Posters

AD CLINICAL TRIALS AND COVID-19

RP01- DEMENTIA RESEARCH PARTICIPATION AND PATIENT PREFERENCES DURING THE COVID-19 PANDEMIC. Lucianne Dobson, Floey Urban, Ross Paterson, Sebastian Crutch, Suzie Barker, Cath Mummery *(Dementia Research Centre, National Hospital For Neurology And Neurosurgery, Queen Square, University College London And University College London Hospital - London (United Kingdom))*

Background: The COVID-19 pandemic has had a significant impact on clinical trials on Alzheimer's disease and other dementia research. At the Dementia Research Centre (DRC), in-person research visits were abandoned for all but clinically essential appointments to protect our staff and highly vulnerable patient groups. Sadly, many projects had to be suspended or terminated. To minimise the impact of the pandemic on our crucial research, we contacted our participants directly to glean their opinions on the impact of COVID-19 on research, and how our practices could be altered to continue safely during the pandemic. **Objectives:** To determine the opinions of our participants on continuing contact and restarting research participation during the COVID-19 pandemic. We were particularly interested in preference for remote or in-person attendance and specific concerns about their own health and COVID-19 risk. We aimed to use information gathered to optimise study design alterations during the pandemic. **Methods:** Current or prospective research participants (dementia patients and healthy volunteers) were contacted with a questionnaire August-September 2020 and responses collated, transcribed and organised October-November 2020. Participants were contacted primarily by email, but also via phone or post if email unavailable. Responses were taken exactly as they were written (or transcribed for phone questionnaires) for analysis. Questions designed for specific responses e.g., yes/no, were analysed quantitatively and presented as "number of participants". Questions designed for open responses, e.g., "comments", were analysed by thematic analysis and qualitative content analysis. **Results:** Five-hundred-and-twenty-seven research participants were contacted with the Research Restart Questionnaire; we received 196 responses (37.2%) and 163 of these participants completed at least part of the questionnaire. We only attempted contact once, to avoid additional burden on vulnerable patients and carers during the pandemic, which resulted in a lower than usual response-rate. Question 1 (Q1) asked participants if they were happy to be contacted about restarting research during the COVID-19 pandemic. The vast majority of questionnaire responders (96.3%) were happy to be contacted about this. Q2 asked if participants would consider attending a research visit in-person at the DRC. Most questionnaire responders (76.7%) said they would, although many expressed concerns. The most common theme of concern was around travel to London/DRC. Forty-one participants were concerned about travelling and using public transport due to increased risk of COVID-19. Q3 asked if participants would consider participating in research remotely, e.g., by telephone or online. The majority of questionnaire responders (89.0%) said they would consider this but there were themes of concern around ability to perform research tasks. Q4 asked if participants have any specific concerns about their own health, e.g., being asked to self-isolate. Most questionnaire responders answered "no" (62.6%) but 39 participants commented on concerns about their own or others' health or COVID-19 risk. Almost two-thirds of participants are not considering themselves to be high risk of COVID-19, e.g., "not been advised to self-isolate"; but there is a strong expectation that our site would be following government guidelines for COVID-19 and that appropriate measures would be in place if they were to attend for a study visit. Q5 asked participants if they had any questions/comments. A large number of participants used this opportunity to make positive comments about the DRC and research participation e.g. "happy to hear from us", "missing taking part in our research", "pleased to hear research is re-starting" and generally thanking us for the "important work (we) do". **Conclusion:** DRC research participants were happy to hear from us during the COVID-19 pandemic and are keen to restart research. The vast majority of our participants would consider attending a research visit at the DRC or participating in research remotely, with a slight preference for remote research overall. There is, however, a lot of concern around travel to London and the DRC, especially using public transport. While the vast majority of our participants would consider taking part in research remotely, many also have concerns about being able to perform research tasks remotely. These concerns include dementia-related communication issues as well as computer proficiency and access to technology. Our participants are complimentary about our research and staff and are looking forward to continuing participation, even during the pandemic while COVID-19 restrictions are in place. If participants can be appropriately supported with travel arrangements, advice on protective measures for COVID-19, and with the practicalities of remote research, many concerns could be eliminated and high research participation rates can be expected during the pandemic. Based on participant preferences, general areas of concern and COVID-19 vulnerability issues, study designs centred around a remote research approach should be employed, where possible. Whilst representing participant opinion as a snapshot at the height of pandemic, the findings from this survey have provided useful insight into participant research preferences during the pandemic and beyond, and will be used to modify current projects, manage subsequent lockdowns/restrictions, and guide future practical/logistical planning and study design at the DRC.

ANIMAL MODEL AND CLINICAL TRIAL

P01- TREATMENT OF ALZHEIMER'S DISEASE BY A PROTEOSOME-BASED ADJUVANT (PROTOLLIN) THAT MODULATES BOTH PERIPHERAL MONOCYTES AND DISEASE-ASSOCIATED MICROGLIA. Panayota Kolypetri[1,2] Lei Liu[1], Estefania Solana[1,2], Christian Gauthier[1,2], Howard L. Weiner[1,2] *(1. Department of Neurology, Ann Romney Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (United States); 2. Evergrande Center for Immunologic Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (United States))*

Background: Amyloid beta (Aβ) accumulation is considered to be the primary initiating event in Alzheimer's disease (AD) pathogenesis. Our previous work has shown that nasal administration of Protollin - a proteosome-based adjuvant acting as a TLR2/TLR4 agonist - leads to reduction

of insoluble, fibrillar and soluble Aβ accumulation in the brain in young and old AD mice (1-4). **Objectives:** We investigated the effects of nasal Protollin on activation and recruitment of peripheral monocytes in the brains of APP/PS1 mice as well as the transcriptional changes microglia undergo in these animals during treatment. We also investigated the impact of Protollin on the transcriptional signature and phagocytic ability of human CD14+ monocytes against Aβ1-42 in vitro. Methods: APP/PS1, APP/PS1-CCR2RFP+/- and APP/PS1-CCR2RFP/RFP transgenic mice received nasal Protollin. Transcriptional profiling of FACS-sorted Ly6Chigh monocytes from cervical lymph nodes (CLN), spleen and bone marrow (BM) as well as Tmem119+ microglia was performed by bulk RNA sequencing. Differentially expressed (DE) genes were analyzed by Ingenuity Pathway Analysis (IPA). In the brain, quantification and visualization of infiltrating immune cells was performed by multi-color flow cytometry and confocal imaging. The phagocytic ability of Protollin-treated FACS-sorted human CD14+ monocytes against HiLyteTM Fluor488-labeled Aβ1-42 was performed using confocal imaging and flow cytometry. Single-cell (sc)-RNAseq analysis of human CD14+ monocytes stimulated with or without Protollin was assessed using the 10x Genomics Chromium technology. **Results:** We examined the in vivo effect of nasal Protollin on peripheral monocytes and microglia from APP/PS1 mice during the initial stages of disease. In the periphery, Ly6Chigh monocytes from CLN, spleen and BM of Protollin treated-mice acquired tissue-specific signatures. IPA analysis showed that DE genes in CLN-derived Ly6Chigh monocytes from treated-mice were involved in cell migration, complement activation and Aβ clearance whereas splenic and BM-derived Ly6Chigh monocytes upregulated genes related to cell migration and M2 polarization. In the brains of Protollin-treated APP/PS1 mice, analysis of the composition of infiltrating immune cells showed a selective, increased recruitment of Ly6Chigh monocytes which were detected adjacent to Aβ aggregates. Of note, an altered transcriptional signature of microglia was identified in treated-animals, marked by significant downregulation of Apoe, Clec7α, Axl, Lyz2, Cst7, Csf1 Trem2 and Itgax, genes related to disease-associated microglia (DAM)/microglial neurodegenerative (MGnD) phenotype (5, 6). Currently, we investigate whether infiltrating monocytes are necessary and/or sufficient to clear Aβ in Protollin-treated mice using the APP/PS1-CCR2RFP/RFP (monocyte deficient) mouse model and by adoptive transfers of Protollin-treated monocytes to APP/PS1 recipient animals. Finally, we addressed the effect of in vitro Protollin stimulation on human CD14+ monocytes. Confocal imaging and flow cytometric analysis showed an increased uptake of HiLyteTM Fluor488-labeled Aβ1-42 in the Protollin-treated group. Sc-RNAseq analysis of CD14+ monocytes allowed us to identify the presence of a Protollin-induced signature on human CD14+ monocytes. **Conclusion:** Our data demonstrate that nasal Protollin induces: 1) tissue-specific transcriptional changes in peripheral Ly6Chigh monocytes which are recruited in the brains of APP/PS1 mice; 2) downregulation of microglial DAM/MGnD-related genes and 3) activation of a transcriptional signature that reprograms human CD14+ monocytes towards a phagocytic phenotype leading to increased Aβ uptake in vitro. Given its safety profile and effect on both animal models of AD and human monocytes, a phase 1 single ascending dose trial of nasal Protollin in early AD is planned for the fall of 2021. Protollin represents a novel immunologic approach to clear Aβ in AD. **References:** 1. D. Frenkel, R. Maron, D. S. Burt, H. L. Weiner, Nasal vaccination with a proteosome-based adjuvant and glatiramer acetate clears beta-amyloid in a mouse model of Alzheimer disease. Journal of Clinical Investigation 115, 2423-2433 (2005). 2. D. Frenkel et al., A nasal proteosome adjuvant activates microglia and prevents amyloid deposition. Ann. Neurol. 63, 591-601 (2008). 3. D. Frenkel et al., Scara1 deficiency impairs clearance of soluble amyloid-beta by mononuclear phagocytes and accelerates Alzheimer's-like disease progression. Nat Commun 4, 2030 (2013). 4. V. Lifshitz et al., Immunotherapy of cerebrovascular amyloidosis in a transgenic mouse model. Neurobiol. Aging 33, 432 e431-432 e413 (2012). 5. H. Keren-Shaul et al., A unique microglia type associated with restricting development of Alzheimer's disease. Cell 169, 1276-1290 (2017). 6. O. Butovsky and H.L. Weiner, Microglial signatures and their role in health and disease. Nat Rev Neurosci 19, 622-635 (2018). The authors declare there is no conflict of interest.

RP02- FAM171A2 ASSOCIATES WITH ALZHEIMER' S DISEASE BY FUNCTIONING AS A CARRIER THAT FACILITATES AB42 CLEARANCE THROUGH CEREBRAL ENDOTHELIUM. Han Sida, Yu Jintai, Cui Mei, Dong Qiang *(Department Of Neurology, Huashan Hospital, Fudan University - Shanghai (China))*

In a previous research, a SNP in FAM171A2 gene was revealed to increase the risk of neurodegenerative diseases including AD, with the molecular mechanisms remaining to be further elucidated. The FAM171A2 protein displays high and endogenous expression on the cerebral endothelium, a region key for Aβ clearance, and is usually affected in AD. Thus, we hypothesized that FAM171A2 could influence the processes of AD by regulating endothelial functions. A series of experiments were conducted to test the hypothesis. We first analyzed the expression of endothelial FAM171A2 comparing the wild-type control and AD animal models. Compared with normal controls, an increase of endothelial FAM171A2 was observed in AD. Next, we knocked down the level of endothelial FAM171A2 in APP/PS1 mice by adeno-associated virus with icam2 specific promotor and studied if it may change AD-related cognitive impairments and neuropathology. Indeed, we found that Morris water maze, novel objective recognition and nesting tests indicated aggravated cognitive deficits of APP/PS1 mice in the presence of endothelial FAM171A2 knockdown. Furthermore, regarding molecular mechanisms, we utilized brain histological staining which showed that endothelial FAM171A2 knockdown depraved vascular Aβ42 deposit and exacerbated BBB leakage. These in vivo findings indicated endothelial FAM171A2 as an inducer of Aβ42 clearance and BBB integrity. Additionally, we assessed the effects of FAM171A2 on the endothelial Aβ42 endocytosis, transportation and degradation using BMECs. Our results indicated that FAM171A2 displayed chaperon-like properties which directly interacted with Aβ42, and then facilitated its endocytosis and transportation to endosome system . Furthermore, FAM171A2 stimulated the autophagy-lysosomal pathway, which led to increased degradation of Aβ42 in BMECs. In conclusion, our results showed that FAM171A2 functioned as a carrier of Aβ42 which induces its clearance in endothelium, ameliorating vascular impairments and cognitive deficits of AD.

BEHAVIORAL DISORDERS AND CLINICAL TRIALS

P02- MAPPING ITEMS OF THE COHEN-MANSFIELD AGITATION INVENTORY ONTO INTERNATIONAL PSYCHOGERIATRIC ASSOCIATION'S AGITATION DEFINITION: DATA FROM THE BREXPIPRAZOLE PHASE 3. Ross A. Baker[1], Eva Kohegyi[1], Ismail Zahinoor[2] *(1. Otsuka - Princeton (United States), 2. Univ Of Calgary - Calgary (Canada))*

Background: Agitation is a challenge in the treatment of dementia, associated with greater patient and caregiver burden, earlier nursing home placement, and increased morbidity and mortality. The 2015 publication of the International Psychogeriatric Association's (IPA) definition of agitation identified 3 domains: physical aggression, verbal aggression, and excessive motor activity. Most phase 3 studies of agitation use the 29-item Cohen-Mansfield Agitation Inventory (CMAI) to measure changes in agitation after drug treatment. Using a Delphi panel, De Mauleon and colleagues [Z1] (2021) have identified 19 CMAI items that map to the 3 domains of agitation as defined by the IPA. To extend the initial findings, we evaluated changes in the CMAI-IPA [Z2] from two Phase 3 studies of brexpiprazole 2 mg/day for the treatment of agitation in Alzheimer's dementia (AAD). **Objectives:** Understand which items of the Cohen Mansfiled Agitation Inventory, a popular scale in pharmacologic trials for treatment of agitation, map to the International Pscychogeriatric Assocciation consensus definition of agitation. **Methods:** Two 12-week, randomized, double-blind, placebo-controlled, parallel-arm studies (NCT01862640, study 1; NCT01922258, study 2; Grossberg et al., 2019 AJGP). **Intervention:** The subpopulation of trial subjects receiving 2 mg/day of brexpiprazole vs. placebo was analyzed post-hoc. Change in the CMAI-IPA were analysed using MMRM in patients from the 2 mg arm in study 1, and for those titrated to 2 mg in Study 2. **Results:** In Study 1, brexpiprazole 2 mg/day (n=138) demonstrated statistically significantly greater improvement in CMAI-IPA from baseline to Week 12 than placebo (n=131) patients (adjusted mean difference, -2.34; confidence intervals [CI], -4.61 -0.07, p=0.040; MMRM). In Study 2, among patients titrated to the maximum brexpiprazole dose of 2 mg/day (n=77) also demonstrated significantly greater improvements in CMAI-IPA compared with similarly titrated placebo (n=74) patients (-2.79; CI, -5.48 -0.11; p=0.041). **Conclusions:** After treatment with brexpiprazole 2 mg/day for up to 12-Weeks, similar changes in the CMAI-IPA and the previously published 29-item CMAI total score were observed, consistent with the initial validation of the CMAI-IPA. The results suggest the simplified CMAI-IPA scale, mapped to match the IPA domains of agitation, may be useful as an outcome measure in both clinical trials and clinical practice.

P03- VETERANS IN AD PREVENTION CLINICAL TRIALS: AN EVALUATION OF THE ASSOCIATION OF TBI ON MEMORY AND GLOBAL COGNITION. Carol Van Hulle, Madison Rundell, Karen Lazar, Elena Beckman, Noele Brandon, Carey Gleason, Sterling Johnson, Sanjay Asthana, Cynthia Carlsson *(University Of Wisconsin-Madison - Madison (United States))*

Background: Traumatic Brain Injury (TBI) is a risk factor for developing Alzheimer's Disease (AD). TBI occurs more frequently among veterans than non-veterans and therefore warrants special consideration in AD prevention clinical trials of aging Veterans. **Objectives:** To determine if the presence of TBI is associated with poorer cognitive function relative to peers without TBI, we compared baseline performance on tests of memory and global cognition among VA-eligible veterans stratified by probable TBI. **Methods:** Participants were drawn from an on-going 18-month, randomized, placebo-controlled clinical trial studying the effects of high-dose eicosapentaenoic acid (icosapent ethyl) on neuroimaging and cerebrospinal fluid AD biomarkers and cognition; the Brain Amyloid and Vascular Effects (BRAVE) of Eicosapentaenoic Acid Study (NCT02719327). Participants were VA -eligible Veterans ages 50-75 with no diagnosis of memory disorder or impairment. Participants were excluded if they were unable to safely take the study medication or participate in MRI or lumbar puncture procedures. Study analyses included N=114 Veterans who were seen for a prestudy screening and baseline visit. Cognitive assessments were administered prior to randomization. For this analysis, we selected three measures of memory function (Digit Symbol Substitution task, a test of working memory speed; Free and Cued Selective Reasoning test [FCSRT] free recall, a measure of associative memory; Logical Memory Delayed Recall) and one measure of global cognition (Mini Mental State Exam [MMSE]). Criteria for probable TBI was adapted from the DSM-V. Participants were designated as probable TBI based on self-reports of an impact or other event causing rapid movement or displacement of the brain within the skull (blast, accident, fall, bullet wound, or fragment), resulting in loss of consciousness (N=34), loss of memory (N = 11) dazed or confused state (N = 44), concussion or other head injury (N = 34). TBI data were missing for two participants. Participants also completed the Mini International Neuropsychiatric Interview (MINI), which identified current PTSD. Other sufferers of PTSD were identified through self-report or diagnosis indicated in electronic health records. We used Ordinary Least Square (OLS) linear regression with age and education as covariates. Education was coded into 5 categories: No high school diploma, high school diploma or GED; technical school graduate or 2 year college/associate's degree; some college but not a 2 or 4 year degree; 4 year college degree; some post-baccalaureate education. **Results:** Most enrollees in BRAVE are male (N=94, 86%) and white (107, 97%). Mean age is 65.5 years (SD = 6.7). Seventeen enrollees (15%) report no college experience, 29 have an associate's degree or degree from a technical school (26%), 25 report some college experience but no degree (23%), 25 (23%) have a 4 year degree, and 14 reported some post-baccalaureate college (13%). Half (N=55) of enrollees met criteria for TBI; 27 indicated the event occurred during deployment. TBI and non-TBI groups were comparable on age, education, gender, race, and depression rating. Those with TBI had a slightly greater incidence of PTSD diagnosis (18 vs 11, p=.10) and were more likely to report two or more deployments (19 vs 8, p= .07). However, covarying for age and education level, the TBI group did not differ from non-TBI group on Digit symbol substitution (b = 0.87, p = .41), FCSRT free recall (b = -0.53, p = .53), or logical memory delayed (b = 0.81, p= .13). Enrollees with probable TBI scored higher than those without probable TBI on the MMSE (b = 0.63, p = .003, TBI group mean = 28.7 [SD = 1.3], non-TBI group mean = 27.8, [SD = 1.7]). **Conclusion:** Ensuring people from diverse backgrounds join clinical trials is key to advancing health equity. Increasing enrollment of Veterans into AD prevention clinical trials is critical in that they are at higher risk for AD than the general population. In this study, the probable TBI group was indistinguishable from the non-TBI group on baseline measures of memory and outperformed the non-TBI group on measure of global cognition. The criteria used to assign TBI may have been overly broad, although our

sample is in line with national statistics showing that a third of those with probable TBI also have PTSD. TBI has been shown to lower the age of dementia onset, however, the BRAVE sample is relatively young and may not be experiencing even subtle cognitive deficits yet. For this study, probable TBI was reduced to a simple dichotomy, but many factors can affect short- and long-term recovery from TBI including type of injury, age, and existing comorbidities. Incorporating these complexities into future research will be critical to finding effective therapies to prevent or treat AD in Veterans.

P04- LOW DOSE LITHIUM TREATMENT OF BEHAVIORAL COMPLICATIONS IN ALZHEIMER'S DISEASE: LIT-AD RANDOMIZED CLINICAL TRIAL. Davangere Devanand, Elizabeth Crocco, Brent Forester, Mustafa Husain, Seonjoo Lee *(Columbia University Irving Medical Center - New York (United States))*

Background: A case series suggested efficacy for lithium to treat agitation in dementia, but no placebo-controlled trials have been conducted. **Objectives:** To evaluate low-dose lithium treatment of agitation in Alzheimer's disease (AD). **Method:** In a four-site trial, patients with AD and agitation/aggression score ≥ 4 on the Neuropsychiatric Inventory (NPI) were randomized, double-blind, to lithium carbonate 150-600 mg daily or placebo for 12 weeks. Primary efficacy outcome was change in NPI agitation/aggression; secondary efficacy outcome was treatment response (30% reduction in NPI score for agitation/aggression plus psychosis and a Clinical Global Impression (CGI) score of much or very much improved). Safety profile of lithium was assessed. **Results:** Fifty-eight of 77 patients (75.3%) completed the trial. In linear mixed effects model analyses, lithium was not significantly superior to placebo for agitation/aggression. Proportion of responders was 31.6% on lithium and 17.9% on placebo ($\chi 2$=1.26, p=0.26). Moderate or marked improvement (CGI) was greater on lithium (10/38=36.8%) than placebo (0/39=0%, Fisher's exact test p<0.001). In exploratory analyses, improvement on lithium was greater than placebo on NPI delusions and irritability/lability (p's<0.05). Lithium showed greater reduction than placebo in patients with high Young Mania Rating Scale scores (β=5.06; 95%CI,1.18 to 8.94,p=0.01). Oral dose and serum levels demonstrated similar associations with efficacy outcomes. Lithium did not differ significantly from placebo on safety outcomes. **Conclusions:** Low-dose lithium was not efficacious in treating agitation but was associated with global clinical improvement and excellent safety. A larger trial may be warranted of likely lithium-responsive behavioral symptoms that overlap with mania.

RP03- PHARMACOLOGICAL TREATMENT OF NEUROPSYCHIATRIC SYMPTOMS OF DEMENTIA: A NETWORK META- ANALYSIS. Jin-Tai Yu *(Huashan Hospital, Fudan University - Shanghai (China))*

Background: Neuropsychiatric symptoms (NPS) affect nearly all patients with dementia throughout disease progression, bringing negative consequences for the quality of patient care. Pharmacological treatments are feasible and frequently prescribed for alleviating NPS in dementia. However, decision on drug selection is still matters of controversy. **Methods:** A systematic review and network meta-analysis was performed on double-blind randomised controlled trials that were identified from PubMed, MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials for reporting NPS outcomes in dementia patients. We included placebo-controlled and head-to-head trials with commonly used drugs for the treatment of dementia and NPS. Primary outcomes were efficacy (change in overall NPS) and acceptability (treatment discontinuation due to any cause). Secondary outcomes were change in aggressive behaviors, psychosis, and discontinuations due to adverse events. This study is registered with PROSPERO: CRD42019132231. **Results:** We included 59 trials and 15 different drugs. In terms of efficacy, risperidone, and galantamine were more effective than placebo. Galantamine and rivastigmine were associated with more dropouts than placebo, and some active drugs. For secondary outcomes, aripiprazole, risperidone, divalproex, olanzapine, and memantine were more efficacious than placebo for reducing aggressive behaviors. Donepezil, haloperidol, aripiprazole, memantine and risperidone were significantly superior to placebo for psychosis. As for tolerability, olanzapine, divalproex, galantamine, rivastigmine, risperidone, and donepezil were associated with more discontinuations due to adverse events than placebo. Most of the results were rated as low or very low. **Conclusion:** Evidence from our meta-analysis shows that risperidone was more efficacious than placebo with relatively good acceptability. Collectively, our analysis should provide a helpful perspective to assist in treatment decisions.

LRP01- BENEFICIAL EFFECTS OF MASUPIRDINE ON PSYCHOSIS IN PATIENTS WITH ALZHEIMER'S DISEASE, ADDRESSING LIMITATIONS OF CURRENT PHARMACOLOGICAL INTERVENTIONS. Ramakrishna Nirogi, Anil Shinde, Abdul Rasheed Mohammed, Vinod Kumar Goyal, Vijay Benade, Veera Raghava Chowdary Palacharla, Ramkumar Subramanian, Renny Abraham, Pradeep Jayarajan, Jyothsna Ravula, Satish Jetta *(Suven Life Sciences Ltd - Hyderabad (India))*

Background: Neuropsychiatric symptoms (NPS) such as delusions and/or hallucinations (psychosis) occur in 25 to 50% of patients with Alzheimer's disease (AD). NPS are associated with increased caregiver burden, repeated hospital stays, and a more rapid progression of dementia. Although antipsychotics are commonly used off-label to treat psychosis in patients with AD, so far no drug is approved for treatment. Antipsychotics offers modest efficacy and their use accelerate cognitive decline and increases chances of stroke. These limitations warrant newer, safer treatment options with procognitive potential. **Objective:** To evaluate the effect of masupirdine, a serotonin 6 receptor antagonist on psychosis symptoms associated with AD using the 12-item neuropsychiatric inventory (NPI-12) assessment scale. **Methods:** Masupirdine was studied in a multicenter, randomized, double-blind, parallel group, 26-week, placebo-controlled proof of concept phase-2 clinical trial in subjects with moderate AD (NCT02580305). Subgroup analyses were carried out on the delusions and/or hallucinations (psychosis) domains of the NPI-12 scale. Analyses were based on the independent patient subgroups with baseline symptoms and/or symptoms emergence. A mixed-effects model for repeated measures was used to determine the effect of masupirdine on psychosis symptoms in modified intention to treat population. **Results:** In the subgroup of population with baseline psychotic symptoms and/or symptoms emergence, a significant reduction (p<0.05) in psychosis score was observed in the masupirdine 50 mg treatment arm at Week 4 & 13. A trend was observed in the masupirdine 100 mg (p<0.1) treatment arm at Week 26 as compared to placebo treated arm. Effect size (Cohen's d) observed with masupirdine

treatment was 0.32 - 0.50 and 0.25 - 0.39 at the end of 13 and 26 weeks, respectively. Masupirdine also showed beneficial effects on cognition in patients with psychosis. **Conclusion:** Further exploration is warranted to confirm the beneficial effects of masupirdine on psychosis associated with AD.

LRP02- PIMAVANSERIN TREATMENT OF HALLUCINATIONS AND DELUSIONS IN PATIENTS WITH PARKINSON'S DISEASE DEMENTIA: POST HOC ANALYSIS OF THE HARMONY TRIAL. Daniel Weintraub[1], Alberto Espay[2], Vibhash Sharma[3], Pierre Tariot[4], Victor Abler[5], Sanjeev Pathak[5], Srdjan Stankovic[5] *(1. Departments Of Psychiatry And Neurology, Perelman School Of Medicine At The University Of Pennsylvania - Philadelphia (United States), 2. Gardner Family Center For Parkinson's Disease And Movement Disorders, Department Of Neurology, University Of Cincinnati - Cincinnati (United States), 3. Department Of Neurology, University Of Kansas Medical Center - Kansas City (United States), 4. Banner Alzheimer's Institute And University Of Arizona College Of Medicine - Phoenix (United States), 5. Acadia Pharmaceuticals Inc. - San Diego (United States))*

Background: Pimavanserin is a selective serotonin modulator with inverse agonist/antagonist activity at the 5HT2A receptor, and to a lesser extent at the 5HT2C receptor. Pimavanserin 34 mg is approved in the US to treat hallucinations and delusions associated with Parkinson's disease (PD) psychosis and was investigated for the treatment of dementia-related psychosis in HARMONY. HARMONY was stopped early when a prespecified interim analysis met stopping criteria for efficacy and revealed a significantly lower risk of relapse of symptoms of psychosis upon continuing pimavanserin versus placebo in the double-blind phase of the study. HARMONY included a subgroup of patients with PD psychosis with PD dementia treated with pimavanserin 34 mg. A post hoc subgroup analysis of data from these patients can expand on the established efficacy and safety of pimavanserin in patients receiving pimavanserin in line with its currently approved indication. **Objectives:** To describe the efficacy and safety of pimavanserin 34 mg for the treatment of hallucinations and delusions in PD psychosis patients with PD dementia in HARMONY. **Methods:** HARMONY (NCT03325556) was a Phase 3, placebo-controlled, randomized discontinuation study. Participants with dementia and moderate-to-severe psychosis were enrolled. The duration of cognitive impairment and a rating of the severity of dementia (mild, moderate, or severe) were reported by the investigator at screening. Eligible patients received pimavanserin once daily for 12 weeks during the open-label (OL) period. Patients with sustained response (defined as ≥30% reduction in Scale for the Assessment of Positive Symptoms-Hallucinations + Delusions [SAPS-H+D] total score AND Clinical Global Impression-Improvement score of much/very much improved) at weeks 8 and 12 were randomized 1:1 to continue pimavanserin or receive placebo for up to 26 weeks in the double-blind (DB) period. The primary endpoint of time from randomization to relapse of psychosis was analyzed using a Cox regression model. Treatment-emergent adverse events (TEAEs) were collected throughout the duration of the study. Motor function was evaluated using the Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A), with higher scores indicating worsened motor function (range, 0-120), and cognitive abilities were evaluated using the Mini-Mental State Examination (MMSE), with lower scores indicating greater cognitive impairment (range, 0-30). **Results:** 392 patients were enrolled into the OL period of HARMONY. Of the 59 with PD psychosis and PD dementia, 49 received pimavanserin 34 mg and were analyzed here. The mean (standard error [SE]) age was 72.6 (1.08) and 61.2% (n=30) were male. At OL baseline, 32.7% (n=16) of patients exhibited mild dementia, 57.1% (n=28) exhibited moderate dementia, and 10.2% (n=5) exhibited severe dementia. The mean (SE) duration of cognitive impairment at baseline was 3.8 (0.33) years, and mean (SE) MMSE score at baseline was 18.9 (0.74). Patients had a mean SAPS-H+D total score of 23.5 (SE, 1.45) and 36.7% (n=18) had previously received medication to treat psychosis. Most patients (73.5% [36 of 49]) exhibited a sustained response to pimavanserin at weeks 8 and 12 during the OL period and were randomized to pimavanserin (n=16) or placebo (n=20) in the DB period. Of 38 patients evaluated at week 12, 42.1% (n=16) exhibited a complete response to pimavanserin (SAPS-H+D score=0) at week 12. The risk of psychosis relapse was lower in the pimavanserin group than in the placebo group (hazard ratio: 0.052; 95% CI: 0.016, 0.166; 1-sided P<0.0001). At the time the study was stopped, 1 pimavanserin-treated patient and 9 placebo-treated patients had met relapse criteria. In the OL period, 46.9% (n=23) of PD participants experienced any TEAE and 10.2% (n=5) experienced a serious TEAE. The most common TEAEs during the OL period were insomnia (8.2%), somnolence (8.2%), decreased appetite (8.2%), weight decreased (8.2%), fall (6.1%), and urinary tract infection (6.1%). During the DB period, 31.3% (n=5) of pimavanserin-treated and 45.0% (n=9) of placebo-treated patients experienced any TEAE. No patients experienced any serious TEAEs in the DB period. The mean ESRS-A score at OL baseline was 26.2 (SE, 1.89), and the mean change from baseline to week 12 was -1.7 (SE, 0.74). Mean ESRS-A scores at DB baseline (pimavanserin, 27.4 [SE, 3.99]; placebo, 26.3 [SE, 3.14]) and mean change from DB baseline to week 26 were similar in pimavanserin- and placebo-treated patients. The mean MMSE score at OL baseline was 18.9 (SE, 0.74), and the mean change from baseline to week 12 was 0.3 (SE, 0.66). Patients randomized to pimavanserin and placebo had similar mean MMSE scores at DB baseline (pimavanserin, 19.6 [SE, 1.26]; placebo, 19.3 [SE, 1.29]) and exhibited a similar mean MMSE score change from DB baseline to week 26. **Conclusions:** Pimavanserin reduced the risk of psychosis relapse in PD psychosis patients with PD dementia. Pimavanserin was well tolerated and did not have a negative effect on motor or cognitive function. These data support the demonstrated efficacy and safety of pimavanserin for the treatment of hallucinations and delusions in patients with PD psychosis to those with PD psychosis and PD dementia.

CLINICAL TRIALS : COGNITIVE AND FUNCTIONAL ENDPOINTS

P06- NATURAL DISEASE PROGRESSION MODEL OF ALZHEIMER'S DISEASE USING THE INTEGRATED ALZHEIMER'S DISEASE RATING SCALE. Brian Willis, Alette Wessels, Laiyi Chua, Kay Chow, Emmanuel Chigutsa, John Sims, Ivelina Gueorguieva *(Eli Lilly And Company - Indianapolis (United States))*

Background: Disease progression modeling characterizes the change in a clinical endpoint over time, usually in patients with chronic disease. The purpose of such a model is to aid in the design of clinical trials by identifying the traits that may suggest differences in disease progression and help characterize the effect of treatments, especially disease-modifying treatments, on the course of the disease (1). Employing a combination of theory-driven and data-driven approaches, the integrated

Alzheimer's Disease Rating Scale (iADRS), a composite of two widely accepted measures, the Alzheimer's Disease Assessment Scale – Cognitive Subscale 13-item version (ADAS-Cog13) and the Alzheimer's Disease Cooperative Study – instrumental activities of daily living scale (ADCS-iADL), was developed. The iADRS has been validated (2, 3), its statistical properties have been described, (4), and the scale has been used as a clinical outcome measure in previous phase 2 and 3 trials in Alzheimer's disease (AD) (5-7). While several disease progression models have been developed for AD, these models have focused on scales such as the ADAS-Cog (8) or Clinical Dementia Rating – Sum of Boxes (9). To date, the authors are unaware of any disease progression models based on the iADRS. There is a need to evaluate how the iADRS captures the course of AD at different stages of the disease and to understand if, and to what extent, patient-specific factors predict progression, as measured by this endpoint. **Objectives:** To evaluate predictors of AD progression as measured by the iADRS and to explore the relative change in the primary iADRS components (ADAS-Cog13 and ADCS-iADL) over time. **Methods:** Using placebo data from the phase 3 EXPEDITION3, AMARANTH, DAYBREAK-ALZ, and phase 2 TRAILBLAZER-ALZ studies, a disease progression model will be developed using a method similar to that described by Conrado et al.10 Exploratory analyses will be conducted using R4.0.3 and model development will be conducted using NONMEM 7.5.0. The impact of age, gender, baseline Mini-Mental State Examination (MMSE) score, and apolipoprotein E4 carrier status (noncarrier/heterozygous/homozygous) will be investigated as potential covariates in the disease progression model. **Results:** Data from approximately 2500 placebo patients will be included in the model. Modeling results are not yet available for the abstract but will be presented during the meeting. **Conclusion:** Conclusion will be provided during the meeting, after data are available. **References:** 1. Cook SF, Bies RR. Disease progression modeling: Key concepts and recent developments. Curr Pharmacol Rep. 2016;2(5):221-230. 2. Wessels AM, Andersen SW, Dowsett SA, Siemers ER. The integrated Alzheimer's Disease Rating Scale (iADRS) findings from the EXPEDITION3 trial. J Prev Alzheimers Dis. 2018;5(2):134-136. 3. Wessels AM, Siemers ER, Yu P, et al. A combined measure of cognition and function for clinical trials: The integrated Alzehiemer's Disease Rating Scale (iADRS). J Prev Alzheimers Dis. 2015;2(4):227-241. 4. Liu-Seifert H, Andersen S, Case M, et al. Statistical properties of continuous composite scales and implications for drug development. J Biopharm Stat. 2017;27(6):1104-1114. 5. Honig LS, Vellas B, Woodward M, et al. Trial of solanezumab for mild dementia due to Alzheimer's disease. N Engl J Med. 2018;378(4):321-330. 6. Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in early Alzheimer's disease. N Engl J Med. 2021;384(18):1691-1704. 7. Wessels AM, Tariot PN, Zimmer JA, et al. Efficacy and safety of lanabecestat for treatment of early and mild Alzheimer disease: The AMARANTH and DAYBREAK-ALZ randomized clinical trials. JAMA Neurol. 2020;77(2):199-209. 8. Holford NH, Peace KE. Results and validation of a population pharmacodynamic model for cognitive effects in Alzheimer patients treated with tacrine. Proc Natl Acad Sci U S A. 1992;89(23):11471-11475. 9. Samtani MN, Raghavan N, Novak G, Nandy P, Narayan VA. Disease progression model for Clinical Dementia Rating-Sum of Boxes in mild cognitive impairment and Alzheimer's subjects from the Alzheimer's Disease Neuroimaging Initiative. Neuropsychiatr Dis Treat. 2014;10:929-952. 10. Conrado DJ, Denney WS, Chen D, Ito K. An updated Alzheimer's disease progression model: incorporating non-linearity, beta regression, and a third-level random effect in NONMEM. J Pharmacokinet Pharmacodyn. 2014;41(6):581-598.

P07- IADRS: DEMONSTRATION OF CLINICAL MEANINGFULNESS BY ASSOCIATION OF HEALTH-RELATED QUALITY OF LIFE OUTCOME ASSESSMENTS.

