalable alternative for categorizing individuals across the AD continuum. This approach may facilitate more efficient patient selection in clinical trials and improve implementation in broader clinical settings.

Key takeaway message: We have created and validated a biological staging model for Alzheimer's disease using two high-performing plasma biomarkers.

OC05- THE EFFECTS OF LECANEMAB TREATMENT ON SOLUBLE CSF AB PROTOFIBRILS IN CLARITY AD.

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Background: Soluble amyloid-β protofibrils (Aβ-PF) are highly toxic and are in equilibrium with amyloid plaques. Lecanemab is a humanized IgG1 monoclonal antibody that binds with high affinity to Aβ-PF. The Clarity AD phase 3 trial in early Alzheimer's disease (AD) showed that lecanemab reduced amyloid plaques measured by amyloid PET and resulted in less decline on measures of cognition and function compared to placebo (1). Prior studies characterizing Aβ-PF have been conducted in vitro using synthetic peptides or in postmortem brain. Recently, we developed a sensitive immunoassay using lecanemab as the capture antibody that selectively quantifies Aβ-PF in human cerebrospinal fluid (CSF) and found that CSF Aβ-PF levels are significantly increased in AD and correlate with neurodegeneration biomarkers (2). In the current study, we further characterized CSF Aβ-PF in the Clarity AD trial: (1) at baseline, (2) as the target engagement biomarker (in vivo protofibril binding) of lecanemab, (3) longitudinally in the placebo arm (natural history), and (4) by investigating the associations between the change from baseline levels of CSF Aβ-PF and neurodegenerative biomarkers in both placebo and lecanemab-treated subjects. **Methods:** Aβ-PF levels were quantified in the CSF samples collected in the Clarity AD trial using the recently developed immunoassay, which is tolerant to therapeutic lecanemab presence in the CSF and measures total Aβ-PF (pool of free and bound forms). 410 subjects (Placebo = 207, Lecanemab = 203) had a CSF sample at baseline and 253 subjects (Placebo = 127, Lecanemab = 126) had a CSF sample at baseline and at least one post-baseline sample in the core study period (18 months). Other biomarker assessments including amyloid PET, and CSF biomarkers including total tau (t-tau), tau phosphorylated at 181 residue (p-tau181), neurogranin, and microtubule-binding region of tau containing 243 residue (MTBR-tau243) were described previously (3) and used for correlation analyses. **Results:** Baseline CSF Aβ-PF positively correlated with neurogranin, a biomarker of synaptic dysfunction ($r = 0.153$, $p = 0.0127$) and negatively correlated with amyloid PET Centiloid ($r = -0.202$, $p = 0.0005$). In the lecanemab-treatment arm, the CSF total Aβ-PF levels (free and bound) increased relative to placebo at each of the post-baseline assessments ($p = 0.0126$ at 12 months and was numerically higher at 18 month). In the subjects achieving amyloid-negativity defined as Centiloid<30 at 18 months, lecanemab-treatment group demonstrated a larger percent change from baseline in CSF Aβ-PF compared with subjects who remained amyloid-positive (Centiloid>30) at 18 months. In the placebo arm to assess the natural history, there were increases from baseline (%) in CSF Aβ-PF levels which showed the significantly positive correlations with the increases from baseline (%) observed in the CSF levels of neurodegenerative biomarkers including t-tau ($r = 0.286$, $p = 0.0069$) and neurogranin ($r = 0.262$, $p = 0.0138$) as well as the biomarkers related to AD tau pathology including p-tau181 ($r = 0.304$,

$p = 0.0040$) and MTBR-tau243 ($r = 0.252$, $p = 0.0155$). In the lecanemab-treatment arm, even though we observed an increase in total CSF Aβ-PF levels, there were no significant associations between the changes from baseline (%) in CSF Aβ-PF and the neurodegenerative or tau-related biomarkers. **Conclusions:** Clarity AD results confirmed previously demonstrated positive correlation of soluble Aβ-PF with neurodegeneration biomarkers. In contrast, we found that soluble Aβ-PF is negatively correlated with amyloid-PET, suggesting that Aβ-PF is a toxic species generated upstream of plaques in the amyloid cascade. The observed increase in total CSF Aβ-PF levels with lecanemab-treatment demonstrates target engagement, and mobilization of Aβ-PF from amyloid plaques (pharmacodynamic effect), confirming the unique dual mechanism of lecanemab targeting Aβ-PF and plaques. Finally, we demonstrated that lecanemab treatment disrupts the association between CSF Aβ-PF and AD biomarkers changes observed in the placebo arm, suggesting neutralization of Aβ-PF toxicity by lecanemab.

Keywords: Amyloid-β protofibrils, lecanemab, Clarity AD, cerebrospinal fluid, target engagement.

Clinical Trial Registry: NCT03887455 (ClarityAD); https://clinicaltrials.gov.

Disclosures: All authors are employees of Eisai.

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Key takeaway message: The increase in total CSF Aβ protofibril (Aβ-PF) levels with lecanemab treatment demonstrated target engagement and mobilization of lecanemab targeting Aβ-PF, confirming the unique dual mechanism of lecanemab targeting Aβ-PF and plaques.

OC11- COMBINING ENDOGENOUS CSF MTBR-TAU243 AND PLASMA PTAU217 ENHANCES PREDICTION OF CONTINUOUS REGIONAL TAU PET BURDEN IN AMYLOID-POSITIVE EARLY ALZHEIMER'S DISEASE.

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Background: Tau PET imaging provides critical insights into Alzheimer's disease (AD) staging and progression. However, its limited accessibility underscores the need for scalable fluid biomarkers that accurately reflect neurofibrillary tangle (NFT) burden. Plasma % phosphorylated to non-phosphorylated tau217 (%pTau217) has recently been shown to predict regional tau PET standardized uptake value ratio (SUVR) in early AD (Devanarayan et al., 2025). Separately, cerebrospinal fluid (CSF) MTBR-tau243 has demonstrated specificity for tau tangle pathology (Horie et al., 2023). This study evaluated whether combining plasma %pTau217 with CSF MTBR-tau243 improves the prediction of continuous regional tau PET SUVR in amyloid-positive individuals with early AD. **Methods:** Plasma pTau217 and non-phosphorylated tau217 were quantified by C2N Diagnostics using immunoprecipitation followed by mass spectrometry (IP/MS). CSF MTBR-tau243 was measured in both its tryptic (digested peptide) and endogenous (in vivo-derived) forms using the same IP/MS platform; the latter is referred to as eMTBR-tau243. Data were obtained from the phase-III clinical trial of lecanemab, which included amyloid-β-positive participants in the early stages of AD with available tau PET imaging. The dataset comprised 242 individuals with plasma %pTau217 data, 80 with CSF MTBR-tau243 data, and 57 with both biomarkers available. Tau PET imaging was performed using the [18F]MK6240 tracer to quantify regional SUVRs, corresponding to Braak stages and cortical regions. A stochastic gradient boosting algorithm was used to develop a multivariate model for simultaneously predicting tau PET SUVR values across multiple brain regions corresponding to Braak stages and cortical areas. This unified modeling approach enabled joint learning across regions. All models included age, sex, and ApoE ε4 status. Model performance was evaluated using 20 iterations of 10-fold stratified cross-validation. Additional analyses assessed whether incorporating cognitive assessments, structural MRI, amyloid PET, other CSF biomarkers (Ab42, pTau181, NfL, Neurogranin), or other plasma biomarkers (Ab42/Ab40, pTau181, GFAP, NfL) improved prediction. **Results:** Combining plasma %pTau217 with CSF eMTBR-tau243 significantly improved the prediction of regional tau PET SUVR, achieving area under the receiver operating characteristic curve (AUROC) values up to 97.6%. This integration enhanced classification accuracy by 4 to 7 percentage points across Braak stages I–VI and cortical regions. Correspondingly, the R^2 values increased by 5 to 11 percentage points, reaching a maximum of 0.67 ($p < 0.05$), indicating robust predictive performance for both early and advanced tau pathology. Models using CSF eMTBR-tau243 alone yielded R^2 values between 0.42 and 0.57, with AUROC values ranging from 76.2% to 93.1% across SUVR thresholds of 1.1, 1.25, 1.5, and 1.75. Notably, the inclusion of cognitive scores, amyloid PET Centiloid, MRI-derived regional volumes, or additional fluid biomarkers did not significantly enhance model performance. These findings suggest that the combined plasma %pTau217 and CSF eMTBR-tau243 capture most of the predictive signal for regional tau burden across all Braak stages. In a simulated clinical trial screening scenario, the combined biomarker model reduced the number of required tau PET scans by up to 70% while maintaining a 5% false negative rate. Although reliance on CSF-based screening may limit scalability, these results support the potential of a fully plasma-based approach. Assuming successful translation of eMTBR-tau243 to plasma, similar predictive performance could enable rapid and less invasive trial enrollment. **Conclusions:** Combining CSF eMTBR-tau243 with plasma %pTau217 effectively predicts continuous regional tau burden in amyloid-positive individuals with early AD. This biomarker combination offers a promising and scalable alternative to tau PET imaging for disease staging and participant selection in clinical trials. While the invasiveness of CSF sampling limits its practicality for routine screening, a plasma-based eMTBR-tau243 assay (Horie et al., 2025) will be evaluated in future studies. Ongoing work will focus on validating these findings in larger and more diverse cohorts, assessing longitudinal performance, and establishing a fully blood-based biomarker panel for broader clinical and research applications.

Key takeaway message: This study shows that combining plasma % pTau217 with CSF eMTBR-tau243 robustly predicts regional tau PET burden, enabling their use to reduce PET scans and optimize clinical trial design in early Alzheimer's disease.

OC14- LONGITUDINAL TRAJECTORIES OF PLASMA P TAU217 IN COGNITIVELY UNIMPAIRED OLDER ADULTS USING A FULLY AUTOMATED PLATFORM.

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Background: Plasma phosphorylated tau 217 (p-tau217) holds significant promise as a biomarker for detecting early Alzheimer's disease pathology before the onset of clinical symptoms. However, large-scale

longitudinal data in cognitively unimpaired (CU) populations are limited, which restricts our understanding of preclinical biomarker trajectories and their potential to predict cognitive decline. Accurately tracking p-tau217 changes is therefore critical for establishing reference ranges, identifying at-risk individuals before symptom onset, and optimizing prevention trial design, particularly by generating estimates of progression rates that drive power and sample size calculations. To ensure the most sensitive and reliable measurements, we conducted a large-scale head-to-head comparison—assessing cross-sectional diagnostic accuracy and longitudinal performance—across four fully automated platforms, which mirror the systems most likely to be adopted globally in routine clinical laboratories. Additionally, we utilized the top-performing assay to directly assess longitudinal p-tau217 trajectories in CU older adults, characterizing biomarker dynamics prior to symptom onset and providing data necessary for the design of prevention trials. **Methods:** Initial head-to-head comparisons included 4784 plasma samples using research-use-only versions of Lumipulse G1200 (Fujirebio), Elecsys cobas e801 (Roche Diagnostics), Atellica IM (Siemens Healthineers), and DxI 9000 (Beckman Coulter), in 1687 CU and 207 CI individuals from the Wisconsin Registry for Alzheimer's Prevention (WRAP) and Alzheimer's Disease Research Center (ADRC). Cross-sectional accuracy of p-tau217 was benchmarked against amyloid PET positivity (>24.1 Centiloids (CL). Longitudinal performance on each platform was evaluated with mixed-effects models, focusing on estimated annual p-tau217 rates of change. Building on these findings, we are currently analyzing an additional 5000 longitudinal p-tau217/Aβ42 Roche Elecsys cobas e801 measurements in CU older adults (ages 50-80, APOE4 carriers and non-carriers) from various well-characterized cohorts. This analysis will quantify biomarker trajectories, account for biological variation and reference change values, and link preclinical biomarker changes to cognitive outcomes. **Results:** In the entire population, the Roche Elecsys cobas e801 platform exhibited significantly higher diagnostic accuracy (AUC = 0.94, 95% CI: 0.91–0.96) for amyloid PET positivity compared to other platforms, and when using the p-tau217/Aβ42 ratio (AUC = 0.95, 95% CI: 0.92-0.97). In CU participants only, Elecsys cobas e801 had an AUC of 0.92 (0.89–0.96). In CI individuals, all assays showed similar performance (AUCs >0.91). In longitudinal mixed-effects analyses assessing how p-tau217 and p-tau217/Aβ42 trajectories differ by amyloid status, the Elecsys cobas e801 assay provided the best fit (AIC = −2600; BIC = −2558) and had an annual increase in amyloid PET–positive individuals of 0.03 pg/mL per year. Adding Aβ42 did not improve the longitudinal model fit. We will also present results from our ongoing analysis of an additional 5000 longitudinal p-tau217 and Aβ42 Roche Elecsys cobas e801 measurements in CU older adults, examining the trajectories and their relationships with cognitive performance and other relevant clinical variables. Estimates of progression rates from this analysis will be used to derive effect-size calculations and determine sample size requirements for primary and secondary prevention trials. **Conclusions:** The Roche Elecsys cobas e801 platform demonstrated superior cross-sectional diagnostic performance for the p-tau217/Aβ42 ratio among fully automated platforms. Although adding the ratio did not improve longitudinal results, Roche p-tau217 alone still outperformed others in terms of model fit. By applying this assay to a large longitudinal dataset of CU older adults, we will generate a detailed characterization of preclinical p tau217 and Aβ42 trajectories, define prognostic thresholds, and calculate sample size and endpoint recommendations for primary and secondary prevention trials. These insights will critically inform the design and timing of preventive Alzheimer's trials in preclinical populations.

Keywords: Plasma p-tau217, biomarkers, Alzheimer's disease, fully automated immunoassays, prevention clinical trials.

Disclosures: NJA has given a paid scientific presentation for Beckman. EMR is a cofounder and advisor of AlzPath, which has licensed it plasma pTau217 capture antibody for use on several immunoassay platforms. He was not involved in the performance of the assay or the resulting data analysis.

Key takeaway message: Among fully-automated platforms, Roche Elecsys cobas e801 p-tau217/Aβ42 had the highest cross-sectional accuracy and the best longitudinal fit for CU trajectories, and planned analyses will provide important information on progression-rates and guide future Alzheimer's prevention trial design.

OC19- ALPHA-SYNUCLEIN DETECTION: A VERSATILE EV-BASED PLASMA ASSAY FOR DETECTING MODIFIED A-SYNUCLEIN IN SYNUCLEINOPATHIES WITHOUT PRE-ENRICHMENT.

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Background: Parkinson's disease (PD) and other synucleinopathies (e.g. DLB, MSA) are marked by the abnormal accumulation of alpha-synuclein (αSyn) into insoluble fibrils and Lewy bodies in the brain and/or CNS. A wide variety of Post-translational modifications (PTMs) including phcsphorylation at serine-129, are increasingly recognized for their complementary roles in the pathogenesis of these diseases, influencing αSyn aggregation, toxicity, and disease progression. Detection of brain-derived, brain pathology related αSyn in peripheral biofluids has been limited by invasive sampling (e.g., cerebrospinal fluid), or labor-intensive seed amplification requiring extended processing times. The Sunbird αSyn™ assay (Sunbird Bio, Cambridge/MA, USA) addresses these limitations with a brain enriched extracellular vesicle (EV)-based platform that directly quantifies modified αSyn from neat plasma without EV isolation. This EV-based immunodetection method enables highly specific and sensitive measurement of multiple αSyn PTMs, offering a scalable, non-invasive biomarker solution for synucleinopathies. Importantly, the technology has the potential to be implemented on standard automated immunoassay analyzers, supporting broader clinical applicability. **Methods:** The Sunbird assay uses a proprietary EV-capture strategy coupled with immunodetection of αSyn PTMs (e.g., phospho-Ser129). It operates on standard EDTA plasma without the need for pre-enrichment. The assays were tested in three independent clinical feasibility cohorts:

• Cohort 1: 34 early-stage PD patients (Hoehn & Yahr stages 1–2; 23M/11F, aged 46–84) and 21 age-matched controls (9M/12F, aged 58–86) from a subset of the Australian Parkinson's Disease Registry (APDR, Florey Institute, 2012-2015). • Cohort 2 (exploratory): 32 symptomatic PD patients (H&Y stages 1–4; 21M/11F, aged 47–87) and 12 healthy controls (8M/4F, aged 58–86) from a subset of the Australian Parkinson's Disease Registry (APDR, Florey Institute, 2012–2015), evaluated with an assay targeting an additional disease-associated αSyn PTM. • Cohort 3 (confirmatory): 41 symptomatic PD patients (H&Y stages 1–4, 19M/22F, aged 45-80) and 38 age - and gender-matched healthy controls (20M/19F, aged 54-79) from a subset of the Australian Parkinson's Disease Registry (APDR, Florey Institute, 2012–2015), tested with the same disease-associated αSyn PTM assay. **Results:** This study evaluated a novel extracellular vesicle (EV)-based plasma assay for detecting post-translationally modified α-synuclein (αSyn) species relevant to synucleinopathies. The assay directly quantifies EV-bound αSyn from neat plasma, without requiring EV isolation or pre-enrichment, and was tested across three independent clinical cohorts: Cohort 1 included 34 early-stage Parkinson's disease (PD) patients and 21 age-matched controls. The ratio of EV-bound phosphorylated αSyn at serine 129 (pS129) to total EV-bound αSyn differentiated PD patients from controls with an area under the curve (AUC) of 0.802. Cohort 2 served as an exploratory study using an alternative disease-associated αSyn PTM assay. Among 32 symptomatic PD patients and 12 controls, this novel PTM assay achieved an AUC of 0.84, indicating strong diagnostic performance. Cohort 3 was a confirmatory study of the Cohort 2 assay in an independent set of 41 symptomatic PD patients and 38 matched controls. The performance was replicated with an AUC of 0.80, supporting robustness and reproducibility. Notably, soluble (non-EV-bound) αSyn

markers yielded poor discrimination (AUC = 0.534). Analytical validation of the pS129 assay demonstrated high precision (<4% coefficient of variation across replicates), excellent reproducibility (<5% variability across operators, lots, and days), stability under multiple freeze-thaw cycles, and resistance to red blood cell lysis interference. The assay is compatible with both standard chemiluminescent and fluorescent plate readers. **Conclusions:** This EV-based plasma assay enables robust, non-invasive detection of modified αSyn species that is reflective of brain pathology without EV isolation. Demonstrated across multiple cohorts and PTMs, the assay technology offers potential for early diagnosis, disease monitoring, and therapeutic stratification in synucleinopathies. Additionally, detecting αSyn PTMs in plasma may aid in identifying AD patients with Lewy body co-pathology, supporting differential diagnosis and clinical trial stratification. Ongoing validation and assay optimization—including cut-off determination and testing in independent cohorts—will be presented at CTAD 2025.

Keywords: Blood-based, alpha-synuclein, post-translational modification, Parkinson's disease.**Disclosures:** Carine Lim, Huiling Ko, Brian Minie, Nicole Tsang, Nicholas Ho and Huilin Shao are employees of Sunbird Bio Singapore, Richard Batrla is employee of Sunbird Bio Cambridge, MA, USA. The Sunbird αSyn™ (plasma) assay is for research use only and has not received regulatory approval.

Key takeaway message: A novel EV-based plasma assay detects modified α-synuclein without pre-enrichment, enabling non-invasive, scalable, and highly specific biomarker assessment for synucleinopathies, validated across three clinical cohorts with strong diagnostic performance.

OC20- POPULATION CHARACTERISTICS AND IMPLICATIONS OF IMPLEMENTATION STRATEGIES FOR BLOOD-BASED BIOMARKERS IN ALZHEIMER'S DISEASE ACROSS HEALTHCARE SETTINGS: INSIGHTS FROM A PROSPECTIVE, GLOBAL, MULTICENTER STUDY.

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Background: Blood-based biomarkers (BBBMs) could streamline the Alzheimer's disease (AD) patient pathway by facilitating diagnosis, treatment, and care; they are increasingly important performance indicators for triaging tests. Amyloid pathology prevalence affects the predictive values of BBBMs, and varies across population demographics/characteristics, factors that are crucial for BBBM implementation. We describe characteristics of populations likely to receive BBBMs as triaging tools across healthcare settings, using data from a prospective, global, multicenter study reflective of routine clinical practice. Additionally, we discuss implementation strategies for BBBMs to rule-in/rule-out patients. **Methods:** Data were from Roche's RD006263 study, designed to validate BBBMs for early amyloid pathology in patients aged 55–80 years with subjective or objective cognitive impairment. The population approximated routine clinical practice across baseline characteristics and comprised patients from primary and secondary/tertiary care settings. For each healthcare setting, amyloid pathology prevalence (point estimates and 95% two-sided Wilson confidence intervals [CI]) was determined by positron emission tomography visual read. The effect of clinical diagnosis (subjective cognitive decline [SCD]; mild cognitive impairment [MCI]; mild dementia [MD]), Mini-Mental State Examination (MMSE) scores (MMSE 28–30: cognitively normal; MMSE 25–27: MCI; MMSE <25: moderate-to-severe cognitive impairment), and age (55–69 years; 70–80 years) on amyloid pathology prevalence was assessed. **Results:** In total, 1290 patients (mean age 69.3 years [standard deviation 6.5]) heterogeneous across sex, race/ethnicity, and comorbidities were included. Of these, 558 (43.3%) were from primary care and 732 (56.7%) from secondary/tertiary care. Overall, amyloid pathology prevalence was lower in primary care (11.6% [95% CI 9.25%–14.6%]) versus secondary/tertiary care (30.7% [95% CI 27.5%–34.2%]). In primary care, 244 (43.7%) patients were clinically diagnosed with SCD, 289 (51.8%) with MCI, and 12 (2.2%) with MD; in secondary/tertiary care, 226 (30.9%) patients were clinically diagnosed with SCD, 435 (59.4%) with MCI, and 64 (8.7%) with MD. Amyloid pathology prevalence was higher in patients with more advanced disease (ie, MCI and MD) across healthcare settings; prevalence per disease stage was lower in primary care (SCD: 7.0% [95% CI 4.4%–10.9%]; MCI: 15.6% [95% CI 11.8%–20.2%]; MD: 8.3% [95% CI 0.4%–35.4%]) versus secondary/tertiary care (SCD: 11.5% [95% CI 7.97%–16.3%]; MCI: 36.8% [95% CI 32.4%–41.4%]; MD: 60.9% [95% CI 48.7%–71.9%]). In primary care, patients generally had higher MMSE scores (215 [38.5%] MMSE 28–30, 234 [41.9%] MMSE 25–27, and 109 [19.5%] MMSE <25), suggesting milder cognitive impairment, versus patients in secondary/tertiary care (330 [45.1%] MMSE 28–30, 222 [30.3%] MMSE 25–27, and 180 [24.6%] MMSE <25), whose scores suggest clinically measurable cognitive impairment. Amyloid pathology prevalence was also higher in patients who were classified as mildly and moderately-to-severely cognitively impaired based on MMSE scoring (ie, MMSE 25–27 and < 25) across healthcare settings; prevalence was lower in primary care (MMSE 28–30: 12.6% [95% CI 8.8%–17.7%]; MMSE 25–27: 9.0% [95% CI 5.9%–13.3%]; MMSE <25: 15.6% [95% CI 10.0%–23.6%]) versus secondary/tertiary care (MMSE 28–30: 15.2% [95% CI 11.7%–19.4%]; MMSE 25–27: 36.9% [95% CI 30.9%–43.5%]; MMSE <25: 51.7% [95% CI 44.4%–58.9%]). Mean age was 69.0 years and 69.5 years in primary and secondary/tertiary care, respectively. Older patients (70–80 years; n = 651) were more likely to have more advanced disease versus younger patients (55–69 years; n = 639). In primary care, 3.1% of patients aged 70–80 years had MD and 17.3% had MMSE <25, versus 1.3% and 21.5% of patients aged 55–69, respectively. In secondary/tertiary care, 11.3% of patients aged 70–80 years had MD and 29.4% had MMSE <25, versus 5.9% and 19.1% of patients aged 55–69, respectively. Amyloid pathology was more prevalent in older patients; in primary care, 18.1% of patients aged 70–80 years had possible amyloid pathology versus 6.0% of patients aged 55–69 years. In secondary/tertiary care, 41.2% of patients aged 70–80 years had possible amyloid pathology versus 18.8% of patients aged 55–69 years. **Conclusions:** In this population reflective of routine clinical practice without exclusion of comorbidities, amyloid pathology prevalence was lower in primary versus secondary/tertiary care; more patients in more advanced disease stages (based on clinical diagnosis and MMSE scores) were seen in secondary/tertiary care versus primary care. More advanced disease stages and increased age were associated with higher amyloid pathology prevalence. Mean age was similar across healthcare settings. When assessing the risk of amyloid pathology using BBBMs, negative and positive predictive values (NPV/PPV) depend on test sensitivity/specificity but also patient risk profile, which relies on healthcare settings/age. In higher-prevalence settings (secondary/tertiary care), higher PPVs and reduced NPVs are expected when implementing BBBMs. In lower-prevalence settings (primary care), higher NPVs and lower PPVs are expected. As high PPVs are desirable for rule-

in tests and high NPVs are desirable for rule-out tests, the effective implementation of rule-in/rule-out tests may be supported in higher-prevalence and lower-prevalence settings, respectively. Implementation of BBBMs into the AD diagnostic pathway may improve treatment/management, quality of life, and cost-efficiency by streamlining confirmatory testing, preventing unnecessary assessments, and reducing diagnosis timelines. This study offers a realistic view of amyloid pathology prevalence across healthcare settings.

Keywords: Amyloid pathology prevalence, blood-based biomarker implementation, care setting, disease stage.

Disclosures: Imke Kirste: IK is an employee of Roche Diagnostics Solutions. Sayuri Hortsch: SH is an employee of Roche Diagnostics GmbH. Craig Ritchie: CEO, Founder and Majority Share Holder: Scottish Brain Sciences, Edinburgh, UK. Jeffrey L. Dage: JLD is an inventor on patents or patent applications assigned to Lilly relating to the assays, methods, reagents and/or compositions of matter for P-tau assays and Aβ targeting therapeutics. JLD has/is served/serving as a consultant or on advisory boards for AbbVie, Alzheimer's Disease Drug Discovery Foundation, AlzPath, Inc., Cognito Therapeutics, Inc., Dolby Family Ventures, Early is Good, Eisai, Gate Neurosciences, Gates Ventures, Genotix Biotechnologies Inc, Karuna Therapeutics, Lilly, MindImmune Therapeutics, Inc., Neurogen Biomarking, Prevail Therapeutics, Quanterix, Rush University, Spear Bio, Tymora Analytical Operations, and University of Kentucky. JLD has received research support from ADx Neurosciences, Fujirebio, Lilly, and Roche Diagnostics in the past 2 years. JLD has received speaker fees from LabCorp and Lilly. JLD is a founder and advisor for Dage Scientific LLC and Monument Biosciences. JLD has stock or stock options in AlzPath, Inc., Genotix Biotechnologies, Lilly, MindImmune Therapeutics, Inc., Monument Biosciences, and Neurogen Biomarking. Kristian Steen Frederiksen: KSF has given lectures in symposia sponsored by Eisai/Bioarctic, Novo Nordisk, and Roche Diagnostics Danmark and served on advisory boards or as consultant for Eisai/Bioarctic, Lilly Novo Nordisk, and Roche Diagnostics (fees paid to institution). Marc Suárez-Calvet: MS-C has received in the past 36mo consultancy/speaker fees (paid to the institution) from by Almirall, Lilly, Novo Nordisk, Quanterix, and Roche Diagnostics. He has received consultancy fees or served on advisory boards (paid to the institution) of Grifols, Lilly, Novo Nordisk, and Roche Diagnostics. 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, ALZpath, Avid Radiopharmaceuticals, Fujirebio, Janssen Research & Development, Lilly, Meso Scale Discovery, and Roche Diagnostics; MS-C did not receive any personal compensation from these organizations or any other for-profit organization. Marwan N. Sabbagh: MNS has collaborated with Roche. Clara Quijano-Rubio: CQ-R is an employee of Roche Diagnostics International Ltd. Third-party medical writing support, under the direction of the authors, was provided by Pozisa Majaja, MSc, of Ashfield MedComms (Johannesburg, South Africa), an Inizio company, and was funded by Roche Diagnostics International Ltd (Rotkreuz, Switzerland).

