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SYMPOSIA

Clinical Trial Alzheimer's Disease

S1- CTAD 2022 FLUID BIOMARKER SYMPOSIUM: RECENT ADVANCES IN PLASMA AND CSF ALZHEIMER BIOMARKERS TO IMPROVE CLINICAL PRACTICE AND TRIALS. R. Bateman[1], M. Mielke[2], O. Hansson[3], K. Blennow[4] *(1. Washington University School Of Medicine - St. Louis (United States), 2. Wake Forest University School Of Medicine - Winston-Salem (United States), 3. Lund University - Lund (Sweden), 4. University Of Gothenburg - Gothenburg (Sweden))*

Presentation 1: *Relationship between blood plasma and CSF measures of Aβ 42/40, tau, and NfL species for tracking drug effects in clinical trials of Alzheimer's disease*, Randall J. Bateman (Washington University School of Medicine, St. Louis, MO, (United States))

Background: Recent advances in the development of novel Alzheimer's disease (AD) measures of amyloid, tau, and neurodegeneration in blood have enabled the ability to track drug effects in clinical trials of AD. The discoveries of novel tau species in brain, CSF, and blood, such as specific phospho-tau (p-tau) and truncated species including the microtubule binding region (MTBR) region that comprises tangles, have greatly expanded our understanding of tau biology, target development, and drug effect tracking. Longitudinal Aβ, tau, and neurofilament light chain (NfL) changes previously measured in CSF are now being measured accurately in blood, enabling the ability not only to screen and enroll much larger and diverse populations, but also to design secondary and primary prevention trials and measure drug effects. These advances promise to accelerate treatment and prevention development for AD. **Methods:** We analyzed blood plasma measures of Aβ42/40, multiple p-tau species, and NfL in sporadic AD and dominantly inherited AD cohorts and determined concordance with CSF, amyloid and tau aggregation measures by Positron Emission Tomography (PET) scans, and clinical and cognitive measures in local and international clinical cohorts. Some of these measures were also used to measure plaque-removing drug effects. **Results:** The findings indicate that CSF and blood plasma Aβ42/Aβ40 ratio and phosphorylation of specific tau species (e.g., p-tau217, p-tau181) mirror decreases in amyloid plaques with anti-amyloid antibody treatments as measured by amyloid PET. Further, findings from CSF suggest that quantitative measures of tau aggregation can be made with specific tau MTBR fragment species, enabling tracking tau aggregation effects separately from amyloid effects. **Conclusions:** Our results demonstrate that biomarkers to track soluble or aggregated amyloid, and now tau aggregation, are highly precise measures of brain amyloidosis, tauopathy, and neurodegeneration. Use of these novel biomarkers can enable larger and more diverse AD studies and improve the understanding of drug impacts on pathophysiology in clinical trials.

Presentation 2: *Consideration and use of AT(N) blood-based biomarkers for community screening*, Michelle M. Mielke, Department of Epidemiology and Prevention, Wake Forest University School of Medicine, Winston-Salem, NC (United States))

A major benefit of the use of blood-based biomarkers in screening for Alzheimer's disease pathology, or diagnosis, is that collection of blood is less invasive and costly than cerebrospinal fluid or neuroimaging markers, and more feasible at the primary care levels where most individuals will present with cognitive symptoms. Blood-based biomarkers of amyloid (A), phosphorylated tau (T), and neurofilament light (N) are already clinically available or nearing clinical use. This talk will highlight some next steps needed before the biomarkers can be implemented for screening or diagnosis at the population level: 1) the identification of factors that may affect the interpretation of the biomarkers (e.g., sex, race/ethnicity, co-morbidities), 2) further discussion regarding how to include the biomarkers in clinical care (e.g., measurement of all 3 biomarkers, development of algorithms or 1 biomarker suitable), and 3) disclosure and ethical considerations.

Presentation 3: *Implementation of plasma biomarkers into clinical practice and trials*, Oskar Hansson (Lund University, (Sweden))

Plasma biomarkers for Alzheimer's disease (AD) have already been started to be used in clinical practice and trials. In this presentation I will summarize the Alzheimer's Association appropriate use recommendations for plasma AD biomarkers, and the key steps needed to be taken before widespread use in e.g. primary care. I will show head-to-head comparisons of different p-tau assays, revealing the high performance of certain mass spectrometry-based assays. I will also show how plasma p-tau217 can be used to drastically lower the need for CSF and PET assessments in the clinical diagnostic work-up of patients with cognitive impairment and still retain a very high diagnostic accuracy. Further, I will describe high-performing plasma-based algorithms for detection of preclinical AD, as well as prediction of cognitive decline in such an early AD population. Longitudinal analyses show that especially plasma p-tau217 is a promising marker for detecting change in AD pathology during the preclinical disease stages. Finally, the effects of potential confounding factors (such as kidney disease) on plasma AD biomarkers will be described, and their effects on the clinical performance will be shown. In summary, plasma AD biomarkers, especially certain p-tau assays, seem to be able to revolutionize the clinical practice and trials in the coming years.

S2- DECENTRALIZED APPROACHES FOR CLINICAL TRIALS ON ALZHEIMER'S DISEASE. H. Massett[1], J. Langbaum[2], P. Maruff[3], R. Lee[4], E. Lee[4], A.M. Wessels[5], K.C. Holdridge[5], M.B. Ferguson[5], R. Yaari[5] *(1. National Institute on Aging - Baltimore, MD (United States), 2. Banner Alzheimer's Institute - Phoenix, AZ (United States), 3. Cogstate Ltd - Melbourne, VIC (Australia), 4. Irvine Clinical Research - Irvine, CA (United States), 5. Eli Lilly and Company - Indianapolis, IN (United States))*

Introduction: Decentralized trials (DCTs) offer flexibility typically limited in traditional trial design, which may increase geographical and ethnic/racial diversity in trial populations,

improve participant engagement and retention, and reduce trial cost. The first DCTs were conducted in the early 2000s and trials with remote designs have exponentially increased within the past 5 years. The need for DCTs was further intensified by the COVID-19 pandemic when trial participants were unable to visit or access facilities for clinical trial assessments, which prompted the FDA to suggest draft guidance on DCT methods to clarify best practices for remote data collection methods. Research utilizing DCT approaches continues to identify both potential benefits and challenges of decentralizing trial research. Clinical trials focused on Alzheimer's disease (AD) pose specialized challenges to remotely assessing cognitive outcomes. This symposium will feature presentations focused on examples of DCTs addressing AD and cognitive health measures, including benefits and limitations of DCTs in the AD population.

Presentation 1: *Remote assessments in a follow-on study from TRAILBLAZER-ALZ*, Jessica Langbaum (Banner Alzheimer's Institute, Phoenix, AZ, (United States))

The comparison of remote, at-home to in-clinic administration of cognitive and functional assessments most often used in clinical trials remains a gap in the literature. To address this, the TRAILBLAZER-EXT (NCT04640077) study Part A was conducted as a multicenter, randomized, non-drug, multiple crossover design that evaluated the reliability of at-home, video teleconferencing (VTC) assessments of cognitive and functional abilities. Participants with AD underwent alternating at-home and in-clinic visits. The reliability of VTC compared with on-site administration of the ADAS-Cog13, ADCS-ADL, MMSE, and CDR-SB was assessed by estimating the intraclass correlation coefficient between the two test modalities. The results from these comparisons will be presented.

Presentation 2: *Effects of supervision on cognitive and functional assessment outcomes,* Paul Maruff (Cogstate Ltd, Melbourne, VIC, (Australia))

Clinical and cognitive outcomes validated for their sensitivity to early AD must be altered slightly for their administration in telehealth settings. Performance on various cognitive and functional tests were compared between in-clinic and telehealth assessment contexts in a sample of community dwelling, cognitively unimpaired (CU, N=31; mean age (SD)= 67 (9); 16 females) or MCI (CDR 0.5, N=23, mean age (SD)= 69 (13); 16 females) adults recruited from the Australian Dementia Network (ADNET) online registry and the Australian Imaging Biomarkers and Lifestyle (AIBL) study. Recruited participants completed the CDR, Cogstate PACC tests [International Shopping List Test (ISLT), Continuous Paired Associate Learning Test (CPAL), International Digit Symbol Substitution test-Medicines (IDSSTm)], the C3 battery, and the MOCA in-clinic and telehealth assessment contexts with context order randomized and CDR raters blinded to clinical status. For the CDR, there was high agreement in clinical classification between in-clinic and telehealth contexts (Kappa=0.93). Associations between scores on the individual neuropsychological tests in the two assessment contexts were also high (R-value range: 0.87-0.92). Magnitudes of impairment in the MCI group compared to the CU group on the neuropsychological tests ranged between -1 to -1.8 and were not significantly different when derived from in-clinic or telehealth contexts. Based on the results, clinical and neuropsychological tests commonly used to assess adults with early AD (preclinical and MCI) are valid for administration using telehealth contexts.

Presentation 3: *Decentralized approaches in TRAILBLAZER-ALZ 3*, Roy Yaari (Eli Lilly and Company, Indianapolis, IN (United States))

The TRAILBLAZER-ALZ 3 (TB3) (NCT05026866) study is an ongoing Phase 3 research trial with a decentralized design, testing donanemab in preclinical AD. This talk will provide an overview of key decentralized design characteristics utilized in the study. The remote screening process, which includes mobile research units and health fairs, uses the modified Telephone Interview for Cognitive status (TICS-m) to help select for cognitively unimpaired individuals. Plasma AD assays assess an AD biomarker as part of the inclusion screening criteria and minimize participant burden. Optional remote genetic counseling for APOE disclosure is offered as well as two optional sub-studies testing amyloid PET and tau PET. Clinical outcomes are assessed throughout the study using central raters who administer the Clinical Dementia Rating scale (CDR) to study partners and participants, and psychometric examinations to study participants. Self-administered tests are proctored remotely by a centralized study coordinator who also helps coordinate and facilitate all remote appointments for the participant and study partner. Infusion and imaging centers outside of traditional study «sites» are available in order to improve participant convenience and access throughout the study. In addition to key DCT design elements, screening data influenced by the DCT design will be presented.

Presentation 4: *Investigator experience in a decentralized clinical trial on Alzheimer's disease,* Ralph Lee (Irvine Clinical Research, Irvine, CA (United States))

The investigator experience is particularly valuable when it comes to identifying and addressing practical considerations with DCTs. An experienced brick and mortar site, Irvine Clinical Research, will share challenges and opportunities faced in participating in its first DCT conducted within the TRAILBLAZER-ALZ 3 study design. The site conducted in-person trial screening events using mobile research units (MRUs) off-site in the community. A fully site investigator-staffed outreach model and an outsourced model were both tested. The outcomes, effect on diversity of participants, and operational challenges of this decentralized approach will be discussed and may help to identify key approaches to further refine future DCT designs.

READOUTS
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TOPLINE RESULTS OF PHASE III GRADUATE I & II PIVOTAL TRIALS WITH SUBCUTANEOUS GANTENERUMAB. R. Bateman[1], J. Smith[2], M.C. Donohue[3], P. Delmar[4], R. Abbas[4], S. Salloway[5], J. Wojtowicz[4], K. Blennow[6,7], T. Bittner[4,8], S.E. Black[9,10], G. Klein[11], M. Boada[12], T. Grimmer[13], A. Tamaoka[14], R.J. Perry[15], R.S. Turner[16], D. Watson[17], M. Woodward[18], A. Thanasopoulou[4], C. Lane[2], M. Baudler-Klein[4], N.C. Fox[19,20], J.L. Cummings[21], P. Fontoura[4], R.S. Doody[4]
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Objectives: GRADUATE I and II are two identically designed ongoing global Phase III parallel-group, placebo-controlled, randomized trials investigating the efficacy and safety of subcutaneous gantenerumab in people with early AD (i.e., mild cognitive impairment [MCI] due to AD or mild AD dementia), as well as its effect on biomarkers of AD pathology and neurodegeneration. **Methods:** Eligible participants (50–90 years) were diagnosed with MCI due to AD or mild AD dementia; demonstrated abnormal memory using the Free and Cued Selective Recall Test; met criteria for the Mini-Mental State Examination (MMSE≥22) and the Clinical Dementia Rating –Global Score (0.5 or 1); with evidence of amyloid positivity confirmed by Aβ positron emission tomography (PET) scan or cerebrospinal fluid (CSF) analysis. Participants were randomized 1:1 to subcutaneous gantenerumab or placebo, administered at the study site or at home using home nursing. Gantenerumab was up-titrated over a 36-week period to a target dosage of 510 mg every 2 weeks (Q2W), irrespective of apolipoprotein E ε4 (APOE ε4) genotype. The primary endpoint was the change from baseline to Week 116 in Clinical Dementia Rating scale – Sum of Boxes (CDR-SB). Secondary confirmatory efficacy endpoints evaluated the change from baseline to Week 116 in cognition and function, including the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog 13), Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) and Functional Activities Questionnaire (FAQ). In addition to the safety assessments, the studies also included further secondary and exploratory efficacy measures, as well as Tau and amyloid PET, and cerebrospinal fluid (CSF) and plasma biomarker assessments. **Results:** In total, 1,965 participants (n = 985 for GRADUATE I; n = 980 for GRADUATE II) from 288 sites across 30 countries were enrolled. Data will be presented on baseline demographics and disease characteristics for both GRADUATE I and II studies. The presentation will focus on the top-line efficacy, safety and biomarker results of the two studies. **Conclusion:** Results of GRADUATE I and II will build on evidence from previous studies and provide a robust dataset informing the overall benefit:risk profile of subcutaneous gantenerumab in early AD. **References:** Klein G, et al. J Prev Alzheimers Dis 2021;8:3–6. Roche.com. Roche's anti-amyloid beta antibody gantenerumab granted FDA Breakthrough Therapy Designation in Alzheimer's disease. Accessed online at: https://www.roche.com/investors/updates/inv-update-2021-10-08 on 6 October 2022. **Acknowledgement:** «GRADUATE I and GRADUATE II participants, their families, clinical investigators and the gantenerumab study group»

TACKLING AGITATION IN ALZHEIMER'S DEMENTIA: BREXPIPRAZOLE PHASE III TRIAL RESULTS. G. Grossberg[1], D. Lee[2], M. Slomkowski[2], N. Hefting[3], D. Chen[2], K. Larsen[3], E. Kohegyi[2], M. Hobart[2], J. Cummings[4]
(1. Department of Psychiatry and Behavioral Neuroscience at Saint Louis University School of Medicine - St. Louis, Missouri (United States), 2. Otsuka Pharmaceutical Development & Commercialization Inc. - Princeton, New Jersey (United States), 3. H. Lundbeck A/S - Valby, Copenhagen (Denmark), 4. Chambers-Grundy Center for Transformative Neuroscience at School of Integrated Health Sciences University of Nevada Las Vegas (UNLV) - Las Vegas, Nevada (United States))

Background: Agitation is highly prevalent among patients with Alzheimer's dementia, in community and long-term care settings (1, 2). The presence of agitation in Alzheimer's dementia (AAD) increases the risk of institutionalization (3), negatively impacts patient quality of life, and increases caregiver distress (4). Currently, there are no FDA-approved pharmacological treatments for the management of AAD. Brexpiprazole, which acts on noradrenergic, serotonergic, and dopaminergic neurotransmitter systems (5), has been investigated as a potential AAD therapy. **Objectives:** To assess the efficacy, safety, and tolerability of brexpiprazole in patients with AAD based on results of a recently completed Phase III trial, together with two previously completed Phase III trials. **Methods:** The first two trials (NCT01862640, NCT01922258), completed in 2017, were 12-week, randomized, double-blind, placebo-controlled, parallel-arm trials of brexpiprazole versus placebo in patients with AAD (6). Patients were required to have a baseline Neuropsychiatric Inventory (NPI) Agitation/

Aggression domain score of ≥4. One trial investigated fixed doses of brexpiprazole (0.5, 1 or 2 mg/day [0.5 mg/day arm discontinued]), whereas the other investigated a flexible dose (0.5–2 mg/day). The third trial (NCT03548584), completed in 2022, also had a 12-week, randomized, double-blind, placebo-controlled, parallel-arm design, but differed in terms of the dose administered (2 or 3 mg/day), and agitation requirements, which comprised the NPI criterion, the International Psychogeriatric Association (IPA) provisional definition, and a criterion based on Cohen–Mansfield Agitation Inventory (CMAI) Factor 1. In all three trials, change in CMAI Total score was the primary endpoint, and change in Clinical Global Impression − Severity of illness (CGI-S) score, as related to agitation, was the key secondary endpoint. Safety was also assessed. **Results:** In the first fixed-dose trial, the highest brexpiprazole dose (2 mg/day) demonstrated statistically significant improvement versus placebo in CMAI Total score change from baseline to Week 12 (least squares mean difference [LSMD], -3.77; p=0.040); the 1 mg dose did not separate from placebo. In the flexible-dose trial, although brexpiprazole 0.5–2 mg/day was not superior to placebo on CMAI Total score, a post hoc analysis of patients titrated to the 2 mg dose showed reduced agitation versus placebo (LSMD, -5.06; p=0.012). A post hoc analysis of both trials indicated that patients who did not meet CMAI Factor 1 criteria at baseline had insufficient baseline agitation severity to show measurable change over time. Hence, the third trial investigated higher doses (2 or 3 mg/day [3 mg tested for efficacy and safety, per FDA request]) in an enriched sample who met CMAI Factor 1 criteria at baseline. In the third trial, brexpiprazole 2 or 3 mg/day demonstrated statistically significant improvement versus placebo from baseline to Week 12 in CMAI Total score (LSMD, -5.32; p=0.0026) and CGI-S score as related to agitation (LSMD, -0.27; p=0.0078). Pooled response rate across the three trials (CMAI criteria) was higher with brexpiprazole versus placebo. Across all three trials, the incidence of treatment-emergent adverse events (TEAEs) was 51.1% with brexpiprazole (all doses pooled) and 45.9% with placebo. Across all three trials (pooled), no single TEAE had an incidence >5% with brexpiprazole (all doses pooled) and more than in placebo-treated patients. TEAEs that occurred in ≥2% of patients receiving brexpiprazole and more than in placebo-treated patients were insomnia (3.7% versus 2.8%), somnolence (3.4% versus 1.8%), nasopharyngitis (2.7% versus 2.6%), and urinary tract infection (2.6% versus 1.5%). The incidence of falls was 1.7% (brexpiprazole) versus 2.6% (placebo). Overall, 6.3% of patients receiving brexpiprazole discontinued treatment due to TEAEs, versus 3.4% receiving placebo. Six brexpiprazole-treated patients (0.9%) and one placebo-treated patient (0.3%) died during double-blind treatment; no deaths were considered related to brexpiprazole treatment. **Conclusion:** Across three Phase III trials in patients with AAD, brexpiprazole doses of 2 or 3 mg/day showed a statistically significant improvement versus placebo on agitation in Alzheimer's dementia. Brexpiprazole was generally well tolerated, which is of critical importance in this vulnerable patient population. **References:** 1. Halpern et al. Using electronic health records to estimate the prevalence of agitation in Alzheimer disease/dementia. Int J Geriatr Psychiatry 2019;34(3):420–431. 2. Fillit et al. Impact of agitation in long-term care residents with dementia in the United States. Int J Geriatr Psychiatry 2021;36(12):1959–1969. 3. Cloutier et al. Institutionalization risk and costs associated with agitation in Alzheimer's disease. Alzheimers Dement (N Y) 2019;5:851–861. 4. Khoo et al. The impact of neuropsychiatric symptoms on caregiver distress and quality of life in persons with dementia in an Asian tertiary hospital memory clinic. Int Psychogeriatr 2013;25(12):1991–1999. 5. Maeda et al. Brexpiprazole I: in vitro and in vivo characterization of a novel serotonin–dopamine activity modulator. J Pharmacol Exp Ther 2014;350(3):589–604. 6. Grossberg et al. Efficacy and safety of brexpiprazole for the treatment of agitation in Alzheimer's dementia: two 12-week, randomized, double-blind, placebo-controlled trials. Am J Geriatr Psychiatry 2020;28(4):383–400.

ROUNDTABLES
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ROUNDTABLE 1- INVESTMENTS IN INNOVATION: ADVANCING THE PATH FORWARD TO NEW ALZHEIMER'S TREATMENTS. N. Bose[1], H. Fillit[2], L. Barker[3], P. Scheltens[4] *(1. Gates Ventures, Seattle, WA (United States), 2. Alzheimer's Drug Discovery Foundation (ADDF), New York City, NY (United States), 3. Dementia Discovery Fund (DDF), London (United Kingdom), 4. LSP Dementia Fund at EQT Life, Alzheimer Centre Amsterdam (University Medical Centre Amsterdam, Amsterdam (The Netherlands))*

Topline summary: Over six million people in the United States and 55 million globally are living with Alzheimer's and related dementias, and that number is expected to grow substantially with an aging population. There is a large global unmet medical need with few effective treatments available for patients, creating an urgency to accelerate efforts to develop novel and effective therapies that target a whole host of underlying pathologies that contribute to Alzheimer's. It is important to foster collaboration across various sectors – government, academia, industry, and philanthropy – combine resources and capital, and utilize innovative and creative approaches to successfully conquer this disease. This roundtable will pull expertise from four influential global investment organizations – all with a venture-minded approach that span across drug discovery and development to commercialization – focused on identifying and investing in innovative, impactful therapies. The will panel will discuss where we are now in the field and where we want to be 10 years from now and more importantly, the path forward, which is only possible when leading scientists and entrepreneurs are connected and have access to capital. The panel will cover their interests, approach, resources, and funding opportunities to support and accelerate research of new drugs, technologies, and breakthrough innovations. Lastly, they will discuss recommendations and provide evidence where these have been used in practice. Recommendations include: • Leveraging the modern era of Alzheimer's research to explore drugs beyond amyloid and tau proteins and focusing the next phase of research, based on the biology of aging, which is centered on promising drugs that target a host of underlying pathologies that contribute to Alzheimer's. • Highlighting the need for more rigorously designed clinical trials enabling the field to more rapidly and efficiently evaluate whether a drug should move to the next stage of clinical development. • Emphasizing the importance of biomarkers as it relates to drug development and precision medicine, with an emphasis on the need for new biomarkers that can measure the impact of each biology of aging target, and the drugs designed to treat them

ROUNDTABLE 2- THE ALZHEIMER'S DISEASE PATIENT PATHWAY FROM A SEX AND GENDER LENS.
F.C. Quevenco[1,2], M.C. Tartaglia[3], M. Carrillo[4], P. Ferrell[5], P. Poulsen[6], A. Santuccione Chadha[2,7], M.T. Ferretti[2], M.F. Iulita[2,8] *(1. Roche (Switzerland), 2. Women's Brain Project (Switzerland), 3. University Of Toronto (Canada), 4. Alzheimer's Association (United States), 5. Eli Lilly (United States), 6. Novo Nordisk (Denmark), 7. Altoida (United States), 8. Memory Disorders Unit, Hospital Sant Pau - Barcelona (Spain))*

The topic of sex differences is now positioned as a top priority in neurology research, particularly in the context of precision medicine and personalized care. There is a growing literature about sex differences in Alzheimer's disease manifestations, highlighting sex and gender-specific factors that are not captured in a standard patient pathway. A patient pathway takes a patient-centric approach to describe an individual's journey from symptom onset to treatment completion. It is a crucial resource for persons living with Alzheimer's disease, physicians, and clinical trial sponsors. When considering sex and gender differences, there are likely deviations between a male and female patient journey. To address this, an ongoing study led by the Women's Brain Project and collaborators is mapping a comprehensive patient pathway that is able to capture these differences. The goal of this symposium is to discuss the importance of why this patient pathway is needed in Alzheimer's disease and why it is relevant for clinical trials by inviting different stakeholders.

ORAL COMMUNICATIONS

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OC1- ACI-35.030 AND JACI-35.064, TWO NOVEL ANTI-PHOSPHO-TAU VACCINES FOR THE TREATMENT OF ALZHEIMER'S DISEASE: INTERIM PHASE 1B/2A DATA ON SAFETY, TOLERABILITY AND IMMUNOGENICITYE.
J. Streffer[1,2], J. Mermoud[1], O. Sol[1], M. Vukicevic[1], E. Fiorini[1], E. Gollwitzer[1], V. Hliva[1], D. Hickman[1], J. Gray[1], P. Donati[1], M.P. Lopez Deber[1], J. Rongère[1], A. Pfeifer[1], M. Kosco-Vilbois[1], P. Scheltens[3] *(1. AC Immune SA - Lausanne (Switzerland), 2. University of Antwerp - Antwerp (Belgium), 3VUMC - Amsterdam (Netherlands))*

Background: Tau deposition is a key pathological feature of Alzheimer's disease (AD) and other neurodegenerative disorders. The spreading of Tau neurofibrillary tangles across defined brain regions is associated with cognitive decline in AD. It is hypothesized that Tau spreading throughout the brain involves extracellular phosphorylated Tau (pTau). Immunotherapy offers the potential to interfere with the spreading of Tau neuropathology and prevent or reduce cognitive impairment. In particular, active vaccination targeting pTau species that seed pathological aggregation, represents an attractive strategy for long-term treatment and potentially prevention of AD as well as other Tauopathies. **Objectives:** This Phase 1b/2a clinical trial, NCT04445831, aims to evaluate two first-in-class anti-pTau vaccine candidates, ACI-35.030 (i.e., liposome-based) and JACI-35.054 (i.e., conjugate-based) for the treatment of AD. We report here interim results of immunogenicity as well as safety and tolerability. **Methods:** This currently ongoing multicenter, double-blind, randomized, placebo-controlled study evaluates the safety, tolerability and immunogenicity of different doses of two anti-pTau vaccines, ACI-35.030 and JACI-35.054, in subjects with early AD. The antibody response is evaluated using ELISAs and measuring binding of the antibodies generated over time to the immunizing peptide, i.e., pTau, as well as against brain derived paired helical filaments (ePHF) and non-phosphorylated Tau. Epitope profiling is also employed using a specifically developed assay to cover phosphorylated and nonphosphorylated epitopes. Each dose-level sub-cohort comprises 8 subjects randomized in a 3:1 active/placebo ratio with the option to expand sub-cohort(s) up to 24 subjects to enlarge the assessment of safety, tolerability and immunogenicity. The study population is characterized as 50-75 year-old, male and female subjects with a diagnosis of mild AD or MCI due to AD according to NIA-AA criteria, CSF Aß42 levels consistent with AD pathology, a CDR global score of 0.5 or 1 and a MMSE score ≥ 22. Subjects receive injections of ACI-35.030 (Cohort 1), JACI-35.054 (Cohort 2) or placebo (Cohorts 1 and 2) at weeks 0, 8, 24 and 48. **Results:** 41 subjects have been randomized in the 3 dose-levels of cohort 1, and 16 subjects in the 2 dose-levels of cohort 2. Both vaccines are considered safe and well tolerated as no clinically relevant safety concerns associated related to the study vaccines have been observed at the time of abstract submission. Subjects immunized with the liposomal vaccine, ACI-35.030, show a high, specific and sustained anti-pTau and anti-ePHF IgG response, with an apparent dose-response between the low- and mid-dose with evidence of immunoglobulin class switch from IgM to IgG. Individual responder rates were high and consistent, especially for anti-pTau and ePHF antibodies. Over time, the data demonstrates that the IgG response matures towards a stronger preference for binding ePHF, the more pathologic species while concomitantly lowering antibody titers towards the non-pathological, non-phosphorylated Tau. Subjects immunized with the conjugate vaccine, JACI-35.054, display a high anti-ePHF and anti-pTau IgG response with no apparent dose-effect observed between the low- and mid-dose. The IgG response shows maintained binding capacity to both pTau and the non-pathological, non-phosphorylated Tau. To further profile the antibody response for breadth and selectivity towards pathological pTau, epitope mapping was performed on the subjects' sera after 3 vaccinations. For ACI-35.030, the IgG response of the subjects was relatively homogenous displaying a broad epitope coverage as binding occurred across the pTau sequences tested and importantly, without end terminal specificity or substantial binding to nonphosphorylated sequences. The subjects vaccinated with JACI-35.054 demonstrated a more heterogeneous response with a strong disproportional binding to end terminal antibodies. These results further elucidate the differences produced by the two vaccines as well as the conclusion of IgG maturation with ACI-35.030 and not JACI-35.054 over time. Finally, as expected, no antibody responses are observed in placebo-treated subjects. **Conclusions:** The clinical study is successfully ongoing despite the challenges of being performed during the restrictions of the Covid-19 pandemic demonstrating that vaccination with either ACI-35.030 or JACI-35.054 is safe and well tolerated, inducing IgG responses to the immunizing peptide as well as ePHF. However, overall ACI-35.030 emerges as the superior vaccine candidate in terms of responder rate, number of immunizations to achieve the initial antibody titer, homogeneity of the antibody response across subjects, epitope coverage, with evidence of antibody maturation towards pathologic forms of Tau. As both vaccines contain the same antigenic peptide sequence, the differences observed so far in antibody response can be ascribed to the different technologies used to present the antigenic peptide to the immune system.

OC02- RESULTS OF A PHASE 2/3 PLACEBO-CONTROLLED, DOUBLE-BLIND, PARALLEL-GROUP, RANDOMIZED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF 12 WEEK TREATMENT WITH THE PHOSPHODIESTERASE 9 (PDE9) INHIBITOR IRSENONTRINE (E2027) IN SUBJECTS WITH DEMENTIA WITH LEWY BODIES. M. Irizarry[1], R. Lai[2], S. Hersch[1], K. Pinner[2], S. Dhadda[1], L. Kramer[1] *(1. Eisai Inc. - Nutley (United States), 2. Eisai Ltd. - Hattfield (United Kingdom))*

Objectives: To assess the safety and efficacy of irsenontrine for treatment of cognition in patients with Dementia with Lewy Bodies (DLB). **Methods:** Study 201 was a phase 2/3, 12-week study in subjects with DLB (N=196) randomized 1:1 to irsenontrine 50 mg or placebo. The co-primary endpoints were change from baseline in the electronic Montreal Cognitive Assessment (eMoCA) and the electronic Clinician's Interview Based Impression of Change Plus Caregiver Input (eCIBIC-plus) at 12 weeks. Secondary outcomes included the Neuropsychiatric Inventory (NPI), Mini-Mental State Examination (MMSE), Cognitive Function Inventory (CFI), and the Clinician's Global Impression of Change – Dementia with Lewy Bodies (CBIC-DLB). **Results:** The study did not meet its primary objective of determining the superiority of irsenontrine compared with placebo on both the cognitive endpoint of MoCA and the global clinical endpoint of CIBIC-Plus after 12 weeks of treatment in the overall population. The irsenontrine group tended to show less decline from Baseline to Week 12 in the MoCA total score in the overall population compared with the placebo group, but the difference between treatment groups was not statistically significant (MMRM analysis: least square (LS) mean difference [95% CI] of 0.181 [-0.716, 1.078], p=0.69). Subjects in the irsenontrine group showed minimal improvement in the CIBIC-Plus compared with the placebo group at Week 12; the difference between treatment groups was not statistically significant (GLMM analysis: odds ratio [95% CI] of 1.018 [0.695, 1.492]; p=0.83). Secondary efficacy endpoints did not show a significant treatment difference between irsenontrine and placebo in the overall population. Exploratory post-hoc analyses suggested that irsenontrine performed better than placebo on the primary efficacy endpoints in a key subgroup of subjects without amyloid copathology (identified by plasma amyloid Aβ42/40 ratio ≥0.092 [C2N assay], N=26 and 30 for the placebo and irsenontrine groups, respectively): For subjects without amyloid copathology ("pure DLB"), irsenontrine treatment resulted in an improvement from Baseline to Week 12 MoCA compared with a decline in the placebo group. The difference approached statistical significance (LS mean difference [95% CI] of 1.567 [-0.024, 3.157]; p=0.05). For subjects without amyloid copathology, the irsenontrine group tended to show greater improvement in CIBIC-Plus at Week 12 compared with the placebo group, with more subjects showing improvement in the irsenontrine group compared with the placebo group: odds ratio (95% CI) of 1.596 [0.753, 3.386]; p=0.47. In the small number of subjects for whom data were available (n=4), 9 weeks of irsenontrine treatment resulted in an average of 168% increase in cGMP in the CSF. Irsenontrine was generally well-tolerated with similar incidence rates of Serious Adverse Events (SAEs) and Treatment Emergent Adverse Events (TEAEs) between the irsenontrine and placebo groups. Worsening DLB, dizziness, somnolence, orthostatic hypotension, and aggression occurred with a higher incidence in the irsenontrine group (3.0% to 5.1%) compared with the placebo group (0% to 1.0%). **Conclusions:** In the overall DLB population, 12 weeks treatment with irsenontrine 50 mg daily did not improve cognition relative to placebo. The suggestion of efficacy in the "pure" DLB subgroup, lacking AD co-pathology, generated the hypothesis that irsenontrine preferentially increases CSF cGMP in pure DLB relative to mixed DLB due to relative preservation of synapses (the site of action of PDE9 inhibition) in patients lacking amyloid co-pathology. This hypothesis is explored in the translational medicine Study 203.

OC03- HMTM TOPLINE RESULTS OF PHASE 3 LUCIDITY – THE FIRST TAU AGGREGATION INHIBITOR. B. Schelter[1,2] *(1. TauRx Therapeutics Ltd - Aberdeen (United Kingdom), 2. University of Aberdeen - Aberdeen (United Kingdom))*

LUCIDITY interim data are currently being analysed and this symposium will provide an opportunity to present new data analysis not yet in the public domain. **Part 1:** History of HMTM and its development (Prof Claude Wischik). Hydromethylthionine mesylate (HMTM) is a tau aggregation inhibitor shown to have exposure-dependent pharmacological activity on cognitive decline and brain atrophy in two completed Phase 3 trials in mild/moderate Alzheimer's disease (AD). The role of tau pathology in AD and the mode of action of HMTM will be presented. Context will be provided using data from 2 completed Phase 3 clinical trials in AD. **Part 2:** Update on the interim data, including safety, key endpoints and biomarkers (Prof Bjoern Schelter). The ongoing Phase 3 LUCIDITY trial (NCT03446001) investigates 16 mg/day as monotherapy as the optimal treatment regime compared to placebo. The trial comprises a 12-month double-blind, placebo-controlled phase followed by a 12-month modified delayed-start open-label treatment phase. The trial is being conducted across 76 clinical research sites in North America and Europe. It recruited 598 subjects in total with probable AD or MCI-AD with 545 in the final version of the protocol. Participants were assigned randomly to receive HMTM at doses of 16 mg/day, 8 mg/day or placebo at a 4:1:4 ratio during the double-blind phase. All participants in the open-label phase receive the 16 mg/day dose. The study has co-primary clinical outcomes comprising the 11-item Alzheimer's Disease Assessment Scale (ADAS-cog11) and the 23-item Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL23). Secondary biomarker measures include whole-brain atrophy measured by MRI and temporal lobe 18F-fluorodeoxyglucose positron emission tomography. 470 participants completed the 12-month placebo-controlled phase by April 2022. During this symposium updates will be provided from ongoing interim data analysis of the double blind and open label phases of LUCIDITY. **Part 3:** What does this mean for the AD landscape? (Dr Richard Stefanacci). LUCIDITY is the only late-stage clinical trial targeting tau pathology. The trial is novel in design as it includes individuals with mild – moderate AD and MCI under the same protocol. A unique feature among tau- and amyloid-targeting approaches in development is that HMTM is an oral drug which has a proven benign safety profile including lack of ARIA risk. The possibility for a medication to come to market to treat a broad range of AD severity and be accessible to patients presents a significant opportunity to transform the AD treatment landscape. This presentation will consider the extent of the potential transformation of the patient pathway that HMTM could provide.