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Background: There are noted limitations associated with the use of current assessment tools in the study of patients with early Alzheimer's disease (AD). The 2018 FDA guidance (Early Alzheimer's disease: developing drugs for the treatment), stated that an integrated scale that adequately and meaningfully assesses both daily function and cognition in early AD patients is acceptable as a single primary outcome measure. The integrated Alzheimer's Disease Rating Scale (iADRS), a composite of two widely accepted measures, the Alzheimer's Disease Assessment Scale – Cognitive Subscale 13-item version (ADAS-Cog13) and the Alzheimer's Disease Cooperative Study – instrumental activities of daily living scale (ADCS-iADL) was developed. The iADRS has been validated [1, 2], the statistical properties described [3], and it has been used as a clinical outcome measure in previous phase 2 and 3 trials in AD [4-6]. Data from the validation study [1] as well as clinical trials demonstrated the iADRS was effective in capturing clinical progression from MCI throughout moderate AD, as well as treatment effects across the early disease spectrum. Given that iADRS effectively and robustly captures decline over a broad spectrum of disease, it can be assumed that slowing clinical progression as measured by the iADRS is inherently clinically meaningful. In addition, clinical meaningfulness can also be supported by establishing an association of changes on the iADRS with changes on important domains and outcomes of disease, such as quality of life. Here we aim to understand the association between iADRS point changes in clinical trials and changes in health-related quality of life measures. **Objectives:** To assess clinical meaningfulness of treatment benefits, and the relationship of the iADRS composite measure to health-related quality-of-life measures (HRQOL). **Methods:** Data from the GERAS-EU, EXPEDITION-3 (NCT01900665) and AMARANTH (NCT02245737) studies will be used for analysis. The RUD-lite results will be used to assess the healthcare resource utilization of patients and their study partners and to determine the level of formal and informal care attributable to AD. (such as study partner time spent assisting patients with activities of daily and time spent supervising). The QOL-AD will be used to index the patients' health related quality of life. Quantile regression analysis and general linear models will be used to analyze the performance of the iADRS on these HRQOL outcomes at baseline and change from baseline to 18 months. **Results:** Estimates are still under analysis but will be presented during the scientific congress. **Conclusions:** Conclusions will be available once analyses are completed, and data is available. **References:** 1. Wessels AM, Siemers ER, Yu P, et al. A combined measure of cognition and function for clinical trials: the Integrated Alzheimer's Disease Rating Scale (iADRS). J Prev Alzheimers Dis 2015;2:227-41. 2. Wessels AM, Andersen SW, Dowsett SA, et al. The Integrated Alzheimer's Disease Rating Scale (iADRS) Findings from the EXPEDITION3 Trial. J Prev

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P08- REPEATED ADMINISTRATION OF AUTOLOGOUS ADIPOSE TISSUE-DERIVED STEM CELLS IMPROVED COGNITIVE FUNCTION IN ALZHEIMER'S DISEASE. Kazuo Shigematsu[1, 2], Kazunari Ishii[3], Naoyuki Komori[2], Kenichi Tahara[4], Hisakazu Yamagishi[5] *(1. Minami Kyoto Hospital - Joyo (Japan), 2. Nagitsuji Hospital - Kyoto (Japan), 3. Department Of Radiology, Kindai University Faculty Of Medicine - Osakasayama (Japan), 4. Takara Bio Inc - Kusatsu (Japan), 5. Kyoto Prefectural University Of Medicine - Kyoto (Japan))*

Background: Patients treated with intravenous autologous adipose stem cells (ADSCs) for the treatment of chronic obstructive pulmonary disease showed not only improvement in respiratory function but also improvement in skin amyloidosis, leading to the hypothesis that ADSCs may improve Alzheimer's disease. Based on this hypothesis, we conducted a therapeutic study of ADSC administration for Alzheimer's disease. In Japan, according to the Act on Securing Safety of Regenerative Medicine and Other Related Matters, regenerative medicine research and treatment can be carried out after approval from the Committee on Specified Regenerative Medicine and Other Related Matters and permission from the Ministry of Health, Labor and Welfare. **Objectives:** Although the safety of ADSCs has already been confirmed in ALS and COPD patients, the objective of this study is to confirm that ADSCs are safe for Alzheimer's disease patients and to evaluate the effects on cognitive function and changes in β-amyloid and p-tau. ADSCs have neprilysin activity, which is a β-amyloid-degrading enzyme, and intravenously administered ADSCs cross the blood-brain barrier and accumulate in brain lesions. When β-amyloid is degraded and removed, other characteristics of ADSCs, such as nerve repair, anti-inflammatory effects, secretion of various growth factors, and improved blood flow, may improve cognitive function. **Methods:** Three patients with Alzheimer's disease who had β-amyloid in the brain confirmed by amyloid PET had about 10 g of abdominal subcutaneous adipose tissue collected under local anesthesia. After culturing in a medium containing no serum from others, 5-9x10^7 ADSCs were administered intravenously 5-6 times at approximately 1-month intervals. Before the start of treatment (baseline) and approximately every month after each treatment, neurological findings, cognitive function assessment, and interviews from caregivers and the patients were conducted. Blood tests, respiratory function tests, MRI, and electrophysiological tests were performed as appropriate. Safety was checked for at least 3 months after the last dose. Written consent was obtained from all patients or surrogates in advance. Approval was obtained from the Ethics Committee of the implementing medical institution. In compliance with the Act on Securing the Safety of Regenerative Medicine and Other Related Matters, the therapeutic research was conducted after receiving approval from the Special Committee for Regenerative Medicine, Kouseikai Takeda Hospital specific authorized regenerative medicine and notifying the Ministry of Health, Labour and Welfare. **Results:** All patients were conscious, ambulatory, and had no depressive tendencies during the entire course of treatment. No adverse events, including any abnormal changes in blood laboratory values, were observed. After administration of ADSCs, one patient recalled being in a sorority in school. Another patient started to work in a field near his house, which he had been unable to do, and was able to return home by himself from the field without wandering. The other didn't get any worse, at least from the family's point of view. The pre-treatment Clinical Dementia Ratings were 2, 3, and 3, respectively, and the Montreal cognitive assessments (MoCA) were 10, 5, and 3, respectively. The MoCA scores changed with each ADSC treatment: 19, 23, 23, 22, 22, 20 in case 1, 5, 8, 6, 7, 8, 10 in case 2 and 5, 7, 8, 9, 11, 7 in case 3. Amyloid PET showed a decrease in beta-amyloid in one patient, almost no change in one patient, and an increase in the other patient. The course of tau PET also showed a corresponding change. There was no headache, disorientation, nausea, vomiting, tremor, or gait disturbance, and no amyloid-related imaging abnormalities (ARIA) on MRI. **Conclusion:** Intravenous administration of ADSCs could be safely repeated in patients with Alzheimer's disease. No adverse effects were observed. No worsening of symptoms was observed during the course of the study. Although the lack of a control group and the small number of cases in this study are insufficient to verify the efficacy of this treatment, the MoCA and interview results suggest that this treatment is promising. The reduction in β-amyloid, even in one case, may also be of some significance. In addition, it is interesting to note that the change in p-tau corresponded to the change in β-amyloid. ADSCs may enter the brain and affect both β-amyloid, which is deposited outside neurons, and p-tau, which is deposited inside neurons. Cognitive function may be improved by ADSCs administration. However, changes in cognitive function may not necessarily be related to β-amyloid or p-tau deposition. This therapeutic study provides a rationale and feasibility for future validation studies. **Conflicts:** none

P09- THE INFLUENCE OF LEVEL OF EDUCATION ON INSTRUMENTAL ACTIVITIES OF DAILY LIVING IN PATIENTS WITH ALZHEIMER'S DISEASE. Carina Wattmo *(Clinical Memory Research Unit, Department Of Clinical Sciences, Malmö, Lund University - Malmö (Sweden))*

Background: According to the "brain-reserve hypothesis" in Alzheimer's disease (AD), patients with more years of education are expected to have higher cognitive status during adulthood. Hence, they might have a relatively larger burden of AD pathology and a more advanced level of the disease when dementia is clinically evident. Higher educated people would also be expected to perform better on standardized cognitive tests that use a single threshold to identify dementia, such as Mini-Mental State Examination (MMSE). These factors might lead to a later manifestation of the typical symptoms of AD and detection of the disease. Thus, diagnosis and treatment might occur in a later stage, which may impair the results of AD therapy. The period in which higher educated individuals experience clinical AD might be shortened, with faster disease progression and earlier death. A higher education level has been associated with more rapid cognitive decline in several studies; however, the relationships between functional abilities and education are less investigated. **Objectives:** This long-term study aimed to investigate the potential associations between years of education and aspects of Instrumental Activities of Daily Living (IADL) capacity in AD. **Methods:** The

Swedish Alzheimer Treatment Study (SATS) is a prospective, observational multicenter study used for assessing longitudinal effectiveness of cholinesterase inhibitor (ChEI) treatment in a routine clinical setting. Among the 1,258 outpatients clinically diagnosed with probable or possible AD, 1,021 had mild-to-moderate AD (MMSE score, 10–26) at the start of ChEI therapy (baseline). Of these, 767 individuals had lower (<=9 years) and 252 had higher (>9 years) education level, and education level was missing for 2; thus, 1,019 patients were enrolled in the present study. Participants were assessed for cognitive (MMSE) and functional performance (IADL and Physical Self-Maintenance Scale [PSMS]) at baseline and every 6 months for 3 years. The date of death was recorded over 20 years. Cox proportional-hazards regression was used to determine characteristics that affected survival: sex, number of apolipoprotein E ε4 alleles, solitary living, duration of AD, age at baseline, specific concomitant medications, and cognitive and functional abilities at baseline and their rates of deterioration. **Results:** The IADL status at baseline was worse in patients with lower education than those with higher education, mean (95% confidence interval [CI]) 16.3 (15.9–16.7) vs. 14.9 (14.2–15.6) points, $p < 0.001$. The higher educated group demonstrated faster IADL progression, but not cognitive decline, from the 24-month assessment and onwards ($p < 0.011$). The IADL capacity was already markedly impaired at baseline; about 45–65% of the participants with higher education and 55–75% of those with lower education were dependent on assistance to perform these activities (IADL score, 2–5). The percentage of patients with impairment in the individual IADL items: "ability to use telephone," "shopping," "mode of transportation," and "responsibility for own medications" and "ability to handle finances," was significantly lower at baseline in the higher educated cohort. After 3 years, the IADL capacity had deteriorated further; 70–90% of the remaining participants still living at home in both groups could not perform these tasks independently. No significant difference in any of the individual IADL items was found between the groups. Thus, the patients with higher education showed faster deterioration in the abovementioned tasks during the 3-year study. After 20 years of follow-up, 733 (96%) of the participants with lower education and 231 (92%) of those with higher education had died, $p = 0.017$. Patients with lower education were older at death than those with higher education, mean (95% CI) 82.9 (82.4–83.3) vs. 80.2 (79.2–81.2) years, $p < 0.001$). In the Cox regression models, risk factors for shorter lifespan in all individuals were male sex, older age, and faster basic ADL progression. In the lower educated cohort, use of antidiabetics or antihypertensive/cardiac therapy, worse cognitive or basic ADL capacity at baseline, and more rapid cognitive decline were independently observed to decrease survival time. In participants with higher education, lower IADL performance at baseline predicted shorter life expectancy. **Conclusion:** The present study highlights the clinical importance of functional evaluations in AD. Participants with lower education, who were ~2.5 mean years older, had worse functional status at baseline than those with higher education; however, the higher educated group deteriorated faster over a longer time in several individual IADL items. The patients with higher education were almost 3 years younger at death, on average. Common risk factors for death, such as use of antihypertensive/cardiac therapy or antidiabetics and cognitive impairment, were found in lower educated, but not in higher educated individuals. IADL capacity at baseline was an important predictor of survival in participants with higher education only. These results indicate that the consequences of dementia, such as cognitive and functional outcomes and comorbidities, have different impacts on the course of AD and prognosis in patients with various levels of cognitive reserve.

P10- LOW-DOSE WHOLE BRAIN RADIATION THERAPY FOR EARLY ALZHEIMER'S DEMENTIA: EARLY RESULTS FROM A PHASE IIA TRIAL. Leland Rogers[1], Sarah Lageman[2], John Karis[3], Minesh Mehta[4], James Fontanesi[5] *(1. Gammawest Cancer Services - Salt Lake City, Ut (United States), 2. Virginia Commonwealth University - Richmond, Va (United States), 3. Barrow Neurological Institute - Phoenix, Az (United States), 4. Miami Cancer Institute - Miami, Fl (United States), 5William Beaumont Hospital - Auburn Hills , Mi (United States))*

Background: Based upon favorable clinical outcomes in patients with systemic amyloidosis treated with low-dose radiation therapy (RT), and also upon improvements in amyloid burden and cognition in murine Alzheimer's models, we launched a human trial of low-dose whole brain RT (LD-WBRT) for early AD defined by NINCDS-ADRDA criteria. Florbetapir and FDG PET findings consistent with AD were also required for enrollment. **Objectives:** Pilot evaluation of neurocognitive, imaging, and safety outcomes from a phase IIa trial of LD-WBRT for early Alzheimer's dementia (eAD). **Methods:** Patients with a clinical diagnosis of dementia consistent with eAD defined by NINCDS-ADRDA criteria were further evaluated for trial enrollment. Neurocognitive function (NCF), psychological function (PF), and quality of life (QOL) assessments were measured and evaluated. NCF was measured using a battery of validated assessments (WTAR, MMSE-2, HVLT-R, BVMT-R, WAIS-IV Digit Span and Coding, Trailmaking Parts A+B, COWAT, Semantic Fluency, and Grooved Pegboard, BNT, and JLO), PF via PHQ-9 and GAD-7, and QOL with QOL-AD and QUALID. Participant and informant ratings of cognition were documented using ECOG questionnaires. Participants underwent a screening physical examination, and screening as well as pre-treatment NCF, PF and QOL assessments. The capacity to complete these assessments was required for study enrollment, as were screening Florbetapir and FDG PET imaging with confirmatory findings. Each patient received LD-WBRT (2Gyx5). Post-treatment evaluations included 6wk, 3mo, 9mo, and 12mo physical exams, NCF, PF, and QOL assessments (BNT and JLO only at baseline and 12mo), and 6mo FDG and Florbetapir PET. Toxicities were assessed at each visit. Additionally pre-planned Data Safety and Monitoring Committee (DSMC) evaluation was performed per protocol. We anticipated, as a function of the natural history of the disease, that learning and memory as well as naming skills would decline somewhat over a year in early AD, while other neurocognitive functions would largely remain stable. The other cognitive domains were evaluated to rule out more advanced AD, and to evaluate for adverse events of radiation therapy. **Results:** Five patients (2 male, 3 female, median age 73.2 years, age range 69-77 years) with eAD were treated with LD-WBRT (2Gy x 5). Every patient completed all study assessments. Comparing pre-treatment and 12-month MMSE-2 T-scores, 3 patients improved, 1 remained stable, and only 1 declined. Skills expected to wane in early AD (naming, learning & memory) remained broadly stable at 1 year in 4 of 5, with trends for improved verbal learning in 3 participants. The one participant who declined in these measures and on Grooved Pegboard and Semantic Fluency, met the lowest-end inclusion criteria and was the oldest, 77 years at the time of study entry. BVMT-R learning and memory, generally stable over time, improved in 1 patient, with numeric

improvements from 9 to 12 months observed in each patient. Processing speed (Grooved Pegboard, WAIS-IV Coding, Trailmaking A), attention (WAIS-IV Digit Span), visuospatial skills (JLO, BVMT-R Copy), executive functions (Trailmaking A+B, lexical fluency), mood (PHQ-9, GAD-7) and QOL (QOL-AD, QUALID, ECOG) assessments remained stable, with the exception of some declines in semantic fluency suggestive of temporal lobe dysfunction. All 5 patients showed improvements in several domains at 9 to 12 months. Patient-reported QOL (QOL-AD, QUALID, ECOG) assessments remained stable, as did informant-reported assessments. Additionally, PET imaging remained stable with possible modest improvements in hippocampal amyloid and parietotemporal FDG. Results were independently reviewed by the Data Safety Monitoring Committee, and no safety issues other than transient epilation were encountered. **Conclusion:** Four of the initial 5 patients with eAD treated with LD-WBRT experienced stability to improvement in MMSE-2, naming and learning & memory scores, stability in executive function, processing, mood, and QOL, and stability to possible improvement in PET imaging. We are now seeking to open a phase III trial with randomization between observation and LD-WBRT. Follow-up beyond 1-year will be required to determine whether improvements in several functional domains at 9 to 12 months and possible improvements in imaging are sustained.

P11- AMBAR TREATMENT EFFECT SIZE COMPARED TO MONOCLONAL ANTIBODY STUDY EFFECT SIZES. Samuel Dickson[1], Suzanne Hendrix[1], Jessie Nicodemus Johnson[1], Miquel Barcelo[2], Merce Boada[3,4], Oscar Lopez[5], Laura Nunez[2], Carlota Grifols[2], Antonio Paez[2] *(1. Pentara Corporation - Millcreek (United States), 2. Grifols - Barcelona (Spain), 3. Universitat Internactional De Catalunya - Barcelona (Spain), 4. Instituto de Salud Carlos III - Madrid (Spain), 5. Universitat Internactional De Catalunya - Pittsburgh (United States))*

Background: AMBAR (Alzheimer's Management By Albumin Replacement) study demonstrated clinically relevant effect with plasma exchange and albumin replacement (PE-A) with and without IVIG across primary (ADAS-Cog and ADCS-ADL) and secondary global measures (CDR-SB and ADCS-CGIC). Statistically significant effects were seen in the primary model for ADCS-ADL, CDR-SB and ADCS-CGIC. **Objectives:** In this study we compare the statistical evidence on these measures to AD comparator trials, specifically Aducanumab (ENGAGE)1, Aducanumab (EMERGE)1, BAN2401 (Study 201)2, Solanezumab (Expedition 1-3)3,4, Gantenerumab (Scarlet RoAD)5, and Donanemab (TRAILBLAZER-ALZ)6. **Methods:** Comparator studies: Clinical effect sizes were collected for the studies listed above from the cited publications. AMBAR: AD patients (N=347) were randomized (1:1:1:1) to one of the three different PE-A treatments or placebo (sham PE-A). We analyzed the performance of active (pooled PE-A-treated groups) relative to placebo overall as well as stratified by mild (Baseline MMSE > 19)/moderate (Baseline MMSE <=19) status. Changes from baseline were analyzed using a mixed model for repeated measures (MMRM). **Results:** Effect size in ADAS-Cog ranged from 34.8% slowing in the Sola Expedition 1+2 mild individuals to 62% slowing in the AMBAR moderate individuals. ADCS-ADL ranged from 15.4% slowing (Sola Expedition 3) to 63.5% slowing in AMBAR moderate individuals. CDR-SB ranged from 15.4% (Sola Expedition 3) to 53.7% slowing (AMBAR moderate individuals). However, among the nine clinical trials and subgroups compared in this study only 2 (AMBAR-moderate population and EMERGE) reached significance on all 3 clinical outcomes and their comparison shows the AMBAR clinical effect sizes are 35%, 24%, and 30% larger than Aducanumab EMERGE for ADAS-Cog, ADCS-ADL, and CDR-SB respectively. **Conclusions:** Overall, the statistical support for AMBAR PE-A was comparable to the comparator studies for all 3 clinical measures, however comparison of clinical effect sizes indicated the AMBAR treatment was substantially more robust for all 3 clinical measures. Literature Cited: 1. Haeberlein, S. B. et al. Emerge and Engage topline results: Phase 3 studies of aducanumab in early Alzheimer's disease. Alzheimer's Dement. 16, 47259 (2020). 2. Swanson, C. J. et al. Dt-01-07: Treatment of Early Ad Subjects With Ban2401, an Anti-Aβ Protofibril Monoclonal Antibody, Significantly Clears Amyloid Plaque and Reduces Clinical Decline. Alzheimer's Dement. 14, P1668–P1668 (2018). 3. Doody, R. S. et al. Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease. N. Engl. J. Med. 370, 311–321 (2014). 4. Siemers, E. R. et al. Phase 3 solanezumab trials: Secondary outcomes in mild Alzheimer's disease patients. Alzheimer's Dement. 12, 110–120 (2016). 5. Ostrowitzki, S. et al. A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. Alzheimer's Res. Ther. 9, (2017). 6. Mintun, M. A. et al. Donanemab in Early Alzheimer's Disease. N. Engl. J. Med. 384, 1691–1704 (2021).

LP01- VALIDATION OF THE LEARNING RATIO DERIVED FROM THE RAVLT IN EARLY-ONSET ALZHEIMER'S DISEASE FROM THE LEADS STUDY. Dustin Hammers[1], Taylor Diedrich[1], Sara Nemes[1], Ani Eloyan[2], Joel Kramer[3], Paul Aisen[4], Maria Carillo[5], Bradford Dickerson[6], Gil Rabinovici[3], Liana Apostolova[1], Leads Leads Consortium[1] *(1. Indiana University - Indianapolis (United States), 2. Brown University - Providence (United States), 3. University Of California San Francisco - San Francisco (United States) - San Francisco (United States), 4. University Of Southern California - Los Angeles (United States), 5. Alzheimer's Association - Chicago (United States), 6. Mass General Brigham Harvard - Boston (United States) - Boston (United States))*

Background: The Learning Ratio (LR) is a novel learning slope score that was developed to identify learning more accurately by considering the proportion of information learned after the first trial of a multi-trial learning task. Specifically, instead of traditional learning slope scores that are calculated as some derivation of the difference in learning between the final trial and the first trial, LR is calculated as the number of items learned after trial one divided by the number of items yet to be learned. In dividing by the information left-to-learn, this metric incorporates the opportunity for future learning in its calculation of learning slope, which varies depending upon an individual's success at Trial 1 (e.g., individuals obtaining higher scores at Trial 1 have fewer items available for subsequent learning). The final score reflects the percent of available information learned after Trial 1. **Objectives:** Although research on LR in samples of late-onset Alzheimer's disease (LOAD) has been promising, little to no information on LR in the context of early-onset Alzheimer's disease (EAOD) exists. Therefore, the goal of this study was to establish criterion validity for this LR metric by showing (1) that its performance is negatively impacted in more severe disease states associated with EOAD, and (2) that it outperforms traditional learning slope scores in EOAD. **Method:** Data from 314 older participants from the multi-center Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) were included in the current analyses. Overall, participants were classified as being cognitively normal (CN; n = 82), amyloid-positive EOAD (n = 168), and amyloid-negative

Early-Onset Non-Alzheimer's Disease (EOnonAD; n = 64). All learning slope scores were derived from the Rey Auditory Verbal Learning Test (RAVLT), which is a verbally-presented list-learning task of 15 items repeatedly presented across five learning trials. Calculations of the learning slopes for each participant were as follows: the raw learning score (RLS) equaled the Highest Trial score (of Trials 2 through 5) – Trial 1 score, the learning over trials (LOT) score was computed as the sum of Trials 1 through 5 minus the value of Trial 1 multiplied by 5, and LR was calculated as RLS / (Maximum trial score possible – Trial One score). Trial 1 score – another common measure of learning – was the number of items obtained during Trial 1. Learning slopes and scores were compared between diagnostic groups using analysis of covariance with an alpha of .01, and comparison between learning values was conducted by converting effect sizes to Cohen's d and examining the overlap of 95% Confidence Intervals (CIs). **Results:** Significant differences existed between groups for demographic variables of age, education, sex, and ethnicity. Specifically, the CN group was older than the EOAD group (ps < 0.001), and the CN group was more highly educated (ps < 0.001), female (p = 0.004), and ethnically diverse (p < 0.001) than both the EOAD and EOnonAD groups. When controlling for age, education, sex, and ethnicity, significant differences were observed between groups for all learning scores: LR (p < 0.001, Cohen's d = 1.94), RLS (p < 0.001, Cohen's d = 1.39), LOT (p < 0.001, Cohen's d = 1.41), and Trial 1 (p < 0.001, Cohen's d = 1.26). For LR, RLS, and LOT, CN participants performed better than EOnonAD participants, who performed better than EOAD participants (all ps < .001). For Trial 1, CN participants performed better than both EOnonAD and EOAD participants (all ps < .001), but statistical difference between EOnonAD and EOAD participants did not remain after correcting for multiple comparisons (p = .02). Upon direct comparison, the magnitude of the omnibus effect for LR (Cohen's d 95% CIs = 1.75 – 2.13) was stronger than for RLS (Cohen's d 95% CIs = 1.21 – 1.56), LOT (Cohen's d 95% CIs = 1.24 – 1.59), and Trial 1 (Cohen's d 95% CIs = 1.09 – 1.43). Comparable results were observed when comparing between CN and EOAD groups (LR Cohen's d 95% CIs = 2.15 – 2.61; RLS Cohen's d 95% CIs = 1.43 – 1.84; LOT Cohen's d 95% CIs = 1.43 – 1.84; and Trial 1 Cohen's d 95% CIs = 1.18 – 1.57). **Conclusions:** These results provide evidence of criterion validity for the novel learning slope calculation LR, by establishing that LR performances derived from the RAVLT are consistently worse in more severe disease states. Examination of 95% CIs additionally indicates that this effect is greater for LR than for the traditional learning metrics assessed, above and beyond the impact of demographic variables. Further, our findings suggest that LR possesses utility for measuring learning in participants with EOAD, which is similar to previous research in LOAD samples. Future investigation is encouraged to assess other forms of validity of LR in EOAD (e.g., convergent validity) to more thoroughly consider the incorporation of the RAVLT LR into clinical decision making. No conflicts are necessary to report.

LP02- SENSITIVITY OF THE PRECLINICAL ALZHEIMER'S COGNITIVE COMPOSITE (PACC), PACC5, AND REPEATABLE BATTERY FOR NEUROPSYCHOLOGICAL STATUS (RBANS) TO AMYLOID STATUS IN PRECLINICAL ALZHEIMER DISEASE -ATABECESTAT PHASE 2B/3 EARLY CLINICAL TRIAL. Kate Papp[1], Hany Rofael[2], Amy Veroff[3], Mike Donohue[4], Shunran Wang[4], Christopher Randolph[5], Ellen Grober[6], H. Robert Brashear[7], Gerald Novak[8], Karin Ernstrom[4], Rema Raman[4], Paul Aisen[4], Reisa Sperling[1], Gary Romano[8], David Henley[9] *(1. Harvard Medical School - Boston (United States), 2. Janssen Research And Development - Titusville (United States), 3. Consultant - Bethesda (United States), 4. University Of Southern California - San Diego (United States), 5. Medavante - Hamilton (United States), 6. Albert Einstein College Of Medicine - Bronx (United States), 7. University Of Virginia - Charlottesville (United States), 8. Janssen - Titusville (United States), 9. Indiana University School Of Medicine - Indianapolis (United States))*

Background: Cognitive composites commonly serve as primary outcomes in Alzheimer's disease (AD) secondary prevention trials. **Objective:** The objective of this study was to evaluate the association between amyloid (Aβ) burden level (+/-) and performance on three separate composite endpoints: the Preclinical Alzheimer's Cognitive Composite (PACC), the PACC plus semantic fluency (PACC5), and the Repeatable Battery for Neuropsychological Status (RBANS). **Methods:** Screening data from the randomized, double-blind, placebo-controlled phase 2b/3 atabecestat EARLY study in participants with preclinical AD was used in this analysis. The EARLY study was conducted at 143 centers across 14 countries. 3,569 cognitively unimpaired older adults with Clinical Dementia Rating global score = 0 were screened for inclusion in the EARLY study. Participants were divided into those with non-pathological Aβ levels (Aβ-, n=2824) and those with pathological levels of Aβ (Aβ+, n=745) based on florbetapir uptake or levels of cerebrospinal fluid (CSF) Aβ1-42.Analysis of Covariance models controlling for age, sex, and education were used to examine the difference in PACC, PACC5, and RBANS between Aβ groups. The nonparametric bootstrap was used to compare sensitivity of composites to differentiate between Aβ status. **Results:** Of 3,569 participants, 2,116 were women (59%), 3006 were Caucasian (84%), and mean (SD) age was 68.98 (5.28) years. Aβ+ participants performed worse compared with Aβ- participants on each of the cognitive composites though the magnitude of the Aβ effect was generally small. The Aβ+/- effect size for the PACC (Cohen's d=-0.15) was statistically significantly greater than that for the RBANS (d=-0.097) while the PACC5 effect size (d=-0.139) was numerically larger than that for the RBANS. When examining subscores from the composites, memory tests (i.e., FCSRT, Visual Reproduction) and speeded processing (i.e., Digit-Symbol/ Coding on the PACC/ RBANS) exhibited the largest Aβ+/- effect sizes. **Conclusions:** Cross sectional relationships between Aβ and cognition among clinically unimpaired older adults are detectable on multi-domain cognitive composites but are relatively small in magnitude. The Aβ+/- group effect was statistically larger for PACC and marginally larger for PACC5 as compared with the RBANS. However, interpretation of composite sensitivity to Aβ status cross-sectionally cannot be generalized to sensitivity to change over time.

RP04- IMPROVING SCREENING EFFICIENCY THROUGH ALTERNATE STORY RECALL. Thomas Doherty[1], Robert Smith[2], Michael Smith[3], Shau-Yu Lynch[4], Jeri Morris[5], Chad Swanson[4] *(1. Worldwide Clinical Trials - London, England (United Kingdom), 2. Worldwide Clinical Trials - Canet, France (United Kingdom), 3. Worldwide Clinical Trials - Charlotte, Nc (United Kingdom), 4. Eisai Inc. - Woodcliff Lake, Nj (United States), 5. Roosevelt University Chicago - Chicago, Il (United States))*

Background: CLARITY AD is an 18-month treatment (core study), multicentre, double-blind, placebo-controlled, parallel-group study with open-label extension in subjects with early AD. To be eligible for the study, subjects must have objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the Wechsler Memory Scale IV-Logical Memory (WMS-LMII). Finding impairment in line with trial eligibility requirements is often challenging. Utilising a psychometric measure that is concordant, prior to screening into a clinical trial, greatly reduces the likelihood of a patient screen failing at an initial study visit on cognitive scales. Prior work has shown the validity of an alternate form of the WMS-LM, often termed the Morris paragraphs. The alternate Morris paragraphs were developed in concordance with the phonetic and psychometric principles applied to the original WMS story recall. Subsequently these versions were translated into US/ Central American Spanish as well as cultural adaptations for the UK, Australia & Canada. Each of these new versions was completed and validated by the original author. **Objectives:** The purpose of this study is to evaluate the utilisation of the alternate Morris paragraphs as a pre-screening tool for the Clarity AD and its impact on the WMS-LMII screen failure rates. **Methods:** Validated versions of the alternate Morris paragraphs, appropriate for country and primary language, were given to sites participating in the Clarity AD program for use prior to consent. Sites staff were trained on the alternate Morris paragraphs by trained neuropsychologists. No prior experience of scales was mandated for those administering this measure. Sites were instructed to assess potential subjects four weeks prior to the undertaking of screening procedures for Clarity AD. Subsequently, at the investigator's discretion, but primarily based upon scores on this measure, subjects were then consented, and formally screened for the Clarity AD study, whereby they underwent cognitive testing on the WMS-LMII. Screen failure rates were compared pre and post implementation of the alternate Morris paragraphs, for sites that utilised it within this program. Analysis of the comparison of the psychometrics properties of the alternate Morris paragraphs and the WM-LMII, comprised of t-tests, correlation analyses and Bland and Altman plots. **Results:** Approximately 679 subjects did not progress to screening for Clarity AD as a result of their score on the alternate Morris paragraphs. Overall 197 subjects progressed and were screened on Clarity AD having been pre-screened previously on the alternate Morris paragraphs. The overall results of implementing this measure prior to screening resulted in a 11% (40%-29%) reduction in the 4-month moving average of the screen failure rate on the WMS-LM II. Site level reductions in screen failures on this measure were also down by an average of 13%. Psychometric analysis showed significant differences between the delayed recall from the alternate Morris paragraph and from the logical memory stories ($t(1,195) = -4.59$, $p=0.0001$). Correlation analysis revealed a significant, yet moderate, positive relationship between the two measures of delayed recall ($r=0.64$). Subjects scored nearly 2 points higher on the logical memory as compared to the similar AP measure however, relative differences among subjects were similar. Further analysis utilising Bland & Altman (1968) methods of agreement showed reasonable agreement between these two measurements with a mean difference (MD) of -1.73 points, an upper limit of agreement (ULOA) of 8.63 and a lower limit of agreement (LLOA) of -12.1. **Conclusion:** Overall, the purpose of implementing this measure was achieved by reducing the screen fail rates at these sites who underwent training and subsequently implemented this measure as part of their pre-screening process. These reductions in screen failures validate the use of this measure within this context for sites to find suitable impairment on the WMS-LMII. By placing the WMS-LMII at the start of the screening process and implanting the alternate Morris paragraphs prior to this, screening efficiency was enhanced. This current study demonstrates the concurrent fundamental underlying constructs between the Morris alternate paragraphs and the WMS-LMII and shows the applicability of the use of the Morris alternate paragraphs in future screening procedures. **Conflict of interests:** TD, RS & MTS are employees of Worldwide Clinical Trials. CS, SYL are employees of Eisai & Jeri Morris is an employee of Roosevelt University Chicago

CLINICAL TRIALS: IMAGING

P12- AN AUTOMATED MRI FACE-REMOVAL PIPELINE TO ANONYMIZE PATIENT SCANS FOR CLINICAL TRIALS. Lukasz Kidzinski[1], Thomas Cajgfinger[2], Kevin Thomas[1], Luc Bracoud[2], Po-Han Chen[3], Shao-Yu Lin[3], Joonmi Oh[1], Chun-Chiang Shen[3], Chris Conklin[4], Joël Schaerer[2], David Scott[1], Joyce Suhy[1] *(1. Bioclinica - San Mateo (United States), 2. Bioclinica - Lyon (France), 3. Bioclinica - Taiwan (Taiwan, Province of China), 4. Bioclinica - Princeton (United States))*

Background: MRI data are collected throughout clinical trials to determine patient's eligibility, monitor their safety and assess treatment efficacy via quantitative analyses. While patient safety is of utmost importance, data privacy is of equal importance. Scientific and public attention was raised some years back that using modern face-recognition software in combination with 3D MRI data, determining patient's identity may be possible [i], [ii].The aim of this work was to create a pipeline to automatically blur patient's face, preventing automated facial recognition without impacting neither clinical diagnosis nor quantitative analyses. **Methods:** To blur the face without affecting other structures, our procedure consisted of three steps: segmentation of the brain, identification of a cut-off plane and finally blurring: - For brain segmentation, we use a U-Net inspired segmentation network trained on 359 brain volumes from the Calgary-Campinas-359 dataset [iii]. - For identifying a cut-off plane, we take a convex hull of 2D brain mask projected on the sagittal plane and find a line anterior to the brain [iv]. We find the plane perpendicular to the sagittal plane, crossing the cut-off line. - Voxels on the face side of the cut-off plane are blurred, while those on the brain side remain unaltered. Face voxels are blurred proportionally to their perpendicular distance from the cut-off plane. The anterior distance between the brain and the cut-off plane is adjusted to ensure that no brain voxels are altered. The standard deviation of the gaussian blur is adjusted to protect patient identity while still enabling robust downstream analyses. Validation of the method was two-fold. First, a random sample of blurred 3D scans were overlayed on top of original scans in order to visually ensure that the privacy objective was met. Then, various analyses were repeated and compared with and without defacing. - Brain

volume analysis: 3DT1 data from 193 patients (101 Cognitively Normal, 73 MCI and 19 AD) from the ADNI-3 database (http://adni.loni.usc.edu/adni-3/), with 3 visits each (Baseline, Month 12 and Month 24) were selected. Brain volume was assessed using Freesurfer 6.0, while volume change over time (e.g. atrophy) was measured using both Boundary Shift Integral (BSI) and Tensor Based Morphometry (TBM) techniques. - PET SUVr quantification: 80 random ADNI-3 patients with MRI/PET pairs were processed, to evaluate the impact on MRI/PET registration and SUVr quantification. - Diffusion Tensor Analysis: 40 random ADNI-3 patients with 3DT1 and DTI scans were analyzed to assess the impact on 3DT1/DTI registration and DTI map quantification. To assess the impact of blurring for each endpoint, the following was checked, where relevant, between original and blurred results: - Comparability, using Pearson correlation; - Group-separation between CN, MCI and AD patients assessed by pair-wise t-tests and ANOVA; - Registration stability using Mutual information between registered data (MRI with PET, and 3DT1 with DTI); - Temporal linearity using average Pearson coefficient of longitudinal results (longitudinal R^2). **Results:** Visual QC confirmed that face blurring was not impacting brain tissue for any of the cases reviewed (N=98 scans), thus having no influence on clinical diagnosis. For brain segmentation, FreeSurfer success rate after face removal on ADNI-3 was about 99%, which is higher than without face removal. All cases that failed after face removal also failed without it. Correlation between volumes was near-perfect for all FreeSurfer structures and for the whole brain ($r>0.99$). No statistically significant differences were found before and after face blurring ($p>0.5$). Results of brain atrophy analysis showed no impact of face blurring on endpoints ($r>0.98$) for any brain structure for both BSI and TBM methods. No statistically significant differences were found ($p>0.5$). Performance metrics such as group separation or longitudinal R^2 showed no differences either. Mutual information from PET/MRI rigid registration was almost unchanged after face blurring, with no outliers ($r>0.99$) and no statistically significant differences ($p>0.5$). Correlation of whole cortex SUVr was near perfect ($r>0.99$). Mutual information from DTI/3DT1 rigid registration was also comparable before and after blurring ($r\sim0.99$) with no significant differences ($p>0.2$). White matter ADC/FA histogram statistics were again highly correlated ($r>0.99$). **Conclusions:** A fully automated pipeline for face removal of 3D T1-weighted MRI sequences was proposed. This method showed very high reliability and did not have any impact on subsequent qualitative review, as well as various quantitative assessments (analysis of brain volume and volume change over time, multi-modal registration, PET quantification, DTI analysis). These results support the deployment of this additional anonymization step whenever required as part of data sharing requirements. [i] Schwartz et al., Identification of Anonymous MRI Research Participants with Face-Recognition Software, N Engl J Med 2019; [ii] NY Times Oct. 23rd 2019, You Got a Brain Scan at the Hospital. Someday a Computer May Use It to Identify You; [iii] Lucena et al., Convolutional Neural Network for Brain MR Imaging Extraction Using Silver-Standards Masks, Artif Intell Med. 2019; [iv] Schimke et al., Quickshear defacing for neuroimages, Proceedings of the 2nd USENIX conference on Health security and privacy, 2011

P13- FREE WATER IMAGING AS A TOOL FOR UNDERSTANDING ALZHEIMER'S DISEASE.

Richard Parker, Richard Joules, Robin Wolz *(Ixico Plc - London (United Kingdom))*

Background: Diffusion MRI (D-MRI) has proved invaluable for the study of Alzheimer's Disease (AD), probing tissue structural properties at scales beyond the reach of more rudimentary MR sequences and allowing for advanced 3D modelling of nerve bundle trajectories. An emerging application of D-MRI is free water imaging – a modelling strategy that breaks the acquired D-MRI signal down into the separate contributions of the intra- and extra-cellular spaces, thereby providing a non-invasive look at how pathological processes may selectively impact these different environments. In the context of AD, it has been suggested that hallmark neuroinflammatory mechanisms may have a much greater impact upon the extra-cellular compartment, and so the free water technique may allow us to capture this particular dimension of the disease with high specificity. Here, we introduce a pipeline for the analysis of in-brain free water content via D-MRI scan data, incorporating steps for the minimisation of common artefacts (subject motion, EPI distortion, eddy currents), characterisation of intra- and extra-cellular compartments via a two-tensor fitting scheme (Hoy et al., 2014), then combination with atlas volumes to create endpoint measures for 200+ gray and white matter regions-of-interest (ROIs). In addition to being automated and configurable, the pipeline is fully-integrated into IXICO's regulatory-compliant trial management software, TrialTracker™: a web-based tool for data upload, storage, analysis and quality assessment. **Objectives:** to demonstrate pipeline validity through application to the study of Alzheimer's-type dementia. Given the putative role of neuroinflammation in AD, we hypothesised that estimates of in-brain free water content would distinguish subjects with/without dementia, with differences being localised to key AD-related structures. Additionally, we aimed to demonstrate that the process of free water correction (calculation of endpoints only from the intra-cellular portion of the D-MRI signal, producing endpoints that are better-related to the intrinsic tissue microstructure) can substantially alter the pattern of results obtained from AD/CN comparative analysis, emphasising that measurements derived from conventional D-MRI reflect an entanglement of intra- and extra-cellular diffusion effects. **Methods:** D-MRI and T1-weighted MRI for 82 cognitively-normal older adults (CN, average age=70.65, no. males=24), 45 adults with Mild Cognitive Impairment (MCI, average age=71.22, no. males=29) and 10 adults with Alzheimer's Disease (AD, average age=71.69, no. males=5) was downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. T1-weighted images were segmented into anatomical subregions, using IXICO's LEAP pipeline (Wolz, et al., 2010), before being entered into our free water pipeline alongside the unprocessed D-MRI data. ROI-averaged diffusion statistics were subsequently contrasted across the controls and AD/MCI subjects using the permutation test. Initial analysis was performed using commonly-derived diffusion tensor statistics fractional anisotropy (FA) and mean diffusivity (MD). Group comparison analysis was then repeated, but this time using variants of FA/MD that had been free water-corrected (fwcFA, fwcMD). In the second analysis we additionally compared the free water index: a measure of the relative volumes of intra and extra-cellular spaces within imaging voxels. Based on the extant literature, we restricted

analysis to 9 ROIs that have been implicated in the pathogenesis of AD and 7 control regions. Results significant at the $\alpha<.05$ were then ranked according to p-value (carried out separately for the corrected/uncorrected analyses). **Results:** CN/AD comparative analysis was supplemented by the addition of free water estimation/correction. MD in the hippocampus was the most significant difference in the uncorrected analysis, but non-significant following free water correction, suggesting that previously-reported alterations in hippocampal MD are driven by changes within the extra-cellular matrix. Accordingly, the hippocampal free water index became one of the best-ranked separators in the second analysis. A similar trend was observed for the splenium region. This trend was not universal however - for the superior longitudinal fasciculus (SLF) tract, fwcMD was one of the best-ranked separators, suggesting that intrinsic microstructural change to this white matter region is a core feature of AD. For the FA metric the pattern of informative regions remained largely the same. In both free water uncorrected/corrected analyses, significant group differences were seen in the corpus callosum (genu and splenium), SLF, fornix, and parahippocampal cingulum. Free water correction may provide subtle alteration to FA results: in the uncorrected analysis, hippocampal FA was ranked as the 12th-best significant separator. In the free water corrected analysis, hippocampal FA was one of the top separators. **Conclusions:** we present a pipeline for free water analysis and demonstrate its potential for improving the specificity Alzheimer's Disease analysis. The fully-automated nature of our pipeline, coupled with its integration into the TrialTracker platform, allows for high-throughput application in phase 2 and 3 clinical trials in a regulatory-compliant manner. **References:** Hoy, A.R., Koay, C.G., Kecskemeti, S.R. and Alexander, A.L., 2014. Optimization of a free water elimination two-compartment model for diffusion tensor imaging. Neuroimage, 103, pp.323-333. Wolz, R., Aljabar, P., Hajnal, J.V., Hammers, A., Rueckert, D. and Alzheimer's Disease Neuroimaging Initiative, 2010. LEAP: learning embeddings for atlas propagation. NeuroImage, 49(2), pp.1316-1325.