Key takeaway message: In a population representative of routine clinical practice, amyloid pathology prevalence varied based on healthcare setting, disease stage, and age. Implementation of BBBMs taking these factors into consideration may improve the AD patient pathway.

OC32- BREAKING BARRIERS IN EARLY ALZHEIMER'S DISEASE DIAGNOSIS: THE POWER OF THE IN VITRO DIAGNOSTIC ELECSYS PT181P IMMUNOASSAY IN A POPULATION REFLECTIVE OF REAL-WORLD CLINICAL PRACTICE.

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Background: Early diagnosis of Alzheimer's disease (AD) is crucial for optimizing patient management, patient outcomes, and quality of life. Currently approved disease-modifying therapies for AD target amyloid-β (Aβ); therefore, identifying the presence of amyloid pathology is critical for diagnosis and treatment. Confirmatory amyloid testing by positron emission tomography (PET) and cerebrospinal fluid (CSF) assessment is expensive, of limited availability, and often perceived as invasive. Blood-based biomarkers (BBBMs) are emerging as powerful tools that harbor the potential to increase access to early AD diagnosis. To enhance the effective use of BBBMs in real-world clinical practice, performance validation in a population representative of clinical practice is essential. This study validated the plasma tau phosphorylated at threonine 181 (pTau181p) cutoff using the Elecsys® Phospho-Tau (181P) plasma immunoassay (pT181p; Roche Diagnostics International Ltd, Rotkreuz, Switzerland) to rule out amyloid pathology in a population reflective of clinical practice in terms of sex, race and ethnicity, comorbidities, and healthcare setting. **Methods:** This prospective, multi-center study (RD006263) included 18 clinical sites across the US, Europe, and Australia; recruitment of the validation cohort was conducted between 11 July 2023–17 December 2024. Patients aged 55–80 years presenting with cognitive complaints or objective memory impairment with unknown symptom etiology were enrolled. Mini-Mental State Examination, Quick Dementia Rating System, Clinical Dementia Rating, and/or clinical diagnosis were used to determine patients' clinical stage to identify those with subjective cognitive decline (SCD), mild cognitive impairment (MCI), or mild dementia. Patients with concomitant medications and comorbidities were permitted. pTau181p levels were measured in samples obtained from eligible patients using the pT181p immunoassay. The pT181p cutoff of 0.934 pg/mL, previously established in an independent population, was validated. Clinical performance was assessed with respect to amyloid pathology status, defined by amyloid-PET visual read (tracers: 18F-florbetapir, 18F-florbetaben, or 18F-flutemetamol), or by the Elecsys CSF pTau181/Aβ42 ratio, which was measured using the Elecsys Phospho-Tau (181P) CSF and Elecsys β-Amyloid (1-42) II CSF immunoassays (Roche Diagnostics International Ltd). The receiver operating characteristic-area under the curve (ROC-AUC), negative predictive value (NPV), positive predictive value (PPV), negative percent agreement (NPA), and positive percent agreement (PPA) were calculated. **Results:** Of 787 patients enrolled, 650 had a valid amyloid-PET result; 43.8% were male, mean age was 69.3 years (standard deviation [SD]: 6.42), and 94.0% had known comorbidities. For the clinical stage assessment, 40.8% were diagnosed with SCD, 53.1% with MCI, 4.6% with mild dementia, and 1.5% had a missing diagnosis. Regarding race, 74.2% of patients were White and 20.2% were Black or African American; the remainder were Asian (2%), Middle Eastern (0.3%), or other (3.4%). Regarding ethnicity, 18.3% were Hispanic or Latino and 61.1% were not, the remainder had unknown (0.15%) or missing ethnicity data (20.5%). Forty-eight percent of patients were reflective of primary care and 52% of secondary/tertiary care. Patient demographics and characteristics for 529/787 patients with a valid CSF pTau181/Aβ42 ratio measurement were similar to the 650/787 patients with a valid amyloid-PET result (401 patients had both valid amyloid-PET and CSF analysis results). In patients with a valid amyloid-PET result (n = 650), the mean pTau181p concentration was 0.995 pg/mL (SD: 0.501) and in amyloid-PET positive (n = 146) and negative (n = 504) individuals, it was 1.48 pg/mL (SD: 0.534) and 0.855 pg/mL (SD: 0.393), respectively. In patients with a valid CSF pTau181/Aβ42 ratio result (n = 529), the mean pTau181p concentration was

0.959 pg/mL (SD: 0.513) and in CSF pTau181/Aβ42 ratio positive (n = 148) and negative (n = 381) patients, it was 1.33 pg/mL (SD: 0.565) and 0.815 pg/mL (SD: 0.410), respectively. The AUC value for pTau181p with respect to amyloid-PET was 0.854 and with respect to the CSF pTau181/Aβ42 ratio was 0.818. The amyloid positivity prevalence observed in patients with a valid amyloid-PET result in the validation cohort was 22.5%. The NPV and PPV with respect to amyloid-PET were 93.8% (95% confidence interval [Cl] 91.3–95.6) and 46.6% (95% CI 42.7–50.5), respectively; the NPA was 72.2% (95% CI 68.2–76.0), and the PPA was 83.6% (95% CI 76.7–88.7). The amyloid positivity prevalence based on the CSF pTau181/Aβ42 ratio was 28.0%. The NPV and PPV with respect to the CSF pTau181/Aβ42 ratio were 88.8% (95% Cl 85.6–91.3) and 55.8% (95% CI 50.7–60.8), respectively; the NPA was 76.9% (95% CI 72.4–80.9), and the PPA was 75.0% (95% CI 67.5–81.3). NPV, indicative of the rule-out performance of the test, was unaffected by low estimated glomerular filtration rate and other comorbidities. **Conclusions:** The pT181p immunoassay cutoff was validated in a diverse patient population reflective of real-world clinical practice in terms of sex, race, and ethnicity, inclusive of comorbidities, and representative of primary and specialist care. These results highlight the high performance of the pT181p immunoassay as a tool to rule out amyloid pathology in individuals in the early stages of cognitive decline in all healthcare settings. Consequently, these results support the potential of the pT181p immunoassay to streamline access to amyloid pathology confirmation and thus enhance patient management, quality of life, and health economic outcomes, evidencing its relevance as an in vitro diagnostic device for implementation in the AD diagnostic pathway.

Keywords: Amyloid pathology, in vitro diagnostic, rule-out, tau phosphorylated at threonine 181.

Disclosures: Sayuri Hortsch: SH is an employee of Roche Diagnostics GmbH. David Caley: DC is an employee of Roche Diagnostics Limited. Patrick Menzel: PM is an employee of Roche Diagnostics GmbH. Christopher Rowe: CR provided consultation for Biogen, Cerveau Technologies, Eisai, Enigma Biomedical, F. Hoffmann-La Roche, Ltd., Lilly, Merck, Novo Nordisk and Prothena and received grants paid to his institution from Biogen, Cerveau, Eisai, Enigma, F. Hoffmann-La Roche, Ltd., and Novo Nordisk. He is supported by Austin Health and the National Health and Medical Research Council of Australia. Mark Rapp: MR declares no conflicts of interest. Dag Aarsland: DA has received honoraria from Roche Diagnostics International Ltd for participating in an advisory board. Anna D. Burke: ADB is a consultant for Alector, Eisai, and Lilly, and has received research funding from Alector, Biogen, Cognito Therapeutics, EIP Pharma, Eli Lilly, F. Hoffmann-La Roche, Ltd., and Janssen. Clara Quijano-Rubio: CQ-R is an employee of Roche Diagnostics International Ltd.

Key takeaway message: The pT181p immunoassay cutoff to rule out amyloid pathology was validated in a population reflective of clinical practice, supporting its relevance as an in vitro diagnostic device for implementation in the Alzheimer's disease diagnostic pathway.

OC35- CLINICAL PERFORMANCE OF THE ELECSYS CSF PTAU181/AB42 RATIO FOR CONCORDANCE WITH TAU-PET IN TWO INDEPENDENT COHORTS.

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Introduction: Tau-positron emission tomography (PET) is a promising modality for detecting tau pathology in patients with Alzheimer's disease (AD) (1); however, its broad application is restricted due to high costs and need for complex infrastructure. The extent and distribution of tau pathology provide insights into diagnosis, disease severity, stage, progression risk, and response to therapy in AD patients (2). Moreover, it may be useful for patient stratification and treatment optimization in AD clinical trials (3). In contrast, fluid biomarkers are more accessible and affordable for assessing AD-related pathology compared with tau-PET, enabling broader application in routine clinical diagnostics (4). Although cerebrospinal fluid (CSF) biomarkers as alternatives to tau-PET have been explored, no in vitro diagnostic (IVD)-approved or commercial CSF biomarker assays are currently available for detecting tau pathology in clinical practice. **Methods:** In this study, we determined and validated the optimal cutoff value for the ratio of tau phosphorylated at a threonine residue at position 181 (pTau 181) to β-amyloid (1–42) (Aβ 42) in CSF, measured with the IVD-approved Elecsys® Phospho-Tau (181P) CSF and β-Amyloid (1–42) CSF immunoassays (Roche Diagnostics International Ltd, Rotkreuz, Switzerland), based on its concordance with binary tau-PET status.Clinical performance was explored using CSF measurements and tau-PET scans retrospectively obtained from a subset of subjects with mild cognitive impairment (MCI) and dementia due to AD in two independent cohorts, Alzheimer's Disease Neuroimaging Initiative-2/3 (ADNI-2/3; N = 133) and Swedish BioFINDER-2 (N = 62). **Results:** In the ADNI-2/3 subset, the pTau 181/Aβ 42 cutoff value with the best compromise between positive percent agreement (PPA) and negative percent agreement (NPA) for the tau-PET visual read endpoint was selected. This cutoff and was associated with PPA 88.5% (95% confidence internal [CI] 77.0, 94.6), NPA 82.7% (95% CI 73.1, 89.4) and overall percent agreement (OPA) 85.0% (95% CI: 77.9, 90.0). After adjustment to account for differences between the ADNI-specific pre-analytical protocol and the manufacturer's recommended pre-analytical protocol used in BioFINDER-2, the optimal CSF pTau181/Aβ42 cutoff value was set at 0.037. The adjusted cutoff was validated in the BioFINDER-2 subset, where it was associated with PPA 85.7% (95% CI 70.6, 93.7), NPA 70.4% (95% CI 51.5, 84.1) and OPA 79.0% (95% CI 67.4, 87.3), and the positive and negative likelihood ratios were 2.89 (95% CI 1.59, 5.25) and 0.203 (95% CI 0.0870, 0.474), respectively. **Conclusions:** The present study is the first to evaluate and validate the clinical performance of the adjusted Elecsys CSF pTau 181/Aβ 42 ratio cutoff value in identifying tau pathology using the routine-use pre-analytical protocol. The optimal pTau 181/Aβ 42 cutoff value of 0.037 showed high concordance with tau-PET status in individuals with MCI or dementia due to AD. Hence, the Elecsys CSF pTau 181/Aβ 42 ratio may be a reliable tool for identifying tau pathology in clinical practice.

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Key takeaway message: Due to high concordance with tau-PET

imaging, the Elecsys CSF pTau 181/Aβ 42 ratio might be the first fluid biomarker for identifying tau pathology in clinical practice.

OC37- THE ASSOCIATIONS BETWEEN COGNITIVE DEFICITS AND THE LOCATION OF TAU TANGLES AND THEIR CONSISTENCY ACROSS CLINICAL AND OBSERVATIONAL DATASETS.

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Background: Tau proteins play a central role in the pathological development of Alzheimer's disease (AD). Toxic tangles of hyperphosphorylated tau proteins disrupt normal neuronal functions and result in cognitive decline or dysfunction. This suggests the spatial distribution of tau tangles should correspond to the domain(s) of cognitive impairment based on the known function of different brain regions. Previously, we reported such associations between spatial deposition of tau tangles and performance on the 5 cognitive domains/indices (immediate memory, delayed memory, language, attention and visuospatial) measured using Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) in the Phase 2 Autonomy trial (NCT04619420). In the current analysis, we expanded our investigation to Alzheimer's Disease Assessment Scale–Cognitive subscale-13 item version (ADAS-Cog-13), a different composite cognitive scale measured at screening in Autonomy as well as in a cohort from the Alzheimer's Disease Neuroimaging Initiative (ADNI). We aim to validate the consistency of these spatial associations across tracers and cohorts. **Methods:** Tau deposition was quantified using Standardized Uptake Value Ratio (SUVR) of positron emission tomography (PET) scans from two cohorts using two tau specific tracers: 390 randomized Autonomy participants with mild cognitive impairment (MCI) or mild AD dementia scanned using 18F-MK-6240, and 313 ADNI participants, diagnosed as mild cognitive impairment (MCI) ($n = 233$) or dementia ($n = 80$) scanned using 18F-T807. We used cerebellar gray as the reference region for all SUVR calculations. To compute the associations, SUVR volumes were non-linearly aligned to Montreal Neurological Institute space and smoothed within a gray matter mask by a full width at half max kernel of 12 mm. Participants from both cohorts that were included in the analysis were chosen to have cognitive tests (RBANS and ADAS-Cog-13 in Autonomy; ADAS-Cog-13 in ADNI) taken within 90 days of the corresponding tau PET scans. Voxelwise associations between each cognitive domain and tau PET SUVRs were quantified using Spearman rank-order correlation. Within each RBANS cognitive domain, voxelwise correlation coefficients were subsequently transformed to their rank within the gray matter mask. An RBANS cognitive domain association map is then created by assigning at each voxel its highest ranked cognitive domain. In order to obtain cognitive domain maps using ADAS-Cog-13 questions that are comparable to those from RBANS, we mapped individual ADAS-Cog-13 question scores to RBANS domain subscales as follows: immediate memory: Q1, Q9; delayed memory: Q4; language: Q5, Q8, Q10, Q11, Q12; attention: Q2, Q6, Q13; visuospatial: Q3. Q7 of ADAS-Cog-13 was not mapped as it didn't fit precisely in any single RBANS domain/index. The summation of z-score normalized question scores under each domain was used as the score of that domain. The summation of z-score normalized domain scores was used as the overall assessment of cognition, approximating the RBANS total score. A voxel is considered to map consistently to a cognitive domain between scales or cohorts, if it met the following 2 criteria: 1) Voxel is significantly ($p < 0.05$) correlated with the given domain in both datasets; 2) The given domain is among the top 2 strongest correlated domains for this voxel in both datasets. To control for false discoveries, the same procedure was applied to datasets with shuffled participants, serving as a chance-level control for voxel consistency. The number of consistent voxels in observed cognitive maps is compared against the corresponding chance-level distributions to establish the assessment of the cross-dataset consistency. **Results:** We observed significant (nominal $p < 0.05$) correlation between domain subscales approximated from ADAS-Cog-13 with corresponding tau PET scans in Autonomy (false discovery rate [FDR] $q < 0.05$) and ADNI (FDR $q < 0.05$) in most parts of the brain for immediate memory, delayed memory, language and attention. Associations for the visuospatial were mainly in the occipital area. In the comparisons between domains derived from ADAS-Cog-13 and those from RBANS within Autonomy, and between domains from ADAS-Cog-13 of Autonomy and those from ADAS-Cog-13 of ADNI, we consistently observed the associations reported previously in the Autonomy RBANS analysis: language to left temporal, visuospatial to occipital, delayed memory to basal medial temporal, immediate memory to frontal, and attention to frontal and parietal. In our dataset-to-dataset comparisons across two cohorts, two cognitive scales, and two tau PET tracers, we observed consistency in maps of ranked associations between tau tangles and cognitive domains with hallmark features that align with the functional anatomy of the brain. **Conclusions:** We tested and validated the correlation between the spatial distribution of tau tangles and cognitive performance described previously in the Autonomy RBANS analysis. Here we extend this work to another cohort using ADAS-Cog-13 and with a different PET tracer and found consistent correlation patterns. Maps of ranked correlations align with known functional anatomy of the brain. Our results are consistent with the presence of tau tangles– or a correlate - negatively impacting local neuronal function. This suggests preventing the spread of tau tangles to tau naïve brain regions may provide disease interception by slowing the progression to additional cognitive domains.

Keywords: Tau, cognitive assessments, neuroimaging.
Clinical Trial Registry: NCT04619420.

Disclosures: Xingjian Zhang, Ritobrato Datta, Maggie Fedgchin, Jennifer Bogert, Janice Wong, David Henley, Gayle Wittenberg and Ziad S. Saad: Employee of Johnson & Johnson and may hold stocks or stock options in Johnson & Johnson.

Key takeaway message: Our results demonstrate the close association of the spatial distribution of tau tangles with the cognitive impact on brain function.

OC42- MAPPING THE PATHOGENESIS OF ALZHEIMER'S DISEASE IN DOWN SYNDROME: IMAGING, FLUID BIOMARKERS, COGNITION, AND SEX DIFFERENCES FOR CLINICAL TRIAL DESIGN.

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Background: The presence of trisomy 21 and increasing age are critical risk factors for Alzheimer's disease (AD) in individuals with Down syndrome (DS), with nearly all developing AD-related neuropathology by age 40 (1,2). Characterizing age-related changes in AD biomarkers is essential for early detection, identifying windows of vulnerability, and optimizing the timing of interventions and clinical trials. In this study, we examined age-related trajectories of AD biomarkers, including PET-amyloid (Centiloid), PET-tau (temporal meta-ROI tau load), plasma neurofilament light (NfL), plasma pTau217, plasma glial fibrillary acidic protein (GFAP), hippocampal volume (MRI), and episodic memory performance (mCRT-FRS). We hypothesized that fluid and PET biomarkers reflecting AD pathology would increase with age, while hippocampal volume and memory would decrease. We further aimed to quantify inflection points in these age-associated trajectories, assess spatial patterns of age-related change, and examine sex-specific differences in AD pathogenesis. **Methods:** We included data from 454

participants (mean age = 43 ± 9.9 years; 45% female) enrolled in the Alzheimer's Disease Biomarkers Consortium – Down Syndrome (ABC-DS). Participants underwent structural T1-weighted magnetic resonance imaging (MRI) and positron emission tomography (PET) scans with 18F-florbetapir (FBP), 11C-Pittsburgh Compound B (PiB), and 18F-Flortaucipir (FTP). All T1-weighted images were processed using FreeSurfer to obtain hippocampal volumes. FBP and PiB standardized uptake value ratios (SUVRs) were harmonized using the Centiloid scale. FTP SUVRs were partial volume–corrected and quantified in the temporal meta-ROI, a composite region that includes the entorhinal cortex, amygdala, parahippocampal gyrus, fusiform gyrus, and inferior and middle temporal gyri. Plasma biomarkers (NfL, GFAP, and pTau217) were measured using a single-plex plate on the ultra-sensitive single-molecule array (Simoa) HD-X platform. We used the modified Cued Recall Test – Free Recall Score (mCRT-FRS) to assess memory performance. Piecewise left-null regression analysis was used to examine inflection points in the association between age and each biomarker. Voxelwise analyses were conducted to assess spatially resolved age-related changes in FTP and FBP SUVRs. VBM analysis was used to examine associations between age and regional atrophy. Sex differences were assessed by including interaction terms and conducting stratified analyses. Covariates included study site and sex, unless stratified. **Results:** We identified a critical window for biomarker acceleration in individuals with DS, spanning approximately 35.3 to 42.5 years of age. Within this window, inflection points were observed for Centiloid (35.29 years), hippocampal volume (36.00), plasma GFAP (36.28), episodic memory (mCRT-FRS; 37.41), plasma NfL (37.61), plasma pTau217 (39.00), and FTP SUVR in the temporal meta-ROI (42.54). Sex-stratified analyses revealed differences in both the timing and sequence of these inflection points. Males showed a broader range (34.5–43 years) compared to a narrower, slightly earlier window in females (34–42 years). The most pronounced sex differences were seen in pTau217, NfL, and memory performance trajectories. Females showed an earlier inflection point for pTau217 (males: 43 years; females: 37.78 years) and later inflection points for plasma NfL (males: 36.54 years; females: 40.80 years) and memory scores (males: 35.89 years; females: 41.00 years). Voxelwise analyses of FTP SUVRs revealed age-related increases in the temporal and frontal regions, with females exhibiting stronger associations than males. Amyloid PET (FBP) SUVRs were most strongly associated with age in the temporal, frontal, and precuneus regions, with no significant associations in the occipital areas. VBM analyses showed that age-related gray matter atrophy was most pronounced in the temporal, frontal, and parietal cortices. **Discussion:** These findings highlight a non-linear, sex-specific progression of AD biomarkers in DS, with a clearly defined midlife window of rapid pathological change. Piecewise regression enabled precise detection of inflection points, capturing subtle shifts that traditional linear approaches may overlook. Spatial analyses via voxelwise FTP and VBM further illustrated consistent age-related involvement of temporal and frontal regions. Importantly, although females showed higher tau levels at younger ages, they experienced later inflection points in memory decline, suggesting potential sex-specific resilience mechanisms. Notably, the dissociation between tau burden and NfL and memory decline in females highlights the need for sex-specific frameworks in AD risk modeling and intervention planning. These insights are essential for optimizing the timing and design of clinical trials in individuals with DS, a population at uniquely high risk for AD.

Keywords: Down syndrome, image biomarkers, plasma biomarkers, sex differences, disease progression modeling, tau pathology. **References:**

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Key takeaway message: Our study reveals a critical midlife window (ages 35-42) for accelerated Alzheimer's biomarker changes in Down syndrome, with sex-specific differences. These insights are valuable for optimizing the design and implementation of clinical trials and interventions.

LB01- PLASMA BIOMARKERS TO IDENTIFY AND PREDICT EARLY AMYLOID ACCUMULATION IN COGNITIVELY UNIMPAIRED INDIVIDUALS: ENRICHMENT FOR STRATIFIED EARLY-STAGE PREVENTION TRIALS.

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Background: Amyloid-targeting therapy (ATT) for very early prevention of Alzheimer's disease may need personalized treatment regimens depending on individualized risks. For example, secondary prevention (stage 1 AD, i.e., established amyloid pathology without symptoms) may require high-intensity ATT, while primary prevention (before stage 1 AD) may suffice with low-intensity ATT. To guide such tailored treatment approaches, we need to be able to stratify cognitively unimpaired individuals into three groups: 1) those with established stage 1 AD, 2) those who are still without AD but who are at clearly increased risk of developing stage 1 AD in the coming years, and finally 3) those without AD who are not at increased risk (and should likely not have any therapy). For this type of stratification to be feasible, tools leverage scalable methods, e.g., blood biomarkers are needed. Consequently, we investigated whether blood biomarkers (alone or together with other scalable variables) can accurately separate these three groups of cognitively unimpaired individuals. We also tested whether changing from negative to positive plasma p-tau217 over time is a meaningful indicator of preclinical AD. **Methods:** Plasma p-tau217 and Aβ42/Aβ40 were measured with immunoassays and mass spectrometry-based methods. We analyzed baseline plasma data from BioFINDER-2 (N = 466 cognitively unimpaired) together with amyloid PET at baseline and after 4 years. We developed predictive algorithms (using baseline plasma biomarkers) to identify individuals likely to be amyloid PET-positive at baseline (^{3}30 centiloids, preclinical AD), amyloid PET-negative at baseline but accumulating amyloid over 4 years (≥3 centiloids/year increase over 4 years, at risk for developing preclinical AD), or stable amyloid PET-negative (low risk of developing preclinical AD). We also analyzed longitudinal plasma data from BioFINDER-1 (N = 235 cognitively unimpaired) and tested if change in plasma p-tau217 from negative to positive over 4 years was associated with amyloid positivity (by CSF Aβ42/Aβ40). **Results:** Among 466 cognitively unimpaired participants in BioFINDER-2, 16% were amyloid PET-positive at baseline, 11% were amyloid-PET negative but exhibited amyloid PET-accumulation over time, and 73% were amyloid-PET negative and did not show signs of amyloid accumulation over time. Compared to those who were amyloid PET-positive at baseline, or those who remained amyloid PET-negative over time, amyloid PET-negative accumulators were enriched among those with intermediate levels in plasma p-tau217 (especially for mass spectrometry-based assays). Amyloid PET-positives at baseline were mainly seen among those with clearly elevated levels in plasma p-tau217 already at baseline. A random forest model using baseline plasma p-tau217, Aβ42/Aβ40, and APOE ε4 achieved i) a PPV of 58% for identifying future amyloid accumulators among amyloid PET-negatives (compared to 11% base prevalence in a test-set), ii) a PPV of 76% for identifying baseline amyloid PET-positives (compared to 15% base prevalence in a test-set) and iii) a PPV of 93% for identifying amyloid PET-negative non-accumulators (compared to 74% base prevalence in a test-set). In BioFINDER-1, 13% of individuals converted from negative to positive plasma p-tau217 over 4 years. Among converters, 82% were CSF Aβ42/Aβ40 positive compared to 18% of non-converters ($p < 0.001$). **Conclusions:** A plasma-based algorithm deployed at baseline can highlight individuals who have a negative amyloid PET scan at baseline, but are at risk for amyloid accumulation over time

(individuals who may benefit from low intensity ATT, for primary prevention). The algorithm can also identify individuals at high risk for a positive amyloid PET scan already at baseline (stage 1 preclinical AD; these individuals may benefit from high intensity ATT, as secondary prevention of AD). Longitudinal increases in plasma p-tau217, from negative to positive levels, are also associated with early-stage amyloid pathology. These approaches enable plasma-biomarker informed personalized treatment strategies in the earliest stages of AD. Incorporating these strategies in trials (and in the future in clinical practice) may increase the feasibility of cost-effective interventions for early AD. We are now establishing a new large cohort study (BioFINDER – Preclinical AD; NCT06121544) to extend and validate our findings. At CTAD, we will present baseline screening data from the first 5000 individuals (non-demented) recruited in this new cohort study.

Key takeaway message: Plasma biomarkers can stratify individuals in different risks for current or future preclinical AD. This can be used for early identification and stratification of AD to optimize individualized interventions.

LB12- PLASMA BRAIN DERIVED P-TAU217 OUTPERFORMS OTHER P-TAU BIOMAKERS IN IDENTIFYING ABNORMAL BRAIN AMYLOID BURDEN AND PREDICTS FASTER COGNITIVE DECLINE.