OC04- JANSSEN SIMOA PLASMA P217+TAU ASSAY AS A PRECISION PRESCREENING TOOL IN AUTONOMY PH2 ANTI-TAU MONOCLONAL AB TRIAL IN EARLY ALZHEIMER'S DISEASE. G. Triana-Baltzer[1], Z. Saad[1], S. Moughadam[1], R. Slemmon[1], M. Quiceno[1], D. Henley[1], H. Kolb[1] *(1. Janssen Research & Development - San Diego (United States))*

Background: It is hypothesized that anti-amyloid or anti-tau therapies should be most effective in Alzheimer's Disease (AD) when initiated early in disease. CSF and PET-based measures have proven utility in identifying subjects with AD pathology even prior to clinical symptom manifestation, however they are burdensome to the patient and costly. Phosphorylated tau (p-tau) as measured in CSF, and most recently plasma, has emerged as one of the most sensitive and specific biomarkers for AD pathology and appears to predict amyloid and tau PET positivity as well as gross cognitive state. Janssen has developed a highly sensitive and precise assay for measuring p217+tau in plasma, with good ability to predict amyloid and tau PET status with a cutoff of ≥0.1 pg/ml. This assay is unique from others specific for phosphorylated T217 in that it has enhanced signal when tau is phosphorylated at neighboring amino acids as well, as is often found in pathological tau species. We have studied the utility of this non-invasive assay for clinical trial enrollment with confirmation of performance via comparison to tau PET. **Objectives:** The Autonomy trial (63733657ALZ2002) seeks to enroll early AD (MCI/mild AD dementia) patients who are tau PET positive (standardized uptake value ratio (SUVR) Z-score > 1 in bilateral inferior temporal cortex) but without having widespread tau tangles [SUVR Z-score > 5 in each of Braak 4, 5, and 6 regions of interest (ROI)]. Patients within this range are further stratified into high and low groups based on SUVR in the Braak 4 ROI. We report on the performance of the Janssen Simoa plasma p217+ tau assay as a prescreening tool for identifying patients who are likely tau PET positive. **Methods:** The plasma p217+tau assay developed on Simoa platform was validated at Quanterix (Billerica, MA) and performed on screening samples from participants presenting with early AD in weekly batches. Technical performance across the initial 55 batches was evaluated. Participants presenting with plasma p217+tau levels ≥ a pre-specified cutoff of 0.1 pg/ml progressed to tau PET (18F-MK6240) screening. Concentrations of plasma p217+tau in this population and prevalence of tau PET positivity in the plasma p217+tau positive participants was studied. To assess the assay's ability to predict participant stratification, we performed a post-hoc ROC analysis using one year's worth of screening data. **Results:** From February 2021 to April 2022, 55 batches of plasma p217+tau screening were performed at Quanterix. A panel of 3 peptide Quality Control (QC) samples (0.1, 0.4, and 1.6 pg/ml) were run in duplicate in each batch revealing excellent intra-run precision (average CV = 6.0, 4.5, and 5.5%, respectively) and inter-run precision (7.6, 6.6, and 13.3% CV, respectively). Precision was also acceptable with clinical trial samples, as amongst N=725 plasma samples the mean CV was 7.9% (0-120% range), with an estimated LLOQ of 0.030 pg/ml (based on mean concentration where CV>20%). Of the 787 early AD patients in which plasma p217+tau was measured, 72% had levels ≥0.1 pg/ml, and hence were slated to have tau PET imaging performed. Of the 346 patients imaged to date, 86% were tau PET positive and 64% satisfied the trial tau PET eligibility criteria of intermediate tau burden. While assay screening performed as expected, 59% of eligible patients were in the high stratum. ROC analysis shows the plasma p217+tau assay can predict patient stratum with an AUC of 0.8, making it possible to use the assay for further patient enrichment for a desired stratification profile. **Conclusion:** Accurate, sensitive, and precise measurement of p-tau isoforms in plasma has emerged as the most promising non-invasive method for detecting aberrant amyloid and tau processes. Longer fragments of multi-phosphorylated tau, containing at least phosphorylation at amino acid 217, have been reported as one of the isoforms most associated with AD pathology and may begin accumulating in CSF and plasma 10-20 years before cognitive decline. Janssen has developed a robust and highly sensitive assay to measure plasma p217+tau which can quantify signal in all early AD participants, suggesting utility for pre-screening participants for anti-tau trials such as Autonomy. Pressure testing of the plasma p217+tau assay in the Autonomy phase-2 clinical trial has shown good precision within and between batches, and demonstrated the ability to enrich populations for tau PET positivity. This "low friction" tool should enable faster and more efficient AD clinical trial enrollment now, and due to its ability to quantify signal in even preclinical AD could potentially be used in the future as a tool to identify the earliest stages of disease in the general population. Additional work should focus on refining cutoffs to stage AD subjects based on time to onset of clinical symptoms and/or amyloid and tau PET progression. **Conflicts of Interest:** GTB, ZSS, SM, RS, MQ, DH, and HCK are employees of Janssen R&D.

OC05- LONG TERM AND ECONOMIC OUTCOMES FOR MIRTAZAPINE AND CARBAMAZEPINE VERSUS PLACEBO: NEW DATA FROM THE SYMBAD RCT. S. Banerjee On Behalf Of The Symbad Group[1] *(1. University Of Plymouth - Plymouth (United Kingdom))*

Background: Agitation is common in people with dementia and impacts negatively on the quality of life of both people with dementia and carers. Non-drug patient-centred care is the first-line treatment, but there is a need for other treatment when this fails. Current evidence is sparse on safer and effective alternatives to antipsychotics. We assessed efficacy and safety of mirtazapine (an antidepressant) and carbamazepine (an anticonvulsant) prescribed for agitation in dementia. Here we present new data from the SYMBAD trial including those on carbamazepine and long-term and economic outcomes. **Objectives:** To assess the safety, clinical and cost effectiveness of mirtazapine and carbamazepine in the treatment of agitation in dementia (Cohen Mansfield Agitation Inventory (CMAI) score), with 12 weeks follow up the primary outcome, and long-term follow up at 6 and 12 months. Registered ISRCTN17411897 and ClinicalTrials.gov NCT03031184, funded by UK National Institute for Health Research. **Methods:** Pragmatic, phase III, multi-centre, double blind, superiority, randomised, placebo-controlled trial of the clinical and cost-effectiveness of mirtazapine and carbamazepine over 12 weeks. Approved by Hampshire A South Central Research Ethics Committee (15/SC/0606) and MHRA (58810/0001/001-0001). Eligible participants randomised to receive either mirtazapine (target dose 45mg), carbamazepine (target 300mg), or placebo. Participants eligible if the following criteria were met: (i) clinical diagnosis of probable or possible Alzheimer's disease; (ii) co-existing agitated behaviours; (iii) evidence the agitated behaviours have not responded to management; (iv) CMAI score of 45+; (v) written informed consent from participant or consultee if capacity lacking; and (vi) availability of suitable informant. Exclusion criteria: (i) currently on antidepressants, anticonvulsants, or antipsychotics; (ii) contraindications

to mirtazapine or carbamazepine; (iii) second degree atrioventricular block; (iv) bone marrow depression or hepatic porphyria; (v) case too critical for randomisation (eg suicide risk or risk of harm to others); and (vi) females of childbearing potential. Participants were drawn from 26 UK sites, allocated in a 1:1:1 ratio to receive placebo or carbamazepine or mirtazapine, each with treatment as usual. Random allocation block stratified by centre and type of residence with random lengths. The trial was double-blind, with drug and placebo identically encapsulated. Analyses were based on intention-to-treat, the primary outcome (CMAI at 12 weeks) was analysed using a general linear regression model including baseline CMAI score as a covariate. General linear regression models were created for secondary outcomes. The primary outcome for the economic evaluation was the incremental cost per 6-point difference in CMAI score at 12 weeks, from a health and social care system perspective. Due to slower than expected recruitment the carbamazepine arm was discontinued in August 2018 with 1:1 randomisation to mirtazapine or placebo thereafter. **Results:** Between January 2017 and February 2020, 244 participants were recruited and randomised to either the mirtazapine (n=102), the placebo (n=102), or the carbamazepine arm (n=40). Mean CMAI scores at 12 weeks were not significantly different between participants allocated to receive mirtazapine and placebo (adjusted mean difference -1.74, 95% CI -7.17 to 3.69, p=0.53). The number of controls with adverse events (65/102 [64%]) was similar to that in the mirtazapine group (67/102 [66%]). There were more deaths in the mirtazapine group (n=7) by week 16 than in the control group (n=1), with post-hoc analysis suggesting this was of marginal statistical significance (p=0.065), but this difference did not persist at 6- and 12-month follow-up. At 12-week follow-up, the costs of unpaid care by the dyadic carer over the prior 6 weeks were significantly higher in the mirtazapine than placebo group (difference: £1,120 (95% CI £56, £2,184)). In the cost-effectiveness analyses mean raw and adjusted outcome scores and costs of the complete cases samples showed no differences between groups. The cost effectiveness analyses showed no evidence of benefit of mirtazapine over placebo. The carbamazepine arm had only 40 randomisations, we therefore lack the statistical power for the planned comparisons with placebo, however exploratory analyses using the same modelling as for mirtazapine versus placebo showed there was also no evidence of any benefits compared to placebo at 12 weeks (adjusted mean difference 2.46, 95% CI -5.01 to 9.93, p=0.52) or at long-term follow-up, with similar levels of adverse events reported. **Conclusions:** This is a trial with negative findings and clinical implications. The data suggest that mirtazapine is not clinically effective or cost-effective (compared to placebo) for clinically significant agitation in dementia. Our findings suggest that there is no reason to use mirtazapine for people with dementia who experience agitation. The data also provide no signal that carbamazepine might have any positive effect on agitation in dementia above that seen in the placebo group and no evidence of long-term benefit of either drug. These data bring into question the use of antidepressants for agitation in dementia.

OC06- COMBINATION OF REGIONAL FLORTAUCIPIR QUANTIFICATION AND EVENT-BASED MODELING IN CLINICAL TRIAL ANALYSES.

I. Higgins[1], A. Morris[1], J. Sims[1], M. Mintun[1], S. Shcherbinin[1] *(1. Eli Lilly and Company - Indianapolis (United States))*

Background: Positron emission tomography (PET) imaging of brain tau burden, topography, and propagation is used to evaluate Alzheimer's disease (AD) progression and treatment response. Regions of interest (ROIs) brain analysis for tau levels may be more sensitive than global whole brain tau estimates (Leuzy et al, Molecular Psychiatry, 2019). Topographic PET staging methods can incorporate a priori established ROI sequences (e.g. Braak staging and Lobar Classification, Schwarz et al, Alzheimer's & Dementia, 2018) and data-driven methodologies, such as an Event-Based Model (EBM, Fonteijn et al, Neuroimage, 2012, Young et al, Brain, 2014, Berron et al, Brain, 2021) that can deliver an ordering scheme in a discrete-event dynamic system to determine a sequence from which a set of ROIs transition to abnormally high tau burden. **Objectives:** Assess an ordered sequence of cortical atlas-based brain regions reflecting tau propagation across the Alzheimer's disease spectrum. Examine data from an interventional trial with donanemab (Mintun et al, NEJM, 2021) for the potential utility of EBM in the efficacy measurements on tau PET. **Methods:** Baseline flortaucipir PET scans from 1238 participants from observational and interventional trials were combined to develop and validate the model. Analyzed images were collected in 1) observational phase 2/3 18F-AV-1451-A05 study (NCT02016560); 2) EXPEDITION 3 phase 3 solanezumab trial (NCT01900665); 3) NAVIGATE-AD phase 2 trial with BACE inhibitor (NCT02791191); 4) AMARANTH phase 2/3 trial with lanabecestat (NCT02245737); and 5) DAYBREAK-ALZ phase 3 trial with lanabecestat (NCT02783573). Flortaucipir images pertaining to 57 elderly cognitive normal participants, 229 participants with mild cognitive impairment (MCI), and 936 participants with AD were included in the consolidated cross-sectional dataset. As regional outputs, standardized uptake value ratios (SUVRs) were calculated with respect to a reference signal intensity in white matter (PERSI, Southekal et al, JNM, 2018) and to an average signal in cerebellar gray matter region (Pontecorvo et al, Brain, 2017). Bilateral cortical ROIs from the Automated Anatomical Labeling (AAL, Tzourio-Mazoyer et al, Neuroimage, 2002) brain atlas were utilized as targets. The EBM assessed each brain region in our consolidated cross-sectional dataset as either "tau unburdened" or "tau burdened", where Gaussian probability density functions governed the distribution of tau SUVRs under these two settings. A brain region experienced "an event" when it switched from normal/unburdened to abnormal tau levels. The ordered sequence of regions was determined from the regional tau SUVR dataset. The EBM ran for 250,000 iterations, where at each step the algorithm swapped the positions of two brain regions and accepted the new sequence if the data fit improved. A simple subject-level resampling scheme permitted estimation of numerous ordered sequences from which regional variation about the characteristic sequence was evaluated. A permutation test was used to determine whether the characteristic sequence was better supported by data than a randomly ordered sequence. To assess the robustness of EBM performance, sensitivity analyses were conducted by varying the reference signal utilized in SUVR measurements. The sequence was also applied to post hoc exploratory analyses of tau PET data from 172 participants with baseline PET scans collected in the multicenter, randomized, double-blind, placebo-

controlled phase 2 TRAILBLAZER-ALZ trial (NCT03367403), to assess the efficacy of donanemab in early, symptomatic patients with AD (Mintun et al, NEJM, 2021). **Results:** EBM-generated sequences for temporal, parietal, and frontal lobe AAL ROIs were generally consistent with previously reported staging schemes (Schwarz et al, A&D, 2018), in that tau largely propagated along the temporal-parietal-frontal axis as AD progressed. Specifically, EBM placed the inferior temporal region at the beginning of the tau spread sequence followed by lateral temporal and parietal regions. All nine frontal ROIs were positioned at the end. The characteristic sequence was largely unchanged when the cerebellar crus was used as the reference region rather than PERSI. In TRAILBLAZER-ALZ post hoc exploratory analyses, regional SUVR values using cerebellar gray as a reference suggested that SUVR values showed more pronounced separation between placebo and donanemab-treated participants in regions identified later in the EBM sequence. Specifically, a significant separation was observed in frontal, temporal, and parietal ROIs ($p<0.05$), but there was no significant difference in tau change in "earlier" inferior temporal ROIs ($p>0.05$). Overall, more slowing in tau was observed ($p<0.001$) across the EBM sequence in participants treated with donanemab relative to placebo. **Conclusions:** Our analyses suggest that EBM can provide useful information in multi-regional analyses of flortaucipir images by ordering brain regions according to the pathologic sequence of tau progression. The EBM approach may better illustrate the therapeutic effect of AD treatment on tau PET by providing evidence of tau spread (Schwarz, Neurotherapeutics, 2021) to complement global tau measures. Larger trial data can further confirm these observations. **Conflict of Interest:** Ixavier A. Higgins is an employee and stockholder of Eli Lilly and Company.

OC07- LONGITUDINAL TAU PET INCREASE IS HIGHEST IN BRAIN REGIONS WITH STRONGEST FUNCTIONAL CONNECTIVITY TO REGIONS WITH MOST NFT AT BASELINE: AN INDEPENDENT VALIDATION. Z.S. Saad[1], R. Datta[1], C. Rowe[2], H.C. Kolb[1] *(1. Janssen R&D, Johnson & Johsnon - San Diego (United States), 2. Austin Health and University of Melbourne - Melbourne (Australia))*

Background: Tau PET is the gold standard for in-vivo quantification of tau Neuro Fibrillary Tangles (NFT), which along with amyloid plaques and neurodegeneration, constitute the pathological hallmarks of Alzheimer's Disease (AD). Since NFT presence and accumulation is heterogenous across patients and brain regions, assessments need to be individualized. Identifying regions most likely to show NFT progression can improve detection of treatment effects and result in smaller trials. **Objectives:** Franzmeier et al. (1) showed based on Flortaucipir PET that future NFT increases were highest in brain regions with the strongest functional connectivity to regions with the highest NFT levels at baseline. We have performed an independent validation of this work using MRI and Tau PET data obtained with a different tracer, MK6240, and an in-house implementation of the analysis pipeline. **Methods:** NFT levels were quantified using MK6240 SUVR in 232 brain regions (reference region: cerebellar gray). Longitudinal tau PET data was analyzed from 18 amyloid positive MCI patients who fit the profile for inclusion in Janssen's Autonomy trial, and 36 Cognitively Normal (CN), amyloid negative subjects as controls. Quantification pipeline was implemented using FreeSurfer (2) and AFNI (3) software. For each subject, NFT epicenter consisted of regions with the top 10% of NFT levels that are at least one standard deviation above uptake in CN controls. All remaining regions were assigned a rank based on the strength of their average functional connectivity to the epicenter. Functional connectivity matrix for 232 cortical and sub-cortical regions (4, 5) was derived using resting state FMRI data from 500 healthy subjects available from the Human Connectome Project ((6, 7). Rank of connectivity to the epicenter was used to group regions into four quartiles Q1 to Q4, with Q1 having the strongest connectivity. **Results:** In the CN amyloid negative cohort, average annualized SUVR changes were close to 0 across quartiles with means and standard deviations of: Q1=-0.02 (0.04), Q2=-0.01 (0.04), Q3=-0.01 (0.04), Q4=-0.01 (0.03). In contrast, SUVR change for the MCI cohort was highest at Q1 and progressively lower across the four quartiles: Q1=0.05 (0.07), Q2=0.04 (0.07), Q3=0.03 (0.07), Q4=0.01 (0.09). Epicenter SUVR change of 0.01 (0.06) was comparable to that in Q4. In the MCI cohort, SUVR changes in Q1 and Q2 were nominally significantly greater than 0 ($p<0.05$) with effect sizes of 0.74 and 0.53, respectively. **Conclusions:** We have validated a patient-centered approach (1) for predicting future NFT increases using the patient's specific pattern of Tau NFT at BL and whole brain functional connectomics. This validation, conducted using independent pipelines, patient cohorts, and a different PET tracer, confirms that NFT increases are largest in brain regions with the strongest functional connectivity to the epicenter at BL. This precision approach may increase the efficiency of AD clinical trials. **References & Acknowledgements:** 1. Franzmeier et al., Nat Commun. 2020; 2. Reuter et al., Neuroimage. 2012; 3. Cox RW, Comput Biomed Res. 1996; 4. Schaefer et al., Cereb Cortex. 2018; 5. Tian et al., Nat Neurosci. 2020; 6. Glasser et al., Neuroimage. 2013; 7. Smith et al., Neuroimage. 2013. The authors would like to acknowledge the following institutions for contributing the imaging data to the Cerveau consortium: University of Wisconsin, Massachusetts General Hospital, Biogen Inc. Author conflicts of interest statements: ZSS, RD, and HCK are employed by Janssen Pharmaceuticals and may hold stock or stock options. Author CR has received research grants from NHMRC, Enigma Australia, Biogen, Eisai and Abbvie. He is on the scientific advisory board for Cerveau Technologies and consulted for Prothena, Eisai, Roche and Biogen Australia.

OC08- INDIVIDUALISED TAU-PET MEASURES MIGHT BE SUPERIOR TO GROUP LEVEL MEASURES WHEN DETERMINING CHANGE IN TAU DEPOSITION OVER TIME IN ALZHEIMER'S DISEASE. A. Leuzy[1], A. Pichet-Binette[1], J. Vogel[2], G. Klein[3], E. Borroni[3], M. Tonietto[3], O. Strandberg[1], N. Mattsson-Carlgren[1], S. Palmqvist[1], E. Stomrud[1], R. Ossenkoppele[1], R. Smith[1], O. Hansson[1] *(1. Clinical Memory Research Unit, Department of Clinical Sciences, Lund University, Malmö, Sweden - Lund (Sweden), 2. Penn/CHOP Lifespan Brain Institute, University of Pennsylvania, Philadelphia, PA, USA - Philadelphia (United States), 3. F. Hoffmann-La Roche Ltd, Basel, Switzerland - Basel (Switzerland))*

Background: Though clinical trials in Alzheimer's disease (AD) typically use change in cognition as a primary outcome, the use of longitudinal tau positron emission tomography (PET) as a (secondary) outcome is becoming increasingly more common. Regions of interest (ROIs) are typically used to summarize change in tau-PET signal over time. To date, most ROIs have been based on neuropathological studies or data-driven approaches where the same ROI is used for each subject (i.e., group-level ROI). However, given the inter-individual heterogeneity in spatial patterns of tau-PET, a key question is whether the use of subject-specific (i.e., individualized) ROIs might offer any advantages over group-level ROIs in AD clinical trials. **Objectives:** To i) compare longitudinal change

in tau-PET estimated using group-level vs. individualized ROIs; ii) assess the number of patients required to detect a 25% reduction in the rate of change of either regional tau-PET or cognition across the different clinical stages of AD using group-level or individualized ROIs. **Methods:** Our sample consisted of 215 participants from BioFINDER-2 with longitudinal (baseline, 2-year) tau-PET using [18F]RO948 and longitudinal cognition. This included 97 Aβ-positive cognitively unimpaired individuals (preclinical AD), 77 Aβ-positive MCI patients (prodromal AD) and 41 patients with mild AD dementia (Mini-Mental State Examination [MMSE] ≥ 22). Longitudinal cognitive measures included MMSE and the modified Preclinical Alzheimer's Cognitive Composite (mPACC). Annual change in [18F]RO948 standardized uptake value ratio (SUVR) was calculated ROI-wise as the difference between follow-up and baseline, divided by baseline uptake and multiplied by the time interval between scans in years: ([follow-up SUVR – baseline SUVR] / baseline SUVR) × 100 / Δtime. Group-level ROIs included i) five ROIs reflecting event-based modelling stages (data-driven stages) and ii) six ROIs reflecting Braak stages; iii) a temporal meta-ROI and iv) a whole-brain composite-ROI. Individualized ROIs included i) epicenter (top 10% of regions with highest tau at baseline), ii) Q1 (top quartile of regions closest to subject-specific epicenter based on functional connectivity), iii) probability-based approach (Gaussian mixture modelling was performed on cross-sectional data to extract probabilities of being tau-positive across individual FreeSurfer ROIs; percent change in SUVR was then calculated for different probability intervals, with selection based on the interval that provided the highest annual percent change in SUVR). A final individualized approach was used based on calculating change in tau-PET in iv) highest data-driven stage that showed abnormal tau-PET signal at baseline using Gaussian mixture modelling-based cut-offs. Change in MMSE and mPACC were calculated as slopes derived from linear mixed models. Power calculations were performed using group-wise analyses (preclinical AD, prodromal AD, mild AD dementia) of tau-PET and cognition data to determine sample size estimates for an intervention with a hypothetical intervention effect of 25%. **Results:** Using the group-level ROIs, the greatest changes in tau-PET SUVR were seen using the data-driven stage I (preclinical AD, 5.14%), II (prodromal AD, 6.23%) and IV (mild AD dementia, 8.90%), which encompassed medial temporal, temporal and frontal lobe regions, respetively. In comparison to group-level ROIs, higher annual change in tau-PET SUVR was seen using individualized ROIs, with the approach iv ("highest data-driven stage approach") performing best in all groups (preclinical AD, 6.4%; prodromal AD, 8.67%; mild AD dementia, 10.72%). In comparison to longitudinal cognition as an outcome, tau-PET using best-performing group-level ROIs as an outcome resulted in greater sample size reductions (preclinical AD: data-driven stage I, 58% fewer subjects compared to mPACC and 63% compared to MMSE; prodromal AD: data-driven stage II, 54% fewer subjects compared mPACC and 65% compared to MMSE; mild AD dementia: data-driven stage IV, 64% fewer subjects compared mPACC and 51% compared to MMSE). Using the best performing individualized ROI (highest data-driven stage) resulted in even greater differences compared to cognitive measures (74% for preclinical AD compared to mPACC, 71% for prodromal AD and 67% for mild AD dementia compared to MMSE). **Conclusion:** Using longitudinal tau-PET as an outcome in early phase trials require fewer participants when compared to cognitive decline in AD clinical trials. If using longitudinal tau-PET as outcome, individualized ROIs appear to carry an advantage over group-level ROIs.

OC09- PREVALENCE AND LONGITUDINAL CLINICAL OUTCOMES OF VISUALLY 18F-FLORTAUCIPIR PET-POSITIVE INDIVIDUALS ACROSS THE ALZHEIMER'S DISEASE SPECTRUM. A. Moscoso[1], F. Heeman[1], V. Camacho[2], M. Van Essen[3], M.J. Grothe[4], L. Lin[5], I. Mainta[6], F. Ribaldi[7], M.D. Devous[8], M.J. Pontecorvo[8], G.B. Frisoni[7], V. Garibotto[7], M. Schöll[1] *(1. Wallenberg Centre for Molecular and Translational Medicine, University of Gothenburg - Gothenburg (Sweden), 2. Department of Nuclear Medicine, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain. - Barcelona (Spain), 3. Department of Clinical Physiology, Sahlgrenska University Hospital, 413 45 Gothenburg, Sweden. - Gothenburg (Sweden), 4. Movement Disorders Group, Institute of Biomedicine of Seville-IBiS, Seville, Spain. - Sevillla (Spain), 5. Department of radiology, the third affiliated hospital of sun yat-sen university. - Guangzhou (China), 6. Division of Nuclear Medicine, Geneva University Hospitals, Geneva, Switzerland. - Genève (Switzerland), 7. Geneva Memory Center, Department of Rehabilitation and Geriatrics, Geneva University Hospitals, Geneva, Switzerland - Genève (Switzerland), 8. Avid Radiopharmaceuticals, Philadelphia, PA, USA - Philadelphia (United States))*

Background: The advent of positron emission tomography (PET) imaging with [18F]flortaucipir has allowed in-vivo visualization of aggregated tau in Alzheimer's disease (AD). Recently, a visual interpretation method for [18F]flortaucipir was developed and validated using neuropathological data, showing that tau-PET positivity can be regarded as a marker of advanced Braak stages (V-VI). This led to the approval of [18F] flortaucipir by the US Food and Drug Administration (FDA) as the first PET radiopharmaceutical indicated to 'estimate the density and distribution of aggregated neurofibrillary tangles'. In the clinical trials realm, this visual tau-PET positivity is one of the key eligibility criteria for inclusion in Donanemab trials. Yet, despite the relevance of this novel visual interpretation method, relevant variables for trialists such as the prevalence of visual tau-PET positivity across the AD spectrum or the longitudinal outcomes associated to visual tau-PET-positivity have not been investigated before. **Objectives:** 1) To estimate the prevalence of visual tau-PET positivity across the AD spectrum. 2) To establish the longitudinal clinical course of visually tau-PET-positive individuals across the AD spectrum. **Methods:** We included cognitively unimpaired individuals and patients with mild cognitive impairment (MCI) and AD dementia from five observational cohort studies — Alzheimer's Disease Neuroimaging Initiative (ADNI), Harvard Aging Brain study (HABS), A4 study, AVID's A05 study and Geneva Memory Clinic cohort — all of which had available FTP PET scans (n=1828, 1219 unimpaired, 425 MCI, and 184 AD dementia). Furthermore, Aβ status, established with Aβ-PET, was available in 1724 participants (94%), and longitudinal clinical and cognitive data was obtained for 523 unimpaired (median follow-up: 2 years) and 372 impaired (median follow-up: 1.5 years) participants. A trained reader (AM), blinded to clinical and imaging information, scored each [18F]flortaucipir PET scan as either negative or positive, and additionally classified positive [18F]flortaucipir PET scans as either moderate or advanced AD patterns. Multinomial generalized additive models (GAM) were fitted to obtain prevalence estimates of each [18F]flortaucipir AD pattern. Linear mixed models were used to estimate cognitive decline trajectories across Aβ- and visual tau-PET groups (A±vTAU±). **Results:** Among all cognitively unimpaired individuals, the prevalence of visual tau-PET positivity was 13.4%, with similar prevalence of moderate and advanced AD patterns (6.1% and 7.3%, respectively). The prevalence

of tau-PET-positivity increased non-linearly with age from ~5% at 65 years to 17% at 90 years. Tau-PET positivity was strongly dependent on Aβ status, showing high specificity (97.8%) for Aβ pathology. In the Aβ-positive unimpaired cohort of the A4 study, 24% of the participants were tau-PET-positive. In longitudinal analyses, A+vTAU+ unimpaired individuals showed the fastest rates of cognitive decline (Aβ+/vTAU+: ΔPACC3 = -0.34/y, p=0.02; Aβ+/vTAU-: ΔPACC3 = -0.16/y, p=0.06; Aβ-/vTAU- as reference). In cognitively impaired individuals, the overall prevalence of tau-PET positivity was 38.1% for MCI and 71.2% for AD dementia, with a much higher relative prevalence of the advanced pattern compared to the moderate (only 8.0% of MCI and 5.4% of AD dementia participants showed a moderate pattern). For both MCI and AD dementia participants, the prevalence of the advanced pattern decreased with age while that of the moderate pattern increased with age. As for unimpaired individuals, tau-PET positivity was highly specific for Aβ pathology (95%). In the longitudinal analysis, only the advanced AD pattern was significantly associated with faster clinical deterioration in MCI or AD dementia patients as measured by longitudinal MMSE, CDR-SB or ADAS-Cog 11. There were no significant differences between the clinical trajectories of A-vTAU- and A+vTAU- individuals. **Conclusion:** Our large-scale study provides the first robust estimates of the prevalence and longitudinal clinical outcomes of tau-PET positive individuals as defined using a clinically applicable, FDA-approved method. These estimates indicate that a non-negligible fraction of the cognitively unimpaired elderly population is tau-PET positive, indicative of advanced Braak stages. This prevalence increases even more among Aβ-positive unimpaired persons, with approximately 1 out of 4 unimpaired Aβ-positive being tau-PET-positive in the A4 study. Together with the fact that tau-PET-positive subjects show the fastest rates of clinical decline, this relatively high prevalence of unimpaired individuals in advanced Braak stages may be relevant for prevention trials using anti-amyloid therapies. The fact that A-vTAU- and A+vTAU- impaired individuals had similar longitudinal clinical outcomes suggests that the advanced AD pattern, and not amyloid pathology, is the main driver for AD-related clinical symptoms.

OC10- CONCORDANCE OF VISUAL AND QUANTITATIVE ANALYSIS FOR AMYLOID PET IMAGING WITH THREE 18F TRACERS IN THE CHARIOT-PRO SUBSTUDY.

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Background: Assessment of amyloid burden has been essential in the selection of patients most likely to be informative of safety and efficacy in clinical trials of amyloid-directed therapy. Three 18F PET tracers are approved for assessment of amyloid status through visual interpretation; quantitative thresholds of Standard Uptake Value Ratios (SUVR) have been defined for each, and a common centiloid (CL) scale has been derived from the linear relationship among the SUVRs of each tracer. While it may be desirable to choose a specific tracer for use within a single clinical trial, the long duration of these studies and their geographic range may require one to use 2 or more approved tracers, and the potential impact of this on consistency of performance needs to be explored. **Objectives:** To compare the performance of three 18F amyloid tracers in an observational trial, the CHARIOT-PRO Substudy (CPSS). **Methods:** The CPSS aims to assess the rate of longitudinal cognitive change in equal numbers of cognitively unimpaired elders with and without biomarker evidence of increased cerebral amyloid burden (A+ and A-, respectively). Participants were recruited at 2 centers in the UK, Imperial College London and the University of Edinburgh; the majority had amyloid assessment via PET. PET exams were acquired using a uniform scanning protocol that minimizes between-site differences in PET systems, as characterized with a Hoffman phantom exam. All exams were acquired in 3D mode, with correction for attenuation (CT-based), scatter and random coincidence. Visual assessments of the scans were performed by one of 3 neuroradiologists in a central laboratory, according to the prescribing information for each tracer, blinded to SUVR. Quantitative analysis involved coregistration of the image to each participant's baseline 3DT1 MRI. A composite SUVR was calculated as the volume-weighted average across FreeSurfer target and reference subregions derived from native-space MRI. The thresholds for amyloid positivity for each tracer were: Florbetapir, > 1.14 referred to whole cerebellum; Florbetaben, > 1.20 referred to cerebellar gray matter; and Flutemetamol > 1.21 referred to whole cerebellum. Composite SUVRs were then re-scaled to centiloid units, using linear regression derived by the central laboratory. PET positivity was determined using a hybrid approach. Concordant visual and quantitative assessments were accepted as A+ or A-, respectively. A negative visual read with an above threshold SUVR was considered A+. In case the visual read was positive and SUVR was below threshold, a second reader considered both results and made a final determination via consensus with the first reader. In case the SUVR was deemed unreliable, results were determined by consensus of 2 visual readers. Agreement between the visual read and SUVR were quantified by the kappa statistic. The sensitivity and specificity of the SUVR threshold defined for each tracer was calculated with respect to the results of the visual read, and an optimized SUVR cutpoint for predicting visual reads was determined by ROC analysis. Similarly, sensitivity and specificity were derived for a CL value of > 22 relative to the visual read, and this was compared to the optimized CL values resulting from ROC analysis. **Results:** A total of 1170 participants had amyloid PET, of whom 1112 had complete visual reads and SUVR (207 A+, 905 A-). Overall concordance was 95.5% and kappa = 0.837, indicating good agreement, but 49 of the 50 discordant cases were visual positive (V+) and SUVR negative (SUVR-). Thus, the visual read identified a higher proportion of participants as A+ (18.6%) than did SUVR (14.3%). Concordance was nominally higher for Florbetapir (n=178, A+=20.8%, concordance=98.3%, kappa=0.948) than for Florbetaben (n=615, A+=17.7%, concordance=95.1%, kappa=0.812) and Flutemetamol (n=319, A+=18.6%, concordance=94.7%, kappa=0.807). With respect to the visual read, the defined cutpoints yielded a sensitivity/specificity of 94.6%/99.3% for Florbetapir, 67.9%/100% for Florbetaben, and 70.1%/100% for Flutemetamol. These observations suggested that the defined SUVR cutoffs for the latter 2 tracers, derived from limited data available in 2015 and 2014 respectively, were too conservative. ROC analysis identified less stringent SUVR thresholds for each tracer (> 1.115 for Florbetapir and Florbetaben, and > 1.08 for Flutemetamol).; in the pooled population, sensitivity/specificity were 94.7%/96.6%. Using a defined threshold CL value > 22, 20.1% of the pooled population was identified as A+, with a sensitivity/specificity of 94.2%/96.7%. ROC analysis yielded an

identical CL threshold of > 22. **Discussion:** Use of a universal CL threshold of 22 units allowed for a consistent mapping of quantitative to qualitative assessments in a study that used 3 different amyloid tracers for participant selection. While there was no direct within-subject tracer comparison in this study, the concordance of the visual assessment with a CL cutoff of 22 across tracers suggests their performance is comparable and supports the use of multiple tracers for patient selection in clinical trials. ZSS, GN, and SB are employed by Janssen and may hold stock or stock options; LB and DS are employees of Clario but declare no conflicts.