P14- IMPACT OF AGE AND APOE4 CARRIER STATUS IN SUBJECTS AT-RISK FOR AD ON MICROHEMORRHAGES, WHITE MATTER LESIONS AND BRAIN VOLUME: PRELIMINARY ANALYSES.

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Background: The apolipoprotein ε4 allele (APOE4) is a major genetic risk factor for Alzheimer's disease (AD), with APOE4 carriers comprising ~65% of AD patients. APOE4 increases beta amyloid (Aβ) monomer production, diminishes clearance and increases their aggregation into soluble neurotoxic oligomers. Homozygotes have shown high rates of fibrillar amyloid pathology, high Aβ oligomer burden, and early cognitive decline. The Generation Program comprised two pivotal phase II/III studies in a cognitively unimpaired population at increased risk for developing Alzheimer's disease based on age and APOE genotype (i.e., presence of the APOE ε4 allele). Generation Study 1 focused on APOE4 homozygotes (HM), while Generation Study 2 also allowed for APOE4 heterozygotes (HT), with an age-range of 60 to 75 years old. The program was discontinued in 2019 due to safety findings observed with the BACE inhibitor. **Objectives:** Focusing on participants at-risk for AD screened for the Generation Program studies, we aimed at studying the influence of age and APOE4 homozygosity on microhemorrhages, white matter lesions and brain volume. Note that these analyses are preliminary and will be completed by amyloid status and other clinical variables once those are cleaned and released officially. **Methods:** We included 718 HM subjects (488 screened for the Generation Study 1 and 230 for Generation Study 2) and 921 HT subjects screened for Generation Study 2. Each subject was scanned using a standardized MRI protocol, including a 3D T1-weighted sequence following ADNI-1 recommendations (MP RAGE (Siemens), 3D TFE (Philips) and 3D Fast SPGR (General Electric) with 1.25×1.25×1.2 mm3 voxel resolution) and 2D Axial FLAIR and T2* Gradient Echo sequences (5 mm slices, 0.5 mm interslice gap, 0.94×0.94 mm2 in-plane resolution, TE adjusted by field strength to homogeneize sensitivity). 3DT1 data were processed using FreeSurfer v5.3 in order to measure the volume of all brain structures as well as intracranial volume, for normalization purposes. Whole brain fraction (WBF), ventricular fraction (VF) and hippocampal fraction (HVF) were derived. FLAIR and T2* data were reviewed by blinded neuroradiologist as part of central eligility reading activities, in order to report the number of microhemorrhages (MH) and extent of white matter lesions (WML) using the Wahlund Age-Related White Matter Changes scale. WML volume was also automatically estimated using FreeSurfer WM hypoteintensities category, to benefit from a rough quantitative estimate. Relationship between age, APOE4 status, scanner field strength, and each of the variables of interest (MH, WML, WBF, VF and HVF) was studied by fitting linear models. Correlations between age and each variable of interest were analyzed by Pearson's correlations, for HM and HT separately. **Results:** 89% of HT subjects presented with no microhemorrhages, as opposed to 87% HM subjects. 99% had 4 microhemorrhages or less irrespective of APOE4 status. Age and APOE4 status were significant predictors of microhemorrhage count. Thanks to TE adjustment across field strength, no significant difference was observed between 1.5T and 3T scanners. Number of microhemorrhages was weakly associated with age ($r=0.11$, $p=0.02$) for HM subjects. For HT subjects, microhemorrhages weren't associated with age. Age, APOE4 status and field strength were all significant predictors of WML extent. White matter lesion extent showed a weak correlation with age ($r=0.13$ to 0.27, $p<0.001$), both for HM and HT subjects, irrespective of field strength. WML volume results showed a moderate correlation to ARWMC score ($r=0.5$, $p<0.001$) and confirmed the associations. Whole brain, ventricles and hippocampus all showed weak to moderate correlations to age ($r=0.19$ to 0.42, $p<0.001$), both for HM and HT subjects, irrespective of field strength. One exception was HVF at 1.5T, showing no relationship to age. Age and HM status were significantly associated to larger ventricles and smaller hippocampi, when looking at subjects scanned at 3T (Adjusted $R=0.26$ to 0.31, $p<0.001$). **Conclusions:** The Generation Program is the largest cohort to date of APOE4 homozygotes and heterozygotes. While this program was discontinued, this population remains a valid target to learn from for new disease-modifying therapies and prevention trials. Results presented here confirmed the hypothesis that APOE4 homozygotes exhibit more advanced neurodegeneration. Nevertheless, further analyses also accounting for amyloid status should complement current analyses to validate this conclusion.

P15- TOWARDS COMPUTER-ASSISTED DETECTION OF ARIA-E OCCURRENCE. Thomas Cajgfinger[1], Luc Bracoud[1], Derk Purcell[2], Joël Schaerer[1], Marco Lyons[3], Szofia Bullain[3], Jakub Wojtowicz[4], Chris Conklin[5], David Scott[6], Joyce Suhy[6], Gregory Klein[4] *(1. Bioclinica - Lyon (France), 2. California Pacific Medical Center - San Francisco (United States), 3. Roche/genentech Product Development, Neuroscience - Basel (Switzerland), 4. Roche Pharma Research And Early Development - Basel (Switzerland), 5. Bioclinica - Princeton (United States), 6. Bioclinica - San Mateo (United States))*

Background: Amyloid-Related Imaging Abnormalities, also known as ARIA, are radiologic concepts, which were introduced after the detection of unexpected edema-like phenomena (ARIA-E) and/or hemosiderin deposits (ARIA-H), in participants of Alzheimer's disease clinical trials exposed to amyloid-modifying therapies in the early 2010's. A decade later, we are starting to understand the pathophysiology of these imaging findings. With the first FDA-approval of a novel therapy targeting amyloid beta plaques, together with the development of several other promising candidates, ARIA may be under increased scrutiny, as although these phenomena are mostly transient and asymptomatic, they require careful monitoring and prompt identification in order to control for and prevent potentially deleterious effects. In all clinical trials to date where subjects were at-risk for ARIA, highly specialized, blinded, central neuroradiologist readers have been involved in the safety monitoring of the scheduled MRI scans, which aimed at revealing the presence of ARIA, even in the absence of symptoms. While the most severe ARIA cases are radiologically obvious and would be readily identified in association with such treatment, more subtle presentations are common and require specific expertise for early detection. Should non-specialized radiologists contribute to this safety monitoring when treatments are administered at a larger scale, any tool that will aid the detection of the more subtle findings could be highly beneficial. To aid real-world monitoring of ARIA, we aimed at applying modern Artificial Intelligence-based techniques, which are the state-of-the art methods for efficient lesion detection in various therapeutic areas, in order to automatically flag cases exhibiting ARIA-like patterns. **Methods:** T2-FLAIR, T2*-Gradient Echo (5 mm axial slices, no gap, 256×256 matrix) and 3D T1-weighted (Sagittal, 0.98×0.98×1.20 to 1.20×1.20×1.20 mm3 resolution) MRI sequences from 501 participants from the Marguerite RoAD and Scarlet RoAD gantenerumab studies (NCT02051608 and NCT01224106) were selected, each with a Screening scan and a total of 1229 follow-up scans (282 with ARIA-E, and 947 without). ARIA samples were selected to have a balance of ARIA-positive and negative cases, and do not represent the ARIA rate from the studies. Semi-automated segmentation of ARIA-E was performed by a single trained neuroradiologist, using intensity-based drawing and editing tools. Bounding boxes of these delineated areas were automatically derived. Two different approaches were then engaged, after randomly splitting these input data into training and validation sets: - Method 1: 3D Deep Learning algorithm (DeepMedic) on 3DT1 and FLAIR images to segment ARIA lesions, trained on visits with and without ARIA-E lesions. Any lesion whose volume is larger than a pre-determined threshold (based on the maximum Youden's index of the ROC curve of the validation set) is considered as an ARIA-E candidate. - Method 2: 2D Deep Learning algorithm (RetinaNet) to find bounding boxes of ARIA-E lesions on FLAIR slices. Predicted bounding boxes are filtered using the probabilities given by the algorithm. Presence of ARIA-E is determined when at least one slice contains a predicted lesion whose probability is above a pre-determined threshold (same strategy as above). Algorithm performance was assessed using Dice coefficient (relevant for DeepMedic only, in order to estimate the ability to automatically match radiologist delineations, which is beyond simple detection) and ROC curves (to assess optimal sensitivity and specificity of each method). **Results:** Dice results of the DeepMedic method were quite modest (39%), illustrating the fact that defining clear boundaries is a challenging and somewhat subjective task, in particular for the ARIA-E subtype consisting mainly of swelling (as opposed to parenchymal and/or sulcal edema) or when edema borders are diffuse. Nevertheless, AUC from the ROC was encouraging (0.942, Sensitivity = 95.7%, Specificity = 81.8%). Coming to the RetinaNet approach, AUC from the ROC was a little lower (0.909, Sensitivity = 86.5%, Specificity = 87.5%). As expected, false negative cases corresponded to subtle findings with very focal and faint areas of hyperintensity. It was determined via various experiments that the most efficient pre-processing steps consisted of bias field correction and brain extraction. Attempts at adding T2* GRE data into the model did not help detection further. **Conclusions:** An AI-based framework was developed in order to help pre-detect the occurrence of ARIA-E on FLAIR MRI scans. While results are promising, detection of the most subtle cases remains a challenge, which untrained radiologists may also face in a real-world setting. Expanding the training set to a larger cohort of subjects may help improve detection accuracy further.

P16- ALLOPREGNANOLONE AS A REGENERATIVE THERAPEUTIC FOR ALZHEIMER'S DISEASE: PHASE 2 PROOF-OF-CONCEPT CLINICAL TRIAL USING HIPPOCAMPAL VOLUME AS A SURROGATE ENDPOINT. Gerson Hernandez[1], Lon Schneider[2], Dawn Matthews[3], Kathleen Rodgers[1], Claudia Lopez[1], Yvette Wang[1], Adam Raikes[1], Gary Cutter[4], Roberta Brinton[1] *(1. Center For Innovation In Brain Science, University Of Arizona - Tucson (United States), 2. Keck School Of Medicine Of Usc - Los Angeles (United States), 3. Adm Diagnostics - Chicago (United States), 4. Uab School Of Public Health - Birmingham (United States))*

Background: In clinical trials much emphasis has been given to the biomarkers that are specific for hallmark Alzheimer's disease (AD) proteinopathies and consequently have been used as therapeutic targets. For drugs that target neurogenesis and neuroprotection, imaging biomarkers play increasingly important roles in assessing drug effects and target engagement. Brain imaging biomarkers are definitive indicators of neurodegeneration or neuronal injury and are used for staging severity of AD. Brain atrophy throughout the process of AD is well documented with the temporal lobe and hippocampus affected early in the degenerative process. Whole brain and hippocampal atrophy detected by magnetic resonance imaging (MRI) are widely used biomarkers for diagnosis and assessment of disease progression in AD. The association between hippocampal atrophy and AD is supported by substantial clinical, imaging and pathological evidence and hence measures of change over time in hippocampal volumetric structures are considered reliable predictors of future cognitive decline and further progression to AD. The value of hippocampal volume imaging measures has been noted by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) which have validated and accepted hippocampal volume as an imaging biomarker suitable for the purpose of aiding in the design of clinical trials in mild to moderate AD. Given that

hippocampal volume is a well-established imaging biomarker predictive of cognitive decline although not itself a measure of cognition, we propose its use as a surrogate endpoint to test the efficacy of allopregnanolone as a regenerative therapeutic for mild AD. **Objectives:** 1) To conduct a phase 2 clinical trial using rate of change in hippocampal volume as a surrogate endpoint to test the efficacy of allopregnanolone as a regenerative therapeutic for mild AD. 2) To assess change in cognition and function. 3) To assess change from baseline in neuroimaging markers: key AD brain structure volumes, white matter tract volume and integrity, intrinsic connectivity, and cerebral blood flow. 4) To assess safety and tolerability of allopregnanolone. **Methods:** Allopregnanolone as regenerative therapeutic is a Phase 2 multi-center, double-blind, parallel-group, randomized-controlled clinical trial. A total of 20 sites will recruit 200 participants with mild AD, 100 participants per treatment arm. Eligible participants are male or female, age 55 to 80 years old, diagnosed with probable AD, with a MMSE between 20–26 and APOE e4 genotype (3/4 and 4/4). Participants will be randomized to 4 mg Allo (administered intravenously over 30 minutes, once per week) or matching placebo, 1:1 allocation, for a 12-month period. After 12 months, all participants in the placebo group will be crossed-over to receive Allo for the remainder of the study (6 month open-label phase). Brain imaging to evaluate the primary endpoint will be conducted at baseline, 6 and 12 months. A critical component of this trial is that all imaging sites participating in the trial are capable of performing both basic and advanced MRI sequences required in the protocol. Hence, all clinical sites will either have in-house imaging capabilities or will have access to a pre-qualified imaging center that is in close proximity to the clinical site. All participating imaging sites will have been pre-qualified and trained by ADMdx imaging group. **Results:** Primary Endpoints: - Mean rate of change in hippocampal volume at 12 months. Secondary Endpoints: - Paired associates learning total errors adjusted (PAL TEA) from Cambridge Neuropsychological Test Automated Battery (CANTAB) after 12 months of treatment. - CANTAB composite score at 12 months. - Alzheimer's Disease Assessment Scale-Cognition11 (ADAS-Cog11) at 12 months. - Alzheimer's Disease Cooperative Study– Instrumental Activities of Daily Living Scale (ADCS-iADL) at 12 months. - Safety and tolerability after 12 and 18 months of treatment. Exploratory Endpoints: - Regional brain volumes, white matter fiber tract diffusion measures as determined by DTI, average intrinsic connectivity as determined by resting state fMRI, and cerebral region cerebral blood flow. - Blood-based biomarkers of target engagement. - Other cognitive and functional measures: Clinical Dementia Rating sum of boxes (CDR-SB) score, ADAS-Cog14 score, MMSE score, Neuropsychiatric Inventory-Questionnaire (NPI-Q) score, EuroQol 5-Dimension / 5-Level (EQ-5D-5L) health-related quality of life scale scores, Quality of Life-Alzheimer's Disease (QoL-AD) score, Zarit Burden Interview (ZBI) Questionnaire score at 12 and 18 months. - Comparison of change from baseline to 6, 12 and 18 months in open label treatment participants switching from placebo to Allo at 12 months in the above endpoints. **Conclusions**: Herein we present the design of a phase 2 proof-of-concept trial to assess the efficacy of allopregnanolone as a regenerative therapeutic using an imaging surrogate endpoint. Results from this study will validate previous findings indicating that allopregnanolone may exert both regenerative and neuroprotective effects on structure and connectivity in the Alzheimer's brain. **Acknowledgements:** National Institute on Aging R01 AG057037 to RDB and LS and Alzheimer's Drug Development Foundation to RDB. Syneos Health as contract research organization.

P17- SAFETY, TOLERABILITY AND CEREBRAL BLOOD FLOW AFTER SINGLE DOSES OF THE B2-AGONIST, CLENBUTEROL, IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT OR PARKINSON'S DISEASE.

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Background: Early-stage deficiency in the noradrenergic system of the brain is a common pathogenic mechanism in multiple neurodegenerative disorders including Alzheimer's and Parkinson's Disease (Braak et al., J Neuropathol Exp Neurol 2011; 70:960). Depletion in noradrenergic signalling, originating largely from neurons in the locus coeruleus, may lead to reduced neuronal activity in key cortical and limbic areas including the prefrontal cortex, thalamus, hippocampus and amygdala. This can have a significant impact on associated functions including attention, learning and working memory. Activation of excitatory receptors of the ascending noradrenergic system, and β2-adrenergic receptors in particular, could therefore be promising therapeutic targets in neurodegenerative disorders. However, as long-term daily exposure to β2-agonists will impart undesirable peripheral effects (including tachycardia, hyperglycaemia and hypokalaemia), co-administration of a peripherally restricted β-blocker may be beneficial to control the cardiovascular and metabolic effects of chronic treatment. **Objectives:** The objectives of this study were to evaluate the safety and effects on cerebral activity of the β2-adrenoceptor agonist clenbuterol in patients with Mild Cognitive Impairment (MCI) or Parkinson's Disease (PD). Cerebral blood flow (CBF), which is tightly coupled to neuronal activity and metabolic responses, was measured by magnetic resonance imaging using single-delay pseudo-continuous arterial spin labeling (pCASL MRI). The pre-administration of a low dose of nadolol, a non-selective β-blocker with minimal brain penetration, was also evaluated on the cardiovascular, metabolic and CNS effects of clenbuterol as a secondary endpoint. **Methods:** Eight patients with neurodegenerative disorders (7 with MCI, 1 with PD) between the ages of 58 and 71 years (mean [SD] = 60.9 [4.3] years) were enrolled in the study. All patients received a first dose of 80μg clenbuterol during the first study visit and a second dose of 80μg clenbuterol during the second study visit following a 7-day washout. Half of the patients were pre-treated with a dose of 1mg nadolol 2.5 hours before clenbuterol in the second study visit. The remaining 4 patients did not receive nadolol during the second visit. Safety and tolerability effects were evaluated by frequent ECGs, vital sign measurements and safety labs. During both study visits, a pCASL MRI scan was acquired prior to (baseline), and 3 hours after the administration of clenbuterol. CBF changes from baseline to post-dose were calculated and expressed as the Mean Relative Difference (MRD) in perfusion. The primary regions of interest, chosen due to their relevance for cognition or alertness, were a combined cortical region (cortex), combined sub-cortical region (subcortical), striatum, thalamus, amygdala and hippocampus.

Results: Following the first treatment with clenbuterol, significant increases in CBF were seen in the hippocampus (20.3%, p=0.001), thalamus (13.1%, p=0.004) and amygdala (14.3%, p=0.005). This response was mostly maintained in the 4 subjects who received clenbuterol monotherapy during the second study visit (MRD of 18.6±15.1% for hippocampus, 21.0±10.8% for the thalamus and 8.1±11.5% for amygdala). In the 4 subjects who received nadolol on the second visit, the central effect of clenbuterol on CBF remained present following the pre-administration of 1mg nadolol (MRD of 16.2±5.2% in the thalamus, and 13.7±5.9% in the hippocampus). Single doses of 80μg clenbuterol were safe and well tolerated. Several of the known side effects of β2-agonists were observed, including increases in heart rate (mean [SD] = 12.9 [8.2] bpm), tremor (4/8), and palpitations (1/8). These peripheral cardiovascular and metabolic effects were mostly eliminated by the low dose of nadolol administered 2.5 hours before clenbuterol. **Conclusion:** In patients with MCI or PD, clenbuterol administration resulted in significant increases in CBF in the hippocampus, thalamus and amygdala. Increases in CBF are expected under conditions of increased neuronal activity. This phenomenon of neurovascular coupling arises from integrated responses from multiple cell types, many of which are known to express β2 receptors, including neurons, cerebral blood vessels, microglia, oligodendrocytes and astrocytes. The observed increases in CBF may therefore suggest that the deficiency in the noradrenergic system that arises early in neurodegenerative disease progression may be at least partially restored by direct β2 receptor activation with clenbuterol. Clenbuterol's effects on CBF were evident both in the absence and presence of the peripherally restricted β-adrenoceptor antagonist, nadolol, suggesting that they are centrally mediated. Clenbuterol was safe and well tolerated, with effects on heart rate and reported adverse events similar to the β2-agonist class. Pre-treatment with a low dose of nadolol mitigated these peripheral effects, thereby confirming meaningful β2 adrenoceptor antagonism in the periphery even at the low dose administered, while maintaining the central effects on CBF.

P18- MILD BEHAVIORAL IMPAIRMENT CORRELATES OF COGNITIVE IMPAIRMENTS IN OLDER ADULTS WITHOUT DEMENTIA: MEDIATION BY AMYLOID PATHOLOGY. Yan Sun[1], Jintai Yu[2], Lan Tan[3] *(1. Department Of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao, China. - Qingdao (China), 2. Department Of Neurology And Institute Of Neurology, Huashan Hospital, State Key Laboratory Of Medical Neurobiology And Moe Frontiers Center For Brain Science, Shanghai Medical College, Fudan University, Shanghai, China. - Shanghai (China), 3. Department Of Neurology And Institute Of Neurology, Huashan Hospital, State Key Laboratory Of Medical Neurobiology And Moe Frontiers Center For Brain Science, Shanghai Medical College, Fudan University, Shanghai, China. - Qingdao (China))*

Objective: Neuropsychiatric symptoms (NPSs) mainly manifested as disturbances of mood, perception, and behavior linked with neurodegenerative disease, which are regarded as noncognitive or behavioral and psychiatric symptoms of dementia. The relationship between mild behavioral impairment (MBI) and Alzheimer's disease (AD) is intricate and still not well investigated. The purpose of the study is to examine the roles of the AD imaging pathologies in modulating the associations of MBI with cognitive impairments. **Methods:** We analyzed 1129 participants (563 [49.86%] female), who had measures of Neuropsychiatric Inventory Questionnaire (NPI-Q), cognition, and amyloid PET AD biomarkers from the Alzheimer's disease Neuroimaging Initiative (ADNI). We assess the longitudinal neuropathological and clinical correlates of baseline MBI via linear mixed-effects and Cox proportional hazard models. The mediation analyses were used to test the mediation effects of AD pathologies on cognition. **Results:** We found that MBI was associated with worse global cognition as represented by MMSE (p<0.001), and higher β-amyloid burden (p<0.001). β-amyloid partially mediated the effects of MBI on cognition with the mediation percentage varied from 14.67 to 40.86% for general cognition, memory, executive, and language functions for non-dementia individuals. However, no significant associations were discovered between MBI and tau burden or neurodegeneration. Furthermore, longitudinal analyses revealed that individuals with MBI had a faster increase in brain amyloid burden (p<0.001) and a higher risk of clinical conversion (HR = 2.42, 95%CI= 1.45 to 4.01 p<0.001). **Conclusion:** MBI could be an imperative prediction indicator of clinical and pathological progression. In addition, amyloid pathologies might partially mediate the influences of MBI on cognitive impairments and AD risk. Examining neurobehavioral outcomes was highly recommended to link the pathological process to clinical symptoms, which contribute to delineate a time course and depict the impact of it on functional decline prior to overt symptom onset.

P19- REGIONAL AMYLOID ACCUMULATION PREDICTS MEMORY DECLINE IN INITIALLY COGNITIVELY UNIMPAIRED INDIVIDUALS. Lyduine Collij[1], Sophie Mastenbroek[1], Gemma Salvadó[2], Alle Meie Wink[1], Pieter Jelle Visser[1], Frederik Barkhof[1], Bart Berckel Van[1], Isadora Lopes Alves[1] *(1. Amsterdam Umc - Amsterdam (Netherlands), 2. Barcelonabeta Brain Research Center - Barcelona (Spain))*

Background: The current shift towards (early) secondary intervention AD trial designs warrants the need for detection of subtle changes of both amyloid-β (Aβ) burden and cognitive functioning. This study investigated the longitudinal trajectory of global and regional Aβ measurements and their value in predicting cognition in initially cognitively unimpaired (CU) subjects. **Methods:** We included 133 CU subjects with available longitudinal cognition (MMSE: 2-13 assessments, 7.9±2.5 years; neuropsychological memory tasks: 2-5 assessments, 4.0±1.9 years) and [11C]PiB PET imaging (2-5 scans, 4.4±1.9 years) from the Open Access Series of Imaging Studies (OASIS-3) cohort. Baseline and annualized distribution volume ratio's (DVR) were computed for a global composite and three early Aβ accumulating regions of interest (ROI), i.e. precuneus, orbitofrontal cortex, and insula. Gaussian Mixture Modelling was used to derive a data-driven cut-off of Aβ-PET positivity (Aβ+) of the global baseline PET measures, which was based on the mean plus two standard deviations from the left Gaussian (i.e. 'normal') distribution (DVR>1.12). First, we investigated the relationship between baseline amyloid burden and annualized slope for the global ROI. Next, linear mixed effect models were used to examine the predictive value of global and early regional Aβ measurements (i.e. Aβbaseline, Aβslope, and Aβbaseline*slope) on global cognition (MMSE) and several aspects of memory performance (i.e. immediate and delayed episodic memory, working memory, and semantic memory). All analyses were controlled for age, sex, years of education, and time between baseline PET and first cognitive assessment. Model preference was based on the Akaike Information Criterion (AIC) and Bayesian Information

Criterion (BIC). Bonferroni correction was set at p<0.01. **Results:** Based on global amyloid burden, 30.1% of subjects were Aβ+ (i.e. DVR>1.12) at the time of the first PET-scan. A non-linear relationship was observed between baseline amyloid burden and slope, where an initial increase in amyloid burden corresponded to increasing yearly rates of change, reaching a peak of accumulation around 1.31 DVR, and subsequently a slowing of the accumulation rates upon further increases in amyloid burden. At baseline, subjects had a mean MMSE score of 28.9±1.3 and cognitive performance did not differ between Aβ-negative (Aβ-) and Aβ+ individuals for all cognitive tests, except for the immediate episodic memory task (Logical Memory IA; Aβ-:14.4±3.8; Aβ+:12.9±3.9, p=.045). Mixed effects analyses showed that baseline global amyloid burden did not predict changes in MMSE score. In turn, Aβ burden in the precuneus ROI could predict MMSE performance over time (βbaseline=-0.29, t=-3.7, p<.001; βslope=-9.71, t=-2.2, p=0.030; βinteraction=8.71, t=2.6, p=.011), where a decline in global cognition was only apparent in subjects with both high amyloid burden and low accumulation rates, i.e. those in which the Aβ accumulation process has already reached a plateau. In contrast, subjects with similarly high baseline amyloid burden but who were still undergoing significant Aβ accumulation have similar cognitive decline profiles to those who are still Aβ-. Precuneal slope and the interaction term were both marginally predictive of changes in immediate (βslope=-60.95, t=-2.0, p=.053; βinteraction=53.39, t=2.1. p=.038) and delayed episodic memory (βslope=-65.45, t=-2.2, p=.030; βinteraction=53.14, t=2.2, p=.031). In the Aβ- at baseline group (N=93), LOFC slope and the interaction term significantly predicted changes in semantic (βslope=-439,43, t=-2.93 p=0.004; βinteraction=393.13, t=2.91, p=0.005) and marginally in working memory performance (βslope=-171.97. t=-2.13, p=0.038; βinteraction=-147.62, t=2.02 p=0.048). In this group, amyloid accumulation was not associated with a decline in cognitive functioning, but rather a possible lack of learning effect, which was observed for the stable subjects. **Conclusions:** Quantifying longitudinal and regional changes in Aβ can predict future cognitive functioning in initially CU individuals. For individuals with established amyloid pathology, longitudinal Aβ measures help to identify those subjects most likely to show cognitive decline within the short timelines of clinical trials. This is crucial information for secondary prevention trials, since these rely on the inclusion of asymptomatic Aβ+ subjects and have cognitive performance as the main outcome measure. In turn, our results illustrate that regional longitudinal PET measures are able to identify subjects at the beginning of the amyloid accumulation process, even when they are classified as Aβ-negative at their baseline visit. Importantly, in this group the effect of amyloid burden and accumulation on cognitive functioning seems to be related to an absence of learning effect, rather than objective cognitive decline. The presenting author has no relevant disclosures regarding this abstract.

LP03- NOVEL WHITE MATTER IMAGING MEASURES OF NEUROINFLAMMATION, AXONAL DENSITY AND DEMYELINATION AS POTENTIAL BIOMARKERS FOR TRIALS IN THE AD SPECTRUM: VALIDATION IN THE LARGESCALE LONGITUDINAL MULTICENTER ADNI STUDIES. Maggie Roy[1], Matthieu Dumont[1], Jean-Christophe Houde[1], Raymond Tesi[2], Christopher Barnum[2], Maxime Descoteaux[1], Alzheimer's Disease Neuroimaging Initiative Alzheimer's Disease Neuroimaging Initiative[3] *(1. Imeka Solutions Inc - Sherbrooke (Canada), 2. Inmune Bio, Inc - San Diego (United States), 3. Alzheimer's Disease Neuroimaging Initiative - San Diego (United States))*

Background: Alzheimer's disease (AD) is considered a disease of gray matter, although white matter (WM) degeneration has been observed for decades in AD. WM microstructure deterioration has even been reported before measurable hippocampal atrophy in persons at risk of AD. Moreover, histological studies of WM in AD show: 1- increased extracellular space and microglia activation 2- dystrophic axons and lower axonal density 3- granulation and loss of myelin sheaths. With the recent advances in diffusion MRI (dMRI), three quantitative WM measures highly sensitive to the microstructural changes listed hereinabove were developed: i- free-water, a biomarker of neuroinflammation ii- apparent fiber density, a marker of axonal integrity iii- tissue radial diffusivity, a marker of myelin content. Our objective was first to characterize these new biomarkers cross-sectionally in the AD spectrum in a largescale dataset and describe their associations with cognitive outcomes. Secondly, we aimed to establish the dynamics of these three markers over a 24-month period. **Methods:** All ADNI cohorts with dMRI were included (ADNI-GO, ADNI2, ADNI3), 594 subjects (304 NC, 207 MCI and 83 AD) analyzed cross-sectionally and 3, 6, 12 and 24 months follow-up acquisitions processed in 51 NC, 78 MCI and 37 AD. In the MCI group, 15 subjects converted to AD over the 24 months. From the dMRI, free-water, fixel-based apparent fiber density and tissue radial diffusivity maps were computed. Then, a composite quantitative track-specific score (AD-bundles) was calculated combining the WM bundles altered in AD (fornix, cingulum, arcuate, uncinate, inferior fronto-occipital and inferior longitudinal fasciculi, genu and splenium of the corpus callosum). WM measures were analyzed with a general linear model using age, sex, ApoE4 status, intracranial volume and WM hyperintensities volume as covariates. Associations with cognitive scores were determined using partial correlation controlling for the above five covariates. **Results:** At baseline in AD-bundles, free-water was 53% higher in AD vs NC (partial η2= 0.10; P= 0.001), and 26% higher in MCI vs NC (partial η2= 0.05; P= 0.007) after controlling for all covariates. When combining all subjects, baseline cognitive scores were associated to free-water in AD-bundles with a moderate effect size: ADAS-Cog 13 (partial r= 0.37; P= 0.002), trail making test part A (partial r= 0.30; P< 0.001), verbal fluency categorical (partial r= -0.33; P< 0.001) and immediate memory recall (partial r= -0.26; P< 0.001). When the fornix was analyzed individually, the ROC curve from baseline free-water had an excellent accuracy to discriminate AD from NC (AUC= 0.84; P< 0.0001). A free-water value of 0.56 in the fornix (free-water fraction of 56%) represented a likelihood ratio of 3.2. At baseline, fiber density in the fornix was 14 % lower in AD vs NC (P< 0.001) and 10% lower in AD vs MCI (P= 0.005). Baseline tissue radial diffusivity in the fornix was 5% higher in AD vs NC (partial η2= 0.10; P= 0.013). Longitudinally, in AD patients, free-water was increased by 7.7, 11.1 and 16.7% (although not significant) at 6, 12 and

24 months respectively compared to baseline. At 24 months, changes were significantly higher in AD vs MCI (P= 0.021). Fornix changes in free-water at 24 months were higher in AD vs NC (partial η2= 0.10; P= 0.028). In AD patients, fiber density in the fornix was decreased by 2.3, 4.3 and 4.4% at 6, 12 and 24 months respectively. Fornix reductions in fiber density at 24 months were larger in AD vs NC (partial η2= 0.22; P= 0.001) and MCI vs NC (partial η2= 0.15; P< 0.001), with a large effect size. At 24 months, tissue radial diffusivity increase in the fornix was higher in AD vs NC (P= 0.044). At baseline, MCI which later converted to AD had 11% higher free-water (P= 0.001), 14% lower fiber density (P= 0.003) and 10% higher radial diffusivity (P= 0.009) compared to MCI stable, where only fiber density was still significant after controlling for all covariates (P= 0.034). **Conclusions:** The decline of these WM imaging measures in AD patients suggest neuroinflammation, axonal deterioration and demyelination, as reported in histological studies. The free-water measure was an excellent classifier of AD patients, which could also allow to select a subpopulation of participants with neuroinflammation in AD clinical trials targeting the immune system. A composite score of AD-bundles allowed to reduce inter-subject variability and was associated to global cognition, episodic memory, executive function and processing speed in the AD continuum. In MCI, the three biomarkers in the fornix, especially fiber density, may be predictive of conversion to AD. In clinical trials, stabilizing (or even reversing decline) fiber density and tissue radial diffusivity measures would suggest tissue repair, strengthened axons and potential remyelination. Considering the insight into the brain microstructure and the related neuropathological processes that these three WM biomarkers provide, clinical trials would benefit to include them as endpoints for the screening and/or drug efficacy assessment in MCI and AD patients.

LP04- MRI MEASURES OF WHITE MATTER PATHOLOGY IN AD CLINICAL TRIALS – CASE STUDY FROM THE XPRO1595 PHASE 1 TRIAL IN ALZHEIMER'S PATIENTS WITH NEUROINFLAMMATION. Maxime Descoteaux[1,2], Maggie Roy[1], Matthieu Dumont[1], Jean-Christophe Houde[1], Parris Pope[3], R.j Tesi[3], C.j Barnam[3] *(1. Imeka Solutions Inc - Sherbrooke (Canada), 2. Université de Sherbrooke - Sherbrooke (Canada), 3. Inmune Bio Inc - San Diego (United States))*

Background: Alzheimer's Disease (AD) leads to widespread brain atrophy, a pathological process typically associated with loss of gray matter. However, loss of white matter (WM), consisting of myelinated axons, is an early event in the disease process preceding the loss of gray matter. In addition, WM can be repaired. With recent advances in diffusion MRI, it is now possible to quantify white matter microstructure and its deterioration in neurodegenerative disease using non-invasive virtual dissection and biopsy tools. XPro1595 is a brain penetrable, dominant-negative TNF analogue that selectively inhibits proinflammatory soluble TNF (solTNF) while preserving the neuroprotective effects of transmembrane TNF. XPro1595 is a next generation tumor necrosis factor (TNF) inhibitor that selectively neutralizes soluble TNF, the TNF species that drives chronic inflammation and disease. In addition to its role within the immune system, TNF acts as a neuromodulator and is critical for white matter plasticity in the CNS. In preclinical studies, XProTM had a profound effect on WM including sparring of axonal loss and promoting remyelination. We examined the effect of XProTM on white matter metrics of neuroinflammation (free-water), axonal density (apparent fiber density) and myelin (tissue radial diffusivity) and compared these to traditional CSF biomarkers in a Phase1b trial in AD patients with biomarkers of inflammation to determine the best approach to assess WM in proof of biology clinical trials. **Methods:** 16 participants were enrolled in an open-label multi-dose trial of XPro1595. Patients needed one or more biomarkers of inflammation to enroll - CRP ≥ 1.5mg/dl, HgbA1C ≥ 6%, ESR ≥ 10 sec or be ApoE4+ve. All patients received 12 weeks of therapy; 5 patients received >50 weeks of therapy in an extension trial at 1mg/kg/QW; the dose planned for the Phase II trial. MRI was assessed every three months. MRI acquisitions were done in 4 sites in Australia, using 3T Siemens and GE systems. 3D T1-weighted images were acquired at 1 mm isotropic and diffusion MRI were acquired at 2 mm isotropic with b-value = 1000 mm2/s, 30 uniform directions and 1 b=0 image. Processing: Diffusion MRI processing from raw DICOM data to virtual dissection of white matter bundles implicated in AD (CC2, CC7, ILF, IFOF, AF, UF) were reconstructed. These "AD bundles" are based on 20+ years of literature and results showing alterations of diffusion MRI and white matter in the AD pathology. Quantitative tractometry (track-specific statistics) was done using local diffusion MRI microstructure indices of free-water (a proxy of neuroinflammation), apparent fiber density (AFD – a proxy of axon integrity) and tissue radial diffusivity (RDt – a proxy to myelin content) in the AD bundles as composite biomarkers of neuroinflammation, axon regeneration and remyelination respectively. **Results:** MRI metrics showed a progressive improvement over 12 months in all white matter metrics; including: i) a 46% reduction in free-water (neuroinflammation), ii) 17% increase in AFD, iii) a 17% reduction in RDt, iv) and an increase in total WM volume and left temporal lobe volume increased. These measures correlated with multiple protein CSF biomarkers of neuroinflammation and neurodegeneration. **Conclusions:** Non-invasive advanced MRI virtual dissection and biopsy tools can quantify the degree of white matter loss and repair and specify the exact location. In this Phase 1b trial, we showed that XPro1595 improves white matter structure within WM bundles that are specifically affected in AD. Improvement was observed as early as 12 weeks and continued for 50 weeks. High correlation with gold standard CSF protein neuroinflammatory and neurodegenerative biomarkers validate the use of non-invasive MRI tools to measure WM pathology. Together, these data demonstrate the superiority of WM metrics over traditional CSF analysis of WM biomarkers. **Disclosures:** MD is CSO and shareholder of Imeka Solutions Inc, J-CH is shareholder and employee at Imeka. MR is consultant and MD is employee at Imeka Solutions Inc. RJT and CJB are both employees shareholders at INmune Bio.