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Background: While blood p-Tau217 have demonstrated promising clinical utility in identifying abnormal brain amyloid burden, recent studies have reported increases in blood p-Tau, including p-Tau217, in patients with amyotrophic lateral sclerosis (ALS) (1,2). This may be attributable to the phosphorylation of peripheral tau (high-molecular-weight [HMW] tau; “big tau”), suggesting that p-Tau released from degenerating peripheral nerves and denervated muscle fibers can increase blood p-Tau217 levels independently of Alzheimer's disease (AD) pathology. This poses a limitation for currently available commercial p-Tau217 immunoassays, which use detection antibodies that capture both high- and low-molecular-weight (LMW) tau («total tau»). In this context, it is postulated that an assay using a detection antibody specific for LMW tau, the predominant form in the central nervous system, could preferentially measure brain derived-p-Tau217 (BD-p-Tau217). Such an approach may mitigate this confounder, providing better sensitivity and specificity, and potentially outperforming total-p-Tau217 by achieving higher diagnostic performance. In this study, we aim to perform a head-to-head comparison of plasma BD-p-Tau217 and total-p-Tau217, as well as other p-Tau isoforms (p-Tau181 and p-Tau231), in detecting amyloid positivity (Aβ+) on positron emission tomography (PET). Furthermore, we evaluated the references ranges for abnormal amyloid burden and assessed the prognostic performance of the plasma BD-p-Tau217 reference ranges. **Methods:** This study included 213 participants recruited from memory clinics and the community in Singapore (mean [SD] age, 73 [7] years; 121 females [57%]; 44 cognitively normal [21%], 107 cognitively impaired no dementia [50%], and 62 dementia [29%]). Plasma samples were analyzed using commercially available Nucleic Acid Linked Immuno-Sandwich Assay (NULISA) central nervous system panel from Alamar Biosciences. Brain amyloid status was determined using visual assessment of amyloid PET scans (Aβ- [n = 139] versus Aβ+ [n = 74]; interval between amyloid PET and blood collection, mean [SD] months = 35 [24] months). Diagnostic performance for detecting PET Aβ+ was assessed using area under the receiver operating characteristic curve (AUC). P-values for comparison of AUCs were derived from DeLong tests. To determine the reference ranges for Aβ-PET positivity, we used a three-range strategy comprising a lower reference point to rule out AD (95% sensitivity; low-risk for PET Aβ+) and a higher reference point to rule in AD (95% specificity; high-risk for PET Aβ+). Alternatively, a binary reference point for Aβ-PET positivity was derived based on maximizing the Youden index. To assess the associations between plasma BD-p-Tau217-derived risk groups and longitudinal cognitive performance, we used linear mixed-effects (LME) models with Mini-Mental State Examination (MMSE) or Clinical Dementia Rating Sum-of-Boxes (CDR-SB) as outcome, including as predictors the plasma BD-p-Tau217-derived risk groups, time, age, sex and years of education, as well as an interaction between risk groups and time. **Results:** Plasma BD-p-Tau217 demonstrated excellent diagnostic performance in identifying PET Aβ+ (AUC [95% CI] = 0.965 [0.942, 0.987]), outperforming all other brain derived and total-p-Tau isoforms (AUC = 0.823 to 0.937, all $p \leq 0.008$), including total-p-Tau217 (AUC [95% CI] = 0.935 [0.901, 0.969]; $p = 0.003$). Using a three-range approach to determine reference ranges, plasma BD-p-Tau217 (lower threshold: plasma BD-p-Tau217 $\leq$ 11.603 NPQ; higher threshold: plasma BD-p-Tau217 $\geq$ 11.850 NPQ) achieved a positive predictive value (PPV) and negative predictive value (NPV) of 90% and 97% respectively. The proportion of participants in the intermediate-risk group was 7% (n = 14). In contrast, while plasma total-p-Tau217 achieved similar PPV of 89% and NPV of 96%, the proportion of participants in the intermediate-risk group increased to 23% (n = 49). Remarkably, when a binary reference point was applied, plasma BD-p-Tau217 (threshold: plasma BD-p-Tau217 $\geq$ 11.691 NPQ) achieved both a specificity and sensitivity of 92%, as well as a PPV and NPV of 86% and 96% respectively. We next assessed the prognostic utility of the plasma BD-p-Tau217-derived three-range reference (mean [SD] follow-up duration = 52 [13] months). Cognitive performance declined in both the low- (n = 127) and high-risk (n = 72) groups over time, with significantly higher rates in the high-risk group compared with the low-risk group (β [95%], MMSE: low-risk = −0.178 [−0.345, −0.011], high-risk = −1.00 [−1.23, −0.770], $p < 0.001$; CDR-SB: low-risk = 0.297 [0.166, 0.429], high-risk = 1.10 [0.917, 1.28], $p < 0.001$). We also assessed the prognostic utility of the plasma BD-p-Tau217-derived binary reference. Similar results were observed: cognitive performance declined in both groups over time (n = 134 and 79 for the low-risk and high-risk groups, respectively), with significantly higher rates in the high-risk group (β [95%], MMSE: low-risk = −0.203 [−0.365, −0.041], high-risk = −0.945 [−1.17, −0.726], $p < 0.001$; CDR-SB: low-risk = 0.311 [0.181, 0.440], high-risk = 1.05 [0.874, 1.22], $p < 0.001$). **Conclusions:** Plasma BD-p-Tau217 demonstrated superior diagnostic performance for detecting abnormal brain amyloid burden on PET compared to other plasma p-Tau biomarkers. Using either a three-range or binary reference, plasma BD-p-Tau217 yielded high sensitivity (>90%), specificity (>90%), PPV (>85%), and NPV (>95%). Notably, the three-range approach resulted in only 7% of individuals in an intermediate zone requiring confirmatory PET testing. Longitudinally, individuals in the plasma BD-p-Tau217-derived high-risk group exhibited faster cognitive decline. Our findings highlight the clinical potential of plasma BD-p-Tau217, though further validation in larger, independent cohorts is needed.

Keywords: Plasma brain derived p-Tau217, diagnosis, amyloid, prognosis.

Disclosures: The authors declared no competing interests.

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Key takeaway message: Plasma brain derived p-Tau217, measured by a novel commercial assay, outperforms other plasma p-Tau biomarkers, including total p-Tau217, and shows strong potential as both a diagnostic and prognostic biomarker for Alzheimer's disease.

LB15- ALZHEIMER’S DISEASE BLOOD BIOMARKERS MEASURED

THROUGH REMOTE CAPILLARY SAMPLING CORRELATE WITH COGNITIVE PERFORMANCE IN OLDER ADULTS.

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Background: The most robust Alzheimer's Disease blood biomarker is p-tau217, which shows highest accuracy for detection of amyloid pathology (1,2). However, with only 0.1% of people with early cognitive decline accessing specialist healthcare, there is a need to adapt biomarker testing to enable broader patient groups to benefit from this emerging diagnostic technology (3,4). Specifically, there is a need to scale them for use in primary care and for self-testing at home in the community. This also aligns to a need to identify amyloid positive patients for clinical trials, which is currently challenging due to the lack of early detection technologies. Self-administered microfluid blood sampling technologies have now been developed for measurement of AD blood biomarkers including p-tau217 through at-home fingertip collection using dried blood spot cards (5,6). Recent work has demonstrated robust feasibility and validation of this method, showing correlations between venous and capillary blood biomarkers and good validity for unsupervised sampling (5). An important next question is whether the capillary biomarker test correlates satisfactorily with clinical symptoms, particularly cognitive and functional impairment, and with diagnostic criteria. Computerised cognitive assessment offers the means of measuring cognitive performance at home, raising the potential for community-based early detection through remote blood and digital biomarkers (7). **Methods:** This concurrent validation study recruited 174 participants who were cognitive healthy, had Mild Cognitive Impairment or Alzheimer's Disease from clinical sites in the UK. All participants provided a capillary blood sample using an at-home dry blood spot kit without clinical supervision, and a subgroup of 41 participants provided a venous blood sample. All participants completed the online PROTECT Cognitive Test System, a computerised system of neuropsychology tests of Delayed Picture Recognition (episodic memory), Digit Vigilance (attention) and Verbal Reasoning (executive function) (8). Functional and global impairment was measured with the well-established Instrumental Activities of Daily Living (IADL) and IQCODE assessments. Blood samples were processed and analyzed for ptau217 using the single molecule array technology (2). Data was subjected to Spearman's R analysis to examine correlation between ptau217 and cognition and function. A Receiver Operator Characteristic analysis was undertaken and an optimum ptau217 threshold was defined at a pre-specified threshold of 85%. Patients falling above and below this threshold were compared for cognition and function using *t*-test analysis. Participants also completed a feedback questionnaire to capture user experience and acceptability of the remote sampling technology. **Results:** The plasma and capillary ptau217 biomarkers showed good correlation ($r = 0.763$, P-0.002). Analysis showed significant correlations between capillary p-tau217 and cognitive performance in the domains of Memory ($P < 0.001$), Attention ($P = 0.019$) and Executive Function ($P = 0.021$) and with function (IQCODE $P < 0.001$, IADL $P < 0.001$). The ROC analysis identified a ptau217 85% specificity threshold which had a sensitivity of 35%. This threshold identified 34 (20%) patients in the cohort as high risk. Individuals with p-tau217 levels above this threshold had significantly more impaired cognitive function (Memory $P = 0.02$, Attention $P = 0.048$) and functional impairment (IQCODE $P = 0.017$, IADL $P = 0.001$) than those below it. Participant feedback on completion of the fingerprick tests at home showed a high level of compliance and willingness to complete the tests, with 78% reporting they would be likely to use these tests as part of routine healthcare. **Conclusions:** These results highlight the potential clinical utility of the p-tau217 capillary marker and provide confidence in the acceptability and feasibility of the technology for patients. They also provide additional confidence in the robust correlation of capillary ptau217 with venous biomarkers. The findings raise the potential for provision of a remote screening method for identifying 20% of individuals likely to be biomarker positive for AD and with a high likelihood of impairments in cognition and function. With further validation, such a technology could lead to a step change in clinical diagnosis and recruitment for clinical trials requiring early-stage patients and individuals who are amyloid positive. This approach could be well-positioned as a triage tool to optimize the clinical pathway and enable early detection of the highest risk individuals in the community, particularly in combination with ongoing community-based monitoring. Further work is needed to replicate and build upon this work, to validate these findings in an independent cohort, determine the longitudinal predictive value of the capillary p-tau217 biomarker and to establish a triage and monitoring process. Specifically, it will be important to examine its use alone or in combination with computerized neuropsychology as a triage tool in the community and primary care and as a potentially transformational approach to improve clinical trial recruitment.

Keywords: Tau217, biomarker, neuropsychology, correlation, sensitivity, remote, detection.

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

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Key takeaway message: Remotely collected capillary blood biomarker ptau217 correlates with plasma ptau217 and cognition, and identifies high risk individuals. This could offer a scalable means of triaging patients for early diagnostics and clinical trials.

LB16- STAGE-SPECIFIC PROGNOSTIC ROLES OF PLASMA BIOMARKERS IN ALZHEIMER'S DISEASE.

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Background: Current indications for anti-amyloid therapy in Alzheimer's disease (AD) are based on initial biomarker status, while treatment efficacy is evaluated through longitudinal cognitive trajectories. While group-level analyses support treatment benefit, prognosis within the same biomarker-defined group is heterogeneous and may require more nuanced approaches in practice. For instance, individuals with Aβ PET positivity but slower decline might warrant a more conservative approach, and treatment effects may be overestimated if such heterogeneity is ignored. Previous studies have used group-based trajectory modeling (GBTM) to dissect heterogeneity in cognitive decline, focusing mainly on imaging markers. In this study, we extended this approach by including plasma biomarkers, which are scalable, biologically informative, and capture amyloid, tau, and processes such as neuroinflammation. We aimed to assess their prognostic utility in distinguishing cognitive trajectory classes across the AD spectrum. **Methods:** We included 1399 participants (253 cognitively unimpaired [CU], 828 mild cognitive impairment [MCI], 318 dementia of the Alzheimer type [DAT]) from the Korea Registries to Overcome dementia and Accelerate Dementia research (K-ROAD) cohort. Participants underwent plasma biomarker assays (Aβ42/40, phosphorylated tau [pTau] 181, pTau217, pTau231, glial fibrillary acidic protein [GFAP], neurofilament light chain [NfL]), Aβ PET, and MRI. Median follow-up was three Clinical Dementia Rating–Sum of Boxes (CDR-SB) assessments. Distinct CDR-SB trajectories were identified within each diagnostic group using GBTM, with class number chosen by model fit criteria. Baseline characteristics, including Aβ PET and plasma biomarkers, were compared across classes. Predictors of class membership were evaluated using multivariable logistic regression with backward selection, including variables significant at baseline. Longitudinal Mini-Mental State Examination (MMSE) trajectories by class were further analyzed with linear mixed-effects models. **Results:** In CU, two classes were identified: slower decliners ($N = 216$) and faster decliners ($N = 37$). Faster decliners had higher Aβ PET positivity (62% vs 31%, $p < 0.05$), smaller hippocampal volume, lower Aβ42/40, and higher plasma pTau, GFAP, and NfL ($p < 0.05$ for Aβ42/40, pTau181, pTau231; $p < 0.001$ for others). Only GFAP was retained as an independent predictor, along with age, APOE ε4 carrier status, years of education, and MMSE (GFAP, odds ratio [OR] = 1.01, $p < 0.05$; age, OR = 1.19, $p < 0.001$; APOE ε4, OR = 5.00, $p < 0.05$; education, OR = 0.84, $p < 0.05$; MMSE, OR = 0.76, $p < 0.05$). In MCI, two classes were also identified (slower, $N = 434$; faster, $N = 394$). Faster decliners had higher biomarker burden, including Aβ PET positivity (75% vs 47%; all $p < 0.001$). In regression models, only plasma pTau217 and hippocampal volume were retained, along with age, APOE ε4, and MMSE (pTau217, OR = 2.18, $p < 0.001$; hippocampal volume, OR = 0.99, $p < 0.05$; age, OR = 1.04, $p < 0.05$; APOE ε4, OR = 1.92, $p < 0.05$; MMSE, OR = 0.51, $p < 0.001$). In DAT, two classes were identified with different intercepts but parallel slopes. Compared with the early group ($N = 251$), the advanced group ($N = 67$) had higher plasma pTau, GFAP, and NfL ($p < 0.001$ for pTau217 and GFAP; $p < 0.05$ for NfL), whereas other biomarkers did not differ. No plasma or imaging biomarkers were retained in regression models; only APOE ε4, education, and MMSE remained significant (APOE ε4, OR = 0.17; education, OR = 1.36; MMSE, OR = 0.49, all $p < 0.001$). Longitudinal MMSE trajectories paralleled these findings. **Conclusions:** Across the AD spectrum, plasma GFAP in CU and pTau217 in MCI were independent predictors of faster decline, whereas Aβ PET positivity did not retain prognostic significance after adjustment. Importantly, Aβ PET positivity was not fully deterministic: many slower decliners were Aβ positive, and not all faster decliners were. In DAT, groups differed in baseline severity but not in rate of decline, and demographic factors, including MMSE, remained significant across stages. These findings show that treatment indications based solely on Aβ PET positivity and a single MMSE cutoff encompass heterogeneous prognostic subgroups. They also suggest that stage-specific plasma biomarkers may help identify high-risk patients. Extending previous research, our findings support a dual-axis approach—combining expected cognitive trajectory with biomarker status—for more personalized treatment decisions. This is particularly relevant because anti-amyloid therapy, while disease-modifying, is not curative and carries non-negligible risks, underscoring the need for careful patient selection and shared decision-making. Concordant CDR-SB and MMSE patterns support construct validity, though external replication is needed for generalizability.

Keywords: Plasma biomarkers, prognosis, Alzheimer's disease, trajectory modeling.

Key takeaway message: Stage-specific plasma biomarkers—GFAP in CU and pTau217 in MCI—predicted faster decliner class membership beyond Aβ PET positivity. A dual-axis approach combining expected cognitive trajectory with biomarker status may personalize anti-amyloid therapy decisions.

LB17- MULTI-BIOMARKER PLASMA CLOCKS FOR PREDICTING ALZHEIMER DISEASE SYMPTOM ONSET.

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Background: Plasma biomarker « clocks » offer accessible alternatives to PET imaging for staging Alzheimer disease (AD) progression and predicting symptom onset (1). These approaches model biomarker trajectories over time to estimate an individual's position along the disease timeline. While single-biomarker clocks show promise, multi-biomarker approaches may enhance predictive accuracy and analytical robustness. Two computational frameworks have emerged for constructing plasma clocks: Temporal Integration of Rate Accumulation (TIRA) and Sampled Iterative Local Approximation (SILA). However, direct comparison of these methods using multiple plasma biomarkers remains unexplored. We systematically compared TIRA and SILA approaches using plasma % p-tau217, GFAP, and NfL to predict cognitive symptom onset across two independent cohorts (2). **Methods:** We analyzed longitudinal plasma biomarker trajectories from cognitively unimpaired and impaired participants in the Knight ADRC ($n = 618$) and ADNI ($n = 307$) cohorts. Both TIRA and SILA algorithms convert longitudinal biomarker data into disease timelines by modeling rate of biomarker change over time. We first established biomarker abnormality thresholds using receiver operating characteristic analyses in the ADNI cohort (%p-tau217: 5.07%; GFAP: 267 pg/mL; NfL: 14.0 pg/mL), which served as origin points of each clock (time = 0). The range of consistent change for each plasma biomarker was identified. We evaluated clock performance through three complementary approaches: correlation analyses between estimated and observed biomarker conversion timing, inter-method concordance between TIRA and SILA, and predictive accuracy for clinical symptom onset (progression from Clinical Dementia Rating® [CDR®] = 0 to CDR>0 with an AD syndrome). Linear regression models assessed relationships between the age at plasma biomarker abnormality

(as estimated by the clock model) and the age at actual symptom onset, while Cox proportional hazards models examined the estimated age at plasma biomarker abnormality predicted time to cognitive impairment. All statistical models incorporated the estimated ages for all three plasma biomarkers (%p-tau217, GFAP, and NfL) simultaneously as predictors in combined multi-biomarker models. Additionally, all analyses were done with and without key demographic covariates (sex, education, APOE ε4 status) to assess the effect of covariates on predictions. **Results:** Both TIRA and SILA successfully generated plasma clocks for plasma %p-tau217, GFAP, and NfL using data from the Knight ADRC and ADNI, producing coherent disease timelines when aligned to their respective abnormality thresholds. The two algorithms demonstrated very high concordance, with estimated biomarker positivity ages correlating at $r = 0.906\text{-}0.976$ across all comparisons. In participants who converted to biomarker positivity during follow-up, the estimated conversion ages strongly correlated with the observed conversion ages (%p-tau217: $r = 0.771\text{-}0.955$; GFAP: $r = 0.761\text{-}0.951$; NfL: $r = 0.843\text{-}0.935$), establishing that plasma clocks accurately capture timing. Multi-biomarker models incorporating clock-estimated ages for all three biomarkers were statistically significant predictors of clinical symptom onset timing, demonstrating moderate to strong predictive relationships without demographic adjustment (adjusted $R^2 = 0.231\text{-}0.670$; Spearman $r = 0.528\text{-}0.771$; mean absolute error (MAE) = 2.84-3.47) and similar performance when including demographic covariates (adjusted $R^2 = 0.115\text{-}0.675$; Spearman $r = 0.555\text{-}0.767$; MAE = 2.58-3.17), with consistent results across cohorts and methods. Within these models of combined biomarkers, estimated age at the plasma %p-tau217 threshold emerged as the only statistically significant individual predictor, while GFAP and NfL showed non-significant associations as individual predictors within the multi-biomarker models. In ADNI analyses, higher education ($HR = 0.89\text{-}0.90$, $p < 0.01$) and male sex ($HR = 0.61$, $p < 0.05$) were associated with reduced risk of cognitive decline when combined with estimated age at biomarker abnormality. **Conclusions:** TIRA and SILA algorithms generate highly concordant plasma biomarker clocks that predict onset of AD symptoms. The high inter-method agreement demonstrates robustness across different mathematical approaches. Estimated age at the plasma %p-tau217 threshold emerged as the sole significant predictor, highlighting its superior prognostic value compared to GFAP and NfL. These findings establish plasma clocks as accessible, blood-based tools for biological staging that complement traditional assessments, supporting their utility for patient stratification and clinical trial enrollment.

Keywords: Plasma biomarkers, biomarker clocks, disease progression, %p-tau217, GFAP, neurofilament light (NfL).

Disclosures: K.K.P. has served as a consultant for Eli Lilly and Company. 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/is served/serving as a consultant or on advisory boards for Eisai, Abbvie, Genotix Biotechnologies Inc, Gates Ventures, Gate Neurosciences, Dolby Family Ventures, Karuna Therapeutics, AlzPath Inc., Cognito Therapeutics, Inc., Prevail Therapeutics, Neurogen Biomarking, Spear Bio, University of Kentucky, Rush University, Tymora, and Quanterix. J.L.D. has received research support from ADx Neurosciences, Fujirebio, Roche Diagnostics and Eli Lilly and Company in the past two years. J.L.D. has received speaker fees from Eli Lilly and Company and LabCorp. 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., Neurogen Biomarking, and Monument Biosciences. H.Z. has served on 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, LabCorp, 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 sponsored by Alzecure, BioArctic, Biogen, Cellectricon, Fujirebio, Lilly, Novo Nordisk, Roche, and WebMD, 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). D.M.H. and R.J.B. have equity ownership interest in C2N Diagnostics. D.M.H. and R.J.B. receive income from C2N Diagnostics for serving on the scientific advisory board. D.M.H. is on the scientific advisory board of Genentech, Denali, Cajal Therapeutics, Acta Pharmaceuticals and Switch, and consults for Alnylam, Pfizer, Novartis, and Roche. R.J.B. is a co-inventor on US patent applications: "Methods to detect novel tau species in CSF and use thereof to track tau neuropathology in Alzheimer's disease and other tauopathies" and "CSF phosphorylated tau and amyloid beta profiles as biomarkers of Tauopathies." R.J.B. is a co-inventor on a non-provisional patent application: "Methods of diagnosing and treating based on site-specific tau phosphorylation." R.J.B. is an unpaid scientific advisory board member of Roche and Biogen, and receives research funding from Avid Radiopharmaceuticals, Janssen, Roche or Genentech, Eli Lilly, Eisai, Biogen, AbbVie, Bristol Myers Squibb and Novartis. 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. W.Z.P. is a Co-Chair Emeritus for the FNIH Biomarkers Consortium Neuroscience Steering Committee. 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. S.E.S. has served on scientific advisory boards on biomarker testing and education for Eisai and Novo Nordisk and has received speaking fees for presentations on biomarker testing from Eisai, Eli Lilly, and Novo Nordisk. C.X., M.M.A., D.T., B.S., and J.C.M. have nothing to disclose.

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Key takeaway message: Plasma %p-tau217, GFAP, and NfL clocks can predict Alzheimer symptom onset, with %p-tau217 demonstrating superior prognostic performance, which is relevant to disease staging and clinical trial enrollment.

LB18- LONGITUDINAL ASSOCIATIONS BETWEEN PLASMA P-TAU217 AND AMYLOID PET.

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Background: Plasma biomarkers are increasingly recognized as scalable tools to identify individuals with Alzheimer's disease pathology and to complement PET in trial screening (1-4). Many studies have now demonstrated strong cross-sectional correlations between plasma p-tau217 and amyloid PET, supporting the application of plasma biomarkers to clinical trial recruitment and cohort enrichment (5). Biomarkers are also essential for demonstrating target engagement in trials of Aβ and tau-modifying therapies, which has been primarily assessed using PET imaging. Longitudinal relationships between changes in plasma p-tau217 and amyloid PET are unclear, raising questions of whether measurements of biomarker change over time are interchangeable between modalities. In this study, we investigated the longitudinal correlations between plasma p-tau217 and amyloid PET, examining how these correlations vary across stages of Alzheimer's disease pathology. **Methods:** We included 389 cognitively normal and impaired participants from the ADNI study who were also used by the FNIH Biomarker Consortium. Each participant had at least three plasma samples within 6 months of amyloid PET. Absolute p-tau217 concentrations were measured using four assays: C2N PrecivityAD2, Fujirebio Lumipulse, ALZpath Quanterix, and Janssen LucentAD Quanterix. In addition, plasma %p-tau217, ratio of phosphorylated tau at threonine-217 (p-tau217) to its non-phosphorylated form (np-tau217), was measured with the C2N PrecivityAD2 assay. Amyloid PET scans were acquired with [18F]florbetapir (FBP) or [18F]florbetaben (FBB) and quantified in Centiloids. We defined baseline amyloid PET status using previously validated thresholds (Centiloid $\geq$20 for FBP and $\geq$18 for FBB) (6) and used published cutoffs for plasma p-tau217 and %p-tau217 by Schindler et al. (2). This classification resulted in four groups: Plasma-PET-, Plasma + PET-, Plasma-PET+, and Plasma + PET+. Transitions across visits were calculated by comparing biomarker status (positive vs. negative, according to established thresholds) at each consecutive visit (Visit 1-2 and Visit 2-3) to classify participants as progressors, regressors, stable positive or stable negative. Annualized rates of change for %p-tau217, p-tau217 (across four assays), and Centiloids were estimated with linear models. Between-group differences in demographics were assessed using Kruskal-Wallis tests for continuous variables and Fisher's exact tests for categorical variables. Significant continuous-variable effects were explored with pairwise Wilcoxon tests using Bonferroni correction. Correlations between these changes were then evaluated using Spearman correlations adjusted for age, sex, and APOE-ε4 carriership in the overall sample and within groups stratified by Plasma/PET status. For all the analysis, outliers that were above ±4SD of the measurements were removed, and $p < 0.05$ were considered statistically significant. **Results:** Participants had longitudinal follow-up on 5.52 ± 1.72 years for PET and 5.42 ± 1.79 years for plasma. For simplicity, demographic information across Plasma/PET status groups is presented based on plasma %p-tau217, measured with C2N PrecivityAD2. At baseline, 217 participants were classified as Plasma-PET-, 24 as Plasma + PET-, 26 as Plasma-PET+, and 122 as Plasma + PET+. The four groups differed significantly by age, APOE-ε4 carriership, diagnosis, MMSE and CDR (all $p < 0.001$). Plasma-PET-participants were younger and predominantly cognitively normal, while Plasma + PET + participants were older, more often APOE-ε4 carriers, and more frequently diagnosed with MCI. Across visits, modest number of participants progressed (8-11% becoming positive by plasma %p-tau217 measures and 7-7.5% becoming amyloid PET positive), while negligible numbers of participants regressed (less than 4% for plasma %p-tau217, less than 2% for amyloid PET). Approximately half of participants remained stable negative (48.5-54.5% for plasma %p-tau217, 49.4-54.2% for amyloid PET) and one-third remained stable positive (34.1-37.5% for plasma %p-tau217, 37.0-42.8% for amyloid PET) across three visits. Overall, transitions occurred more often toward biomarker positivity than negativity, consistent with expected disease progression. The correlation between annual rates of change in plasma %p-tau217 and Centiloid was $\rho = 0.31$ (95%CI: 0.22-0.40; $p < 0.0001$). Stratified by baseline Plasma/PET status, the correlation was significant only in the Plasma-/PET-subgroup ($\rho = 0.34$, 95%CI: 0.22-0.46; $p < 0.001$) and was not significant in Plasma-/PET+ ($\rho = 0.33$, 95%CI: −0.09-0.66; $p = 0.09$), Plasma+/PET- ($\rho = 0.23$, 95%CI: −0.24-0.61; $p = 0.29$), or Plasma+/PET+ ($\rho = 0.13$, 95%CI: −0.05-0.31; $p = 0.14$). Within the Plasma-/PET-subgroup, correlations between annual rates of change of plasma p-tau217 and Centiloids were consistent across assays; C2N PrecivityAD2: [$\rho = 0.39$, 95%CI: 0.28-0.50]; AlzPath Quanterix: [$\rho = 0.43$, 95%CI: 0.31-0.53]; Fujirebio Lumipulse [$\rho = 0.30$, 95%CI: 0.18-0.42]; and Janssen LucentAD/Quanterix, $\rho = 0.31$ (95% CI: 0.18-0.43); $p < 0.0001$ for all. No significant correlations were observed in the other Plasma/PET subgroups, regardless of assay. **Conclusions:** In this longitudinal cohort, a modest correlation was observed between annual rates of change in plasma p-tau217 and amyloid plaque accumulation as measured in Centiloid. This relationship was driven almost entirely by the Plasma-PET-group. In contrast, no meaningful correlations were found in the Plasma + PET + group, which is particularly relevant for clinical trials as it mirrors the biomarker profile of placebo arm in anti-amyloid studies. Similar results were observed across all four plasma p-tau217 assays included in this head-to-head study, underscoring the robustness of the findings. The lack of correlations in rates of change for the Plasma+/PET + group demonstrates that while plasma p-tau217 is a promising marker for detecting amyloid positivity, it does not mirror the trajectories of amyloid PET. Taken together, this highlights the stage-dependent value of plasma biomarkers, confirming that plasma biomarkers are useful for enrichment and early monitoring in prevention trials, but do not closely track rates of brain amyloid accumulation, potentially because plasma p-tau217 also reflects tau pathology.