OC11- AMYLOIDIQ QUANTIFICATION STRONGLY AGREES WITH BOTH HISTOPATHOLOGY AND VISUAL READS ACROSS MULTIPLE AMYLOID TRACERS.

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Background: Neuritic plaques formed predominantly of misfolded Amyloid-β (Aβ) are one of 2 pathological hallmarks of Alzheimer's Disease (AD). Amyloid PET imaging with one of the FDA approved amyloid PET radiotracers provides a method to detect Aβ pathology in vivo. Scans are routinely classified as either positive (Aβ+) or negative (Aβ-) by visual assessment (often with a majority read from multiple independent reads). With the advance of quantitative algorithms such as AmyloidIQ, which has shown strong performance in cross-sectional and longitudinal studies, it now becomes possible to provide an automated quantitative assessment of Aβ pathology in the brain. **Objectives:** In this work, we assess the performance of AmyloidIQ against gold-standard post-mortem histopathology data and against visual assessment performed by trained readers for the PET tracers [18F]Florbetaben and [18F]Florbetapir. Within these analyses we also compared the performance of AmyloidIQ with a PET only pipeline and also with an associated structural MRI image available. **Methods:** There were 3 distinct analyses performed on different datasets in this work. In the first, histopathology (either Bielschowsky silver staining (BSS) or Immunohistochemistry (IHC)) was compared to AmyloidIQ quantification of ante-mortem [18F] Florbetaben scans for both PET-MR and PETOnly AmyloidIQ pipelines (PET-MR: n = 80, 25 Aβ-, 35 Aβ+ and PETOnly: n = 88, 35 Aβ-, 54 Aβ+). The second and third were comparisons of AmyloidIQ quantification with visual reads with [18F] Florbetaben (PET-MR: n = 345, 173 Aβ-, 172 Aβ+ and PETOnly: n = 439 , 246 Aβ-, 193 Aβ+) and [18F]Florbetapir (PET-MR and PETOnly: n=610, 313 Aβ-, 297 Aβ+) respectively. The visual reads for both analyses were performed by 5 experienced independent readers. The AmyloidIQ algorithm models spatially normalised SUVR images as the linear combination of two canonical images (carrying capacity image K and non-specific image NS) to produce a single continuous outcome measure, Amyloid Load (AβL), which quantifies the global amyloid burden. AmyloidIQ was successfully run on all scans from all 3 datasets with the only difference between PET-MR and PETOnly pipeline being the spatial normalisation algorithm (PET-MR: nonlinear using DARTEL, PETOnly: affine). Histopathology and visual reads provided a classification of the presence or absence of amyloid pathology (Aβ pathology was considered present, if any of the 6 regions sampled had moderate or frequent neuritic plaques either by BSS or IHC or both) and Aβ+/Aβ- respectively. ROC curve analyses produced optimum thresholds for AβL for classification for both PET-MR and PETOnly pipelines. The accuracy of each methodology was evaluated at these optimum thresholds using both histopathology and visual reads as a gold standard. **Results:** The comparison of AmyloidIQ against post-mortem data yielded a strong agreement (PET-MR: Accuracy 95.0% with sensitivity 94.5% and specificity 96.0% and PETOnly: Accuracy 95.5% with sensitivity 94.4% and specificity 97.1%) at the optimum thresholds (PET-MR: 35.6% and PETOnly: 42.3%). Visual reads also exhibited a strong agreement with AmyloidIQ regardless of the tracer used. More specifically, in the [18F]Florbetapir data, the accuracy of the PET-MR pipeline was 93.4% and the accuracy of the PETOnly pipeline was 93.1%. The optimum AβL thresholds for the two pipelines were similar (PET-MR: 32.5% and PETOnly: 35.6%). The [18F]Florbetaben results were remarkably similar. The accuracy of the PET-MR pipeline was 94.5% at the optimum AβL threshold of 35.6% and the accuracy of the PETOnly pipeline was 93.2% and cut-off at the optimum AβL threshold of 42.3%. **Conclusion:** AmyloidIQ analysis of [18F]Florbetaben scans exhibits a very strong agreement with both histopathology (IHC/BSS) data and visual assessment. Further, AmyloidIQ analysis of [18F]Florbetapir also showed a very strong agreement with visual assessment. AmyloidIQ classification was unaffected without an associated MRI scan which paves the way for the straightforward deployment in the clinical setting. The optimum thresholds found in all circumstances were extremely similar and the carrying capacity image can be calibrated to produce a standardised threshold of 33% across all tracers and pipelines hence providing a global and easily interpretable scale for AβL. This extensive assessment of AmyloidIQ against the gold-standard measures of post-mortem data and visual reads shows that its quantification can be used to both detect amyloid burden in the brain and automate the visual assessment of amyloid PET scans.

OC12- TOPLINE RESULTS OF EXERT: CAN EXERCISE PROTECT AGAINST COGNITIVE DECLINE IN MCI?

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Background: There are currently no effective therapeutic options to delay the progression of Alzheimer's disease (AD). The potential benefits of exercise on brain health in older adults at risk for AD are supported by preliminary studies and warrant further investigation. The EXERT trial (NCT02814526) was a Phase 3, multicenter, randomized single-blind study that examined the effects of regular exercise on cognition and other measures of brain function in a planned sample of 300 older adults with amnestic mild cognitive impairment (MCI). **Objective:** To test whether 12 months of supervised moderate intensity aerobic exercise versus an active control of stretching and balance protected against cognitive decline and other measures of AD progression in adults with MCI. **Methods:** EXERT was conducted at 14 sites and coordinated by the Alzheimer's Disease Cooperative Study (ADCS), in partnership with Wake Forest School of Medicine and the YMCA of the USA (Y-USA) for oversight of intervention delivery. Participants were randomized to complete aerobic exercise (AX) training or stretching, balance, and range of motion (SBR) activities for 18 months. For the first 12 months, exercise was completed with supervision of YMCA trainers twice per week, and independently twice per week. In the final 6 months (Months

13-18), participants completed exercise without supervision. The AX group completed moderate intensity exercise indicated by elevated heart rate (65-70% of heart rate reserve) and ratings of exertion. The SBR group exercised at a lower heart rate (<35% heart rate reserve) and ratings of exertion. Objective measures of adherence were tracked and monitored regularly by exercise specialists (Wake Forest, Y-USA). Outcomes assessments were completed in the clinic at baseline, and at Months 6, 12, and 18. The primary endpoint included outcomes obtained at Months 6 and 12. A modified version of the ADAS-Cog13 that included select subtests with additional measures of executive function (referred to as the ADAS-Cog-Exec) was validated and used as the primary outcome. Additional tests of executive function and memory were administered, blood was collected for AD biomarker analysis, and brain MRI was completed. In addition, 12-month changes in the ADAS-Cog-Exec and Clinical Dementia Rating Sum of Boxes (CDR-SB) were compared for both EXERT intervention groups relative to propensity-matched samples from other cohorts (e.g., ADNI-1) to estimate treatment effects relative to no intervention (i.e., "Usual Care"). **Results:** A total of 296 participants were enrolled from September 2016 to March 2020. Over 31,000 exercise sessions were completed in the 12-month supervised phase of the study, 18,045 of which (58.2%) were supervised by a trainer. For the AX group, 81% of expected supervised sessions were completed; for the SBR group, 87% of expected supervised sessions were completed. During the COVID-19 pandemic when the study was paused, >60% of participants reported continued exercise. The AX and SBR groups were balanced in baseline characteristics; 13.2% represented communities of color, and 40% did not have a college degree. Baseline MMSE and CDR-SB scores indicated that EXERT participants had mild cognitive impairments (mean MMSE=27.9; mean CDR-SB=1.5), and 25% of the sample were APOE4 carriers. Using a modified ITT approach (i.e., ppts must have initiated exercise and completed at least 1 follow-up assessment) to data analysis, neither the AX group nor the SBR group showed cognitive decline on either the ADAS-Cog-Exec or the CDR-SB over 12 months of follow-up. There were no significant treatment differences between AX and SBR on these outcomes. In the Usual Care analysis comparing ADNI-1 and EXERT participants matched on several key variables (demographics, baseline cognitive function, APOE4), ADNI-1 participants showed the expected 12-month decline on the ADAS-Cog-Exec but the EXERT AX and SBR groups did not (ADNI-1: vs. AX: p=0.012; vs. SBR: p=0.00049). **Conclusions:** In past smaller trials, exercise-related benefits were observed showing relative 'protection against decline' vs. the control group that showed expected rates of decline for adults with MCI. In EXERT, the expected 12-month declines for the control group did not occur. Our findings suggest that both exercise interventions stalled cognitive decline for adults with MCI. EXERT is the longest exercise trial in MCI conducted to date, and it is possible that greater 'volume' of exercise provided more protection, regardless of exercise intensity. In addition, both groups were provided with equal amounts of socialization, which may have also protected against decline. These results are particularly noteworthy given that the trial was conducted during the COVID-19 pandemic. **Funding:** NIH/NIA U19 AG010483

OC13- SENOLYTIC THERAPY TO MODULATE THE PROGRESSION OF ALZHEIMER'S DISEASE (STOMP-AD) – PILOT STUDY RESULTS ON CENTRAL NERVOUS SYSTEM PENETRANCE AND ALZHEIMER'S DISEASE BIOMARKERS.

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Objectives: Cellular senescence, a hallmark of biological aging, is a novel therapeutic target for neurodegenerative disease, which leverages the geroscience approach to disease prevention and treatment. Accumulation of senescent cells across tissues, including the brain, increases with aging. Senescent cells can produce a noxious secretome of cytokines and chemokines, which propagates inflammation and induces tissue dysfunction if not efficiently cleared by immune system. In the brain, senescent cells frequently colocalize with neuropathology. Preclinical studies have demonstrated that pharmacological ablation of senescent cells dampens inflammation, reduces ventricular enlargement, preserves neuronal and synaptic density, attenuates neuropathological burden, and improves cognitive behavior. However, the safety and efficacy of this novel therapeutic approach, referred to as "senolytics", in humans with cognitive impairment remains unestablished. Herein, we conducted a vanguard open-label clinical trial of senolytic therapy for Alzheimer's disease. The primary objectives were to evaluate the safety profile of intermittent orally-administered dasatinib and quercetin and determine central nervous system penetrance of the compounds. We also aimed to gain preliminary data into treatment effects on cognitive function, fluid biomarkers of AD pathogenesis, and senescence-associated inflammation. **Methods:** Participants with a clinical diagnosis of early-stage AD (CDR Global = 1) were enrolled in an open-label twelve-week pilot trial of intermittent orally-delivered dasatinib (100 mg) and quercetin (1000 mg). Safety was continuously monitored with adverse event reporting, vitals, and laboratory work. Plasma and cerebrospinal fluid (CSF) levels of dasatinib and quercetin were assessed before treatment and within four hours after final study drug administration using HPLC with tandem mass spectroscopy. CSF levels of Ab40, Ab42, phosphorylated tau 181 (p-tau 181), p-tau 231, neurofilament light (NFL), and glial fibrillary acidic protein (GFAP) were assayed using the Simoa HD-X Analyzer. For purposes of rigor, we also used Lumipulse to measure Ab40, Ab42, total tau, and p-tau 181; and capillary electrophoresis for measuring total and phosphorylated tau. Target engagement was assessed by investigating treatment-related changes in plasma and CSF markers of senescence and the senescence-associated secretory phenotype by Meso Scale Discovery Immunoassays. Paired t-tests were used to examine differences in biomarker levels pre- and post-treatment. **Results:** Five participants (40% female) with a mean age of 76±4 years completed the open-label trial. The treatment was well-tolerated with no significant changes in vitals, complete blood counts, and comprehensive metabolic panels (all p>0.05). The primary cognitive endpoints, the CDR Sum of Boxes (CDR SOB, t(4)=2.449, p=0.070) and the Montreal Cognitive Assessment (MoCA, t(4)=-0.196, p=0.854) were stable from pre- to post-treatment. Dasatinib was detected in plasma (t(4)=3.612, p=0.023) and CSF (t(4)=3.123, p=0.035) following treatment. Plasma quercetin levels were higher post-treatment (t(4)=2.847, p=0.047), whereas quercetin levels in CSF were undetectable across timepoints. Simoa results demonstrated

that in four out of five participants, CSF levels of p-tau 181 and the p-tau 181/Ab1-42 ratio decreased from pre- to post-treatment. There was a significant increase in CSF GFAP levels across timepoints (t(4)=3.354, p=0.028). Mean treatment-related changes in all other AD biomarkers did not reach statistical significance (Ab40: t(4)=0.274, p=0.797, Ab1-42: t(4)=-0.092, p=0.931, p-tau 181: t(4)=-1.521, p=0.203, p-tau 181/Ab1-42: t(4)=-0.869, p=0.434, p-tau 231: t(4)=-0.152, p=0.887, NFL: t(4)=-0.096, p=0.928). Lumipulse data indicated that in four out of five participants, Ab1-42 increased and the tau/Ab1-42 ratio decreased, although the results for the whole sample did not reach statistical significance (Ab1-42: t(4)=2.338, p=0.0795, p-tau 181/Ab1-42: t(4)=1.606, p=0.1835). Capillary electrophoresis demonstrated that high molecular weight p-tau 181 significantly decreased in all subjects with treatment (t(4)=2.941, p=0.0424) though the lower molecular weight tau did not change (t(4)=0.8199, p=0.4583). Assays of senescence in plasma and CSF are underway. **Conclusion:** Results from the first clinical trial of senolytic therapy in older adults with AD indicates that the treatment was well-tolerated. Preliminary data from our open-label pilot supports central nervous system penetration of dasatinib. While early results are promising, fully powered, double-blinded, placebo-controlled studies are needed to evaluate the potential of disease modification with the novel approach of targeting cellular senescence in AD.

OC14- A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, PHARMACODYNAMICS AND PHARMACOKINETICS OF TW001 IN ALZHEIMER PATIENTS. R. Van Der Geest[1], A. Lili[1], O. Van Loosbroek[1], A. Almeida[1], M. Oosthoek[2], C. Teunissen[2], S. Sikkes[3], E. Vijverberg[2] *(1. Treeway TW001AD BV - Tilburg (Netherlands), 2. Neurochemistry Laboratory, Department of Clinical Chemistry, Vrije Universiteit Amsterdam, Amsterdam UMC - Amsterdam (Netherlands), 3. Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC - Amsterdam (Netherlands))*

Background: The pathological hallmarks of Alzheimer's disease (AD) are the amyloid-beta (Aβ) plaques and the tau neurofibrillary tangles. Recent failures in phase 3 studies of anti-amyloid agents and tau aggregation inhibitors in patients with early stage, mild or mild to moderate AD suggest that novel approaches to drug development are urgently needed. Oxidative stress has been reported to be a prominent early event in the pathogenesis of AD. Reactive oxygen species (ROS) can alter the physical structures of proteins and accompanied by reactive nitrogen species (RNS) can induce cell membrane lipids to undergo peroxidation under oxidative stress conditions. All these oxidative stress products accumulate and trigger AD development. Accumulated in vitro and in vivo evidence has demonstrated that edaravone, a free radical scavenger with the ability to cross the blood brain barrier, can be effective in AD. In particular, edaravone can reduce oxidative stress in animal models of AD, measured by a reduction of pro-oxidants or products of lipid peroxidation or an increase in antioxidants in different brain regions. Moreover, the studies indicate that there is a neuroprotective effect of edaravone on several other levels that could reduce the rate of AD progression. This is indicated by the effect of edaravone on pro-inflammatory cytokines and on the cholinergic system, the latter being the main system targeted by current medication in the treatment of AD dementia. The intravenous formulation of edaravone is already on the market in a variety of countries (including the US and Japan) initially to reduce neuronal damage caused by Acute Ischemic Stroke (AiS) and later in the treatment of Amyotrophic Lateral Sclerosis (ALS). Treeway B.V. has developed an oral formulation for edaravone (TW001) to overcome the challenges related to intravenously administered edaravone for the treatment of ALS. This formulation is currently being tested in a Pivotal Phase 3 Clinical Trial in Europe. **Objectives:** It is hypothesized that an antioxidant therapy, such as edaravone, might also be a promising treatment strategy for AD, as oxidative stress plays a pivotal role in the development and progression of the disease. Current treatment options for AD, however, do not target oxidative stress. This is the first study that aims to investigate the effect of an antioxidant treatment for early AD. In light of this, Treeway B.V., supported by ADDF, has planned to initiate a Phase IIA clinical trial in AD patients in collaboration with the VU Medical Center and the Brain Research Center in Amsterdam. **Methods:** This is a double-blind, randomized, placebo-controlled, phase IIA proof-of-concept study to evaluate the safety, pharmacodynamics and pharmacokinetics of TW001 in mild AD patients. Although the primary objective of this highly innovative study design is to investigate the effect of oral edaravone on a series of disease and target engagement (e.g., oxidative stress) biomarkers, the study will also explore the early effect of edaravone on a variety of individual biomarkers and surrogate endpoints such as EEG, to define a potential composite biomarker that can be used in subsequent long-term clinical studies. In addition, a newly developed and highly sensitive clinical assessment tool (Cognitive-Functional Composite - CFC), developed by the Alzheimer Center of Amsterdam, will be tested in the study as a clinical outcome measure to potentially detect early changes in cognitive function. **Conflict of interest:** Treeway TW001AD B.V. has received a research grant in November 2019 sponsored by ADDF (reference GC-2013807) for the development of this project.

OC15- PROTEIN BIOMARKERS IN AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE CEREBROSPINAL FLUID IDENTIFY EARLY CHANGES IN BRAIN GLUCOSE METABOLISM AND THE MATRISOME. S. Bian[1], E.K. Carter[1], R. Haque[1], C. Watson[1], B. Gordon[2], L. Ping[1], D. Duong[1], M. Epstein[1], J. Lah[1], B. Roberts[1], A. Fagan[2], N. Seyfried[1], A. Levey[1], E. Johnson[1] *(1. Emory University - Atlanta (United States), 2. Washington University - St. Louis (United States))*

Background: Alzheimer's disease (AD) is characterized by multiple pathological brain alterations beyond amyloid-β (Aβ) and tau dyshomeostasis. How these pathological changes evolve over the course of the disease and are reflected by current AD biomarkers is currently unknown. **Objectives:** To better understand the natural history of AD pathology, we analyzed cerebrospinal fluid (CSF) from autosomal dominant AD (ADAD) mutation carriers and family member controls by targeted mass spectrometry to measure the levels of multiple proteins related to disease. The proteins were mapped to different AD brain pathologies as recently described in a consensus proteomic brain co-expression network of late-onset AD. **Methods:** 59 proteins were measured in 284 ADAD mutation carriers and 183 non-carriers in the Dominantly Inherited Alzheimer Network (DIAN). Measurements were obtained from baseline visits, and protein levels for each subject were placed in a longitudinal framework by the estimated year of disease onset (EYO). To better approximate protein levels sampled at a discrete set of EYO time points, we modeled EYO using a restricted cubic spline transformation with three knots

at the 0.10, 0.50, and 0.90 quantiles. To achieve uncertainty estimates and to account for random effects imposed by shared genetic background, the Bayesian regression model was built using a Markov Chain Monte Carlo algorithm and was applied to model the relationship between protein levels and fixed effects including mutation status, EYO, and the interaction effect. Differences in protein levels between mutation carriers and non-carriers at the 99% confidence interval were inferred using the posterior coefficient estimates from the Bayesian regression model at discrete EYO 0.5 year intervals between -36 and 26. The time at which protein biomarker levels in carriers were noted to diverge from non-carriers was compared to other biomarker changes measured in DIAN. **Results:** 29 proteins out of the 59 targeted for measurement were found to be different between mutation carriers and non-carriers at any EYO time point, with most proteins increased in mutation carrier CSF. Proteins derived from the brain matrisome co-expression module associated with Aβ deposition were among the earliest to change in mutation carriers—earlier than the absolute decreased levels of Aβ42 and nearly 30 years prior to symptom onset—followed by synaptic proteins and proteins associated with glucose metabolism. Markers of glucose metabolism were elevated at approximately the same time point as tau phosphorylated at residues 217 and 181 (pTau217 and pTau181). Multiple proteins associated with inflammation were noted to increase concomitantly with decreases in brain tissue and metabolism as assessed by MRI and metabolic imaging. Decreased levels of proteins from the granin family were found to be associated with cognitive impairment and functional decline. **Conclusion:** Proteomic approaches are able to identify novel brain-based biomarkers for AD. Measurement of these AD biomarkers in DIAN provides insight into the natural history of AD pathophysiology, which begins approximately three decades prior to the onset of cognitive symptoms in ADAD. The authors declare no competing interests. On behalf of the Dominantly Inherited Alzheimer Network.

OC16- LEVERAGING NOVEL TECHNOLOGIES TO DESIGN AND IMPLEMENT MORE PATIENT FOCUSED CLINICAL TRIALS.

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Late-stage Alzheimer's disease (AD) randomized controlled trials (RCTs) are typically characterized by enrolling a large number of participants, high screen failures, and a trial duration commonly ranging from 2 to 4 years. It is then critical to bring efficiency to these late-stage AD clinical trials to accelerate the drug development process while maintaining the reliability of the evidence being generated. Unlearn's novel clinical trial participant-focused approach, called TwinRCTs, enables reducing the number of participants in the control arm for a desired power while maintaining a strict control of type I error rate as with the traditional RCT. Unlearn's approach has received a draft qualification opinion from the European Medicines Agency (EMA) novel methodologies program for a 3-step procedure called PROCOVA, the foundation of our TwinRCTs. The PROCOVA procedure consists of 3 steps: Step 1 is to build and evaluate a prognostic machine learning model for use in a particular planned trial (the Target Trial); Step 2 is to estimate the sample size and plan the Target Trial using PROCOVA for the primary analysis. Step 3, taking place after Target Trial database lock, is to estimate the treatment effect using a linear model while adjusting for the prognostic score. For the Step 1 of the PROCOVA procedure, Unlearn has developed machine learning methods to build models trained with historical data that are highly suitable to be used with the PROCOVA procedure. Among our current models, we have developed an AD model leveraging historical AD data that has been used in collaboration with a number of pharmaceutical companies for determining potential use cases in their existing AD clinical programs. We have shown that for a completed Phase 2 AD clinical trial, Unlearn's approach could enable the reduction of the control arm by more than 20%. TwinRCTs, including the PROCOVA procedure, are faster, participant-focused, and more efficient RCTs that generate regulatory-suitable clinical evidence.

OC17- AMYLOID AND TAU PET POSITIVE COGNITIVELY UNIMPAIRED INDIVIDUALS: DESTINED TO DECLINE?

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Background: A major unanswered question in the dementia field is whether cognitively unimpaired individuals who harbor both Alzheimer's disease (AD) neuropathological hallmarks (i.e., amyloid-beta plaques and tau neurofibrillary tangles) can preserve their cognition over time or are destined to decline. Consequently, there is fundamental disagreement between the National Institute on Aging and Alzheimer's Association (NIA-AA) criteria and the International Working Group (IWG) criteria about the nomenclature for cognitively unimpaired individuals who harbor one or both AD hallmark neuropathological features. For example, a cognitively unimpaired individual with positive Abeta (A+) and tau (T+) biomarkers is classified as "preclinical AD" by the NIA-AA criteria, while the IWG criteria would label such an individual "at risk for progression to AD". **Objective:** In this large multi-center amyloid and tau-PET study (n=1325), we examined the risk for future progression to mild cognitive impairment and the rate of cognitive decline over time among cognitively unimpaired individuals who were amyloid-PET-positive (A+) and tau-PET positive (T+) in the medial temporal lobe (A+TMTL+) and/or in the neocortex (A+TNEO+) and compared them with A+T- and A-T- groups. **Methods:** Participants were recruited from the Mayo Clinic Olmsted Study of Aging (n=680), the Swedish BioFINDER-1 (n=56) and BioFINDER-2 (n=228) studies, the Berkeley Aging Cohort study (n=109), the Harvard Aging Brain Study (n=162), the Australian Imaging Biomarkers and Lifestyle Study of Ageing (n=48) and the Amsterdam Dementia Cohort (n=42). All participants were i) cognitively unimpaired at baseline defined by neuropsychological test scores within the normative range given an individuals' age, sex and educational background, ii) had amyloid-PET available to determine Abeta-status, iii) underwent a tau-PET scan before January 1, 2019, to allow for sufficiently long follow-up duration, and iv) had at least one clinical follow-up visit available. Follow-up data was collected until April 1st, 2022. Abeta-status was determined using center-specific cut-offs or visual read metrics using [18F] flutemetamol, [11C]Pittsburgh compound-B, [18F]florbetapir or [18F]NAV4694 PET. Tau-PET was performed using [18F] flortaucipir across all cohorts, except BioFINDER-2 where [18F]RO948 was used. We computed tau-PET status for a medial temporal lobe (MTL; unweighted average of bilateral

entorhinal cortex and amygdala) and a neocortical (NEO; weighted average of bilateral middle temporal and inferior temporal gyri) region-of-interest. The threshold was determined for each cohort separately, based on the mean+2*standard deviation across all Abeta-negative participants within each cohort. Based on amyloid and tau-PET status we generated four different biomarker groups: A-T-, A+T-, A+TMTL+ (defined as tau-PET positive in the MTL but not in the neocortex) and A+TNEO+ (defined as tau-PET positive in the neocortex and/or in the MTL). First, we examined progression from cognitively unimpaired to mild cognitive impairment (MCI) using Cox proportional hazard models, adjusting for age, sex, education and cohort using A-T- as the reference group. Second, we examined differences in cognitive trajectories between groups on the modified preclinical Alzheimer cognitive composite 5 (mPACC5) and the Mini-Mental State Examination (MMSE) using linear mixed effect models with random intercepts and slopes, adjusting for age, sex, education and cohort. Statistical significance for all models was set at $p<0.05$ two-sided. **Results:** We included 1325 cognitively unimpaired participants, of whom 843 (63.6%) were A-T-, 328 (24.8%) A+T-, 55 (4.2%) A+TMTL+ and 65 (4.9%) A+TNEO+. During clinical follow-up, 26/781 (3.3%) of A-T-, 26/292 (8.9%) of A+T-, 25/51 (49.0%) of A+TMTL+ and 32/60 (53.3%) of A+TNEO+ participants progressed to MCI. Cox proportional hazard models, adjusted for age, sex, education and cohort, showed an increased risk for future progression to MCI in the A+TNEO+ (Hazard ratio [HR]=19.2[95% confidence interval: 10.9-33.7], $p<0.001$), A+TMTL+ (HR=14.6[8.1-26.4], $p<0.001$) and A+T- (HR=2.4[1.4-4.3], $p=0.002$) groups compared to the A-T- (reference) group. Pairwise log-rank tests showed that the A+TMTL+ and A+TNEO+ groups (both $p<0.001$) had steeper survival curves compared to the A+T- group, while the A+TMTL+ and A+TNEO+ groups did not differ from each other ($p=0.19$). Fifty percent of the A+TNEO+ and A+TMTL+ groups had progressed to MCI after 42.8 and 43.6 months, respectively. Linear mixed effect models adjusting for age, sex, education and cohort indicated that the A+TNEO+ (standardized b [stb] of interaction with time in months ± standard error=-0.020±0.002, T=-10.14, $p<0.001$), A+TMTL+ (stb=-0.017±0.002, T=-8.84, $p<0.001$) and A+T- (stb=-0.005±0.001, T=-5.26, $p<0.001$) groups showed faster decline over time on the mPACC5 compared to the A-T- (reference) group. On the MMSE, the A+TNEO+ (b=-0.056±0.005, T=-11.55, $p<0.001$), A+TMTL+ (b=-0.024±0.005, T=-4.72, $p<0.001$) and A+T- (b=-0.008±0.002, T=-3.46, $p<0.001$) groups showed faster decline over time compared to the A-T- (reference) group. The A+TNEO+ (T=-9.51, $p<0.001$) and A+TMTL+ (T=-3.04, $p=0.002$) groups progressed faster than the A+T- group, and the A+TNEO+ group declined faster than the A+TMTL+ group (T=-4.82, $p<0.001$). **Conclusion:** Evidence of advanced AD pathological changes provided by amyloid and tau-PET is strongly associated with short-term (i.e., 3-5 years) cognitive decline in cognitively unimpaired individuals and is therefore of high clinical relevance. This supports the NIA-AA criteria-based classification of A+T+ cognitively unimpaired individuals as "preclinical AD", especially when "T" is defined by PET.

OC18- PLASMA NT1-TAU CORRELATES WITH AGE AND COGNITIVE DECLINE IN TWO LARGE DOWN SYNDROME COHORTS. A.M. Stern[1], K.L. Van Pelt[2], L. Liu[1], A.K. Anderson[1], B. Ostaszewski[1], D.J. Selkoe[1], F. Schmitt[2], E. Head[3] *(1. Ann Romney Center For Neurologic Diseases, Brigham And Women's Hospital, Harvard Medical School - Boston, Ma (United States), 2. Sanders-Brown Center For Aging, Department Of Neurology, University Of Kentucky - Lexington, Ky (United States), 3. Department Of Pathology And Laboratory Medicine, University Of California, Irvine - Irvine, Ca (United States))*

Background: New plasma biomarker assays can predict cognitive decline and pathology in patients with or at risk for Alzheimer disease (AD). There is a need to expand upon novel plasma biomarker profiles in people with Down syndrome (DS), who nearly universally develop AD pathology. We previously found the NT1-tau assay can predict cognitive decline and imaging biomarker changes in sporadic non-DS AD. We have also recently developed plasma assays for Aβ37, Aβ40, and Aβ42. **Objectives:** To determine whether plasma Aβ isoforms and the ratios between them, and NT1-tau, predict cognitive decline in people with DS. **Methods:** The discovery cohort from the University of Kentucky (UKY) consisted of 104 participants with 416 longitudinal plasma samples. After excluding outliers and missing data, 85 participants with 220 observations were included in the analysis. The validation cohort from the Alzheimer's Biomarker Consortium Down Syndrome (ABC-DS) consisted of 297 cross-sectional plasma sample. The NT1-tau assay was run on the Quanterix Simoa HD-X instrument, and the Aβ isoform assays on the SP-X instrument. Linear mixed models first assessed change in biomarkers in the discovery cohort over time, with covariates including baseline age, sex, level of intellectual disability (ID), and consensus diagnosis. No longitudinal effect of time was observed in the linear mixed models, so individual regressions for each biomarker were used in a cross-sectional manner for baseline discovery cohort samples to correlate with age, sex, performance on the Dementia Scale for People with Learning Disabilities (DLD), or consensus diagnosis. The regression models developed in the discovery cohort were evaluated in the validation cohort by comparing the model-predicted vs actual values. **Results:** In the discovery cohort, the Aβ42 and NT1-tau linear regression models demonstrated significant main effects of baseline age (Aβ42: $F(6, 78) = 3.37$, $p = 0.005$, R2adj = 0.14, RMSE = 18.18, $\beta = -0.70$; NT1-tau: ($F(6, 78) = 4.98$, $p < 0.001$, R2adj = 0.22, RMSE = 1.32, $\beta = 0.05$). NT1-tau was not independently associated with DLD-Total or DLD subscores when controlling for age, sex, ID, and clinical diagnosis. However, NT1-tau was significantly associated with DLD-Cognitive ($\beta = 1.76$, R2adj = 0.095, $p = 0.003$), DLD-Social ($\beta = 1.45$, R2adj = 0.11, $p = 0.002$), and DLD-Total ($\beta = 3.20$, R2adj = 0.12, $p = 0.001$) scores when Aβ40, Aβ42, Aβ37 were the only covariates. The linear regression model for NT1-tau developed in the discovery UKY cohort predicted the NT1-tau level in the validation ABC-DS cohort (correlation between actual and predicted NT1-tau $r = 0.38$, $p < 0.001$). **Conclusions:** Plasma NT1-tau and Aβ42 correlate with age in people with DS. Plasma NT1-tau correlates with cognitive decline, and its predictive power holds across two large independent cohorts. **Conflicts of Interest:** DJS is a director of Prothena Biosciences and a consultant to Eisai. KLVP is now an employee of Synaptek, LLC.

OC19- SPECIFIC ASSOCIATIONS BETWEEN PLASMA BIOMARKERS AND POST-MORTEM AMYLOID PLAQUE AND NEUROFIBRILLARY TAU TANGLE BURDEN.