LP05- ANATOMICAL AND FUNCTIONAL CONNECTIVITY OF THE NUCLEUS BASALIS IN ALZHEIMER'S DISEASE. Sergio Becerra[1,2], Sheldon Jordan[1,2], Taylor Kuhn[1,2], Kennedy Mahdavi[1], Jon Haroon[1], Margaret Zielinski[1] *(1. Synaptec Network - Santa Monica, Ca (United States), 2. UCLA - Los Angeles, Ca (United States))*

Background: The nucleus basalis of Meynert (NBM) is the major source of cholinergic innervation to the cerebral cortex and amygdala. Elderly patients have diminished cholingergic activity in the NBM, likely due to reduced cholineacetyltransferase (ChAT) and acetylcholinesterase (AChE) activity. Their NBM neurons are both smaller and less dense than those found in younger individuals. A variety of cognitive disorders, including Alzheimer's disease (AD), are correlated with degeneration of cholinergic neurons. Projections

from the cholinergic neuron complex (Ch4) in the NBM to the cerebral cortex remain largely unmapped, but cholinergic axons have been traced from the NBM through the amygdala and insular cortex to the hippocampus and entorhinal cortex. **Objective:** The degeneration of Ch4 has a profound effect on the pathology of AD, because the disruption of this small group of neurons can perturb neurotransmission in all cortical areas. While the role of Ch4 in cognition is not fully understood, the cholinergic circuitry may provide a window into the cognitive state of AD. Focusing Diffusion Tensor Imaging and fMRI on the NBM can shed light on the potential state of subjects with Alzheimer's disease. We aim to use DTI to provide insight into the white matter projections from the NBM and use resting state fMRI to depict how it is functionally wired. Combining these methods may even provide potential biomarkers for the developmental stage of AD. **Methods:** 38 Alzheimer's patients were identified using the gold standard lumbar puncture method based on amyloid-beta and tau markers. They were split into 2 groups based on CDR scores: 20 subjects who scored 0.5 (very mild) and 18 subjects with a CDR score of 1.0 (mild). 23 healthy, age-matched control participants were also recruited for comparison. All subjects were scanned on a Simmons 1.5T Espree and received an anatomical MPRAGE image, a resting state BOLD (rs-fMRI) image and a 30 direction DTI acquisition . After preprocssing the rs-fMRI, functional connectivity analysis was performed with a seed set for both the left and right NBM. That same seed was used in probabilistic tractography to map out the white matter connections stemming from the NBM. Group analysis was performed in standard MNI space. **Results:** Group analysis between healthy controls and CDR 0.5 group showed that the AD group had a decrease in activity in the thalamus an orbito-frontal region. The same results were observed between healthy controls and the CDR 1.0 AD group. Difference between CDR 0.5 and CDR 1.0 were equivocal. Probabilistic Tractography showed a drastic drop off in both tract density and count corresponding with CDR score from healthy controls. There was a 40% drop off from the control group the CDR 0.5 AD group; there was an additional 25 % drop from CDR 0.5 to CDR 1.0. **Conclusion:** Imaging of the NBM successfully differentiated dementia patients from controls, and additionally was able to capture the level of cognitive decline. While the results are still preliminary, this analysis introduces a new method of observing the progression of AD pathologies. One benefit of this method is that it does not require any special fMRI add on beyond the standard BOLD acquisition. Clinically, this approach may help resting fMRI and DTI classify the progression of neurodegenerative disorders

RP05- COMPARISON OF CT AND MRI BASED STANDARDIZED UPTAKE VALUE RATIO FOR THE AMYLOID PET ANALYSIS IN SUBJECTIVE COGNITIVE DECLINE AND MILD COGNITIVE IMPAIRMENT SUBJECTS. Dong Won Yang, Yun Jeong Hong, Junghee Cho, Young Chul Youn *(Department Of Neurology, College Of Medicine, The Catholic University Of Korea - Seoul (Korea, Republic of))*

Background: FDA approval of aducanumab made the amyloid PET standardized uptake value ratio (SUVR) more important for the diagnosis of Alzheimer's disease and follow-up of its effect to remove amyloid in the brain. 3D T1 MRI imaging is required for accurate SUVR measurement in Alzheimer's disease spectrum disorders. However, 3D T1 MRI is not always acquired along with amyloid PET scanning or is sometimes not available out of special dementia centers. **Objectives:** We develop SUVR methods based on low-dose CT imaging that is acquired along with the amyloid PET scanning and compared its validity and reliability with MRI based SUVR method. **Methods:** 22 Florbetaben PET-positive and 22 negative subjective cognitive decline (SCD) and mild cognitive impairment (MCI) were selected in the single dementia clinic and 3D MRI and low dose CT imaging were acquired for the analysis. SPM12 and MATLAB were used for the SUVR measurement. 3D T1MRI and CT were used for the reregistration with amyloid PET, normalization, and gray matter segmentation. With the visual PET reading as a gold standard, we compared demographic data, MMSE, APOE4, SUVR between groups. Intra-class correlation coefficient (ICC) was used to test the validity of two SUVR methods. **Results:** Mean age and MMSE of 44 subjects were 72.9 and 25.2. Age, education, MMSE were not different between amyloid PET-positive and negative groups. APOE4 was frequent in the PET-positive group (63.6% vs 22.7%) and SUVR MRI (1.220 V.S 1.686), SUVR CT (1.179 V.S. 1.655) were higher in the amyloid PET positive group. The mean of the SUVR MRI and SUVR CT was 1.453 (S.D. 0.272) and 1.417 (S.D. 0.282). ICC between the two methods was 0.981, p=0.0001. The area under the curve (AUC) of SUVR MRI was 0.998 and the AUC of SUVR CT was 0.994. With cut-off value 1.41, the sensitivity and specificity of SUVR MRI was 96% and 100% With cut-off values 1.38 the sensitivity and specificity of SUVR CT were 96% and 96%. **Conclusions:** CT-based SUVR calculation method is valid as much as the MRI-based SUVR method. Further analysis will be needed to test the CT-based SUVR method in the more advanced Alzheimer's disease spectrum disorders with more brain atrophic changes. This study was supported by a grant from the Ministry of Health and Welfare, HI18C0530

RP06- DIAGNOSTIC PERFORMANCE FOR ALZHEIMER'S DISEASE OF THE DEEP LEARNING-BASED CLASSIFICATION SYSTEM USING BRAIN MAGNETIC RESONANCE IMAGING. Bae Jong Bin, Kim Ki Woong *(Seoul National University Bundang Hospital - Seongnam-Si (Korea, Republic of))*

We developed the deep learning-based classification system using structural brain MRI (DLCS) in our previous work. This study aimed to investigate its diagnostic performance for Alzheimer's disease (AD). We retrospectively collected T1-weighted brain MRI of 188 patients with mild cognitive impairment or dementia due to AD and 162 cognitively normal controls. The patients were amyloid beta (Aβ)-positive whereas the controls were Aβ-negative on 18F-florbetaben positron emission tomography. Sensitivity, specificity, positive predictive value, negative predictive value, and area under the receiver operating characteristics curve for AD were 85.6% (95%CI, 79.8–90), 90.1% (95%CI, 84.5–94.2), 91.0% (95%CI, 86.3–94.1), 84.4% (95%CI, 79.2–88.5) and 0.937 (95%CI, 0.911–0.963) respectively, indicating that the diagnostic performance for AD of the DLCS was excellent. DLCS may improve the early detection of AD in individuals who have taken a MRI scan for whatever purpose. **Conflict of Interest:** J.B. Bae and Ki Woong Kim received royalty income from VUNO Inc.

RP06BIS- ASSOCIATIONS OF STAGES OF OBJECTIVE MEMORY IMPAIRMENT (SOMI) WITH ALZHEIMER'S DISEASE BIOMARKERS IN THE A4 STUDY. Ellen Grober[1], Richard Lipton[1], Reisa Sperling[2], Keith Johnson[2], Dorene Rentz[2], Kathryn Papp[2], Paul Aisen[3], Ali Ezzati[1] *(1. Albert Einstein College of Medicine - Bronx (United States), 2. Harvard Medical School - Boston (United States), 3. University of Southern California - San Diego (United States))*

Background: Stages of Objective Memory Impairment (SOMI) based on Free and Cued Selective Reminding Test (FCSRT) performance identifies five sequential stages in the breakdown of episodic memory in preclinical and prodromal Alzheimer's disease (AD) [1]. It was developed based on the extensive review of studies linking FCSRT performance to clinical outcomes and to biological markers. The first three SOMI stages (SOMI 0–2) typically precede clinical dementia by 5 to 8 years and reflect increasing retrieval difficulty, shown by declining free recall (FR) in the context of intact total recall (TR). The next two SOMI stages (SOMI 3, 4) precede clinical dementia by about 2 to 3 years; in these stages cuing fails to recover all of the items missed on FR indicating an impairment of memory storage that defines the core clinical phenotype of AD [2]. We have shown that in persons at SOMI 3 or 4 AD neuropathology is common [3]. SOMI-2 is highly associated with incident clinical AD dementia over 8 years of follow-up [4]. **Objectives:** Among "cognitively unimpaired" older adults from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study, we sought to identify persons at various SOMI stages and to characterize their biomarker status based on imaging markers of amyloid and neurodegeneration used in the NIA-AA Research Framework [5]. **Methods:** FCSRT scores from 4484 cognitively unimpaired participants were used to classify participants into SOMI stages and then to explore differences in β-amyloid (Aβ) pathology as measured by PET imaging. Among the Aβ+ participants, we assessed the relationship of SOMI stage to neurodegeneration, indexed by volumetric MRI measures of the hippocampus, parahippocampal gyrus, entorhinal cortex, and inferior temporal cortex, regions affected by early AD pathology. We used analysis of covariance (ANCOVA) to compare biomarker values of SOMI groups accounting for age, sex, education, and APOE4 status. Post-hoc pairwise uncorrected comparisons were performed to assess differences between groups defined by SOMI. **Results:** Participants had a mean age of 71.3 (SD=4.6) years, were 40.6% male, had 16.6 years of education, and 34.6% were APOE4 positive. In the entire cohort, as SOMI stage increased the proportion of participants who were Aβ+ also increased. Among Aβ+ individuals, those in higher SOMI stages also had higher global amyloid SUVR ($F=8.4$, $p<.001$). Participants in higher SOMI stages were older in age ($F=44.7$, $p<.001$) and more likely to be female ($F=54.0$, $p<.001$). Volumetric MRI was available for 1262 Aβ+ participants. The relationship of volumetric measure differed across SOMI stages: 1) Individuals at higher SOMI stages head smaller hippocampal volumes likely reflecting hippocampal atrophy ($F=3.66$, $p=.003$); 2) Individuals with impairment of memory storage (SOMI-3 and 4) displayed greater atrophy of the inferior temporal cortex compared to those with no storage impairment; and 3) atrophy of the entorhinal cortex was only present in SOMI-4 (significantly different from all other groups with p-value<0.01), but it did not differ among other groups. **Conclusions:** These results indicate that amyloid burden is associated with SOMI stage among individuals who are "cognitively unimpaired". Hippocampal atrophy increases across SOMI stages including those with retrieval but not storage impairment. The development of memory storage impairment is associated with atrophy of inferior temporal cortex but volume loss in entorhinal cortex occurs only with advanced storage issues in SOMI 4. The AD-biomarker differences between SOMI stages supports its relationship to the biological definition of AD [5]. **References:** Grober, E., Veroff, A. E., & Lipton, R. B. (2018). Temporal unfolding of declining episodic memory on the Free and Cued Selective Reminding Test in the predementia phase of Alzheimer's disease: Implications for clinical trials. Alzheimers Dement (Amst), 10, 161-171. Dubois, B., Feldman, H. H., Jacova, C., et al (2014). Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. The Lancet Neurology, 13(6), 614-629. Grober, E., Qi, Q., Kuo, L., et al (2021). Stages of Objective Memory Impairment Predict Alzheimer's Disease Neuropathology: Comparison with the Clinical Dementia Rating Scale–Sum of Boxes. Journal of Alzheimer's Disease, 80, 185-195. Qu, Q., Kuo, L., Resnick, S., Grober, E. (2021). A Bayesian joint model predicting time-to-dementia in the Baltimore Longitudinal Study of Aging, in review Jack, C.

LRP01BIS- SIX RECURRENT AMYLOID RELATED IMAGING ABNORMALITY EPISODES IN A PATIENT TREATED WITH ADUCANUMAB. Jacob Hall[1], Elizabeth Mormino[2], Amanda Ng[2], Athanasia Boumis[3], Jennifer Gaudioso[4], Guido Davidzon[5], Sharon Sha[2] *(1. The Neurology Center Of Southern California - Temecula (United States), 2. Department Of Neurology And Neurological Sciences, Stanford University - Stanford (United States), 3. Stanford Center For Clinical Research, Stanford University - Stanford (United States), 4. Global Alzheimer's Platform Foundation - San Francsico (United States), 5. Division Of Nuclear Medicine & Molecular Imaging, Department Of Radiology, Stanford University - Stanford (United States))*

Background: Aducanumab was approved by the US FDA in 2021 without clear guidance for ARIA management for potential prescribers. **Objectives:** In this case report, we describe a patient who was treated with aducanumab in the PRIME phase 1b clinical trial who developed amyloid related imaging abnormality-edema (ARIA-E) six times. **Methods:** n/a. **Results:** MK is a high-functioning man who presented with slowly progressive short-term memory and word-finding difficulties in 2007 at age 67. He had a history of 1st degree AV block, hypertension and hearing loss. Medications included antihypertensives, memantine and donepezil. He enrolled in PRIME, the phase 1b clinical trial for aducanumab, in late 2014 and was randomized to the placebo arm. He initially scored 27/30 on the mini mental status examination (MMSE) and had a global Clinical Dementia Rating (CDR) score of 0.5 (sum of boxes [SOB]=1.5). APOE genotype was ε3/ε4. Brain MRI revealed subtle hippocampal atrophy. The Florbetapir PET scan was positive, consistent with prodromal Alzheimer's disease. He completed 14 placebo infusions without incident. He entered long-term extension (LTE) in late 2015 and was randomized to titration to 6 mg/kg monthly infusions, the maximum allowed dose for APOE ε4 carriers in early protocol versions. At month 7 of LTE, after four 3 mg/kg doses, he developed asymptomatic, radiographically moderate ARIA-E, prompting dose suspension until resolution at month 10, followed by continued 3 mg/kg dosing. At month 12, he developed asymptomatic mild ARIA-E and dosing continued uninterrupted with resolution at month 15. At month 18, after receiving two 6 mg/kg doses, he again had asymptomatic moderate ARIA-E, prompting dose suspension until resolution at month 21, followed by dose

reduction to 3 mg/kg. At this point, a protocol amendment allowed titration to 10mg/kg, which was accomplished by month 24. At month 26, he developed asymptomatic mild ARIA-E, prompting dose reduction to 6 mg/kg, with resolution at month 28. At month 29, asymptomatic mild ARIA-E recurred, prompting further dose reduction to 3 mg/kg, with resolution at month 32. At month 35, he developed asymptomatic mild ARIA-E and mild ARIA-hemorrhage (ARIA-H) with mild superficial siderosis, prompting dose suspension, with ARIA-E resolution at month 36 and ARIA-H stability through month 39, followed by continued 3 mg/kg dosing. The trial was halted at month 44 of LTE after 31 aducanumab infusions with a cumulative dose of 124mg/kg. **Conclusion:** Despite the controversy of the approval of aducanumab, there is a need to define ARIA management strategies for potential prescribers. ARIA-E occurred in 35% of trial participants receiving aducanumab at 10 mg/kg. APOE ε4 carriers were particularly susceptible, with 42% experiencing ARIA-E compared with 20% in non-carriers. Of the 46 participants who experienced ARIA-E in the phase 1b trial and LTE, recurrent episodes occurred in eight. We present a participant treated with aducanumab over 44 months with 6 asymptomatic ARIA episodes, the most in the three aducanumab trials. Though our participant never achieved sustained maintenance dosing of 10 mg/kg, the Florbetapir PET scan became visually negative at the interval scan following 21 doses with a cumulative dose of 91mg/kg (global SUVR reduction 1.291 to 1.045, using a whole cerebellum reference region. Recent aducanumab Appropriate Use Recommendations propose uninterrupted dosing through asymptomatic mild ARIA (-E and -H) and dose suspension for asymptomatic moderate-severe ARIA. Our participant was managed largely in alignment with these recommendations, although with additional conservative measures taken for later episodes due to number of recurrences. Our participant is an APOE ε4 carrier which may have increased his ARIA risk. Appropriate Use Recommendations suggest a patient-centered discussion and consideration of testing, which may be particularly relevant to this patient. Although this case does not suggest a uniform strategy for ARIA management, it prompts consideration of APOE status, caution and vigilance during dose titration when ARIA is more likely to occur, dose suspension for moderate ARIA-E, and dose reduction or suspension in select circumstances, such as recurrent ARIA. **Acknowledgements:** Biogen provided support for running the clinical trial (PRIME) and Biogen representatives reviewed the manuscript to confirm dosing of the participant.

LRP02BIS- IN VIVO 18F-APN-1607 TAU PET/CT IMAGING OF PATIENTS WITH FRONTOTEMPORAL LOBAR DEGENERATION DUE TO DIFFERENT MAPT MUTATIONS: CROSS-SECTIONAL AND LONGITUDINAL FINDINGS. Xin-Yue Zhou, Jia-Ying Lu, Feng-Tao Liu, Chuan-Tao Zuo, Yi-Min Sun, Jian Wang *(Huashan Hospital, Fudan University - Shanghai (China))*

Background: Frontotemporal lobar degeneration (FTLD) with tauopathy due to MAPT mutations is a highly heterogenous disorder. The ability to visualize and longitudinally monitor tau deposits may be beneficial to understand the disease pathophysiology and predict the clinical course. **Objective:** To investigate the cross-sectional and longitudinal 18F-APN-1607 PET/CT imaging of MAPTmutation carriers. **Methods:** Seven carriers with MAPT mutations (six within exon 10 and one outside of exon 10) and fifteen healthy controls were included. All participants underwent 18F-APN-1607 PET/CT at baseline. Three carriers of exon 10 mutations received follow-up 18F-APN-1607 PET/CT imaging at the annual visit. Standardized uptake value ratio (SUVR) maps were obtained using the cerebellar gray matter as the reference region. SUVR values observed in MAPT mutation carriers were normalized to data from healthy controls. A two-region positivity approach was used as the criterion to define positive 18F-APN-1607 PET/CT findings. **Results:** While the seven study patients had heterogenous clinical phenotypes, all showed a significant 18F-APN-1607 uptake presenting high-contrast signals. However, the anatomical localization of tau deposits varied in patients with different clinical symptoms. Follow-up imaging data – which were available for three patients – revealed worsening patterns of tau accumulation over time, which were noticeably paralleled by a significant clinical deterioration. **Conclusions:** Our data represent a promising step in understanding the usefulness of 18F-APN-1607 PET/CT imaging for detecting the tau burden in MAPT mutation carriers. Our preliminary follow-up data also suggest the potential value of 18F-APN-1607 PET/CT for monitoring the longitudinal trajectories of FTLD due to MAPTmutations.

CLINICAL TRIALS: BIOMARKERS INCLUDING PLASMA

P20- MICROGLIA BIOMARKERS IN ALZHEIMER'S DISEASE. Peng-Fei Zhang *(Qingdao University - Qingdao (China))*

Background and purpose: Early detection of Alzheimer's disease (AD) is extremely important for disease prevention and treatment. Due to the occult nature of the disease, the diagnosis of AD based on clinical symptoms is currently facing increasing challenges. Therefore, the molecular diagnosis model of AD pathological markers has received more and more attention. Microglia are necessary for normal brain function, and the scientific community has a keen interest in their role in pathological mechanisms and continues to study them. There are several AD biomarkers, but there is still a lack of microglia biomarkers that can accurately reflect the pathological changes of preclinical AD with high specificity and sensitivity. The introduction of microglia biomarkers into molecular diagnostic systems based on liquid and neuroimaging will promote the development of scientific research and clinical practice in the future. In addition, the development of novel, specific and sensitive microglia biomarkers will make it possible to develop drugs targeting microglia. This review discusses potential microglia biomarkers that are expected to be used in the diagnosis of AD. **Method :** By consulting the relevant literature in recent years, we have sorted out the research status of microglia and their biomarkers. First, we explored the role of microglia in the pathogenesis of AD. Then, the microglia biomarkers are divided into body fluid and imaging markers, and the advantages and disadvantages of each are discussed. Body fluid biomarkers are divided into cerebrospinal fluid biomarkers and blood biomarkers according to their specificity; neuroimaging is developed from the two most commonly used methods—PET and MRI. Finally, it looks forward to the future development of microglia biomarkers in AD. **Result:** The instability of microglia in the central nervous system may increase the risk of degeneration of the nervous system. Aβ pathology is widely considered to be the initiating factor of the disease. When microglia clears Aβ, it triggers the NF-kB inflammatory pathway, and the released IL-1β damages neurons and aggravates the pathological progression of tau.

Tau pathology will counteract the NLRP3 inflammasome in the cell, forming a vicious circle of tau → NLRP3 → tau, which will eventually cause the instability of microglia and even the degeneration of the nervous system. The liquid biomarkers in AD are the most well-known. The ideal liquid biomarker should have the characteristics of non-invasiveness, simple measurement, repeatability and reliability. Liquid biomarkers are usually obtained from cerebrospinal fluid or blood. Considering the direct contact between cerebrospinal fluid and brain cells, cerebrospinal fluid is a reasonable source for the development of effective microglia biomarkers. sTREM2, CX3CL1, PGRN, and GPNMB are all potential markers in cerebrospinal fluid. Due to the invasiveness and inconvenient availability of cerebrospinal fluid biomarkers, some studies are devoted to the development of blood biomarkers. sTREM2, CX3CL1, and PROS1 are all possible blood biomarkers. The use of neuroimaging to detect the activation of microglia in the body is mainly achieved through PET and MRI technology. PET is currently the most widely used method for in vivo detection of microglia activation. The detection accuracy depends on the tracer. TSPO, CB2R, CSF1R, and P2RY12 have received widespread attention as viable tracers. With the upgrading of MRI technology, some results have been achieved with it to detect microglia in vivo. **Conclusion:** Microglia biomarkers make it possible to monitor the responsiveness of cells to AD pathology. Although it is still difficult to develop effective treatments in a short period of time, the research on microglia biomarkers will undoubtedly deepen our understanding of AD. There are still many challenges in incorporating microglia biomarkers into the research framework. First, the dynamic changes of microglia are not a specific response to AD pathology. Secondly, the relationship between microglia biomarkers and AD pathology is susceptible to other confounding factors. Finally, the accuracy of biomarkers is affected by sample collection and storage. Therefore, it is necessary to further develop new microglia biomarkers and further improve the research framework in the future.

P21- PLASMA NEUROFILAMENT LIGHT AND LONGITUDINAL PROGRESSION OF WHITE MATTER HYPERINTENSITY IN ELDERLY PERSONS WITHOUT DEMENTIA. Yan Sun[1], Jintai Yu[2], Lan Tan[3] *(1. Department Of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao, China. - Qingdao (China), 2. Department Of Neurology And Institute Of Neurology, huashan hospital, Shanghai Medical College, Fudan University, Shanghai, China - Shanghai (China), 3. Department Of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao, China - Qingdao (China))*

Background: White matter hyperintensities (WMH) is highly associated with aging, vascular risk factors, early mortality, frailty and depression, and it may also increase the possibilities of progression to Alzheimer's disease. Plasma neurofilament light protein (NFL) is known as a potential and sensible blood-based neuronal injury marker. It has been reported that symptoms of most neurodegenerative diseases manifest as NFL accumulation, indicating a potential prognostic role of neurodegenerative diseases. The present study aims to determine whether plasma neurofilament light (NFL) protein levels could predict the progression of WMH volume in elderly persons without dementia. **Methods:** The present study included 1029 non-dementia participants from the Alzheimer' Disease Neuroimaging Initiative (ADNI) in which all had measurements of plasma NFL and WMH at baseline and 589 had longitudinal measurements during follow-up. Spearman correlation analyses and regression models were used to assess cross-sectional and longitudinal associations between plasma NFL and WMH. **Results:** Plasma NFL concentration had a moderately strong correlation with WMH at baseline ($r=0.17$, $p<0.001$). We further divided all participants into four quartiles according to their baseline plasma NFL concentration. Comparing with the lowest quartile, the third ($\beta=0.031$, $p=0.039$, 95%CI=1.00-1.06) and the forth ($\beta=0.032$, $p=0.041$, 95%CI=1.01-1.06) quartiles were both associated with increased WMH extent. Longitudinal analyses showed that higher baseline plasma NFL concentration was associated with accelerated progression of WMH ($\beta=0.015$, $p=0.007$). Furthermore, higher change rates of plasma NFL could predict faster progression of WMH in the future ($\beta=0.581$, $p=0.002$). **Conclusion:** The results of the study suggest that plasma NFL level might be used as a noninvasive biomarker to track variation trend in WMH in elderly persons without dementia. The dynamic changes of plasma NFL can be more accurate to predict the further status of WMH.

P22- ALZHEIMER'S DISEASE PATIENTS HAVE IMPAIRED CSF EGRESS DUE TO ATROPHY OF THE CRIBRIFORM PLATE. Douglas Ethell[1, 2], Ricardo Zaragoza[1], Javed Siddiqi[3], Daniel Miuli[4] *(1. Leucadia Therapeutics Inc - Riverside (United States), 2. La Jolla Immunology Institute - San Diego (United States), 3. Desert Regional Med Ctr - Palm Springs (United States), 4. Arrowhead Regional Med Ctr - Colton (United States))*

Alzheimer's disease (AD) patients show cribriform plate (CP) atrophy that reduces CSF-mediated clearance of brain regions where plaques and tangles appear first, specifically the basal forebrain and medial temporal lobe. We evaluated CPs from 620 Subjects from 20-94-years old using high-resolution micro-CT scans, clinical CT scans, U-Net-based deep learning models for semantic segmentation, Procrustes alignment, and cluster analysis. Contrast-enhanced micro-CT revealed a complex conduit system in the CP that acts as a watershed for CSF to flow down its free-energy gradient from CNS to the nasal mucosa, with minimal risk of pathogen entry. Conduits run from the crista Galli's interior to a manifold within the olfactory fossa's back wall, with connections to medium and large apertures in between. CP apertures contain olfactory nerves (CN1) and spongy arachnoid tissue that conveys CSF to the nasal mucosa and its exchange with porous features of a watershed within CP conduits. This configuration provides uniform intermediate pressure across the CP that cushions the drop in CSF pressure drop from subarachnoid (~10 mmHg) to nasal mucosa (-2 to 2 mmHg) and prevents backflow. Subjects with a confirmed AD diagnosis displayed CP atrophy that included watershed degeneration, CN1 nerve loss, and aperture occlusion. The dysregulation of CSF egress caused by CP atrophy reduces inflow from the olfactory tracts and lateral olfactory stria, which carry CSF flux from the basal forebrain and medial temporal lobe. Reductions in CSF outflow from those regions predisposed those brain regions to the accumulation of intercellular aggregates, decreasing egress further. These findings indicate that CP atrophy may play a critical role in accumulating toxic metabolites that seed AD pathology. Analysis of CP morphology presents a non-invasive method to track and predict AD years before cognitive impairment begins, requiring only 20-second CT scans starting at age 50.

P23- LONGITUDINAL PLASMA PHOSPHORYLATED TAU 181 TRACKS DISEASE PROGRESSION IN ALZHEIMER'S DISEASE. Shi-Dong Chen, Qiang Dong, Jin-Tai Yu *(Department Of Neurology And Institute Of Neurology, Huashan Hospital, Shanghai Medical College, Fudan University - Shanghai (China))*

Backgrounds: Recently, blood immunoassays for measurement of blood tau phosphorylated at threonine 181 have been developed and show promising results for the diagnosis of Alzheimer's disease (AD). However, it remains unclear whether plasma phosphorylated tau181 (p-tau181) could serve as the progression biomarker for AD. **Objectives:** To assess plasma p-tau181 as a progression biomarker in AD. **Methods:** We examined longitudinal plasma p-tau181 of 1184 participants (403 cognitively normal (CN), 560 patients with mild cognitive impairment (MCI), and 221 with AD dementia) from Alzheimer's Disease Neuroimaging Initiative (ADNI). **Results:** The plasma p-tau level was increased at baseline for MCI and AD dementia (mean: CN, 15.4 pg/mL; MCI, 18.4 pg/mL; AD dementia, 23.7 pg/mL; $P < .001$) and increased significantly over time at preclinical (Aβ-positive CN), prodromal (Aβ-positive MCI), and dementia (Aβ-positive dementia) stage of AD. A longitudinal increase of plasma p-tau181 was associated with abnormal cerebrospinal fluid biomarker levels(low Aβ42 , high phosphorylated tau, and high total tau, all $P<.001$), amyloid accumulation ($P<.001$) and hypometabolism ($P=.002$) on positron emission tomography, atrophy in structure imaging (small hippocampal ($P=.030$), middle temporal ($P=.008$), and whole brain ($P=.027$) volume, and large ventricular volume ($P=.008$)), and deteriorated cognitive performance (global cognition and memory, language, executive function, and visuospatial function, all $P<.050$) at baseline. Furthermore, longitudinal plasma p-tau181 correlated with concurrent changes of nearly all these AD-related hallmarks and a faster increase in plasma p-tau181 correlated with faster-worsening cognition in all diagnostic groups. Importantly, most associations remained significant in the Aβ-positive group and became non-significant in the Aβ-negative group. **Conclusions:** Longitudinal analyses of plasma p-tau181 suggest its potential as a noninvasive biomarker to track disease progression in AD and to monitor effects of disease-modifying therapeutics in clinical trials.

P24- CAN EEG BIOMARKERS DIFFERENTIATE ALZHEIMER'S DISEASE DEMENTIA VS. NON-AD DEMENTIA?. Pieter Van Mierlo[1,2] *(1. Ghent University - Ghent (Belgium), 2. Epilog Nv - Ghent (Belgium))*

Aim: The aim of the study is to verify whether EEG biomarkers can be used to classify patients with dementia from controls and patients with AD dementia versus patients with non-AD dementia. **Methods:** EEG measurements of 53 AD patients, 49 patients with a different type of non-AD dementia and 83 controls are used. After preprocessing, multiple EEG features, such as spectral power and functional brain connectivity are calculated. Support vector machines (SVM) are applied to classify (i) dementia vs. controls and (ii) AD-dementia vs non-AD dementia based on the EEG features. To evaluate the performance of the model, nested cross-validation is used with the area under the precision-recall curve (AUPRC) as evaluation metric. **Results:** The binary classification of patients with dementia and controls resulted in an average AUPRC of 0.985 for the validation set and 0.965 for the test set. The classification of AD vs. other types of dementia resulted in average AUPRCs of 0.750 and 0.749 respectively for the validation and test set. Patients with dementia had significantly higher power in the delta and theta band compared to controls. To classify AD vs. non-AD dementia functional connectivity features had most discriminative power. **Conclusions:** EEG biomarkers can differentiate between dementia and healthy controls with excellent accuracy. Furthermore, the differentiation between AD and non-AD dementia is possible with a good accuracy, indicating the potential to be used in clinical trials.

P26- CHARACTERIZATION OF ALZHEIMER'S TAU BIOMARKER DISCORDANCE USING PLASMA, CSF AND PET. Guo Yu *(Department Of Neurology And Institute Of Neurology, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China - Shanghai (China))*

Backgrounds: Plasma tau phosphorylated at threonine 181 (p-tau181) has recently emerged as a novel tau biomarker for Alzheimer's disease (AD), and showed disagreement with cerebrospinal fluid (CSF) p-tau181 and tau positron emission tomography (PET). However, it's still unclear whether this discordance could affect disease severity and whether plasma p-tau181 could be used to detect early pathology in AD. **Objectives:** Herein, we investigated tau biomarker discrepancies of AD using plasma p-tau181, CSF p-tau181, and AV1451 PET, and wonder whether discordant plasma and CSF or PET tau indicators denoted different stages of disease severity. **Methods:** In the Alzheimer's Disease Neuroimaging Initiative, 724 non-demented participants were categorized into plasma/CSF and plasma/PET groups. Demographic and clinical variables, amyloid-β (Aβ) burden, flortaucipir-PET binding in Braak regions of interest (ROIs), longitudinal changes in clinical outcomes, and conversion risk were compared. **Results:** Across different tau biomarker groups, the proportion of participants with a discordant profile varied (plasma+/CSF– 15.6%, plasma–/CSF+ 15.3%, plasma+/PET– 22.4% and plasma–/PET+ 6.1%). Within plasma/CSF categories, we found an increase from concordant-negative to discordant to concordant-positive in the frequency of Aβ pathology or cognitive impairment, rates of cognitive decline, and risk of cognitive conversion. However, the two discordant categories (plasma+/CSF– and plasma–/CSF+) showed comparable performances, resulting in similarly reduced cognitive capacities. Regarding plasma/PET categories, as expected, PET positive individuals had increased Aβ burden, elevated flortaucipir retention in Braak ROIs, and accelerated cognitive deterioration than concordant-negative persons. Noteworthy, discordant participants with normal PET exhibited reduced flortaucipir uptake in Braak stage ROIs and slower rates of cognitive decline, relative to those PET positive. Therefore, individuals with PET abnormality appeared to have advanced tau pathological changes and poorer cognitive function, regardless of the plasma status. Furthermore, these results were found only in individuals with Aβ pathology. **Conclusions:** Our results indicate that plasma and CSF p-tau181 abnormalities associated with amyloidosis occur simultaneously in the progression of AD pathogenesis and related cognitive decline, before tau-PET turns positive. **Competing interests:** The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

LP06- EXTRACELLULAR VESICLE BIOMARKERS OF INSULIN SIGNALING ASSOCIATE WITH AGE-RELATED CHANGE IN CSF BIOMARKERS OF ALZHEIMER'S DISEASE IN ADULTS WITHOUT DEMENTIA. Gilda Ennis[1], Erden Eren[2], Yue Ma[1], Corinne Engelman[1], Rozalyn Anderson[1], Ivonne Suridjan[3], Gwen Kollmorgen[4], Cynthia Carlsson[1], Sanjay Asthana[1], Sterling Johnson[1], Henrik Zetterberg[5], Kaj Blennow[5], Barbara Bendlin[1], Dimitrios Kapogiannis[2] *(1. University Of Wisconsin-Madison - Madison (United States), 2. National Institute On Aging - Baltimore (United States), 3. Roche Diagnostics International Ltd - Rotkreuz (Switzerland), 4. Roche Diagnostics Gmbh - Penzberg (Germany), 5. University Of Gothenburg - Gothenburg (Sweden))*

Background: Insulin signaling is essential to neuronal health, facilitating neurogenesis and inhibiting neurodegeneration. A large body of literature indicates that dysregulation of neuronal insulin signaling is associated with dementia due to Alzheimer's disease (AD). In postmortem hippocampal tissue of autopsy-confirmed AD cases, reduced responses to insulin were identified at the level of insulin receptor substrate-1 (IRS-1), and basal levels of phosphorylated forms of IRS-1 and downstream molecules [e.g., pAkt(Ser473)] were higher in AD cases compared with controls (Talbot et al., 2012). In a case-control study of cognitively normal individuals, some of whom eventually developed AD, future AD cases had higher levels of insulin signaling biomarkers, tyrosine and serine 312 phosphorylated IRS-1, in plasma extracellular vesicles (EVs) enriched for neuronal origin (nEVs). Results suggest that impaired neuronal insulin signaling is associated with the clinicopathologic continuum of AD, but it is not clear how insulin signaling biomarkers in nEVs (and by extension, neuronal insulin signaling) may be related to established cerebrospinal fluid (CSF) biomarkers of AD (and by extension, AD pathologic cascades). **Objectives:** We tested whether nEV biomarkers of insulin signaling would moderate the association between age and CSF biomarkers of AD in a sample of middle-aged and older adults without dementia but enriched for AD risk due to parental history of the disease and APOE4 allele carriership. **Methods:** Adults (n= 163) from the Wisconsin Registry for Alzheimer's Prevention (WRAP) were tested. Participants had a mean age of 61.5 years (SD = 6.4) at first lumbar puncture and 38.7% were APOE εX/ε4 allele carriers. By time of last lumbar puncture, 6.1% had mild cognitive impairment and none had been diagnosed with dementia. nEVs were isolated from plasma samples by immunoprecipitation targeting neuronal marker L1CAM. Enrichment for L1CAM was confirmed by flow cytometry analysis and EV-association and neuronal origin were demonstrated by high resolution microscopy demonstrating co-localization with EV markers and neuronal markers, respectively. The following insulin signaling biomarkers were measured in nEVs using electrochemiluminescence assays (Meso Scale Discovery, Rockville, Maryland, USA): a) tyrosine phosphorylated IRS-1 [p(Tyr)-IRS-1], b) insulin-like growth factor 1 receptor (p-IGF-1R), c) insulin receptor (pIr), d) glycogen-synthase kinase 3β phosphorylated at serine 9 [pGSK-3B(Ser9)], and e) protein kinase B phosphorylated at serine 473 [pAkt(Ser473)]. Plasma for nEVs was collected on average 1.1 years (standard deviation = 1.9) prior to first lumbar puncture. Longitudinal CSF (1-5 samples) was collected over a mean of 5 years and was assayed using the Roche NeuroToolKit panel employing either the Elecsys® β-Amyloid (1-42), Total-Tau and Phospho-Tau (181P) CSF immunoassays or robust prototype assays (Roche Diagnostics International Ltd, Rotkreuz, Switzerland). CSF biomarkers of AD were tested as dependent variables and included: Aβ42/Aβ40 ratio, p-tau181/Aβ42 ratio, and p-tau181. CSF biomarkers of neurodegeneration (t-tau, neurogranin, and NfL) were also explored as outcomes. Linear mixed effects models examined nEV biomarkers of insulin signaling as moderators of age-related change in CSF biomarkers of AD. APOE4 allele carrier status and sex were controlled. **Results:** p(Tyr)-IRS-1, pGSK-3B(Ser9), and pAkt(Ser473) significantly moderated the relationship between age and CSF p-tau181/Aβ42 ratio. Higher levels of each nEV biomarker were related to a steeper increase in CSF p-tau181/Aβ42 with increasing age. There were trends ($p \leq .11$) for all nEV insulin signaling biomarkers to moderate the relationship between age and CSF Aβ42/Aβ40 ratio. Results suggested that a higher level of each nEV biomarker was related to a non-significant steeper decline in CSF Aβ42/Aβ40 with increasing age. None of the nEV biomarkers of insulin signaling moderated the relationship between age and CSF p-tau181, t-tau, NfL, and neurogranin. **Conclusion:** In a sample of predominantly asymptomatic adults, higher levels of insulin signaling biomarkers derived from nEVs (putatively suggesting the presence of neuronal insulin resistance in brain tissues) were related to steeper increases in CSF p-tau181/Aβ42 ratio with increasing age, when controlling for APOE4 allele carrier status and sex. Whether AD pathology dysregulates neuronal insulin signaling and induces brain insulin resistance or the latter accelerates the accumulation of AD pathology should be investigated. Treating brain insulin resistance alongside therapies targeting amyloid and/or tau deserves consideration. **Conflict of interests:** IS is a full-time employee and shareholder of Roche Diagnostics International Ltd. GK is a full-time employee of Roche Diagnostics GmbH. HZ has served at scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics and CogRx, has given lectures in symposia sponsored by Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. KB has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu, Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program.