Keywords: Alzheimer's disease, plasma p-tau217, amyloid PET, clinical trials, blood-based biomarkers, longitudinal trajectories. **References:** 1. Brum, Wagner S. et al. «A two-step workflow based on plasma p-tau217 to screen for amyloid β positivity with further confirmatory testing only in uncertain cases.» Nature Aging 3.9 (2023): 1079-1090. 2. Schindler, Suzanne E. et al. «Head-to-head comparison of leading blood tests for Alzheimer's disease pathology.» Alzheimer's & Dementia 20.11 (2024): 8074-8096. 3. Warmenhoven, Noëlle et al. «A comprehensive head-to-head comparison of key plasma phosphorylated tau 217 biomarker tests.» Brain 148.2 (2025): 416-431. 4. Palmqvist, Sebastian et al. «Plasma phospho-tau217 for Alzheimer's disease diagnosis in primary and secondary care using a fully automated platform.» Nature Medicine (2025): 1-8. 5. Therriault J, Brum WS, Trudel L et al. Blood phosphorylated tau for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol. 2025; 24 (9):740-752. https://doi.org/10.1016/S1474-4422(2500227-3). 6. Royse, Sarah K. et al. «Validation of amyloid PET positivity thresholds in centiloids: a multisite PET study approach.» Alzheimer's research & therapy 13.1 (2021): 99.

Key takeaway message: Plasma p-tau217 and amyloid PET are coupled only in the Plasma-/PET-group. After biomarker positivity, the correlation disappears, consistent with rapid biomarker saturation along the amyloid timeline.

LB19- FOUNDATION MODELS FOR THE EARLY DETECTION OF ALZHEIMER'S USING CELL-FREE DNA.

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Background: Blood biomarkers such as plasma phosphorylated tau 217 (pTau 217) are advancing Alzheimer's disease (AD) diagnosis, yet performance can vary across stages and subgroups. Cell free DNA (cfDNA) methylation provides complementary information reflecting the neurobiology of disease that may strengthen diagnostic accuracy. We developed Pleiades, whole genome epigenetic foundation models (90M/600M/7B parameters) trained on 1.9T tokens of methylated and unmethylated human DNA with alignment embeddings and hierarchical attention to reason over cfDNA sets, and evaluated their clinical utility for AD (1,2). **Methods:** We conducted an observational case control study using plasma cfDNA from 81 age and sex matched participants (mild AD dementia or mild cognitive impairment meeting ATN criteria vs cognitively healthy controls). Libraries were prepared with enzymatic methyl seq and sequenced to $>30\times$ depth. We fine tuned Pleiades on cell type–specific differentially methylated regions (DMRs) for microglia, neurons, B cells, and T cells, and performed nested 5 fold cross validation with a hierarchical attention transformer that aggregates fragment level representations to region and sample level embeddings for AD classification. Plasma proteins (Aβ40, Aβ42, neurofilament light, glial fibrillary acidic protein, pTau 181, pTau 217) were measured on Simoa platforms; multi omic models combined pTau 217 with Pleiades predictions (1,3,4). **Results:** In AD vs control classification, Pleiades 7B achieved AuROC of 0.81 (microglia markers), 0.82 (neuronal), 0.82 (B cell), and 0.80 (T cell) across outer folds; simple averaging across cell types yielded AuROC = 0.89. pTau 217 alone reached AuROC = 0.90 in the same cohort. Combining pTau 217 with Pleiades predictions improved performance to AuROC = 0.97, with significant gain over cfDNA alone (Wilcoxon $p = 0.03$) and a trend versus proteomics alone ($p = 0.06$) (1). **Conclusions:** Genome wide cfDNA methylation modelling with Pleiades delivers blood based AD detection approaching state of the art proteomic markers and shows additive value when combined with pTau 217. Results support multi omic screening/stratification strategies for clinical trials, with immediate next steps including multi centre, demographically broader, prospective validation and expanded multimodal pretraining to enhance robustness and interpretability.

Keywords: Alzheimer's disease, cell free DNA, DNA methylation, blood biomarkers.

Disclosures: Several authors are shareholders of Prima Mente.

References: 1. Niki P, Nalmpantis C, Ganbat J O et al. Human whole epigenome modelling for clinical applications with Pleiades. bioRxiv (2025). 2. Loyfer N et al. A DNA methylation atlas of normal human cell types. Nature (2023). 3. Palmqvist S et al. Plasma phospho tau217 for Alzheimer's disease diagnosis. Nature Medicine (2025). 4. Tian W et al. Single cell DNA methylation and 3D genome architecture in the human brain. Science (2023).

Key takeaway message: Foundation modelling unlocks new modalities (cell-free DNA) for the early detection of Alzheimer's Disease.

LB2- ANTI-TAU THERAPEUTIC ANTIBODY, ETALANETUG, REDUCES THE NOVEL BIOMARKER PLASMA EMTBR-TAU243 IN PATIENTS WITH DIAD.

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Background: Etalanetug (E2814) is intended to delay the clinical progression of Alzheimer's disease by binding to the microtubule binding region (MTBR) of tau, which is required for the seeding and spreading of tau pathology. E2814-G000-103 is an open-label, phase 1b/2 study in dominantly-inherited Alzheimer's disease (DIAD) patients (NCT04971733). 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 etalanetug IV every 4 weeks escalating from 750mg, 1500mg, 3000mg, to 4500mg (min of 3 doses/dose level). After ascending to 4500mg, patients received 4500mg for up to 108 weeks. Plasma and CSF were collected every three months for the first year and then at week 108. In addition, plasma was sampled on days 15, 29 and 57, which was during the 750mg dosing period. MTBR-tau243 (243-254 tryptic residue) and eMTBR-tau243 (243-256 endogenous form) were measured by immunoprecipitation with mass spectrometry (IP-MS) as described in Horie et al., Nat Med 2023; Nat Med 2025, respectively. Briefly, the MTBR-tau243 protocol follows a 2-step immunoprecipitation (IP), followed by tryptic digestion and quantification of the 243-254 peptide. In contrast, eMTBR-tau243 is captured by a 1-step IP followed by digestion with ArgC and quantification of the 243-256 peptide. Drug interference experiments were performed at concentrations of E2814 spanning concentrations observed clinical samples and >2X observed concentrations. Plasma was also analyzed from healthy subjects in the E2814-G000-001 phase 1 study, to compare pharmacodynamic effects in a population without tau pathology. **Results:** Drug interference testing demonstrated that eMTBR-tau243 assay performance was not impacted by the presence of etalanetug in CSF or plasma. Pharmacodynamic (PD) effects of etalanetug on eMTBR-tau243 was compared with the tryptic MTBR-tau243 in CSF. The mean reduction for eMTBR-tau243 (−87% non-deamidated, −89% deamidated) was greater than the tryptic MTBR-tau243 (−69%) in DIAD (n = 5). The non-deamidated and deamidated forms of eMTBR-tau243 are highly correlated in CSF (r = 0.99 Pearson, r = 0.97 Spearman, n = 33). While multiple forms of MTBR-tau243 are detectable in CSF, only the deamidated form of eMTBR-tau243 is detectable in plasma. Concentrations of eMTBR-tau243 decreased in plasma after treatment with etalanetug, with a mean reduction of 25% after 2 doses and −78% after 3 doses of the lowest dose tested, 750mg (n = 4). Maximal reduction of greater than 90% was observed and maintained for the duration of treatment. Plasma eMTBR-tau243 was not detectable in healthy subjects treated with placebo or 3 doses of etalanetug up to 4500mg. **Conclusions:** Results support that eMTBR-tau243 in CSF is a more sensitive biomarker than tryptic MTBR-tau243 at detecting the effects of etalanetug on tau pathology. The results observed for eMTBR-tau243 in CSF translate to plasma. This is the first report demonstrating plasma eMTBR-tau243, which is highly correlated with tau PET, can serve as a pharmacodynamic biomarker reflecting mechanism of action of anti-tau therapy. Etalanetug's ability to reduce eMTBR-tau243 in CSF and plasma in mild-to-moderate DIAD participants provide evidence that etalanetug attenuates the propagation of tau pathology.

Keywords: CSF MTBR-tau243, Plasma eMTBR-tau243, anti-tau, Dominantly-inherited Alzheimer's disease.

Disclosures: K Wildsmith, K. Horie, E Andreozzi, J Zhou and L Reyderman are employees of Eisai Inc. K. Horie is an Eisai-sponsored voluntary research associate professor at Washington University and has received a salary from Eisai. K. Horie and R. Bateman may receive income based on technology licensed by Washington University to C2N Diagnostics. 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). P Boyd is an employee of Eisai Europe Ltd.

Key takeaway message: Etalanetug's ability to reduce eMTBR-tau243 in CSF and plasma in mild-to-moderate DIAD participants provide evidence that etalanetug attenuates the propagation of tau pathology.

LB22- NEURON-DERIVED EXTRACELLULAR VESICLE-ASSOCIATED PROBDNF AND COMPLEX V PREDICT RESILIENCE TO COGNITIVE IMPAIRMENT.

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Background: Dementia in the elderly, largely due to Alzheimer's disease (AD) and co-pathologies, has a long preclinical course. While cerebrospinal fluid, positron emission tomography, and soluble blood-based biomarkers help define the preclinical AD stages, they measure proteins that have aggregated and may not reveal upstream biological processes. Plasma neuron-derived extracellular vesicles (NDEVs) provide a neuron-specific window that may reveal important molecular and cellular changes during progression across the AD spectrum. This study aimed to identify biomarkers predictive of cognitive decline and progression from normal cognition to mild cognitive impairment (MCI) or dementia leveraging plasma NDEVs. **Methods:** We analyzed 593 plasma samples from 389 participants (aged 60–85 years), all cognitively normal at baseline (Clinical Dementia Rating – Sum of Boxes [CDR-SB] = 0), from the Cognitive Health in Ageing Register (CHARIOT): Prospective Readiness cOhort (PRO) study. We used blood samples from month 12 and late stages (on average 4 years apart), and cognitive assessment was conducted using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). NDEVs were isolated via immunoaffinity capture for neuronal markers (L1CAM, GAP43, and NLGN3), in which we quantified pathogenic AD proteins (Aβ42, Aβ40, total Tau, p181-Tau, p231-Tau), the neurotrophin intracellular precursor proBDNF, and mitochondrial energy transducer Complex V. Biomarker values were log-transformed and standardized (Z-scores). We sought to identify participants who remained cognitively normal or developed cognitive impairment (CDR-SB $\geq$ 0.5) during follow-up. Cox proportional hazards models were used to estimate associations between baseline biomarker levels and time to first clinical progression. We fitted linear mixed-effects models to assess the relationship between biomarkers measured at 12 months and longitudinal RBANS scores through month 54. Models were adjusted for APOE genotype, age, sex, race, years of education, and time since first visit, with subject ID included as a random effect to account for repeated measures. Analyses were also stratified by APOE ε4 carrier status to assess potential effect modification. **Results:** Among study participants, 147 met the criteria for cognitive impairment (CDR-SB $\geq$ 0.5) at least once during the study. Higher baseline Complex V was associated with better RBANS performance over time (β coefficient 0.03, 95% confidence interval [CI] 0.005–0.06, p = 0.02). Increased baseline proBDNF (hazard ratio [HR] 0.87, 95% CI 0.77–0.99, p = 0.03) and Complex V (HR 0.71, 95% CI 0.58–0.87, p = 0.009) were associated with reduced risk of cognitive decline. NDEV-associated Tau biomarkers were significant only among APOE ε4 carriers, with higher p181-Tau/total Tau (HR 1.36, 95% CI 1.02–1.82, p = 0.04) and p231-Tau/total Tau (HR 1.24, 95% CI 1.01–1.52, p = 0.02) ratios being associated with increased risk of cognitive decline. **Conclusions:** Higher levels of NDEV-associated proBDNF and mitochondrial Complex V predict lower risk of cognitive decline, while phosphorylated Tau identified ε4 carriers at elevated risk. These findings suggest that preserved BDNF signaling and mitochondrial energy generation are associated with resilience to MCI and dementia.

Keywords: Cognitive resilience, neuron-derived extracellular vesicles, blood-based biomarkers.

Clinical Trial Registry: NCT02114372; httsp://clinicaltrials.gov.

Disclosures: This research was supported in part by the Intramural Research Program of the National Institutes of Health (NIH). The contributions of the NIH authors are considered Works of the United States Government. The findings and conclusions presented in this abstract are those of the authors and do not necessarily reflect the views of the NIH or the U.S. Department of Health and Human Services. The CHARIOT study was sponsored by Johnson & Johnson. Andrei Popescu and Zoi Alexopoulou are employees of and hold stock in Merck Sharp & Dohme. Janaky Coomaraswamy receive salary and company stock as compensation for their employment with Takeda Pharmaceutical Company Limited. Janice Wong is a full-time employee of and hold stock in Johnson & Johnson. Gallen Triana-Baltzer and Gerald Novak hold stock in Johnson & Johnson. Lefkos Middleton has received research funding (to Institution) from Johnson & Johnson, Merck, Takeda, Gates Ventures, Davos Alzheimer's Cooperative, NIHR, and UKRI.

Key takeaway message: Plasma neuron-derived extracellular vesicle-associated proBDNF and mitochondrial complex V predict resilience to cognitive decline, while phosphorylated Tau ratios identify APOE ε4 carriers at higher risk, supporting NDEVs as neuron-specific liquid biopsies in preclinical AD.

LB23- OPTIMIZING BLOOD-BASED ALZHEIMER'S DISEASE DIAGNOSIS: A MULTI-MARKER PTAU-217–INCLUSIVE APPROACH.

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Background: Plasma biomarkers for Alzheimer's disease (AD) have emerged as promising tools for noninvasive diagnosis. While phosphorylated tau at threonine 217 (pTau217) is among the most promising plasma biomarkers, reliance on a single analyte may be insufficient for optimal diagnostic accuracy, particularly in heterogeneous populations and at early disease stages. Recent work from our group demonstrated that proteomic signals beyond amyloid and tau can meaningfully contribute to assessing clinical AD status by defining a novel pTau217-independent protein signature (1). In the present study, we leveraged the same richly phenotyped Knight Alzheimer Disease Research Center (ADRC) cohort and its integrated proteomic and clinical dataset. Rather than testing new signatures independent of pTau217, we developed and evaluated a plasma-based multi-marker model that incorporated pTau217 and directly compared its diagnostic performance to pTau217 alone. **Methods:** We analyzed data from 2898 unique Knight ADRC participants, all of whom underwent plasma sampling within six months of comprehensive assessments to assign clinical status as cognitively

unimpaired controls (CO) versus AD; status was assigned by clinicians who had access to a full complement of clinical data including laboratory, imaging, and cognitive testing results. This group was randomly divided into discovery (70%) and replication (30%) cohorts, with stratification based on outcome, sex, and age. Using patient-level proteomic data generated on the SomaLogic platform, we conducted differential abundance analyses within the discovery cohort to identify proteins associated with AD. Prediction models were derived in the discovery cohort with clinical status as the primary outcome. Marker candidates were identified by linear model analysis and reduced to a subset of proteins based on backward elimination guided by variable importance (VIP) scores from a logistic least absolute shrinkage and selection operator (LASSO) regression model. pTau217 was forced into all models, while novel proteins identified during differential abundance analyses and three proteins commonly measured in plasma (amyloid beta 1-42 [Aβ42], glial fibrillary acidic protein [GFAP], and neurofilament light chain [NFL]) were allowed to enter through VIP-based feature selection. Out-of-sample diagnostic performance of pTau217 and multimarker models was assessed using area under the receiver operating characteristic curve (AUC) analysis. Diagnostic performance of our final model was further evaluated using varied AD status criteria. First, an analysis was performed in which 620 patients assigned AD status and a clinical dementia rating (CDR) of 0.5 (i.e., mild cognitive impairment) were excluded, allowing for comparison between cognitively normal and those with at least mild dementia. For a subset of patients, biomarker-derived disease status was also available (361 with amyloid/tau (A/T) CSF status and 387 with amyloid PET), and diagnostic performance for prediction of biomarker status was tested within each of these subgroups. In all cases, multimarker model performance was compared with pTau217 alone, and differences in AUC were assessed using DeLong's test. **Results:** Differential abundance analyses identified 19 proteins with significant associations with clinical AD. Four proteins not commonly measured in clinical practice, neuronal pentraxin receptor (NPTX-R), acetylcholinesterase (ACHE), spindle component 25 (SPC-25) and cardiotrophin 1 (CTF-1) exhibited strongest associations. In predictive modeling, the inclusion of these proteins improved diagnostic performance compared with pTau217 alone. A streamlined model that included pTau217, Aβ42, GFAP and NFL, together with NPTX-R and ACHE, achieved equivalent performance to the larger panel while excluding SPC-25 and CTF-1, thereby yielding a concise and clinically tractable biomarker set. For the primary prediction outcome of clinical status (CO vs AD), pTau217 alone achieved an AUC of 0.80 (95% CI 0.77 – 0.83) during out-of-sample validation on the replication cohort, whereas the multimarker model improved performance to 0.87 (95% CI 0.84 – 0.89, $P = 5.1\times10-10$). When comparing CO with AD in individuals with CDR $\geq$1, pTau217 achieved an AUC of 0.81 (95% CI 0.77–0.85), which increased to 0.90 (95% CI 0.87–0.93, $P = 1.3\times10-10$) with the multimarker model. A similar pattern was observed for CSF A/T classification, where performance improved from 0.94 (95% CI 0.90–0.99) with pTau217 alone to 0.98 (95% CI 0.96–1.0, $P = 0.04$) using the multimarker model. Improvements were more modest for amyloid PET status, with AUC rising slightly from 0.92 (95% CI 0.87–0.97) to 0.93 (95% CI 0.88–0.98, $P = 0.57$). **Conclusions:** A multimarker model that includes four established blood-based protein biomarkers of neurodegenerative disease and two novel proteins identified through proteomics analysis significantly improved performance in classifying clinical AD status compared with p-Tau217 alone. As high-throughput analyzers continue to evolve to support simultaneous measurement of multiple proteins, multimarker approaches may represent an effective path forward for blood-based Alzheimer's disease diagnostics.

Keywords: Blood-based biomarkers, proteomics, Alzheimer's, diagnosis.

Disclosures: JH and SL are employed by Danaher Corporation. JE and TW are employed by Genedata. MA and CC have received grant funding from Danaher Corporation.

Reference: 1. Heo, G. et al. Large-scale plasma proteomic profiling unveils diagnostic biomarkers and pathways for Alzheimer's disease. Nat. Aging 5, 1114–1131 (2025).

Key takeaway message: Plasma pTau217 reliably distinguished Alzheimer's disease, but integrating additional proteins into a multimarker model significantly improved diagnostic accuracy across clinical and biomarker outcomes, underscoring the promise of multiplex assays for noninvasive AD diagnosis.

LB24- pTAU217 PERFORMANCE TO SEPARATE ALZHEIMER'S DISEASE BIOLOGICAL STAGE IS NOT INCREASED BY ADDING DEMOGRAPHIC OR CLINICAL INFORMATION.

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Background: Determining the biological stage of Alzheimer's disease (AD) is essential for understanding development of the disease and for identifying and recruiting clinical trial participants. Blood-based measures of AD biology facilitate efforts to identify biological processes, with pTau217 showing promise as a marker of Amyloid-beta (Aβ) and phosphorylated Tau status in older adults. However, the extent to which levels of pTau217 can be used to indicate stages of tau aggregation, necessary for biological staging of AD, are still unknown. While individual pTau217 biomarker assays have been investigated for their ability to predict AD biological stage (1,2), no studies have compared accuracy of different assays across increasing biological stage, nor have they determined how demographic or concurrent clinical information could improve the accuracy of prediction. The first aim of this study was to compare the accuracy of pTau217 levels for predicting biological AD stage, defined by Aβ-PET (18F-NAV4694) and tau-PET (18F-MK6240), from four different blood-based assays. The second aim was to determine how predictive models could be improved by incorporation of information about age, sex, APOE ε4 carriership, and cognition. **Methods:** The Elecsys® (Roche), Lumipulse G (Fujirebio), Lucent AD® (Johnson & Johnson), and ALZpath Simoa (Quanterix), pTau217 blood-based assays were tested on a cohort of K2-EDTA plasma sample of 279 adults from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of ageing. All AIBL participants had undergone Aβ and tau-PET with blood collected within 12 months of the scans. Participants were classified into five groups reflecting different AD biological stages of increasing severity, based on previously (1,3) validated cut-off values for Aβ (A) and tau (T) PET (A-T-, A + T-, A + TMTL, A + TMOD, A + THIGH). The pTau217/Aβ42 ratios for both Lumipulse and Elecsys were also assessed. Mean levels of each biomarker and their percent increase between stages were computed to quantify differences across the AD biological disease stages of increasing severity, with results from ordinal regression used for comparison of pTau217 models. Linear models were computed for pTau217 (dependent variable), with independent variables added to account for variance explained by age, gender, APOE ε4 carriership, clinical classification (CU/MCI/AD), Clinical Dementia Rating Global score (CDR-GS), Mini Mental Status Examination score (MMSE), and the Pre-clinical Alzheimer's Cognitive Composite score (PACC). Resultant fitted values from each model adding separate combinations of independent variables were then

compared, and the resultant proportional change between stage was assessed. Statistics from receiver operating characteristic analyses for each biomarker/biomarker-covariate assessment for pairwise biological stage classification were compared. **Results:** The average age of participants at sample collection was 74 (SD:8) years, 47% were female, and 49% were APOE ε4 carriers. Biological disease stage classification was as follows, A-T- (n = 113), A + T-(n = 65), A + TMTL (n = 22), A + TMOD (n = 52), and A + THIGH (n = 27). Percent change in mean pTau217 levels between A-T- and A + T-ranged from 80% to 127% (Lucent AD: 80.4%, Elecsys: 110.7%, Lumipulse 101.7%, ALZpath Simoa 127.1%). Moving from A + T-to A + TMTL, pTau217 rose between 14 and 33% (Elecsys: 14%, ALZpath Simoa: 26.3%, Lucent AD: 26.8%, Lumipulse 33.2%). Average increases appeared greater from the A + TMTL to A + TMOD groups, with percent increase rising to as high as 70% (ALZpath Simoa: 25.8%, Elecsys: 29.5%, Lucent AD: 44.1%, Lumipulse 70%), and then, for most assays, greater again for comparison of the A + TMOD to A + THIGH groups (Elecsys: 20.7%, ALZpath Simoa: 31.7%, Lucent AD: 52.2%, Lumipulse 74%). The pTau217/Aβ42 ratio improved group differentiation greater than pTau217 alone. Early in the disease continuum, it increased the A-T- vs A-T+ contrast (Lumipulse +8.3%, Elecsys +36.9%). Later in the disease continuum, comparing A + TMOD to A + THIGH, both ratio's showed increases over and above pTau217 alone (Lumipulse +13%, Elecsys +3.8%). Comparing biomarker increases across biological stage via ordinal regression saw significant differences between most pTau217 assays ($p < 0.0001$), except between Elecsys and ALZpath ($p = 0.72$). Statistical control of variance in pTau217 related to demographic characteristics (age, sex, and APOE ε4) of the sample did not improve models' ability to differentiate between stages relative to models of biomarkers alone. In fact, the trend was towards a worsening with the contrast between A + TMOD and A + THIGH worsening by up to 10.6%. Similarly, no discriminative improvements were seen when clinical classification, CDR-GS, MMSE and PACC score were used as covariates in lieu of demographics, with largest increases seen between A + TMOD and A + THIGH for Lumipulse pTau217/Aβ42 ratio (39%). Inclusion of either demographic or clinical parameters did not affect model accuracy over and above using the biomarker alone across any comparison ($p > 0.03$). **Conclusions:** The use of the blood based pTau217 measure, either alone or combined into a pTau217/Aβ42 ratio, provided good discrimination between AD biological disease stages, although the best discrimination was usually obtained from the pTau217/Aβ42 ratio. These findings suggest that adding demographic or clinical data does not significantly enhance pTau217's ability to distinguish between disease stage. The generalizability of this conclusion requires confirmation in larger real-world cohorts.

Keywords: pTau217, biological stage, Amyloid beta, tau.

Disclosures: JDD has nothing to disclose.

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Key takeaway message: The pTau217/AB42 ratio provided the highest discrimination early (A-T vs A + T-, Elecsys up147%) and later (Lumipulse up 87%) in the disease; adding demographic or clinical information did not improve this discrimination.

LB3- MODULATION OF THE P75 NEUROTROPHIN RECEPTOR IN A PHASE 2A ALZHEIMER'S DISEASE TRIAL REDUCES PLASMA P-TAU217, ENGAGES THE SYNAPTIC PROTEOME, AND PRESERVES VISUOSPATIAL COGNITION.

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Background: Degenerative signalling cascades coupled to the p75 neurotrophin receptor (p75NTR) contribute to pathological tau post-translational modifications, synaptic dysfunction, neurodegeneration, and glial reactivity occurring in Alzheimer's disease (AD). In preclinical models, pharmacological modulation of p75NTR with the small molecule LM11A-31 reduces accumulation of multiple pathological tau species, and rescues amyloid and tau-induced loss of dendritic spines and synapses. LM11A-31 also normalizes synaptic function, as assessed by hippocampal slice long-term potentiation and multiple behavioral tests, and reduces microglial and astrocyte activation. In a phase 2a trial, LM11A-31 slowed gray matter atrophy, preserved cerebral glucose metabolism, and attenuated changes in cerebrospinal fluid (CSF) biomarkers consistent with preserving synapses and reducing glial activation (1). In this presentation, we report novel findings from the phase 2a trial that demonstrate the clinical relevance of p75NTR modulation, including slowing of progression of plasma phosphorylated tau (p-tau), CSF proteomic signatures, and domain-specific cognitive composite scores. **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. Individuals with mild to moderate AD dementia (n = 242) were treated twice daily with placebo, 200mg or 400mg of LM11A-31. Exploratory endpoints included plasma p-tau217 as measured by liquid chromatography-mass spectrometry (LC-MS/MS; C2N Diagnostics LLC, St. Louis), immunoassay measures of plasma GFAP (University of Gothenburg), CSF proteomics as measured by tandem mass tag-based mass spectrometry (TMT-MS; Emtherapro, Atlanta) and psychometrically-validated composite domain scores assessing memory, language, executive function and visuospatial abilities. **Results:** First, we characterized relationships among the biomarker and cognitive endpoints at baseline, demonstrating novel associations between composite domain scores, plasma p-tau217, GFAP, and CSF proteomic modules. When examining longitudinal treatment effects, we observed that 26-week treatment with LM11A-31 significantly decreased plasma p-tau217 compared to placebo. Moreover, CSF proteomic analyses identified 241 proteins altered by LM11A-31 treatment, with those decreased in abundance significantly enriched for synaptic compartments and processes. Analysis of protein co-expression modules, defined in an independent sample of AD patients (2), revealed that LM11A-31 slowed disease progression of modules enriched for neurons, oligodendrocytes, and microglia. Over the 26-week course of the trial, two of the four composite domains (memory and visuospatial ability) exhibited significant decline in the placebo group. Despite the relatively short 26-week treatment duration, a significant effect of LM11A-31 was observed on visuospatial cognition, with participants who received LM11A-31 exhibiting less decline at 12- and 26-weeks compared to participants who received placebo. **Conclusions:** Over 26-weeks of treatment, LM11A-31 slowed progression of key markers of disease, with converging effects on p-tau217, synaptic proteins, glial networks, and visuospatial function. In addition, we observed significant cross-correlations among these novel outcome measures, suggesting that these molecular and cognitive changes are biologically interconnected and may reflect a common treatment-responsive pathway. Overall, these results are consistent with preclinical studies demonstrating that LM11A-31 reduces multiple forms of tau pathology (3,4), promotes synaptic resilience, and attenuates glial activation. This work supports p75NTR modulation as a disease-modifying therapeutic strategy for AD. Larger trials of longer treatment duration are warranted to further evaluate the effects of LM11A-31.