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Background: Multiple plasma biomarkers have been recently developed and have shown promise as diagnostic and prognostic tools for Alzheimer's disease (AD). However, their specific relationship with post-mortem pathological burden is still not fully understood. **Objectives:** We aimed to investigate the specific associations between multiple plasma biomarkers (phosphorylated tau217 [p-tau217], p-tau181, p-tau231, amyloid-β42/40 [Aβ42/40] ratio, glial fibrillary acidic protein [GFAP], and neurofilament light [NfL]) and core pathological measures of AD pathology (amyloid plaques and neurofibrillary tau tangles) assessed at autopsy. **Methods:** We included 132 participants from the Banner Sun Health Research Institute with a post-mortem neuropathological exam and available plasma biomarkers. Plasma p-tau217 and p-tau181 were measured using immunoassay developed by Lilly Research Laboratories (IN, USA); plasma p-tau231 was analysed using in-house single molecular arrays (Simoa) developed at the University of Gothenburg and; Aβ42, Aβ40, GFAP and NfL were analyzed using in-house Elecsys prototype plasma immunoassays (not commercially available, Roche Diagnostics International Ltd). We created a global measure for both plaques and tangles, which were measured in a semi-continuous scale (0–3) in five different regions (hippocampus, entorhinal cortex, and frontal, temporal, and parietal lobes). To assess specific associations between plasma makers and each of the two AD pathological measures, we performed linear regression models with plasma biomarkers as dependent variables and measures of both plaques and tangles as independent variables. The relevance of AD pathology was also assessed using the AD neuropathological change level (ADNC) based on the NIA-AA criteria, which considers presence of both plaques and tangles. We then investigated the diagnostic accuracy of plasma biomarkers in predicting presence (intermediate/high) of ADNC using receiver operating characteristic (ROC) curve analysis. The most parsimonious models for predicting pathological measures were selected based on the corrected Akaike criterion (AICc). We inverted the Aβ42/40 ratio from the usual practice, so that higher standardized betas would represent higher pathology for an easier comparison with the other markers. **Results:** We included 54 participants with none/low ADNC and 78 participants with intermediate/high ADNC. Participants had a mean(SD) age of 84.5(8.6) years at death and 52 (39.4%) were women. In univariate analyses, all markers except NfL were associated with plaques ($0.35 \leq \beta \leq 0.67$, $p<0.001$) and tangles ($0.25 \leq \beta \leq 0.60$, $p<0.011$). When both plaques and tangles were included in the same model, the Aβ42/40 ratio and p-tau231 were associated with plaques (βinverted Aβ42/40[95%CI]=0.57[0.36,0.77]; βp-tau231[95%CI]=0.33[0.10,0.55], both $p<0.001$), while GFAP was associated with tangles (βGFAP[95%CI]=0.34[0.15,0.53], $p=0.001$). In contrast, p-tau217 and p-tau181 were associated with both plaques (βp-tau217[95%CI]=0.51[0.37,0.65]; βp-tau181[95%CI]=0.48[0.32,0.64], both $p<0.001$) and tangles (βp-tau217[95%CI]=0.32[0.17,0.47], $p<0.001$; βp-tau181[95%CI]=0.23[0.06,0.40], $p=0.008$), with p-tau217 showing a significantly higher correlation coefficient with tangles than p-tau181 (βdiff[95%CI]=0.09[0.00,0.18], $p=0.038$). A model combining p-tau217 and the Aβ42/40 ratio showed the highest accuracy for predicting presence of ADNC (AUC[95%CI]=0.89[0.82,0.96], R2=0.62) as semi-quantitative measures of plaques (R2=0.55), while p-tau217 alone showed the highest accuracy to predict semi-quantitative measures of tau tangles (R2=0.45). **Conclusion:** We observed that some plasma biomarkers are strictly associated with only amyloid pathology (the Aβ42/40 ratio and p-tau231) or only tau pathology (GFAP), whereas p-tau181 and, particularly, p-tau217 are independently associated with both pathologies. These results may have important applications for clinical trials targeting one or both hallmarks of AD as they reveal specific associations with actual pathology. We suggest that the combined use of the Aβ42/40 ratio and p-tau217 may be useful in selecting participants for trials targeting amyloid-b pathology, whereas the use of plasma p-tau217 alone may be sufficient for participant selection in trials targeting tau pathology. **Conflicts of interest:** GK is a full-time employee of Roche Diagnostics GmbH. Work at the authors' research center was supported by the Swedish Research Council (2016-00906), the Knut and Alice Wallenberg foundation (2017-0383), the Marianne and Marcus Wallenberg foundation (2015.0125), the Strategic Research Area MultiPark (Multidisciplinary Research in Parkinson's disease) at Lund University, the Swedish Alzheimer Foundation (AF-939932), the Swedish Brain Foundation (FO2021-0293), The Parkinson foundation of Sweden (1280/20), the Konung Gustaf V:s och Drottning Victorias Frimurarestiftelse, the Skåne University Hospital Foundation (2020-O000028), Regionalt Forskningsstöd (2020-0314) and the Swedish federal government under the ALF agreement (2018-Projekt0279). The funding sources had no role in the design and conduct of the study; in the collection, analysis, interpretation of the data; or in the preparation, review, or approval of the abstract.

OC20- SYSTEMIC INFLAMMATION AND REDUCED CEREBRAL AB CLEARANCE TRIGGERED BY PANCREATIC AMYLIN.

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Background: Overexpression or/and impaired clearance of amyloidogenic proteins such as islet amyloid polypeptide (amylin) and β-amyloid (Aβ) are critical pathological pathways

in both type-2 diabetes and Alzheimer's disease (AD). Data from different research teams (including our own) show cerebral amylin deposits in humans with both sporadic and familial AD; however, a potential relationship between blood amylin concentrations and AD pathology remains unclear. **Objectives:** Because amylin deposits can be detected within the cerebral blood vessels in humans with AD, we hypothesized that amylin secreted from the pancreas disturbs cerebral Aβ clearance. To test this hypothesis, we measured blood amylin concentrations in humans with and without AD and assessed the relationships with brain parenchymal and vascular Aβ; transgenic rats were used to determine how pancreatic amyloid-forming human amylin affects cerebral Aβ clearance. **Methods:** Blood and brain tissue were collected as part of the University of Kentucky (UK) prospective cohort study (n=172). Additional formalin fixed temporal cortex tissues from familial AD (fAD) mutation carriers were provided by the Queen Square Brain Bank for Neurological Disorders at UCL Queen Square Institute of Neurology and King's College London. Observer-masked analyses were conducted on blood samples from cohort participants spanning the continuum of being cognitively unimpaired (CU; n=42) to mild cognitive impairment (MCI; n=19) and dementia (DEM; n=19) using amylin ELISA and flow cytometry. The results were communicated to UK-AD Research Center to assess the relationship between blood amylin concentrations and cognitive function. To assess the brain amylin-Aβ relationship, we measured amylin and Aβ42 concentrations in temporal cortex homogenates from persons with sporadic (sAD) (n=42) and CU individuals (n=18) by ELISA. Both plasma and frozen brain tissue were available from 20 participants. Histological evidence of cerebrovascular amylin-Aβ co-localization was tested in fAD (n=27) and sAD (32) brain slices by immunohistochemistry (IHC), confocal microscopy and proximity ligation assay (PLA) with anti-amylin and anti-Aβ antibodies. **Results:** CU, MCI and DEM groups had similar blood glucose concentrations (112.9 ± 5.71 mg/dL vs. 119.1 ± 9.43 mg/dL vs. 113.2 ± 5.10 mg/dL; one-way ANOVA, $P = 0.79$) and age (79.35 ± 2.18 years vs. 81.35 ± 1.78 years vs. 77.60 ± 0.66 years; one-way ANOVA, $P = 0.14$). Blood amylin concentrations were higher in DEM vs. CU groups with estimated medians of 4.33 (2.84-6.56, interquartile range) and 1.53 (1.12-3.43, interquartile range) (Kruskal-Wallis one-way analysis of variance, $P < 0.001$). Blood samples with amylin concentrations in the upper quartile contained increased fractions of CD14+ monocytes positive for amylin, with an estimated mean rank difference of difference of 38 (Kruskal-Wallis one-way analysis of variance, $P < 0.0001$). Confocal microscopic imaging confirmed amylin inclusions in circulating CD14+ monocytes. Brain amylin concentrations were higher in sAD vs. control groups with an estimated difference between medians of 4.653 (unpaired t test, $P<0.01$). Increased brain amylin concentrations were associated with greater Aβ42 concentrations ($r = 0.34$; $P < 0.05$), consistent with the amylin-Aβ42 relationship recently reported in fAD brains. The point estimate of the pairwise correlation coefficient suggests a possible relationship between blood amylin levels and brain amylin accumulation ($r = 0.40$; $P = 0.09$) (potential outliers were excluded from the analysis). The IHC analysis detected amylin in approximately 2/3 of the total blood vessels staining positive for Aβ in AD brains. Aβ deposits were present in perivascular spaces and blood vessel walls, whereas amylin accumulated within the lumen and on the luminal side of blood vessel walls. Confocal microscopic analysis of brain section triple stained with anti-amylin, anti-Aβ, and anti-α smooth muscle cell actin antibodies showed co-localization patterns in which Aβ was present in perivascular areas and amylin within the blood vessel wall. The PLA signal showed an overall consistency with amylin-Aβ colocalization within the arteriolar wall. In rats, pancreatic expression of human amylin indeed induced systemic inflammation, cerebrovascular amylin deposits and local perivascular inflammation. LRP1-mediated Aβ transport across the blood-brain barrier (BBB) and Aβ clearance through interstitial fluid drainage along vascular walls were impaired, as indicated by Aβ deposition in perivascular spaces. At the molecular level, cerebrovascular amylin deposition altered immune and hypoxia-related brain gene expression. **Conclusions:** Three interdependent factors underlie amylin-induced impairment of cerebral Aβ clearance: blood amylin concentrations are increased in dementia vs. cognitively unimpaired individuals; chronically increased concentrations of amyloid-forming amylin in blood promote amylin accumulation in circulating monocytes reflecting systemic inflammation and leading to cerebrovascular amylin deposition; and cerebrovascular amylin deposition disturbs LRP1-mediated Aβ transport across BBB and Aβ clearance through interstitial fluid drainage along vascular walls, as indicated by amylin-Aβ co-localization in blood vessel walls and perivascular spaces. Future studies are needed to clarify these relationships and test whether screening for pancreatic amylin dysregulation could identify people at increased risk for brain microvascular and AD pathologies. Altering pancreas-derived amylin in blood could potentially reduce cerebrovascular amylin deposits, Aβ pathology, and the risk of diabetic brain injury and cognitive impairment.

OC21- PRAZOSIN FOR AGITATION IN ALZHEIMER'S DISEASE: PEACE-AD. E. Peskind[1], M. Raskind[2], R. Thomas[3], G. Jicha[4], N. Patel[5], A. Pierce[6], S. Brangman[7], M. Sano[8], J. Kaye[6], M. Lim[6], M. Au-Yeung[6], M. Herman[9], G. Leger[9], K. Messer[9], H. Feldman[9] *(1. VA Northwest Mental Illness Research, Education and Clinical Center (MIRECC), Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine - Seattle (United States), 2. VA Northwest Mental Illness Research, Education and Clinical Center (MIRECC) and Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine - Seattle (United States), 3. Departments of Family Medicine and Neurosciences, University of California San Diego - La Jolla (United States), 4. Department of Neurology, University of Kentucky - Lexington (United States), 5. Department of Family and Community Medicine, UT Health San Antonio - San Antonio (United States), 6. Department of Neurology, OHSU School of Medicine - Portland (United States), 7. Department of Geriatrics, SUNY Upstate Medical University - Syracuse (United States), 8. Department of Psychiatry, Mount Sinai School of Medicine - New York (United States), 9. Department of Neurosciences, University of California San Diego - La Jolla (United States))*

Background: To evaluate the efficacy and safety of prazosin for the treatment of disruptive agitation in Alzheimer's disease participants residing at home or in a long-term care facility in a national multicenter randomized controlled trial conducted by the NIA-funded Alzheimer's Disease Cooperative Study (ADCS). **Methods:** In this multi-site randomized controlled trial (RCT) in which recruitment was substantially handicapped by the COVID-19 pandemic, participants were randomized to prazosin or placebo using a 2:1 permuted block randomization. Prazosin was titrated over 4 weeks to a maximum possible dose of 4 mg mid-morning and 6 mg at bedtime based on tolerability and persistent agitation. Adverse events and orthostatic blood pressure and heart rate were monitored. Primary outcome

measure was the ADCS-Clinical Global Impression of Change-Agitation (CGIC-A) targeting disruptive agitated behaviors. Secondary outcomes were the 17-item Neuropsychiatric Inventory (NPI), Cohen Mansfield Agitation Inventory (CMAI), ADCS-Activities of Daily Living (ADCS-ADL) for severe dementia, and total number study days completed. An exploratory outcome was the NPI 5-item subscale reflecting agitation. Due to COVID-19 restrictions, methods were adapted to allow for remote consent, participant screening, and outcome and safety assessments. In addition, caregivers were trained to measure blood pressure and heart rate using the Omron automated blood pressure machine. **Results:** Thirty-five participants were randomized 2:1 to prazosin or placebo for 12 weeks. Mixed Models Repeated Measures analysis was performed. There were no significant differences in the CGIC-A or total NPI scores. In the prazosin group, 7 of 18 participants were moderately or markedly improved on the CGIC-A compared to 1 of 4 participants in the placebo group (NS). Change from baseline in CMAI score significantly favored prazosin (-5.5 ± 4.1 [mean ± SEM] in the prazosin group vs. +10.0 ± 6.0 in the placebo group, p=0.04) and the 5-item NPI Agitation subscale numerically favored prazosin (NS). Kaplan-Meier Survival Analysis numerically favored prazosin with 63% of prazosin participants completing all 12 weeks compared to 38% of placebo participants (NS). The adverse event (AE) profile was as anticipated for prazosin; AEs that occurred in >5% of prazosin participants and >2X the occurrence in the placebo group included syncope, dizziness, nausea, and somnolence. Remote consenting, screening, and assessments allowed continuation of the study without the necessity of in-person clinic visits. **Conclusion:** PEACE AD provides some additional evidence of the potential efficacy in this small RCT testing of prazosin in the treatment of disruptive agitation in AD. While the assessment of both efficacy and safety were limited by the small number of participants, particularly in the placebo group, there was some benefit with prazosin seen across measures of behavioral assessment over 12 weeks of treatment, with the expected safety profile. PEACE AD was successfully conducted during COVID 19 using fully remote visits with home dwelling participants and technology support. It demonstrates the feasibility and significant advantages of performing a randomized controlled trial for disruptive agitation in AD using remote technology in home dwelling participants. This approach permitted the inclusion of severely agitated AD outpatients for whom attendance at frequent clinic visits would itself have been extremely challenging. A larger multi-center study of prazosin for moderate-severe disruptive agitation in AD is necessary and warranted to extend these results with lessons from this trial applied in its design and methods. The PEACE-AD study was funded by the National Institute on Aging via the Alzheimer's Disease Cooperative Study (U19 AG010483) with additional support from the Alzheimer's Association (SG-20-690388).

OC22- DEMOGRAPHIC ANALYSIS OF INDUSTRY SPONSORED ALZHEIMER'S DISEASE TRIAL POPULATIONS IN THE UNITED STATES.

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Background: The Food and Drug Administration (FDA) stated in 2020 that "sponsors should enroll participants who reflect the characteristics of clinically relevant populations with regard to age, sex, race, and ethnicity". Moreover, the FDA Guidance recommended that sponsors include a plan for inclusion of clinically relevant populations no later than the end of the Phase 2 meeting for all drugs and biological investigational therapeutics. In view of the significant amount of clinical trial research in Alzheimer's Disease, a comprehensive demographic evaluation of the study populations used in Alzheimer's disease trials seems prudent. **Objectives:** Although it has been noted for at least 30 years that Alzheimer's Disease trials have enrolled predominantly White subjects, a thorough analysis of industry-sponsored, US-based Alzheimer's trials has yet to be performed. The present study therefore evaluated all available demographic data on industry-sponsored Alzheimer's trials of 100 or more subjects, performed solely in the United States. Global Alzheimer trials were excluded since sponsors rarely report demographics on a country by country basis. The objective was to determine if the gender and racial distributions of the trial subjects were representative of the known epidemiological characteristics of Alzheimer's Disease. **Methods:** A search of the ClinicalTrials.Gov website (https://clinicaltrials.gov/) for "Alzheimer's Disease, Industry-sponsored" clinical trials was made on March 31, 2022. A total of 1,145 trials were identified. The trials data were then screened for US only trials with at least 100 enrolled Alzheimer's Disease subjects. Finally, the analysis dataset included all trials that had gender and/or racial demographic results available on either the ClinicalTrials.Gov website or in an associated publication identified via a PubMed search. **Results:** There were 35 identified trials with gender and/or racial demographic results, comprised of nearly 13,000 enrolled Alzheimer's Disease subjects. These trials were completed between 1997 and 2019. The subject enrollment per trial ranged from 100 to 1,649 individuals. The gender distribution was available from 35 trials involving 12,912 subjects. There were 6,970 (54%) females and 5,942 (46%) males in these trials. The racial distribution was available from 24 trials, involving 10,872 Alzheimer's Disease subjects. There were 10,017 (92%) Whites, 341 (3.1%) Black or African Americans, 49 (0.5%) Asians and 464 (4.3%) Others (e.g., Mixed, Unknowns, etc.). The percentage of White subjects per study in the 24 trials ranged from 84%-99%. **Conclusion:** The analysis of 35 industry-sponsored Alzheimer's trials, performed solely in the US, showed an increased frequency of female vs. male participation in the trials. This observation is consistent with the known epidemiology of Alzheimer's Disease. By contrast, the analysis of 24 US only, industry sponsored trials identified a major discrepancy between the racial distribution in the trial subjects compared to the known epidemiology of Alzheimer's Disease in the United States. Large scale epidemiological studies in Alzheimer's Disease across the entire US population have not been performed. However, 92% of Alzheimer's Disease trial subjects have been White over the past 25 years in the United States. This fact is clearly a significant deviation from the known racial demographics of Alzheimer's Disease. These data suggest that significant modifications of subject recruitment methods are needed to increase the enrollment of underrepresented populations into Alzheimer's Disease trials. The consistently high percentage of White subjects per trial, in all 25 studies analyzed, suggests that these racial disparities are a likely result of a recruitment process that has not focused on subject diversity. The result is that an immediate need exists to increase the enrollment of multiple underrepresented populations of Alzheimer's patients in US clinical trials. Based on a review of clinical trial participation barriers in underrepresented populations (e.g., Black or African-America, Hispanic and American Indian), two consistent themes have emerged that limit research participation: mistrust and lack of information. These obstacles can be overcome, but they require a significant and long-term investment in community outreach

programs. In the short-term, information about ongoing trials needs to be communicated effectively to underrepresented communities via local health centers, senior community centers, neighborhood association meetings, pharmacies, churches, etc. Although limited research has suggested that this approach can be successful, more research is needed to determine the optimal ways to inform underrepresented populations about clinical trial research opportunities. A more challenging need is to determine the optimal ways to build trust between the medical research community and historically underrepresented populations in Alzheimer's Disease clinical trials.

OC23- PLASMA BIOMARKER FINDINGS FROM THE ALZHEIMER'S PREVENTION INITIATIVE AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE COLOMBIA TRIAL.
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Background: Crenezumab is an anti-amyloid monoclonal antibody that binds to beta-amyloid (Aβ) oligomers and is hypothesized to prevent the buildup of pathogenic Aβ plaques and to modify Alzheimer's disease (AD) progression with a low risk of amyloid-related imaging abnormalities (ARIA). The Alzheimer's Prevention Initiative (API) Autosomal Dominant AD (ADAD) Colombia trial evaluated crenezumab using clinical and biomarker endpoints in cognitively unimpaired presenilin 1 (PSEN1) E280A mutation carriers recruited from the world's largest ADAD kindred (NCT01998841). Blood-based biomarkers (BBBMs) of amyloid and tau pathophysiology, neurodegeneration, and neuroinflammation have the potential to inform the development of AD-modifying and prevention therapies. **Objectives:** To describe baseline and change from baseline treatment-related BBBM findings from participants of the API ADAD Colombia trial. **Methods:** This randomized, double-blind, placebo-controlled, parallel-group trial evaluated the efficacy, safety, and tolerability of crenezumab in cognitively unimpaired 30–60-year-old Colombian PSEN1 E280A kindred members whose median age of mild cognitive impairment onset is 44 years. The 252 trial participants included mutation carriers who were randomized to crenezumab, mutation carriers who were randomized to placebo, and non-carriers who received placebo distributed in an approximately 1:1:1 ratio. Participants and researchers were blinded to mutation status. While participant inclusion in the trial was independent of baseline amyloid positron emission tomography (PET) findings, 40% of the carriers were found to have a negative amyloid PET scan prior to treatment. While dosing started with 300 mg subcutaneously every 2 weeks, it evolved over time and participants were eventually treated with either crenezumab (up to 720 mg subcutaneously every 2 weeks or 60 mg/kg intravenously every 4 weeks) or placebo for 5–8 years using a common close design. The primary endpoint family included the change in the API ADAD Cognitive Composite Test score and the Free and Cued Selective Reminding Test score. Most of the participants had serial amyloid PET, tau PET, 18F-FDG PET, magnetic resonance imaging, cerebrospinal fluid (CSF) and BBBM measurements and other assessments. Blood samples collected annually were measured using Elecsysâ robust prototype immunoassays. Biomarkers tested included plasma phosphorylated tau (p-tau)181 and p-tau217, which provide information about Aβ plaque burden and Aβ-related tau pathophysiology; plasma neurofilament light (NfL), which provides information about neuronal injury and neurodegeneration; and plasma glial fibrillary acid protein (GFAP), chitinase 3-like 1 (YKL-40) and soluble triggering receptor expressed on myeloid cells 2 (TREM2), which provide information about neuroinflammation. **Results:** After summarizing trial aims and design, participant characteristics, and treatment-related clinical, cognitive, imaging and CSF biomarker findings, we will describe the participants' baseline BBBM and treatment-related BBBM findings, including in mutation carriers with positive and negative baseline Aβ PET scans, and relationships between BBBM and clinical effects. **Conclusion:** The API ADAD Colombia Trial was intended to characterize the efficacy, safety, and tolerability of crenezumab in the prevention of AD; explore the treatment's differential biomarker effects in amyloid-positive and amyloid-negative participants at virtually certain AD risk; clarify relationships between the treatment effects on biomarker and clinical outcomes; provide a shared resource of data and samples for the field; help to establish a new era in AD prevention research; and advance the role of emerging BBBMs in these endeavors.
Conflict of interest statement: Our work on this particular study was supported by NIH grants, F. Hoffmann-La Roche, philanthropic donations to Banner Alzheimer's Foundation, and grants from the state of Arizona. Eric. M. Reiman is a Co-Founder & Advisor of ALZPath. He is a scientific advisor to Alzheon, Aural Analytics, Denali, Retromer Therapeutics, Vaxxinity and has Institutional Research Agreements with F. Hoffmann-La Roche/Genentech, Avid/Lilly.

OC24- NEUROIMAGING DATA FROM A PHASE 2, OPEN-LABEL STUDY OF NE3107 IN PATIENTS WITH COGNITIVE DECLINE DUE TO DEGENERATIVE DEMENTIAS.
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Background: Alzheimer's disease (AD) affects more than 6 million Americans and is associated with substantial healthcare costs and suffering. Unfortunately, therapies targeting neurodegenerative and abnormal protein deposits in the brain, including amyloid beta (Aβ) and phosphorylated tau (P-tau), have shown unclear clinical benefit, and more effective therapies are urgently needed. AD is associated with imbalances or deficiencies in neuronal glutathione levels and significant synapse and dendritic spine loss in parts of the brain, among other neurophysiological deficiencies. During the past decade, chronic inflammation and impaired glucose metabolism have been recognized as important contributors to the pathophysiology of AD. Neuroinflammation, insulin resistance (IR), and Aβ and P-tau pathologies form a feed-forward loop in AD progression. Therefore, targeting neuroinflammation and IR are attractive strategies in the treatment of AD. NE3107 is a well-tolerated, blood-brain permeable oral agent that selectively inhibits several inflammatory mediators and improves insulin signaling. Across several clinical studies, NE3107 increased insulin sensitivity and restored metabolic homeostasis in patients with type 2 diabetes and inflammation.

It was also shown to alter inflammatory biomarkers that have been associated with cognitive decline. Multimodal imaging in patients with dementia has demonstrated certain qualities that would reflect associated changes in brain structure and function. These include change in regional neural dysfunction as shown in arterial spin labeling (ASL), change in interstitial free water and neurite density as found in diffusion tensor imaging - neurite orientation dispersion and density imaging (DTI-NODDI), change in redox stress as reflected in glutathione magnetic resonance spectroscopy (MRS), and change in seed-based functional connectivity of the nucleus basalis of Meynert as found in blood oxygen level dependent (BOLD) imaging. **Objectives:** This is a Phase 2, open-label study to evaluate the potential efficacy of NE3107 in patients with mild cognitive impairment (MCI) or mild dementia using advanced neuroimaging endpoints, AD and inflammatory biomarkers, changes in glucose metabolism, and cognitive performance testing. The primary objective of this study is to evaluate changes in neurophysiological health using multi-modal brain MRIs obtained at baseline and treatment termination (3 months). Secondary objectives of this study include a longitudinal comparison of glucose homeostasis, cognitive impairment as defined by neuropsychological testing, and AD and inflammatory markers. **Methods:** Twenty-three participants were enrolled and received 20-mg oral NE3107 twice daily for 3 months. Participants were between 50-89 years old with MCI or mild dementia (Quick Dementia Rating Scale [QDRS] cutoff range: 1.5-12.5; Clinical Dementia Rating [CDR] score range: 0.5-1). AD markers (Aβ and P-tau) were evaluated at baseline and treatment termination. Primary endpoints evaluated neurophysiological health using multi-modal brain MRIs at baseline and treatment termination, including stabilization or increase in glutathione levels (measured by MRS), enhancement of arterial perfusion (quantified by ASL), increased functional connectivity of the nucleus basalis of Meynert (visualized by seed analysis of BOLD imaging), and improvements in dendritic density and interstitial free water (measured by DTI-NODDI). Secondary endpoints evaluated changes in serological inflammatory markers, glucose and insulin homeostasis, and cognitive functioning—including changes in Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog 12) from baseline at treatment termination. **Results:** Participants had a mean age of 71.6 (SD = 9.63) years and 15 (65%) were females. At baseline, the mean QDRS score was 5.07, 18 (78%) participants had a CDR score of 0.5, and 5 (22%) participants had a CDR score of 1. Results of neuroimaging analyses will be presented at the conference. **Conclusion:** Using an array of advanced neuroimaging techniques to ascertain changes in participants' neurophysiological health before and after treatment with NE3107, this study aimed to demonstrate the potential therapeutic efficacy associated with NE3107 treatment in patients with MCI. Funded by: BioVie Inc. **Disclosures:** ER, KM, KJ, JH, MZ, VV, SB, and SJ have received grant support from BioVie Inc. DG has nothing to disclose. BP has nothing to disclose. CA, CR, and JP are employees of BioVie Inc.

OC25- HOPE4MCI TRIAL TARGETING HIPPOCAMPAL OVERACTIVITY FOR THE TREATMENT OF MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S DISEASE WITH AGB101: BASELINE TAU AND MRI IMAGING CHARACTERISTICS. R. Mohs[1], S. Rosenzweig-Lipson[1], A. Bakker[2], E. Chang[2], N. Rani[2], R. Barton[1], M. Gallagher[1,2] *(1. AgeneBio, Inc - Baltimore (United States), 2. Johns Hopkins University - Baltimore (United States))*

Background: No effective therapies exist to halt or reverse Alzheimer's Disease (AD). With a predicted prevalence of AD cases rising to over 100 million worldwide by 2050, the need for such therapy is urgent. Novel therapies are primarily focused on patients with amnestic mild cognitive impairment (aMCI) due to AD, recognized as a prodromal phase between normal aging and a clinical diagnosis of dementia, as interventions will likely confer the greatest clinical benefit during the early phases of the disease. In addition to tau and amyloid accumulation, hippocampal hyperactivity has been recognized as a characteristic feature of aMCI with strong evidence from both studies of animal models and humans observing that hyperactivity in neuronal circuits contributes to the accumulation and spread of AD pathology and forecasts subsequent cognitive decline. Clinical studies in patients with aMCI have demonstrated that treatment with low dose levetiracetam normalizes hippocampal hyperactivity and improves memory function in these patients (Bakker et al., 2012). The HOPE4MCI trial is a randomized placebo-controlled study of AGB101, a once daily extended-release formulation containing 220 mg of levetiracetam (NCT03486938). **Objectives:** The objective of the HOPE4MCI study is to examine the efficacy of AGB101 compared to placebo in patients with aMCI due to AD using the Clinical Dementia Rating Scale Sum of Boxes score as well as secondary functional and cognitive measures. In addition, the HOPE4MCI trial includes several cutting-edge biomarker measures including longitudinal structural magnetic resonance imaging (MRI), and longitudinal FMK-6240 PET measures of tau in a subset of participants. **Methods:** The HOPE4MCI trial is a multicenter randomized, double-blind placebo-controlled 78-week, fixed dose study of AGB101. Participants are between 55-85 years old, meeting NIA-AA criteria for MCI due to AD based on a corroborated subjective memory complaint, objective memory impairment, and amyloid positivity by PET scan. **Results:** The HOPE4MCI trial is fully enrolled with 164 participants meeting criteria for aMCI due to AD and is expected to complete data collection by the end of 2022. A subgroup of 49 participants completed both structural MRI and FMK-6240 tau PET at baseline. Image analysis of the structural MRI data was completed using Freesurfer generating volumetric measures of the hippocampus, entorhinal cortex, and amygdala and measures of cortical thickness of the entorhinal cortex, areas that show neurodegeneration as a function of disease progression in aMCI. In addition, volume and cortical thickness were obtained for control areas where primary disease related neurodegeneration has not been observed. FMK-6240 Tau PET analysis was similarly completed using Freesurfer, generating measures of tau accumulation in the hippocampus, entorhinal cortex, and amygdala. Previous work using the FMK-6240 tau marker has shown that tau accumulation in these regions can be used to assess disease progression consistent with Braak staging (Pascoal et al., 2020). Results will be presented to show convergence of biomarkers with associations between regional tau accumulation and localized neurodegeneration particularly in the entorhinal cortex. These results will be presented in the context of cognitive

and functional measures obtained from these participants establishing a richly characterized sample of patients with aMCI. **Conclusion:** The current study includes multiple measures relevant to dementia due to AD in a prodromal condition recognized as transitional between normal aging and progression to a clinical AD diagnosis. The use of additional biomarkers in the subset of patients is informative for further characterization of MCI due to AD. The association between structural MRI and FMK-6240 Tau PET in this sample will also be informative bridging to the full dataset of 164 enrollees in which structural MRI was obtained in all participants. In addition, the imaging biomarkers were also obtained within-subject at the end of the 78 week protocol providing additional opportunities to examine change in these measures as a function of treatment (AGEB 101 compared to placebo).
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OC26- DESIGN OF THE ABCA1 AGONIST CS6253 PHASE 1 SAD AND MAD STUDY IN MALE AND FEMALE, APOE4 AND NON-APOE4 CARRIERS TO ASSESS SAFETY, PK AND BIOMARKER EFFICACY.
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Background: Apolipoprotein E (APOE) ε4 genotype, the main genetic late-onset Alzheimer's disease (AD) risk factor, is characterized by the apoE4 protein (as opposed to apoE3) having impaired interaction with astrocyte's ATP-binding cassette transporter A1 (ABCA1). The ABCA1 agonist CS6253 appears to correct this deficit. Current anti-amyloid AD-therapies in development have ARIA side effects in the APOE4 carriers and development of alternative therapies is warranted. The CS6253 IND is now open and a Phase 1 Single Ascending dose (SAD) and Multiple Ascending Dose (MAD) study has been designed to assess safety, PK and efficacy in male and female subjects with and w/o APOE4. Efficacy assessment will be guided by results from mice pharmacology studies and cynomolgus monkey studies showing CS6253 effects on lipoprotein and AD variables related to neuron protection and cognition. **Methods:** SAD: In 4-6 cohorts of 8 subjects (6 active: 2 placebo) CS6253 starting with 1 mg/kg will be administered and plasma and CSF collected simultaneously over 24 hours to assess PK and effect markers. MAD: In 3-4 cohorts of 8 subjects (6 active: 2 placebo) CS6253 will be administered starting with 75% of the SAD maximum tolerated dose. Prior to dosing and in conjunction with the 4th/last dose, plasma and CSF will be collected simultaneously over 24 hours. PK will be analyzed by LC-MS. Plasma and CSF will be analyzed by ELISA for ApoE and Ab42/40 (Simoa). **Results:** In APOE4 targeted replacement mice CS6253 20 mg/kg QOD ip for 6 weeks increased plasma apoE 37% ($p<0.05$). In cynomolgus monkeys CS6253 10 mg/kg IV single and repeat 4 doses increased plasma apoE with concomitant increase in plasma Ab42/40-ratio (all $p<0.05$). Human SAD results are expected the summer of 2023 and human MAD data the fall of 2023. **Conclusion:** The Phase 1 SAD and MAD study of the ABCA1 agonist CS6253 treatment will evaluate safety, PK and biomarker efficacy in male and female subjects with and w/o APOE4. Simultaneous collection and analysis in plasma and CSF of PK and of PD markers including apoE and Ab42/40-ratio will assess clinical potential for this cholesterol-targeting treatment of hereditary APO4-associated AD.

OC27- SIGNIFICANT EFFECTS OF ORAL ALZ-801 ON PLASMA BIOMARKERS OF ALZHEIMER'S DISEASE: 12-MONTH INTERIM ANALYSIS OF PHASE 2 BIOMARKER STUDY IN APOE4 CARRIERS WITH EARLY AD.
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Background: ALZ-801 (valiltramiprosate) is in development as an oral disease-modifying treatment for Alzheimer's disease (AD). ALZ-801 is a brain-penetrant, small molecule inhibitor of amyloid oligomer formation. A fully enrolled Phase 2 study is ongoing in APOE4 carriers with Early AD to evaluate ALZ-801 effects on core AD neuropathologies, including plasma biomarkers of beta amyloid (Aβ) and hyperphosphorylated tau (p-tau). A pivotal APOLLOE4 Phase 3 placebo-controlled study is currently enrolling APOE4/4 homozygotes with Early AD. Advances in blood-based biomarker assays of AD support their use to assess efficacy in drug trials. Plasma p-tau, a marker of Aβ-induced neuronal stress and injury, is elevated in AD, and can be detected using new sensitive assays. Agents that inhibit Aβ toxicity in brain are expected to reduce p-tau release into blood. Indeed, the amyloid antibodies lecanemab and aducanumab, at doses that demonstrate clinical efficacy, both showed significant plasma p-tau181 reduction at 18 months. **Objectives:** To evaluate effect of oral ALZ-801 on core AD pathologies including fluid biomarkers (p-tau181, Aβ42, Aβ40), hippocampal volume (HV), and on clinical outcomes over 2 years of treatment. **Methods:** The Phase 2 biomarker study of ALZ-801 is an ongoing, open-label study at 7 sites in the Czech Republic and the Netherlands. Enrolled subjects (MMSE 22-30, CDR-G 0.5 or 1) have either APOE4/4 or APOE3/4 genotype and prior positive amyloid-PET or CSF biomarkers fulfilling A+/T+ criteria. CSF criteria are ratio of CSF Aβ42/40 ≤ 0.061, and p-tau181 ≥ 61 pg/ml. Subjects receive oral ALZ-801 as 265 mg BID tablets over 2 years and undergo serial assessments of plasma, CSF, volumetric MRI (vMRI), cognitive and functional tests. All fluid biomarker analyses are conducted at the Neurochemistry Laboratory of Dr. Blennow (Molndal, Sweden), and blinded to subject's demographics or genotype. CSF biomarker assays are analyzed using Lumipulse (Fujirebio) and plasma assays utilized Simoa platform. vMRI analyses of HV are conducted at Bioclinica/Clario. Cognitive tests include the Rey Auditory Verbal Learning Test (RAVLT: immediate, delayed and recognition memory) and Digit Symbol Substitution Tests (DSST), and

a composite cognitive Z-score is calculated (3-item RAVLT + DSST). Change from baseline analyses performed on the modified intent-to-treat population (mITT) population includes all observed data, using paired t-tests and 2-sided p-values. The primary biomarker outcome is p-tau181 and total HV is the primary imaging outcome. HV atrophy rate on MRI using tensor-based morphometry is measured on each side, and total HV (left + right) atrophy compared to external control subjects from the ADNI database, who are matched for genotype and disease stage. Interim analyses to detect early biomarker effects of ALZ-801 were pre-specified. **Results:** A total of 84 APOE4 carriers enrolled and received ALZ-801, and 80 and 75 subjects completed 26 and 52 weeks, respectively. The mITT population baseline demographics were mean age 69 years, 51% female, MMSE 26.0, CDR-G 0.6, 70% MCI and 30% Mild AD. Plasma p-tau181 reduction was significant at 13 and 26 weeks and reached -41% at 52 weeks (p=0.016). Plasma Aβ42 and Aβ40 showed significant elevation at 13-26 weeks followed by significant reduction at 52 weeks (both -5%, p =0.002 & p=0.005). Reductions of p-tau181/Aβ42 were significant at each time point (-37%% at 52 weeks, p=0.032). Bilateral HV atrophy at 1 year was reduced by 25% compared to the matched ADNI subjects. The composite cognitive test (RAVLT memory scores + DSST) Z-score improved significantly at 13 and 26 weeks (p=0.002, 26 weeks), and remained numerically above baseline at 52 weeks. The effects on the 3-item RAVLT memory test showed significant correlations to effects on left HV (correlation coefficient 0.3, p=0.01). Most common adverse events were mild nausea and COVID infection, with no drug-related serious events and no events of ARIA-E in 75 subjects at 52 weeks. **Conclusions:** This 1-year interim analysis of ALZ-801 in APOE4 carriers with Early AD shows significant, progressive, and sustained reduction of plasma p-tau181, reaching a robust 41% reduction at 52 weeks. The time course of Aβ42 and Aβ40 changes in plasma suggests clearance of soluble Aβ monomers from brain to plasma, with significant reduction at 52 weeks. These effects are consistent with the molecular mechanism of ALZ-801, namely preventing the formation of soluble toxic amyloid oligomers. The cognitive composite outcome showed initial symptomatic improvement over 26 weeks followed by stability at 1 year compared to baseline. Reduction of hippocampal atrophy compared to matched controls suggests a neuroprotective effect on brain volume and showed significant correlation to memory benefits. The convergence of positive effects on plasma biomarkers, hippocampal volume and clinical benefits supports the disease modifying profile of ALZ-801. These data strengthen the case for a Phase 3 study in APOE4 carriers. The favorable safety, low risk of ARIA-E, and convenience of a simple oral regimen, make ALZ-801 an attractive potential disease-modifying treatment with wide access for AD patients, and very suitable for future AD prevention trials.