LP08- CEREBROSPINAL FLUID BIOMARKERS IN EARLY ALZHEIMER'S DISEASE SUBJECTS WITH APOE4/4 AND APOE3/4 GENOTYPES: BASELINE DATA FROM PHASE 2 BIOMARKER STUDY WITH ORAL ANTI-AMYLOID AGENT ALZ-801. John Hey[1], Susan Abushakra[1], Aidan Power[1], Sterre Rutgers[2], Katerina Sheardova[3], Paul Dautzenberg[4], Niels Prins[2], Ladislav Pazdera[5], Earvin Liang[1], Kaj Blennow[6], Philip Scheltens[7], Jakub Hort[8], Martin Tolar[1] *(1. Alzheon Inc. - Framingham (United States), 2. Brain Research Center - Amsterdam (Netherlands), 3. St. Anne University Hospital - Brno (Czech Republic), 4. Brain Research Center - Den Bosch (Netherlands), 5. Vestra Research Clinics - Rychnov And Knežnou (Czech Republic), 6. Gothenberg University - Molndal (Sweden), 7. Amsterdam University Medical Centers, Alzheimers Center - Amsterdam (Netherlands), 8. Charles University Cognitive Center, Motol Hospital - Prague (Czech Republic))*

Background: Biomarker-based diagnosis of Alzheimer's disease (AD) for drug trials represents a major advance in drug development (Jack, 2018). This diagnostic framework requires evidence of beta amyloid (Aβ) and tau pathology, ±

neurodegeneration (A/T/N system), using PET imaging or cerebrospinal fluid (CSF) biomarkers. The core AD biomarkers in CSF: soluble Aβ42 and Aβ40, and hyperphosphorylated tau (p-tau), become abnormal before the emergence of amyloid plaques and neurofibrillary tangles on PET scans. These biomarkers are useful for patient selection and evaluation of disease-modifying drug effects. ALZ-801 is an oral, brain-penetrant, inhibitor of amyloid oligomer formation, in development as a disease modifying agent. ALZ-801 is being evaluated in an ongoing APOLLOE4 Phase 3 study in Early AD subjects with APOE4/4 homozygous genotype, and in a Phase 2 biomarker study in Early AD subjects with both APOE4/4 homozygous and APOE3/4 heterozygous genotypes. The Phase 2 trial already completed enrollment and will evaluate effects of ALZ-801 on fluid biomarkers, including CSF and plasma biomarkers of Aβ and tau pathologies, microglial and astrocyte activation, and synaptic and axonal injury. **Objectives:** To assess the baseline differences in CSF biomarker profiles in APOE4/4 homozygotes (HM) versus APOE3/4 heterozygotes (HT) with Early AD, and to inform selection of CSF biomarker outcomes for ALZ-801 trials in these genotypes. **Methods:** The ALZ-801 Phase 2 biomarker study is in progress at 7 sites in the Czech Republic and the Netherlands, and enrolled Early AD subjects (MMSE 22-30, CDR-G 0.5 or 1) with either APOE4/4 or APOE3/4 genotypes. Enrollment requires a prior positive amyloid PET or CSF biomarkers fulfilling A+/T+ criteria, and the primary endpoint is CSF p-tau181reduction at 2 years. Subjects receive ALZ-801 over 2 years (265mg BID tablet) and undergo serial assessments of CSF, plasma, volumetric MRI, and cognitive tests. The CSF dataset includes all screened subjects who provided baseline CSF for study inclusion. Biomarker analyses were performed at the Neurochemistry Laboratory (Dr. Blennow, Molndal, Sweden), and were blinded to subject's demographics and genotype. CSF biomarker assays were analyzed using Lumipulse (Fujirebio). CSF enrollment criteria were: Aβ42 ≤ 610 pg/ml with ratio of Aβ42/40 x10 ≤ 0.61, and p-tau181≥ 60 pg/ml. All CSF values (reported in pg/ml) were analyzed with descriptive statistics and linear regression plots versus MMSE score. Biomarker values between genotypes were compared using both parametric and non-parametric tests and 1-tailed p-values. 131 subjects completed screening, and 110 subjects had acceptable clinical tests and brain MRI. 108 subjects provided CSF samples evaluated in this analysis. **Results:** The CSF dataset (N=108) includes 34 homozygotes (19 females/15 males) and 74 heterozygotes (35 females/39 males); difference in proportion of females was not significant. Mean age and MMSE of HM and HT were similar (68.5 versus 67.9 years, p = NS; MMSE 26 in both). Baseline Aβ42 levels in HM and HT were 431 (SD 128) and 548 (SD 258), respectively, p = 0.0072; Aβ42/40 ratios were: 0.40 (SD 0.11) and 0.52 (SD 0.19), p = 0.0002; and p-tau181were 97.3 (SD 47.6) and 80.3 (SD 47.9), p = 0.045. Ratio of CSF p-tau/Aβ42 in HM and HT was 0.24 (SD 0.12) and 0.18 (SD 0.12), p = 0.011. Regression analysis of biomarkers versus screening MMSE was evaluated for Aβ42, Aβ42/40, p-tau, and p-tau/Aβ42, showing distinct profile for each genotype. In HM, the linear regression of CSF Aβ42/40 versus MMSE was flat, while HT exhibited a defined slope. A similar difference in profiles emerged for p-tau181levels versus MMSE. All homozygotes except one subject, had abnormal Aβ42/40 and elevated p-tau at MCI stage (MMSE >26), while 11 HT with MCI were below threshold. Despite similar demographics and MMSE scores, 27% of heterozygotes (20/74) were below A+/T+ threshold, versus only 3% of homozygous subjects (1/34) who were A-/T- and failed screening. **Conclusions:** ALZ-801 Phase 2 biomarker study enrolled Early AD subjects using criteria similar to the ongoing APOLLOE4 Phase 3 study. Analysis of 108 AD patients showed significant baseline differences in CSF biomarker profiles between APOE4/4 homozygotes and APOE3/4 heterozygotes. Almost all homozygotes (>97%) had abnormal p-tau/Aβ42 levels, thereby validating selection of this patient population for the ALZ-801 Phase 3 study. In contrast, one-third of APOE4 heterozygotes had negative CSF biomarkers, indicating the necessity of CSF biomarkers to enroll A+/T+ subjects. These data support the distinct phenotype of APOE4/4 AD subjects, who have higher p-tau/Aβ42 ratios than APOE4 heterozygotes and appear to accumulate a high burden of amyloid and tau pathologies at the pre-MCI stage. Tramiprosate, the active agent in the ALZ-801 prodrug, selectively blocks formation of soluble Aβ oligomers and has shown promising efficacy in APOE4/4 AD subjects with favorable safety, and with no evidence of vasogenic edema or macrohemorrhages (Abushakra, 2017). These data strongly support selection of a genetically-defined population enriched in Aβ pathology for the initial Phase 3 trial of ALZ-801 in AD.

LP09- BRAIN HIPPOCAMPAL VOLUME AND CORTICAL THICKNESS IN EARLY ALZHEIMER'S DISEASE SUBJECTS WITH APOE4/4 AND APOE3/4 GENOTYPES: BASELINE DATA FROM PHASE 2 BIOMARKER STUDY WITH THE ORAL ANTI-AMYLOID AGENT ALZ-801. Susan Abushakra[1], John Hey[1], Luc Bracoud[2], Aidan Power[1], Joyce Suhy[3], Jakub Hort[4], Sheardova Katerina[5], Pazdera Ladislav[6], Rutgers Sterre[7], Scheltens Philip[8], Tolar Martin[1] *(1. Alzheon Inc. - Framingham (United States), 2. Bioclinica - Leon (France), 3. Bioclinica - San Mateo (United States), 4. Charles University - Prague (Czech Republic), 5. St. Anne University Hospital - Brno (Czech Republic), 6. Vestra Research Clinics - Rychnov And Knežnou (Czech Republic), 7. Brain Research Center - Amsterdam (Netherlands), 8. Amsterdam University Alzheimer Center - Amsterdam (Netherlands))*

Background: Hippocampal volume and cortical thickness are widely used imaging biomarkers in trials of disease modifying Alzheimer's disease (AD) agents. Recent late-stage trials of anti-amyloid antibodies have consistently shown increased brain atrophy, and no significant slowing of hippocampal or cortical atrophy. These studies included approximately 15-17% APOE4/4 homozygotes, 50-55% APOE4 heterozygotes, and 30-35% APOE4 non-carriers. APOE4, a major genetic risk factor for sporadic AD, is associated with heterogeneity on pathologic, cognitive and brain atrophy profiles (Emrani, 2020, Abushakra 2020). To date, volumetric MRI (vMRI) results from drug trials have not been reported by APOE genotypes. ALZ-801 is an oral, brain-penetrant small molecule inhibitor of amyloid oligomer formation. Oral ALZ-801 is potentially disease modifying, has favorable long-term safety, and is not associated with vasogenic edema, even in APOE4/4 homozygotes. ALZ-801 is therefore being evaluated in the APOLLOE4 Phase 3 study in Early AD subjects with APOE4/4 homozygous genotype (NCT04770220). We also started a Phase 2 biomarker study in Early AD subjects with both APOE4/4 homozygous and APOE3/4 heterozygous genotypes, in which we examine drug effects on vMRI and AD fluid biomarkers (NCT04693520). This Phase 2 biomarker study already completed enrollment of 84 subjects. **Objectives:** To assess the baseline differences in hippocampal volume (HV) and cortical thickness (CT) in APOE4/4 homozygotes versus APOE3/4 heterozygotes with Early AD, and to inform selection of the primary brain volume outcome in the APOLLOE4 Phase 3 trial, and in a planned trial evaluating ALZ-801 in APOE4

heterozygotes. **Methods:** We analyzed data from the ongoing ALZ-801 Phase 2 AD Biomarker Study being conducted at 7 sites in Czech Republic and the Netherlands. This multi-center study enrolled Early AD subjects (MMSE 22-30, CDR-G 0.5 or 1), who receive ALZ-801 over 2 years and undergo serial assessments of CSF, plasma and vMRI biomarkers. Among 131 screened AD subjects, a total of 110 were clinically eligible and had good quality (evaluable) baseline MRIs. Of these 110 subjects, 108 provided baseline CSF for analysis of amyloid and p-tau biomarkers (A, T respectively). The subset that had positive CSF biomarkers (A+/T+) were enrolled into the study (N=84). All the vMRI analyses were conducted by Bioclinica using previously reported methods (Abushakra et al, 2020). In summary, vMRI data were processed centrally with fully automated methods using FreeSurfer v5.2 for brain segmentation at baseline. Cortical thickness was measured using FreeSurfer, and Mayo AD signature ROI was calculated (Jack et al. 2017). Baseline HV (L+R) and average cortical thickness (Mayo Index) were summarized using descriptive statistics, and compared using independent sample t-tests. HV is presented in mm3, and cortical thickness in mm. Correlations between baseline vMRI biomarkers and clinical characteristics (age and MMSE) were assessed within each APOE4 subgroup using Pearson's correlations. **Results:** The MRI dataset (N=110) included 35 APOE4/4 homozygotes (HM, 18 females/17 males) and 75 heterozygotes (HT, 41 females/34 males). The mean age and MMSE of the HM and HT groups were similar (68.5 vs 67.5 years; MMSE 26.5 vs 26). Baseline HV mean values were similar in homozygotes and heterozygotes: HM was 6786 mm3(SD 1207) vs 7092 mm3(SD 990), p = 0.093 (2-tailed). CT values using Mayo Index were also similar: HM was 2.73 mm (SD 0.17) vs 2.68 mm (SD 0.20), p =0.122 (2-tailed). In heterozygotes, both HV and Mayo Index values were inversely correlated with age (R= -0.49 & -0.47, both p< 0.001), and positively correlated with MMSE (R=0.55 & 0.58, both p< 0.001). While in homozygotes correlations of HV and Mayo Index to age were not significant (R= -0.24 & -0.12, p= 0.174, p= 0.316), but correlations to MMSE were significant (R=0.41 & 0.40, both p< 0.02). Regression analyses of CT vs MMSE were compared between HM and HT, the differences did not achieve statistical significance, but heterozygotes appeared to have more prominent cortical thinning in advanced disease (lower MMSE) group. Heterozygotes showed the strongest correlation in this analysis, for cortical thickness positive correlation with MMSE (0.58, p< 0.001). **Conclusions:** In this cross-sectional analysis of baseline MRI data in Early AD patients, APOE4/4 homozygotes vs APOE4 heterozygotes showed distinct profiles of hippocampal atrophy and cortical thinning with advanced disease and age. In APOE4 heterozygotes, both volumetric measures showed significant and moderate correlations with MMSE, while in homozygotes this correlation was significant but modest. The correlation of cortical thickness to disease stage appears to be steeper in APOE4 heterozygotes than homozygotes. These differences in brain atrophy profiles were apparent despite similar demographic characteristics and disease stage. These findings can be strengthened by analyzing a longitudinal dataset such as ADNI. For a planned Phase 3 trial with ALZ-801 focusing on APOE4 heterozygotes, cortical thinning may be an optimal brain imaging biomarker to assess therapeutic effects of a prospective disease modifying agent.

RP07- LEVELS OF CIRCULATING MEMORY CD8 T CELLS THAT INDUCE AD-LIKE PATHOLOGY IN MICE CORRELATE WITH COGNITION AND DECREASED CSF ABETA42 IN PATIENTS. Christopher Wheeler[1,2], Debby Van Dam[3,4], Yannick Vermeiren[3,4], Hans De Reu[3], Peter Paul De Deyn[3,4], Vicky Yamamoto[2,5] *(1. T-Neuro Pharma, Inc. - Aptos (United States), 2. Brain Mapping Fndn. - Pacific Palisades (United States), 3. University Of Antwerp - Antwerp (Belgium), 4. University of Groningen - Groningen (Netherlands), 5. University Of Southern California - Los Angeles (United States))*

Backgrounds: We previously engineered mice to accumulate age-related, antigen-specific memory CD8 T cells as in humans. These mice spontaneously develop all major hallmarks of AD with aging. Analogous T cells reactive to an epitope on Amyloid Precursor Protein (APP) were found in aging humans, accumulated in AD brain, and decreased in AD blood where their levels accurately tracked the disease in initial analysis. Here, we examine whether levels of these blood T cells are associated with established AD biomarkers. **Objectives:** We specifically sought to assess the extent to which APP-peptide-specific, KLRG1+ CD8 T cell levels in blood corresponded with Aβ1-42, total Tau, and/or pTau181 levels in CSF from the same patients. Correspondence with one or more of these CSF biomarkers could suggest the mechanism(s) by which these T cells impact AD pathophysiology, as well as aid in determining temporal limitations to their ability to track AD along the disease course. **Methods:** Antigen-specific CD8 T cells in blood were quantified by flow cytometric analysis after staining with anti-CD8, anti-KLRG1 and APP peptide-HLA-A2 multimers in normal aging, MCI with or without AD biomarkers, and confirmed late-onset AD patient cohorts (n = 50). Aβ1-42, total Tau, and pTau181 were quantified in CSF, and cognitive performance assessed by MMSE. **Results:** Percentage of APP-specific memory CD8 T cells was significantly decreased with dementia (0.68 + 0.29% for MMSE <25; 1.63 + 0.32% for MMSE >24), reaching minimal levels in AD. Although the paucity of APP-specific CD8 T cells in AD blood precluded meaningful correlations, decreases in the larger parental (KLRG1+) memory CD8 T cell population correlated with decreased CSF Aβ1-42 in AD (r = 0.511; P = 0.003; n = 31). Decreasing APP-specific CD8 T cells in blood also correlated with lower CSF Aβ1-42 in normal aging patients (r = 0.518; P = 0.028; n = 18). No significant correlations between T cell levels and total Tau or pTau181 were observed. **Conclusion:** Our results reveal that age-related memory CD8 T cells in blood decrease with dementia, and in proportion to decreased CSF Aβ1-42 in both AD and normal aging. Given that decreased CSF Aβ1-42 is among the earliest biomarkers for AD, this validates our previous findings that loss of APP-specific memory CD8 T cells from blood accurately tracks the AD continuum in humans. Our findings also support the notion that antigen-specific memory CD8 T cells are associated with the earliest detectable pathologic changes in AD, and as such may represent novel candidates to predict and track the disease.

RP08- SERUM INFLAMMATORY BIOMARKERS IN MILD VS MODERATE PATIENTS UNDERGOING THERAPEUTIC PLASMA EXCHANGE WITH ALBUMIN REPLACEMENT AS A TREATMENT FOR ALZHEIMER'S DISEASE. Ana María Ortiz[1], Carla Minguet[1], Ricardo Gonzalo[1], Laura Núñez[1], Agustín Ruiz[2,3], Oscar L López[4], Mercè Boada[2,5], Antonio Páez[1], Montserrat Costa[1] *(1. Grifols Bioscience Research - Barcelona (Spain), 2. Research Center And Memory Clinic, Fundació Ace, Institut Català De Neurociències Aplicades-Universitat Internacional De Catalunya - Barcelona (Spain), 3. Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Instituto de Salud Carlos III - Madrid (Spain) - Madrid (Spain), 4. Departments Of Neurology And Psychiatry, University Of Pittsburgh School Of Medicine - Pittsburgh (United States), 5. Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Instituto de Salud Carlos III - Madrid (Spain)))*

Backgrounds: There is increasing evidence that Alzheimer's disease (AD) pathogenesis is not restricted to the neuronal compartment but would involve peripheral inflammatory mechanisms. The AMBAR phase 2b/3 trial is a therapeutic approach for mild-to-moderate AD patients (Mini-Mental State Examination [MMSE]:18-26) based on a 14-month program comprising 18 plasma exchange procedures with albumin replacement (PE-Alb) by removing neurotoxic Aβ and other pathological substances, to slow down or even halt AD progression. **Objectives:** The aim of this study was to assess PE-Alb effects on serum inflammatory biomarkers across the AMBAR study, with patients stratified by moderate and mild AD. **Methods:** Twenty-three inflammatory biomarker levels (IFN γ, IL 1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, TNF-α, Eotaxin, MIP-1β, Eotaxin 3, TARC, IP-10, MIP-1α, MCP-1, MDC, MCP-4, SAA, CRP, VCAM-1 and ICAM 1) were measured through three electrochemiluminescence V-plex panels from Meso Scale Discovery. Up to 105 PE-Alb-treated and 37 placebo [sham-PE-Alb] patients were studied. Samples were collected throughout two intervention regimens: an intensive or conventional therapeutic PE-Alb period (TPE: processing 1 plasma volume [2500-3000 mL]; 1 TPE/week for 6 weeks); and a maintenance or low volume PE-Alb [LVPE] period (removal of approximately 1/3 plasma volume [similarly to a plasma donation]; 1 LVPE/month for 12 moths). Serum samples (8 time points) collected from 2016 onwards, were assessed. Evaluable biomarkers, defined as those that were detectable in more than 30% of the samples at baseline and final visit, were analyzed over time as the change from baseline with a mixed model for repeated measures (MMRM) approach stratifying for moderate and mild AD patients (baseline MMSE scores 18-21 and 22-26 respectively). After patient stratification, the sample size of 2 cytokines was insufficient for MMRM analysis. Fixed effects factors for month, treatment group, and month*treatment interaction, with adjustment for age, baseline MMSE, and baseline biomarker levels were used. Patient was included as a repeated factor in the model. Least squares means (LSM) (± standard error of the mean [SEM]) was used to plot the differences vs the baseline. Reported p-values were adjusted by Benjamini-Hochberg procedure to decrease the False Discovery Rate. **Results:** Seventeen out of 23 inflammatory biomarkers in serum resulted evaluable. Across treatment analysis, positive effects on lowering serum inflammatory biomarkers in comparison to placebo were observed within the TPE period (at 1.5-month and/or at intermediate visit [2-month]) and/or in the LVPE period (at 9-month, 13-month and/or 14-month) in both mild and moderate patients. Mixed model estimates showed statistical significance ($p<0.05$) for 11 biomarkers in moderate PE-treated patients and for 4 biomarkers in mild PE-Alb-treated patients compared to placebo. After adjusting for false discovery rate, statistical significance was still present in 7 serum pro-inflammatory biomarkers in moderate AD patients compared to placebo. Again, the positive effects could be observed in both treatment periods. **Conclusions:** PE-Alb procedures used in the AMBAR study (the TPE and the LVPE), reduced the serum pro-inflammatory profile for both mild and moderate AD patients in comparison to placebo. The more marked effects were observed in moderate AD patients. These results support a multimechanistic basis of the AMBAR therapeutic approach that may contribute to slowing AD progression. Further investigation is warranted.

RP09- A POLYGENIC RISK SCORE IS ASSOCIATED WITH ALZHEIMER'S BRAIN PATHOLOGY IN AN AGE-DEPENDENT MANNER. Joseph Quinn[1], Chao-Yi Wu[1], Sahi Kolli[2], Nora Mattek[3], Randall Woltjer[3], Shawn Westaway[3], Jeffrey Kaye[3], Kelly Bakulski[4], Hiroko Dodge[4] *(1. Department of Neurology, Layton Aging And Alzheimer's Disease Center, Oregon Health & Science University - Portland (United States), 2. International Business Machines (ibm) - New York (United States), 3. Department of Neurology, Layton Aging And Alzheimer's Disease Center, Oregon Health & Science University - Portland, Or (United States), 4. Department of Epidemiology At The University of Michigan School of Public Health And Michigan Alzheimer's Disease Center - Ann Arbor (United States))*

Background: Polygenic scores may be a strategy to enrich Alzheimer's disease (AD) prevention trial populations with individuals at high risk of dementia. However, age-dependent differences in AD brain pathology may complicate this approach. **Objective:** To test the hypothesis that the brain pathology predicted by PRS is dependent on age of the participant. **Methods:** All subjects in the Oregon Aging and Alzheimer's Disease Center database with single nucleotide polymorphism data from National Cell Repository for Alzheimer's Disease (NCRAD) were included. At each overlapping genomic position (92,584 variants), we weighted the number of participant variant alleles by the allele's association with Alzheimer's disease (Kunkle 2019) and took the sum. Within the 535-participant sample, the sums were z-score standardized to generate the polygenic scores. Relationships between polygenic scores and quantitative brain pathology were examined, using Braak staging as a measure of neurofibrillary tangle pathology, CERAD staging as a measure of beta amyloid pathology, the presence of Lewy bodies, and cerebrovascular pathology as indicated by small artery infarcts and/or hemorrhages. The associations between polygenic score and each brain pathology were examined in the overall sample with neuropathological data (n=353). Regression models were adjusted for covariates (age, sex, educational attainment, having at least one Apolipoprotein E4 allele versus none). We tested for effect modification of the polygenic score by age among those <75 years at death (n=58) and those ≥75 years (n=295). **Results:** The study sample was 56.4% female, 100% European genetic ancestry, and had an average of 14.7 years of education. The average Braak stage in this sample was 4.6. Multinomial regression models showed that those with Braak stage 5-6, compared with Braak stage 3-4, had 0.3 standard deviation unit higher polygenic risk score (p=0.03). When the group was dichotomized by age, the effect of polygenic score upon Braak stage was not moderated by age (pinteraction=0.22). The average CERAD stage in this sample was 1.6. Those with

CERAD stage 3, compared with CERAD stages 0, 1, and 2, had higher polygenic scores (CERAD score of 3 versus 0, p=0.001; CERAD score of 3 versus 1, p= 0.04; CERAD score of 3 versus 2, p=0.02). The effect of polygenic score upon CERAD stage was suppressed at older ages (pinteraction(CERAD 0 versus 1)=0.03, pinteraction(CERAD 3 versus 1)=0.045), suggesting that a higher polygenic score was associated with higher beta amyloid pathology among those who died before 75 years old in comparison with those who died at/after age 75. For example, for one standard deviation increase in PRS, the odds of having CERAD score of 1 (vs 0) is decreased by 95% if the participant's age at death is 75 or older. A total of 19.1% of this sample had Lewy body pathology. There was no relationship between Lewy body pathology and polygenic score (p=0.39). A total of 19.3% of this sample had small artery infarcts and/or hemorrhages. There was no relationship between cerebrovascular pathology and polygenic score (p=0.19). **Conclusions:** A polygenic score for Alzheimer's disease was associated with multiple brain pathologies, and the influence of the polygenic score upon beta amyloid brain pathology varied with age. If polygenic scores are to be included in clinical trials for prevention of Alzheimer's disease, they may need to be tailored to the age of the study population. **Funding:** NIA P30AG066518, NIA P30 AG053760

RP10- LONGITUDINAL TAU ACCUMULATION IN ALZHEIMER'S DISEASE: PROSPECTIVE 5-YEAR FOLLOW-UP STUDY. Hanna Cho[1], Min Seok Baek[2], Han-Kyeol Kim[1], Jae Hoon Lee[3], Joong-Hyun Chun[4], Young Hoon Ryu[3], Chul Hyoung Lyoo[1] *(1. Department Of Neurology, Gangnam Severance Hospital, Yonsei University College Of Medicine - Seoul (Korea, Republic of), 2. Department Of Neurology, Wonju Severance Christian Hospital, Yonsei University Wonju College Of Medicine - Wonju (Korea, Republic of), 3. Department Of Nuclear Medicine, Gangnam Severance Hospital, Yonsei University College Of Medicine - Seoul (Korea, Republic of), 4. Department Of Nuclear Medicine, Severance Hospital, Yonsei University College Of Medicine - Seoul (Korea, Republic of))*

Background: Tau PET reflecting severity of Alzheimer's disease (AD) is now considered to be a disease stage biomarker for AD. Recent longitudinal studies exhibited a progression of cortical tau burden and a predictability of baseline tau PET for further tau accumulation, cortical atrophy, and even clinical progression in short-term period. We sought to investigate long-term changes in tau burden and predictability of tau PET for long-term disease progression. **Methods:** In a cohort with 273 participants who had completed visit 1 (V1) assessments including two PET (18F-florbetaben and 18F-flortaucipir), MR imaging studies and neuropsychological function tests, 77 Aβ+ participants [9 cognitively unimpaired (CU) and 38 mild cognitive impairment (MCI), and 30 AD dementia (DEM)] completed visit 2 (V2) assessments at two years, and subsequently 39 Aβ+ participants (6 CU, 24 MCI, and 9 DEM) completed visit 3 (V3) assessments at about four years (mean 4.6 years) after the V1 study. After correcting for partial volume effect, we measured regional standardized uptake value ratios (SUVR) values with cerebellar crus median as a reference and regional volumes as well. **Results:** During the short- (V1 to 2) and long-term (V1 to 3) periods, tau burden significantly increased in the widespread cortex, particularly in the medial and lateral temporal cortices. In 33 cognitively impaired patients who completed both V2 and V3 scans, DEM patients exhibited higher global cortical tau accumulation rate (V1 to 2 = 0.066 and V2 to 3 = 0.058 SUVR/year) than MCI patients (V1 to 2 = 0.044 and V2 to 3 = 0.051 SUVR/year). Tau burden at V1 highly correlated with the tau accumulation and volume reduction rates, particularly in the lateral temporal cortex and also correlated with the global cognitive decline rate, particularly in the prefrontal and parietal cortices. Likewise, in both short- and long-term data, tau accumulation rate correlated with the volume reduction and global cognitive decline rates. **Conclusion:** Tau accumulates progressively throughout four years of long-term follow-up period. Progression of tau pathology, cortical atrophy and cognitive decline can be predicted by baseline tau burden. Tau PET is useful imaging biomarker in predicting long-term disease progression.

RP11- ASSESSMENT OF HIGH RISK FOR ALZHEIMER'S DISEASE USING PLASMA BIOMARKERS IN SUBJECTS WITH NORMAL COGNITION IN TAIWAN. Shieh-Yueh Yang *(Magqu Co., Ltd. - New Taipei City (Taiwan, Province of China))*

Background: In Alzheimer's disease (AD), cognitive impairment begins 10-15 years later than neurodegeneration in the brain. Fluid biomarkers are promising candidates for identifying neurodegeneration in people with normal cognition. **Objectives:** In this work, 422 subjects aged 20 to 89 years were enrolled in seven cities around Taiwan. All enrolled subjects were clinically diagnosed with normal cognition. Plasma amyloid β 1-40 (Aβ1-40), Aβ1-42, and total Tau protein (T-Tau) levels were assayed for each subject using immunomagnetic reduction to assess the rick of of dementia. **Measures:** It has been reported that subjects with Aβ1-42 x T-Tau levels higher than 455 pg2/ml2 are assessed as having a high risk of amnesic mild impairment (aMCI) or AD, denoted as HRAD. The results in this study showed that 4.6% of young adults (age: 20-44 years), 8.5% of middle-aged adults (age: 45-64 years) and 7.3% of elderly adults (age: 65-90 years) had HRAD. The percentage of individuals with HRAD dramatically increased in middle-aged and elderly adults compared to young adults. **Conclusions:** This suggests that attention should be paid to preventing cognitive impairment due to Alzheimer's disease, not only in elderly adults but also middle-aged adults. More subjects should be enrolled in the future to validate the percentage of people with normal cognition with HRAD.

RP12- EVIDENCE OF PLASMA BIOMARKERS FOR HIGH RISK OF DEMENTIA IN COGNITIVELY NORMAL SUBJECTS OF POST STROKE, FAMILY HISTORY OF ALZHEIMER'S DISEASE, DIABETES MELLITUS, END-STAGE RENAL DISEASE AND OBSTRUCTIVE SLEEP APNEA. Shieh-Yueh Yang *(Magqu Co., Ltd. - New Taipei City (Taiwan, Province of China))*

Background: Subjects with cardiovascular risks, family history, hypoxia, and other comorbidities are potentially risky for neurodegeneration. Some models of scores using these risk factors at midlife to predict the occurrence of dementia as aged have been developed for clinical assessments. However, there lacks a direct relationship to correlate these risk factors to dementia pathology. In this work, the assays of immunomagnetic reduction (IMR) are utilized for assaying plasma Aβ1-42 and total Tau protein (T-Tau) in risky population. **Methods:** The enrolled subjects include post-stroke subjects (PS, n = 27), individuals with family history of AD (ADFH, n = 35), patients with diabetes (n = 21), end-stage renal disease (ESRD, n = 41) and obstructive sleep apnea (OSA, n = 20). In addition, thirty-seven healthy controls (HC) and sixty-five patients with Alzheimer's disease were enrolled (AD).

Results: The measured concentrations of plasma Aβ1-42 are 14.26±1.42 pg/ml in HC, 15.43±1.76 pg/ml in PS, 15.52±1.60 pg/ml in ADFH, 19.74±2.92 pg/ml in diabetes, 16.52±0.59 pg/ml in ESRD, 15.97±0.54 pg/ml in OSA and 20.06±3.09 pg/ml in AD. HC shows 15.13±3.62 pg/ml for the levels of T-Tau, PS has 19.29±8.01 pg/ml, ADFH has 17.93±6.26 pg/ml, diabetes has 19.74±2.92 pg/ml, ESRD has 21.54±2.72 pg/ml, OSA has 20.17±2.77 pg/ml, and AD has 41.24±14.64 pg/ml. **Conclusions:** The plasma levels of Aβ1-42 and T-Tau in PS, ADFH, diabetes, ESRD and OSA are relatively high as compared to those in NC, but are lower than those in AD. This evidence the high risk for dementia in these groups in the plasma biomarker point of view.

RP13- DYNAMIC CHANGES OF CSF STREM2 IN PRECLINICAL ALZHEIMER'S DISEASE: THE CABLE STUDY. Lingzhi Ma *(Department Of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao, China (China))*

Background: Loss of function of triggering receptor expressed on myeloid cell 2 (TREM2), a key receptor selectively expressed by microglia in the brain, contributes to the development of Alzheimer's disease (AD). **Objectives:** Whether TREM2 levels are pathologically altered during the preclinical phase, and whether cerebrospinal fluid (CSF) soluble TREM2 protein (sTREM2) has a relationship with major pathological processes including Aβ and tau deposition are still unclear. **Methods:** According to the NIA-AA criteria, 659 cognitively normal participants from the Chinese Alzheimer's Biomarker and LifestylE (CABLE) cohort were divided into four groups, stage 0 (normal Aβ1–42, T-tau and P-tau), stage 1 (low Aβ1–42, normal T-tau and P-tau), stage 2 (low Aβ1–42 and high T-tau or P-tau), and suspected non-AD pathology (SNAP) (normal Aβ1–42 and high T-tau or P-tau), to examine changes of CSF sTREM2 in the preclinical AD. Biomarker cut-off was based on the assumption that one-third of adults with normal cognition have AD pathology. **Results:** The level of CSF sTREM2 in the stage 1 decreased compared with the stage 0 ($P < 0.001$), and then increased in the stage 2 ($P = 0.008$). SNAP individuals also had significantly increased CSF sTREM2 ($P < 0.001$). Results of multiple linear regressions also showed positive correlations of CSF sTREM2 with Aβ1–42 ($\beta = 0.192$, $P < 0.001$), T-tau ($\beta = 0.215$, $P < 0.001$) and P-tau ($\beta = 0.123$, $P < 0.001$). **Conclusion:** CSF sTREM2 levels are dynamic in preclinical AD. Aβ pathology is associated with a decrease in CSF sTREM2 in the absence of tau deposition and neurodegeneration. However, tau pathology and neurodegeneration are associated with an increase in CSF sTREM2.

RP13BIS- CEREBROSPINAL FLUID PLATELET-DERIVED GROWTH FACTOR RECEPTOR-B MEASURED IN BIOFINDER 2: A MARKER OF MICROVASCULAR DAMAGE?. Claudia Cicognola[1,2], Shorena Janelidze[1], Danielle Van Westen[3,4], Khazar Ahmadi[1], Oskar Hansson[1,2] *(1. Clinical Memory Research Unit, Lund University (Sweden), 2. Memory Clinic, Skåne University Hospital (Sweden), 3. Diagnostic Radiology, Department Of Clinical Sciences Lund, Lund University (Sweden), 4. Image and Function, Skåne University Hospital, Malmö (Sweden))*

Background: Pericytes align the endothelial cells in the walls of capillaries and venules and are involved in angiogenesis, maintenance of the blood-brain barrier (BBB) and regulation of the cerebral blood flow (CBF) in the brain. Damage to pericytes causes disruption of the BBB and alterations in CBF and potentially promote cerebral amyloid angiopathy (Blanchard et al., 2020). The platelet-derived growth factor receptor-β (PDGFRβ) is exclusively expressed in brain pericytes and serves as a pericyte-specific marker (Miners et al., 2019). When the BBB is damaged, PDGFRβ is released in the cerebrospinal fluid (CSF). In Alzheimer's disease (AD), levels of CSF PDGFRβ have been associated with the severity of clinical symptoms and predicted cognitive decline in APOE ε4 carriers (Nation et al, 2019; Montaigne et al, 2020). **Objectives:** Our aims were to investigate possible associations between baseline CSF PDGFRβ and clinical diagnosis (stratified by Aβ status); CSF to plasma albumin ratio; glial fibrillary acidic protein (GFAP); the volume of white matter lesions (WML); CBF as measured with arterial spin labelling, longitudinal measures of cognition and APOE genotype. **Methods:** The levels of PDGFRβ in CSF were determined in the longitudinal BioFINDER 2 study, including cognitively unimpaired subjects (CU, n=290), as well as patients with subjective cognitive decline (SCD, n=118), mild cognitive impairment (MCI, n=174), AD dementia (n=124), Parkinson's disease (n=45), dementia with Lewy bodies (DLB, n=28) or other types of neurodegenerative diseases (n=87). PDGFRβ was measured in CSF with the Human Total PDGFRβ DuoSet® IC ELISA (R & D). Aβ status was determined using the CSF Aβ42/40 ratio. Longitudinal cognitive measures included Mini Mental State Examination (MMSE) at baseline and at 2 years' follow-up and Preclinical Alzheimer Cognitive Composite (PACC) at baseline and at 1 year's follow-up. **Results:** The CSF levels of PDGFRβ were increased in patients with Aβ+ SCD, Aβ+ MCI, and AD dementia when compared to Aβ- CU ($p<0.05$). PDGFRβ correlated with the CSF/plasma albumin ratio ($r=0.26$-0.35, $p<0.05$) and CSF GFAP ($r=0.35$-0.47; $p<0.05$) in all groups of the AD continuum. In the CU cases, there was an association between PDGFRβ and WML volume ($r=0.25$; $p<0.0001$). Association clusters in different brain regions seen between PDGFRβ and CBF in all brain regions were dependent on the age of the subjects in each diagnostic group. In CU, there was a negative correlation between PDGFRβ and baseline MMSE and PACC ($r=-0.20$, -0.33, respectively; $p<0.0001$ both). No association was seen between baseline PDGFRβ and longitudinal change MMSE or PACC, even after adjusting for baseline test results. No difference in cognitive decline was observed in subjects stratified by APOE ε4 status based on PDGFRβ baseline concentrations. No clear-cut association with Aβ status was seen in the diagnostic groups for any association analyzed. **Conclusion:** The association between PDGFRβ and the CSF/plasma albumin ratio confirms that PDGFRβ is a marker BBB damage. Further, the observed correlation of PDGFRβ with GFAP indicates a role of astrocytosis in the degeneration of pericytes.