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Keywords: Tau, p75 neurotrophin receptor, proteomics, cognitive domains.

Disclosures: NTS, AIL and DMD are co-founders and consultants of Emtherapro. VV and MRM are employees of C2N Diagnostics, LLC. KB has served as a consultant and at advisory boards for Abbvie, AC Immune, ALZPath, AriBio, Beckman-Coulter, BioArctic, Biogen, Eisai, Lilly, Moleac Pte. Ltd, Neurimmune, Novartis, Ono Pharma, Prothena, Quanterix, Roche Diagnostics, Sunbird Bio, Sanofi 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. MW is the vice president for research and development of NeuroScios GmbH. 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. TWS has consulted as a pharmacological/clinical expert for NeuroScios GmbH.

Funding**:** National Institute on Aging (NIA AD pilot trial 1R01AG051596) and PharmatrophiX (Menlo Park, California).

Clinical trial registry: EU Clinical Trials 2015-005263-16; ClinicalTrials.gov NCT03069014.

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Key takeaway message: In a phase 2a AD trial, 26-week treatment with the p75 neurotrophin receptor modulator LM11A-31 slowed progression of plasma p-tau217, CSF synaptic markers, and glial- and neuronally-enriched CSF proteomic modules, while preserving visuospatial cognitive function.

LB4- DIAGNOSTIC PERFORMANCE OF THE FDA-CLEARED LUMIPULSE G PTAU217/ß-AMYLOID 1-42 PLASMA RATIO THRESHOLDS FOR THE DETECTION OF AMYLOID PATHOLOGY.

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Background: The Lumipulse G pTau217/β-Amyloid 1-42 (Aβ42) Ratio is the first FDA-cleared blood biomarker test to aid in the diagnosis of Alzheimer's disease (AD) in symptomatic individuals ≥50 years old. Clinical performance was established in 499 individuals with subjective cognitive decline (SCD), mild cognitive impairment (MCI), dementia, and other cognitive disorders. For detection of amyloid pathology, the pTau217/Ab42 ratio has a reported 98% sensitivity and 91% specificity at the lower (≤0.00370) and upper (≥0.00738) cutpoints, respectively, supporting its use as a confirmatory test of amyloid pathology per current clinical practice guidelines (1). The reported positive predictive value (PPV) was 91.8% (95% CI: 87.8–94.6%), and the negative predictive value (NPV) was 97.3% (95% CI: 93.9–98.8%) at 51.1% amyloid pathology prevalence with 20% intermediate results. This study evaluated the clinical performance claims of the FDA-cleared Lumipulse pTau217/Ab42 Plasma Ratio assay in comparison to a clinically available laboratory-developed test (LDT) utilizing the Lumipulse plasma pTau217 assay alone (2). **Methods:** Two independent cohorts, comprising of individuals with MCI, dementia, and other cognitive disorders, were evaluated. Cohort 1 (n = 252) was a clinical cohort from a prospective study at a tertiary care subspecialty clinic (Mayo Clinic, Rochester, MN) where patients were enrolled if they underwent amyloid-PET and/or CSF p-tau181/Aβ42 testing as part of their clinical evaluation between November 2023–September 2025. Cohort 2 (n = 101) was a risk-enriched AD cohort from the Wisconsin Alzheimer's Disease Research Center (WADRC) and the Wisconsin Registry for Alzheimer's Prevention (WRAP). Plasma pTau217 and Aβ42 were measured at each site using the Fujirebio Lumipulse assays in the LUMIPULSE G1200. The pTau217/Aβ42 ratio results were classified as negative (≤0.00370), intermediate (0.00371–0.00737), or positive (≥0.00738) using the FDA-cleared assay cutpoints. Previously established pTau217/Aβ42 ratio cutpoints were also evaluated, classifying results as negative (≤0.0074), intermediate (0.0075–0.0131), or positive (≥0.0132) (3). Plasma pTau217 assay results (pg/mL) were classified as negative (≤0.185), intermediate (0.186–0.324), or positive (≥0.325) based on previously established cutpoints.2 For cohort 1, amyloid pathology was determined by amyloid-PET (florbetapir F-18) visual read or CSF pTau181/Aβ42 ratio (positive >0.028); a positive result by either modality was considered amyloid-positive (A+). In cohort 2, A+ status was determined by amyloid-PET (^{11}C-PiB) visual read. A+ prevalence was 70% in cohort 1 and 71% in cohort 2. **Results:** In cohort 1, applying the FDA-cleared cutpoints, plasma pTau217/Aβ42 results were positive in 82% of patients (207/252), negative in 4% (9/252), and intermediate in 14% (36/252). Restricting analysis to definitive (positive or negative) outcomes, plasma pTau217/Aβ42 showed 100% sensitivity (95% CI: 98–100%) and 23% specificity (95% CI: 11–39%), with 77% diagnostic accuracy (95% CI: 71–83%). Using the previously established in-house cutpoints, pTau217/Aβ42 was positive in 69% of patients (173/252), negative in 18% (45/252), and intermediate in 13% (34/252). Restricting analysis to definitive outcomes, plasma pTau217/Aβ42 showed 100% sensitivity (95% CI: 98–100%) and 79% specificity (95% CI: 66–89%), with a 94% diagnostic accuracy (95% CI: 90–97%). In contrast, the plasma pTau217 assay was positive in 63% of patients (159/252), negative in 21% (54/252), and intermediate in 15% (39/252). Restricting analysis to definitive outcomes, plasma pTau217 exhibited 98% sensitivity (95% CI: 94–100%) and 84% specificity (95% CI: 72–92%), with 94% diagnostic accuracy (95% CI: 90–97%). In cohort 2, when applying the FDA-cleared cutpoints, plasma pTau217/Aβ42 was positive in 68% (69/101) of participants, negative in 18% (18/101), and intermediate in 14% (14/101). Restricting analysis to definitive (positive or negative) outcomes, plasma pTau217/Aβ42 showed 99% sensitivity (95% CI: 92–100%) and 85% specificity (95% CI: 62–97%). Elevated pTau217/Aβ42 predicted amyloid pathology with 95% diagnostic accuracy (95% CI: 88–98%). Using previously established in-house cutpoints, pTau217/Aβ42 was positive in 45% of patients (46/101), negative in 32% (32/101), and intermediate in 23% (23/101). Restricting analysis to definitive outcomes, plasma pTau217/Aβ42 showed 88% sensitivity (95% CI: 76–96%) and 96% specificity (95% CI: 81–100%) with 91% diagnostic accuracy (95% CI: 82–96%). In this cohort, plasma pTau217 was positive in 48% (49/101) of participants, negative in 29% (29/101), and intermediate in 23% (23/101). Restricting analysis to definitive outcomes, plasma pTau217 showed 89% sensitivity (95% CI: 77–96%) and 96% specificity (95% CI: 79–100%), with 91% diagnostic accuracy (95% CI: 82–96%). **Conclusions:** In this study, the use of the Lumipulse pTau217/Aβ42 Plasma Ratio FDA-cleared cutpoints demonstrated different diagnostic accuracies in a real-world clinical cohort (cohort 1; 77% accuracy) versus a

risk-enriched AD cohort (cohort 2; 95%). Additionally, diagnostic accuracy of the FDA-cleared pTau217/Ab42 ratio cutpoints and established pTau217 cutpoints differed substantially in the real-world clinical cohort (77% vs. 94%), but not in the risk-enriched AD cohort (95% vs. 91%). In contrast, use of previously established in-house pTau217/Aβ42 cutpoints yielded >90% diagnostic accuracy in both cohorts. These findings suggest that the diagnostic performance of FDA-cleared pTau217/Aβ42 ratio cutpoints may vary in real-world clinical cohorts. These findings underscore the importance of independent validation of test performance in real-world settings—even for FDA-cleared assays.

Keywords: Plasma pTau217, plasma pTau217/Aβ42, Fujirebio Lumipulse.

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Disclosures: AAS has participated in advisory boards for Roche Diagnostics, Fujirebio Diagnostics and Siemens Healthineers, and has received speaker honoraria from Roche Diagnostics and Eli Lilly. JAB has received honorarium from Roche Diagnostics and travel funds from Siemens Healthineers. DJF has received speaker honoraria from Beckman Coulter. DRJ reports consultation/advisory board for Novartis, Telix and Cellectar. GSD reports no competing interests directly relevant to this work.His research is supported by NIH (R01AG089380, U01AG057195, U01NS120901, U19AG032438, P30AG062677). He serves as a consultant for Arialys Therapeutics, and as a Topic Editor (Dementia) for DynaMed (EBSCO). He is a co-Project PI for a clinical trial in anti-NMDAR encephalitis, which receives support from NIH/NINDS (U01NS120901) and Amgen Pharmaceuticals. He has developed educational materials for Continuing Education Inc, Ionis Pharmaceuticals, and MJH Life Sciences. He owns stock in ANI Pharmaceuticals. SJM receives funding from the NIH and American Academy of Sleep Medicine Foundation. HB receives funding from NIH and CervoMed. JGR serves as site investigator for trials sponsored by Eisai and Cognition Therapeutics. RCP serves as a consultant for Roche, Genentech, Eli Lilly, Eisai, Novartis, and Novo Nordisk; receives royalties from Oxford University Press and UpToDate, and receives NIH funding.VKR has received research funding from the NIH and the Mangurian Foundation for Lewy Body Disease Research; has provided educational content for Medscape, Expert Perspectives in Alzheimer's Disease, and Roche/ADLM; has received speaker and conference session honoraria from the American Academy of Neurology Institute; is co-PI for a clinical trial supported by the Alzheimer's Association; is site Co-PI for the Alzheimer's Clinical Trials Consortium; and is a site clinician for clinical trials supported by Eisai, the Alzheimer's Treatment and Research Institute at USC, and Transposon Therapeutics, Inc. 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, Enigma, LabCorp, Merck Sharp & Dohme, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Quanterix, Red Abbey Labs, reMYND, Roche, Samumed, ScandiBio Therapeutics AB, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures sponsored by Alzecure, BioArctic, Biogen, Cellectricon, Fujirebio, LabCorp, Lilly, Novo Nordisk, Oy Medix Biochemica AB, Roche, and WebMD, is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, and is a shareholder of CERimmune Therapeutics (outside submitted work). SCJ serves as an advisor to Enigma Biomedical, Eli Lilly, ALZpath, Alamar and Merck. SAK, RERR, and BJB have no disclosures.

Key takeaway message: Differences in diagnostic performance were observed when the Lumipulse pTau217/Aβ42 Plasma Ratio FDA-cleared cutpoints were applied to different cohorts. Our findings suggest that the FDA-cleared pTau217/Aβ42 ratio cutpoints performance may vary in real-world clinical cohorts. These findings underscore the importance of independent validation of test performance in real-world settings—even for FDA-cleared assays.

LB6- IMMUNOASSAY-BASED P-TAU205 IS A BIOMARKER OF TAU-PET ABNORMALITY: A CROSS-SECTIONAL AND LONGITUDINAL STUDY.

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Background: In recent years, soluble p-tau205 has gained significant attention in the Alzheimer's disease (AD) biomarker field (1-10). This specific phosphorylation plays a key role in misfolded tau deposition and is central to the neuropathological definitive diagnosis of AD. Moreover, as a biomarker, p-tau205 emerges at a distinct time point across the AD continuum compared to other soluble p-tau forms (2,5,6,8) and exhibits stronger correlation with tau-PET than other p-tau species (3,7). These features have led to the proposal of p-tau205 as a candidate for biological staging of AD using fluid biomarkers (8,9). Supportive of this perspective, the Alzheimer's Association's new criteria for diagnosis and staging incorporated p-tau205 into the fluid biomarker framework, positioning it as an example of an early-stage marker, emerging between initial markers (e.g., p-tau217) and intermediate-stage markers (e.g., MTBR-tau243) (8). To date, the potential of p-tau205 as a staging biomarker has been investigated primarily through mass spectrometry-based measurements (6,10), which are technically complex. The present study aimed to evaluate whether immunoassay-based cerebrospinal fluid (CSF) p-tau205 could similarly capture staging utility, thereby enhancing its accessibility for use in clinical practice and trials. **Methods:** We used an in-house p-tau205 immunoassay to 2069 CSF samples from two independent cohorts (BioFINDER-2 [n = 1364] and BioFINDER-1 [n = 705]) to examine cross-sectional and longitudinal associations of p-tau205 with imaging and cognitive biomarkers. We further assessed its potential to support AD staging, as well as its ability to predict pathological and clinical progression. Group differences in CSF p-tau205 levels were assessed using ANCOVA with age and sex as covariates, followed by Tukey's post hoc tests. Cross-sectional and longitudinal associations with AD biomarkers were evaluated using linear regression and linear mixed models, respectively, adjusting for age, sex, and education where appropriate, while locally estimated scatterplot smoothing (LOESS) regressions were applied to visualize biomarker progression. CSF biomarkers were dichotomized to define hierarchical AD stages, which were then used in Cox proportional hazards models and Kaplan-Meier curves to examine risk of progression to dementia, with multiple comparisons controlled via FDR correction. **Results:** CSF p-tau205 progressively increase in Aβ-positive compared with Aβ-negative groups ($p < 0.001$ for all; fold change [FC]: FCCU- vs CU+ = 1.91, FCCU- vs MCI+ = 2.32, and FCCU- vs AD = 2.95). In Aβ-positive participants, cross-sectional CSF p-tau205 measurements were associated with Aβ-PET ($R2 = 0.26$), tau-PET ($R2 = 0.29$), cortical thickness ($R2 = 0.14$) and cognition (MMSE, $R2 = 0.14$). Higher baseline concentrations of CSF p-tau205 were associated with longitudinal increases of Aβ and tau-PET tracer uptake (Aβ-PET: $R2 = 0.44$; neocortical Tau-PET: $R2 = 0.33$). CSF p-tau205 had a steeper increase longitudinally in Aβ-positive in comparison with Aβ-negative individuals (time×Aβ-interaction: β[95%CI] = 0.16 [0.12, 0.21], $p < 0.001$). Longitudinal changes in CSF p-tau205 were associated with longitudinal decreases in cortical thickness ($R2 = 0.32$) and cognitive decline (MMSE: $R2 = 0.41$; mPACC: $R2 = 0.46$). Unlike CSF p-tau217, CSF p-tau205 became abnormal almost simultaneously to neocortical tau-PET. When creating a biological staging model for AD, stage-0 was defined by negative CSF biomarkers, stage-1 (only positive Aβ42/40), stage-2 (positive Aβ42/40 and p-tau217), and stage-3 (positive Aβ42/40, p-tau217, and p-tau205).

This staging system classified the severity of AD pathophysiology. Notably, we demonstrated that CSF p-tau205 positivity (stage-3) is associated with more severe cortical atrophy and worsening in cognition, as well as a significantly higher risk of progressing into AD dementia (HR [95%CI] = 6.40 [4.28, 9.59], $p < 0.001$) than stages 1 and 2. **Conclusions:** In this work, we validated immunoassay-based CSF p-tau205 as a biomarker that emerges later in the AD continuum compared to other p-tau forms and can serve as an accessible alternative for tracking and predicting underlying tau pathology. Notably, p-tau205 becomes positive at a similar time as tau-PET in the temporal neocortex, underscoring its potential as a surrogate marker in clinical trials. By integrating CSF p-tau205 into an AD staging framework, we show that p-tau205 positivity provides a meaningful indicator of the disease biological stage and is of high value for predicting longitudinal changes in imaging and cognitive biomarkers. Importantly, this validation was performed using a scalable immunoassay, reinforcing its potential to facilitate patient stratification in clinical trials.

Keywords: CSF, p-tau205, Alzheimer's disease, biomarkers, tau, staging, tangle, cognition.

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Key takeaway message: Immunoassay-based CSF p-tau205 emerges later in the AD continuum than other p-tau forms, aligns with tau-PET, and predicts neurodegeneration and cognitive decline, supporting its high value for disease staging and patient stratification in clinical trials.

LB7- LUMIPULSE PLASMA P-TAU217/AB42 RATIO: ACCURACY ACROSS THE SPECTRUM OF ALZHEIMER'S DISEASE NEUROPATHOLOGIC CHANGES.

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Background: Accurate in vivo detection of intermediate and high Alzheimer's disease neuropathologic changes (ADNC) is key for disease staging and clinical trial enrolment. A visually positive tau-PET scan with the FDA/EMA-approved tracer [18F]flortaucipir (1,2) is considered a reliable proxy of high ADNC (3). Plasma biomarkers such as p-tau217 are emerging as minimally invasive alternatives, especially with the recent FDA approval of the Lumipulse p-tau217/Aβ42 ratio (4) for the assessment of amyloid pathology. This study evaluated the performance of the Lumipulse p-tau217/Aβ42 ratio for detecting intermediate and high ADNC defined by either neuropathologic assessments at autopsy or by visual reads of FDA/EMA-approved tau-PET scans. **Methods:** Post-mortem neuropathologic assessments and ante-mortem plasma p-tau217/Aβ42 measurements (Lumipulse G1200 assay) from 119 ADNI participants were evaluated. In addition, Lumipulse p-tau217/Aβ42 measurements and [18F]flortaucipir tau-PET scans were available in 625 additional ADNI participants. Three trained readers rated the [18F]flortaucipir scans as visually positive/negative using the FDA/EMA-approved interpretation method. An approximate correspondence between AT profiles and ADNC classification was established as follows: A−T− = "no ADNC", A + T− = "intermediate ADNC", and A + T+ = "high ADNC". Amyloid-positivity was defined using the previously neuropathologically verified cut-point of 24.4 Centiloids (CL) (5). Receiver operating characteristic (ROC) curve analysis assessed the biomarkers' discriminative accuracy across ADNC levels. Kaplan–Meier curves and Cox models assessed rates of conversion to Aβ-PET positivity based on CL in p-tau217/Aβ42 ratio–positive cases (intermediate/positive). **Results:** The plasma p-tau217/Aβ42 ratio biomarker demonstrated high accuracy (AUC = 0.93) for discriminating between "no/low/intermediate" and "high" ADNC at autopsy. When applying the FDA-approved two-tier cut-points (negative/intermediate/positive), the ratio identified all "high" ADNC cases (100%) but misclassified 25% of "no" ADNC cases as positive. Among low/intermediate ADNC, classification was inconsistent: only 10% of low ADNC were correctly identified as negative, and only 77% of intermediate ADNC cases were classified as positive. Findings in the in vivo cohort examined with tau-PET further supported these results. Plasma p-tau217/Aβ42 reliably detected A + T+ ("high" ADNC) (88% for CU and 94% for CI), but most A+T− individuals had plasma p-tau217/Aβ42 levels in the intermediate (39% for CU and 24% for CI) or negative range (21% for CU and 10% for CI). False positives were again observed among A− individuals ("no" ADNC), with only 62% correctly identified as negative in CU and 53% in CI participants, indicating a substantial rate of false positives. Accuracy was higher in cognitively impaired (CI) than unimpaired (CU) participants (AUC = 0.96 for CI and AUC = 0.89 for CU). In preclinical AD (A+) individuals, only half of Aβ-PET positive cases were detected (51%) by plasma p-tau217/Aβ42. Among impaired A+ cases, 88% were classified as positive. When testing whether p-tau217/Aβ42-positivity could precede Aβ-PET positivity, we found that among p-tau217/Aβ42-positive but Aβ-PET–negative individuals at baseline with available follow-up Aβ-PET data (n = 95), only 17.4% progressed to Aβ-PET positive within five years, with 80% of the sample never progressing during seven years of follow-up. Neither p-tau217/Aβ42 classification (intermediate vs. positive), age, nor plasma-to-PET interval predicted conversion (HR =

0.64 (95% CI, 0.18-2.30), p = 0.5; HR = 0.99 (95% CI, 0.88-1.11), p = 0.9; HR = 1.01 (95% CI, 0.99-1.03), p = 0.3). By contrast, higher baseline CL values were significantly associated with future progression to A+ (HR = 1.14 (95% CI, 1.07-1.22), p < 0.001). **Conclusions:** Plasma p-tau217/Aβ42 ratio reliably identifies the extremes of ADNC but lacks precision in low/intermediate stages, reflecting limited utility for biological disease staging. Its weaker performance in preclinical individuals—particularly the inability to reliably classify A+ cases—challenges their role in early AD detection. Importantly, false positives were also frequent among A− individuals, which are often interpreted as reflecting earlier detection by plasma biomarkers. Yet, our results demonstrate that most plasma-positive but Aβ-PET–negative cases do not progress to Aβ-PET positivity within five years, confirming that many p-tau217/Aβ42 false positives are indeed false rather than reflecting earlier disease detection. Complementary imaging approaches may therefore be required to improve reliability in early disease stages.

Keywords: Plasma p-tau217/Aβ42, tau-PET imaging, [18F]flortaucipir, Alzheimer's disease neuropathologic changes, Alzheimer's disease.

Disclosures: Nothing to disclose.

References: 1. FDA label for [18F]flortaucipir. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212123s000lbl.pdf, 2020. 2. EMA label for [18F]flortaucipir. https://www.ema.europa.eu/en/medicines/human/EPAR/tauvid, 2024. 3. Fleisher AS, Pontecorvo MJ, Devous MD, Sr. et al. Positron Emission Tomography Imaging With [18F]flortaucipir and Postmortem Assessment of Alzheimer Disease Neuropathologic Changes. JAMA Neurol. 2020. https://doi.org/10.1001/jamaneurol.2020.0528. 4. U.S. Food & Drug Administration. (2025, May 16). K242706 - Lumipulse G pTau217/β-Amyloid 1-42 Plasma Ratio [510(k) Summary]. https://www.accessdata.fda.gov/cdrh_docs/pdf24/K242706.pdf. 5. La Joie R, Ayakta N, Seeley WW et al. Multisite study of the relationships between antemortem [11C]PIB-PET Centiloid values and postmortem measures of Alzheimer's disease neuropathology. Alzheimers Dement. 2019. https://doi.org/10.1016/j.jalz.2018.09.001.

Key takeaway message: Plasma p-tau217/Aβ42 ratio reliably detects high ADNC but performs poorly in preclinical and low/intermediate stages, with frequent false positives. It does not precede Aβ-PET, underscoring the need for complementary imaging in early Alzheimer's detection.

LB8- UNTARGETED PROTEOMICS AND MACHINE LEARNING REVEAL NOVEL BIOMARKER CANDIDATES CAPTURING DIVERSE PERTURBED PATHWAYS IN ALZHEIMER'S DISEASE IN AN AFRICAN AMERICAN COHORT.

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Background: Blood-based biomarkers offer improved accessibility compared to established diagnostic modalities for Alzheimer's disease (AD) (1). However, current blood-based biomarker candidates have not yet been tested comprehensively in diverse populations and represent only a fraction of pathways known to be dysregulated in AD, potentially leading to missed opportunities to identify additional diagnostic biomarkers or novel therapeutic targets (2-5). This study seeks to address these knowledge gaps through untargeted plasma biomarker discovery in an African American (AA) cohort, an underrepresented group in AD research, despite having a disproportionately higher risk of developing dementia relative to non-Hispanic White (NHW) individuals (6,7). **Methods:** Untargeted plasma proteome measurements were generated using the SomaScan 7k platform on plasma samples from AA study participants clinically diagnosed as AD dementia (n = 181) or cognitively unimpaired (CU; n = 142). Machine learning was applied to identify a set of plasma proteins that distinguish between AD dementia and CU. Predictive models were constructed by elastic net regression optimized with nested cross-validation on 6853 proteins and evaluated by receiver operating characteristic analysis. The generalizability of proteins selected by machine learning was assessed in two independent datasets: 1) an external Alzheimer's Disease Research Center plasma cohort of 369 NHW and AA study participants diagnosed as AD dementia or CU, and 2) a multi-ethnic autopsy-confirmed brain proteome cohort from the Accelerating Medicine's Partnership for AD (AMP-AD) (8). Finally, baseline plasma protein levels were evaluated for their ability to predict conversion to amnestic mild cognitive impairment (aMCI) or AD dementia in 30 participants with longitudinal follow-up (median = 9.7 years). **Results:** Thirty-six proteins were selected as best predictors of AD dementia diagnosis. These 36 proteins achieved an area under the curve (AUC) of 0.94 to classify AD dementia in the discovery cohort, a 22% improvement over a model including only age and sex. Replication in an external plasma cohort confirmed their performance, also achieving AUC = 0.94, a 35% improvement over age and sex. Fourteen of the 36 proteins were measured in the AMP-AD brain proteome cohort, yielding an AUC of 0.91 to distinguish between autopsy-confirmed diagnoses of AD and control. Moreover, of the 36 proteins, 11 were significantly associated with AD dementia diagnosis, but not with plasma p-tau217 levels, suggesting that they capture disease processes beyond canonical amyloid and tau pathology. These eleven proteins were enriched for pathways implicated in AD, including synaptic dysfunction, extracellular matrix organization, lipid trafficking, and immune response. Notably, baseline levels of nine of the 36 proteins showed nominal association with conversion to aMCI or AD dementia. **Conclusions:** Data-driven biomarker discovery combining proteomics and machine learning identified a robust panel of plasma proteins that accurately classify AD dementia and reflect diverse biological processes beyond amyloid and tau accumulation. These findings highlight novel blood-based biomarker candidates that could be leveraged to improve diagnostic accuracy, support precision medicine approaches, and enable early detection of AD-related pathology in broad populations. Future work will further evaluate the ability of baseline plasma proteins to predict AD-related cognitive decline in larger, multiethnic, longitudinally followed cohorts.

Keywords: Plasma biomarkers, proteomics, machine learning, health equity, precision medicine, diagnosis, prediction.

Disclosures: The authors report no disclosures relevant to this work.

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Key takeaway message: Untargeted proteomics and machine learning identified 36 plasma proteins that accurately classify AD dementia in an African American cohort, revealing novel biomarker candidates that capture diverse disease processes beyond amyloid and tau pathology.

3.5. Clinical trials: cognitive and functional endpoints

OC41- IMPACT OF NUTRITION, SLEEP AND PHYSICAL ACTIVITY ON PRESERVATION OF INTELLECTUAL FUNCTION IN OLDER FRAILTY ADULTS (INSPIOR): A RANDOMIZED CONTROLLED TRIAL.