OC28- MEASURES OF CORTICAL MICROSTRUCTURE ARE LINKED TO AMYLOID PATHOLOGY IN ALZHEIMER'S DISEASE. N. Spotorno[1], O. Strandberg[1], G. Vis[2,3], E. Stomrud[1], M. Nilsson[2,4], O. Hansson[1] *(1. Clinical Memory Research Unit, Department Of Clinical Sciences, Lund University - Lund (Sweden), 2. Diagnostic Radiology, Institution For Clinical Sciences, Lund University - Lund (Sweden), 3. Memory Clinic, Skåne University Hospital - Malmö (Sweden), 4. Memory Clinic, Skåne University Hospital - Malmö (Sweden))*

Background: Markers of downstream events are a key component of clinical trials of disease-modifying therapies for Alzheimer's disease, especially during later stages to monitor the response of the participants to the treatment. Clinical and cognitive scores are the most obvious primary outcome measures at this point. However, when targeting upstream pathological events, such as Aβ misfolding and accumulation, therapies will likely be more effective during pre-symptomatic or prodromal disease stages before overt and irreversible neurodegeneration become more evident. In this context, clinical readout might become more challenging and putative makers will be of critical importance. Morphological metrics like cortical thickness are established measures of atrophy but are not sensitive enough to detect Aβ-related changes that occur before overt atrophy become visible. Objectives. We aimed to investigate to what extent diffusion MRI can provide sensitive markers of cortical microstructural changes and to test their associations with multiple aspects of the Alzheimer's disease pathological cascade, including both Aβ and tau accumulation, astrocytic activation and cognitive deficits. **Methods:** We applied the mean apparent diffusion propagator model (MAP-MRI) to diffusion MRI data from 492 cognitively unimpaired elderly and patients with mild cognitive impairment from the Swedish BioFINDER-2 cohort. Participants were stratified in Aβ-negative/tau-negative, Aβ-positive/tau-negative, and Aβ-positive/tau-positive based on Aβ- and tau-PET uptake. Cortical regional values of MAP-MRI metrics and cortical thickness were compared across groups. Associations between regional values of MAP-MRI metrics and both Aβ- and tau-PET uptake were also investigated along with the association with plasma level of glial fibrillary acidic protein (GFAP), a marker of astrocytes activation (available in 292 participants). **Results:** Mean square displacement (MSD) from MAP-MRI revealed widespread microstructural differences already between Aβ-negative/tau-negative and Aβ-positive/tau-negative participants with a spatial distribution that closely resembled the pattern of Aβ accumulation, including retrosplenial regions extending to the precuneus, neocortical temporal regions, as well as rostral anterior cingulate and rostral middle frontal cortex (p-values FDR corrected, $p < 0.05$, standardized-β coefficients range: 0.18 – 0.30). In contrast, differences in cortical thickness were clearly more limited (only entorhinal cortex, parahippocampal gyrus and temporal pole p-values FDR corrected, $p < 0.05$). MSD was also highly correlated with both Aβ- and tau-PET uptake even independently from one another and independently from cortical thickness. Further, analysis focusing on a composite ROI encompassing regions that accumulate Aβ early in the disease process confirmed MSD exhibited significantly stronger correlations with Aβ-PET uptake than cortical thickness (significant difference between the β coefficients of MSD and cortical thickness: $p < 0.01$). Similar results were found when focusing on a temporal meta-ROI where MSD was more strongly associated to tau-PET uptake than cortical thickness ($p<0.01$). Regional MSD values were also positively correlated with the glial marker GFAP with a pattern that resemble Aβ accumulation (standardized-β coefficients range: 0.14 – 0.20), and GFAP partially mediated the association between Aβ accumulation and MSD. Further, impairments in executive functions were significantly more associated with MSD extracted from the early-Aβ meta-ROI than with cortical thickness ($p<0.05$). Similarly, impairments in memory functions were significantly more associated with MSD extracted from the temporal meta-ROI, than with cortical thickness ($p<0.05$). Further longitudinal analyses to investigate the possible use of diffusion MRI for tracking disease changes over time are undergoing and the results will be presented at the conference. **Conclusions:** Metrics of cortical microstructural

alteration derived from diffusion MRI are highly sensitive to multiple aspects of the Alzheimer's disease pathological cascade. Of particular interest is the link between MSD, Aβ-PET and GFAP which suggests that MSD might reflect microstructural changes related to the astrocytic response to Aβ aggregation. Therefore, MSD might be an important outcome measure in anti-Aβ treatments clinical trials for detecting drug-induced changes in early Aβ-related microstructural changes. **Competing interest:** The corresponding author has no competing interests to report.

OC29- A BRIEF, AUTOMATED SPEECH-BASED SCREENER FOR MILD COGNITIVE IMPAIRMENT TO SUPPORT ONLINE RECRUITMENT AT SCALE. C. Skirrow[1], J. Weston[1], M. Meszaros[1], U. Meepegama[1], E. Fristed[1] *(1.Novoic - London (United Kingdom))*

Background: Cognitive changes occurring during the early stages of Alzheimer's disease (AD) are reflected in how someone speaks, where sensitive patterns can be extracted using audio- and text-based machine learning models. Automated speech-based testing makes an excellent candidate for at-scale screening and recruitment into larger research projects and clinical trials. Participants can self-administer tests at home in a few minutes using a range of personal mobile devices. Recorded speech samples can be automatically analysed to produce sensitive diagnostic screening data, which can facilitate onward referral for further clinical evaluation in key participant groups. **Objectives:** Develop a short, automated speech-based AI system to screen for MCI based on automatically transcribed speech alone. **Methods:** Data was taken from the AMYPRED-UK (NCT04828122) and AMYPRED-US (NCT04928976) studies, comprising 200 participants age 54-85 with established amyloid beta (Aβ) and clinical diagnostic status (MCI, mild AD or cognitively unimpaired). Participants engaged in optional remote once-daily speech-based assessments for up to 8 days using their own smart devices. Assessments included the Automatic Story Recall Task (ASRT). Responses were recorded and then transcribed manually and using an out-of-the-box Automatic Speech Recognition (ASR) system. Data was extracted from two immediate and one delayed recall of two short ASRT stories administered in the same test session, to emulate a brief screening set-up. Differences in the original story source text and transcribed participant retelling were evaluated via a generalized matching score ("G-match"). G-match is computed in Python as the weighted sum of the cosine similarity between the embeddings of ASRT source text and the transcribed retellings. G-match was evaluated separately for manual and ASR transcribed speech data, in the full sample and after restriction of the cognitively impaired group to those with MCI only. Logistic regression models were trained to predict clinical labels (MCI/mild AD vs. cognitively unimpaired) using 5-fold cross-validation, producing Receiver Operating Curve (ROC) outputs. 95% confidence intervals for Area Under the Curve (AUC) were computed using the standard error of the 5-fold AUC samples. The ASRT models were evaluated relative to a demographic comparison (combining age, gender and years in education), and the Preclinical Alzheimer's Clinical Composite with semantic processing (PACC5), a more extensive supervised clinical assessment battery. The reduction in in-person clinical assessment required with pre-screening using G-match was evaluated in a simulated US population sample age 65+ (MCI prevalence 15.4%), using the sensitivity and specificity of the G-match model for differentiating MCI and cognitively unimpaired participants. **Results:** The participant sample completing the abbreviated test battery, and included in the current analysis comprised 96 adults (N=55 cognitively unimpaired, N=34 MCI, N=7 mild AD; N=48 Aβ positive, N=48 Aβ negative; 51 female, 45 male). The abbreviated assessment battery collected an average of 2.4 minutes of speech per participant. G-match of the brief test battery showed good prediction of MCI/mild AD status using ASR transcripts with AUC=0.87 +/- 0.03. Results remained consistent when restricting analyses to comparisons between MCI and cognitively unimpaired participants alone with AUC=0.82 +/- 0.04. Differences between ASR and manually transcribed data were not statistically significant ($p \geq 0.33$). G-match models were significantly superior to random performance ($p \leq 0.001$), and outperformed the demographic comparison ($p \leq 0.01$). PACC5, a longer, multi-task battery evaluated in-person during a clinical assessment, outperformed G-match for the analysis restricted to the MCI and cognitively healthy group alone (AUC=0.91 +/-0.04, p=0.02), but not for the combined MCI/mild AD group (p=0.26). Screening based on G-match (ASR transcription; sensitivity 0.94 and specificity=0.54 at Youden's index) was simulated in a population sample age 65+. For a targeted sample of MCI patients for research, the ASRT system screening is estimated to reduce the number of in-depth clinical assessments required by 43.2%, but require 5.9% more participants at the recruitment and screening stage. **Conclusion:** Combined with an advanced AI language model, brief speech-based testing offers simple and accessible screening for MCI. Such testing could be used at scale to screen for appropriate patients for treatment, research and clinical trials. The ASRT system does not require trained personnel or specialist equipment and could help to reduce the costs of clinical trials by enriching recruited samples. The ASRT system has potential to reduce the quantity of more in-depth clinical assessments required, reducing clinical resource bottlenecks and costs of research and clinical trials. **Funding and competing interests:** All authors are employees of Novoic and option holders or shareholders of Novoic.

OC30- AB-STRUCTURE AS PRECISE RISK PLASMA BIOMARKER FOR FUTURE CONVERSION TO ALZHEIMER´S DISEASE 17 YEARS IN ADVANCE. K. Gerwert[1,2] *(1. Ruhr-University Bochum - Bochum (Germany), 2. Center for Protein Diagnostics (ProDi) - Bochum (Germany))*

Background: The identification and validation of early-stage biomarkers is coming into focus. Especially, early stage diagnosis in a symptom-free stage before significant amyloid plaques have been formed might provide the best therapy response. In recent years, the development of highly sensitive analytical methods enabled the identification of non-invasive and low costs blood-based biomarkers. Blood-based biomarkers allow beside expensive PET scans and invasive CSF measurements pre-screening of the elder population. In contrast to the widely studied concentration-based analyses of Aβ and P-tau biomarkers in body fluids we have examined Aβ and tau misfolding as structure biomarkers. The misfolding of Aβ from a monomeric/unstructured to a β-sheet enriched isoform is one of the earliest events in AD pathogenesis. With the patented infrared-immuno-sensor (iRIS) we are able to measure the secondary structure distribution of all Aβ isoforms as structure biomarker (1). Initial misfolding of Aβ takes place about 15-20 years before AD is clinically diagnosed and is followed by β-sheet oligomerization and aggregation to much larger fibrils on the nanometer scale. After several years, this Aβ misfolding

becomes visible at the macroscopic scale as deposits in large amyloid plaques. We have shown in a discovery study that the structure biomarker indicates probable Alzheimer's disease in a prospective cohort (1). We extended this to prodromal AD in the BioFINDER cohort (2). Furthermore, we have shown that the structure biomarker is prognostic and predicts the conversion to AD in older adults in the population based ESTHER cohort 14 years in advance (2). There was an added value when including APOEe4 as risk factor for identifying preclinical AD states 14 years before disease onset increasing the AUC over 0.87 (3). Additionally, the combination of other biomarkers such as tau misfolding in CSF or plasma Aβ42/40 showed added values as well. Analyzing tau misfolding in CSF and Aβ misfolding in plasma increases the sensitivity to 89% and specificity up to 97% as compared to clinical diagnosis (4). Beside the general threshold <1644 cm-1 indicating abnormal misfolding in diseased individuals, a second threshold >1646 cm-1 was introduced indicating a normal Aβ secondary structure distribution as observed in individuals without AD (4). Frequencies between both thresholds indicate low misfolding. This analysis enables the risk stratification by means of the misfolding status as already proven on SCD subjects from the Amsterdam dementia cohort (5). **Objectives:** We investigated the performance of Aβ misfolding as a prescreening plasma biomarker for AD development in a population based cohort up to 17 years before clinical manifestation. Additionally, the performance was compared to the concentration biomarkers GFAP, NfL and P-tau181 measured with SIMOA (6). **Methods:** Baseline plasma samples of 308 subjects taken between 2000-2002 were analyzed using the infrared-immuno sensor (iRIS). The obtained structure biomarker results were compared with GFAP, P-tau181 and NfL levels obtained by the SIMOA platform. **Results:** Baseline plasma analysis revealed significant differences for all plasma biomarkers in AD subjects compared to the controls. Additionally, the misfolding biomarker showed the best prognostic performance at 17-year follow-up relative to all concentration biomarkers. Furthermore, a biomarker panel of Aβ misfolding and GFAP levels showed an added value. Interestingly, the prognostic performance of P-tau181 was limited to 8 years before symptom onset. It could not predict AD conversion more than 8 years in advance. **Conclusions:** Aβ misfolding allows the identification of individuals who will develop AD up to 17 years before clinical manifestation. This highlights the potential of the misfolding biomarker as a simple blood biomarker and as a screening method for the aging population, analyzing symptom-free stages and determining the risk of future AD development. Thus, prevention and early intervention of Alzheimer's can be achieved. **References:** 1. Nabers A, et al. J.Biophotonics. 2016;9(3):224-34. 2. Nabers A, et al. EMBO.Mol.Med. 2018May;10(5). 3. Stocker H, et al. Alzheimer's and Dementia. 2020;16:283–91. 4. Nabers A, et al. Alzheimer's and Dementia (Amst). 2019 Mar 12;11:257-263. 5. Stockmann J and Verberk I et al. Alz Res and Ther. 2020, 6. Beyer L and Stocker H, et al. Alzheimer's and Dementia. 2022, in press

OC31- NVG-291 PHASE 1 RESULTS AND PHASE 1B/2A STUDY DESIGN IN INDIVIDUALS WITH MILD COGNITIVE IMPAIRMENT OR MILD DEMENTIA DUE TO ALZHEIMER'S DISEASE.

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Background: Chondroitin sulfate proteoglycans (CSPGs) are increased at sites of central nervous system (CNS) damage, including regions with beta-amyloid plaques and neurofibrillary tangles of Alzheimer's disease (AD). CSPGs inhibit neural repair mechanisms, in part through their interaction with the receptor protein tyrosine phosphatase sigma (PTPσ). NVG-291 is a subcutaneously (SC) administered peptide that modulates PTPσ. In various animal models of CNS damage, NVG-291 treatment resulted in functional improvements due to enhanced axonal regeneration, plasticity, and remyelination. It is hypothesized that NVG-291 treatment of individuals with impaired cognition due to AD will lead to improved function of CNS neurons as a result of enhanced plasticity and strengthened synaptic connections, which may be measured using functional brain imaging techniques. **Objectives:** Present Phase 1 results (healthy subjects) and Phase 1b/2a study design (subjects with mild cognitive impairment or mild dementia due to Alzheimer's disease). **Methods:** The single ascending dose (SAD) portion of the Phase 1 trial in healthy subjects enrolled 37 subjects in 6 dose cohorts of NVG-291 or placebo. The multiple ascending dose (MAD) portion of the study is dosing up to 18 subjects randomly assigned into 3 dose cohorts to receive NVG-291 or placebo SC once-daily for 14 days. Additional subjects treated with open-label NVG-291 are undergoing cerebrospinal fluid (CSF) analysis to measure NVG-291 concentration. NVG-291 doses being investigated in the MAD portion of the study exceed human equivalent levels that showed efficacy in animal models. The primary objective of the multicenter Phase 1b/2a trial is to assess the safety, tolerability and pharmacokinetic profile of NVG-291 in subjects with AD. Secondary objectives are to investigate the biological effects of NVG-291 by assessing change in the standardized uptake value ratio of 18F-fluorodeoxyglucose (18FDG) in a pre-specified region of interest and by voxel-based subtraction analysis using 18FDG-positron emission tomography; and to assess change in cognition using the AD Assessment Scale-Cognitive Subscale (ADAS-Cog) 13 and Clinician Interview-Based Impression of Change, plus caregiver interview (CIBIC-plus). Exploratory objectives include assessment of cerebral resting state functional connectivity using functional magnetic resonance imaging Blood Oxygenation Level Dependent (BOLD) sequences and to assess episodic/working memory, reaction time, learning, executive function and activities of daily living using additional cognitive instruments. The Phase 1b/2a trial will enroll ~80 subjects aged 55-85 with mild cognitive impairment or mild dementia due to AD, mini-mental state exam score 22-28, abnormal paragraph recall, and evidence of AD biology. Subjects will be randomized 1:1 to NVG-291 or placebo administered by daily SC injection x 12 weeks, followed by no intervention for 12 weeks. **Results:** NVG-291 has been safe and well-tolerated through 6 completed SAD cohorts and two completed MAD cohorts. In the SAD cohorts, all adverse

events (AEs) were mild and transient; the most common AE was injection site related. Blinded analysis of safety in the MAD (dose cohorts 1 and 2) has shown that AEs were mild except for a single event of moderate migraine; the most common AE was injection site related. There were no serious AEs, and no effect on vital signs or ECGs in any subjects, and NVG-291 has shown promising pharmacokinetic characteristics. **Conclusion:** NVG-291 appears well tolerated after administration of multiple ascending doses in healthy subjects. Upon completion this year, the Phase 1 study will establish the safety/tolerability/pharmacokinetics of NVG-291 to support advancement to the Phase 1b/2a clinical trial in subjects with mild cognitive impairment or mild dementia due to AD. The Phase 1b/2a study in AD will assess change in functional and advanced structural imaging measures and cognition following treatment, with the trial expected to initiate in late 2022. **Disclosures:** DM and JT are employees of NervGen. MF, BL, GP, RS, MW, HZ, and JC are paid consultants of NervGen

OC32- INTRODUCTION TO THE VERI-T TRIAL: A PHASE 1 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER TRIAL OF VERDIPERSTAT IN PATIENTS WITH SVPPA DUE TO FTLD-TDP. P. Ljubenkov[1], A. Staffaroni[1], L. Vandevrede[1], J. Rojas-Martinez[1], M. Koestler[1], A. Porsteinsson[2], M.B. Pascual[3], J. Masdeu[3], I. Grant[4], D. Irwin[5], D. Knopman[6], R. Bowser[7], M. Grossman[5], I. Qureshi[8], A. Boxer[1] *(1. UCSF Memory and Aging Center - San Francisco (United States), 2. University of Rochester - Rochester (United States), 3. Houston Methodist - Houston (United States), 4. Northwestern University - Chicago (United States), 5. University of Pennsylvania - Philadelphia (United States), 6. Mayo Clinic Rochester - Rochester (United States), 7. Barrow Neurological Institute - Phoenix (United States), 8. Biohaven Pharmaceuticals - New Haven (United States))*

Background: Nuclear depletion and cytoplasmic accumulation of TAR DNA-binding protein 43 (TDP-43) is a major cause of dementia, present in about 20% of patients with Alzheimer's disease and about half of patients with frontotemporal dementia. There is currently an unmet need for dementia clinical trials targeting sporadic TDP-43 pathology, but TDP-43 mislocalization is typically difficult to diagnose prior to autopsy. The semantic variant of primary progressive aphasia (svPPA) is over 80% predictive of frontotemporal lobar degeneration with TDP-43 mislocalization (FTLD-TDP) and is thus an ideal cohort in which to conduct the first wave of therapeutic trials targeting sporadic TDP-43 pathology. Potential therapeutic targets in FTLD-TDP include oxidative stress, which promotes mislocalization of TDP-43 in neurons. Verdiperstat is a potent, oral, CNS-penetrant, myeloperoxidase inhibitor that reduces production of oxidative species from microglia. The Veri-T trial (NCT05184569) will explore the therapeutic potential of verdiperstat in the first clinical trial to focus on patients suffering from svPPA. The Veri-T trial is also the first clinical trial to leverage the recruitment resources of the ARTFL LEFFTDS Longitudinal FTLD (ALLFTD) research network of clinical centers. **Objectives:** The primary objective of this study is to determine the safety and tolerability of verdiperstat in patients svPPA due to FTLD-TDP. The secondary objective of this study is to determine the pharmacokinetic (PK) profile of verdiperstat in patients with svPPA. Exploratory objectives will include investigation of verdiperstat's effects on candidate pharmacodynamic markers and candidate markers of efficacy for future trials in patients with FTLD-TDP. Exploratory endpoints include plasma myeloperoxidase activity, cerebrospinal fluid (CSF) biomarkers of glial activity (chitinase-family proteins), neurodegeneration (neurofilament light chain), and unbiased CSF proteomics (via SOMAmer reagent assays), as well as volumetric MRI changes unique to svPPA, and cognitive and language impairment measures assessed via ALLFTD's Smartphone app. **Methods:** This is a multisite, phase 1, randomized, double-blind, placebo-controlled trial. N=64 participants with svPPA will be randomized 1:3 to placebo or oral verdiperstat (titrated to a dose of 600mg BID) for 6 months of double-blind therapy. Neuropsychological assessments, plasma and CSF, and volumetric brain imaging will be collected prior to and upon conclusion of treatment. Recruitment will occur at 5 ALLFTD research network clinical centers. **Results:** The first participant was randomized April 19th, 2022 and recruitment remains ongoing. To date, no dose-limiting toxicities have occurred. **Conclusion:** The Veri-T trial examines the safety, tolerability and pharmacokinetic properties of verdiperstat in svPPA and explores novel pharmacodynamic biomarkers and outcome measures that could be employed in future efficacy studies targeting sporadic FTLD-TDP.

OC33- A PHASE 1, OPEN-LABEL, 52-WEEK, MULTICENTER STUDY TO EVALUATE THE SAFETY AND BIOCHEMICAL EFFICACY OF AAV GENE THERAPY (LX1001) IN PATIENTS WITH APOE4 HOMOZYGOTE ALZHEIMER'S DISEASE – INTERIM DATA. M. Kaplitt[1], P. Leopold[2], E. Noch[3], J. Ivanidze[4], L. Chazen[4], R. Crystal[2], S. Kaminsky[2], H. Bowe[2], M. Wang[2], D. Ballon[4], J. Dyke[4], D. Sondhi[2], S. Gandy[5], G. Giannantoni-Ibelli[6], J. Barth[6] *(1. Department of Neurological Surgery, Weill Cornell Medical College - New York (United States), 2. Department of Genetic Medicine, Weill Cornell Medical College - New York (United States), 3. Department of Neurology, Weill Cornell Medical College - New York (United States), 4. Department of Radiology, Weill Cornell Medical College - New York (United States), 5. Departments of Neurology and Psychiatry, Icahn School of Medicine at Mt Sinai - New York (United States), 6. LEXEO Therapeutics, Inc. - New York (United States))*

Background: Alzheimer's disease (AD), a progressive neurodegenerative disorder, is associated with a strong genetic risk resulting from polymorphisms of the apolipoprotein E (APOE) gene. The APOE4 allele is a well-recognized genetic risk factor for late-onset AD. While this allele increases risk and reduces the age of AD onset, the E2 allele decreases risk and delays the age of AD onset. APOE4 homozygotes have a 15-fold greater risk of developing AD compared with the APOE3 homozygotes, the most common genotype. The marked reduction in AD risk among APOE2/E4 heterozygotes suggests a potential protective effect of APOE2, yet only 5% of the population carry an APOE2 allele. LX1001 is an adeno-associated viral vector (AAV) investigational gene therapy (AAVrh.10hAPOE2) designed to deliver the protective apolipoprotein E2 (APOE2) gene into the central nervous system of APOE4 homozygous AD subjects in order to halt or slow the disease progression, mediated by the APOE4 allele. **Objectives:** The primary objective of this first-in-human trial is to evaluate the safety of LX1001 administered into the cerebrospinal fluid (CSF) at the craniocervical junction (via CT-guided C1-C2 or intracisternal route), given the equipoise regarding the potential effects of both overexpressing APOE2 in the AD brain and of widespread CSF delivery of AAV vectors in the degenerating human brain. This trial is also designed to evaluate the feasibility of converting CSF from the APOE4 homozygous profile to an APOE4/E2 profile as a biomarker

of successful gene delivery. Additional secondary endpoints include analysis of other CSF AD biomarkers, including Aß42, total tau (T-tau), and phosphorylated tau (P-tau) along with amyloid-targeted PET, structural MRI imaging, and cognitive tests. **Methods:** This is a Phase 1, open label, dose-finding study evaluating the safety and tolerability of LX1001 in AD. LX1001 is being evaluated in three ascending single-dose cohorts (5.0E10, 1.6E11 and 5.0E11 gc/ml CSF), with the dose for each subject determined based on CSF volume measured by MRI. Each of 3 dose cohorts consists of ~5 APOE4 homozygotes. Enrollment criteria include APOE4 homozygous genetic profile, age 50 years or older, positive amyloid-targeted PET, CSF biomarkers consistent with AD, and mild cognitive impairment to mild or moderate dementia due to AD. After completing this study, subjects are invited to enroll into an extension study for evaluation of long-term safety and efficacy for an additional 4 years post gene transfer. **Results:** A total of five subjects were dosed in the low-dose (5E10 gc/ml CSF) cohort. Based on data available to date, among all subjects in cohort 1 (n=5, age 59-73 years, with MCI or moderate dementia due to AD), treatment with LX1001 was well-tolerated with no serious adverse events reported to date. Follow-up data for evaluation of efficacy are available for 4 subjects, aged 59-73 years, with MCI or moderate dementia due to AD. Preliminary data for cohort 1 demonstrated that post-vector administration APOE2 was expressed in CSF in all 4 subjects with follow-up data ≥ 3 months. Both subjects with 12-month data demonstrated a decline in the CSF T-Tau and P-Tau. One subject showed a CSF T-Tau reduction from baseline over 12-months of ~20% and CSF P-Tau reduction of ~9%. The other subject showed a CSF T-Tau reduction from baseline over 12-months of ~4% and CSF P-Tau reduction of ~14%. **Conclusion:** LX1001 is the first investigational gene therapy to directly address APOE, a well-recognized genetic risk factor of AD. Initial data in the low-dose cohort supports technical feasibility of conferring APOE2 expression in the CNS of human APOE4 homozygotes and indicates that there were no serious adverse events from either CSF delivery of LX1001 or from documented expression of APOE2 in these subjects. These data support further exploration of APOE2 gene therapy as a potential therapeutic for APOE4 homozygous AD patients. **Conflicts of Interest:** None at this time.

OC34- PRELIMINARY EVIDENCE FOR RELIABILITY AND VALIDITY OF THE INTERPERSONAL FUNCTIONING AND DAILY ACTIVITIES QUESTIONNAIRE (IFDAQ) IN THE A4/LEARN PRE-RANDOMIZATION SAMPLE.

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Introduction: There is an unmet need for patient-reported measures reflecting relevant domains of treatment benefit in early Alzheimer's disease (AD) that have been developed using best practices, including appropriate input from persons with Mild Cognitive Impairment (MCI) and caregivers. The Cognition Working Group (WG) of the Critical Path Institute's Patient-Reported Outcome (PRO) Consortium developed a new PRO instrument, intended as a "fit-for-purpose" efficacy endpoint measure in clinical trials in prodromal AD or MCI due to AD. Using a targeted literature review, focus groups, and interviews, concepts of importance for complex activities of daily living (cADLs) and interpersonal functioning (IF) were identified. Using FDA feedback, advice from clinical experts, and concept elicitation interviews in 79 MCI, probable AD and non-impaired controls, and 65 informants, a conceptual framework was developed for a draft measure (the Interpersonal Functioning and Daily Activities Questionnaire (IFDAQ)) that included both cADL (16 items e.g., managing finances and planning skills) and IF domains (10 items e.g., conversational skills) (Gordon et al., 2016). Each item had response options of "Never" (0), "Rarely" (1), "Sometimes" (2), "Often" (3), and "Always" (4) to measure the frequency with which people with early AD experience difficulties in each domain. **Objectives:** To provide initial evidence for the reliability and validity of the IFDAQ using a large dataset derived from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's study (A4) and the Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN) studies' pre-randomization data. The A4 Study is a secondary prevention trial in preclinical AD and has a companion observational study called LEARN. The A4 study aims to prevent or slow the onset of AD symptoms in healthy adults with amyloid-beta plaque to see if treatment can show a benefit in preventing or slowing cognitive decline i.e., progression from clinical stages 1 and 2 (preclinical) to clinical stage 3 (prodromal or MCI). **Methods:** The IFDAQ was included in A4/LEARN and is part of the assessment schedule for two pre-randomization visits conducted within 90 days of each other (Screening Visits 1 and 3 (Note: Amyloid PET imaging occurred at Screening Visit 2, followed by disclosure of amyloid status)). Analyses were performed on the total score (26 items, range 0-104) and the IF (10 items, range 0-40) and cADL (16 items, range 0-64) subscales. Reliability was evaluated using Cronbach's alpha for internal consistency and ICC (A,1) for test retest. Validity was evaluated using known groups validity (t-test and Cohen's d) at Visit 1 comparing between the group with CDR Global =0 and that with CDR Global =0.5. **Results:** Data were available for a total of N=6203 participants (mean age 71.5 (SD 4.8); 58% female; mean years of education 16.5 (SD 2.93), with IFDAQ data available for N=5402 participants at Visit 1 and N=4264 participants at Visit 3. Item level missing data increased marginally over the length of instrument with a maximum of 4.3% of data missing for the final item (#26). Internal consistency reliability was high for the cADL and IF subscales (α=0.90 (95% CI 0.89, 0.90) and α=0.87 (95% CI 0.87, 0.88), respectively), and the total score (α=0.93 (95% CI 0.93, 0.93)). Test-retest reliability was adequate for the cADL and IF subscales (ICC=0.76 (95% CI 0.75, 0.77) and ICC=0.75 (95% CI 0.74, 0.76), respectively), and the total score (ICC=0.78 (95% CI 0.77, 0.79)). Known groups validity analyses showed statistically significant differences between CDR Global =0 (N=5230) and CDR Global =0.5 (N=101) groups at Visit 1 (unequal variances t-test p<0.001). Higher scores indicating worse participant reported function were seen in the CDR 0.5 group for cADL (Cohen's d=1.06; mean 12.6 (SD 6.79) and mean 16.7 (SD 7.72) respectively), IF (Cohen's d=0.68; mean 10.3 (SD 5.34 and mean 12.4 (SD 6.10) respectively), and the total score (Cohen's d=0.97; mean 22.9 (SD 11.20) and mean 29.2 (SD 12.66) respectively). **Conclusion:** Initial analyses of the IFDAQ in a largely cognitively normal population undergoing screening for the A4 secondary prevention trial in

preclinical AD and the companion observational study LEARN, support its validity and reliability as a PRO measure assessing interpersonal function and complex ADLs. In the know groups validity analyses a larger difference was evident for cADL items versus IF items, which may suggest cADL difficulties were more prominent and/or reflect concept coverage in the CDR. The IFDAQ has potential utility for the measurement of early changes in the frequency with which people with predementia/prodromal AD (clinical stages 1-3) experience difficulties in complex ADLs and interpersonal functioning. **References:** Gordon, M. F. et al. (2016) 'Development of a patient-reported outcome instrument to assess complex activities of daily living and interpersonal functioning in persons with mild cognitive impairment: The qualitative research phase', Alzheimer's and Dementia. doi: 10.1016/j.jalz.2015.04.008. **Disclosures:** Chris J Edgar is a fulltime employee of Cogstate.

OC35- APOE-TARGETED EPIGENOME THERAPY FOR ALZHEIMER'S DISEASE. B. Kantor[1,2], O. Chiba-Falek[1,3] *(1. Duke University - Durham (United States), 2. CLAIRIgene LLC - Durham (United States), 3. CLAIRIgene - Durham (United States))*

Background: There is an urgent need to refocus Alzheimer's disease (AD) drug discovery on new targets and shifting the paradigm of AD drug development towards precision medicine. Apolipoprotein E gene (APOE) is the strongest and most reproducible genetic risk factor for late-onset Alzheimer's disease (LOAD). Moreover, 50% reduction in APOE levels showed beneficial effects in AD cellular and mouse models. Thus, APOE gene holds promise as a potential therapeutics target for LOAD. **Objectives:** In this study we developed an epigenome therapy platform to reduce APOE expression generally and APOEe4 allele specifically by targeted modification of the epigenome landscape within APOE locus. **Methods:** Our gene therapy strategy is based on CRISPR/deactivated (d)Cas9 editing technology fused with an effector molecule and delivered by viral-based vehicles. Our gRNAs were designed to target regulatory elements within the APOE promoter/intron 1 region and in exon 4 sequence overlapping the SNP that defines the APOEe4 allele. We evaluated our epigenome therapy platform in vitro using human hiPSC-derived neurons and in vivo by stereotactic injection of reporter gene into the hippocampus of mice. **Results:** The viral dCas9-repressor vector showed decreased APOE-mRNA and protein overall levels in hiPSC-derived neuronal model. To specifically target the APOEe4 allele we utilized the VRER-dCas9 protein. Evaluation of the system specificity showed a reduction in APOE-mRNA levels in the hiPSC-derived neurons with the e4 allele while there was no effect in the isogeneic hiPSC-derived neurons homozygous for the e3 allele. Moving onto in vivo studies in mice, administration of the viral dCas9-repressor vector and the green fluorescent protein (GFP) reporter gene into the hippocampus showed a significant decrease in GFP expression with strong repression effect, demonstrating promising preliminary data. Collectively, our results provided in vitro and in vivo proof-of-concept for the utility and efficacy of the APOE-targeted epigenome therapy. **Conclusions:** Our epigenome therapy strategy for fine-tuning of APOE expression based on dCas9 technology is translational toward the development of a therapeutics approach to prevent and/or delay LOAD onset. Furthermore, the technology offers the opportunity to refine the platform for the development of gene-specific and even allele- and cell-type- specific therapies, and by that enables the advancement of strategies for precision medicine in LOAD.