LRP03- PRE-ANALYTICS OF THE AB1-42/AB1-40 RATIO IN FRESH AND FROZEN SAMPLES USING AN OPTIMIZED CSF COLLECTION PROTOCOL. Rianne Esquivel[1], Sara Ho[2], Jacqueline Darrow[2], Amanda Calabro[1], Sara Gannon[1], Parmi Thakker[2], Francesca De Simone[1], Abhay Moghekar[2] *(1. Fujirebio Diagnostics Inc - Malvern (United States), 2. Johns Hopkins School Of Medicine - Baltimore (United States))*

Background: Cerebrospinal fluid (CSF) biomarkers β-amyloid1-42 (Aβ1-42) and β-amyloid1-40 (Aβ1-40) have shown high concordance with amyloid PET when used as the ratio Aβ1-42/Aβ1-40 (amyloid ratio). While Aβ1-42 differentiates individuals who have amyloid burden in the brain from those who do not by decreasing in the CSF, Aβ1-40 remains constant and normalizes the measurement of

amyloid on an individual level to compensate for high and low amyloid producers. Normalization is also necessary to compensate for amyloid loss due to the tendency of amyloid protein to aggregate and adsorb to surfaces. In this study we examined the ability of Aβ1-42/Aβ1-40 to compensate for concentration loss along a specified collection protocol in pre-selected polypropylene tubes. Additionally, the change in Aβ1-42/Aβ1-40 concentration was analyzed under fresh and frozen conditions to determine the feasibility of a single cutoff between sample conditions. **Methods:** Freshly collected CSF samples obtained in Sarstedt 72.703.600 (tube A) and 62.610.018 (tube B) polypropylene tubes from patients at the Johns Hopkins Center for CSF Disorders were subjected to laboratory specific protocols. Aβ1-42 and Aβ1-40 concentrations were measured using the LUMIPULSE G1200 (Fujirebio Diagnostics Inc., Malvern, PA). Tubes were filled to 80% fill volume and CSF were analyzed post centrifugation (2000 xg, 10 minutes, 5 ± 3°C). **Results:** An optimized CSF collection protocol was examined to compare fresh and frozen sample pre-analytics. Prior studies indicated direct collection by gravity drip into Sarstedt tubes 62.610.018 or 72.703.600, no mixing of fresh samples or roller mixing after freezing, and direct testing on an automated platform as optimal for reduction of Aβ1-42 loss. While centrifugation is optional but not recommended it was included in this study as no difference was seen between centrifuged and non-centrifuged samples (Hansson et al, 2020). Aliquots (n=4) from ten patients were measured in tube A and tube B in duplicate to obtain baseline fresh concentrations. During fresh testing, within tube variation was minimal for both individual analytes and amyloid ratio. Between tube variation was significant for fresh testing for individual analytes for 3 out of 10 patients for Aβ1-42 and 7 out of 10 patients for Aβ1-40. No significant differences were observed between the amyloid ratio between tube types (unpaired T test). Using Bland-Altman to examine between tube variation the amyloid ratio further minimized bias between tubes (Aβ1-42: -1.0% +/-3.4%; Aβ1-40: -1.6%+/- 2.5%; Aβ1-42/ Aβ1-40: 0.6% +/-1.5%). Aliquots from the same patient of thawed and roller mixed frozen samples were compared to the fresh aliquots in each tube. Fresh and frozen bias between tube A was minimized using the amyloid ratio (Aβ1-42: -5.5% +/-4.7%; Aβ1-40: -4.2%+/- 3.7%; Aβ1-42/ Aβ1-40: -1.3% +/-2.4%) Fresh and frozen bias between tube B was minimal between individual analytes and remained low using the amyloid ratio (Aβ1-42: -2.1% +/-2.1%; Aβ1-40: -0.2%+/- 2.1%; Aβ1-42/ Aβ1-40: -2.2% +/-2.9%). **Conclusion:** In this study we saw no significant differences between tubes and between fresh and frozen samples when using the Aβ1-42/Aβ1-40 ratio. Individual amyloid proteins did have significant variability in tube A between fresh and frozen testing. However, the amyloid ratio did compensate for this variability. Under an optimized CSF collection protocol, it is feasible to use a single cutoff for the Aβ1-42/Aβ1-40 ratio in fresh and frozen samples. **Conflicts of Interest:** This study was funded by Fujirebio Diagnostics Inc. FD, AC, SG, and RE are employed by Fujirebio Diagnostics Inc.

LRP04- PRE-ANALYTICAL EFFECTS OF CAP CONTACT AND MIXING ON CSF AB1–42, AB1–40, AND PTAU181 CONCENTRATIONS WHEN MEASURED ON AN AUTOMATED CHEMILUMINESCENT PLATFORMY.

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Background: Core cerebrospinal fluid (CSF) biomarker concentrations for β-amyloid1-42 (Aβ1-42) β-amyloid1-40 (Aβ1-40), and ptau181 are valuable in the diagnosis of Alzheimer's Disease (AD). Through use of automated assays and the reduction of analytic variability the true impact of pre-analytic variables on amyloid loss can be observed. In this study the effect of sample mixing and extended sample cap contact on Aβ1-42, Aβ1-40 and ptau181 concentrations and commonly used ratios Aβ1-42/Aβ1-40 and ptau181/Aβ1-42 was evaluated in freshly collected CSF with preselected tubes with optimal pre-analytic characteristics for amyloid collection. The utility of the ratios to correct for pre-analytical variability and bring concentrations within +/- 5% of baseline was examined based on recently published Alzheimer's Association International Guidelines for CSF handling. **Methods:** Freshly collected CSF samples obtained in Sarstedt 72.703.600 (tube A) and 62.610.018 (tube B) polypropylene tubes from patients at the Johns Hopkins Center for CSF Disorders were subjected to laboratory-specific protocols. Aβ1-42, Aβ1-40, and ptau181 concentrations were measured using LUMIPULSE G1200 (Fujirebio Diagnostics Inc., Malvern, PA). Tubes were filled to 80% fill volume and CSF was analyzed post centrifugation (2000 g, 10 minutes, 5 ± 3°C). To assess the effect of mixing method on biomarker concentration, samples were frozen at -80°C and thawed before being inverted, vortexed, roller mixed, or left unmixed prior to analysis. Extended sample cap contact was evaluated by storing samples upright or upside down at 4°C for 1 week or upright or upside down at -80°C for 1 month. **Results:** Prior tube comparison studies established Sarstedt tubes 72.703.600 and 62.610.018 as optimal for reduction of Aβ1-42 loss under specific conditions. Mixing of samples after thawing by vortexing for at least 10 seconds, roller mixing, or inverting 10x is critical. Unmixed samples had lower concentration than mixed samples and resulted in significant concentration loss for all three analytes in both tube types. Additionally, significant concentration loss was observed for individual analytes Aβ1-42 and Aβ1-40 in tube A but not tube B when roller mixing (Aβ1-42: p=0.008; Aβ1-40: p=0.002), vortexing (Aβ1-42: p=0.004; Aβ1-40: p=0.010) or inverting 10x (Aβ1-42: p=0.004; Aβ1-40 p=0.037). In tube B Aβ1-42 or Aβ1-40 concentrations were not significantly lower under any mixing condition. Surprisingly, ptau181 demonstrated significant concentration loss when roller mixing in tube A (p=0.004). However, for all three analytes when mixing conditions were compared using one-way ANOVA (Kruskal-Wallis multiple comparison test) no significant differences were observed and some concentration loss may be due to the additional impact of freezing and thawing rather than mixing. In tube A the Aβ1-42/Aβ1-40 ratio was able to compensate for concentration loss and brought samples to within +/-5 % of baseline for all four conditions (no mixing: Mean -1.7% CI -4.0%-0.6%; Invert 10x: Mean: -2.6% CI -4.5% - -0.7%; Vortex 10s: Mean: -1.4% CI -3.5% – 0.7%; Roller Mixing: Mean: -1.4% CI -3.1% – 0.3%). In tube B the Aβ1-42/Aβ1-40 ratio brought all samples except unmixed (Mean 6.6% CI 1.3% – 11.8%) to within +/-5 of baseline. The ptau181/Aβ1-42

ratio was less able to compensate for concentration loss. In tube A only under roller mixing did concentration remain within +/- 5 percent of baseline (Mean 1.8% CI -0.7% – 4.3%) and for Tube B only inverting 10x remained +/- 5% from baseline (Mean 2.0% CI -0.2% – 4.2%). Cap contact did not significantly impact biomarker concentrations at 4°C. In tube A some concentration loss was observed for Aβ1-40 at -80°C upright (p=0.01) and upside down (p=0.02). However, literature indicates Aβ1-40 is more impacted by long term storage and freezing and thus cap contact may not be responsible for this concentration loss. The Aβ1-42/Aβ1-40 ratio was able to compensate for Aβ1-40 concentration loss and maintain concentration within +/-5% of baseline at -80°C in both conditions (upright mean: 2.7% CI 0.9% – 4.4%; upside down mean: 2.3% CI 0.2% – 4.3%)) whereas the ptau181/Aβ1-42 ratio did not (upright mean: -4.9% CI -18.9% – 9.0%; upside down mean: 4.0% CI 0.5% – 7.5%). In tube B all three analytes experienced significant concentration loss at -80°C upright but not upside down. The Aβ1-42/Aβ1-40 ratio was able to compensate for this effect (mean 2.2% CI 0.1%- 4.4%) but ptau181/Aβ1-42 could not (mean -4.2% CI -9.6% – 1.2%). **Conclusion:** Our data suggests that while mixing samples after thawing is critical, the mode of mixing does not significantly impact concentration. The Aβ1-42/Aβ1-40 ratio was able to compensate for concentration loss after thawing under multiple mixing conditions whereas ptau181/Aβ1-42 was inconsistent in the ability to compensate. Interestingly, while cap contact in these tubes did not appear to significantly impact concentration the study did reveal an issue with tube 62.610.018 storage at -80°C upright that affects individual analyte concentration. This issue needs further examination with additional studies. However, the Aβ1-42/Aβ1-40 ratio was able to compensate for this concentration change and measurement of Aβ1-40 alongside Aβ1-42 is important to normalize amyloid loss especially for -80°C storage. **Conflicts of Interest:** This study was funded by Fujirebio Diagnostics Inc. FD, AC, SG, and RE are employed by Fujirebio Diagnostics Inc.

LRP05- EVALUATE THE UTILITY OF SAPPHIRE II SCANNING COMPARED TO QUANTITATIVE BETA AMYLOID PET SCANS IN MCI AND MILD AD SUBJECTS.

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Background: Alzheimer's disease (AD) is the most common cause of dementia and sixth leading cause of death in the US. Recent research has led to a detailed understanding of AD pathogenesis and emerging treatments that target the underlying pathology. Testing and eventual implementation of new AD treatments depend on developing new diagnostics for accurate and early detection and disease monitoring. Currently, AD diagnosis largely relies on clinical assessment of late-emerging neurocognitive deficits when the underlying pathology is already well established. The NIA recognizes development of reliable, easy-to-use AD diagnostics as a high-priority objective. We present herein our progress on the development of an innovative drug-device combination eye scanner that detects AD-specific β-amyloid (Aβ) pathology in the ocular lens for early AD detection and monitoring. Cognoptix Sapphire II eye scanning technology is based on discovery of AD-specific Aβ pathology in the ocular lenses of patients with pathologically confirmed AD, but not in other neurodegenerative diseases or normal aging. This discovery provided the first evidence of AD pathology outside the brain. Subsequent research found that AD-related pathology occurs years to a decade earlier in the lens than brain in Framingham Eye Study participants. The Sapphire II technology employs a proprietary topically applied fluorescent ligand (Aftobetin) that binds AD-linked Aβ pathology in the lens and is noninvasively detectable by fluorescent ligand eye scanning (FLES) spectroscopy. The Sapphire II system enables early beta amyloid detection in individual patients with high reliability. Proof-of-concept validation has been established in two Phase 2 clinical trials that showed high NPV (100%) and PPV (94%) predictive values for AD diagnosis and accurate detection of MCI confirmed by amyloid-PET imaging. **Objective:** This current study evaluates the utility of Sapphire II scanning compared to quantitative beta amyloid PET scans in MCI and mild AD subjects. 34 participants (24 MCI and 10 mild AD patients) were studied. All MCI and AD subjects underwent cognitive testing and quantitative beta amyloid PET scans. **Methods:** The SAPPHIRE II system is a combination of a fluorescent ligand (Aftobetin), formulated as a medical imaging ointment, applied to the lower eye lid, and a Fluorescent Laser Eye Scanning (SAPPHIRE II) Device. The eye is scanned to detect a highly specific shifted fluorescent signature signal of the medical imaging ointment bound to beta amyloid. Quantitative amyloid PET data (Amyvid) were compared to quantitative fluorescent signal (FLES scores). Analyses (from study PRT 0036) included a comparison of SAPPHIRE II FLES scores to PET amyloid imaging SUVr scores on a subset of the subjects enrolled in the study in which SUVr values were available. Current literature supports a cutoff of in the range of 1.10 to 1.17 for PET (florbetapir) quantitative SUVr when correlating to a binary scan of positive or negative. Our analyses explored which SUVr and FLES cutoff values were most effective. **Results:** No serious adverse events were reported. The SAPPHIRE II System device, and ophthalmic ointment, used in this study posed no observed safety risk. We performed an optimization of both SUVr and FLES cutoffs on the mild AD and MCI dataset. The intent of cutoff optimization was to determine appropriate cutoffs to pre-specify for an upcoming pivotal study. The ideal range for FLES was found to be between 0.887 and 0.912. The ideal SUVr cutoff was found to be 1.12 given the fit of the dataset in the Receiver Operating Characteristic (ROC) curve with AUC of 0.70. There were only few subjects with low FLES and low SUVr scores as well as high FLES and high SUVr scores, somewhat limiting the power of these results. Nonetheless, a positive correlation was observed between FLES and PET SUVr with 70.6% congruency in FLES and SUVr scores overall. Sensitivity, specificity, accuracy, PPV and NPV values that correspond to cutoff scenarios 1) FLES=0.883, FLES=0.887, and FLES=0.912 compared with PET SUVr=1.12 were obtained. Although 100% sensitivity can be achieved with FLES=0.887, this cutoff may not offer physicians an optimal differential tool for diagnosis. We concluded that a FLES cutoff of 0.912 achieved a reasonable balance of sensitivity (74%) to specificity (73%) with 74% accuracy, while yielding a high PPV (85%) and reasonable NPV (57%) with $p<0.05$ given the small dataset for mild AD and MCI patients. **Conclusion:** Data generated by Cognoptix provides confidence that SAPPHIRE II is based on rationally founded scientific evidence and there is good correlation of AD-associated β-amyloid pathology in the lens of the eye with corresponding AD-associated β-amyloid pathology in the brain as documented by quantitative PET amyloid imaging.

CLINICAL TRIALS: METHODOLOGY

P27- PLACEBO-EFFECT SIZE IN SYMPTOMATIC ALZHEIMER'S DISEASE CLINICAL TRIALS.

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Background: As in all soft-endpoint CNS indications, also in AD one can observe a placebo effect in randomized, placebo-controlled trials, even though not quite as large as in pain or depression studies. It is important to understand the size and time-course of the placebo response in AD studies to more precisely calculate the sample size of future trials and to also determine the optimal observational period. **Objectives:** Assess the effect size of a placebo-response in published symptomatic AD studies to better understand the need for any placebo-minimizing measures in future AD trials with a placebo-arm. **Methods:** Studies evaluating the efficacy of symptomatic donepezil versus placebo in AD, using the MMSE and ADAS-cog score as outcome at 6 (available in 6 of 9 studies), 12 (7 of 9 studies) and 24 weeks (4 of 9 studies) after baseline were identified in PubMed by using the search terms: ((donepezil[Title]) AND ((alzheimer disease[Title] OR alzheimer's disease[Title])) AND (placebo[Title] OR efficacy[Title]) and analyzed. The search limits were further set for clinical trials, multicenter studies, and RCTs in English on humans. Only symptomatic treatment trials were evaluated since only in this setting a placebo-response can be clearly differentiated from a treatment effect. From a total of 40 initially identified studies, nine studies qualified for this analysis, all published between 1996 and 2018. **Results:** The selected studies included 2002 patients (63% female, 37% male; average age 74,85 years; average baseline MMSE score: 18,70 and ADAS-cog score: 22,53). A placebo effect (+0,25 to +1,77 points in MMSE; -0,81 to -1,96 points in ADAS-cog) at week 12 and (+0,5 to +1,9 points in MMSE; -2,18 to -3,45 points in ADAS-cog) at week 24 was detected in these studies. The highest placebo effect was observed within 6-12 weeks after baseline. **Conclusion:** The amount of the placebo-response in AD is rather limited and not further increasing after a peak at weeks 6-12. This is indicative of a "perceived" placebo effect, triggered by items such as: patient, caregiver and rater expectations, inflation of baseline ratings, the attempt to please the site staff and sponsor, etc. The effect size in disease-modifying therapies may be different, based on a different level of expectations, but is also more difficult to estimate based on the impacted slope of disease progression in the active treatment group. A "true" placebo effect which would impact AD pathophysiology should last longer or even increase over time. Specific placebo-effect minimizing measures such as rater and participant training seem to be less relevant than in other CNS indications such as pain. Vice versa, the placebo effect in AD does not have sufficient size to be used for therapeutic purposes – again in contrast to other CNS indications where a placebo-treatment may provide a well-tolerated alternative to pharmacotherapy. **Conflicts of Interest:** Nadine Mader declares not to have any conflict of interest, Peter Schueler is staff of the global CRO ICON

P28- EFFECTS OF ORALLY ADMINISTERED NICOTINAMIDE RIBOSIDE ON BIOENERGETIC METABOLISM, OXIDATIVE STRESS AND COGNITION IN MILD COGNITIVE IMPAIRMENT AND MILD ALZHEIMER'S DISEASE.

Isabella Santangelo, Morgan Green, Regan Patrick, David Harper, Tao Song, Chenyanwen Zhu, Boyu Ren, Brent Forester, Fei Du *(Mclean Hospital - Belmont (United States))*

Background: Alzheimer's Disease (AD) is a neurodegenerative disease affecting millions of people worldwide, thus representing a significant health and economic burden. Recently, there has been a push to develop more effective AD treatments. One potential strategy involves enhancing brain bioenergetics, or the metabolism of fuel molecules to create and use energy through glycolysis and oxidative phosphorylation (OxPhos). The regulation of mitochondrial turnover and function in the brain becomes compromised as we age, and it has become increasingly accepted that these metabolic alterations are antecedent to hallmark AD pathology, including amyloid-beta (Aβ) plaques and neurofibrillary tangles. An overlapping set of mechanisms involving redox dysregulation, oxidative stress, and mitochondrial dysfunction may be related to mild cognitive impairment (MCI) and AD. Nicotinamide adenine dinucleotide (NAD) has been identified as a promising molecular target for bioenergetic treatments because it is required for many redox reactions. The redox ratio (RR, i.e. NAD+/NADH) is used as a marker of the system's ability to carry out ATP synthesis. NAD+ levels decrease over time as we age, which compromises energy production within the mitochondria, impairs clearance of damaged mitochondria, and impacts our brain's capacity to respond to oxidative stress. Since mitochondrial dysfunction and oxidative stress are believed to play a role in the pathophysiology of age-related diseases, boosting NAD levels could be an effective AD treatment. Nicotinamide Riboside (NR), is a naturally occurring, commercially available vitamin B3- based NAD+ precursor supplement. Several lines of evidence suggest that NR is a mitochondrially-favored NAD+ precursor. Data have supported the safety and efficacy of using NR to increase NAD+ levels in humans, but these studies have not measured the RR at critical tissue sites, such as the brain, to determine the therapeutic potential of oral NR supplementation. This study proposes a novel intervention strategy for patients with MCI or mild AD. We focus on targeting redox dysregulation and oxidative stress in the brain using NR—an over the counter, orally bioavailable, and safe vitamin supplement. **Objectives:** Our primary objective is to validate the effect of NR supplementation on NAD+ levels and RR in the brain of patients with MCI or mild AD. Our secondary aim is to quantify the impact of NR supplementation on downstream markers of mitochondrial function and oxidative stress in MCI and mild AD patients. Our third, exploratory aim, is to correlate neuroimaging measurements with clinical assessments. **Methods:** A 12-week open-label, clinical trial of NR supported by the National Institute on Aging (R01AG066670, Du/Forester), we plan to enroll a total of 50 participants - 25 with MCI and 25 with mild AD, all with at least one copy of the APOE ε4 allele. Participants will be asked to take 1,000 mg NR daily over 12-weeks, and they will come in for three scanning visits. We will use novel neuroimaging approaches —spectroscopy on a 4T scanner to enable in vivo measurement of NAD+, NADH and RR, as well as the markers of mitochondrial function with functional ties to NAD, including creatine kinase (CK), ATPase,

and glutathione (GSH)—a molecule essential for cellular repair. Our primary outcome measures are NAD+ levels and RR. Our secondary outcome measures are CK/ATPase activity and GSH levels. Our exploratory outcome measures include the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) for cognition and the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) for daily functioning. **Results:** Previous clinical trials of NR pharmacokinetics in humans support the safety and efficacy of using NR to increase NAD+ levels in the plasma. Emerging data also sheds light on the important health benefits this supplementation could have. We recently received preliminary spectroscopic data following a course of NR supplementation in healthy volunteers (N=4) which observed elevations in NAD+ and RR after two weeks of NR supplementation. Only a small difference of downstream effects, CK/ATPase activity and GSH levels, were observed, which could be due to the short period of NR treatment. We hypothesize that oral NR will increase NAD+ and RR in the medial prefrontal cortex and will increase GSH levels and CK/ATPase activity in the brain. For our exploratory aim, we hypothesize that oral NR will improve cognitive status and functional abilities, as measured by the RBANS and ADCS-ADL. **Conclusion:** We are investigating NR to target redox dysregulation and oxidative stress in the brain in those with MCI or mild AD. We aim to document and quantify the neurobiological and clinical effects of NR supplementation in MCI and mild AD using in vivo brain imaging techniques. This novel intervention strategy has thus far received minimal empirical attention and could represent an alternative strategy for treating MCI and mild AD by focusing on brain bioenergetics. Early detection and then repair of neural dysfunction at this critical stage could significantly alter disease course and improve functional outcomes.

P29- EFFECTS OF EXCLUSION CRITERIA ON DISEASE MODIFYING CLINICAL TRIALS FOR ALZHEIMER'S DISEASE. Aaron Ritter, Joel Adu-Brimpong, Marwan Sabbagh, Jiong Shi, Justin Miller, Jessica Caldwell *(Cleveland Clinic - Las Vegas (United States))*

Background: The clinical syndrome of Alzheimer's disease (AD) is a byproduct of likely multiple, complex biochemical processes. The biological heterogeneity underlying AD manifest in significant variations in clinical features (symptoms, age of onset, etc.) and disease course. Medical comorbidities, both related and unrelated to underlying AD processes may also have a significant impact on an individual's cognitive and functional abilities. In order to reduce the potential masking effects that clinical heterogeneity and medical comorbidity may have on clinical trial outcomes, exclusionary criteria for AD trials have become increasingly restrictive. A potential unintended consequence of overly restrictive exclusion criteria is to limit the generalizability of findings from AD clinical trials, whose participants may only represent a subgroup of individuals with AD, and, thus, do not accurately resemble "real world" AD populations. Previous literature has shown that only a small percentage of individuals with clinically-defined AD met criteria for clinical trial participation. This research was conducted in the 1990s before the development of AD biomarkers. There has been little research into the effects of commonly used exclusion criteria on the ability participate in research studies of biomarker-based, disease modifying agents (DMTs). **Objectives:** The overall objective of this study was to explore how the application of commonly used exclusion criteria impact clinical trial populations for disease modifying therapies for AD. Specifically, we wanted to see how exclusion criteria impact the demographic makeup and clinical characteristics of individuals who would otherwise meet inclusion criteria (i.e. they had both the clinical diagnosis and biomarker evidence of AD). We also wanted to understand how clinical trial populations may differ in their rates of cognitive and functional decline. **Methods:** We used the National Alzheimer's Coordinating Center Database (NACC). Although the NACC database is not entirely reflective of the general public it was chosen because biomarker status is collected, individuals are well characterized and followed longitudinally, and it lacks strict exclusion criteria. To conduct this study, we first identified all the individuals in the NACC who would hypothetically meet inclusion criteria for typical, early AD clinical trials. We included all individuals with the following: 1) biomarker evidence of amyloid pathology (positive amyloid PET or CSF or CERAD score of 2 or greater on neuropathology); 2) were staged as mild cognitive impairment (MCI) or mild dementia (Clinical Dementia Rating (CDR)score of 0.5-1); 3) and a clinical diagnosis of MCI or mild AD due to Alzheimer's disease. We then applied exclusion criteria to this cohort using a composite of criteria derived from five of the most recent high profile DMT trials in early AD populations (accessed through clinicaltrials.gov). To measure the impact of each exclusionary criteria, we applied each exclusion individually. To measure the total effect of exclusion criteria, we then applied each criteria sequentially. We also compared the clinical, demographic, and disease course of those who would be eligible for AD DMTs against those who would be excluded. **Results:** We found that only 8% of individuals in the NACC who otherwise meet general inclusion criteria (amyloid pathology and correctly staged as MCI or mild dementia due to AD) would be eligible for clinical trial participation. Low scores on global cognitive tests such as the Montreal Cognitive Assessment or Mini Mental Status Examination (53%), active depression (38%), uncontrolled hypertension (28%), use of anticoagulants (20%) and concurrent diagnosis of FTD or LBD (21%/19%) were the most common reasons for excluding individuals. Individuals who meet eligibility criteria were more likely to be younger, male, married, and more highly educated than those who were excluded. They also performed better on neuropsychological testing and had statistically significant slower rates of cognitive decline. **Conclusions:** Only a small percentage of individuals with clinical and biomarker-defined AD meet exclusion criteria used for clinical trials of DMTs. This suggests that exclusion criteria have a significant constraining effect on clinical trial populations that may limit the generalizability of findings from DMT trials. Our study may actually underestimate the effects of exclusionary criteria given that we used individuals already participating in a research study as a proxy for the general public. Clinical trial design should consider the impact of generalizability when defining exclusion criteria for AD and regulators should consider this when making recommendations both about design and a potential agent's approval.

P30- CARING FOR BEHAVIORAL SYMPTOMS OF DEMENTIA (CBD): A NEW INVESTIGATION INTO CANNABIDIOL FOR THE TREATMENT OF ANXIETY AND AGITATION IN ALZHEIMER'S DEMENTIA. Kaitlin Mcmanus, Rosemary Smith, Regan Patrick, David Harper, Staci Gruber, Brent Forester *(Mclean Hospital - Boston (United States))*

Background: Alzheimer's disease (AD) is a debilitating neurodegenerative disease accounting for 60-80% of

dementia cases worldwide. In the United States alone, 12.7 million Americans are predicted to develop AD by 2050. The neuropsychiatric symptoms (NPS) of dementia affect up to 97% of AD patients over the course of their disease. A common NPS is agitation, characterized by problem behaviors that include combativeness and restlessness. Agitation is associated with greater caregiver burden, shorter time to institutionalization, and anxiety. Anxiety symptoms affect 25-70% of the dementia population, and this wide range speaks to the challenges in differentiating anxiety from agitation. Despite the pervasiveness of anxiety and agitation in the AD population, there are no FDA-approved medications that treat the NPS of AD. Current treatments for these symptoms include time-intensive behavioral therapies and prescription of off-label antipsychotic medications that include an FDA warning of increased mortality in this population. Thus, the need for developing safe and efficacious treatments for anxiety and agitation in AD is dire. One potential treatment is cannabidiol (CBD), the major non-intoxicating constituent of cannabis sativa and industrial hemp, a variety of the cannabis plant that contains <0.3% delta9-tetrahydrocannabinol (THC), the main intoxicating constituent in cannabis, by weight. CBD modifies the endocannabinoid system and is thought to modulate effects via a variety of pathways, including the 5-HT serotonergic system, μ-opioid receptors, and TRPV1/TRPV2 receptors. Studies have demonstrated CBD's ability to attenuate acute responses to stress in rats, act as a panicolytic in rats, and attenuate anxiety in humans. The utilization of CBD may extend beyond its role as an anxiolytic, as preclinical studies suggest widespread therapeutic impacts of CBD, including its potential ability to offer neuroprotective properties and inhibit tau hyperphosphorylation. Despite pre-clinical and animal evidence that CBD could modify neurodegeneration and behavioral symptoms in AD, no human clinical trials have investigated the impact of CBD on anxiety or agitation in AD. **Objectives:** The present open-label clinical trial seeks to address this gap in knowledge by assessing the efficacy and tolerability of a high-CBD/low-THC sublingual solution as a treatment for anxiety and agitation in older adults with Alzheimer's disease. We hypothesize that twice daily treatment with the solution will be safely tolerated and associated with a statistically significant reduction in anxiety and agitation symptoms compared to baseline. **Methods:** We are conducting an 8-week open-label clinical trial of an industrial hemp-derived custom-formulated high-CBD/low-THC sublingual solution developed by Dr. Staci Gruber, PhD, at McLean Hospital. We are recruiting 12 research participants with mild to moderate AD and behavioral symptoms of anxiety with or without agitation. Our primary efficacy outcome measures are the anxiety domain of the Neuropsychiatric Inventory-Clinician Version (NPI-C), the Generalized Anxiety Disorder-7 Item Scale (GAD-7), and the Beck Anxiety Inventory (BAI), for which we consider both patient and caregiver reports of the subject's anxiety. Our secondary safety outcome measures include monitoring for serious adverse events and medication side effects, cognitive decline estimates from the Mini Mental Status Exam (MMSE), and the emergence of delirium from the Family and 3D Confusion Assessment Methods (FAM-CAM; 3D-CAM). Agitation and aggression domains of the NPI-C, scores on the Cohen-Mansfield Agitation Inventory (CMAI), and caregiver burden estimates from the Zarit Caregiver Burden Interview are included as exploratory measures. Linear mixed-effects models will be constructed for each of the behavioral scales listed as primary or exploratory outcomes. Our primary and exploratory outcome measures will be tested using a multiple degree-of-freedom comparison of scores. Post-hoc, single degree-of-freedom tests will compare baseline scores with subsequent scores. **Results:** One subject completed the 8-week trial thus far; their singular experience provides preliminary support to our hypotheses. This subject experienced a reduction in anxiety at Week 8 compared to baseline as measured by the primary efficacy outcome measures (anxiety domain of NPI-C: 80.0% decrease; GAD-7: 100.0% decrease; BAI Subject: 50.0% decrease; BAI Caregiver: 100.0% decrease). The subject did not experience any serious adverse side effects as measured by our secondary safety outcome measures during this 8-week treatment phase; there were reports of increased talkativeness and laughing during this phase that were possibly related to the study product used, but not considered serious. Exploratory outcome measurements revealed a decrease in agitation at Week 8 compared to baseline (agitation domain of NPI-C: 76.9% decrease; aggression domain of NPI-C: 75.0% decrease; CMAI: 27.8% decrease). **Conclusion:** Safe and effective treatments for the neuropsychiatric symptoms of anxiety and agitation in older adults with AD are needed. With no current FDA-approved treatments for these behavioral symptoms, patients with AD risk ineffective therapies or mortality-associated antipsychotic treatments to address their NPS. Treating anxiety and agitation in these patients not only alleviates their symptoms but could also reduce caregiver burden and lengthen the time to institutionalization. CBD is a promising anxiolytic treatment that could advance our available treatment options for anxiety and agitation in AD.

P31- ECT-AD TRIAL: CHALLENGES TO STARTUP & RECRUITMENT. Maria Lapid[1], Brent Forester[2], George Petrides[3], Adriana Hermida[4], Louis Nykamp[5], Martina Mueller[6], Regan Patrick[2] *(1. Mayo Clinic - Rochester, Mn (United States), 2. Mclean Hospital - Belmont, Ma (United States), 3. Northwell Health/zucker Hillside Hospital - Glen Oaks, Ny (United States), 4. Emory University Healthcare - Atlanta, Ga (United States), 5. Pine Rest Christian Mental Health Services - Grand Rapids, Mi (United States), 6. Medical University Of South Carolina - Charleston, Sc (United States))*

Background: The Electroconvulsive Therapy (ECT) for Agitation in Alzheimer's Dementia (AD) (ECT-AD) study is a multi-site, NIH-funded, single-blind, randomized controlled trial to investigate the safety and efficacy of ECT in severe and treatment refractory agitation and aggression in AD. Agitation is present in up to 90% of individuals with dementia, which increases morbidity and mortality and contribute to caregiver stress and burden. There are no FDA-approved treatments for severe agitation in people with advanced dementia. First-line behavioral interventions are not effective in severely agitated patients, and off-label use of psychotropics have limited efficacy and higher risk for adverse effects. There is preliminary evidence that acute electroconvulsive therapy (ECT) can be safe and effective in reducing agitation in this population. **Objectives:** The aims of the study are (1) To compare the relative efficacy of up to 9 ECT treatments plus usual care (ECT+UC) versus Simulated ECT plus Usual Care (S-ECT+UC) in reducing severe agitation in participants with moderate to severe AD; and (2) To compare the relative tolerability/safety outcomes of ECT+UC versus S-ECT+UC participants with moderate to severe AD. An exploratory aim is to explore the stability of agitation reduction and global functioning at 1, 3 and 6 months following the randomized phase, and then for a fourth visit 12 months after the randomized phase. **Methods:** Inclusion criteria include diagnosis of Alzheimer's

Dementia according to NIA-AA criteria, age 55 - 89 years, MMSE ≤ 15, Cohen-Mansfield Agitation Inventory Nursing Home Version (CMAI) score of >5 on at least one item of aggression or a physical nonaggressive item that holds potentially dangerous consequences, at least three failed pharmacological interventions from different drug classes at therapeutic doses, with authorized legal representative able and willing to give informed consent. Participants are randomized 1:1 to ECT+UC or Simulated-ECT+UC. Treatment with acute course of ECT consists of up to 9 sessions, administered 3 times per week or less. The primary efficacy outcome is CMAI total score, assessed at baseline, after 3rd ECT/S-ECT (Time 1), after 6th ECT/S-ECT (Time 2), and after 9th ECT/S-ECT (Time 3). Secondary efficacy outcomes include Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change Scale (ADCS-CGIC), Neuropsychiatric Inventory, Clinician Version (NPI-C), and Pittsburgh Agitation Scale (PAS). Tolerability is assessed with Severe Impairment Battery-8 (SIB-8), and safety is assessed with Confusion Assessment Method (CAM). For the 12-month naturalistic observational phase, the CMAI, Clinical Global Impression-Severity (CGI-S), Zarit Caregiver Burden Interview (ZARIT), Quality of Life in Late-Stage Dementia Scale (QUALID), and Barthel Index (BI) are measured at baseline-2 and months 1, 3, 6, and 12. **Results:** The study is ongoing. Notable challenges related to study startup included: (1) regulatory aspects related to securing an investigational device exception (IDE) from the FDA, (2) approval from a single IRB when multiple sites from different states are involved, and (3) adapting to unplanned safety and regulatory considerations due to the COVID-19 pandemic. Major challenges to recruitment thus far have included: (1) COVID-19-related delays (e.g., reduced bed counts, establishing appropriate safety procedures for patients and staff, etc.), (2) family/caregiver AND clinician reticence to referring acutely agitated patients to a research trial – and potentially being randomized to the placebo/simulated ECT arm – versus immediately starting a clinical course of ECT, (3) family/caregiver lack of interest in ECT (e.g., fear of side effects, poor prior experience with ECT, prefer to see if medication adjustments are effective, etc.), (4) unexpectedly high rate of patients with non-AD dementia diagnoses in recruitment pool (per clinical criteria) resulting in ineligibility. **Conclusion:** In this presentation, we will describe the challenges to study startup and recruitment that are being encountered in the ECT-AD trial, and describe ongoing strategies to manage the challenges. The investigators have no conflicts of interest to disclose. This study is supported by the NIA (grant number 5R01AG061100).

P32- THE IMPACT OF MMSE ADMINISTRATION ERRORS ON MMSE CHANGE ONE YEAR AFTER RANDOMIZATION: A PRELIMINARY ANALYSIS OF POOLED DATAY. David Miller[1], Xingmei Wang[1], Alan Kott[2] *(1. Signant Health - Blue Bell, Pa (United States), 2. Signant Health - Prague (Czech Republic))*

Background: Audio recording of eCOA MMSE administration offers a unique opportunity to identify both scale administration and/or scoring errors. Administration errors have the potential to impact a subject's performance on individual tasks and as a result, on the overall MMSE score as well. We have previously identified a large percentage of screening and baseline visits be affected by administration errors (Miller, Kott, 2020), but the impact on actual score changes after randomization has not been investigated. **Objective:** To assess whether and to what extent the presence of administration errors at the time of randomization and/or at 1 year post-randomization had any effect on the overall MMSE score change from baseline. **Methods:** MMSE baseline data and data collected a year after randomization were pooled from 3 randomized double-blind clinical trials in mild to moderate Alzheimer's disease. We classified visits as having an administration error if upon audio review, an administration error was identified in at least one MMSE domain. The impact of the presence of the administration error(s) at baseline and/or year 1 visit was estimated using a generalized linear model that had main effects of the administration errors and protocol, and baseline MMSE score was included as a covariate. **Results:** Our dataset was gleaned from 2,089 subjects with both baseline and one year after randomization MMSE data available. The average change in the blinded data at year 1 visit in MMSE was a worsening of 1.7 points (+/-3.1). Baseline administration errors were recorded in 225 cases (10.8%) while administration errors recorded one year after randomization were identified in 252 cases (12.1%). Baseline administration errors were significantly associated with the presence of administration errors at one year after randomization ($p < 0.05$), though both errors co-occurred in only in 39 cases (1.9%). While correcting for baseline MMSE score and trial, the presence of an administration error at baseline resulted in a decrease in the MMSE worsening by 0.47 points while the presence of an administration error 1 year after randomization further increased the worsening by 0.6 points. Both effects were statistically significant at alpha level of 0.05. **Conclusion:** Our data indicate that the presence of administration errors has a significant effect on MMSE change from baseline one year after randomization. The presence of baseline errors was associated with a significant reduction in the amount of worsening in the MMSE compared to subjects who did not have an administration error at baseline. In contrast, the presence of an administration error at 1 year after randomization was associated with a significant worsening in the MMSE change. The somewhat puzzling differential effect of the administration errors at baseline and year 1 visit may be potentially explained by the fact that the MMSE scores are on average lower in the presence of an administration error than when no administration error was identified. If true, subjects with an administration error identified at baseline would be expected to 'worsen less' compared to subjects without an administration error at baseline. And similarly, subjects who recorded an administration error one year after randomization would be expected to worsen more, which is what we see in our data. These results need to be considered preliminary and require independent replication.

P33- THE ANEED STUDY: AMBROXOL IN NEW AND EARLY DEMENTIA WITH LEWY BODIES. Arvid Rongve *(Helse Fonna - Haugesund (Norway))*

Background: The mechanisms by which GBA and APOE mutations result in PD, DLB and AD are not fully understood; however, there is evidence that it may be connected to reduced levels of GCase enzyme activity. CNS penetration has been confirmed for Ambroxol and has been shown to increase glucocerebrosidase activity and protein levels in animal and human studies. Ambroxol may act by increasing transcription factor EB, the regulator of the CLEAR pathway involved in lysosomal biogenesis and by acting as a chaperone for GCase. **Method:** We will execute a national multicenter phase IIa RCT clinical intervention study with Ambroxol in prodromal and mild DLB in seven Memory Clinics across Norway. We will include persons living with prodromal (DLB-MCI) or

mild DLB with MMSE >=15 to Ambroxol or placebo. We will stratify participants based on genotypes for APOE and the CSF biomarker amyloid-beta. **Results:** The ANeED-study has received funding from the national Norwegian health authorities. Formal approvals for ethics, data protection and Medicine Agency are granted and first patients will be included during spring 2021. We are currently building a national platform in Norway to be able to run clinical intervention studies in neurodegenerative disorders like AD and DLB. We are building a PPI program to recruit patients and caregivers to clinical studies. **Conclusion:** We are now starting a phase IIa study with Ambroxol in Norway. APOE, GBA and GCase are central to the disease process in both PD, PDD, DLB and AD. Patients, caregivers and health providers now need to be offered participation in clinical trials also when diagnosed with one of the α-synucleinopathies. Preliminary data find Ambroxol to be potentially disease modifying in these disorders, and potential collaborators for a phase III study in DLB in Europe and the US are welcome to contact.