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Background: Alzheimer's disease is the leading cause of dementia, and early intervention in the precursor stage of the disease, mild cognitive impairment (MCI), is important. Lifestyle factors and genetic factors such as the APOE gene are involved in the onset of the disease. Previously, the FINGER trial demonstrated that a 2-year multi-domain intervention, incorporating physical activity, cognitive training, and dietary guidance, improved cognitive performance and slowed decline in older adults at risk for dementia (1). Large-scale studies have also been conducted to collect lifestyle habits by Wearable devices (2). This study aimed to evaluate the effectiveness of personalized lifestyle notifications, based on wearable device recorded data, in improving health outcomes—specifically cognitive function and protection of dementia onset—among older adults, compared to usual care. In this study, we conducted a stratified analysis for each genotype in order to evaluate the association between improvements in lifestyle habits, such as exercise, sleep and nutrition, and the preservation of the intellectual function, as measured by the Montreal Cognitive Assessment (MoCA) score. The aim was to identify risk factors and develop effective intervention methods. **Methods:** In a 6-month randomized controlled trial, 355 older adults (aged 65+), including those with frailty tendancies whose frailty score was more than 1 in a simple 5 score evaluation based on Japanese-CHS standard (3). They were randomly assigned to an intervention group (n = 178) or a control group (n = 177). The intervention group wore Fitbit Charge 5 devices and received lifestyle alerts with rule-based personalization, using thresholds derived by human experts, throughout the 6-month period. The intervention group also received regular nutritional balance optimization alerts based on their dietary records from Asuken-app (Tokyo, Japan) for 6 months. The control group did not receive any notifications and the use of Fitbit and Asuken was limited in duration. Those in the intervention group who wished to participate received nutritional supplements containing protein and dietary fiber to improve their nutritional balance. This dietary supplement in the form of small meatballs (16.7g each x 6/day) containing 17.1 g of protein, 3.8 g of dietary fiber, 180 mg of anserine and 56 mg of carnosine as imidazole dipeptide per day. We found that the number of individuals with ApoE4 who recovered to a score of 0 on the Clinical Dementia Rating (CDR) scale increased significantly with imidazole dipeptide intake compared to those in the control group who did not take it (4). The study was approved by GSFS of The University of Tokyo Ethics Committee (approval number: 22-360). **Results:** In the intention-to-treat analysis (ITT: n = 178 intervention, n = 177 control), the intervention group showed significant improvements in general cognitive function (MoCA scores increased by 1.0 (95% CI: 0.6 to 1.4) vs 0.2 (−0.2 to 0.6) in the control group, $p = 0.004$). In the per-protocol set analysis (PPS: intervention: n = 140; control: n = 138), the results were similar. Frailty scores were also significantly improved in the intervention group compared to the control group in both ITT and PPS analyses ($p < 0.01$). In terms of nutrition, protein and fiber intakes showed significant increases ($p < 0.001$), confirming an optimized dietary balance. In terms of exercise activity, the intervention group showed a significant decrease in the sedation time ($p < 0.001$) compared to the control group. Stratified analyses were conducted for each stratum factor using the change in MoCA scores as the objective variable: subjects suspected to MCI, APOE4 carriers and non-carriers suspected of having MCI. The results showed a significant increase in the amount of change in MoCA scores before and after the intervention in MCI group, compared to the control group. However, effect size analysis revealed a moderate effect size for individuals suspected of having MCI who were not APOE4 carriers, and a large effect size for individuals suspected of having MCI who were APOE4 carriers. The number of individuals with ApoE4 who recovered to cognitive normality based on MoCA scores (more than 26 score) increased significantly with this lifestyle improvement notification based on lifelog data, compared to the control group. Moreover, a multiple regression analysis showed that increased nutrient intake, activity time and sleep duration were effective in restoring the cognitive function of individuals with MCI and ApoE4 to normal levels. **Conclusions:** This study provides evidence that personalized, multifaceted, Fitbit-based lifestyle interventions can effectively preserve cognitive function, with notable improvements in MoCA scores in particular. Although combined interventions, such as the Finger study, have been shown to be effective in preventing dementia, there have been challenges in using them as an actual health care service for dementia prevention due to the large human burden on service providers. In the present study, the collection of lifelog data and the corresponding multifaceted and personalized lifestyle guidance were conducted entirely online using digital devices in order to reduce the human burden, and the effectiveness of this system was confirmed. Comprehensive lifestyle interventions incorporating exercise, sleep and nutrition, based on wearable technology, could be valuable in promoting healthy ageing and preventing the onset of dementia, particularly among individuals at higher risk of Alzheimer's disease, such as those with mild cognitive impairment (MCI) who carry the ApoE4 gene.

Keywords: Wearable technology, fitbit, personalized lifestyle notifications, cognitive function, frailty, older adults, healthy aging, comprehensive intervention, MoCA.
Clinical Trial Registry: NCT06135740; https://clinicaltrials.gov.
Data Deposition: medRxiv, 2025.03. 14.25323203. **Disclosures:** TH received a grant from Google and NH Foods.

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Key takeaway message: The six-month, personalized, multifaceted lifestyle intervention based on Fitbit (nutrition, sleep and physical activity) showed significant improvements in the MoCA score, particularly

among individuals with mild cognitive impairment (MCI) who carry the ApoE4 gene.

3.6. Health economics and clinical trials

OC39- ESTIMATED BUDGET IMPACT OF A SCREENING AND TREATMENT PROGRAM FOR PRECLINICAL ALZHEIMER'S DISEASE IN THE U.S. OVER 15 YEARS.

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Background: Pharmacologic treatments to reduce the risk of progression from preclinical Alzheimer's disease (AD) to early-stage symptomatic AD are in advanced clinical trials. While prior research has suggested that the treatments could be cost-effective, concerns remain about affordability given the large potentially eligible population. We predict the annual and cumulative budget impact for the US over 15 years using a hypothetical screening and treatment program. **Methods:** We assumed that the cognitively unimpaired population aged 55-79 would undergo testing with a p-tau217 blood test annually except for individuals with cardiac implants or life expectancy <10 years. The tercile with the highest p-tau217 levels, for which sensitivity and specificity would be 0.9, would be treated with 9 doses of a hypothetical treatment in the first year and a single maintenance dose in subsequent years until progression to early-stage disease, plus one MRI at baseline and then annually together with a brief cognitive assessment and a repeat blood test until progression to early-stage AD. We used a structured expert consultation process to obtain estimates for participation in the screening program and then uptake of treatment if the screening test showed an abnormal result in years 1, 5, 10, and 15 after initiation. The panel included 13 experts (3 primary care physicians, 2 geriatricians, 2 geriatric psychiatrists, 2 neurologists, 1 neuropsychologist, and 3 AD specialists). The experts were instructed to use the "best case" assumptions that the treatment would reduce the risk of progression to early-stage AD by 50%, and that both the test and the treatment were FDA approved, covered by health insurance and recommended by guidelines. They received a briefing document with data on historic uptake of screening programs and a literature review on uptake of treatment based on screening results and were asked to provide their estimates in two rounds. In the first round, they provided their ratings independently and were given the opportunity to make comments and ask questions. In the second round, they received their own estimates, the median estimate and the average absolute difference for the median of the entire group, and all comments and questions with answers, and were asked for their final estimates. We used the final median estimates for the uptake assumptions in our model. Costs of tests and services are based on 2025 Medicare rates and list prices and were $211.32 for a brain MRI without contrast, $130.40 for infusion delivery, $126.21 for the blood test, and $97.18 for an office visit. We assume the cost for the hypothetical treatment to be $2300 per dose. All costs were inflated by 3% annually. Annual budget impact of the hypothetical treatment was calculated as cost of tests and treatment minus reduced medical and social care costs from fewer cases with manifest cognitive impairment. Of note, the cost of treating individuals, who have progressed to early-stage AD, is not considered, as the current analysis intends to only analyze the budget impact of the preclinical program. **Results:** The final estimates for participation in screening were 20% in year 1, 40% in year 5, 60% in year 10 and 70% in year 15 and the corresponding estimates for treatment uptake 30%, 40%, 60% and 60%. Of 90 million individuals, 15 million would be eligible for and 3.1 million (3.4%) would undergo screening in year 1, of which 140,000 (0.2%) would receive treatment. The numbers would increase to 10 million screened and 1.3 million treated by year 15. Net direct program cost, i.e., spending less savings from reduced early-stage AD, would be $3.8 billion in year 1, and decline to $2.1 billion in year 5, as fewer individuals enter the program. before turning net negative with $118 million in savings in year 10. Savings would reach $1.8 billion in year 12 and $4.1 billion in year 15. Cumulative budget impact over 15 years is projected to be $14.7 billion. **Conclusions:** Even under our "best case" assumptions, screening for and treating preclinical AD would result in modest annual average budget impact of $1 billion over 15 years, corresponding to $750 per treated individual. Less favorable conditions at the inception of the prevention program would reduce its budget impact but also its benefits to patients, payers and society: As prior analyses have shown, the economic value to payers in terms of preserved Quality-Adjusted Life-Years in addition to the cost offsets and to society in terms of reduced burden on caregivers will exceed program costs. In addition, not all the cost-savings from treatment will have materialized within the 15-year timeframe.
Key takeaway message: Even under optimistic assumptions for approval and coverage, screening for and treating preclinical AD would result in modest annual average budget impact of $1 billion over 15 years, corresponding to $750 per treated individual.

LB14- THE VALUE OF EARLIER INITIATION OF ANTI-AMYLOID THERAPY FOR AD.

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Background: Background: Novel anti-amyloid therapies for Alzheimer's disease (AD) can slow disease progression (1,2). Emerging blood-based biomarker tests are expanding screening and diagnostic options, which could facilitate timely treatment initiation. Research investigating the potential complementary value of these innovations is needed to inform monitoring and treatment strategies that will maximize societal benefit while containing costs. This study quantifies the long-term societal value of anti-amyloid therapy and the potential gains in value that could be achieved from earlier treatment initiation, consistent with improving monitoring of biomarkers and cognition. **Methods:** We used the Future Elderly Model (FEM)—an established and well-validated dynamic microsimulation—to estimate the long-term health and economic impacts of donanemab treatment among participants of TRAILBLAZER-ALZ 2, the pivotal phase 3 trial of donanemab (1). FEM is based on nationally representative data including the Health and Retirement Study (HRS). We estimated models of Clinical Dementia Rating–Sum of Boxes (CDR-SB) progression using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). To construct the simulation cohort, we used ADNI data to estimate the clinical trial participants' CDR-SB two years before trial entry, and then used HRS to create a simulant population matching the trial participants' baseline characteristics and estimated recent trajectory of CDR-SB. Treatment was modeled as a 29% slowing of CDR-SB progression, consistent with TRAILBLAZER-ALZ 2. We simulated individuals' remaining life without treatment (Status Quo) and counterfactual treatment scenarios: (i) Baseline Treatment initiated treatment at the clinical trial baseline (mean age 73); (ii) Earlier Treatment initiated treatment two years before trial baseline (mean age 71); (iii) additional scenarios explored initiating treatment starting as early as the presymptomatic stage (mean age 65). We quantified the total value of treatment for individuals' remaining life compared to Status Quo, including impacts on the quality of life of the persons living with AD and their care partners, medical costs, caregiving costs, and earnings. Total value was calculated as the present value at treatment initiation using a 3% discount rate and reported in 2024 USD. In sensitivity analyses, we varied the magnitude of the treatment effect

(rate of slowing) and the persistence of the treatment effect. **Results:** The simulated trajectory of CDR-SB closely aligned with the trajectory observed in the clinical trial placebo group. Total lifetime value of donanemab in the Baseline Treatment scenario relative to Status Quo was $102,000 per treated individual. Total lifetime value in the Earlier Treatment scenario was $156,000, representing a 55% increase in value resulting from two-year earlier treatment initiation. Gains in patient quality of life were the largest source of value (41%-46%), followed by reductions in medical costs (24%-27%), reductions in caregiving costs (22%-25%), gains in quality of life of care partners (6%-7%), and higher lifetime earnings (1%). Reductions in medical costs were driven by 11%-15% reductions in Medicaid spending, stemming from significantly lower nursing home use with 0.8 and 1.2 more years spent living in the community in the Baseline and Earlier Treatment scenarios, respectively. In analyses varying the treatment effect magnitude (rate of slowing) and persistence, the gains that resulted from innovations improving these two parameters were compounded when combined with earlier treatment. In additional analyses, scenarios initiating treatment at symptom onset and presymptomatic stages resulted in up to double the total value compared to Baseline Treatment, depending on treatment effect assumptions. **Conclusions:** With current anti-amyloid therapies and screening technology, we estimate there is substantial societal value to be gained from improving monitoring and treatment initiation timing. Back of the envelope calculations suggest that, for the 12.7 million Americans projected to be living with AD in 2050 (3), donanemab-like treatment could generate up to $1.3 trillion in total lifetime value if administered as in the clinical trial and $2.0 trillion if initiated just two years earlier; the availability of earlier treatments targeting the presymptomatic stage could further increase value.

Keywords: Health economics, societal value, microsimulation, anti-amyloid therapy.

Disclosures: The USC Schaeffer Center for Health Policy & Economics received funding from Lilly; the authors retained full control of research design, analyses, and conclusions. Dr. Chapel is supported by the USC Schaeffer Center—which receives funding from foundations, government agencies, individuals, and corporations, including Lilly—and grants from NIH. Dr. Aisen has research grants from NIH, the Alzheimer's Association, Lilly and Eisai, and consults with Merck, Roche, Genentech, Abbvie, Biogen, ImmunoBrain Checkpoint, AltPep, Bristol Myers Squibb, Johnson&Johnson, New Amsterdam and Neurimmune. In the last three years, Dr. Goldman reports grants from American Heart Association, Alexion, Amgen, Biomarin, Blue Cross Blue Shield of Arizona, Blue Cross Blue Shield of Massachusetts, BrightFocus, Bristol Myers Squibb, California Hospital Association, Cedars-Sinai Health System, Charles Koch Foundation, CommonSpirit, Edwards Lifesciences, Gates Ventures, Genentech, Gilead Sciences, Incyte, Johnson & Johnson, Lilly, National Institute on Aging, National Institute of Diabetes and Digestive and Kidney Diseases, Novartis, Pfizer, RA Capital, and Roche; personal fees from Edwards Lifesciences, and GRAIL. He is a co-founder of EntityRisk and holds equity in the company.

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Key takeaway message: Earlier initiation of anti-amyloid therapy, consistent with improved monitoring of cognition and biomarkers, could substantially increase the long-term societal value of treatment.

3.7. Epidemiology and clinical trials

OC01- THE EFFECT OF HERPES ZOSTER VACCINATION AT DIFFERENT STAGES OF THE DEMENTIA DISEASE COURSE: IMPLICATIONS FOR DEFINING THE STUDY POPULATION OF CLINICAL TRIALS.

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Background: Using unique natural experiments, our group has previously found that live-attenuated herpes zoster (HZ) vaccination reduced the incidence of new diagnoses of dementia in Wales and Australia. To inform future clinical trials, it is crucial to understand at which stage of the disease course of dementia the HZ vaccine has its effect. Representing the two opposing ends of the dementia disease course, the aims of this study were twofold: to determine the effect of HZ vaccination on i) new diagnoses of mild cognitive impairment (MCI) among individuals without any record of cognitive impairment, and ii) deaths due to dementia among individuals living with dementia. **Methods:** In Wales, individuals who had their eightieth birthday just after the start date of the HZ vaccination program (September 1 2013) were eligible for HZ vaccination in the National Health Service for one year whereas those who had their eightieth birthday just before were ineligible for life. This eligibility rule created comparison groups immediately on either side of the September 2 1933 date-of-birth eligibility threshold who should be similar in their health characteristics and behaviors. We used regression discontinuity analysis in detailed country-wide electronic health record data from primary care in Wales, linked to hospital records and death certificates. **Results:** Among our study cohort of 282,557 individuals who did not have any record of cognitive impairment at baseline, HZ vaccination eligibility and receipt reduced the incidence of a new MCI diagnosis by 1.5 (95% CI: 0.5 – 2.9, $p = 0.006$) and 3.1 (95% CI: 1.0 – 6.2, $p = 0.007$) percentage points over nine years, respectively. Similarly, among our study cohort of 14,350 individuals who were living with dementia at baseline, being eligible for and receiving HZ vaccination reduced deaths due to dementia by 8.5 (95% CI: 0.6 – 18.5, $p = 0.036$) and 29.5 (95% CI: 0.6 – 62.9, $p = 0.046$) percentage points over nine years, respectively. The protective effects of HZ vaccination for both MCI and deaths due to dementia were larger among women than men. **Conclusions:** Our findings suggest that the live-attenuated HZ vaccine has a beneficial effect at both ends of the disease course of dementia. There is, therefore, an evidence base from natural experiments for clinical trials of HZ vaccination to be conducted among participants without any cognitive impairment, those with MCI, as well as those with an existing diagnosis of dementia.

Keywords: Herpes zoster, vaccination, immunization, mild cognitive impairment, dementia, natural experiment, quasi-experiment. **Disclosures:** The authors declare that they have no conflicts of interest.

Key takeaway message: There is an evidence base from natural experiments for clinical trials of HZ vaccination to be conducted among participants without any cognitive impairment, those with MCI, as well as those with an existing diagnosis of dementia.

3.8. Animal model and preclinical trials in AD

LB27- BQ-141, A FIRST-IN-CLASS ORAL TAU STABILIZER, ROBUSTLY INHIBITS TAU SPREADING AND MODULATES TRANSLATIONAL BIOMARKERS IN A SEED-AND-SPREAD MODEL.

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Background: Tau aggregation and propagation are central drivers of Alzheimer's disease and related tauopathies. While several therapeutic strategies have previously reduced tau pathology in mouse models, no orally available approach has so far demonstrated inhibition of tau spreading in vivo. BQ-141 is a novel, brain-penetrant small molecule designed to stabilize native monomeric tau, thereby preventing pathological misfolding and seeding. **Methods:** Efficacy of BQ-141 was assessed in a tau seed-and-spread mouse model (hTau [P301S] brain

homogenate injection). Animals received oral BQ-141 or vehicle once daily for 6 weeks. Tau pathology was quantified using AT8 immunohistochemistry in ipsilateral and contralateral hippocampal regions. Cerebrospinal fluid (CSF) and plasma were analyzed using the human CNS NULISA® biomarker panel. **Results:** BQ-141 significantly reduced AT8-positive tau pathology by ~40% in the ipsilateral hippocampus (***$p = 0.0002$) and by ~47% in the contralateral side (*$p = 0.029$), demonstrating robust inhibition of tau aggregation and spreading. In CSF, BQ-141 lowered inflammatory (IL-6, PGF) and synuclein-related (pS129-α-synuclein) markers. In plasma, seven biomarkers fulfilled strict translational criteria and were significantly modulated, including reduced oligomeric α-synuclein ($p = 0.0035$), decreased IL-13 and CRH, and increased NPY and Calbindin-2. The strongest effect was observed for BACE1 ($p = 0.0005$), suggesting normalization of APP metabolism. **Conclusions:** This study provides the first evidence that an orally available small molecule can not only reduce tau aggregation but also robustly inhibit tau spreading in vivo. The parallel modulation of translational CSF and plasma biomarkers further underscores the disease-modifying potential of BQ-141. These findings support BQ-141 as a promising first-in-class therapeutic candidate for IND-enabling studies in Alzheimer's, PSP, and other tauopathies.

Keywords: Tau, Alzheimer's disease, small molecule, seed-and-spread model, biomarkers, neuroinflammation.

Disclosures: This work was supported by the German Federal Agency for Breakthrough Innovation (SPRIND). The author is an employee of brainQr Therapeutics GmbH. No additional conflicts of interest are declared.

Declaration of generative AI and AI-assisted technologies in the writing process: During the preparation of this abstract, the authors used ChatGPT (OpenAI, San Francisco, USA) to improve readability and clarity. After using this tool, the authors reviewed and edited the content and take full responsibility for the final version.

Key takeaway message: BQ-141, a first-in-class oral tau stabilizer, significantly reduced tau pathology and spreading by up to 47% in vivo and modulated translational CSF/plasma biomarkers, supporting its development for Alzheimer's and related tauopathies.

3.9. New therapies and clinical trials

OC04- THE SMART-HS STUDY: A TARGETED THERAPEUTIC STRATEGY FOR LATE DISEASE.

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Background and Objective: Limbic-predominant age-related TDP-43 encephalopathy (LATE) is an increasingly recognized yet underdiagnosed neurodegenerative condition that mimics Alzheimer's disease (AD). Autopsy studies have shown that LATE neuropathologic change (LATE-NC), characterized by TDP-43 proteinopathy without concurrent Alzheimer's disease pathology, affects 10–26% of individuals over 85 years old and is strongly associated with cognitive impairment. However, traditional drug development pipelines—relying on large, lengthy, and costly trials with broad inclusion criteria—have not been optimized to address LATE's unique clinical and biological profile. Recent genetic studies have linked specific single-nucleotide polymorphisms in the ABCC9 gene, encoding the SUR2 subunit of the ATP-sensitive potassium channel (K_ATP), with increased risk for LATE. Nicorandil, a specific agonist for this channel approved for angina and congestive heart failure in many countries, offers a promising therapeutic avenue. While it is under investigation in other disease contexts for its tissue-protective and metabolic effects, this is the first trial to repurpose nicorandil for modulating ABCC9 pathway specific to LATE, presenting a novel opportunity for disease modification. This Phase 2a clinical trial—SMART-HS—aims to assess the safety, tolerability, and preliminary efficacy of nicorandil in patients with probable LATE. The study also aims to explore K_ATP channel modulation as a novel mechanistic target in LATE, repurpose an existing, well-characterized drug (nicorandil) to accelerate the development of a disease-modifying intervention, identify the optimal disease stage (early cognitive impairment) for intervention and implement a biologically-informed, resource-efficient "go/no-go" strategy to evaluate drug relevance, potentially reducing trial duration and cost compared to traditional outcome-based models. **Methods:** SMART-HS is a randomized, double-blind, placebo-controlled, multicenter Phase 2a trial. A total of 63 participants, aged ≥70 with mild cognitive impairment (MCI), CDR of 0.5–1, were enrolled based on strict inclusion/exclusion criteria designed to enrich for LATE while excluding other neurodegenerative pathologies (utilizing UDPRS =< 7, Hachinski score =< 4 & AD biomarkers negative). Participants were randomized to receive either oral nicorandil 20 mg daily or placebo over a 24-month period. The primary endpoint is safety and tolerability, while secondary endpoints include efficacy measured by hippocampal atrophy on MRI and changes in cognitive performance. Exploratory aims include identifying additional MRI markers suggestive of LATE and peripheral proteomic signatures to better understand LATE and potential treatment effects. All study personnel, including investigators, participants, and assessors, were blinded to group allocation. **Results:** Recruitment for the study is now complete. Of the 133 individuals screened, 63 (47.4% of the total screened) were successfully randomized (59% female, 96% Caucasian, with a mean age of 78 years and a maximum age of 94). Among the 73 screen failures, the majority (59%) were excluded due to the presence of AD-related biomarkers. Other reasons for screen failure included withdrawal of consent (17.8%), CDR scores outside the eligible range (<0.5 or >1; 14.3%), and various other criteria (11%). **Conclusions:** SMART-HS is the first clinical trial to target LATE as a distinct neurodegenerative disease, demonstrating that a mechanistically driven intervention can be pursued even in the absence of established biomarkers. By applying rigorous clinical inclusion/exclusion criteria, we were able to approximate a biologically relevant population, setting a precedent for rational drug development in underrecognized dementias. Notably, this study was designed before the release of formal clinical diagnostic criteria for LATE, yet our framework closely aligns with the newly proposed definitions, underscoring its validity and potential for broader application in other neurodegenerative diseases with no confirmatory biological biomarkers. This trial highlights a practical approach to studying neurodegenerative diseases that lack definitive biomarkers, while also establishing the feasibility of repurposing nicorandil—guided by genetic and pharmacologic rationale—as a potential disease-modifying therapy for LATE. The implementation of a "go/no-go" design enables early determination of biological relevance and therapeutic potential, reducing the time and cost typically associated with large, traditional trials. By integrating early-stage targeting, imaging, and proteomic markers, SMART-HS introduces an efficient and scalable model that may accelerate therapeutic discovery in related conditions. Ultimately, this trial illustrates a paradigm shift in clinical trial design—anchored in precision patient selection and mechanism-based therapy—that could reshape the future of dementia research and treatment. **Keywords:** Clinical trials, AD mimics, LATE, Nicorandil.

Disclosures: The study is funded by NIH/NIA 1R01AG061111-01.

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Key takeaway message: SMART-HS is the first clinical trial targeting LATE using a repurposed K_ATP channel agonist, demonstrating a novel, biomarker-independent strategy for precision therapy design and early-stage assessment of disease-modifying potential.

OC24- AMYLOID-RELATED IMAGING ABNORMALITIES IN AN ONGOING PHASE 1 STUDY OF MIVELSIRAN, AN INVESTIGATIONAL RNA INTERFERENCE THERAPEUTIC TARGETING AMYLOID PRECURSOR PROTEIN, IN PATIENTS WITH ALZHEIMER'S DISEASE.

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Background: Amyloid-related imaging abnormalities (ARIA) are common treatment-emergent adverse events observed in patients with Alzheimer's disease (AD) treated with amyloid-beta (Aβ)-targeting monoclonal antibodies. Treatment with recently approved Aβ-targeting monoclonal antibodies has been shown to significantly increase the risk of ARIA-edema/effusions (ARIA-E), both in isolation and concurrently with ARIA-hemosiderin with microhemorrhages or superficial siderosis (ARIA-H). This risk is particularly increased in patients with a greater baseline burden of microhemorrhage or superficial siderosis, which can be indicative of cerebral amyloid angiopathy (CAA), and in patients who are APOE4 carriers. In contrast, isolated ARIA-H without concurrent ARIA-E occurs at similar rates in monoclonal antibody- and placebo-treated patients. Mivelsiran is an investigational RNA interference therapeutic in development for AD and CAA that targets amyloid-beta precursor protein (APP). In contrast to the monoclonal antibodies that promote active Aβ clearance, mivelsiran reduces the production of APP and downstream Aβ species. In this ongoing Phase 1 study, we sought to describe ARIA occurrence in patients with early-onset AD (EOAD) who received mivelsiran. **Methods:** We report data from an ongoing double-blind, placebo-controlled Phase 1 study (NCT05231785) of mivelsiran in patients with EOAD confirmed via cerebrospinal fluid (CSF) biomarkers or Aβ positron emission tomography. Evidence of ARIA or CAA at baseline did not exclude patients from enrolling, nor were participants excluded by APOE genotype. The study is being conducted in a single ascending dose part and a multiple dose part. The primary endpoint is safety and tolerability, and additional endpoints include change from baseline in CSF levels of soluble APPβ. Patients in the study undergo brain magnetic resonance imaging (MRI) at baseline and months 1, 3, and 6. MRIs are centrally read for ARIA by blinded radiologists. ARIA occurrence is reported using descriptive statistics. **Results:** As of 21 May 2025, 53 patients with EOAD were enrolled in the single ascending dose part of the study. The mean age was 62 years (standard deviation, 5), and 24% of patients were female. The baseline Clinical Dementia Rating global score was 0 in 1.9%, 0.5 in 79.2%, and 1.0 in 18.9% of patients. Fifteen patients received placebo, and 38 received a single dose of mivelsiran ranging from 25 mg to 150 mg. Patients receiving mivelsiran had robust and durable reductions in CSF soluble APPβ, with peak mean reductions from baseline up to 85.4% at Month 2. Microhemorrhages or superficial siderosis at baseline were reported in 1/13 patients (7.7%) randomized to placebo and 2/35 patients (5.7%) randomized to mivelsiran. As of 21 May 2025, no treatment-emergent ARIA-E events have been reported among patients receiving mivelsiran (0/38) or placebo (0/15). In total, 2 patients developed new ARIA-H through Month 6; both had received mivelsiran (2/38, 5.2%). One of these patients had pre-existing microhemorrhage and superficial siderosis at baseline, while the other patient did not have either present at baseline. These findings were not reported as drug-related adverse events by the investigators. No symptomatic events were reported as related to ARIA. Additional data, including from the multiple dose part, will be presented. **Conclusions:** No ARIA-E and low rates of ARIA-H were observed in patients with EOAD who received mivelsiran in a trial population that did not exclude patients with baseline microhemorrhage or superficial siderosis of any severity. New ARIA-H occurred in mivelsiran-treated patients at a comparably low rate to that reported in placebo arms of previous trials in patients with AD (1,2). Mivelsiran is a novel investigational therapeutic for AD and CAA, which does not currently show evidence of increased risk of ARIA.