OC36- CONFOUNDING FACTORS OF ALZHEIMER'S DISEASE PLASMA BIOMARKERS AND THEIR IMPACT ON CLINICAL PERFORMANCE. A. Pichet Binette[1], S. Janelidze[1], N. Cullen[1], J.L. Dage[2], R.J. Bateman[3], H. Zetterberg[4,5], K. Blennow[1], E. Stomrud[1], N. Mattsson-Carlgren[1], O. Hansson[1] *(1. Clinical Memory Research Unit, Faculty Of Medicine, Lund University - Lund (Sweden), 2. Department Of Neurology, Indiana University School Of Medicine - Indianapolis (United States), 3. Department Of Neurology, Washington University School Of Medicine - St. Louis (United States), 4. Department Of Psychiatry And Neurochemistry, The Sahlgrenska Academy, University Of Gothenburg - Gothenburg (Sweden), 5. UK Dementia Research Institute, University College London - London (United Kingdom))*

Background: Plasma biomarkers will likely revolutionize the diagnostic work-up of Alzheimer's disease (AD). However, before widespread clinical use, it is important to determine which, if any, confounding factors might affect the levels of these biomarkers, and their clinical utility. Here we studied whether common comorbidities, as well as proxies of kidney function (plasma creatinine) and blood volume (body mass index [BMI]) confounded the levels of several state-of-the-art plasma biomarkers for AD and neurodegeneration. **Objectives:** First, we investigated associations between plasma biomarkers levels and comorbidities/medication use, creatinine, and BMI, which allowed us to identify key potential confounding factors. Second, we studied whether the performance of plasma biomarkers was improved when adjusting for such potential confounding factors in two contexts: i) associations between individual plasma biomarkers and their CSF counterparts, and (ii) the ability of plasma biomarkers to predict conversion to AD dementia or all-cause dementia in non-demented individuals. **Methods:** Participants with plasma and CSF biomarkers, creatinine, BMI, and medical history data from the Swedish BioFINDER-1 (n=748) and BioFINDER-2 (n=421) cohorts were included. Beta-amyloid (Ab42, Ab40), phosphorylated tau (p-tau217, p-tau181), neurofilament light (NfL), and glial fibrillary acidic protein (GFAP) were measured in plasma and CSF, using high-performing assays (mass-spectrometry [MS], Meso Scale Discovery or Sioma for plasma and all Elecsys assays for CSF, apart from p-tau217). For plasma Ab, results were validated across three assays, including the WashU-IP-MS. Linear regression models first assessed associations for plasma biomarkers with BMI, creatinine, and comorbidities. Next, we used bootstrapping to assess if models with or without confounding factors as covariates (linear regressions for plasma-CSF correspondence and logistic regressions for progression to dementia) were significantly different. **Results:** In both cohorts, creatinine and BMI, but not comorbidities or medication use, were the main factors associated with plasma biomarkers. Creatinine was positively correlated with NfL and GFAP in both cohorts (average standardized coefficients of 0.2, all $p<0.05$). In BioFINDER-1, creatinine was also positively correlated with p-tau217 and p-tau181 (average standardized coefficients of 0.14, all $p<0.05$). BMI was negatively correlated with NfL, GFAP, and to a lesser extent with p-tau217 and p-tau181 in both cohorts (average standardized coefficients of -0.15, all $p<0.05$). No associations were found with the Ab42/Ab40 ratio. Adjustment for BMI and creatinine had minor effects in models predicting either the corresponding levels in CSF or subsequent development of dementia. In both cohorts, NfL was the main biomarker for which accounting for confounding factors consistently improved the plasma coefficient (by 6 to 10%) in relation to

CSF. Smaller improvements (2-3%) were seen when accounting for confounding factors with the Ab42/Ab40 ratio, only on MS-based assays. Regarding progression to subsequent dementia, plasma p-tau217 and NfL odds ratio were improved by 4.5% to discriminate between stable participants and those progressing to AD dementia or all-cause dementia respectively. However, the discriminative accuracies between models (AUC of 0.82 for p-tau217 and 0.71 for NfL) were virtually the same, with a maximum change in AUC of 0.01. **Conclusion:** In two large cohorts, creatinine and BMI were related to certain plasma biomarkers levels. Still, the improvements in models were modest when including these two confounding factors, suggesting their limited clinical relevance for the majority of individuals.

OC37- ADUCANUMAB AND LECANEMAB LABEL INSOLUBLE, FIBRILLAR, DIFFUSIBLE AB AGGREGATES IN AQUEOUS EXTRACTS OF HUMAN ALZHEIMER DISEASE BRAIN. A.M. Stern[1], A.L. Meunier[1], W. Liu[1], M. Ericsson[2], D.J. Selkoe[2] *(1. Ann Romney Center For Neurologic Diseases, Brigham And Women's Hospital, Harvard Medical School - Boston (United States), 2. Harvard Medical School Electron Microscopy Core - Boston (United States))*

Background: Monoclonal antibodies that bind aggregated forms of Aβ are FDA-approved or are completing confirmatory phase 3 trials, and some may enter the clinic in common use in the next few years. Detailed studies have described their binding to synthetic Aβ and in vitro-derived aggregates thereof, but less is known about the nature of aggregates these antibodies bind in human brain. Binding and removing small aqueously soluble "oligomers" has been proposed to be one mechanism of action for these antibodies and an attractive target for future generations. Lecanemab has been shown to bind small oligomeric synthetic Aβ species aggregated in vitro, but in human subjects it reduces amyloid PET signal, which measures large fibrillar forms of Aβ. **Objectives:** We sought to describe the quantity, size and shape of aggregates bound by clinical antibodies in the aqueous fraction of extracts from human AD brain tissue. **Methods:** Aqueous extracts of postmortem AD and control cortical tissue were prepared by mincing and then soaking in TBS buffer followed by ultracentrifugation, retaining the supernatant. Immunoprecipitation followed by denaturation and detection with an Aβ42-specific ELISA were used to quantify Aβ species in the extracts reactive to therapeutic antibodies. Extracts were adsorbed onto carbon-coated grids, and immuno-electron microscopy with protein A-gold was used to study binding of therapeutic antibodies to Aβ fibrils found in the aqueous extracts. **Results:** Aducanumab, lecanemab, and bapineuzumab all immunoprecipitated the majority of Aβ detectable in aqueous AD brain "soaking" extracts. Negative staining and immunogold transmission EM revealed the presence of pelletable, fibrillar Aβ species in aqueous "soaking" extracts of all thirteen human AD brains examined. Aducanumab, lecanemab, and bapineuzumab all decorated these Aβ fibrils. Lecanemab immunoprecipitation of Aβ did not occur from the supernatants of very high ultracentrifugation speeds (250,000 - 475,000 g) but did occur from supernatants prepared at lower speeds (20,000 – 100,000 g). **Conclusions:** At least some oligomers present in aqueous diffusible extracts of AD brain are fibrillar and can bind therapeutic monoclonal antibodies. The fibrils are lost with very high-speed ultracentrifugation. The results suggest that the mechanism of action of therapeutic anti-amyloid antibodies may in part be due to binding insoluble Aβ aggregates. This agrees with the observation of robust clearance of amyloid PET by these antibodies, including lecanemab. **Disclosures:** DJS is a director of Prothena Biosciences and a consultant to Eisai.

OC38- A MULTIMODAL CLINICAL AND LIFESTYLE INTERVENTION INDUCES MULTIOMIC SYSTEMIC EFFECTS AND IMPROVES COGNITIVE OUTCOMES IN ALZHEIMER'S DISEASE. J.C. Roach[1], L.E. Edens[1], S. Rajbhandari[1], J. Hara[2], J. Bramen[3,4], M.K. Rapozo[5], C. Funk[1], W.R. Shankle[2,6,7,8], L. Hood[1] *(1. Institute For Systems Biology - Seattle, Washington (United States), 2. Pickup Family Neurosciences Institute, Hoag Memorial Hospital Presbyterian - Newport Beach, California (United States), 3. Pacific Brain Health Center, Pacific Neuroscience Institute - Santa Monica, California (United States), 4. Department of Translational Neurosciences and Neurotherapeutics, Saint John's Cancer Institute - Santa Monica, California (United States), 5. Providence St. Joseph Health - Renton, Washington (United States), 6. Shankle Clinic - Newport Beach, California (United States), 7. Department of Cognitive Sciences, University of California - Irvine, California (United States), 8. EMBIC Corporation - Newport Beach, California (United States))*

Background: The Coaching for Cognition in Alzheimer's (COCOA) trial was a prospective randomized clinical trial (RCT) to test the effect of a multimodal intervention on individuals in the early stages of cognitive decline. Participants met criteria for at least one definition of either Alzheimer's disease (AD) or a condition on the AD spectrum. AD and other dementias result from the interplay of multiple interacting dysfunctional biological systems. The motivation for COCOA was to test the hypothesis that personalized multimodal lifestyle and clinical interventions could ameliorate cognitive decline in this population. Coached interventions in COCOA were tailored to personal, clinical, and molecular data for each individual – representing a form of precision medicine. Standard of care, including pharmaceutical combination therapy, was available to all individuals enrolled in the trial; the intervention arm received personalized coaching for combination lifestyle interventions and cognitive training in addition to this standard of care. **Objectives:** Our overarching objective is to establish (or disprove) causal paths connecting specific interventions (or combinations of them) through intermediate molecular subsystems to neurological subsystems that promote cognition. Parts of this epistemological argument should include: (i) evidence that multimodal interventions improve cognition, such as a significant change in an RCT primary outcome measure, (ii) evidence that multimodal interventions impact particular endophenotypes, including description of the particular molecular analytes comprising these endophenotypes, and (iii) evidence connecting these endophenotypes to beneficial neurological and cognitive outcomes. Our goal for the resulting knowledge is to enhance the design of future clinical trials, tweak or overhaul recommendations for multimodal interventions, and stimulate broader adoption of lifestyle interventions already suspected or known to ameliorate cognitive decline. **Methods:** COCOA's trial design is as described (1). COCOA's primary outcome measure is the Memory Performance Index (MPI), a measure of cognition. The MPI is a summary statistic of the MCI Screen (MCIS). Secondary outcome measures include the Functional Assessment Staging Test (FAST), a measure of function. In addition to testing a hypothesis of improvement in a primary cognitive outcome endpoint, COCOA was also designed to produce dense omics data to enable epistemological analyses

and exploration (2). We analyzed an interim data freeze from COCOA spanning a full year of trial participation for all participants. These data included cognitive outcome measures, clinical labs, targeted serum proteomics, and comprehensive serum metabolomics. We integrated these data into a combined omics dataset and analyzed them as a connected system, using both pre-existing knowledge graphs and connections learned from the data. Dimensionality reduction techniques included multidimensional scaling, principal components analysis, and force-directed network layout. Gene set and metabolite set enrichment analyses were performed on connected subsystems. Significance was computed for subsystems as well as for individual analytes. New results were contextualized and integrated with prior knowledge using knowledge graphs summarizing existing biomedical knowledge. **Results:** In aggregate, both the primary cognitive outcome measure (MPI) and the functional outcome measure (FAST) significantly improved in cases compared to controls. Omics data from the 42 participants with at least two omic timepoints were considered. The multimodal intervention impacted (significantly different between cases and controls) analytes spanning overlapping systems including metabolic, immune, cardiovascular, and neurologic function. The most significant of these subsystems had functions related to protein and amino acid metabolism. A subset of the most significant proteins had neurotrophic function. A distinct set of analytes, particularly cardiovascular proteins, were correlated with better cognitive outcomes across all individuals (both cases and controls). **Conclusion:** Multimodal lifestyle interventions have broad impacts on many physiological systems; these impacts are reflected in hundreds of serum analytes. In aggregate, individuals receiving these interventions have better cognitive outcomes than those who do not. One possible interpretation is that some single aspect of the multimodal intervention, potentially different in each person, may convey the bulk of causal benefit. However, it is more likely that improving general health across a wide variety of connected organ systems improves multiple functions that work synergistically to improve cognitive health. These functions appear to include cardiovascular health and neurotrophic support. More generally, improved overall energetics and protein synthesis may fundamentally enable systems in the body that have been degraded by other processes, have become underpowered to maintain homeostasis, and have allowed the body to veer towards a path of cognitive decline and dementia. Revitalization of these basic metabolic processes may enhance allostasis and improve cognitive outcomes. Progression of AD may be delayed, halted, or reversed (ameliorated) in some individuals. These insights may be generalizable to other conditions of aging. Additional work remains for the analysis of this and future COCOA data freezes. Our existing results facilitate design of future clinical trials and may guide refinements to personalized multimodal interventions. **References:** 1. Roach et al. The Coaching for Cognition in Alzheimer's (COCOA) Trial: Study Design. Alzheimers Dement. In Press. 2. Roach et al. 2022. Dense data enables twenty-first century clinical trials. Alzheimers Dement. e12297.

OC39- ADVANTAGES OF NEXT GENERATION SUPRAANTIGEN® PLATFORM LIPOSOMAL VACCINES TO IMMUNIZE AGAINST PATHOLOGICAL TARGETS OF ALZHEIMER'S DISEASE.

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Background: Alzheimer's disease (AD) and certain related neurodegenerative diseases are silent pandemics that are expanding in step with our ageing global population. Amyloid plaques, composed of misfolded Abeta species such as neurotoxic pyroGlu-Abeta and oligomeric Abeta, are one of the early hallmarks of AD, appearing when people are pre-symptomatic and proliferating as disease progresses. In addition, early in the disease, Tau forms neurofibrillar tangles, rich in aggregated phosphorylated (p)Tau, the deposition of which tracks with loss of cognition and neurodegeneration. For over a decade, we have been evolving our liposome-based SupraAntigen® vaccine platform, comparing it to commonly used approaches, such as protein-conjugate-based vaccines, to create best-in-class vaccines that can slow disease progression as well as delay or prevent disease onset. **Objectives:** Development of vaccines that safely generate sustained, conformation-specific antibody titers with preferences for the pathological species of Abeta and Tau. Evaluation of these vaccines in mice, non-human primates (NHP) and AD patients. **Methods:** For Abeta, several vaccines were generated as follows: a liposome-based SupraAntigen® vaccine (i.e., optimized ACI-24) containing the antigenic peptide Abeta 1-15, an adjuvant and a universal T-helper cell peptide; and CRM-conjugated vaccines containing various antigenic Abeta peptides (e.g., ACC-001) or full-length Abeta (i.e., AN1792) mixed with adjuvant. Mice and NHPs were vaccinated as follows: mice, 3 times every 2 weeks and plasma collected one week post immunization; cynomolgus monkeys, 5 times monthly and serum collected one week post immunization. ELISA-based assays assessed the binding to various forms of Abeta. Epitope mapping was carried out assessing the binding to 8 amino acid long peptides of Abeta. For Tau, various vaccines were generated as follows: a liposomal-based SupraAntigen® vaccine (i.e., ACI-35.030) containing an antigenic phosphorylated peptide pTau, adjuvants and a universal T-helper cell peptide: and a CRM-conjugated vaccine containing an antigenic phosphorylated Tau peptide. NHPs were immunized at 0, 1, 3 and 6 months and serum collected one and three weeks after each immunization. ELISA-based assays assessed the binding to various forms of Tau. Epitope mapping was carried out assessing the binding to the peptides of non-phospho- and phospho-Tau. **Results:** When immunizing mice and NHPs with vaccines containing the various Abeta peptides, all animals developed anti-Abeta 1-42 titers. However, only the liposomal-based optimized ACI-24 induced a homogenous and robust response to the Abeta-toxic species, pyroglutamate (pyroGlu-Abeta). Furthermore, this protective IgG response was maintained over time and could be consistently boosted. Additional profiling of the antibody response by epitope mapping revealed the superior broad coverage of the repertoire, as only optimized ACI-24 induced antibody responses to different short peptides including the mid-domain of Abeta 1-15, while the other vaccines generated antibodies that bound mainly to the very N-terminal sequence

of Abeta. For the Tau targeting vaccines, ACI-35.030 and the CRM-conjugated vaccine induced similar IgG titers to the immunizing peptide, as well as ePHF. However, ACI-35.030 induced antibodies with a strong preference towards the phospho peptide and low binding to the non-phospho peptide, while the CRM-conjugated vaccine induced a strong response to the non-phospho peptide. This was in line with the epitope mapping data, which demonstrated strong binding to the phosphorylated residues for the ACI-35.030-induced antibodies. In contrast, the CRM-conjugated vaccine induced limited coverage mainly recognizing a truncation-specific open end amino acid of the Tau peptide sequence. Importantly, both vaccines showed a favorable safety profile and did not induce Tau-specific T-cell activation. Further evaluation of the 2 Tau targeted vaccines in AD patients confirmed similar specificity of the induced antibodies observed in the NHPs. **Conclusions:** For both Abeta and Tau targeting vaccines, the liposome-based SupraAntigen® vaccines demonstrated a superior quality of the IgG repertoire generated post-immunization. The responses in NHPs were well tolerated, homogenous, robust and boostable over time, while broadly engaging relevant pathological epitopes. For Abeta, the liposome-based SupraAntigen® vaccine generated the highest titers of antibodies specifically targeting pyroGlu-Abeta. For Tau, only the liposome-based SupraAntigen® vaccine matured a repertoire of antibodies that broadly recognized species containing the pathological pTau. Taken together, the SupraAntigen® vaccine technology platform, using carefully chosen target peptides combined with adjuvants and universal T-helper cell peptides, creates a broad and safe antibody response to the key pathological species which translates to best-in-class clinical vaccine candidates.

OC40- U-P53AZ IN PROGNOSTICATION OF EARLY ONSET ALZHEIMER'S DISEASE UP TO 6 YEARS IN ADVANCE OF THE CLINICAL DIAGNOSIS. S. Piccirella[1], L. Van Neste[2], C.H.R.I.S. Fowler[3], C.M.A.S. Masters[3], J.U.R.G.E. Fripp[4], J.D. Doecke[4], C. Xiong[5], D. Uberti[6], P. Kinnon[1]
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Background: The unfolded conformational variant of the p53 protein is a potential prognostic biomarker of Alzheimer's dementia (AD) (U-p53AZ), previously observed in individuals in the prodromal and clinical AD stages. Diadem have developed AlzoSure® Predict (Piccirella et al, 2022), a simple, non-invasive, rapid blood-based test that allows the assessment of cognitive decline to AD-dementia up to 6 years in advance of any clinical symptoms by detecting the concentration of a specific sequence peptide, AZ284®, from U-p53AZ. **Objectives:** This study aims to confirm the prognostic performance of U-p53AZ in the onset of AD and to compare this with other AD biomarkers. **Methods:** In this retrospective study, we evaluate the prognostic performance U-p53AZ (detected by AlzoSure® Predict) in plasma samples from individuals participating in the Australian Imaging, Biomarkers and Lifestyle (AIBL) cohort. AlzoSure® Predict is a LC-MS/MS based method that detects a specific peptide belonging to the U-p53AZ protein, called AZ284®. AlzoSure® Predict is a CE-IVD marked test, recently designated as breakthrough device by the FDA. At baseline, this cohort consists of 237 cognitively normal subjects, including both those without and with subjective memory complaints (NMC/SMC), 98 individuals with mild cognitive impairment (MCI), 141 patients with AD, and 3 other dementia patients that were followed up every 18 months. The performance of U-p53AZ was compared with other AD biomarkers, i.e. amyloid status assessed by calibrated centiloid, tau protein, ApoE4 allele status, age, and gender. To evaluate the prognostic potential , Cox proportional hazards regression models were developed for the beforementioned markers. **Results:** The prognostic value of U-p53AZ was evaluated in the longitudinal AD patient subset of the AIBL cohort, removing all individual that were already diagnosed with AD at baseline. The value of AZ284® relative to other biomarkers was evaluated by fitting Cox proportional hazards models. The other risk factors that were explored include centiloid, ApoE4, tau, age, and gender, in addition to combinations of these. While AZ284® data is available for a total of 338 men and women, comparisons can only be made on subjects with a complete marker profile. Because information on tau is lacking for many, this biomarker is addressed separately. First, AZ284® was compared with 294 subjects for which amyloid, age, gender, and ApoE4 are available, of which 36 develop AD over time. In terms of individual risk factors, AZ284® clearly outperforms the other risk factors with a concordance (C) index of 95.3% ± 0.9% (standard error) (all $p < .0016$). The best multi-risk factor model includes AZ284® ($p<.0001$), amyloid ($p<.0001$), and age ($p=.0096$), resulting in a C-index of 94.3% ± 1.6%. Gender and ApoE4 were not significant and did not result in any improvement of the model and were hence not included. Similarly, the best model that does not include AZ284® consists of amyloid ($p<.0001$) and age ($p=.0007$), with a C-index of 86.4% ± 3.1%. This model has a significantly lower performance compared to the model with AZ284® ($p<.0001$), demonstrating the significance and synergistic performance of AZ284®. The comparison with tau protein was more difficult, since this biomarker was only available for a limited subset of the subjects. When the maximum difference in sample collection for AZ284® and tau protein was limited to 1 year, only 29 subjects were eligible, of which only 2 developed AD over time. To increase the patient number, in particular those that develop AD, AZ284® and tau were compared without time restriction. It is important to note that the lead time for AZ284® is significantly larger compared to that of the tau sample, i.e. samples were taken significantly longer before the final diagnosis ($p < .0001$), which is also the case for those subjects that develop AD ($p=.0418$), creating a slight bias in favor of tau since the time-to-event of the AZ284® was used for all. This allowed to compare both biomarkers on a set of 64 subjects, of which 6 developed AD over time. In this subset, AZ284® performs similarly compared to the larger population, with a C-index of 95.7% ± 2.1%. Total tau and p-tau 181 were assessed, both as binary marker (positive vs negative) or using the actual concentration. For both, the actual concentration performed better than the binary marker, with C-indices 88.3% ± 4.6% vs .65.8% ± 10.1% and 77.7% ± 8.8% vs 63.6% ± 10.2%, respectively. Except for total tau concentration ($p=.0841$), AZ284® significantly outperformed tau protein (total tau binary: $p=.0024$; p-tau binary: $p=.0013$; p-tau concentration: $p= .0303$). **Conclusion:** The present study confirms the prognostic performance of U-p53AZ for AD. Despite the small sample size, the trend clearly indicates that AZ284® is the strongest performing biomarker and would be recommended as an integral part of any biomarker-based model. More details are available on: https://link.springer.com/article/10.14283/jpad.2022.52.

OC41- IWHELD: AN RCT OF A NOVEL DIGITAL NON-PHARMACOLOGICAL INTERVENTION TO IMPROVE QUALITY OF LIFE AND REDUCE ANTIPSYCHOTICS IN 741 PEOPLE LIVING IN NURSING HOMES DURING THE COVID-19 PANDEMIC. C. Ballard[1], J. Mcdermid[1], A. Sweetnam[1] *(1. University of Exeter - Exeter (United Kingdom))*

Background: Inconsistent quality of care in nursing homes has long been recognised as a challenging area that requires urgent action and its impact on quality of life in people living with dementia. These enduring issues have been compounded by the emergence of and ongoing pressures of the COVID-19 pandemic on nursing home settings. People living in nursing homes and long-term care facilities are often frail and have complex needs, many with dementia, neuropsychiatric symptoms, and/or other physical conditions and have been disproportionately impacted by the pandemic, affecting not only residents but also their families and the care workforce. Whilst high prescribing rates of antipsychotics in the early 2000s for people living with dementia in nursing homes had significantly reduced in recent years, the pandemic has seen a rebound increase in use. Implementation of evidence-based training and support for nursing staff into real world practice in nursing home settings is a major challenge. Digital approaches provide real potential to addressing the barriers, particularly over the difficult period of the COVID-19 pandemic. **Objectives:** In response to the COVID-19 crisis, to rapidly develop and implement a nursing home intervention programme to include virtual coaching, peer networking and solution sharing, alongside evidence-based elements focussing on person-centred care, personalised activities, and reduction of unnecessary antipsychotic medications. **Method:** iWHELD is a first-of-its-kind digital programme evolving the principles of the WHELD intervention combining person centred care, social interaction, movement, and antipsychotic review with virtual coaching and a digital resource for nursing homes. The entirely remote intervention utilising a Dementia Champion model supported by live virtual coaching set within a digital resource hub and peer networking platform was compared to usual care in a 16-week randomised control cluster study of 741 people with dementia across 149 nursing homes in the UK. The primary outcome evaluated quality of life (using the DEMQOL-Proxy) and secondary outcomes included the use of antipsychotic drugs and neuropsychiatric symptoms (using the Neuropsychiatric Inventory NH). **Result:** The average age of residents was 84.5 years (71% female). 64% of participating nursing homes had experienced a COVID-19 outbreak. At baseline, 28% of residents were prescribed an antipsychotic (a significant 55% increase compared to pre pandemic in previous WHELD RCT trial in 2014). 36/72 (53%) of nursing homes allocated to the active treatment arm engaged successfully with the digital intervention, with 563 residents completing the treatment period. There was significant benefit in quality of life for residents receiving the iWHELD intervention compared to those in the control group (DEMQOL-Proxy 4.76 ± 15.03 point advantage, p=.006, Cohen's D effect size 0.32). There was also a significant reduction in antipsychotic use in the iWHELD treatment group from 49% to 31% compared to no change in the group receiving usual care (p=0.046). Analysis of neuropsychiatric symptoms indicates a significant benefit for the treatment group with respect to delusions (p= .01) with no significant differences in hallucinations or agitation in the intervention group compared to those receiving usual care indicating no significant worsening of these symptoms in the context of a significant reduction in antipsychotic prescriptions. **Conclusion:** For this current large scale RCT, we successfully designed, recruited, and delivered a novel digital programme in 149 nursing homes with 741 residents and over 200 staff as part of a rapid response COVID-19 initiative. The iWHELD intervention with live virtual coaching delivered through a Dementia Champion achieved better than 50% engagement, which compares favourably with previous studies of digital interventions in other therapeutic areas. The iWHELD intervention conferred significant benefit in quality of life as well as significant reductions in antipsychotic use without any worsening of neuropsychiatric symptoms and significant benefit with respect to delusions. This study provides an important potential approach to both improving wellbeing and quality of life and to safely reducing the rise in antipsychotic use in nursing home residents with dementia that has become a major challenge during the COVID-19 pandemic. The iWHELD digital format provides a potential solution for wide-scale rollout into real world settings.

OC42- MAKING DIGITAL MEASURES FIT-FOR-PURPOSE IN ALZHEIMER'S TRIALS. F. Cormack[1], J. Sorinas[2], C. Meunier[3] *(1. Cambridge Cognition - Cambridge (United Kingdom), 2. Novartis - Basel (Switzerland), 3. DiMe - San Francisco (United States))*

Background: Developing novel cognitive tasks or adapting existing cognitive tasks to novel technology requires an iterative and cumulative approach to validation in order to develop measures which are fit for purpose, particularly in the context of virtual clinical trials, where scalable, robust and repeatable testing are needed. Three key aspects of this are considered here: 1) the technical feasibility across device, which encompasses the accuracy of automated scoring 2) participant acceptability 3) analytical validation, focused on psychometric properties. Here we illustrate these three aspects of task development. We conducted a series of large (a total of 2,868 participants) home-based feasibility studies deploying a device-agnostic web-based technology for administering and scoring verbal neuropsychological tests (Verbal Paired Associates and Digit Span Forwards and Back and Serial Subtraction). We describe the methods developed to support automated stimulus generation to enable repeated longitudinal assessment and robust automated scoring in home settings. Technical feasibility and robustness of these methods were assessed through manual review of responses. Participant acceptability was assessed through post-test questionnaires, and the suitability of the tasks for repeat remote administration, was assessed through repeated administration of parallel forms. Qualitatively, participants reported that the automated instructions were clear and easy to understand, and that the tasks were challenging but enjoyable. We observed expected effects of task difficulty and demographic variables on task performance. We also present data on the psychometric properties of assessments, supporting the psychometric properties of the tasks and the suitability of the tests for repeat, remote administration. Together, these results illustrate developing cognitive assessment technology for use in decentralised clinical trials. Specifically, the constraints of scalable, repeatable, and robust testing were met through a combination of specifically designed algorithms to generation stimuli, and score responses, together with iterative refinements to the user interactions to ensure ease of use for participants in the absence of trained raters.

LATE BREAKING
Clinical Trial Alzheimer's Disease

LB1- TAU PET ASSOCIATED WITH PLASMA P-TAU217 AND COGNITIVE TESTING IN PRECLINICAL AD: SCREENING DATA FROM THE AHEAD STUDY A3 AND A45 TRIALS. K. Johnson[1], A. Schultz[1], R. Rissman[2], O. Langford[2], E. Thibault[1], M. Meyer[3], K. Kirmess[3], M. Irizarry[4], J. Zhou[4], M. Donohue[2], R. Raman[2], P. Aisen[2], R. Sperling[1,5], A.3.4.S. Team[6] *(1. Massachusetts General Hospital - Boston (United States), 2. University of Southern California - San Diego (United States), 3. C2N Diagnostics - St. Louis (United States), 4. Eisai - Nutley (United States), 5. Brigham and Women's Hospital - Boston (United States), 6. ACTC - Many Sites (United States))*

Background: The emergence of more accurate plasma AD biomarkers will substantially improve screening efficiency for prevention trials. Our work in the AHEAD 3-45 Study screening cognitively unimpaired participants has recently demonstrated that plasma Aβ42/40 and p-tau217 are highly predictive of positive amyloid PET status (18F-NAV4694 PET > 20CL eligibility). In addition, plasma p-tau measures could also enable prediction of tau deposition on Tau PET, subsequent cognitive decline, response to specific therapeutic mechanisms, or as a trial inclusion criterion. **Objective:** In this study, we investigated the ability of plasma p-tau measures to predict level of tau deposition estimated with 18F-MK6240 Tau PET in cognitively unimpaired individuals who were eligible (>20CL on amyloid PET) for the AHEAD Study A3 and A45 trials. **Methods:** The AHEAD Study has a shared screening platform for both the A3 (20-40 CL) and the A45 (>40CL) trials. Only individuals who showed >20CL on NAV PET and were otherwise eligible for the AHEAD trials moved forward in screening and underwent tau PET imaging with MK6240. Samples with both plasma and PET data available in the U.S. as of March 2022 (prior to the introduction of plasma measures to determine eligibility to continue in AHEAD screening) were sent to C2N Diagnostics for batch analysis of Aß42/40, and both the phosphorylated (p-tau) and non-phosphorylated (np-tau) forms of tau181 and tau217 using C2N's mass spectrometry platform. A concentration ratio of p-tau to np-tau was calculated to normalize for differing np-tau concentrations at each epitope (p-tau181r and p-tau217r). We tested two Tau PET aggregate regions representing tau deposition at the early and mid-stages of AD tauopathy: the medial temporal allocortex (MTL: amygdala, entorhinal, parahippocampal) and inferolateral temporal/parietal neocortex (NEO: inferior temporal, fusiform, middle temporal, inferior parietal). Tau PET was quantified with the standardized uptake value ratio (SUVr; 4mm eroded cerebral white matter reference). InVicro generated NAV4694 centiloid values for global amyloid PET quantification. Pearson correlations and multivariate linear models were calculated to predict baseline Tau PET composites and the subsample z-scored Preclinical Alzheimer's Cognitive Composite score (PACC-5). None of the p values are adjusted for multiple comparisons in these exploratory analyses. **Results:** There were 303 AHEAD 3-45 amyloid eligible (>20CL) participants with plasma and screening Tau PET data available: age 69.5±5.5 years, 66% female, 75% APOE ε4 carriers, and education 16.4+2.7 years. Across the full Tau PET sample, p-tau217r showed consistently stronger associations with both Tau PET composite regions than p-tau181r. The p-tau217r correlated with Tau PET SUVr in both MTL (r=0.35; p<0.0001) and NEO (r=0.43;p<0.0001) composites. The NAV amyloid PET also correlated with MTL (r=0.33; p>0.0001) and NEO (r=0.27;p<0.0001). Interestingly, in a multivariate model with age and APOE ε4 included, p-tau217r and amyloid NAV CL were significant independent predictors of both Tau PET composites, with stronger associations observed for ptau217r over NAV CL: MTL (ptau217r estimated β=0.088, t=4.49, p<0.0001; NAV CL β=0.003, t=2.89, p=0.004); and NEO (p-tau217r β=0.104; t=6.49, p<0.0001; NAV β=0.002, t=2.13, p=0.034). Among the full Tau PET sample, 93 individuals were eligible for the A3 trial (20-40 NAV CL) and 210 were eligible for A45 (>40 NAV CL). Among the A3 subset, p-tau217r was correlated with both MTL (r=0.27, p=0.0088) and NEO (r=0.30, p=0.0035). NAV CL was marginally correlated with MTL (r=0.20, p=0.054) but not with NEO (r=0.13, p=NS). Among the A45 subset, p-tau217r was correlated with MTL (r=0.28, p<0.001) and NEO (r=0.42, p<0.0001) Tau PET composites. NAV CL was also correlated with Tau PET MTL (r=0.20, p=0.003) and NEO (r=0.23, p=0.001) composites in the A45 subset. Finally, we evaluated the association of amyloid NAV, Tau PET composites, and p-tau plasma measures with screening PACC-5 score, with age, sex, and education covaried. Across the full Tau PET sample and within the A45 subsample alone, only the NEO Tau PET composite was associated with screening PACC-5 (β= -0.18; p=0.0006). No association with cognition at screening was observed with NAV CL, MTL Tau PET, p-tau181r, or p-tau217r. **Conclusions:** In this sample of cognitively unimpaired participants who were all amyloid eligible for the AHEAD 3-45 Study, p-tau217r predicts tau deposition as measured by Tau PET imaging, above and beyond amyloid levels. Neocortical Tau PET burden was associated with screening cognitive testing, even within the restricted range of normal cognition required for eligibility in the AHEAD Study. These results suggest that plasma p-tau217r measures may be useful in identifying those preclinical AD individuals with evidence of Tau pathology, whereas Tau PET may be valuable for tracking cognitive outcomes. In particular, these markers should enable efficient screening and sensitive outcomes for upcoming trials targeting tau mechanisms at very early stages of AD.