P34- AGE AFFECTS CLINICAL OUTCOME IN ALZHEIMER'S DISEASE TRIALS. Steven Targum[1], Lisa Fosdick[2], Kristin Drake[3], Paul Rosenberg[4], Anna Burke[5], David Wolk[6], Kelly Foote[7], Wael Asaad[8], Marwan Sabbagh[9], Gwenn Smith[4], Andres Lozano[10], Constantine Lyketsos[4]
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Background: Subject selection is a critical factor in the execution of a successful clinical trial. Beyond the diagnostic and symptom severity criteria applied, demographic factors may also affect the outcome. It is well established that participants with probable mild Alzheimer's disease (AD) have heterogeneous etiologies and clinical presentations that could affect the trajectory of their clinical course during a trial. Age is one factor that may affect treatment outcome. **Objectives:** We examined age as a moderator of treatment outcome in an exploratory study of deep brain stimulation targeting the fornix (DBS-f) region in participants with AD. **Methods:** The Advance study was conducted at 7 clinical trial sites in the United States and Canada between May 2012 and June 2015 (clinicaltrials.gov (NCT01608061). ADvance was an exploratory phase II feasibility study in which the primary objective was to evaluate the safety and tolerability of DBS-f in participants with probable mild AD by assessing device and/or therapy related adverse events after 12 months. Study participants between the ages of 45-80 were eligible for the study based upon meeting diagnostic criteria for probable AD according to the NIA/Alzheimer's Association criteria, documentation of progressive functional decline over at least one year, having ADAS-cog-11 scores between 12-24 and a Clinical Dementia Rating Scale (CDR) global rating of 0.5 or 1.0. In addition, all eligible participants needed to be taking a stable dose of a cholinesterase inhibitor for at least 60 days prior to signing the informed consent. Biomarkers were not part of the subject selection criteria. The target site for neurosurgical implantation of the DBS electrodes was just anterior and in juxtaposition to the post commissural fornix (DBS-f). A Model 37601 Activa PC pulse generator battery and Model 3387 Leads with Model 37085 extensions (supplied by Medtronic, Inc.) was implanted in all participants who continued to meet randomization criteria at the baseline visit. All participants were eligible for a one-year extension with DBS-f "on" stimulation following the 12-month double-blind study period. **Results:** Forty-two participants between the ages of 48-80 were implanted with DBS electrodes and randomized 1:1 to double-blind DBS-f stimulation ("on") or sham DBS-f ("off") for 12 months. The intervention was safe and well tolerated and met the primary objectives of the study. However, the selected clinical measures (ADAS-cog-13 and CDR-Sum of Boxes (CDR-SB) did not differentiate between the "on" and "off" groups in the intent to treat (ITT) population. There was a significant age by time interaction with the ADAS-cog-13: b= -0.41; SE 0.18; p= 0.028. Six of the 12 enrolled participants <65 years old (50%) markedly declined on the ADAS-cog-13 in contrast to only 2 of the 30 participants ≥65 years old (6.7%) regardless of treatment assignment (p = 0.005). The DBS-f "on" group did worse than the "off" group on all clinical measures in the <65 age cohort. Cohen's d effect size estimates (ES) favored DBS-f "off" versus "on" in the <65 age cohort on all of the outcomes. On the other hand, the DBS-f "on" group did better than the "off" group on all clinical measures in the ≥65 age cohort. Although not statistically significant, the ES for the ADAS-cog-13 favoring the DBS-f "on" treatment group increased from 0.00 in the entire ITT population to 0.58 in the 30 participants ≥65 years old, and the ES for the CDR-SB favoring the DBS-f "on" increased from 0.09 to 0.52. The mean change score difference on the integrated Alzheimer's disease assessment scale (iADRS) between the DBS-f "on" and "off" groups was 0.4 in the ITT population but increased to a 21.4-point difference favoring the DBS-f "off" group in the <65 age cohort (ES= 1.41). Alternatively, in the ≥65 age cohort, the mean iADRS change score revealed a 9.3-point difference favoring the DBS-f "on" group versus the DBS-f "off" group. The ES for the iADRS improved from +0.02 in the ITT population to -0.52 favoring DBS-f "on" in the ≥65 age cohort. **Conclusion:** The findings highlight the challenges associated with subject selection in clinical trials for AD. This exploratory study allowed AD participants with a wide age range (between 45-80) that included 12 individuals < 65 years old (30% of the study population). Faster disease progression in younger AD participants with different AD sub-types may have influenced the results. Biomarker confirmation and genotyping to differentiate AD subtypes is important for future clinical trials.

P35- EFFECTS OF INCLUSION/EXCLUSION CRITERIA ON ETHNOCULTURAL AND SOCIOECONOMIC COMPOSITION OF PARTICIPANTS IN AN ALZHEIMER'S DISEASE CLINICAL TRIAL: ANALYSIS OF HEALTH AND RETIREMENT STUDY (HRS) DATA. Miriam T. Ashford[1], Mohammed U. Kabeto[2], Caroline R. Wixom[3,4,5], Rachel L. Nosheny[6], Michael W. Weiner[7], David R. Weir[8], Kenneth M. Langa[8,9,10] *(1. Northern California Institute For Research And Education (ncire), Department Of Veterans Affairs Medical Center - San Francisco (United States), 2. Department Of Internal Medicine, University Of Michigan - Ann Arbor (United States), 3. General Medicine, Department Of Internal Medicine, University Of Michigan - Ann Arbor (United States), 4. Department of Medicine, University of California San Francisco - San Francisco (United States), 5. Department of Neurology, University of California San Francisco - San Francisco (United States), 6. Department Of Psychiatry, University Of California San Franciscof - San Francisco (United States), 7. Department Of Radiology And Biomedical Imaging, University Of California San Francisco - San Francisco (United States), 8. Institute For Social Research, University Of Michigan - Ann Arbor (United States), 9. Department of Medicine, University of Michigan - Ann Arbor (United States), 10. Institute for Healthcare Policy and Innovation, University of Michigan - Ann Arbor (United States))*

Background: Randomized control clinical trials (RCTs) are considered the gold standard for testing the safety, efficacy, and effectiveness of new Alzheimer's disease (AD) treatments. The focus of RCTs is increasingly on the asymptomatic (prevention trials) or early symptomatic (prodromal AD) disease stages. The generalizability of AD treatment RCTs to all individuals likely to receive the tested treatments may be limited by stringent eligibility criteria. Those from minoritized ethnocultural groups and lower education attainment are chonically underrepresented in Alzheimer's RCTs, but the extent to which they are excluded based on common exclusion criteria such as medical comorbities or medications is understudied. **Objectives:** The aim of this study was to identify how AD prevention trial medical exclusion criteria affect the eligibility and inclusion of underrepresented ethnoculural and socioeconomic populations (URPs). To do this, we applied the exclusion criteria from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's study(A4) to the nationally-representative sample of older adults enrolled in the Health and Retirement Study (HRS). **Methods:** We operationalized the exclusion criteria from the A4 study, which is an ongoing large, multisite prevention trial of cognitively unimpaired older adults with elevated brain amyloid. Our study included 10 A4 study medical condition exclusion criteria (including dementia and other related drugs, current serious or unstable illness, serious infection, primary or recurrent malignant disease, history of HIV, chronic conditions, major unstable conditions, schizophrenia) which were operationalized using HRS and linked Medicare administrative data. The HRS is an ongoing longitudinal panel study that surveys a nationally representative sample of approximately 20,000 adults (aged 51+) in the United States. We included individuals who were covered by a Medicare fee-for-service, Part A & B plan for at least 80% of the prior year , were alive and were aged 66-85 in December 2016. This excludes participants who were enrolled in Medicare Health Maintenance Organization plans for more than 20% of the prior year. HRS sampling weights were applied to account for the complex sampling design of the HRS. We compared the following characteristics of individuals that would be included or excluded from the A4 study based on medical exclusion criteria: age, gender, ethnocultural group (non-Latinx white, non-Latinx Black, Latinx, other), education in years (<12, 12, 13-15, 16+), net wealth (<$31,000, $31,001-$145,000, $145,001-$385,000, >$385,000), and living arrangement (married/have partner, unmarried living with other, unmarried living alone). **Results:** Of 11,148 HRS respondents with linked Medicare data and alive by December 2016, 3,950 (35.2%) made the study inclusion criteria described above. The average age was 75.9 (standard deviation=5.5), 59.6% were female, 6.6% were Latinx, 13.1% were non-Latinx Black, 78.0% were non-Latinx white, and 2.0% identified as Other, 25.8% had 16+ years of education, 31.3% had a net wealth of >$385,000, and 61.8% were married/had partner. Almost half in the sample (1,561 ,49.5%) had one or more A4 medical exclusion criteria. The most common exclusion criteria were "current serious/unstable illnesses (cardiovascular, hepatic, renal, gastroenterologic, respiratory, endocrinologic, neurologic, psychiatric, immunologic, hematologic)" (n=710, 18%) and "primary or recurrent malignant disease (last-5 years)" (n=692, 17.5%). Comparison of those included and excluded based on A4 criteria showed significant differences in age, gender, ethnocultural group, education, net wealth, and living arrangement. Higher percentages of non-Latinx Black (47.4%) and Latinx (45.6%) individuals were excluded compared to non-Latinx white (39.0%) (p<.001). Further, a higher percentage of individuals with lower education (e.g., <12 years: 55.2%) was excluded compared to indiviuals with higher education (e.g., 16+ years: 33.8) and a higher precentage of indiviuals with lower net worth (e.g., <$31,000: 48.5%) was excluded compared to individuals with a higher net worth (e.g., >$385,000: 37.0%). **Conclusion:** Taken together, among participants in a large national populations-based study, the proportion of participants from ethnocultural and socioeconomic URPs was higher in the excluded group, based on A4 study medical exclusion criteria, compared to included group. More studies are needed to understand the complex relationship between URP ethnocultural status, socioeconomic status, and other factors, and how these and other factors, such as discrimination and structural racism, impact medical conditions and exclusion from AD RCTs. It is critical that this analysis is replicated and extended using other samples, databases, and exclusion criteria from other AD studies.

P36- A MACHINE LEARNING TOOL TO ENRICH EARLY ALZHEIMER'S DISEASE CLINICAL TRIAL COHORTS. Angela Tam, César Laurent, Christian Dansereau *(Perceiv Research Inc - Montreal (Canada))*

Background: Although cognitive changes are typical primary and secondary outcomes in Alzheimer's disease clinical trials, a significant proportion of trial patients will not exhibit cognitive decline throughout the duration of a trial. This can negatively impact a trial's ability to detect differences between placebo and treatment groups leading to failure to meet its endpoints. **Objectives:** We aim to make clinical trials more efficient and of better quality through outcome-based population enrichment. We use machine learning models to identify individuals who will have stable cognitive trajectories and remove these individuals prior to randomization to obtain a population that will give clinical trials the best chance to reach their endpoints. **Methods:** We trained a machine learning prognostic pipeline to classify decliners from stable individuals on 1329 individuals with a clinical diagnosis of mild cognitive impairment or Alzheimer's dementia from the ADNI (adni.loni.usc.edu) and NACC (naccdata.org) datasets. Decliners

were defined as individuals who had increased CDR-SB scores at 24 months of follow-up compared to their baseline scores. Age, sex, APOE4 carriership, and volumes from anatomical brain regions extracted from MRI at baseline were used as input features. The model was trained and tested with nested 5-fold cross-validation. We also evaluated the generalizability of this model on an independent dataset that comprised the placebo arm of a Phase 3 clinical trial (n=125). **Results:** In the pooled ADNI and NACC dataset, 479 individuals (36% of the sample) did not actually decline on the CDR-SB at 24 months of follow-up. The whole sample had a mean (± std) observed change of 1.63 ± 2.65 points on the CDR-SB at 24 months compared to baseline. Using this full cohort, a power analysis showed that a clinical trial would need to enroll 432 individuals in order to detect a 30% difference in CDR-SB between treatment and placebo groups at 80% power. The predictive model flagged 362 individuals as stable (27% of the sample) and 967 individuals as decliners, and it achieved a mean (± std) AUC of 76.4 ± 0.87. The predicted stable group had a mean observed change of 0.30 ± 1.56 on the CDR-SB at 24 months compared to baseline. On the other hand, the predicted decliners had a mean observed change of 2.13 ± 2.68. Using a sample size power analysis, we estimated that for that enriched cohort of decliners, only 278 individuals would be required for enrollment to detect a treatment effect. By removing the predicted stable individuals, it is possible to reduce a clinical trial sample size by 36% (from n=432 to n=278) compared to enrolling the full sample of eligible candidates while retaining the same detection power. We also replicated these findings in subsamples selected for amyloid positivity and having specific ranges of cognition at baseline (e.g. baseline global CDR of 0.5-1, baseline MMSE of 20-30) by matching inclusion-exclusion criteria of past clinical trials. In an independent dataset obtained from the placebo arm of an 18-month Phase 3 clinical trial where 29% of individuals remained stable, the model achieved 75.28 AUC at classifying stable individuals (n=13) and decliners (n=112). As a whole, the sample experienced a mean change of 1.54 ± 2.05 points on the CDR-SB at 18 months compared to baseline. Using the full cohort, 311 individuals would be needed to adequately detect treatment effects according to our power analysis. However, the predicted stable individuals had a mean observed change of -0.12 ± 2.01 on the CDR-SB at 18 months, whereas the predicted decliners had a mean observed change of 1.73 ± 1.97. With this enriched cohort of decliners, a power analysis found that a clinical trial would need to recruit only 228 individuals. By selecting only the decliners for enrollment, we can achieve a 27% reduction in sample size compared to the estimated n=311 that was calculated from including both stable individuals and decliners. **Conclusion:** Our machine learning model can successfully identify individuals with mild cognitive impairment or Alzheimer's dementia who will likely remain cognitively stable from those who are at high risk of decline over the course of 24 months. This tool can be used in clinical trials to favour the enrollment of individuals who are more likely to exhibit cognitive decline during the trial, thereby improving the quality of the population recruited in the trial while allowing for smaller sample sizes and faster recruitment time. Our tool allows clinical trials to reduce their sample sizes by as much as 36% (compared to enrolling all eligible participants).

P37- ENHANCING THE ENROLLMENT OF UNDERREPRESENTED MINORITY POPULATIONS IN CLINICAL TRIALS THROUGH THE GLOBAL ALZHEIMER'S PLATFORM FOUNDATION'S® (GAP'S) DIVERSITY AND INCLUSION PROGRAM. Tamiko Rodgers, Leigh Zisko, John Dwyer, Judith Jeter, Cyndy Cordell *(Global Alzheimer's Platform Foundation - Washington Dc (United States)*

Background: Clinical trials that reflect the populations most likely to use the drug are important to assess safety and efficacy. Treatment effects cannot be fully investigated and understood without adequate representation of the entire population. Despite efforts to boost enrollment of underrepresented minority (URM) populations in clinical trials by broadening eligibility criteria and making trial participation less burdensome, URM participation remains low and does not represent the population in the United States (United States Census Bureau Quick Facts https://www.census.gov/quickfacts/fact/table/US/PST045219; 2020 Drug Trials Snapshot https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots). Diverse representation in Alzheimer's disease (AD) clinical trials is particularly important because of the higher prevalence of AD in some URM groups including Black and Hispanic Americans (2021 Alzheimer's Disease Facts and Figures https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf.). The Global Alzheimer's Platform Foundation® (GAP) is developing a Clinical Trial Diversity and Inclusion Program for sites participating in its network (GAP-Net). **Objectives:** GAP's Clinical Trial Diversity and Inclusion program seeks to improve awareness, recruitment, knowledge, and access of AD clinical trials for URM populations. **Methods:** GAP's approach to broadening engagement of diverse populations focuses on addressing key barriers at a local level. Key barriers include lack of awareness of research to promote health, knowledge of the purpose of the research, and access to the research (Multi-Regional Clinical Trials (MCRT) Center of Brigham and Women's Hospital and Harvard 2021 Guidance Document https://mrctcenter.org/diversity-in-clinical-research/). The initial program will focus on 4 GAP-Net sites located in communities in Illinois, Florida, and Missouri that are accessible to minorities and have established community relationships. Community mapping is a systemic approach to gathering demographic information about how the URM community operates around each site so community-specific strategies can be built that enable long-term success. GAP will help sites map and identify minority community-based healthcare professionals, physicians, trusted leaders, influencers, and community-based organizations in the site's city and surrounding counties. GAP will also incorporate census data and other metrics to inform sites about where URM populations reside in their communities. Traditional barriers to clinical trial participation – such as access to public transportation – will also be reviewed. GAP will help sites initiate and maintain relationships with the appropriate identified organizations. Relationship building helps sites form and maintain long-term relationships with community partners such as local healthcare providers (HCPs), organizations, and minority leaders to support a referral pathway. Referring physicians are often a trusted source of information about clinical trials, and patients may be more likely to participate if recommended by their HCP (Curr Probl Cardiol. 2019;44(5):148-172). It is essential for success in building and establishing trust to maintain long-term relationships with community partners. Ongoing community engagement allows the involvement of

sites and community-based organizations to develop long-term, sustainable strategies for improving URM participation in clinical research. Key community organizations include healthcare and AD-focused groups, places of worship, and local chapters of national organizations. Joint participation of sites and community-based organizations in activities such as local health fairs, educational webinars, and community outreach events can lead to increase awareness and knowledge. Materials such as culturally sensitive tools, social media content, presentations for HCPs, and print materials can be leveraged during these activities. **Results:** Program implementation began April 2021and the following outcomes will be measured: - Minority recruitment outcomes by study type (observational or therapeutic). - Level of engagement with identified community leaders and local organizations. Level of engagement between the site and community organizations will be categorized by inform, consult, involve, collaborate, and co-lead (Mayo Clin Proceed. March 2021;96(3):733-743). - Information related to how each minority participant heard about the study (referral source) will also be evaluated. Interim results will be shared during CTAD's 2021 Annual Conference. **Conclusions:** While the lack of diversity in clinical trials has often been recognized as a moral and scientific issue, approaches to improve diversity have largely been unsuccessful. Achieving diversity in clinical trials will require a community-specific approach that addresses all barriers to participation (Mayo Clin Proceed. March 2021;96(3):733-743). Furthermore, any community-specific strategies need to be constructed in such a way as to enable long-term success. Key learning's from GAP's Diversity and Inclusion Program will inform the development of future diversity and inclusion programs not only for AD trials but for trials in other therapeutic areas. **References:** Alzheimer's Association. 2021 Alzheimer's Disease Facts and Figures. https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf. Accessed May 18, 2021. Bierer BE, White SA, Meloney LG, Ahmed HR, Strauss DH, Clark LT. Achieving Diversity, Inclusion, and Equity in Clinical Research Guidance Document. Version1 .1. Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center). mrctcenter.org/diversity-in-clinical-research/. Published January 2021. Accessed May 18, 2021. Clark LT, Watkins L, Piña IL, et al. Increasing Diversity in Clinical Trials: Overcoming Critical Barriers [published correction appears in Curr Probl Cardiol. 2021 Mar;46(3):100647]. Curr Probl Cardiol. 2019;44(5):148-172. doi:10.1016/j.cpcardiol.2018.11.002 US Census Bureau. United States Census Bureau Quick Facts. https://www.census.gov/quickfacts/fact/table/US/PST045219. Updated August 27, 2019. Accessed May 18, 2021. US Food and Drug Administration. 2020 Drug Trials Snapshots Summary Report. https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots. Published February 2021. Accessed May 18, 2021. Wieland, ML. Njeru JW, Alahdab F, Doubeni CA, Sia IG. Community-Engaged Approaches for Minority Recruitment Into Clinical Research: A Scoping Review of the Literature. Mayo Clin Proceed. March 2021;96(3):733-743. doi.org/10.1016/j.mayocp.2020.03.028

P38- COMPREHENSIVE EVALUATIONS OF SOME MIXED MODELS FOR CLINICAL TRIAL ANALYSIS IN ALZHEIMER DISEASE. Guoqiao Wang *(Washington University In St Louis - St Louis (United States))*

Background: Clinical trials for sporadic Alzheimer disease (AD) generally use mixed models for repeated measures (MMRM) with the time variable being categorical as the primary efficacy analysis model. MMRM is well-accepted by regulatory agencies due to its minimal restrictions on the disease progression. However, inferences using MMRM focus on the between-group contrast at the pre-determined, end-of-study assessments, are less efficient (e.g. less power) given that participants who drop out before the end-of-study assessments don't contribute directly to the treatment efficacy inference. Other models such as the closely related linear mixed effects with random intercept and/or slope (LME) model with first-order polynomial time and/or second-order polynomial time as continuous variables utilize all available assessments and are more efficient, but with less popularity due to the assumption of linear or quadratic disease progression. Additionally, the MMRM/LME model controls the heterogeneous disease progression by including relevant covariates, but a better model may be needed to improve the efficiency of this strategy. To use the data more efficiently, three key areas should be evaluated using real clinical trial data: (i) does the real data meet the linear or quadratic disease progression assumption? (ii) Could alternative models that bridge the gap between MMRM and LME be used? (iii) Is there a better way to accommodate for the heterogeneous disease progression? These questions will be answered using simulations based on both hypothetical data and real trial data. **Objectives:** To evaluate the validity of model assumptions as well as the efficiency (i.e., power difference) of 7 models including a novel proportional MMRM model. **Methods:** First, we simulate hypothetical clinical trials based on 3 outcomes: the CDR SB, ADAS-cog, and MMSE of the placebo data of EXPEDITION 1-2 trials using well-established simulation methods. Then we compare the behavior of 7 models in terms of power; validity of model assumptions; and treatment effect pattern during the follow-up period. The models under evaluation include: (i) MMRM with efficacy inference at the pre-determined last study visit (MMRM-last-visit), which is the primary efficacy analysis model in most AD trials; (ii) MMRM with efficacy inference using data from all post-baseline visits (MMRM-all-visits); (iii) Linear mixed effects (LME) model with the constraint that the baseline mean is the same between the treatment and the placebo group (constrained LME); (iv) LME without the constraint about the baseline mean (unconstrained LME); (v) proportional MMRM with the assumption that the treatment effect in the post-baseline visits is approximately proportional to the mean change from baseline of the placebo group (pMMRM); (vi) Constrained LME with quadratic time (time*time) in the model (constrained quadratic LME); and (vii) Unconstrained LME with quadratic time (time*time) in the model (unconstrained quadratic LME). For each simulated trial using EXPEDITION 1-2 data, the assumption of linear disease progression will be tested by comparing the LME models with/without quadratic time. Furthermore, we evaluate the efficiency of each model when the trial population is heterogeneous by comparing covariate adjusted MMRM/LME model to two-part pMMRM model (i.e., equivalent to modeling participants with baseline MMSE 22-24 and baseline MMSE 25-28 simultaneously with two MMRM models). **Results:** Based on simulated hypothetical clinical trials with a proportional, disease-modifying treatment

effect (% reduction in placebo mean change from baseline), the power ranks of these models from high to low are: (i) constrained LME and pMMRM, (ii) MMRM-all-visits, and (iii) MMRM-last-visit and unconstrained LME. More simulations and analyses are ongoing and results for quadratic LME models will be added. Despite using all the data, the unconstrained LME model has similar power to MMRM using only last-visit data. Results based on EXPEDITION 1-2 actual data will also be presented. **Conclusion:** In addition to the traditional MMRM with efficacy inference at the last visits (MMRM-last-visit), several alternative models that have minimum or reasonable model assumptions with added benefits of power are possible and can be considered. When disease modifying treatment effects do exist, MMRM-all-visits has more power (>10%) than the MMRM-last-visit despite the same model assumption. Like MMRM, pMMRM does not require any parametric disease progression pattern, and it has much more power (>10%) than MMRM-last-visit under the assumption that the treatment effect (% reduction of the placebo decline) is approximately proportional. Simultaneously and separately modeling the heterogeneous trial cohorts in one model (such as the two-part pMMRM) could yield more power (5%-15%) than the traditional covariate adjusted model.

P39- PREDICTING AMYLOID POSITIVITY USING MACHINE LEARNING-BASED RISK SCORES. Kellen Petersen, Ali Ezzati, Richard Lipton, Ellen Grober *(Albert Einstein College Of Medicine - Bronx (United States))*

Background: Alzheimer's disease (AD) is the most common neurological disease leading to dementia and currently has no cure. The ATN framework has been proposed as a biomarker-based approach to defining and understanding AD in living persons. The biomarkers used are categorized as follows: 1) "A" represents β-amyloid (Aβ) accumulation, believed to be the initial pathology of AD, measured by amyloid positron emission tomography (PET) or cerebrospinal (CSF) Aβ42; 2) "T" represents pathologic tau measured by tau PET or CSF phospho-tau; and 3) "N" represents neurodegeneration or neuronal injury. As this framework has been widely adopted, predicting the accumulation of Aβ is essential in both research and clinical settings for early intervention with amyloid targeted treatments. **Objective:** The objective of this work was to develop and test the performance of different Positive Aβ Risk Scores (PARSs) for prediction of Aβ positivity in cognitively unimpaired individuals for use in research or clinical settings. **Methods:** We developed a practical machine learning-based risk score for predicting Aβ positivity. Using data obtained for 4134 individuals enrolled in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study, the sample was first divided into training and test sets. We assigned each of the seventeen different variables to one of four categories: demographics, subjective measures, objective measures, and genetic information in the form of APOE4 status. Combinations of these categories formed the feature-sets used for developing different risk score models. Models were developed by first finding the importance ordering of variables based on the Gini Index from implementation of a Random Forest algorithm. Variables were iteratively included, based on this ordering, in risk score models derived from coefficients of logistic regression models. Final risk score models were found by keeping variables that improved the model area under the ROC curve (AUC) by at least 1%. **Results:** Performance of the final models were then measured using the independent test set. Three risk score models were derived from different combinations of features (feature-sets) including demographics, subjective measures, objective measures, and APOE4 status: Model 1 consisted of age, BMI, and family history and had an AUC of 0.60; Model 2 had an AUC of 0.61 and included Free Recall in addition the variables of Model 1; Model 3 attained an AUC of 0.73 and consisted only of age, BMI, and APOE4 status. With a prevalence of 33% in the test set, Model 3 showed the highest performance metrics in comparison with other models: sensitivity = 72%, specificity = 62%, positive predictive value (PPV) = 48%, negative predictive value (NPV) = 82%, and accuracy = 65%. Models 1 and 2 had PPVs 22% (7 percentage points) above prevalence while Model 3 had a PPV 47% (15 percentage points) above prevalence. While the percentage of amyloid positive individuals in the bottom two quartiles of points for each model were similar, the percentage of amyloid positive individuals with risk score points in the third quartile were 42%, 44%, and 65%, respectively, and the percentage of amyloid individuals in the fourth quartile of points for risk score Models 1, 2, and 3 were 71%, 60%, and 90%, respectively. **Conclusion:** In conclusion, we presented an approach that can be used by both researchers and clinicians to develop simple and practical risk scores for the important task of predicting Aβ positivity. We implemented this approach to derive three risk score models for predicting Aβ positivity and reported the performance of each model. **Conflicts of Interest:** The authors have no conflicts of interest to report except Ellen Grober, Ph.D. receives a small royalty for commercial use of the Free and Cued Selective Reminding Test with Immediate Recall. The test is available at no cost for research or clinical activities from the Albert Einstein College of Medicine.

P40- DETERMINING THE PROBABILITY OF SUCCESS IN A CLINICAL DEVELOPMENT PROGRAM FOR A DISEASE MODIFYING AD TREATMENT. Suzanne Hendrix, Newman Knowlton, Jessie Nicodemus Johnson, Sean Hennessey, Samuel Dickson *(Pentara Corporation - Salt Lake City (United States))*

Background: The failure rate in Alzheimer's disease studies is exceptionally high, particularly with disease modifying treatments. Many factors lead to this high failure rate. But the recent successful phase 3 study of aducanumab (EMERGE) brings up the question of how large a treatment effect needs to be to successfully complete an AD clinical development program. **Objectives:** To determine the approximate probability of successful completion of a clinical development program for stage 3 Alzheimer's disease. **Methods:** We define a traditional clinical development program as a phase 1 study for target engagement, a phase 2 dose finding / proof of concept study, and two phase 3 pivotal studies, with assumed sample sizes of 40, 250, and 1000 per arm as "high Ns" and sample sizes of 20, 75 and 400 per arm as "low Ns". We defined success in phase 1 as an effect that is directionally in favor of active (although we acknowledge that phase 1 success is often based on biomarkers). In phase 2, success was defined as a trend in favor of active treatment ($p<0.20$, two sided), and in phase 3, success was defined as $p<0.05$ two sided for each of two studies. The primary endpoint is assumed to be ADAS-cog or CDR-sb over an 18-month study and means and standard deviations for a placebo arm were estimated from 5 phase 3 studies of monoclonal antibodies in early or mild AD. **Results:** Our estimated effect size across primary and secondary outcomes based on pooled ENGAGE and EMERGE studies for Aducanumab, is 19% slowing of disease progression. The probability of a successful development program based on a

single primary endpoint of ADAS-cog is estimated to be 1.2% for the low N, and 9.5% for the high Ns. The probability of success with CDR-sb as a single primary endpoint is 1.5% for the low Ns, and 12.1% for the high Ns. Assuming an effect size of 35%, the probability of a successful development program with ADAS-cog is 15.4% for the low Ns, and 57.5% for the high Ns. Using the CDR-sb increases these probabilities to 19.0% and 62.4%, respectively. Using the smaller sample sizes approaches 50% chance of success (48.5%) with an effect size of 50% slowing of progression. **Conclusion:** Alzheimer's disease is a challenging disease to treat, and disease modifying effects – which are expected to result in slowed progression -- are particularly difficult to detect, resulting in many clinical trial failures. Even with relatively large effect sizes and large clinical trial sample sizes, the chance of failure for active compounds is quite high.

LP10- PRECLINICAL AD RESEARCH AND THE ELECTRONIC MEDICAL RECORD (EMR): BALANCING CONFIDENTIALITY AND PARTICIPANT SAFETYY.

Seth Gale[1], Judith Heidebrink[2], Jonathan Graff-Radford[3], Joshua Grill[4], Gregory Jicha[5], Jason Karlawish[6], William Menard[7], Milap Nowrangi[8], Susi Sami[9], Shirley Sirivong[4], Sarah Walter[10] *(1. Brigham And Women's Hospital - Boston (United States), 2. University Of Michigan - Ann Arbor (United States) - Ann Arbor (United States), 3. Mayo Clinic - Rochester (United States), 4. University Of California - Irvine (United States), 5. University Of Kentucky - Lexington (United States), 6. University Of Pennsylvania - Philadelphia (United States), 7. Butler Hospital, Memory And Aging Center - Providence (United States), 8. Johns Hopkins University - Baltimore (United States), 9. Case Western Reserve University - Cleveland (United States), 10. Alzheimer's Therapeutic Research Institute, University Of Southern California - San Diego (United States))*

Background: The pathology of Alzheimer disease (AD) begins years before the onset of overt symptoms. Early AD pathologic changes can be detected in vivo by biomarker tests, including molecular imaging and cerebrospinal fluid assays. "Preclinical AD", which remains functionally a research construct, describes this condition, where biomarker results indicate the presence of pathological hallmarks of AD in the absence of symptoms. Conceptually, preclinical AD can be considered a "risk state" for developing cognitive/functional impairment rather than "clinical" AD itself, even while both are defined, in part, by the same biomarkers. This overlap in tests that characterize both a research-identified condition and a symptomatic disease, along with the potential for harms to research participants arising from unwanted disclosure of preclinical AD status, presents a host of ethical and care delivery challenges for researchers and clinicians. Principal among these is that preclinical AD status determination occurs mostly in research settings and involves sensitive information, including study names themselves and AD biomarker test results, placing participants at risk of stigma and discrimination if disclosed. Simultaneously, treatments used in preclinical AD trials may cause sequelae that require emergent or longitudinal care outside of research, and disclosure of relevant, sensitive study information to treating clinicians is often needed to deliver safe and optimal care. Thus, research data, stored in electronic medical records (EMRs), present an ethically complex junction between optimized research confidentiality and the protection of participant safety and interests. **Objective:** The Internal Ethics Committee (IEC) of the NIA-funded Alzheimer Clinical Trials Consortium (ACTC), along with ACTC Coordinating Center staff, assessed the ethical and practical challenges related to use of EMRs for research in preclinical AD. The aims were: 1) to provide ACTC member sites and the broader AD research community with a rich framework for understanding this topic, and, 2) to generate a "Guidance Document" and educational Webinar containing considerations and suggestions for how researchers might best utilize EMRs to balance their ethical obligations in preclinical AD research. **Methods:** The review was catalyzed by requests for advice from study personnel at ACTC member sites on best practices for the use of information systems in preclinical AD research. It became clear that research staff are actively negotiating with their IT and administrative teams, developing creative solutions to protect participant privacy. Subsequently, a working group composed of IEC members and select ACTC staff was formed to discuss ACTC sites' experiences with EMRs, confidentiality considerations for different kinds of research data, and challenges related to information flow within electronic systems pertaining to preclinical AD research participants. Working group members then conducted a review of relevant AD clinical research and ethics literature to inform subsequent discussions and preparation of educational materials and reccomendations. **Results:** By consensus, the working group created a "Guidance Document" and a live/recorded Webinar to collate conclusions from their discussions and review. These materials provide an ethical framework for understanding the responsibilities of researchers who conduct studies in preclinical AD. Researchers must protect the confidentiality of study participants who have preclinical AD, but also make clinically-relevant research data easily available for care decisions outside of research. In policy and practice, study teams and institutions might appeal to individual research participants' autonomy and directly engage them in decisions about data documentation, contingent on the capacity for individualization in their EMR. Individual-level engagement would also ensure transparency and participants' comprehensive understanding of the risks of disclosure/non-disclosure. The personal, medical risks of not including data that might reveal preclinical AD status within a clinically-utilized EMR could be weighed against the societal risk of harms to that individual if wider, unwanted disclosure of their preclinical AD status occurred, including discrimination with insurance coverage, misdiagnosis, or stigmatization. The working group recommended that researchers and IT teams create a separate record for research and clinical information, or, embed research information in the clinical EMR, with added features of digital "protection" to dissuade common access. The "Guidance Document" and Webinar provide further details on the risk of including specific types of preclinical AD research information within the clinical EMR. **Conclusion:** With increasing attention on AD prevention, individuals with preclinical AD are being readily identified in research settings and sensitive health information is stored in EMRs. It is essential for the AD research community, institutions, and study sponsors, to mitigate potential harms that can arise from unwanted disclosures outside of research, while also facilitating access to research data that is needed to optimize clinical care. Researchers must use clear language in their informed consent to communicate potential risks to confidentiality when EMRs are being utilized. Broader discussion within the AD research community and dissemination of best practices for managing preclinical AD research are key in ensuring that researchers honor the bioethical principle of respect for persons and its attendant obligations to protect participant confidentiality and welfare.

LP11- PLANNING FOR SUCCESS: A THREE-STEP PROCESS TO DEFINE PHASE II TRIAL SIZE AND DURATION USING A PATIENT ENRICHMENT STRATEGY USING PHASE I DATA AND PUBLIC DATABASES. CJ Barnum[1, 2], Descoteaux Maxime[3], Roy Maggie[4], Dumont Matthieu[4], Jean-Christophe Houde[4], Melanie Buitendyk[5], Judith Jaeger[6], Rj Tesi[1] *(1. Immune Bio Inc - Boca Raton (United States), 2. Imeka Solutions Inc - Sherbrooke (Canada), 3. Université De Sherbrooke - Sherbrooke (Canada), 4. Imeka Solutions Inc - Sherbrooke (Canada), 5. Cato-Sms - Wilmington (United States), 6. Cognition Metrics Llc - Springfield (United States))*

Background: CNS drug development can learn many lessons from the "best practices" used in oncology drug development campaigns. Each year many more new drugs are approved for the treatment of cancer than the treatment of neurologic diseases. While there are many possible reasons for this, we believe the success in oncology is based on more innovative use of biomarkers and patient enrichment strategies in their clinical trial design. Put simply, oncology drug development carefully matches the drug's mechanism-of-action (MOA) with the patient population they are studying. This strategy is a trade-off between market size and development risk - both are decreased. In today's era of precision medicine, this trade-off improves clinical success and more importantly, that patients receive the right treatment. **Methodology:** The development of XProTM for the treatment of AD used a stepwise oncology-like approach for the drug development. The Phase I was designed to determine if XProTM, a drug targeting neuroinflammation, could decrease biomarkers of neuroinflammation in the target population. If the answer to the first question was yes, the Phase II trial would determine if decreasing neuroinflammation will affect cognition. This resulted in a three-step process. First, inclusion criteria were developed to enrich enrollment for AD patients with neuroinflammation (ADi), matching the disease process with the drug MOA. This step occurred before the first patient was enrolled in the Phase I trial. The second step was to confirm, comparing data from the phase 1 trial with existing data bases, the success of the enrichment strategy in the Phase 1 study. Did the trial enroll only patients with neuroinflammation as part of their AD pathology? The final step was to explore existing data bases for patients similar to those enrolled in the Phase I trial to determine the speed and variability of the disease progression rate to determine size and duration needed for a successful Phase II trial. **Results:** The sponsors did not want to require MRI or CSF collection as part of the screening criteria; the first is expensive, the second discourages participation. The sponsor opted for easily obtained laboratory data to determine if the AD patient had a high probability of having neuroinflammation contributing to their AD. The patient needed one or more of a CRP≥1.5mg/L, ESR≥10sec, HgbA1c>6% or be ApoE4 positive. Half of the patients referred for the clinical trial did not have any of the 4 inclusion criteria - a screen failure rate was 50%. During the clinical trial, neuroinflammation was assessed at 12 weeks by CSF (OLINK 48 cytokine panel) and up to 12 months by MRI measure of free water (FW) in white matter AD bundles (IMEKA) with decreases of 15% and 46% respectively in the dose planned for the Phase II trial (1mg/kg once a week by subcutaneous injection). Next, patients in the trial were compared with patients in the ADNI database with MRI FW data without regard for any other inclusion criteria. Patients from the ADNI cohort had substantially less neuroinflammation as measured by MRI FW than the AD patients that were enrolled in the Phase 1 study and validated the patient enrichment strategy. The second step was to determine the impact of ADi on cognitive decline in our target clinical cohort, mild ADi. Leveraging the ADNI database, we plotted the rate of cognitive decline in the ADAS-Cog, CDR-SB, and Early Mild Alzheimer's Cognitive Composite (EMACC) as a function of neuroinflammation. The Phase I patient profile was overlaid on the "rate of progression" to provide an estimate of speed and severity of cognitive deterioration in a group of patients with the clinical profile defined by the Phase I trial. The subset of AD patients from the public database with neuroinflammation as part of their pathology declined more quickly and had less variability than patients without neuroinflammation. These results were used in the statistical planning to define trial size (n) and duration (time in months). **Conclusions:** 1) A patient enrichment strategy using peripheral biomarkers of inflammation resulted in an AD clinical trial population with a high incidence of neuroinflammation as part of their AD pathology. 2) Patients in the ADNI database with neuroinflammation measured by neuroinflammatory biomarkers had more rapid cognitive decline with less variability. 3) Using data from the first two steps, a 6 month, 200 patient biomarker directed, blinded, placebo control Phase II trial was designed. In summary, patient enrichment strategies combined with analysis of public patient databases allows for smaller, shorter Phase II trial designs. This approach should decrease size, duration and cost of AD development.