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Key takeaway message: In this ongoing Phase 1 study of the novel APP-targeting RNA interference therapeutic mivelsiran, no treatment-emergent amyloid-related imaging abnormalities (ARIA)-edema/effusion events and no symptomatic ARIA cases have been observed in patients receiving mivelsiran or placebo.

OC26- ABCA1-AGONIST TREATMENT BY CS6253 AND EFFECTS ON PLASMA TOTAL AND ISOFORM-SPECIFIC APOLIPOPROTEIN E IN ELDERLY MEN AND WOMEN.

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Background: Low plasma apoE predicts Alzheimer's disease (AD) risk above and beyond APOE genotype. The apolipoprotein E (apoE) mimetic/ABCA1 agonist CS6253 has shown favorable effects on apoE and amyloid transportation in mice and monkeys. The Phase 1 single ascending dose (SAD) and multiple ascending dose (MAD) showed safety and favorable pharmacokinetics (PK). Here we present CS6253's effects from the Phase 1 MAD on plasma total apoE and apoE isoforms, and plasma small High-Density Lipoproteins (HDL). **Methods:** CS6253 or placebo was administered every 72 hours for three doses to men and women aged 50 years and older ($n = 16$), stratified 1:1 by presence of at least one APOE4 allele. Plasma and cerebrospinal fluid (CSF) were collected before any dosing via lumbar puncture and continuously via CSF catheter for 24 hours in conjunction with the 3rd/last dose. ApoE and Aβ42/40 were analyzed using NulisaSeq (Alamar), HDL particle size by 1D-gel electrophoresis (Boston Heart), and apoE isoforms by mass spectrometric immunoassay (Isoformix). **Results:** CS6253 transiently increased plasma small HDL particles ($p > 0.05$). CS6253 increased plasma total apoE by approximately 15-20% over 72 hours ($n = 12$) ($p < 0.05$). In the six subjects with APOE4/E3 genotype, the baseline plasma apoE4/E3 ratio was below 1.0; this ratio was increased by CS6253 treatment ($n = 4$) ($p < 0.02$), an effect that was not observed with placebo ($n = 2$). Additionally, the plasma Aβ42/40 ratio increased by 18% over 72 hours, primarily due to an increase in Aβ42 ($p < 0.05$). **Conclusions:** It was previously reported that CS6253 in the Phase 1 SAD-MAD study demonstrated excellent safety, tolerability, and PK. Consistent with previous findings in mouse and non-human primate models, we demonstrate here that CS6253 increased plasma small HDL particles and apoE levels, and that in APOE4/E3 carriers, the plasma apoE4/E3 ratio increased. Furthermore, CS6253 increased the plasma Aβ42/40 ratio, suggesting enhanced amyloid clearance. The apoE mimetic and ABCA1 agonist CS6253 may have therapeutic utility in AD by correcting impaired cholesterol transport.

Keywords: Apolipoprotein E, ABCA1 agonist, CS6253, Cholesterol transport, NCT05965414, Amyloid.

OC27- EFFICACY AND SAFETY OF XANOMELINE AND TROSPIUM CHLORIDE FOR COGNITIVE IMPAIRMENT IN ALZHEIMER'S DISEASE (MINDSET-1 AND MINDSET-2).

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Background: Alzheimer's disease (AD) is the most common cause of dementia (1) and is characterized by progressive cognitive decline, including impairment of memory, semantic, and executive abilities (2-4). Unmet need remains in the AD therapeutic landscape, as treatments that further improve cognitive function and address neuropsychiatric symptoms are needed (5). In previous research, the M1/M4 preferring muscarinic receptor agonist xanomeline improved cognition and psychosis in people living with AD, but cholinergic adverse events (AEs) associated with peripheral muscarinic receptor activation halted further assessment (6-8). The dual M1/M4 preferring muscarinic receptor agonist xanomeline combined with the peripherally restricted muscarinic receptor antagonist trospium chloride (X/T) is the first muscarinic agonist approved to treat schizophrenia (9). In the EMERGENT trials in schizophrenia, X/T reduced symptoms of psychosis, patients with baseline cognitive impairment showed improvement in cognitive symptoms, and there was lower risk for the AEs associated with conventional antipsychotics (10,11). Together, its mechanism of action and historical clinical data suggest that X/T may be effective in treating AD symptoms. Our aim is to evaluate the efficacy and safety of X/T for the treatment of cognitive impairment in AD (12,13). **Methods:** MINDSET-1 (NCT06976216) and MINDSET-2 (NCT06976203) are identical, global, phase 3, randomized, double-blind, placebo-controlled, parallel-group trials to evaluate the efficacy and safety of X/T for the treatment of cognitive impairment associated with mild to moderate AD (12,13). Inclusion criteria include individuals aged 60-85 years with a primary confirmed diagnosis of stage 4 or 5 AD, confirmed diagnosis of AD pathology, Mini-Mental State Examination score 12-22. Participants on acetylcholinesterase inhibitors and/or memantine must be on a stable dosage for $\geq$12 weeks prior to screening and maintain the dose for the trial duration. Exclusion criteria include a significant or severe medical condition, primary psychiatric diagnosis (eg, major depression, schizoaffective disorder, or bipolar disorder), previous exposure to X/T or currently undergoing treatment with disease-modifying anti-amyloid therapies for AD in the past 6 months, and significant pathological findings on brain magnetic resonance imaging at screening (12,13). Participants will be randomized 1:1 to either placebo or X/T. Total trial duration is approximately 57 weeks, including up to 5 weeks for screening, 24 weeks for treatment, and a 4-week safety follow-up period, with an optional 24-week open-label extension period. Participants will be titrated to the maximum suitable X/T dose based on tolerability, with the option to reduce the dose based on tolerability. **Results:** MINDSET-1 and MINDSET-2 will each enroll approximately 586 participants (12,13). The primary endpoints are change from baseline to week 24 in Alzheimer's Disease Assessment Scale–Cognitive Subscale 11 (ADAS-Cog11) and Clinician's Interview-Based Impression Plus Caregiver Input (CIBIC+) at week 24 (12,13). Secondary efficacy endpoints are change from baseline in Alzheimer's Disease Cooperative Study–Activities of Daily Living scale (ADCS-ADL) and Neuropsychiatric Inventory (NPI) total score at week 24. Safety measures include incidence of AEs, serious AEs, AEs of special interest, AEs leading to trial drug intervention discontinuation, AEs leading to trial discontinuation, and AEs leading to death, as well as clinically significant changes in vital signs, electrocardiogram tests, Columbia-Suicide Severity Rating Scale (C-SSRS) tests, and safety laboratory tests (12,13). **Conclusions:** X/T has the potential to be a first-in-class treatment for cognition in AD, with a unique mechanism of action based on muscarinic receptor agonism.

Disclosures: JLC has provided consultation to Acadia, Acumen, ALZpath, Annovis, Artery, Axsome, Biogen, Biohaven, Bristol Myers Squibb, CervoMed, Eisai, Fosun, GAP Foundation, Green Valley, Hummingbird Diagnostics, IGC, Janssen, Kinoxis, Lighthouse, Lilly, Lundbeck, LSP/eqt, Merck, MoCA Cognition, Novo Nordisk, NSC Therapeutics, Optoceutics, Otsuka, Praxis, ReMYND, Roche, Scottish Brain Sciences, Signant Health, Simcere, Sinaptica, T-Neuro, TrueBinding, and Vaxxinity pharmaceutical, assessment, and investment companies. JLC is co-founder of CNS Innovations and Mangrove Therapeutics. JLC owns the copyright of the Neuropsychiatric Inventory. JLC is supported by NIA R35AG71476; NIA R25AG083721-01; Alzheimer's Disease Drug Discovery Foundation (ADDF); Ted and Maria Quirk Endowment; Joy Chambers-Grundy Endowment. WPH is a full-time employee and equity holder at Engrail Therapeutics and a former employee of Bristol Myers Squibb. DL, JS, and CL are employees of Bristol Myers Squibb.

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Key takeaway message: MINDSET-1 and MINDSET-2 are identical, phase 3, randomized, double-blind, placebo-controlled, parallel-group trials evaluating the efficacy and safety of xanomeline and trospium chloride for the treatment of cognitive impairment in Alzheimer's disease.

LB10- PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIP OF THE GAMMA-SECRETASE MODULATOR NIVEGACETOR IN PRE-SYMPTOMATIC CARRIER PARTICIPANTS OF THE PSEN1 E280A MUTATION.

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Background: Gamma-secretase modulators (GSMs) are a promising therapeutic approach to treat and/or delay the onset of Alzheimer's disease (AD) since they reduce the production of longer, amyloidogenic amyloid-beta (Aβ) peptides (such as Aβ42) and increase the production of shorter, non-amyloidogenic species (such as Aβ37 and Aβ38) (1-3). Nivegacetor (RO7269162) is a novel, potent, and selective oral GSM in clinical development for sporadic AD (4). In the Entry-into-Human study in healthy volunteers, nivegacetor demonstrated a favorable safety and tolerability profile. Additionally, its pharmacokinetic (PK) properties supported once-daily oral administration. After single and multiple doses up to 14 days, the molecule also showed the characteristic pharmacodynamic (PD) effect expected for a GSM, reducing Aβ42 and Aβ40 monomers and increasing Aβ38 and Aβ37 monomers in both cerebrospinal fluid (CSF) and plasma (1,4,5). A Phase IIa study in sporadic AD is currently ongoing that is investigating safety, tolerability, and effects of nivegacetor on AD-related biomarkers (ClinicalTrials.gov Identifier:

NCT06402838) (6,7). Autosomal-dominant Alzheimer's disease (ADAD) accounts for < 1% of all AD cases and is the result of fully penetrant, autosomal-dominant mutations of genes coding for either gamma-secretase subunits (presenilin 1 [PSEN1] or presenilin 2 [PSEN2]) or the amyloid precursor protein (APP) (8). ADAD and sporadic AD have many clinical and neuropathological features in common, and it is assumed that they would respond to the same treatments (8). However, since PSEN1 and PSEN2 are subunits of the gamma-secretase enzyme and APP is its substrate, mutations in these three genes could alter the enzyme's sensitivity to a small molecule modulator (9). In vitro preclinical studies showed that the PSEN1 E280A mutation showed sensitivity to GSMs comparable to that of the wild-type allele, while the PSEN2 N141I and PSEN1 L166P mutations demonstrated lower sensitivity (10). This Phase Ib study was designed to investigate the PK, PD, and safety of nivegacetor and characterize the PK/PD relationship in carriers of the PSEN1 E280A mutation in Colombia to inform further clinical studies (ISRCTN Identifier: ISRCTN75434529). **Methods:** This Phase Ib, single-center, adaptive, repeated-dose study enrolled 15 presymptomatic mutation carrier participants and five cognitively unimpaired noncarrier participants aged 18–25 from the Colombian PSEN1 E280A kindred. Genotype status was kept unknown to participants and investigators by enrolling noncarrier family members. All participants received once-daily oral doses of nivegacetor for seven consecutive days in three sequential, dose-escalating cohorts (70 mg, 120 mg, and 230 mg). Plasma and CSF samples were collected to assess the PK and the effects of nivegacetor on Aβ isoforms (Aβ42, Aβ40, Aβ38, Aβ37), and safety data were recorded. **Results:** Nivegacetor was safe and well tolerated following daily oral administration of doses up to 230 mg for seven days. A total of 35 adverse events (AEs) were reported by 15 out of 20 participants, with no severe AEs and two moderate AEs considered related to the drug (vomiting and tension headache). No serious AEs or discontinuations were reported. The PK profile was consistent with previous findings in healthy volunteers and supports once-daily dosing. Nivegacetor demonstrated robust, dose-dependent PD effects. In CSF, treatment led to marked reductions in Aβ42 and Aβ40 levels, alongside pronounced increases in Aβ37 and Aβ38 levels. Similar dose-dependent reductions in Aβ42 and Aβ40 levels were observed in plasma in PSEN1 E280A mutation carrier participants. In this group, the maximum mean percentage change from baseline in plasma levels of Aβ42 was achieved on Day 7 at around 4 hours post dose and levels were reduced by 49%, 56%, and 72% (versus baseline) following daily oral administration of 70 mg, 120 mg and 230 mg nivegacetor, respectively. The magnitude of all Aβ changes in plasma and CSF was comparable between PSEN1 E280A mutation carrier participants and noncarrier participants. A strong correlation was also observed between Aβ monomer changes in plasma and in CSF. **Conclusions:** This study provides the first characterization of the PK/PD relationship of nivegacetor in presymptomatic carrier participants of the PSEN1 E280A mutation. The results demonstrate that nivegacetor robustly modulates gamma-secretase processivity in this population, with PK/PD and safety/tolerability profiles comparable to those observed in healthy volunteers. In conclusion, the presence of the PSEN1 E280A mutation in the drug's target enzyme did not significantly alter its PD effects. These findings provide important data to inform dose selection for future efficacy trials of nivegacetor in individuals with the PSEN1 E280A mutation.

Keywords: Gamma secretase modulator, autosomal-dominant Alzheimer's disease, pharmacokinetics, pharmacodynamics. **Disclosures:** Agnès Poirier, Enrique Gaspar, Dominik Lott, Irene Gerlach, Thomas Mueggler, Stefan Sturm, Tayo Bodede, and Rosanna Tortelli are employees of F. Hoffmann-La Roche Ltd and own stock or stock options in F. Hoffmann-La Roche Ltd. Tianxu Yang, Agnès Portron, and Stella Yilmaz are employees of F. Hoffmann-La Roche Ltd. David Aguillón is supported by grants from National Institutes of Health (NIH). He reports receiving payment or honoraria from Eli Lilly Colombia for serving on an advisory board. Robert Alexander is supported by grants R01AG058468, R01AG055444, and R01AG074983 from the National Institute on Aging (NIA). He reports his institution has received grants or contracts from Eli Lilly and Roche. He reports receiving consulting fees from Lundbeck, Vigil Neurosciences, and Novartis. He reports serving as a member of the Data Safety Monitoring Board for the ImmunoBrain study IBC-01-01. David Gordon has consulted and/or received honoraria/personal fees from Roche for work related to the clinical study [ISRCTN75434529] stated in the abstract. He reports his institution has been awarded an R01 grant from the National Institutes of Health based on intellectual property from the Roche clinical study; that will support another study not sponsored by Roche. Kalbinder Mahil has no conflicts of interest to disclose. This study was funded by F. Hoffmann-La Roche Ltd. Editorial support for the development of this abstract was provided by Thywill Sabblah, PhD, funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

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Clinical Trial Registration: https://www.isrctn.com/ISRCTN75434529.

Key takeaway message: Nivegacetor was safe and showed robust, dose-dependent Aβ modulation in presymptomatic PSEN1 E280A carriers. The PK/PD relationship was comparable to non-carriers, showing the mutation does not alter nivegacetor's effect.

LB11- ORAL BLARCAMESINE PHASE IIB/III TRIAL CONFIRMS IDENTIFIED PRECISION MEDICINE PATIENT POPULATION – SIGNIFICANT BROAD CLINICAL AND QUALITY OF LIFE IMPROVEMENTS FOR EARLY ALZHEIMER'S DISEASE PATIENTS.

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Background: There are no approved oral disease-modifying treatments for Alzheimer's disease (AD) with the ability to prolong time in a stable disease state and with clinically meaningful outcomes clear to patients and caregivers. **Methods:** Blarcamesine, for which Market Authorisation Application (MAA) is currently under review by EMA, underwent a randomized, double-blind, placebo-controlled, 48-week Phase IIb/III ANAVEX2-73-AD-004 trial with prespecified gene or GWAS identified genetic variant populations related to the mechanism of the pharmacological intervention. **Results:** Treatment of Blarcamesine demonstrated significant clinical benefit in all primary, secondary and exploratory clinical endpoints in two Precision Medicine populations ABCLEAR2 and ABCLEAR3, representing up to ~70% of the global population. ABCLEAR3 blarcamesine group vs. placebo at Week 48 (ADAS-Cog13 difference of −4.179; P = 0.0005; ADCS-ADL difference of +3.131; P = 0.0111; CDR-SB difference of −1.076; P = 0.0002; QoL-AD Patient improvement from baseline of 0.334 and difference of 1.848; P = 0.0095). The clinical outcomes were strongest in the blarcamesine 30 mg cohort (ADAS-Cog13 difference of −4.739; P = 0.0004; ADCS-ADL difference of +4.245; P = 0.0024; CDR-SB difference of −1.414; P < 0.0001; QoL-AD Patient improvement from baseline of 0.182; and difference of 1.651; P = 0.0392). No ARIA events were reported. There were no deaths related to the study drug (1). **Conclusions:** Blarcamesine

group vs. placebo was 75.9% reduction in decline at 48 weeks in the total blarcamesine group and was 84.7% in the 30 mg dose group by, respectively on the prespecified co-primary cognitive endpoint ADAS-Cog13 in the ABCLEAR3 population. Blarcamesine demonstrated consistently significantly improved clinical effect for all clinical endpoints, which was in accordance with significant and further reduced brain atrophy. Furthermore, a significant absolute improvement in Quality of Life (QoL-AD) scores indicating a reversal of negative trajectory for Alzheimer's disease patients from baseline to end of trial was observed. Evidenced by the Precision Medicine paradigm, including in a prespecified ABCLEAR1 population, a consistent significant improvement for all clinical endpoints in the ABCLEAR2 and ABCLEAR3 populations, respectively, was demonstrated. Coupled with a convenient once daily, oral pill administration, blarcamesine restoring impaired autophagy could represent a novel treatment option for up to ~70% of early AD patients benefiting from further improved outcomes using directed Precision Medicine to alleviate significant medical and economic burden.

Key takeaway message: Blarcamesine, Precision Medicine, autophagy, randomized clinical trial, GWAS, ADAS-Cog, ADCS-ADL, CDR-SB, QoL-AD.

LB21- ESTIMATING THE 10-YEAR TIME-SAVINGS BENEFITS OF LECANEMAB TREATMENT.

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1. Pentara Corporation - Millcreek (United States), 2. Eisai Inc. - Nutley (United States).

Background: Monoclonal antibodies (mAbs) against amyloid-b have been shown to significantly slow the rate of cognitive and functional decline in early Alzheimer's disease (AD) clinical trials. Throughout the open label extension (OLE) phase of the CLARITY-AD study, lecanemab (which acts by targeting toxic soluble Ab species as well as insoluble plaques) has previously been shown to provide ongoing benefits out to 48 months, with time savings of 11 months by the end of this OLE period when compared to a historical, matched external control population from ADNI. To contextualize the continued benefits of treatment beyond 48 months, data from the CLARITY-AD OLE was used to model disease progression with or without treatment for up to 10 years. **Methods:** Clinical Dementia Rating-Sum of Boxes (CDR-SB) data from participants in the observational ADNI study were used to model progression curves through the course of Alzheimer's disease, estimated out to 10 years. The observed treatment effect results from the CLARITY-AD 48-month OLE were used to modify these progression curves to represent the benefits of treatment over 10 years, and the effects of stopping treatment at time points before 10 years. The slowing rates of progression were estimated from a Bayesian Gaussian Process model fitted on summarized slowing data from 19 studies of mAbs against amyloid-b for AD treatment and then adjusted to the rates of slowing with lecanemab treatment. This model accounted for the severity of AD when treatment was initiated and the duration of treatment. Estimated slowing rates were taken from the model at the baseline severity observed in CLARITY-AD OLE, with adjustments made for the efficacy of lecanemab. Slowing rates after treatment discontinuation were estimated using data from the 19 mAb studies, in which participants were taken off treatment and a decrease in the accumulation of treatment benefit was observed. **Results:** Continuing treatment with lecanemab led to a greater delay in progression compared to stopping treatment. Similar to the time savings over 48 months that was observed for the CLARITY-AD OLE, our model estimated approximately 12 months of time savings over 48 months, thus validating our model. Next, when starting treatment at the MCI and mild AD stages and looking at disease slowing benefit over 10 years, ongoing lecanemab treatment is estimated to delay progression by 2.5 years when treatment is continued for 10 years, while stopping treatment after 1 year is estimated to delay progression by 1 year over 10 years. In CLARITY-AD participants at the earliest stages of disease (defined as having low-amyloid at baseline), those who continue treatment for 10 years are projected to have time savings of 4.4 years, while those who stopped after 1 year are expected to have time savings of 1.8 years over 10 years. These results from the low-amyloid sub-group suggest that initiating treatment early leads to additional delays in progression and additional time saved. Based on these models, each additional year on therapy after 1 year could delay disease progression by an additional 1.9 months over 10 years for the full group. Our model projects that an individual treated for 10 years will have 44% less disease progression over the treatment period. **Conclusions:** Lecanemab is most effective when starting early and continuing for as long as possible. Models built from the full CLARITY-AD population suggest that individuals who initiate treatment with lecanemab at the earliest signs of disease (the low amyloid group) will see the greatest delay of disease progression. Further, these models indicate that each additional year on lecanemab could further delay disease progression compared to stopping treatment, even long after plaque is expected to have been cleared.

Keywords: Amyloid, disease progression, time-savings, lecanemab.

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

Key takeaway message: Models suggest that initiating lecanemab at the earliest signs of disease will provide the greatest delay of disease progression and that each additional year on lecanemab could further delay disease progression compared to stopping treatment.

3.10. Translational research

LB30- DISCOVERY OF BLOOD-BASED MICRORNAS THAT CHARACTERIZE CEREBRAL AMYLOID ANGIOPATHY.

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Background: Cerebral Amyloid Angiopathy (CAA) is an underdiagnosed cerebrovascular condition that contributes to lobar intracerebral hemorrhage and cognitive decline (1). CAA is a common comorbidity in Alzheimer's disease (AD) and is also implicated in amyloid-related imaging abnormalities (ARIA) observed in patients treated with anti-amyloid therapies. Current diagnostic approaches rely on a combination of clinical and imaging-based features; however, the v2.0 Boston criteria for probable CAA demonstrate only 64.5% sensitivity, leaving more than one-third of cases undetected (2). While cerebrospinal fluid (CSF) Aβ40 levels offer modest discriminatory value (AUC 0.83), lumbar puncture is invasive and impractical for population-level screening (3). Blood-based, plasma Aβ measures, such as the Aβ42/Aβ40 ratio, have inadequate sensitivity (48.5%) for CAA detection (4). Therefore, new blood-based biomarkers are needed for early, accurate, and scalable screening of CAA. MicroRNAs (miRNAs) are established diagnostic tools in oncolo654y and are under investigation in several neurological diseases (5,6). We therefore hypothesized that circulating plasma miRNAs could classify CAA with clinically useful accuracy. **Methods:** Blood plasma samples were obtained from participants enrolled in the Massachusetts Alzheimer's Disease Research Center. CAA severity was scored on postmortem brain tissue using the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) and corresponding clinical and neuropsychological measures. Total RNA was extracted from plasma, and small RNA libraries were prepared and sequenced on an Illumina platform (paired-end, 95 bp). Raw reads underwent adapter trimming, quality filtering, and alignment to miRBase v22 and hg38. Unique molecular identifiers were applied to collapse PCR duplicates. Canonical miRNAs and isomiR variants were quantified, with low-abundance features excluded (counts per million $\leq$2 in $\geq$75% of samples). Normalization was performed using trimmed mean of M-values (TMM), and batch effects were corrected with ComBat. Feature

selection followed a filter–wrapper approach: (i) univariate ROC analysis (AUC $\geq$0.60, FDR-adjusted $p < 0.10$), followed by (ii) L1-penalized logistic regression with nested cross-validation. The final classifier was trained on 90% of the dataset and tested on an independent 10% holdout cohort. Diagnostic performance was evaluated by ROC-AUC with bootstrap-derived 95% confidence intervals. **Results:** In this initial proof-of-concept study, the resulting miRNA panel distinguished CAA cases from controls with an AUC of 0.843 ($p < 0.0001$) in the independent test set. At a balanced cutoff, the classifier achieved 95% sensitivity, 37% specificity, 75% positive predictive value (PPV), 79% negative predictive value (NPV), with an odds ratio of 11.25. Subgroup analyses demonstrated consistent performance across moderate and severe CAA, sex, and APOE ε4 status. Feature importance analysis identified reproducible contributions from a subset of miRNAs implicated in vascular integrity, endothelial function, and amyloid processing pathways. **Conclusions:** These early findings suggest that plasma microRNAs may serve as a promising blood-based classifier of CAA, with performance exceeding existing blood biomarkers. However, larger and independently collected cohorts will be critical to confirm robustness, reproducibility, and clinical utility. Given the high performance of many recent Alzheimer's blood-based assays (e.g., p-tau217), these results should be viewed as a preliminary but encouraging step toward a scalable diagnosis of CAA. If validated, this assay could aid clinical trial design, by enabling stratification or enrichment based on CAA burden and informing ARIA-risk management, thereby reducing outcome variability without sacrificing generalizability. Beyond CAA, blood-based microRNAs hold potential for characterizing other brain pathologies and comorbidities, offering a broad platform for advancing precision diagnostics in neurology (7).

Keywords: microRNA, biomarker, cerebral amyloid angiopathy.
Data Deposition: Data can be shared upon reasonable request.
Disclosures: DWS and NCF are shareholders of Gatehouse Bio who received grants from the Alzheimer's Drug Discovery Fund and the Carol & Gene Ludwig Family Foundation. AWB is a shareholder of AbbVie. SEA received an R21 grant from the NIH. PKW and SEA declared no competing interests.

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Key takeaway message: Plasma microRNAs show early promise as a blood-based classifier of CAA, exceeding current fluid biomarkers. If validated, this scalable assay could enable diagnosis, improve ARIA-risk management, and support trial stratification in Alzheimer's disease.

3.11. Beyond amyloid and tau

OC15- PROTEIN-BASED DIAGNOSIS AND ANALYSIS OF CO-PATHOLOGIES ACROSS NEURODEGENERATIVE DISEASES: LARGE-SCALE AI-BOOSTED CSF AND PLASMA PROTEOMIC CLASSIFIER.