LB2- PLASMA LEVELS OF ABETA42/40 AND P-TAU217 RATIOS INCREASE ACCURACY OF AMYLOID PET PREDICTION IN PRECLINICAL AD. R.A. Rissman[1,2], O. Langford[2], M. Donohue[2], R. Raman[2], S. Abdel-Latif[2], M. Meyer[3], K. Kirmess[3], J. Braunstein[3], M. Irizarry[4], K. Johnson[5], P. Aisen[2], R. Sperling[6], T. Ahead 3-45 Study[7] *(1. UC San Diego - La Jolla, Ca (United States), 2. University of Southern California - San Diego, Ca (United States), 3. C2N Diagnostics - St. Louis, Mo (United States), 4. Eisai - Indianapolis, In (United States), 5. Massachusets General Hospital, Harvard University - Boston, Ma (United States), 6. Brigham and Woman's Hospital, Harvard - Boston, Ma (United States), 7. ACTC - San Diego, Ca (United States)*

Background: Our prior data from the A4 and AHEAD Study, and that from other groups demonstrates that plasma Aβ42/40 quantification by mass spectrometry can serve as a reliable biomarker for predicting elevated brain amyloid detected by PET. We studied the value of adding plasma p-tau measures to our plasma Aβ42/40 algorithm to further streamline identification of eligible participants and reduce burden and trial cost. **Objective:** To determine if the addition of plasma p-tau181 and/or p-tau217 concentrations can improve plasma Aβ42/40 algorithms to correctly identify participants with amyloid burden of >20 centiloids with the NAV4694 tracer among individuals screening for participation in the AHEAD preclinical AD trial. **Methods:** Plasma amyloid and

tau measures were quantified by C2N Diagnostics using mass spectrometry-based analytical platforms. Participant plasma samples (N=1085) collected prior to the introduction of plasma Aβ42/40 testing during screening were used. Plasma samples for these analyses consisted of those with sufficient amyloid PET levels (n = 364; 33%) to be eligible for AHEAD and those who screen failed (n = 747; 67%). C2N quantified Aβ (Aβ42/40) and various tau species, including both the phosphorylated (p-tau) and non-phosphorylated (np-tau) forms of tau181 and tau217. A ratio of p-tau to np-tau was also calculated for each epitope (p-tau181r and p-tau217r) to normalize for inter-individual differences in np-tau concentrations. We conducted Receiver Operating Characteristic (ROC) curve analyses for each of these biomarkers against amyloid status defined by amyloid PET status (>20 centiloids). We also fit a Mixture of Experts model to assess the value of including p-tau181r and p-tau217r in the existing predictive algorithm (Aβ42/40, Age and APOE) for amyloid PET status using NAV4694. **Results:** This sample of N =1085 contained 67% Female, 13.5% Hispanic, 3.7% Black or African American with a mean age of 67.6 (SD = 6.1) years. 45% of the participants had at least one APOE4 allele. The Area Under the Curve (AUC) for plasma Aβ42/40 was 0.87 (95% CI; 0.84, 0.89), consistent with prior reports. For plasma tau markers, we observed AUCs of 0.74 (95% CI; 0.71, 0.77) with p-tau181, to 0.91 (95% CI; 0.90, 0.93) with p-tau217r. The model including covariates p-tau217r, Aβ42/40, Age and APOE improved AUC to 0.95 (95% CI; 0.93, 0.96). **Conclusions:** These findings demonstrate that the addition of plasma p-tau/np-tau concentration ratios for tau181 and tau217 species greatly improved the utility of plasma testing for amyloid PET positivity, with p-tau217r conferring the greatest improvement. Our data suggests that consideration of plasma p-tau217r in addition to Aβ42/40 ratio can dramatically improve anti-amyloid clinical trial screening burden and timelines for participant recruitment. In addition to determining how our results can be applied to other amyloid tracers and varying levels of neuropathology as informed by Aβ and tau PET, our current priorities involve expanding these findings to underrepresented populations to determine whether the specific levels and cutoffs of plasma Aβ and p-tau species and their relation to PET amyloid positivity are similar across different racial, ethnic and other underrepresented groups.

LB3- TRAILBLAZER-ALZ 4: TOPLINE STUDY RESULTS DIRECTLY COMPARING DONANEMAB TO ADUCANUMAB ON AMYLOID LOWERING IN EARLY, SYMPTOMATIC ALZHEIMER'S DISEASE.

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Background: The amyloid cascade in Alzheimer's disease (AD) involves the production and deposition of amyloid beta (Aβ) as an early and necessary event in the pathogenesis of AD (1). Both donanemab and aducanumab have demonstrated the ability to reduce brain amyloid plaque burden and potentially slow clinical decline (2, 3). Recently, the FDA provided accelerated approval for aducanumab for the treatment of early symptomatic AD based on its ability to reduce Aβ plaques (4) as a surrogate biomarker reasonably likely to predict a clinical benefit to AD patients. **Objectives:** The primary outcome of TRAILBLAZER-ALZ 4 (NCT05108922) evaluated the potential superiority of donanemab treatment compared to aducanumab on the percentage of participants with amyloid plaque clearance (≤24.1 Centiloids (CL)) at 6 months in the overall study population and subpopulation of participants with intermediate tau deposition. **Methods:** TRAILBLAZER-ALZ-4 is a multicenter, phase 3, open-label, active comparator study of participants with early symptomatic AD (n=148), randomized 1:1 to receive donanemab (700 mg IV Q4W for first 3 doses, then 1400 mg IV Q4W for subsequent doses) or aducanumab (per USPI4: 1 mg/kg IV Q4W for first 2 doses, 3 mg/kg IV Q4W for next 2 doses, 6 mg/kg IV Q4W for next 2 doses and 10 mg/kg IV Q4W for subsequent doses). The overall study duration is 18 months with the primary endpoints assessed at 6 months. Eligible participants are considered to have early symptomatic AD with a mini-mental state examination score of 20-30 (inclusive) and Clinical Dementia Rating-global score of 0.5 or 1.0. Other eligibility criteria included elevated Aβ as detected by florbetapir F18 PET scan, age 50-85 years; and consent to apolipoprotein E (APOE ε4) genotyping. Magnetic resonance imaging (MRI)-based exclusions included >4 microhemorrhages, superficial siderosis, and severe white matter changes; use of anti-coagulation agents was not permitted. Participant randomization was stratified by amyloid burden at baseline and APOE ε4 status. A flortaucipir F18 PET scan was also performed to identify a subpopulation with an intermediate tau level. Intermediate tau deposition was defined as an initial flortaucipir scan with moderate AD patterns based on visual assessment and neocortical standardized uptake value ratio (SUVR) between 1.10 and 1.46, inclusive, or advanced AD patterns and neocortical SUVR ≤ 1.46. Key secondary objectives include assessment of the superiority of donanemab treatment compared to aducanumab brain amyloid plaque levels percent and mean change at 6 months. Beyond standard safety assessments, MRI assessments monitored amyloid-related imaging abnormalities (ARIA) occurrence. **Results:** The analysis set was defined as those with at least one dose of donanemab (N=71) or aducanumab (N=69). There were N=27 participants defined as having intermediate tau in the donanemab group compared to N=28 in the aducanumab group. Baseline demographics and characteristics were well-balanced across treatment groups. Upon assessment of florbetapir F18 PET scans at 6 months, 37.9% of donanemab-treated participants achieved amyloid clearance compared to 1.6% of aducanumab-treated participants (p<0.001). In the intermediate tau subpopulation, 38.5% of donanemab-treated participants achieved amyloid clearance compared to 3.8% of aducanumab-treated participants (p=0.008). Percent change and mean change in brain amyloid levels for participants on donanemab were -65.2% +/- 3.9% (baseline: 98.29 +/- 27.83 CL, change: -62.10 +/- 3.69 CL), and -17.0% +/- 4.0% (baseline: 102.40 +/- 35.49 CL, change: -16.41 +/- 3.77 CL) for participants on aducanumab (p<0.001). In the intermediate tau subpopulation, percent and mean change in brain amyloid levels for participants on donanemab were -63.9% +/- 7.4% (baseline: 104.97 +/- 25.68 CL, change: -64.08 +/- 7.34 CL) and -25.4% +/- 7.8% (baseline: 102.23 +/- 28.13 CL, change: -23.82 +/- 7.70 CL) for participants on aducanumab (p≤0.001). 62.0% of participants treated with donanemab reported an adverse event (AE) and there were no serious AEs due to ARIA. In the aducanumab group, 66.7% of participants reported an AE, and there were 1.4% serious AEs (one event) due to ARIA. The incidence of ARIA-E in the donanemab group was 21.1%, with 2.8% symptomatic ARIA-E (13.3% of those with ARIA-E). In the aducanumab group, ARIA-E incidence

was 23.2%, with 4.3% symptomatic ARIA-E of all participants in the aducanumab group (18.8% of those with ARIA-E). The incidence of ARIA-H in the donanemab group was 19.7% and in the aducanumab group was 17.4%. Infusion-related reactions (IRRs) were reported by 7.0% of the donanemab group; in the aducanumab group, 2.9% of participants reported IRRs. **Conclusions:** The TRAILBLAZER-ALZ 4 study provides the first active comparator data on amyloid plaque clearance in patients with early symptomatic AD. There were significantly more participants reaching amyloid clearance and significantly greater amyloid plaque reductions with donanemab compared to aducanumab at 6 months. Both agents showed similar safety profiles to their previous studies. **References:** 1. Selkoe DJ. JAMA. 2000;283(12):1615-1617. 2. Mintun MA, et al. NEJM. 2021;384(18):1691-1704. 3. Budd Haeberlein S, et al. JPAD. 2022;9(2):197-210. 4. Aducanumab-avwa prescribing information. ADUHELM (fda.gov).

LB4- CSF MTBR-TAU243 IS A NON-AMYLOID SPECIFIC BIOMARKER OF NEUROFIBRILLARY TANGLES OF ALZHEIMER'S DISEASE. K. Horie[1,2], G. Salvadó[3], N. Barthélemy[1], Y. Li[1], B. Saef[1], C. Chen[1], H. Jiang[1], B. Gordon[1], T. Benzinger[1], D. Holtzman[1], S. Schindler[1], O. Hansson[3,4], R. Bateman[1] *(1. Washington University School of Medicine - St. Louis (United States), 2. Eisai Inc. - Nutley (United States), 3. Lund University - Lund (Sweden), 4. Skåne University Hospital - Malmö (Sweden))*

Background: Neurofibrillary tangles (NFTs) are a key pathological hallmark of Alzheimer's disease (AD) and are comprised of hyper-phosphorylated tau (p-tau) and microtubule binding region of tau (MTBR-tau) species. While the levels of soluble p-tau species such as p-tau181, 217, and 231 in cerebrospinal fluid (CSF) and blood are widely used as indicators of AD tau tangles, recent studies indicate that these soluble p-tau species are more strongly associated with amyloid plaques than tau tangles. We previously discovered that CSF MTBR-tau species containing the residue of 243 (MTBR-tau243) located in the upstream region of the MTBR was the fluid biomarker most highly correlated with tau tangles as measured by positron emission tomography (PET) in a small cohort (Horie et al., Brain, 2021). **Objectives:** We aimed to establish a non-amyloid dependent CSF biomarker to specifically quantify NFTs in AD. We measured the novel biomarker, MTBR-tau243, in CSF samples from two cohorts: 1. The Swedish BioFINDER-2 study and 2. The Knight Alzheimer Disease Research Center (Knight ADRC). Furthermore, we compared CSF MTBR-tau243 and p-tau as predictors of amyloid pathology, tau pathology and cognitive function. **Methods:** BioFINDER-2 (n=448) and Knight ADRC (n=219) participants underwent a lumbar puncture within two years of an amyloid PET (Flutemetamol or Florbetapir/Pittsburgh Compound-B, respectively) and/or tau PET (RO6958948 or Flortaucipir, respectively) scan. CSF was subjected to sequential immunoprecipitation with anti-N-terminal to mid-domain antibodies for p-tau analyses (p-tau181, 205, 217, and 231) and a specific antibody targeting the upstream region of MTBR for MTBR-tau243 analyses, then evaluated via mass spectrometry. Spearman correlations were used to evaluate the relationships of CSF biomarkers with amyloid PET, tau PET measures, and the Mini-Mental State Examination (MMSE). To identify the combination of CSF biomarkers that best predicted amyloid and tau PET measures, linear regression with the Least Absolute Shrinkage and Selection Operator (LASSO) variable selection method was used. The longitudinal rates of changes for the CSF tau species were compared among groups that were amyloid and tau positive vs. negative groups at baseline. **Results:** The majority of participants were amyloid positive (A+, 59% for BioFINDER-2 and 62% for the Knight ADRC); 70% of BioFINDER-2 and 35% of Knight ADRC were cognitively impaired. Longitudinal CSF collected 2 years after the baseline CSF was available for 223 participants from BioFINDER-2. In both the BioFINDER-2 and Knight ADRC cohorts, CSF MTBR-tau243 concentration was the biomarker most strongly correlated with NFTs as measured by tau PET even in the amyloid-positive group (Spearman Rho=0.83 and 0.70, respectively) and was the least correlated with amyloid plaques as measured by amyloid PET in the same group (Rho=0.49 and 0.48, respectively). CSF p-tau205 occupancy was also highly correlated with NFTs even in the amyloid-positive group (Rho=0.78 and 0.70, respectively) but had a stronger association with brain amyloidosis in the same group (Rho=0.67 and 0.60, respectively) than MTBR-tau243. Linear regression with LASSO selection suggested that the combination of MTBR-tau243 level and p-tau205 occupancy was the best predictor of tau PET (adjusted R2=0.75 and 0.65, respectively), while the combination of p-tau217, 205 occupancies and Aβ42/40 was the best predictor of amyloid PET (adjusted R2=0.77 and 0.69, respectively). Notably, CSF MTBR-tau243 was the most highly correlated with the MMSE (Rho=-0.62 and -0.53, respectively) across all CSF tau measures. Linear regression with LASSO selection suggested that the combination of MTBR-tau243 level and p-tau205 occupancy was the best predictor of MMSE (adjusted R2=0.41 and 0.35, respectively), which was only slightly inferior to tau PET (adjusted R2=0.43 and 0.44, respectively). In longitudinal analyses of the BioFINDER-2 cohort, MTBR-tau243 exhibited the most significant increase in rate of change according to disease progression between amyloid-positive tau-positive (A+T+) and the other two groups (A-T-: Cohen's d=1.48, p<0.001; A+T-: Cohen's d=1.13, p<0.001), while p-tau205 and the other p-tau species (i.e., 181, 217, and 231) exhibited no significant change and even decreases in the rates of changes between A+T- and A+T+ groups. **Conclusion:** These findings suggest that CSF MTBR-tau243 reflects changes in tau pathology that occur at a later stage in AD progression than brain amyloidosis and could be used to stage AD tauopathy and track the effects of tau-targeting therapies independent of amyloid effects. The combination of CSF MTBR-tau243 and p-tau205 occupancy explained most of the total variance in tau PET and predicted MMSE almost as accurately as tau PET, which suggests high clinical utility of a biomarker panel containing MTBR-tau243. The mechanisms underlying these findings add to the growing understanding of AD pathophysiology and strategies for novel tau-targeting AD therapies.

LB5- TOP-LINE RESULTS FROM THE 2-YEAR SYSTEMATIC MULTI-DOMAIN ALZHEIMER'S RISK REDUCTION TRIAL (SMARRT). K. Yaffe[1], E. Vittinghoff[1], S. Dublin[2], C. Peltz[1], L. Fleckenstein[2], D. Rosenberg[2], D. Barnes[1], B. Balderson[2], E. Larson[3] *(1. University of California, San Francisco - San Francisco, Ca (United States), 2. Kaiser Permanente Washington Health Research Institute - Seattle, Wa (United States), 3. University of Washington - Seattle, Wa (United States))*

Background: Modifiable risk factors account for 30-40% of dementia; yet, few trials, especially multi-domain, have demonstrated that risk reduction interventions can improve these risk factors and in turn, cognitive outcomes. We conducted the NIH-funded Systematic Multi-domain Alzheimer's Risk Reduction Trial (SMARRT), a 2-year

randomized pilot trial to test a personalized, pragmatic, multi-domain dementia risk reduction intervention in an integrated healthcare delivery system. (NCT03683394). **Objective:** To determine whether a 2-year personalized multi-domain risk reduction intervention benefits cognition and behavioral risk factors compared to a health education group. **Methods:** We recruited 172 older adults at higher risk for dementia (age 70-89, subjective cognitive complaints, low-normal performance on a brief telephone cognitive screen, and ≥ two targeted modifiable risk factors) from primary care clinics of Kaiser Permanente Washington (KPWA). Modifiable risk factors that counted towards eligibility and were targeted by the intervention included poorly controlled diabetes or hypertension, use of risky prescription medications, physical inactivity, social isolation, poor sleep, smoking, and depression. Participants were randomly assigned to the SMARRT intervention or to a Health Education (HE) control. The intervention consisted of personalized risk reduction goals with health/nurse coaching for those target goals. Personalized intervention was based on the prevalence of risk factors as well as personal preference for risk reduction priority and strategy. The primary outcome was change in a composite cognition score (initially assessed in person and then due to the COVID-19 pandemic, by phone); pre-planned secondary outcomes were change in risk factors and quality of life measures. Participants were evaluated at baseline, 6, 12, 18, and 24 month assessments. Analyses of all outcomes were by intention-to-treat and used linear mixed models to compare changes from baseline, averaged across the four follow-up visits. **Results:** The mean age of participants was 75.7 years (sd 4.8), 63% were women and 19% were non-White; the mean number of risk factors at enrollment was 2.5 (0.6). Intervention participants had a mean of 20 (sd 3.8) contacts with the health coach or study nurse during the 2-year intervention. The trial recently was completed, and we will present top-line results on the primary and secondary outcomes. We will also present data on safety and adherence. **Conclusion:** The recently completed SMARRT study is the first NIH-funded personalized multi-domain trial testing a risk reduction intervention with cognitive and behavioral outcomes among high-risk older adults. Results from this trial will be critical for guiding risk reduction strategies for cognitive aging.

LB6- TWO-YEAR PROGNOSTIC UTILITY OF PLASMA P217+TAU IN THE ALZHEIMER CONTINUUM.

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Background: Plasma p217+tau is a novel biomarker that detects tau phosphorylation at threonine 217 and is augmented by phosphorylation at threonine 212. P217+tau has shown high predictive accuracy for CSF and PET amyloid-β (Aβ) and tau status. However, the association of p217+tau with longitudinal cognition and its comparative performance to neuroimaging biomarkers of Aβ and tau in predicting prospective cognitive decline has not yet been investigated. **Objectives:** We examined whether p217+tau can 1) predict prospective cognitive decline on multiple well-established measures of cognition; 2) be a better predictor of cognitive decline than neuroimaging biomarkers of Aβ (18F-NAV4694) and tau (18F-MK6240); 3) provide a (pre)screening strategy to decrease sample size, and therefore cost, of therapeutic trials aiming to slow cognitive decline. All objectives were investigated in a cognitively unimpaired and a cognitively impaired cohort to assess performance of p217+tau in early and later stages of the Alzheimer's Disease (AD) continuum. **Methods:** 134 cognitively unimpaired (CU) participants and 41 age-matched patients with cognitive impairment (CI: i.e., mild cognitive impairment or mild dementia) were included. Participants underwent blood sampling, 18F-MK6240 tau PET, and 18F-NAV4694 Aβ-PET at baseline. PET were quantified in Centiloid (CL) for Aβ scans and SUVR in the mesial temporal (Me), temporo-parietal (Te), and meta-temporal (MetaT) regions for tau scan using CapAIBL. Clinical and neuropsychological assessments (MMSE, CDR-SB, AIBL-PACC) were performed at baseline and follow-up (2 ± 0.6 years). Multivariable linear models were used to evaluate the association of baseline biomarkers with change in cognition (individual cognitive slopes calculated via robust linear models), after adjusting for baseline age, sex, APOE ε4, and years of education. Standardised beta coefficients (β) and their corresponding p values are reported. Binary p217+tau (pT-/pT+), Aβ (A-/A+), and tau (T-/T+) groups were created using 80% sensitivity thresholds to identify cognitive decliners. Power analysis was performed in CI to estimate sample size required to detect a 30% slope reduction on CDR-SB, with 90% power. Sample size and associated screening cost for the pT+ group was compared to those for A+ and T+ PET groups. **Results:** In the CI group, plasma p217+tau was a significant predictor of change in MMSE ($\beta = -0.51$, $p = 0.002$) and CDR-SB ($\beta = 0.57$, $p < 0.001$), with the effect size larger than Aβ-PET CL (MMSE $\beta = -0.43$, $p = 0.021$; CDR-SB $\beta = 0.37$, $p = 0.045$) but lower than MetaT tau SUVR (MMSE: $\beta = -0.59$, $p < 0.001$; CDR-SB: $\beta = 0.64$, $p < 0.001$). In the CU group, plasma p217+tau did not correlate with decline in AIBL-PACC score over two years ($\beta = -0.08$, $p = 0.36$;), similar to Aβ-PET CL ($\beta = -0.05$, $p = 0.58$) while MetaT tau SUVR was associated with cognitive decline ($\beta = -0.19$, $p = 0.031$). In CI, the biomarker thresholds based on 80% sensitivity to detect positive CDR-SB slope were 131.1 fg/ml for pT+, 1.12 SUVR for T+Me, 1.2 SUVR for T+Te, 1.18 SUVR for T+MetaT and 62 CL for A+ group. Screening pT+ CI participants into a therapeutic trial — aiming at slowing cognitive decline— led to 29% reduction in sample size compared to screening with PET for A+ and 4-16% reduction compared to screening with PET for T+ (for different ROIs). Using plasma p217+tau for trial selection rather than a PET scan would translate to a >75% test cost saving assuming a blood test cost one fifth of a PET scan, owing to both the lower cost of the test and the smaller cohort size required for the trial. In a therapeutic trial recruiting PET T+MetaT, p217+tau pre-screening followed by PET would save 4% of the PET cost in the CI group, compared to 38% in the CU group. **Conclusion:** This data suggests that substantial cost reduction can be achieved using plasma p217+tau alone to select participants with MCI or mild dementia for a clinical trial designed to slow cognitive decline by 30% over two years,

compared to participant selection by PET. Cognitive decline in CI participants that were pT+ was slightly steeper than that in PET T+ or A+; therefore, savings would result from the lower cost of the test and the smaller cohort size required for the trial. Cost-effectiveness of using p217+tau for pre-screening in MCI and mild dementia can only be achieved if the plasma p217+tau test costs far less than one fifth of the PET scan but increases the number needed to screen and this may negate any saving from lower test cost. In contrast, in the cognitively unimpaired population, p217+tau was not able to predict cognitive decline over two years, but it provided significant cost-saving if used as a pre-screening measure for PET A+ or T+. In CU, only tau PET predicted two-year cognitive decline. These findings require replication in larger cohorts.

LB7- ALZ-NET: USING REAL WORLD EVIDENCE TO DEFINE THE FUTURE OF ALZHEIMER'S TREATMENT AND CARE. M. Carrillo[1], G. Rabinovici[2], M. Rafii[3] *(1. Alzheimer's Association - Chicago (United States), 2. Memory and Aging Center, Departments of Neurology, Radiology & Biomedical Imaging, University of California, San Francisco - San Francisco (United States), 3. Alzheimer's Therapeutic Research Institute, Keck School of Medicine of the University of Southern California - San Diego (United States))*

Background: There are over 100 therapies being tested in clinical trials for Alzheimer's disease (AD) today. With potential therapies undergoing regulatory review and a growing drug development pipeline, the field is in a new phase of treatment. Once approved and used in the community, it will be important to track longitudinal clinical and safety outcomes of novel therapies in large numbers of diverse patients being cared for in real-world clinical practice. **Methods:** The Alzheimer's Association, American College of Radiology, American Society of Neuroradiology, the Department of Biostatistics, Brown University School of Public Health and the Critical Path Institute, along with international clinical, research and imaging experts, have launched the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET). ALZ-NET builds on successes of networks developed in other neurologic and systemic diseases, and leverages the groundwork from the IDEAS and New IDEAS studies. These have demonstrated large-scale, real-world data collection in dementia practice is feasible for addressing critical research questions regarding dementia care. Networks of dementia clinics and imaging facilities will provide ALZ-NET's foundation and will expand over time to include a variety of clinical practices. Patients about to start or already receiving treatment with a novel FDA-approved AD therapy will be eligible to enroll in ALZNET. ALZ-NET is structured to collect a data set that aligns with patient care, agnostic of therapy and care setting, including, baseline demographic, medical, neurologic, genetic and biomarker data. Every 6-12 months, patients will be followed longitudinally with MMSE or MoCA (required), AD8 (optional), FAQ (required) and NPI-Q (optional). Trajectories for cognition, function and behavior over time will be evaluated, assessing the patient-specific predictors of response, including clinical response to individual drugs or combination of drugs. ALZ-NET will track all adverse events (CTCAE grade≥3), unexpected and serious adverse events. A central repository will collect baseline and longitudinal neuroimaging (MRI, PET). Existing databases will track health outcomes and resource utilization. Patients will be followed until withdrawal of consent, death or lost to follow-up. All data collection and sharing will be fully compliant with research participant protections, privacy and patient/provider autonomy. **Results:** ALZ-NET will collect longitudinal clinical and safety data for enrolled patients treated with novel FDA-approved AD therapies and will track long-term health outcomes (effectiveness and safety), associated with use in real-world settings. ALZ-NET aims to assess the clinical course of people from a variety of backgrounds and communities, to achieve representativeness beyond the populations historically enrolled in clinical trials. ALZ-NET has partnered with clinical sites providing care in diverse practice settings to serve as the network's initial vanguard sites. These clinical sites are the first to enroll patients into the network and provide clinical and imaging data on the use of currently approved FDA therapy for AD. ALZ-NET continues to invite sites who already, or will, offer these therapies to their patients. Participating sites have multi-disciplinary clinical expertise and an infrastructure to support the use of novel FDA-approved AD therapies consistent with the safety monitoring outlined in applicable FDA approved labels. Aspects of a qualified participating site include: access to accredited and appropriate radiological services for diagnostic and safety brain imaging; access to infusion services; access to emergency services; and access to standard cognitive, behavioral, and functional assessments used in dementia care. Efforts have been made to minimize patient and site burden while still ensuring collection of a rigorous core dataset that can be used to answer critical research questions. ALZ-NET is designed to work collaboratively and in conjunction with affiliated studies conducted by academia, industry, federal or ALZ-NET project teams. Affiliated studies could be designed to answer broad or specific questions regarding treatment. Data are being collected in a regulatory grade manner to maximize the potential for how data can be used and applied for all stakeholders. **Conclusions:** ALZ-NET is actively engaging and expanding the network of sites, allowing for the collection of real-world data from enrolled patients receiving novel FDA-approved AD therapies. It is designed to answer questions for therapies available now and those on the horizon including: tracking longitudinal change of treatment (or treatments); identifying responders and non-responders or predictors of response and non-response to specific therapeutics; and comparing aggregated data on outcomes across mechanisms of action and within classes of therapeutics. Over time, ALZ-NET will be used to study clinical outcomes and resource utilization using claims and EHR. ALZ-NET will be a resource for evidence gathering, information sharing, and education across clinical and research communities, encouraging innovative, inclusive research and supporting opportunities to improve care. **Note:** This abstract is submitted on behalf of the ALZ-NET Project Team: Ali Atri, Banner Sun Health Research Institute; Jerome Barakos, Sutter Health California; Sharon Brangman, SUNY Upstate Medical University; Kirk Daffner, Harvard Medical School; Rebecca M. Edelmayer, Alzheimer's Association; Constantine Gatsonis, Brown University School of Public Health; Gregory Jicha, University of Kentucky; John Jordan, American College of Radiology / American Society of Neuroradiology / Providence Little Company of Mary Medical Center-Torrance; Jennifer Lingler, University of Pittsburgh School of Nursing; Oscar Lopez, University of Pittsburgh School of Medicine; Andrew W. March, American College of Radiology; Anton P. Porsteinsson, University of Rochester School of Medicine; Katherine Possin, Memory and Aging Center, University of California, San Francisco; Klaus Romero, Critical Path Institute; Stephen Salloway, Butler Hospital / Warren Alpert Medical School of Brown University; Mary Sano, Mount Sinai School of Medicine; Sudhir Sivakumaran, Critical Path Institute;

Heather Snyder, Alzheimer's Association; Rade B. Vukmir, Alzheimer's Association; Christopher Whitlow, Wake Forest School of Medicine / American College of Radiology; Consuelo Wilkins, Vanderbilt University Medical Center; Charles Windon, Memory and Aging Center, University of California, San Francisco. **Disclosures:** Maria C. Carrillo is a full-time employee of the Alzheimer's Association. She has a daughter that is a full-time graduate student in the USC Neuroscience program. Gil Rabinovici receives research support from Avid Radiopharmaceuticals, GE Healthcare, Genentech, and Life Molecular Imaging; served on SAB for Eli Lilly, Genentech, and Roche; serves on DSMB for Johnson & Johnson; is an Associate Editor for JAMA Neurology. Michael Rafii receives research support from Eli Lilly and Eisai Inc.; chairs DSMBs for Alzheon and Biohaven; serves on the SAB for Embic; provides consultation to AC Immune SA and Keystone Bio.

LB8- TOP LINE DATA OF ANAVEX®2-73 (BLARCAMESINE) RANDOMIZED, DOUBLE-BLIND, MULTICENTER, PLACEBO-CONTROLLED PHASE 2B/3 IN PATIENTS WITH EARLY ALZHEIMER'S DISEASE (AD). S. Macfarlane[1], T. Grimmer[2], T. O'brien[3], E. Hammond[4], W. Kaufmann[4], E. Fadiran[4], C. Missling[4] *(1. Hammoncare - Melbourne (Australia), 2. THU Munich - Munich (Germany), 3. Monash University, Alfred Health - Melbourne (Australia), 4. Anavex Life Sciences - New York (United States))*

Background: ANAVEX®2-73 (blarcamesine) is a novel, oral, investigational sigma-1 receptor (SIGMAR1) agonist with multimodal activity with previously demonstrated dose-dependent target engagement by positron emission tomography (PET) imaging as well as reduction of pathological inflammation, amyloid beta, and tau. A prior Phase 2a ANAVEX®2-73 study in patients with Alzheimer's disease (AD) (1) demonstrated reduction in rates of cognitive (MMSE) and functional (ADCS-ADL) decline in participants with higher ANAVEX®2-73 plasma concentration (doses up to 50 mg once daily). This effect was also observed in the cohort carrying the common SIGMAR1 wild type (WT) gene variant (80-84% of worldwide population), which would be an additional confirmation of the biological relevance of the SIGMAR1 activation (2). Furthermore, in a transcriptomics analysis (RNAseq) of a randomized, placebo-controlled dementia study in patients with Parkinson's Disease Dementia (PDD), levels of pathways and genes, which are down-regulated in AD pathology were significantly increased by the therapeutic effect of ANAVEX®2-73 ($p<0.005$) (3). **Objectives:** The ANAVEX®2-73-AD-004 study was an international, randomized, double-blind, multicenter, placebo-controlled Phase 2b/3 clinical study in participants with early AD, which included biomarkers of both drug response and AD pathology (4). Here we report efficacy over 48 weeks of ANAVEX®2-73 administration on reduction in cognitive (ADAS-Cog) and functional (ADCS-ADL) decline as well as the effect of the common SIGMAR1 wild type (WT) gene variant on efficacy outcome measures. **Methods:** 509 patients with early AD were randomized 1:1:1 to oral target doses of 30 mg, 50 mg ANAVEX®2-73 or placebo, once daily. The primary endpoint was reduction in cognitive and functional decline, assessed from baseline, over the 48-week period as evaluated by co-primary efficacy endpoints ADAS-Cog and ADCS-ADL in participants receiving ANAVEX®2-73 compared to placebo. Key secondary efficacy endpoint was reduction in cognitive decline as measured by the CDR-SB from baseline to end of treatment (48 weeks). Safety of ANAVEX®2-73 in this study was also evaluated. **Results:** The top line results of the study are expected to be available around the time of the CTAD 2022 conference. **Conclusions:** The conclusions of the study are expected to be available around the time of the CTAD 2022 conference. **References:** 1. Hampel et al. A precision medicine framework using artificial intelligence for the identification and confirmation of genomic biomarkers of response to an Alzheimer's disease therapy: Analysis of the blarcamesine (ANAVEX2-73) Phase 2a clinical study. Alzheimer's Dement. 2020;00:1–14; 2. Excluding the cohort carrying the SIGMAR1 rs1800866 gene variant (16%-20%): https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=rs1800866; 3. https://www.anavex.com/_files/ugd/79bcf7_c5813c517d9f4ca5aacbeb719508827a.pdf; 4. ClinicalTrials.gov Identifiers: NCT03790709, NCT02756858.