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Background: Diagnosing the four most common neurodegenerative diseases (NDs), Alzheimer's disease (AD), Parkinson's disease (PD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD), is challenging because clinical phenotypes overlap, and mixed pathologies are frequent. Cerebrospinal fluid (CSF) or plasma assays for amyloid-β and phosphorylated tau (ptau) are sensitive for AD, yet reliable fluid markers for α-synuclein- or TDP-43-driven disorders remain elusive. Binary "case-versus-control" models do not account for co-existing pathologies, so there is a need to develop new molecular models that can be used for multi-disease prediction that are also able to quantify mixed pathologies. Large-scale proteomics now quantifies thousands of proteins per sample, enabling data-driven, multi-class diagnostics. An effective model must (i) handle several NDs simultaneously, (ii) assign interpretable probabilities that capture overlapping pathologies, (iii) generalize across cohorts without retraining or imputation, and (iv) extend to related conditions such as autosomal dominant Alzheimer's disease (ADAD) and Parkinson's Disease Dementia (PDD), and (v) capture neuropathological and cognitive end-points. **Methods:** We leveraged proteomic data (SomaScan) from more than 4500 CSF and plasma samples to develop and validate an explainable, boosting-based multi-class AI-classifiers. We comined all proteins present in the 7K and 5K panels in order to make this model easy to implement across studies. After identifying disease-specific proteins, feature numbers were further reduced to 400 (CSF) and 700 (plasma) by applying a variance threshold ($\sigma^2 > 0.01$) followed by F-test ranking. A gradient-boosted classifier (LightGBM (1) with SMOTETomek (2) balancing method) was trained on 70% of the discovery data to output joint probabilities for AD, PD, FTD, DLB, and cognitively normal (CO). The trained classifier, applied without retraining or imputation, was evaluated on >10,000 independent samples from GNPC v1.3, ROSMAP, and Indiana ADRC, accurately identifying established diagnoses across heterogeneous cohorts. The model high performance was also tested in samples from ROSMAP and Knight-ADRC by analyzing the association of the different disease probabilities with and standard neuropathological trails and cognitive measures. Finally, cases labelled as "Unknown," "MCI" or "other" were re-classified: most were reassigned to the single diagnosis supported by biomarkers or neuropathology, like CSF AT status, ptau217, Amyloid PET Imaging, or Braak Stage. **Results:** Regarding the model performance, in the 30% held-out testing subset, the CSF classifier achieved a weighted AUC-ROC of 0.97 (macro AUC 0.95; overall accuracy 88%), whereas the plasma model reached 0.88 (macro AUC 0.79; overall accuracy 73%). All CSF per-class AUCs exceeded 0.91; in plasma, AUCs for the major diagnostic groups (AD, PD, CO) were $\geq$ 0.88. When internal full dataset (training + testing) was evaluated, both models maintained AUCs > 0.96 and accuracies > 88% for the major disease groups. Notably, AD diagnosis was supported by amyloid- and tau-based biomarkers, whereas PD, FTD, and DLB remained purely clinically defined, a limitation given the lack of equally specific biomarkers and the symptomatic overlap among these disorders. Without retraining or imputation, we applied the models to related diagnostic categories and external cohorts. Autosomal-dominant AD (ADAD, $n = 114$) samples showed a mean AD probability of 0.65 and a secondary PD signal (0.23), suggesting concomitant α-synuclein pathology. Prodromal PD samples were classified as PD in 96.4% of cases (mean PD probability 0.94). Parkinson's-disease dementia (PDD) samples split between PD (0.64) and AD (0.28) probabilities, consistent with mixed pathology. In ROSMAP plasma, the model distinguished neuropathologically confirmed AD from controls with an AUC of 0.80, and similar biomarker concordance was observed in Indiana-ADRC. Across the multi-site GNPC dataset, CSF AUCs were 0.84 (AD) and 0.72 (CO); plasma AUCs were 0.72 (AD) and 0.74 (PD). Exploring into the neuropathological trails and

cognitive tests, model outputs tracked independent biological measures: in CSF, higher final CDR, Braak stage, and neuritic-plaque burden were associated with AD probabilities. In ROSMAP plasma, AD probability increased with plaque and tangle burden, decreased across more favorable CERAD and NIA–Reagan grades, and was inversely related to Mini-Mental State Examination (MMSE) and episodic-memory scores. Clinical controls or "unknown" cases re-classified as CO were enriched for A-T- status and amyloid-PET negativity (73.2% in both CSF groups). Conversely, those re-classified as AD were enriched for ptau217-or amyloid-positive profiles (79.8% of clinical controls, 75.8% of unknowns). Exemplary re-classified AD cases exhibited Braak stage 5, CERAD 1, high NIA–Reagan likelihood, marked episodic-memory decline and MMSE < 24, underscoring the clinical validity of the model's assignments, and with the statistically significance tests. Samples shifted to the PD category exhibited severe parkinsonism and satisfied CAPIT diagnostic criteria. **Conclusions:** High-throughput aptamer proteomics now lets us profile thousands of proteins at once. Using these data, we built the first fluid-based atlas spanning AD, PD, FTD, DLB and CO individuals, and distilled it into an individual-level interpretable five-class model. The classifier not only distinguishes the diseases with high accuracy but also yields a continuous probability vector that quantifies mixed pathology. Performance remained strong in >10,000 external samples, and probabilities tracked gold-standard neuropathology (neuritic plaques, Braak, NIA-Reagan) and cognition (MMSE, episodic memory). Because it depends only on protein levels, the model is agnostic to age, sex, genotype and cohort, enabling plug-and-play use in observational studies and trials. A single blood draw can refine inclusion criteria, stratify participants and monitor treatment effects, advancing fluid proteomics from single markers to a systems-level precision-medicine tool for neurodegeneration.

Keywords: Large-scale proteomics, biomarker, neurodegenerative diseases, clinical trial.

Clinical Trial Registry: None.

Data Deposition: None.

Disclosures: CC has received research support from GSK and EISAI. CC is a member of the scientific advisory board of Circular Genomics and owns stocks. CC is a member of the scientific advisory board of ADmit. There is an invention disclosure for the prediction models, including protein IDs, alternative proteins and weights, cut off and algorithms. CC has served on scientific advisory for GSK and Novo Nordisk.

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Key takeaway message: A multi-class AI classifier using CSF and plasma proteomics distinguishes AD, PD, DLB, FTD, and controls, quantifies mixed pathologies, and generalizes across 10,000+ samples, supporting scalable precision diagnostics for neurodegeneration.

OC16- IDENTIFYING AND STRATIFYING ALZHEIMER'S DISEASE USING CIRCULAR RNA BIOMARKERS IN BLOOD.

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Background: Circular RNAs (circRNAs) are covalently closed non-coding RNAs especially enriched in the brain and shown to be dysregulated in Alzheimer's disease (AD). Early detection of AD is critical in delaying irreversible neurodegeneration. We previously found several circRNAs correlated with AD severity measurements in the cortex. The high stability and tissue-specific regulation of circRNAs and their ability to cross the blood-brain-barrier highlight their utility as blood-based diagnostic biomarkers, therapeutic targets, and disease progression trackers for brain disorders. Using the current largest transcriptomic whole blood dataset, we analyzed the utility of blood circRNAs to accurately diagnose AD and predict risk of disease progression and benchmarked the models with currently developed plasma protein biomarkers. **Methods:** We generated whole blood bulk RNA-seq ($n = 1234$) from the Knight ADRC and performed cross-sectional models of clinical status to identify circRNAs associated with AD. CircRNAs were called and QCed using two circRNA bioinformatic tools. Logistic regression models were used to identify blood circRNAs associated with clinical diagnosis of AD and related-phenotypes. Prediction models were created for clinical status and later tested against amyloid PET and CSF biomarker positivity. The models included samples with available biomarker data from CSF (Aβ42 and pTau181; 283 A-T-, 181 A + T+), brain imaging (Amyloid PET; 520 A-, 256 A+), and plasma (pTau217; 502 T-, 413 T+). The circRNA model was also evaluated for its ability to assess risk of disease progression (610 CO, 78 AD progressors). Sensitivity analyses were done and stratified by sex and APOE status. To further validate the model's diagnostic performance, it was evaluated in individuals with autosomal dominant AD and across diverse genetic ancestries. Furthermore, specificity analyses were performed against PD, DLB, and FTD. Prediction models were performed using 100 iterations of undersampling to balance the sample sizes of the cases and controls per phenotype. **Results:** A total of 34 blood circRNAs passed status FDR correction as being differentially altered in clinically diagnosed AD patients vs healthy controls. These 34 circRNAs include some derived from AD-GWAS significant loci, and is overall enriched for synaptic function pathways. As blood is a medically relevant tissue for diagnosis, we inferred diagnostic accuracy of the 34 FDR significant blood circRNAs using regression modeling. This circRNA model, utilizing a single cutoff, was initially developed solely based on clinical diagnosis. Recent biomarker development studies assess biomarkers related to amyloid accumulation rather than clinical status to identify individuals with underlying AD pathology. For this reason, we evaluated the accuracy of circRNA for biomarker-defined status. The model generated a robust AUC of 0.945 in Amyloid and Tau (AT) biomarker confirmed patients vs AT biomarker negative controls, and 0.825 for PET amyloid positivity, demonstrating strong discriminatory power that is comparable to the current standard of care modalities. Moreover, the model showed similar high performance in both sexes, as well as in APOE4+ and APOE4-individuals, and perfectly classified AD cases from controls in 92 African Americans. We further validated the model in autosomal dominant AD (ADAD) using blood samples from individuals in the independent Dominantly Inherited Alzheimer Network (DIAN) cohort. Between affected ADAD mutation carriers ($n = 48$) and non-carriers ($n = 132$), the blood circRNA model had an AUC of 0.928 (0.994 for females) in differentiating ADAD from non-carriers. Additionally, we further sought to determine the AD specificity of the model compared to non-AD dementias ($n = 276$ PD, $n = 26$ DLB, $n = 11$ FTD). The AD blood circRNA model did not show any significant predictive value in non-AD dementias (PD AUC = 0.440, PD + DLB + FTD AUC = 0.450, PD + DLB AUC = 0.449, PD + FTD AUC = 0.432) vs AD dementia, thus confirming its specificity to AD-associated dementia. Lastly, we explored the capabilities of circRNAs to predict progression to symptomatic AD. We

interrogated a subset of samples from patients who at the time of blood draw progressed from control to AD by the last clinic visit and compared it to a model using plasma pTau217 alone. The pTau217 model had lower AUC (AUC = 0.788; HR = 2.27, 95% CI: 1.04-4.96) compared to the blood circRNA model (AUC = 0.87; 2.92, 95% CI: 1.63-5.23) using the same patient samples. Moreover, correction for sex resulted in further improvements in the ability of the circRNA model to predict risk of AD progression in asymptomatic individuals (AUC = 0.956 for male and AUC = 0.927 for female). **Conclusions:** Identifying circRNAs with strong associations to the pathophysiology and etiology of AD is advancing diagnostic research and enhancing our understanding of AD circRNA expression across disease progression. These results support the use of blood-based circRNAs as non-invasive and scalable biomarkers for detecting AT pathology, with robust performance when compared to brain imaging, CSF, and other plasma biomarkers. These results suggest that the 34 identified brain-derived circRNAs offer a novel and comprehensive approach for accurately and reliably diagnosing AD with the added specificity to distinguish among different forms of dementia and possibly predicting disease progression over time. Further studies are needed to validate the model's performance across different types of co-morbidities and risk factors.

Keywords: Alzheimer's disease, circular RNA, pTau217, blood-based biomarkers.

Disclosures: BP is a consultant for Circular Genomics. CC has received research support from GSK and EISAI. CC is a member of the scientific advisory board of Circular Genomics and owns stocks. CC is a member of the scientific advisory board of ADmit. CC has served on scientific advisory for GSK and Novo Nordisk. NM is a co-founder and Chief Scientific Officer with equity in Circular Genomics. The rest of the authors declare no competing interest.

Key takeaway message: Identifying circRNAs with AD predictive ability will further AD diagnostic research and lead to a better understanding of how AD circRNA expression changes throughout disease progression.

OC17- LARGE-SCALE PLASMA PROTEOMIC PROFILING UNVEILS DIAGNOSTIC BIOMARKERS AND PATHWAYS FOR ALZHEIMER'S DISEASE.

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Background: Proteomic studies have been instrumental in identifying brain, cerebrospinal fluid, and plasma proteins associated with Alzheimer's disease (AD). Although most AD proteomic studies focus on the brain or cerebrospinal fluid (CSF), very few studies have been conducted in plasma. These plasma proteomic studies have analyzed around <700 AD cases and controls. Plasma ptau217 is very effective at predicting amyloid positivity but is a proxy for brain amyloidosis, not overall dementia. New anti-Aβ therapies can remove Aβ deposits as seen in amyloid PET scans, and studies show ptau217 levels decrease with amyloid removal, even if neurodegeneration continues. Therefore, additional biomarkers beyond tau and Aβ are needed to track overall disease status and learn whether they could be employed to develop innovative predictive models. **Methods:** A large-scale study examined nearly 7000 plasma proteins from 1270 people with clinical Alzheimer's disease (AD) and 2096 cognitively normal individuals. A three-stage approach was used (discovery, replication, and meta-analysis) to identify proteins associated with AD. This method identified 456 significant aptamers (416 proteins) that showed consistent results in both discovery and replication stages, that were further validated using two external datasets (ROSMAP and GNPC), confirming their reliability. These results were then compared with some well validated CSF biomarkers as well as amyloid imaging. **Results:** Among the 416 proteins identified in the study, including 168 proteins (193 aptamers) novel proteins associated with Alzheimer's disease (AD). These included proteins like SPC25, CLU, and PPBP involved in signal transduction, and SPARC, NCAM1, and VEGFA involved in endothelial pathways. Additionally, 122 proteins (123 aptamers) from this study have support from previous plasma studies. In order to develop Aβ and tau-independent biomarkers, we used AI to identify seven-proteins that predicted clinical AD and biomarker status. As Alzheimer's disease pathology may starts between 15 and 20 years before onset, current biomarker development is focused on identifying individuals with AD pathology based on Amyloid-PET or CSF amyloid/tau status. The predictive power for the seven-protein model was significantly higher than that for clinical status, showing an AUC of 0.88 for amyloid positivity, 0.89 for CSF amyloid/tau status, and 0.88 for plasma ptau217 status. In addition, when testing if this model could identify those individuals that were cognitively normal at blood draw but later would progress to symptomatic AD, we found a strong association (hazard ratio = 2.71; p = 1.99×10-4), confirming that in fact this model can identify people with AD pathology and not only clinical status. To further compare our predictive model with well-established AD biomarkers, we analyzed plasma ptau181, ptau217, Aβ40, Aβ42, NEFL, and GFAP measured using the Alamar/Nulisa. The seven-protein model (AUC = 0.794) demonstrated comparable predictive power to ptau217 (AUC = 0.79) and surpassed Aβ40, Aβ42, NEFL, GFAP, and ptau181. This model was further validated in orthogonal platforms including Alamar and Olink and replicated in four independent cohorts. Further analysis of the predictive performance of this model with other non-AD dementia was examined and showed low overlap with Parkinson's Disease (PD) and Dementia with Lewy Bodies (DLB), but not with Frontotemporal Dementia (FTD). Larger studies on these groups are needed to create disease-specific predictive models to better assess how specific the current model is for Alzheimer's disease. **Conclusions:** In summary, this large-scale plasma proteomic study identified proteins associated with AD, developed a robust prediction model that accurately predicted AD status, that also identify individuals that progress to symptomatic AD. Amyloid-targeting therapies, like Lecanemab and Donanemab, are designed to reduce amyloid plaques in the brain, which are a hallmark of Alzheimer's disease. Therefore, biomarkers that are a direct proxy of AD pathology such as CSF Aβ, tau or plasma ptau217 may become negative as amyloid plaques are being removing. Here we present a model that is independent of Aβ, or ptau217 that may address this problem, is robust, replicable and specific to Alzheimer's disease. **Key takeaway message:** This large-scale plasma proteomic study identified proteins associated with AD, developed a robust prediction model that accurately predicted AD status, that also identify individuals that progress to symptomatic AD.

OC18- BIOMARKERS ASSOCIATED WITH RESPONSE TO TREATMENT OF EARLY STAGE AD WITH PEPINEMAB, ANTI-SEMA4D BLOCKING ANIBODY.

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Background: Semaphorin 4D (SEMA4D) is upregulated in diseased or damaged brains during progression of Alzheimer's Disease (AD) and Huntington's Disease (HD) (1). Engagement of SEMA4D with its Plexin B1/B2 receptors triggers astrocyte reactivity and a chain of downstream pathogenic events that drive disease progression, including microglial activation (2-3), disruption of vascular integrity (4), and synaptic dysfunction (1). Multiple lines of genetic evidence have reported an association between activation of the SEMA4D/PlexinB1 signaling pathway and amyloid plaque load, tau tangle density, and cognitive decline in AD (5-7). Pepinemab, a SEMA4D blocking antibody, was well tolerated and demonstrated evidence of clinical benefit in a previously completed Phase 2 study in patients with HD. Pepinemab prevented

metabolic decline, reduced levels of plasma GFAP, and slowed cognitive decline ($p = 0.007$) (8). These results suggested that preventing astrocyte activation and reducing brain inflammation with pepinemab could be an attractive alternative or complement to anti-Aβ or tau-targeted treatments for AD. **Methods:** The randomized, double-blind, SIGNAL-AD trial was designed to evaluate safety and efficacy of pepinemab in people with MCI or mild dementia due to AD. 50 individuals were randomized 1:1 to pepinemab or placebo, and treated for 12 months by IV infusion, Q4W. Key eligibility criteria included amyloid positive (PET or CSF), CDR-GS 0.5-1, MMSE 17-26. The primary objective of the study was safety and tolerability. Additional prespecified assessments included target engagement, plasma fluid biomarkers, multiplex proteomic analysis of CSF, as well as cognitive measures and subgroup analyses for baseline MMSE 22-26 and 17-21. **Results:** Pepinemab was well tolerated with no discontinuations. Drug levels in CSF were detected at or above target saturation levels with direct evidence of target engagement via presence of drug/target complexes. Additional evidence of target engagement was observed through downstream effects of antibody treatment, including reduction in key biomarkers associated with neuroinflammation (plasma GFAP), synaptic loss (CSF SNAP25), tau accumulation (plasma p-tau 217 and CSF GAP-43) and AD disease progression in a prespecified subgroup of early stage patients with baseline MMSE scores of 22-26 with positive trends of change in multiple cognitive measures for this population. Proteomic Olink analysis of CSF identified additional biomarkers linked to the frequency of an astrocyte subpopulation (Ast10) reported by others to be regulated by the SEMA4D/PlexinB1 signaling pathway and associated with cognitive decline (5). **Conclusions:** Statistically significant changes in biomarkers associated with astrocyte reactivity, microglial activation, compromised vasculature, tau spreading and accumulation, as well as positive trends in cognitive measures were observed for subjects with late MCI and mild dementia due to AD. The results support an important role for SEMA4D/PlexinB1 signaling in triggering a chain of pathogenic events that drive disease progression and identify plasma and CSF fluid biomarkers that may predict response to treatment with this non-amyloid and non-tau targeted agent.

Clinical Trial Registry: NCT04381468; https://clinicaltrials.gov.

Keywords: SEMA4D and PLXNB1 signaling, clinical trial biomarkers, reactive astrocytes, neuroinflammation.

Disclosures: M Zauderer and E. Evans are employees, stockholders, and officers of Vaccinex., T. Fisher, L. Balch, V. Mishra, E. Gersz, J. Leonard, C. Mallow are employees and stockholders of Vaccinex.

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Key takeaway message: Significant changes in biomarkers associated with astrocyte reactivity, microglial activation, compromised vasculature, tau spreading and accumulation were observed in subjects with late MCI and mild dementia due to AD treated with pepinemab, anti-SEMA4D blocking antibody.

OC28- STOMP AND STAMINA CLINICAL TRIALS OF SENOLYTICS IN ALZHEIMER'S DISEASE TREATMENT AND PREVENTION.

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Background: Senolytics—agents that selectively eliminate senescent cells—have emerged as a promising geroscience-guided strategy for preventing and treating Alzheimer's disease (AD) (1). In preclinical models, senescent cells accumulate in the aging brain and contribute to neuroinflammation, tau and amyloid pathology, and cognitive decline. Intermittent senolytic treatment reduces pathology and improves cognitive function. Building on this foundation, early-phase human studies have begun to evaluate the feasibility, safety, and biological activity of senolytics in both symptomatic and at-risk older adults. Here, we describe findings from two Phase 1 trials and discuss ongoing efforts to translate senolytics toward clinical application in AD (2-4). **Methods:** Two open-label Phase 1 trials—SToMP-AD and STAMINA—evaluated 12 weeks of intermittent oral dasatinib plus quercetin (D + Q) in older adults. SToMP enrolled participants with symptomatic AD and assessed central nervous system (CNS) penetrance, safety, CSF and plasma biomarkers, and brain imaging. STAMINA enrolled older adults with mild cognitive impairment (MCI) and slow gait speed and evaluated changes in cognition, physical function, and blood-based biomarkers. Both studies measured senescence-associated secretory phenotype (SASP) factors, inflammatory and AD-related proteins, and markers of neuronal injury. In SToMP, an exploratory transcriptomic immune stress signature, the conserved transcriptional response to adversity (CTRA), was also assessed. Pre-to post-treatment comparisons were analyzed using paired t-tests or Wilcoxon signed rank tests. **Results:** SToMP enrolled 5 individuals with AD (mean age 72 ± 4 years, 60% female); STAMINA enrolled 12 individuals with MCI (mean age 77 ± 8 years, 58% female). Senolytic treatment was well tolerated, with no serious adverse events. Plasma levels of D and Q increased in all SToMP participants, and D was detected in CSF in 80% (range 0.281–0.536 ng/mL), confirming CNS exposure; Q was not detected in CSF. In SToMP, plasma inflammatory markers—including SASP factors—decreased following treatment, a trend that was similarly observed in STAMINA. In SToMP, CSF levels of IL-6 and GFAP increased, while the CTRA gene expression profile decreased in four of five participants, suggesting downregulation of systemic immune stress. In STAMINA, reductions in plasma TNF-α significantly correlated with improvements in MoCA scores ($r = -0.65$, $p = 0.02$). **Conclusions:** These Phase 1 studies support the safety, feasibility, and biological activity of senolytic therapy in older adults with or at risk for AD. Plasma-based reductions in inflammation and SASP factors, CNS penetrance of dasatinib, and early signals of cognitive benefit offer a foundation for ongoing clinical development. A Phase 2 randomized controlled trial of D + Q in AD is now underway to further evaluate target engagement and clinical outcomes; interim findings will be presented (5). Together, these studies contribute to growing momentum in the field to develop senolytics as a novel disease-modifying approach targeting fundamental aging processes in AD.

Keywords: Senolytics, Alzheimer's disease, aging biology, prevention, treatment, geroscience.

Clinical Trial Registry: NCT04063124, NCT05422885, NCT04685590.

Disclosures: The authors report no competing interests.

References: Riessland M et al. (2024) Nat Rev Drug Discov. 23 (11):817-837. 1. Gonzales MM et al. (2023) Nat Med. 29 (10): 2481-2488. 2. Millar CL et al. EBioMedicine 2025 Mar:113:105612. https://doi.org/10.1016/j.ebiom.2025.105612. 3. Garbarino VR et al. (2025) Neurotherapeutics. Apr 23:e00591. https://doi.org/10.1016/j.neurot.2025.e00591. 4. Riessland M et al. (2023) J Prev Alzheimers Dis. 10 (4):633-646.

Key takeaway message: Together, these studies highlight the growing momentum in the field to target the biology of aging as a therapeutic approach for Alzheimer's disease and showcase the importance of identifying the optimal disease stage for intervention.

OC29- PLEIOTROPIC EFFECTS OF THE CNS-SELECTIVE M1 MUSCARINIC AGONIST NSC001: FROM RAPID SYMPTOMATIC RELIEF TO LONG-TERM DISEASE MODIFICATION IN ALZHEIMER'S DISEASE (AD).

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Objectives: Cholinergic dysfunction emerges early in AD and is a well-validated therapeutic target. M1 muscarinic receptors are key regulators of cognitive function and disease progression, highlighting the therapeutic promise of selective M1 agonists. NSC001 (AF267B), a highly rigid, M1-selective and specific orthosteric partial agonist, has completed preclinical safety and toxicology and has shown across multiple animal models promising effects in pharmacology studies aligned with cholinergic activity (e.g. cognitive deficits, beta-amyloid and tau pathologies, and alpha-synuclein aggregation). Four Phase 1 clinical studies were conducted in healthy volunteers to assess safety, tolerability, and pharmacokinetics (PK). **Methods and Results:** The single and multiple ascending dose double-blind and placebo-controlled trials, showed a maximum tolerated dose of 35 mg once daily (od) in younger subjects and 20 mg od in the elderly, with 15 mg being well-tolerated. A 28-day MAD trial in 60 elderly subjects confirmed excellent tolerability across doses of 5-15 mg od, with no dose-dependent cholinergic adverse reactions. PK data from previous studies were reproduced. PK on Days 1 and 28 demonstrated excellent blood-brain barrier penetration (CNS/plasma ratio 0.9) of NSC001, linear dose-exposure, and no drug accumulation. Exploratory measures on AD biomarkers showed a significant reduction of CSF p-tau and total tau at 10 and 15 mg. Quantitative EEG included alpha slow-wave index and theta/beta ratios indicating increased alpha and decreased delta activity correlated to drug exposure, suggesting potential cognitive benefits and CNS target engagement. **Conclusions:** NSC001 represents a novel, multi-modal therapeutic approach in AD and related neurodegenerative disorders, combining rapid cognitive-enhancing activity with disease-modifying effects. NSC001 has entered a Phase 2a proof-of-concept trial in patients with mild to moderate AD, with up-titration from 10 to 40 mg od. The trial will explore safety, PK, AD biomarkers, and cognitive effects, with results informing a future Phase 3 program.

Key takeaway message: NSC001, a selective M1 agonist with excellent safety, brain penetration, and linear PK, reduces CSF tau and modulates EEG biomarkers— is now advancing into Phase 2a trials for Alzheimer's disease.

LB28- RESULTS OF ASURE: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, PHARMACODYNAMICS, PHARMACOKINETICS AND EXPLORATORY ACTIVITY OF TW001 IN PATIENTS WITH ALZHEIMER'S DISEASE.

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Background: Alzheimer's disease (AD) involves multiple pathological processes, including oxidative stress and neuroinflammation. Edaravone reduces these processes and shows neuroprotective effects in preclinical AD models. TW001 is a proprietary oral formulation of edaravone and a potential disease-modifying therapy for AD. **Methods:** ASURE is a Phase IIa, multicenter, randomized, placebo-controlled study evaluating safety, pharmacodynamics, pharmacokinetics (PK) and exploratory activity of TW001 (oral edaravone) in patients with early AD (NIAA-AA criteria). Patients received TW001 once daily for 90 days. Primary endpoints were safety and oxidative stress biomarkers. Exploratory endpoints included AD biomarkers (Aβ40/42, tau epitopes, markers of neurodegeneration and neuroinflammation in CSF and plasma), cognitive and functional measures, and EEG. **Results:** Patients were enrolled at six sites in the Netherlands and Croatia. Ninety-five patients were screened; 61 were randomized of which 58 completed the study (TW001 n = 32, placebo n = 29). Mean age was 67.6 years; baseline Mini Mental State Examination (MMSE) averaged 25 across groups. Treatment compliance was high at 100%. PK analysis on Day 1 in TW001-treated patients showed plasma exposure (Cmax, AUC) consistent with previous Phase I studies. Treatment with TW001 at a daily dose of 100 mg was safe and well tolerated, with no unexpected findings. **Conclusions:** ASURE is the first study investigating the effect of TW001 in AD patients. Results demonstrated excellent safety, compliance and target exposures enabling further clinical investigation of the effect of oxidative stress and neuroinflammation in AD. Detailed biomarker, cognitive and functional, and EEG results will be presented at CTAD.

Keywords: Alzheimer's disease, oxidative stress, edaravone, ASURE, TW001, Treeway.

Clinical trial registry: NCT05323812.

Disclosures: Treeway TW001AD B.V. has received a research grant in November 2019 sponsored by ADDF (reference GC-2013807) for the development of this project. Dr Vijverberg has received consultancy fees (paid to the university) for New Amsterdam Pharma, Treeway, ReMynd, Vivoryon, Biogen, Vigil Neuroscience, ImmunoBrain Checkpoint, Muna Therapeutics, Esai, Eli Lilly, CogRX, Therini, UCB and Roche. Within his university affiliation he is the PI of studies sponsored by DIAN, AC immune, Alnylam, CogRX therapeutics, New Amsterdam Pharma, Janssen, UCB, Roche, Vivoryon, ImmunoBrain, GSK, MSD, Biogen, Alector, Eli Lilly, AriBio Fuij Film Toyama, GemVax.

Key takeaway message: The ASURE study is the first study to investigate TW001 in patients with Alzheimer's Disease. The study showed that TW001 was well tolerated and achieved target exposures in Alzheimer's patients. Efficacy data will be presented at CTAD.