LB9- HIGHER SENSITIVITY AMYLOID-PET DETECTION OF THE EARLIEST FOCAL BETA-AMYLOID ACCUMULATION USING SPATIAL EXTENT. M.E. Farrell[1], E.G. Thibault[1], J.A. Becker[1], J.C. Price[1], K. Gong[1], A.P. Schultz[1], M.J. Properzi[1], R.F. Buckley[1,2], H.I.L. Jacobs[1], B.J. Hanseeuw[1,3], R.A. Sperling[1,2], K.A. Johnson[1,2] *(1. Massachusetts General Hospital - Boston, Ma (United States), 2. Brigham & Women's Hospital - Boston, Ma (United States), 3. Cliniques Universitaires Saint-Luc, Université Catholique de Louvain - Brussels (Belgium))*

Background: The key to the prevention of Alzheimer's disease may lie with intervening at the earliest possible point in the pathological cascade, before neurodegeneration at the earliest signs of beta-amyloid (Aβ). The current gold standard for measuring Aβ deposits in the brain relies on average measures of global neocortical burden using PET, which fails to detect earlier focal Aβ deposits and likely leaves a limited time window before neurodegeneration. Importantly, it may be possible to reliably measure Aβ below global AbPET thresholds by changing two key aspects of Aβ-PET measurement: where we look and how we measure. Prior studies indicate focusing on early-accumulating regions can aid detection of early focal Aβ, but heterogeneity across studies in where Aβ begins accumulating has impeded the development of a reliable and generalizable early Aβ PET aggregate. In the present study, we sought to allow greater flexibly by incorporating more early Aβ regions, aggregating across all regions that are reliably associated with future Aβ-PET accumulation using longitudinal PIB-PET from initially globally Aβ- adults from the Harvard Aging Brain Study (HABS). However, while an expanded early Aβ aggregate may allow greater flexibility, doing so may also dilute the early focal signals we aim to detect. To avoid this dilution, we shifted our summary Aβ from the standard measure of average burden to a measure of the spatial extent of Aβ deposits. We hypothesized that measuring the number of regions with elevated Aβ within a larger set of reliable early Aβ regions would allow for greater sensitivity to focal early Aβ deposits than requiring the average burden across the entire aggregate to surpass a detection threshold. **Objective:** To demonstrate the improved sensitivity and specificity of measuring spatial extent within a set of reliable early Aβ regions to predict which individuals will progress to global Aβ positivity in the future and assess its potential for improved targeting of individuals with early Aβ in clinical trials. **Methods:** Longitudinal Pittsburgh Compound B (PIB)-PET data from 160 clinically normal (CN) older adults from HABS with globally Aβ- PET scans at baseline were used to identify all regions for which baseline elevated PIB was not significantly associated with future local decline (a sign of vulnerability to signal noise) and was significantly associated with increasing future global PIB slope. The mean burden and spatial extent in different potential aggregates based on these results were tested

for their ability to predict progression to global Aβ+ in 3 years using receiver operate characteristic (ROC) curve analysis and beyond (up to 8 years) using survival analysis. The replicability and generalizability of these results were validated in an external sample of 208 initially globally Aβ- CN older adults from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Power analyses determined the number of the individuals that would need to be screened to enroll 200 participants to detect a 50% change in Ab burden over 1 year with 80% power based on 4 possible approaches to defining the lower bound for early Aβ deposits: 1) the current global Aβ threshold, 2) a lowered global Aβ threshold, 3) mean burden in the optimized early Aβ aggregate, and 4) spatial extent in the global Aβ burden. **Results:** A large aggregate of reliable and predictive regions (bilateral medial frontal/parietal, cingulate, lateral parietal/occipital and left lateral frontal/parietal) developed within HABS provided high sensitivity in predict progression to global positivity while maintaining high specificity in HABS (SE=.88, SP=.97) and ADNI (SE=1.00, SP=.91), though its slight advantage in specificity over other large aggregates is small compared with the 2.5x increased rate of early detection conferred by switching from a measure of mean burden to extent (SEextent=.88, SEmean=.35). Using Spatial extent in the early Aβ aggregate resulted in a 73% reduction in the number of individuals that would need to the screened relative to a standard global Aβ threshold (nstandard=4340, nextent=1193), a 44% reduction relative to a lowered global threshold (n = 2146) and 51% relative to using the mean burden in the early Aβ aggregate (n=2543). **Conclusion:** Our findings demonstrate that measures of spatial extent across a broad set of neocortical regions are far more sensitive to detect early Aβ than traditional measures of average burden in two independent samples. These extent measures display great potential for improved targeting of early Aβ in both clinical trials and research into the earliest stages of amyloidosis and AD pathogenesis.

LB10- SAMPLE SIZE ESTIMATES FOR PRECLINICAL AD INTERVENTION TRIALS BASED ON WISCONSIN REGISTRY FOR ALZHEIMER'S PREVENTION LONGITUDINAL PET AMYLOID, PLASMA P-TAU217, AND COGNITIVE ASSESSMENT DATA. R. Langhough Koscik[1], D. Norton[1], T. Betthauser[1], L. Du[1], E. Jonaitis[1], K. Cody[1], B. Hermann[1], K. Mueller[1], R. Chappell[1], B. Christian[1], S. Janelidze[1], N. Mattsson-Carlgren[1], O. Hansson[1], S. Johnson[1]
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Background: Data increasingly show that progression from amyloid onset to Alzheimer's disease (AD)-dementia spans many years. Our study and others have demonstrated that preclinical cognitive decline is related to brain amyloid burden and how long amyloid has been present. Thus, an ideal intervention window for amyloid therapies may be at the earliest signs of amyloid accumulation, before cognitive decline has reached clinical impairment. This study uses longitudinal data from the Wisconsin Registry for Alzheimer's Prevention (WRAP) to inform sample size estimates for preclinical AD trial designs aiming to slow amyloid accumulation and slow or delay tau accumulation and cognitive decline. **Methods:** WRAP, a longitudinal cohort study of persons who were without dementia at cognitive baseline (mean(sd) age=54(6)), is enriched for AD risk via oversampling for parental AD history (~72%). WRAP participants complete biennial cognitive assessments and blood draws; a subset complete positron emission tomography (PET) amyloid scans. PET amyloid burden was quantified from eight bi-lateral ROI's using the tracer 11C-Pittsburgh Compound B to obtain a global PiB DVR value from each scan; DVR was then used to get estimated amyloid onset age and imputed DVR's corresponding to ages at cognitive and plasma sampling (Betthauser et al, 2022). Longitudinal plasma P-tau217 was assayed in a PET subset (Meso Scale Discovery platform). To assess the effect of baseline amyloid on expected progression on various trial-relevant outcomes, we stratified observations into groups defined by PiB DVR at each assessment age. Groups (and corresponding DVR ranges) included amyloid negative (Aneg; DVR<1.13), sub-threshold-to-low-amyloid-positive (subApos; DVR≈[1.13, 1.2); and amyloid-positive (Apos; Global PiB DVR≥1.2). Visit-level data were included in estimates for each group if: the DVR was in that group's range; the participant was between 50-80 years and cognitively unimpaired (CU) at first visit in that group; and the participant had at least two visits for the outcome of interest. A single participant could in this way contribute in more than one group. We used linear mixed effects models to estimate group-specific slope and error for Global PiB DVR, plasma P-tau217 and a set of cognitive composites and individual tests considered sensitive to AD-related change (fixed effect: years since baseline measurement; random within-person intercepts and slopes). The fixed effects slope estimates were then used to estimate sample sizes needed to detect a range of possible treatment effects for PiB, plasma and cognitive outcomes for trials targeting CU subApos samples and CU Apos samples (power=80%; assuming 3-year PiB and plasma follow-up and 6-year cognitive follow-up). Treatment effects were calculated as percent change relative to slope estimates within the subApos and Apos groups (i.e., representing attenuation towards 0 in treatment group); for the subApos group, we also calculated sample sizes for treatment effects relative to the Aneg slopes (representing attenuation to normal preclinical age-related change in the treatment group). We report samples sizes needed per treatment arm (25% treatment effect) for the five cognitive outcomes with lowest estimates from a set that included three cognitive composites and eight individual tests. **Results:** In the Aneg sample, longitudinal data from 109, 93, and 330 participants, respectively, contributed to slope estimates for PiB, plasma, and cognitive outcomes (median baseline ages by outcome:62, 62, and 55). In the subApos sample, longitudinal data from 13, 28, and 68 participants contributed to PiB, plasma, and cognitive estimates (median baseline ages: 65, 65, and 61). Sample sizes needed per treatment arm to detect a 25% reduction in worsening relative to 0/aNeg are, by cognitive outcome: Digit Symbol Substitution test, 441/2697; Harvard Aging Brain Study processing speed composite (HABS-PS, Trails A and Digit Symbol), 1373/2573; WRAP 3-test preclinical Alzheimer's Cognitive composite (PACC3; RAVLT learning, Logical Memory II, Digit Symbol Substitution), 1903/8716; WRAP 5-test PACC (PACC3 plus MMSE and CFL fluency), 2015/3242; and log(Trails B) time, 6738/5206. In the Apos sample, longitudinal data from 20, 46, and 61 participants, contributed to estimates for PiB, plasma, and cognitive outcomes (median baseline ages 66, 64, 59). Sample size needed per treatment arm to detect a 25% reduction in worsening relative to 0 are, by outcome: PiB, 117; plasma p-tau217, 377; Digit Symbol, 190; PACC5, 843; PACC3, 905; Logical Memory II, 1545; and HABS-PS, 1960. For both target samples, powering to detect such cognitive change corresponds to >80% power to detect PiB and plasma p-tau217 effects of ~10% or higher. **Conclusion:** Sample size requirements for cognitive outcomes vary widely depending on the cognitive measure, the baseline amyloid range of trial participants and whether treatment effects are based on attenuation to zero or to trajectory estimates

of those who are amyloid negative (i.e., presumably healthy controls). Our estimates suggest that a processing speed composite or the Digit Symbol task contributing to it may out-perform more commonly used preclinical AD composites. Studies that are adequately powered to detect slowing in preclinical cognitive decline will be adequately powered to detect clinically meaningful PiB and plasma P-tau217 treatment effects.

LB11- CEREBROSPINAL FLUID BIOMARKER EFFECTS FROM A FIXED-DOSE COMBINATION OF SODIUM PHENYLBUTYRATE AND TAURURSODIOL IN ALZHEIMER'S DISEASE: RESULTS FROM THE PEGASUS TRIAL. S.E. Arnold[1,2], N. Knowlton[3], V.J. Williams[4], J.M. Burns[5], M. Crane[6], A.J. Mcmanus[1], S.N. Vaishnavi[7], Z. Arvanitakis[8], J. Neugroschl[9], K. Bell[10], B.A. Trombetta[1], B.C. Carlyle[11], P. Kivisäkk[2,12], R.E. Tanzi[13,14], K. Leslie[15,16] *(1. Department of Neurology, Massachusetts General Hospital, Boston, MA, USA - Boston (United States), 2. Harvard Medical School, Boston, MA, USA - Boston (United States), 3. Pentara Corporation, Millcreek, UT, USA - Millcreek (United States), 4. Department of Medicine, University of Wisconsin-Madison, School of Medicine and Public Health, Madison, WI, USA - Madison (United States), 5. University of Kansas Alzheimer's Disease Center, Kansas City, KS, USA - Kansas City (United States), 6. Genesis Neuroscience Clinic, Knoxville, TN, USA - Knoxville (United States), 7. Department of Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA - Philadelphia (United States), 8. Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA - Chicago (United States), 9. Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA - New York (United States), 10. Department of Neurology, Columbia University, New York, NY, USA - New York (United States), 11. Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, England, United Kingdom - England (United Kingdom), 12. Department of Neurology, Massachusetts General Hospital, Boston, MA, USA; Harvard Medical School, Boston, MA, USA - Boston (United States), 13. Harvard Medical School, Boston, MA, USA - Boston (United Kingdom), 14. Department of Neurology, Genetics and Aging Research Unit, McCance Center for Brain Health, Massachusetts General Hospital, Harvard University, Boston, MA, USA - Boston (United States), 15. Amylyx Pharmaceuticals, Inc., Cambridge, MA, USA - Cambridge (United States), 16. Present address: Division of Biology and Biological Engineering Graduate Program, California Institute of Technology, Pasadena, CA, USA - Pasadena (United States))*

Background: An oral, fixed-dose combination of sodium phenylbutyrate and taurursodiol (PB and TURSO) is hypothesized to simultaneously mitigate endoplasmic reticulum stress and mitochondrial dysfunction, pathways relevant in neurodegenerative diseases. Oral PB and TURSO was shown to significantly slow functional decline and prolong survival in a randomized, placebo-controlled trial in amyotrophic lateral sclerosis (ALS). Preclinical studies have shown activity of PB and TURSO individually and in combination in animal models of Alzheimer's disease (AD). PEGASUS (NCT03533257) was the first-in-indication clinical trial designed to evaluate the safety and biologic activity of PB and TURSO in AD, with an aim of informing the design of future studies of PB and TURSO in AD and other neurodegenerative diseases. **Objective:** Report final safety and full biomarker results from PEGASUS. **Methods:** PEGASUS was a phase 2, multicenter, randomized, double-blind, placebo-controlled trial enrolling adults aged 55 to 89 years with mild cognitive impairment or mild to moderate dementia (baseline Montreal Cognitive Assessment [MoCA] score ≥8) with supporting biomarkers of AD pathology. Participants were randomized to receive oral PB and TURSO or matching placebo for 24 weeks and were permitted to continue on stable dosing regimens of standard-of-care AD medications. The primary outcome of the study was safety and tolerability of PB and TURSO. The secondary outcome was efficacy assessed using a global statistical test for change from baseline to week 24 combining 3 univariate end points: Mild/Moderate Alzheimer's Disease Composite Scale (MADCOMS), Functional Activities Questionnaire, and hippocampal volume on volumetric magnetic resonance imaging. Exploratory outcome measures consisted of cerebrospinal fluid (CSF) biomarkers, namely, changes from baseline in core AD biomarkers (amyloid beta species [Aβ42, Aβ40, and Aβ42/Aβ40 ratio], total tau [t-tau], and phospho-tau 181 [p-tau]) as well as biomarkers of neurodegeneration (neurofilament light chain, fatty acid binding protein-3 [FABP3]), synaptic integrity (neurogranin), inflammation and immune modulation (interleukin [IL]-6, IL-8, IL-15, monocyte chemoattractant protein-1, glial fibrillary acidic protein, chitinase 3–like protein 1 [YKL-40]), neurovascular/neuropil remodeling (matrix metalloproteinase-10), oxidative stress (8-hydroxy-2′-deoxyguanosine [8-OHdG]), and metabolic dysregulation in the brain (24S-hydroxycholesterol, leptin, soluble insulin receptor). Based on feasibility, a sample size of approximately 100 participants was chosen. Mean between-group differences in change from baseline at week 24 were compared between active and placebo arms for all efficacy outcomes and declared significant if P<.05 without multiplicity adjustment. No hypothesis testing was performed for safety variables. **Results:** A total of 95 participants with an average age of 70.7 years were randomized (PB and TURSO, n=51; placebo, n=44). Approximately 67% of participants were receiving donepezil and 37% participants were receiving memantine at baseline for cognitive impairment. Baseline demographics and biomarker values were generally well matched between the groups; however, participants randomized to PB and TURSO had evidence of greater baseline cognitive impairment based on mean Alzheimer's Disease Assessment Scale–Cognitive Subscale, MoCA, and MADCOMS scores (all P≤.007 vs placebo). No new safety signals were observed compared to the previous study in ALS, despite the older participant population in PEGASUS. Adverse events were predominantly gastrointestinal. This study was not powered to see differences in clinical efficacy end points, and no significant between-group differences were observed for the primary or secondary clinical end points. However, mean (SD) changes from baseline to week 24 directionally favored PB and TURSO versus placebo for the core AD biomarkers Aβ42/Aβ40 ratio (+0.004 [0.004] vs –0.005 [0.004]; P=.005), t-tau (–64.9 [15.5] vs +8.82 [15.2] pg/mL; P<.0001), and p-tau (–14.6 [3.0] vs –0.27 [2.9] pg/mL; P=.0002), as well as FABP3 (–344.6 [85.9] vs +102.9 [80.6] pg/mL; P=.0004), neurogranin (–81.2 [16.5] vs –8.3 [15.9] pg/mL; P= .0003), IL-15 (–0.02 [0.08] vs +0.25 [0.07] pg/mL; P=.01), YKL-40 (–14,635.4 [3954.0] vs +1507.9 [3776.8] pg/mL; P=.004), and 8-OHdG (+0.31 [0.16] vs –0.13 [0.15]; P=.006). Other biomarkers did not show significant mean between-group differences. **Conclusions:** Compared with placebo, PB and TURSO significantly improved CSF amyloid, tau, and neurodegeneration markers and other biomarkers relevant to AD pathophysiology. Results from PEGASUS provide the first-in-human evidence for a treatment effect of PB and TURSO on AD pathology and pathways of inflammation, synaptic function, oxidative stress, and neurodegeneration, complementing preclinical studies that showed a biologic effect

for PB and TURSO both individually and in combination in AD models. Taken together, these findings may be used to inform the design of subsequent trials and provide support for further clinical development of PB and TURSO for AD and other neurodegenerative diseases. **Disclosures:** Conflicts of interest will be listed in the presentation at CTAD.

LB12- USE OF A BLOOD-BASED BIOMARKER TEST IMPACTS CLINICAL DECISION MAKING AMONG NEUROLOGISTS EVALUATING PATIENTS WITH SYMPTOMS OF COGNITIVE IMPAIRMENT. J. Braunstein[1], M. Monane[1], K. Johnson[2], B.J. Snider[3], R. Scott Turner[4], J. Drake[5], D. Jacobs[6], J. Ortega[1], J. Henderson[1], T. West[1] *(1. C2N Diagnostics - St Louis (United States), 2. Duke University - Durham (United States), 3. Washington University - St Louis (United States), 4. Georgetown University - Washington (United States), 5. Lifespan - Providence (United States), 6. Neurological Services of Orlando - Orlando (United States))*

Background: A critical need exists for early, accurate diagnosis of Alzheimer's disease (AD) to guide patients to current and emerging anti-AD therapies as well as to rule out AD to allow for other diagnostic considerations. There is also a need for safe, less resource-intensive, easily accessible, and broadly available tests that identify the presence or absence of brain amyloid plaques, a pathologic hallmark of AD. Blood-based biomarkers (BBMs) offer advantages over imaging and cerebrospinal fluid (CSF) measurements, potentially fulfilling these unmet needs. The PrecivityAD™ blood test quantifies plasma concentrations of amyloid beta 42 and 40 (Aβ42 and Aβ40) and determines the presence of apolipoprotein E (ApoE)-specific peptides to establish the APOE genotype. The Aβ42/40 ratio + APOE genotype + patient's age are used to calculate the Amyloid Probability Score (APS), which is the test result, by way of a validated regression model. The PrecivityAD blood test has demonstrated 92% sensitivity and 77% specificity in a large trial incorporating patients from the Plasma Test for Amyloidosis Risk Screening (PARIS) study (NCT02420756), a prospective add-on to the Imaging Dementia–Evidence for Amyloid Scanning study, as well as the MissionAD study (BCT02956486). While clinical validity for the PrecivityAD blood test has been demonstrated, this study focuses on clinical decision making associated with results of BBM testing. **Objectives:** The study objective is to assess patient selection and score interpretation of the PrecivityAD blood test and the APS as well as post-test changes in diagnostic certainty and management of symptomatic patients being evaluated for AD or other causes of cognitive decline. **Methods:** The Quality Improvement PrecivityAD (QUIP I) Clinician Survey (NCT05477056) is a prospective, single cohort study conducted at outpatient sites among patients 60 years and older presenting to a neurologist with signs or symptoms of mild cognitive impairment (MCI) or dementia. All patients received PrecivityAD blood testing and an APS result. The APS reflects the likelihood that a patient, on a scale of 0-100, will be amyloid positive on an amyloid PET scan, with low APS (0-35), intermediate APS (36-57), and high APS (58-100) as established score categories representing low, intermediate, and high likelihood of amyloid PET positivity, respectively. Physician surveys focused on quality improvement were conducted after receipt of the test results. Collected data included subject demographics, APS result, diagnostic certainty pre- and post-blood testing, and planned drug therapy. **Results:** Participating clinicians from 13 sites submitted 272 surveys between March 2021 and July 2022. The surveys reflected patients with a median age of 73 years old, 56% female, and 90% white. The mean APS was 45 (range 0-100): 46% (n=125) patients had low scores, 14% (n=39) had intermediate scores, and 40% (n=108) had high scores. The mean probability of AD diagnosis was rated by physicians as 63% pre-test and 52% post-test ($p<0.0001$). The mean probability of physicians' estimates of AD changed pre-test to post-test from 56% to 20% (low APS group), 63% to 47% (intermediate APS group), and 70% to 89% (high APS group) ($p<0.0001$). Anti-AD drug therapy was noted in 50% of patients pre-test and 57% of patients post-test; however, 25% (69/272) of patients had planned changes in anti-AD drug therapy. Of note, 85% (33/39) of patients with increased drug therapy were in the high APS group, and 93% (28/30) of patients with decreased drug therapy were in the low APS group ($p<0.0001$). **Conclusions:** In summary, the PrecivityAD blood test showed clinical utility in its association with physician decision-making around diagnostic certainty and drug therapy management in patients evaluated for mild cognitive impairment or dementia, with 86% of patients deriving clinically useful low or high APS results. Low APS patients were evaluated by neurologists to have lower AD likelihood post-test and were less likely to be managed with anti-AD drugs, consistent with ruling out AD. High APS patients were judged by neurologists to have higher AD likelihood post-test and were more likely to be managed with anti-AD drugs, consistent with ruling in AD. While previous studies have demonstrated that the use of amyloid PET and CSF biomarkers have been associated with changes in diagnostic confidence of AD as well as changes in anti-AD drug therapy, this study is one of the first to show clinical management changes using a BBM test assessing the presence or absence of brain amyloidosis among symptomatic patients being evaluated for AD or other causes of cognitive decline.

LB13- PHASE 1 PHARMACOKINETIC AND CNS TARGET ENGAGEMENT PROPERTIES OF THE ORALLY ADMINISTERED O-GLCNACASE INHIBITOR ASN51 IN HUMANS. R. Schubert[1], R. Pokorny[1], B. Permanne[1], P. Fang[1], V. Teachout[1], M. Nény[1], S. Ousson[1], J. Hantson[1], A. Sand[1], R. Ahmed[1], M. Schneider[1], J.F. Stallaert[1], A. Quattropani[1], E. Yuen[1], D. Beher[1] *(1. Asceneuron - Lausanne (Switzerland))*

Background: Inhibition of the O-linked-β-N-acetylglucosaminidase (OGA) enzyme blocks the removal of O-linked GlcNAc carbohydrate moieties from the hydroxyl groups of serine and threonine residues on target proteins. One protein that is markedly O-GlcNAcylated in response to OGA inhibition is the microtubule associated protein tau. Tau is best known for its central role in the onset and progression of neurofibrillary tangle (NFT) pathology in Alzheimer's disease (AD) and related forms of dementia. The O-GlcNAcylation of tau proteins prevents their incorporation into insoluble NFTs and maintains tau in a soluble state (O-tau). The ability of orally administered OGA inhibitors to slow the development of neurofibrillary tangle pathology in vivo across multiple preclinical tauopathy models has raised the visibility and potential of this new therapeutic class. Recent work has further shown that O-GlcNAcylation slows the aggregation of α-synuclein proteins by increasing the amount of O-synuclein, with therapeutic implications for Parkinson's disease and related disorders. ASN51 is a novel, oral, brain-penetrant, active-site-directed, reversible OGA inhibitor that is being evaluated as a clinical candidate for the treatment of Alzheimer's and Parkinson's disease. **Objectives and Methods:** Two Phase 1 studies examined the human safety,

tolerability, pharmacokinetic, pharmacodynamic and CNS target engagement properties of ASN51 in healthy volunteers. The first study, ASN51-101, was a randomized, double-blind, placebo-controlled safety, tolerability, pharmacokinetic and pharmacodynamic study of oral ASN51 in healthy young volunteers administered single doses of 20 mg and 50 mg and in healthy elderly volunteers administered ten daily doses of 20 mg. The second study, ASN51-102, was an open-label OGA positron emission tomography (PET) study in healthy adult volunteers administered two single doses of 5 to 15 mg, to determine the relationship between plasma concentration and brain target engagement of ASN51. **Results:** ASN51 was safe and well tolerated throughout the two clinical studies, reaching meaningful plasma and CSF concentrations. Exposures increased in proportion to dose with plasma half-lives in the multiple dose healthy elderly cohort ranging from 38 to 48 hours in steady state. The O-GlcNAcylation of PBMC proteins after ASN51 administration was measured as a surrogate biomarker of O-tau and was >2-fold the baseline value 8 hours after administration of a single 20 mg dose. The OGA PET study indicated that single daily doses of 10 mg can yield OGA enzyme occupancies >95% occupancy at trough. **Conclusions:** Altogether, the Phase 1 data suggest that daily doses of 10 mg or lower will maintain a therapeutic level of OGA inhibition with elevated O-tau and O-synuclein throughout the entire day. ASN51 thus demonstrates safety, pharmacokinetic and pharmacodynamic target engagement properties that are ideal for a once-daily, low dose CNS therapy. Based on ASN51's optimal safety and human pharmacology profile in Phase 1, ASN51 is being advanced to a Phase 2A tau PET proof of mechanism biomarker study in early symptomatic AD patients.

LB14- ANALYSIS OF 15 SOFTWARE PIPELINES FOR VALIDATION OF [18F]FLORBETABEN PET QUANTITATION. A. Jovalekic[1], N. Roe-Vellve[1], N. Koglin[1], M. Lagos Quintana[1], A. Nelson[2], M. Diemling[3], J. Lilja[3], J.P. Gomez Gonzalez[4], V. Dore[5], P. Bourgeat[5], A. Whittington[6], R. Gunn[6], A. Stephens[1], S. Bullich[1] *(1. Life Molecular Imaging - Berlin (Germany), 2. MIM Software - Cleveland (United States), 3. Hermes Medical Solutions - Stockholm (Sweden), 4. QuBiotech - A Coruna (Spain), 5. CSIRO - Brisbane (Australia), 6. Invicro - London (United Kingdom))*

Background: Amyloid positron emission tomography (PET) with [18F]florbetaben is an established tool for detecting Aβ deposition in the brain in vivo and has been approved for routine clinical use since 2014 as Neuraceq® based on visual assessment (VA) of PET scans. Quantitative measures are however commonly used in the research context, with many of the available PET software packages capable of calculating amyloid burden both on a regional and a composite level, allowing continuous measurement of amyloid burden in addition to the approved dichotomous VA. **Objectives:** This study aimed to provide scientific evidence of the robustness and additional value of florbetaben PET quantification, with a focus on Centiloid-based analysis. The diagnostic performance (i.e., sensitivity and specificity) of quantification against the histopathological confirmation of Aβ load was estimated and compared to the effectiveness of the approved VA method. Additionally, the concordance between visual and quantitative evaluation of florbetaben PET scans was assessed. The reliability and comparability of the different analytical pipelines was further tested. **Methods:** This is a retrospective analysis of florbetaben PET images that had been acquired in previous clinical trials. The study population consisted of 589 subjects with at least one available florbetaben PET scan. Florbetaben PET scans were quantified with 15 analytical pipelines using nine software packages (MiMneuro, Hermes BRASS, Neurocloud, Neurology Toolkit, statistical parametric mapping (SPM8), PMOD Neuro, CapAIBL, non-negative matrix factorization (NMF), AmyloidIQ (Whittington et al., 2019)) that used several metrics to estimate Aβ load (SUVR, Centiloid, amyloid load and amyloid index). Six analytical methods reported Centiloid (MiMneuro (Piper et al., 2014), standard centiloid pipeline (Klunk et al., 2015, Rowe et al., 2017), Neurology Toolkit, SPM8 (PET-only), CapAIBL (Bourgeat et al., 2018), NMF (Bourgeat et al., 2021). For some software packages, different analytical methods were tested using different reference regions, for example, without using the T1-weighted MRI scan. All the scans were quantified in batch mode to minimize operator intervention. The operators were different for each software package and blinded to the diagnosis of subjects, demographics, visual PET assessment, histopathology results and all other clinical data. All results were quality controlled. **Results:** The mean sensitivity, specificity and accuracy was 96.1±1.6%, 96.9±1.0% and 96.4±1.1%, respectively, for all quantitative methods tested. Centiloid-based approaches yielded a comparable mean sensitivity, specificity and accuracy of 96.1±1.6%, 97.4±1.2% and 96.7±1.2%, respectively. The mean percentage of agreement between binary quantitative assessment across all 15 pipelines and visual majority assessment was 92.4±1.5%. For the Centiloid-based sub-analysis the mean percentage of agreement with visual majority assessment was 93.2±0.4%. Substantial agreement was observed across software packages using different measures. Intra-software reliability based on re-analysis of selected scans (n=84) ranged between R2=0.98 and 1.00. **Conclusion:** Results from this retrospective analysis demonstrate that software quantification methods, for example Centiloid analysis, can complement visual assessment of florbetaben PET images. Such robust, validated methods could enable readers to augment their visual analysis with optional quantitative tools. Adjunct use of quantification software tools could be beneficial for newly trained or inexperienced operators in instances when images are visually assessed with relatively low confidence, or when amyloid levels of patients are close to «pathology» thresholds, or in longitudinal studies for studying amyloid accumulation or removal. Based on this study, quantification of [18F]florbetaben PET as an adjunct to visual assessment was recently approved by the European Medicines Agency (EMA) in the EU for Neuraceq®. **References:** Bourgeat, P., et al., Implementing the centiloid transformation for (11)C-PiB and beta-amyloid (18)F-PET tracers using CapAIBL. Neuroimage, 2018. 183: p. 387-393. Bourgeat, P., et al., Non-negative matrix factorisation improves Centiloid robustness in longitudinal studies. Neuroimage, 2021. 226: p. 117593. Klunk, W.E., et al., The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. Alzheimers Dement, 2015. 11(1): p. 1-15 e1-4. 27. Piper, J., A. Nelson, and A. Javorek. Evaluation of a Quantitative Method for Florbetaben (FBB) PET Using SUVR. in EANM. 2014. Rowe, C.C., et al., (18)F-Florbetaben PET beta-amyloid binding expressed in Centiloids. Eur J Nucl Med Mol Imaging, 2017. 44(12): p. 2053-2059. Whittington A, and Gunn RN. Amyloid Load: A More Sensitive Biomarker for Amyloid Imaging. J Nucl Med. 2019. 60(4):536-540.

LB15- RESULTS FROM A CLINICAL STUDY OF AN ANTI-GALECTIN-3 MONOCLONAL ANTIBODY IN PATIENTS WITH MODERATE TO SEVERE ALZHEIMER'S DISEASE. D. Sun[1], G. Haig[1], S. Rasool[1] *(1. Truebinding Inc - Foster City (United States))*

Background: Galectin-3 has been reported to be highly expressed in Alzheimer's disease (AD) brain tissues. Our studies elucidated its intrinsic ability of acting as glue to promote oligomerization of Abeta, pTAU and other amyloid proteins in vitro. It's antagonist monoclonal antibodies showed dramatic cognition improvement and plaque reduction in AD mice after only two-week treatment Inhibition of Galectin-3 is a novel approach to the treatment of AD. The hypothesis is disease reversal, not halting disease progression. Gal-3 is a ubiquitous endogenous protein involved the pathology of certain neurodegenerative, metabolic, and immunologic disorders. TB006 is a humanized IgG4 type monoclonal antibody with high affinity and selectivity for Gal-3. Preclinical studies in Tg mice demonstrated dramatic cognitive improvement and plaque reduction with only two weeks of treatment. In a SAD study in healthy volunteers, doses of up 5000 mg (~70 mg/kg) were safe and well tolerated. Dosing of the clinical lead antibody TB006 in a single ascending dose (SAD) study in healthy volunteers up to 5000mg (70mg/kg) was safe and well tolerated. This phase 1b/2a study was conducted in moderate to severe AD patients to assess the safety, tolerability, PK and efficacy of five weekly TB006 doses. **Methods:** This was a seamless Ph 1b/2a double-blinded, placebo controlled, multicenter study. AD patients with a screening MMSE <24 and without confounding neurologic or psychiatric disease were eligible. In Ph 1b, 3 groups (140 mg, 420 mg, 1000 mg) of 8 patients in sequential ascending fashion received either weekly TB006 (6) or placebo (2) infusions for 5 doses. In Ph 2a, 1 participants16 were to be randomized (1:1) to receive either TB006 (1000mgthe highest safe and tolerated dose from Part 1) or placebo weekly for 5 doses. Ph 2a used the clinical dementia rating -sum of boxes (CDR-SB) score as the primary endpoint. Other endpoints were the mini-mental state examination (MMSE), neuropsychiatric inventory (NPI), CDR battery and plasma and imaging (MRI/PET) biomarkers. Cognition testing was done at baseline and on Days 15, 364, 64, and 104. Safety assessments were conducted at each visit. The sample size provided 80% power to detect a mean difference between TB006 and placebo of 0.25 point at Day 104 on the CDR-SB. **Results:** 157 patients, including 24 in Part 1, were randomized at 15 US sites. ; Nine9 subjects prematurely discontinued. TB006 was safe and well tolerated at all dose levels. There were 9 severe adverse events (SAEs), including 1 death. None were related to TB006 treatment. Most other AEs were mild, sporadic and self-limiting. Patients in Group 3 (1000 mg), as well as all placebo patients in Ph 1a were included in the efficacy analysis. The primary endpoint was met. Patients receiving TB006 showed a dramatic0.9 point reduction on the CDR-SB score compared with placebo ($p<0.015$). Secondary efficacy endpoints were equally robust. Mean efficacy endpoint scores in the placebo group remained consistent throughout the observation period. **Conclusion:** TB006 demonstrated evidence of AD reversal in this short-term treatment study. TB006 was safe and well tolerated.

LB16- PHASE 1 PREVENTIVE ADJUVANTED TAU VACCINE, AV-1980R. S. Schneider[1], A. Ghichikyan[2], R. Alexander[3], H. Zetterberg[3], E. Reiman[3], D. Tosun[4], M. Agadjanyan[2] *(1. USC - Los Angeles (United States), 2. Institute for Molecular Medicine - Huntington Beach (United States), 3. Banner Alzheimer's Institute - Phoenix (United States), 4. University of California San Francisco - San Francisco (United States))*

Objectives: Results from active and passive immunotherapy in early Alzheimer's patients demonstrate that monoclonal antibodies decrease Aβ and tau pathology. A recent report stated that treatment with anti-amyloid mAb lecanemab reduced cognitive decline by 0.45 CDR-SB points. This facilitates the shift from treatment to prevention, and aligns with a long-standing tenet that safe and immunogenic preventive Aβ and/or tau vaccines should be initiated in cognitively unimpaired participants with preclinical AD. **Methods:** GMP grade AV-1980R was manufactured. Edematous changes, meningeal changes, micro-hemorrhages and meningoencephalitis, and brain atrophy assessed by MRI will be analyzed. Anti-tau cellular and humoral responses will be assessed by ELISPOT and ELISA, respectively. Plasma Aβ42/40, P-tau181, P-tau217, and P-tau231, neurofilament light chain, GFAP will be measured by SIMOA technology. **Results:** This is a randomized, multicenter, double-blind, placebo-controlled, multiple ascending dose trial consisting of 64 cognitively unimpaired individuals at risk of MCI due to AD (preclinical) determined by PET scan and blood biomarkers to determine the safety and tolerability of AV-1980R/A at 20, 100, and 300 μg, i.m. doses. Participants are injected four times at 0, 4, 12, 36 weeks and followed up for a 44-week period. to determine the safety and tolerability of AV-1980R/A at 20, 100, and 300 μg, i.m. doses. Participants will be injected four times and followed up for 44-weeks. Primary outcome is Treatment-Emergent Adverse Events (TEAEs) or Serious Adverse Events (SAEs). Secondary outcomes are humoral and cellular immune responses and blood biomarkers. **Conclusion:** Passive mAb immunotherapy for cognitively unimpaired people is impractical due to the complexity and need for frequent administration of very high doses. Safe and immunogenic active vaccines are suitable candidates for preventing the accumulation of tau pathology and potentially delaying onset of illness. We are evaluating for the first-time preventive vaccine, AV-1980R/A targeting the phosphatase-activating domain (PAD) of pathological tau.