LP12- PREFERENCES FOR DISCLOSURE OF BIOMARKER AND GENETIC RESULTS IN ALZHEIMER'S RESEARCH: FEEDBACK FROM A PARTICIPANT ADVISORY BOARD. Sarah Walter[1], Adam Boxer[2], Joshua D. Grill[3], Jason Karlawish[4], Shaffer Elizabeth[1], Jaimie Ziolkowski[5], Paul Aisen[1] *(1. alzheimer's Therapeutic Research Institute, University Of Southern California - San Diego (United States), 2. university Of California, San Francisco - San Francisco (United States), 3. university Of California, Irvine - Irvine (United States), 4. university Of Pennsylvania, Perlman Medical School - Philadelphia (United States), 5. university Of Michigan - Detroit (United States))*

Background: The Alzheimer's Clinical Trials Consortium (ACTC) has the mission to provide an optimal infrastructure to accelerate the development of effective interventions for Alzheimer's disease and related disorders (ADRD). ACTC launched the Research Participant Advisory Board in 2020 with the aim of improving the design and conduct of clinical trials by integrating feedback from participants. The Advisory Board is comprised of twelve members, with 75% women and 58% from racial and ethnic groups typically under-represented in dementia research. Members reside in both urban and rural settings across the United States. The advisory board includes individuals with a diagnosis of mild Alzheimer's disease (AD), individuals with elevated risk for AD, and both former and current care partners of people with dementia. A majority of members have participated in research, with two members describing themselves as 'research curious'. **Objectives:** To share recommendations generated by discussions with the ACTC Research Participant Advisory Board around the disclosure of biomarker and genetic results. **Methods:** Board Members were invited to join a videoconference where an ACTC investigator presented on the status of the field and answered questions. Feedback was collected in separate small group discussions, held via videoconference. Discussion questions were developed in collaboration with the study team and the ACTC Internal Ethics Committee. The meetings were

recorded and transcribed. The feedback was summarized and is shared here, and with the ACTC investigators. **Results:** Each of the advisory board members expressed interest in learning their biomarker and genetic results, regardless of their cognitive complaints. Participants expressed a high level of confidence in medical settings and expected accurate results would be shared both by researchers and clinicians. Prior to disclosing results, participants recommended that researchers define any medical terms being used and take the time to actively verify that participants understand the terms. Although keenly interested themselves to learn their results, board members urged flexibility, citing examples of friends and relatives who chose not to join research because the study required disclosure of amyloid status. Reasons to decline participation included a preference not to know, as well as concerns for legal protection and risk to privacy. They recommended that researchers include care partners in the disclosure process. One member, a Latina woman caring for her mother, shared that for her culture, it was more acceptable for the care partner and not the person with the diagnosis to be disclosed results. Her recommendation was for researchers to ask the participant and family their preferences for who to include in the disclosure process. Although participants have an assumption of standardization, they also grasped that measuring biomarkers is complex and that results could be impacted by instrumentation, or the experience and training of individuals involved. They expressed a desire to learn their own results, even if the clinical relevance is not fully understood. Participants shared their expectation that the scientific evidence and clinical utility of biomarkers will evolve, and they were prepared to follow those changes. Participants agreed that where learning had a potential to impact study outcomes, researchers should disclose at the end of the study. However, there was concern that longer studies may require an unreasonable amount of time for participants to wait. Participants also urged researchers to be cautious where information conflicts with a prior diagnosis, and to consider meeting with the participant, care partners and diagnosing physician to discuss what the results could mean for clinical care. **Conclusion:** The feedback from ACTC Research Participant Advisory board indicates that many participants are eager to learn their results and are willing to tolerate uncertainties and evolving understandings of what biomarker or genetic results mean. They cautioned researchers to consider cultural differences, to ask for participant and care partner preferences for who to include in disclosure process, and to design studies with the option to learn or not learn one's biomarker or genetic status. Underlying the feedback received from this board was an expectation for transparency driven by respect for the individual and their care partners. By requesting input before the trial designs are set, ACTC investigators were able to integrate feedback into study design. Participant feedback should be considered at multiple timepoints throughout studies, as better tools to predict risk, track disease progression and treat or prevent disease emerge. ACTC is funded by a Cooperative Agreement from the National Institute on Aging, National Institutes of Health (ACTC grant (NIH/NIA U24 AG057437, Aisen / Sperling / Petersen, Multi-PI). The authors declare that there is no conflict of interest..

RP14- THE ADATAVIEWER: EXPLORING ALZHEIMER'S DISEASE COHORT DATA. Yasamin Salimi[1,2], Daniel Domingo-Fernández[1], Carlos Bobis-Álvarez[3], Martin Hofmann-Apitius[1,2], Colin Birkenbihl[1,2] *(1. Department Of Bioinformatics, Fraunhofer Institute For Algorithms And Scientific Computing (scai) - Sankt Augustin 53754 (Germany), 2. Bonn-Aachen International Center for IT, Rheinische Friedrich-Wilhelms-Universität Bonn - Bonn 53115 (Germany), 3. University Hospital Ntra. Sra. De Candelaria - Santa Cruz De Tenerife 38010 (Spain))*

Background: There exist a plethora of studies that have collected patient-level data in the field of Alzheimer's disease (AD). Much of the data-driven research that has been previously conducted was based on a single cohort dataset. Due to the variability across cohort studies in patient demographics, restrictive recruitment criteria (i.e. exclusion and inclusion criteria), and regional influences, a myriad of concerns naturally arise regarding the generalizability of conclusions obtained from such single-cohort works. To evaluate the reproducibility of the results derived from these studies, it is vital to validate the research using independent cohort datasets. However, as the AD cohort datasets do not necessarily share a set of common features or measurements, it is first required to make them interoperable at a variable level. Previous attempts in the neurodegeneration research community to establish data catalogs at the metadata level lack information on interoperability between studies at the level of individual features. In order to really solve the harmonization and interoperability issue in the Alzheimer patient-level data arena, we implemented a systematic approach for the mapping of study data at the variable (feature) level. **Objectives:** The selection of cohort studies that could be relevant for any data-driven research is a time-consuming task as it requires access to the datasets and investigation of measurement availability. Additionally, not all of the measurements have been collected for all the participants, thereby posing a potential restriction on the usability of the datasets. To enable artificial intelligence (AI) based modeling in the AD field and in particular to facilitate the identification of suitable independent control studies, we generated a comprehensive data and feature catalog called ADataViewer. This catalog contains the majority of the widely used, published AD cohort studies; ADataViewer allows comparison of these datasets at the feature level. The interface we developed enables for interactive selection of relevant cohort studies according to well-defined variables (e.g. endpoints or biomarkers) that are relevant for the underlying scientific question. Our goal was to accelerate and assist researchers in identifying potentially comparable training and validation cohorts by identifying those which share common sets of features. Thus, this endeavor paves the foundation for further comprehensive investigations. **Methods:** We have harmonized all the common features present in 20 widely recognized and studied cohort datasets. All features in all studies were mapped wherever possible and all information was organized longitudinally along a standardized time scale. Through meticulous manual curation, we have also mapped each feature to standardized ontologies, whenever possible, to improve semantic operability. Finally, we developed a publicly available web application that enables interactive exploration of the investigated cohorts on a feature level: the ADataViewer. **Results:** We compared the availability of collected measurements among the investigated datasets on modality as well as feature level. Through manual curation, we successfully mapped more than 1,000 individual features across the 20 cohort datasets. Our investigation revealed that

in some cases, certain features were not collected even though they had been reported in the study metadata. A dedicated tool called "StudyPicker", enables the identification of relevant cohorts by entering features of interest; the output is a ranked list of cohorts based on the availability of those features. StudyPicker enables the selection of the most relevant cohort given a specific aim of a modeling and mining task, therefore expediting the researcher's most tedious steps into one effortless task. Additionally, using a variety of visualizations, we enable users to trace selected features over time for each cohort study. These views are advantageous because the number of available samples for each feature over time is directly visible. Often, the measurements for a cohort study were normalized before the datasets were shared with the researchers; this could restrict the interoperability of the datasets. Motivated by this potential limitation as well as a general interest to compare distributions, we presented the measurements of each mapped feature using box plots for all study cohorts. Our visualization tool allows the user to compare the distribution of each feature across the investigated cohorts and ultimately informs the user of the interoperability of the datasets. **Conclusion:** To our knowledge, ADataViewer is the first fully mapped AD data catalog that comprises 20 cohort studies and enables interactive dataset exploration at feature / variable level. Using StudyPicker, researchers can select the most appropriate datasets to the aim of their studies before applying for the datasets; in essence, they know what they can ask for in the data before they have the data at hand. The harmonized, feature-based mapping catalog is publicly available, thus allowing researchers to leverage this semantically aligned resource to make distinct datasets interoperable and conduct analyses across multiple datasets.

RP15- WHAT MIGHT INTRINSIC CHANGES IN SCREEN TO BASELINE CDRS IN ALZHEIMER'S CLINICAL TRIALS SIGNIFY: AN EXPLORATORY ANALYSIS. Alan Kott[1], David Miller[2] (*1. Signant Health - Prague (Czech Republic), 2. Signant Health - Blue Bell (United States)*)

Background: We have previously reported that only one third of subjects entering mild to moderate AD trials show a consistent unidirectional change across cognitive domains in the MMSE between Screening and Baseline. The remaining two thirds of subjects show a mixed pattern of change with some domains improving and some worsening. The largest difference between the change in total score and the absolute 'intrinsic' changes across all domains were observed in cases where the total score change was minimal. **Objective:** To determine whether and to what extent changes in individual CDR domains correspond with the direction and magnitude of total CDR-SB score change between Screening and Baseline in Alzheimer's Disease (AD) clinical trials. **Methods:** Screening and baseline data were pooled from 6 randomized double blind clinical trials in mild to moderate Alzheimer's disease. Absolute CDR-SB score change and individual absolute domain changes between Screening and Baseline were calculated as was the difference between the absolute CDR-SB score change and the sum of absolute score changes in the individual CDR domains (intrinsic difference). We classified CDR-SB change as absent, questionable (0.5 point change), minimal (1 - 1.5 point change), and clinically meaningful (>=2 point change). Chi square test was used to analyze the data and evaluate the association of CDR-SB change with intrinsic differences. **Results:** Our dataset consisted of 2,830 pairs of CDR-SB ratings collected at screening and baseline. No change between screening and baseline in CDR-SB was present in 1,026 cases (36.3%). Questionable change was present in 1,048 cases (37%), minimal in 632 cases (22.3%) and clinically meaningful in 124 cases (4.4%). The largest CDR-SB change between screening and baseline observed in the dataset was of 5.5 points. No difference between the sum of individual domain changes and the CDR-SB change was observed in 2,313 cases (81.7%), a 1 point difference in 435 cases (15.4%), a 2 point difference in 77 (2.7%) of cases and finally a 3 point difference in 5 cases (0.2%). Intrinsic differences were unevenly distributed in the data with the majority of them happening when CDR-SB showed no or questionable change between screening and baseline ($chi2(3) = 64.4129$; $p < 0.001$). **Conclusion:** Our data indicate that over 36.3% of subjects show no change in the CDR-SB between screening and baseline. However, in these subjects we identified changes in opposite direction within the scale itself (improvement and worsening at the same time) in 24.5% of subjects. In the remaining 63.3% of subjects, the intrinsic changes within the CDR exceeded the sum of boxes absolute change in 15.3% of instances. As was the case for the MMSE, the largest intrinsic changes were observed in the case when the CDR-SB did not change or changed by 0.5 point only. Our data endorse that a total score stability in the CDR-SB may not be an accurate measure of stability and that domain changes should be carefully examined to verify stability. Potential explanations of intrinsic changes in the CDR include unstable living conditions affecting the subject's cognitive and functional performance, rater change as well as scale administration and/or scoring errors. Further analyses are necessary to understand the phenomenon of intrinsic changes better and assess the impact of these changes on data once subjects are randomized. **Conflict of interest:** Both authors are full time employees of Signant Health

RP15BIS- OPTIMIZATION OF CLINICAL TRIAL DESIGN FOR COMBINATION THERAPIES USING VIRTUAL PATIENTS. Hugo Geerts[1], Mike Walker[2], Rachel Rose[1] *(1. Certara - Berwyn, Pa (United States), 2. Certara - Sheffield Uk (United Kingdom)))*

Background: There is increasing interest in combination therapy treating the complex clinical phenotype of Alzheimer's disease. Such a combination therapy ideally would be optimized for the patient specific disease state. However the sheer number of combinations and conditions far exceeds the capabilities of clinical trials; we propose to use advanced mechanistic computational modeling of 'virtual twins' to support the clinical development of such therapeutic combinations, in particular amyloid and tau modulating strategies. **Methods:** Quantitative Systems Pharmacology combines PK simulations with advanced pharmacodynamic modeling of downstream effects on relevant biomarkers and clinical outcome. Amyloid aggregation dynamics and spatio-temporal tau progression is modeled based on a combination of preclinical and clinical datasets. Oligomeric amyloid levels affects glutamate and nicotinic neurotransmission and tau hyperphosphorylation affecting both tau release from presynaptic nerve endings as well as intraneuronal oligomerization. Spatial progression of misfolded tau protein is modelled using slow axonal transport, together with tau degradation and oligomerization with endogenous tau. Release from pre-synaptic nerve ending and uptake by post-synaptic neurons is calibrated using in vitro cell culture experiments. Coupling between these two pathologies is calibrated using available biomarker data from clinical trials. Finally, we simulate anticipated functional outcome in an ADAS-Cog calibrated neuronal circuit for cognitive dysfunction based

on the interaction of tau oligomers with voltage-gated ion channels. **Results:** We first simulate the natural history of amyloid aggregation suggesting a precipitous drop in monomer Ab42 CSF about 15-20 years before the plateauing of higher order aggregates in the brain. Implementing APOE genotype in the clearance pathway shows a 5-10 year delay in this aggregation for an non-APOE4 carrier. The model of spatial Tau progression is first calibrated using data from preclinical animal models and further extrapolated to the clinical situation using brain connectomics. We further show that tau pathology dominates amyloid effects in neuronal firing activity as shown in preclinical transgene mouse models. Clinical interventions using monoclonal antibodies or small molecules are modeled using a PBPK platform. Finally, we simulate a number of clinical trial scenarios where amyloid modulating agents are combined with tau modulating agents in a staggered design, affecting different processes of the tau pathology at different time points. **Conclusion:** The introduction of advanced computer modeling of the biological processes involved in amyloid and tau pathology in a virtual patient platform likely allows to identify key pharmacodynamic interactions and improve clinical trial design.

RP16- EVALUATING THE EFFECTIVENESS OF A DIGITAL THERAPEUTIC TO REDUCE ALZHEIMER'S RISK: A RANDOMIZED CONTROLLED TRIAL. Mark Mcinnis[1], Richard Isaacson[2], Robert Krikorian[3] *(1. Retain Health - Bedford (United States), 2. Alzheimer's Disease Education Consultants - Miami Beach (United States), 3. University Of Cincinnati Academic Health Center - Cincinnati (United States))*

Background: Alzheimer's disease (AD) develops over an extended asymptomatic period, known as Stage 1 AD, where pathologic changes begin in the brain without noticeable decline in cognition. In the United States alone, there are currently 46 million people in Stage 1 AD. This period represents a window of opportunity for prevention or delay of dementia due to AD given that there are a host of modifiable AD risk factors. Several randomized controlled trials (RCTs) have shown that multi-domain intervention (e.g., physical exercise, dietary change, vascular risk factor control) can maintain cognitive function and reduce the risk of cognitive impairment with aging. A recent study demonstrated that modifiable risk reduction via individualized, multi-domain clinical recommendations improved cognition and lowered calculated AD risk. These data suggest that personalized lifestyle changes can improve cognition and reduce one's risk of developing AD. However, these studies involved substantial resources in terms of personnel and costs of care delivery. To target an ever-growing population at risk for AD, an effective, pragmatic approach with the capacity for broader reach is needed. We created a digital therapeutic to provide individualized, evidence-based risk reduction education while monitoring outcomes longitudinally. The software incorporates key components of the Transtheoretical Model of Behavior Change, a model that has been successfully applied in a variety of studies to drive behavioral change related to lifestyle. **Objective:** The objective of this study is to evaluate the effectiveness of a proprietary digital therapeutic tool to reduce users' calculated risk AD. The primary outcome will be change from baseline on a validated AD risk index. Secondary outcomes include change from baseline in performance on an associative memory test, and other self-reported measures such as costs of lifestyle changes and user satisfaction. **Methodology:** Participants will be recruited using targeted advertising. Electronic informed consent will be obtained from all participants prior to joining. Users will be screened for age, family history of AD, access to a compatible digital device, and the presence of at least one modifiable risk factor for AD. At baseline, users will be asked to complete a welcome interview questionnaire that examines the users' risk factor profile. Participants will then be randomized to one of three groups: (1) access to the full software protocol, (2) access to select features of the software, and (3) an information-only control group. **Results:** The study is currently in progress and an update on the trial will be forthcoming. **Conclusion:** The study software is a digital therapeutic that aims to scale multi-domain AD risk reduction and improve access to individualized care. This research addresses goals of the National Alzheimer's Project Act to prevent and effectively treat AD by 2025.

RP17- CLINICAL TRIAL PROTOCOL OF BROMOCRIPTINE IN ALZHEIMER'S DISEASE WITH PRESENILIN 1 (PSEN1) MUTATIONST. Haruhiko Banno[1], Takayuki Kondo[1], Taro Okunomiya[1], Yoko Amino[1], Akiyoshi Nakakura[1], Ryuji Uozumi[1], Harue Tada[1], Akihiro Shindo[2], Takakuni Maki[1], Manabu Ikeda[3], Yuishin Izumi[4], Kazutomi Kanemaru[5], Kenji Ishii[6], Kazue Shigenobu[7], Yoshihide Sunada[8], Toshifumi Watanabe[9], Osamu Uchikawa[10], Ryosuke Takahashi[1], Hidekazu Tomimoto[2], Haruhisa Inoue[1] *(1. Kyoto University - Kyoto (Japan), 2. Mie University - Tsu (Japan), 3. Osaka University - Suita (Japan), 4. Tokushima University - Tokushima (Japan), 5. Tokyo Metropolitan Geriatric Medical Center - Tokyo (Japan), 6. Tokyo Metropolitan Institute Of Gerontology - Tokyo (Japan), 7. Asakayama Hospital - Sakai (Japan), 8. Kawasaki Medical School - Kurashiki (Japan), 9. Time Therapeutics, Inc. - Kyoto (Japan), 10. Towa Pharmaceutical Co.,ltd. - Osaka (Japan))*

Background: Pathogenic variants in the PSEN1 gene are the most frequent cause of early-onset Alzheimer's disease (AD). Most of the AD patients with mutations in the PSEN1 gene (PSEN1-AD) experience onset in their 20s to 50s, and their cognitive function deteriorates rapidly, leading to death within several years. Medications for PSEN1-AD are limited to symptomatic therapies and no established radical treatments are available. To develop therapeutic compounds for PSEN1-AD, we previously established induced pluripotent stem cells (iPSCs) from patients with PSEN1-AD. iPSCs were established by introducing a small number of genes into patients' cells. Established iPSCs can differentiate into any type of cell in the body and proliferate indefinitely. We established an iPSC-based screening system by modelling Aβ phenotypes of PSEN-1AD. We utilized an existing drug library the safety and pharmacokinetic profile of which had already been confirmed clinically and approved for use in human. After the screening, we found bromocriptine to be the most potent modifier of Aβ production for PSEN1-AD neurons among existing drugs. Bromocriptine is an already approved drug with few safety concerns and a long history of usage in clinical settings. Bromocriptine was approved for the treatment of Parkinson's disease (approved dosage 22.5mg/day), pituitary tumor, and hyperprolactinaemia, and was proven to penetrate the blood-brain barrier. Based on iPSC studies, as we hypothesized that bromocriptine might attenuate the clinical symptoms of PSEN1-AD patients, we decided to conduct a clinical trial to evaluate the safety and efficacy of the first-time administration to PSEN1-AD patients as an investigator-initiated clinical trial (exploratory study). **Objectives:** In this study, we used an enrichment strategy with iPSCs to select the study population, and we will investigate the safety and efficacy of an orally

administered dose of bromocriptine in patients with PSEN1-AD. **Methods:** This is a multi-center, randomized, placebo-controlled trial. AD patients with PSEN1 mutations and a Mini Mental State Examination-Japanese (MMSE-J) score of ≤ 25 will be randomly assigned, at a 2 : 1 ratio, to the trial drug or placebo group (≥ 4 patients in TW-012R and ≥ 2 patients in placebo). Owing to the ethical issue for patients assigned to the placebo group, unequal randomization will be employed. This clinical trial consists of a screening period, double-blind phase (9 months), and extension phase (3 months). The double-blind phase for evaluating the efficacy and safety is composed of the low-dose maintenance period (10 mg/day), high-dose maintenance period (22.5 mg/day), and tapering period of the trial drug. Additionally, there is an open-labelled active drug extension period for evaluating long-term safety. Primary outcomes are safety and efficacy in cognitive and psychological function. For cognitive function, Severe Impairment Battery-Japanese (SIB-J) will be evaluated. For psychological function to evaluate behavioral and psychological symptoms of dementia (BPSD), Neuropsychiatric Inventory (NPI) will be assessed. Also, exploratory investigations for the efficacy of bromocriptine by neurological scores and biomarkers will be conducted. Secondary endpoints include Mental Function Impairment Scale (MENFIS), MMSE-J, Disability Assessment for Dementia (DAD), Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III, Apathy Evaluation Scale Informant Version, plasma Aβ protein, plasma neurofilament light chain protein (NfL), plasma total tau and plasma phosphorylated tau protein, cerebrospinal fluid Aβ (CSF Aβ), cerebrospinal fluid total tau and phosphorylated tau protein (CSF total/p-tau), and blood bromocriptine concentration. In addition, wearable physical activity meter, measurement with finger tapping device, brain amyloid PET, brain tau PET, Upper Motor Neuron Burden Score (UMNB), and plasma Aβ-related peptides will be assessed as reference endpoints. Due to the COVID-19 pandemic in 2020, we amended our protocol to make it possible to deliver study drugs if a participant cannot visit a medical facility. For participant retention and safety reasons, a participant will have 10 phone-call-visits in addition to monthly onsite-visits. This trial registration numbers are jRCT2041200008 (Japan Registry of Clinical Trials), and NCT 04413344 (ClinicalTrials.gov). **Results:** This ongoing clinical trial started to enroll participants in June 2020 and will end in March 2022. This study will be conducted at 6 academic hospitals and 1 community hospital in Japan. **Conclusion/** This study is the first to use bromocriptine for PSEN1-AD patients, and it presents both a low- and a high-dose safety verification as well as cognitive, neuropsychiatric and biomarker-based efficacy detections. The trial design includes enrichment of the patient population by iPSC technology. Digital biomarkers will potentially reduce participants' and caregivers' burden in future trials. This is an investigator-initiated clinical trial for the safety and early efficacy evaluation with a small number of participants. Therefore, a large-scale study will be needed in the following phases. **Conflict of Interest:** HB reports funding for this clinical trial from Time Therapeutics, Inc., trial drugs from Towa Pharmaceutical Co., Ltd., during the conduct of the study; personal fees from Sumitomo Dainippon Pharma Co., Ltd., outside the submitted work.

LRP06- IMPACT OF GENDER ON THE WILLINGNESS TO CONSIDER PARTICIPATING IN CLINICAL TRIALS AND UNDERGO A LUMBAR PUNCTURE IN MIDDLE AGED INDIVIDUALS AT RISK OF ALZHEIMER 'S DISEASE.

Lidia Canals-Gispert[1], Alba Cañas-Martínez[1], Gema Huesa[1], Marc Suárez-Calvet[1,2,3], Marta Milà-Alomà[1,2,3], Eider Arenaza-Urquijo[1,2,3], Davide Cirillo[4], Annemarie Schumacher Dimech[4,5], Maria Florencia Iulita[4,6], Julie Martinkova[4,7], Maria Carmela Tartaglia[4], Gonzalo Sánchez-Benavides[1,2,3], Carolina Minguillón[1,2,3], Karine Fauria[1,2,3], Maria Teresa Ferretti[4], Anna Brugulat-Serrat[1,2,3] *(1. Barcelonabeta Brain Research Center - Barcelona (Spain), 2. IMIM (Hospital del Mar Medical Research Institute) - Barcelona (Spain), 3. Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable (CIBERFES) - Madrid (Spain), 4. Women's Brain Project - Guntershausen (Switzerland), 5. Department of Health Sciences and Medicine, University of Lucerne - Lucerne (Swaziland), 6. Sant Pau Memory Unit, Department of Neurology, Hospital de la Santa Creu i Sant Pau, Biomedical Research Institute Sant Pau, Universitat Autònoma de Barcelona - Barcelona (Spain), 7. Cognitive Center, Department Of Neurology, Second Faculty Of Medicine, Charles University, And Motol University Hospital - Prague (Czech Republic))*

Background: There is growing evidence that gender influences the early diagnosis and research participation in preclinical Alzheimer's disease (AD) studies. However, whether gender-related factors affect the willingness to undergo diagnostic procedures in the early stage of the AD continuum has not been fully explored. This study aims to determine the role of gender to consider participating in clinical trials and undergoing specific procedures in the context of AD prevention research studies. Due to preexisting social inequities between males and females, the participants' characteristics that predict their willingness to participate, such as education, marital, education and caregiver status, are expected to differ by gender. **Methods:** The ALFA parent cohort represents a sample of cognitively unimpaired middle-aged participants at higher risk of AD from Spain. 2544 participants from the ALFA parent cohort (age 45-75 years, 1606 [63.1%] females) underwent a structured phone call interview to determine their willingness to undergo clinical trial-related procedures (magnetic resonance imaging [MRI], positron emission tomography [PET], lumbar puncture [LP], and cognitive assessments) and the possibility to participate in AD prevention clinical trials. Gender was collected self-reported. As gender-related factors, years of education, employment (active, temporally inactive, and inactive), marital (single/divorced/widower, married/couple) and caregiver status (yes, no) data were gathered. We performed stepwise logistic regression models to study the interaction between gender and those factors in the willingness to undergo clinical trial-related procedures and participate in clinical trials. **Results:** Women were younger (women M=59.0 (±6.7) vs men M= 59.6 (±6.7), p=0.03) and had lower education (women M=13.2 (±3.5) vs men M=13.8 (±3.4), p<0.01) than men. In addition, there was a higher number of women caregivers (women 15% vs men 8%, p<0.01), women single/divorced/widower (women 24% vs men 14.2%, p<0.01), as well as not gainfully employed (women 22.6% vs men 20.9%, p=0.03). With regard to clinical trial-related procedures, we found a significant gender difference to undergo an LP but not other procedures. Men showed greater willingness (men 87.7% vs women 83.1%, X2 =9.44, p<0.01) to undergo an LP than women. Regarding gender-based factors, women with greater years of education (OR 1.07; 95% CI [1.00-1.15]; p=0.04)

were significantly less willing to undergo an LP. Men also showed a greater willingness to consider the possibility to participate in a clinical trial (95%, X2=9.12; p<0.01). However, caregiver women (OR 2.82; 95% CI [1.13-7.00]; p=0.03) and women married/couple (OR 5.27; 95% CI [1.18-23.61]; p=0.03) showed greater willingness than their men counterparts. **Conclusion:** Our results showed gender differences in the willingness to undergo clinical trial-related procedures and to consider participating in clinical trials in a context of an AD research program. Specifically, men were more willing to undergo an LP and consider being involved in AD-related clinical trials. Moreover, we showed that gender-related factors analyzed could predict this willingness, and these factors differ among women and men. In women, higher levels of education predict less willingness to undergo LP. Regarding the possibility to participate in a clinical trial, caregiver status and having a partner predicted a higher willingness in women but not in men. Understanding gender-related differences may help achieve higher participation in clinical research for men and women. Therefore, our results add evidence to the urgent need to design recruitment strategies accounting for gender-based factors, particularly those related to education, marital status, and caregiving.

LRP07- QYPREDICT®: ADDED VALUE TO PATIENT SELECTION STRATEGIES AND STATISTICAL ANALYSIS IN CLINICAL TRIALS ON ALZHEIMER'S DISEASE.

Jorge Samper-Gonzalez[1], Marwan Sabbagh[2], Philippe Scheltens[3], Elizabeth Gordon[1], Antoine Movschin[1], Nicolas Guizard[1], Clarisse Longo Dos Santos[1], Enrica Cavedo[1], Alireza Atri[4,5], Bruno Dubois[6] *(1. Qynapse - Paris (France), 2. Cleveland Clinic Lou Ruvo Center For Brain Health - Las Vegas, Nv (United States), 3. Amsterdam University Medical Center - Amsterdam (Netherlands), 4. Banner Sun Health Research Institute, Banner Health - Sun City, Az (United States), 5. Brigham and Women's Hospital, Harvard Medical School - Boston, Ma (United States), 6. Institute Of Memory And Alzheimer's Disease (im2a), Centre Of Excellence Of Neurodegenerative Disease (coen), Icm, Cic Neurosciences, Ap-Hp, Department Of Neurology, Hôpital De La Pitié-Salpêtrière, Sorbonne University - Paris (France)*

Background: A substantial proportion of patients enrolled in clinical trials (CT) for Alzheimer's Disease (AD) do not progress clinically over the course of the trial. Insufficient clinical progression can significantly reduce the power to detect positive treatment effects of experimental drugs or interventions. The suboptimal selection of patients, who clinically progress within the duration of CTs, has been a key contributor to the high failure rate of disease-modifying trials for AD (Yiannopoulou KG et al., Biomedicines. 2019). Artificial intelligence approaches, such as those employed in Qypredict®, provide promising tools to improve the success likelihood for selection of leveraged patient populations who would be more likely to clinically progress during the timeframe of AD CTs. **Objectives:** To evaluate, using CT simulations, the benefit of using QyPredict®, a tool comprising multiple feature engineering and machine learning algorithms, to refine patient selection in terms of success probability. To assess, using CT simulations, the influence of the inclusion of a predictive score (such as QyPredict®) into statistical analysis on trial success probability. **Methods:** This study focused on cognitive decline as measured using the CDR-SOB as the outcome of interest. Baseline features of MCI from different domains were retrieved and constructed from the ADNI database to inform the model: demographic data, clinical data (MMSE, ADAS-Cog11, CDR-SOB), imaging data (T1 MRI and derived QyScore® markers from automated structural MRI analysis, amyloid PET), genetic data (APOE4 alleles) and fluid biomarkers (CSF amyloid markers). We used QyPredict® to predict the probability that CDR-SOB score would increase by 1+ points within 12 months. We will refer to this probability as QyPredict® score. Our CT simulation consisted of several steps. Firstly, the ADNI database (n=1987) was filtered according to CT inclusion criteria to obtain a cohort of eligible subjects. The simulated CT inclusion criteria were: age (55 – 85 years old), MMSE (score 24 – 30), CDR (score = 0.5) and positivity of amyloid markers. Next, 1000 subjects were sampled with replacement from this eligible cohort and were randomly split into a treatment (n=500) and a placebo (n=500) arm. Then, the outcome in the treatment arm was artificially modified to account for an expected treatment effect of 25% reduction on CDR-SOB decline over a 12-month period. Finally, a statistical analysis, that used Least Square means difference from linear models that adjusted for covariates, compared placebo versus treatment arms to determine if the trial was a success or a failure. To achieve statistical robustness, the simulations were performed 1000 times (all steps after filtering by inclusion criteria). Success rate was calculated as the ratio of successful simulated trials. To observe the added value of using our prediction model, two approaches were followed. First, QyPredict® score (ranging from 0 to 1) was incorporated in the inclusion criteria. Multiple QyPredict ® probability scores were investigated to ascertain optimal tradeoff between stricter criteria for probable decline (and hence improved detection of a positive treatment effect) and the associated increased screen failures. We investigated selecting patients above different QyPredict ® probability scores until additional improvements of the model performances plateaued. Based on this, only patients with a QyPredict® score demonstrating probability of clinical progression more than 0.1, or > 0.2 or > 0.3 were included as eligible subjects for separate simulations. Second, QyPredict® score was used as an additional covariate in the linear models. **Results:** CT simulations without including QyPredict resulted in a success rate of 52.2% as a baseline performance. After including QyPredict® score as part of the inclusion criteria with thresholds of 0.1, 0.2 and 0.3, the trial success rates increased to 56%, 81% and 90.4%, respectively. To achieve these increased success rates the number of subjects needed to be screened to reach enrollment of 1000 subjects subsequently increases by +4.6%, +25.3% and +51.5%, respectively. Although initial screening numbers increased, it provides a performance increase of 3.8%, 28.8% and 38.2%, respectively (p<0.001) for detecting a positive treatment effect, when compared to baseline, without QyPredict® score. Adding QyPredict® score only as a covariate in the statistical analysis provided a success rate of 59.9%, representing an increase of 7.7% (p<0.001) with respect to baseline with no additional screening cost. **Conclusion:** The use of QyPredict® score as part of the inclusion criteria in this CT simulation significantly improved the probability of trial success, while increasing screening failure rates due to excluding those who would be less likely to clinically progress. These results support the promising potential of the combined use of QyPredict® to improve design and power of AD clinical trials, and the likelihood of detecting positive treatment effects and achieving trial success.

LRP08- A FULLY VIRTUAL TRIAL DESIGN IN TIMES OF COVID-19: EARLY LESSONS LEARNED FROM THE REACTION STUDY IN AGE-RELATED COGNITIVE DECLINE. Christian Camargo[1], Katalina Mcinerney[1], Danielle Counotte[2], Tatjana Rundek[1] *(1. University Of Miami Miller School Of Medicine - Miami (United States), 2. Danone Nutricia Research - Utrecht (Netherlands))*

Background: Alzheimer's Disease (AD) is the most common cause of dementia, and the risk of developing AD increases with age. Age-related cognitive decline (ARCD) refers to the cognitive changes that can occur in individuals as a consequence of aging. Research suggests that the underlying mechanism behind ARCD is a loss of synaptic plasticity and altered dendritic spine morphology. Similarly, the cognitive changes in AD are also thought to arise from impaired synaptic plasticity and dendritic spine loss. Therefore, increasing synaptic plasticity and rescuing dendritic spine density may be a viable strategy for slowing ARCD, and preventing or treating AD-related cognitive changes. Souvenaid contains a specific combination of precursors and cofactors for phospholipid biosynthesis, and has shown beneficial effects on memory, cognition, and brain atrophy in prodromal AD [1]. In addition, the data from this previous study suggest a stronger effect would be expected in participants at earlier stages of prodromal AD. **Objectives:** Given Souvenaid has not yet been tested in individuals with ARCD, the REACTION (Reducing the Effects of Aging on Cognition with Therapeutic Intervention of an Oral multi-Nutrient combination) pilot study was developed. While finalizing the study design, the COVID19 pandemic hit, which quickly prompted the study to become fully virtual with screening and outcome visits to take place via telemedicine. **Methods:** REACTION is a 6-month single-center randomized, double-blind placebo-controlled pilot clinical trial. The study design specifically factors in local COVID-19 restrictions. We plan to recruit 60 participants aged 55-89 with age-related cognitive decline, who will be screened and randomized to the oral multi-nutrient combination (Souvenaid) or placebo on a 1:1 basis. The main outcome of this trial is feasibility (recruitment rate and time, adherence rate and retention rate). Other outcomes include memory (e.g. Ray Verbal Learning Task), cognition (e.g. Oral Trail Making Test), and quality of life (e.g. Amsterdam IADL Questionnaire) outcome measures. **Results:** In the first three months of recruitment, we have contacted 50 individuals who expressed interest in study participation. As of September 17, 2021, we have enrolled 13 participants. An additional 4 participants, expected to enroll, are awaiting a 24-30 day wash-out period given prior supplement use. There have been 2 withdrawals from the study due to desire to return to supplement use, and 5 individuals who initially expressed interest did not enroll due to unwillingness to discontinue current supplement use. **Conclusions:** With the rapidly growing prevalence of ARCD and limited pharmacological curative treatment options currently available, nutritional interventions may potentially play an important role to prevent or delay the onset of ARCD. Recruitment of healthy, aging individuals for this pilot trial remains underway. The COVID19-induced necessity to switch to a fully virtual platform has enabled the participation of individuals who were otherwise hesitant about participating in in-person clinical research studies. Early observations suggest prior supplement use and supplement preference in a subset of individuals of this "worried-well" aging adult population may affect the final decision to participate **References:** 1. Soininen et al 2021 https://doi.org/10.1002/alz.12172

LRP09- AN ASSESSMENT OF THE STATISTICAL RELIABILITY OF DATA-DRIVEN DECOMPOSITION FOR THE USE OF MULTI-MODAL ANALYSES. Kristen Knight[1,2], Nicole Lazar[3], Liang Liu[4] *(1. UCSF Department of Radiology and Biomedical Imaging - San Francisco, CA (United States), 2. VA Advanced Imaging Research Center, San Francisco Veteran's Administration Medical Center - San Francisco, Ca (United States), 3. PennState Department of Statistics - University Park, PA (United States), 4. UGA Department of Statistics - Athens, GA (United States))*

Background: Advanced knowledge on the pathogenesis of dementia has led to large-scale data collection efforts, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI). Research supports the underlying complex biological process of AD involving changes across a combination of biomarkers that are often present prior to severe cognitive decline. The complex pathology of AD, newly available large data sources, and advances in computation have spurred the use of data-driven techniques that permit a joint analysis of multiple sources of data. However, when straying from parametric assumptions, the derivations of the novel learning algorithms produce stochastic estimates. This study examines the statistical reliability of results derived from data-driven decomposition techniques and seeks to formulate hypothesis-driven disease group comparisons from the fused features. **Methods:** Structural and functional neuroimaging data are paired with single nucleotide polymorphisms (SNP) from 135 patients who are either cognitively normal (CN) or have received a mild cognitive impaired (MCI) or Alzheimer's disease (AD) diagnosis. Decomposition methods of joint and parallel independent component analysis (ICA) are applied individually on FDG-PET, structural MRI (sMRI), and SNP data, then for the possible pairwise and three-way combinations of the data. Four optimization techniques that permit data-driven learning are used under the two decomposition structures. Data are bootstrapped with randomized initial values of the algorithms 30 times and ICA is run on each 50 times. In order to assess statistical reliability, the results of the ICA runs are grouped using agglomerative clustering, and the centroids are extracted as the final ICA loading vectors. The cluster compactness index (I_c) per component are derived as a measure of cluster tightness and separability. On a scale of (0,1), indices closer to 1 indicate higher statistical reliability of the estimates. Spatial maps of the fused data features are observed and compared among the clinical diagnosis groups. **Results:** Single modalities overall showed a lower cluster compactness than two-way and three-way decomposition models, with the SNP data showing low statistical reliability ranging between (0.35, 0.46). Improvement was observed for two-way analyses involving SNP information with FDG-PET and sMRI modalities, ranges of (0.89, 0.97) and (0.91, 0.99), respectively. The highest amount of statistical reliability was achieved for three-way decomposition, (0.94, 0.99). Spatial maps were identified using the IC centroids and highlighted regions of the brain known to succumb to brain atrophy in the later disease stages, especially in the medial temporal lobe. T-tests were run on components from the respective modality combinations to determine whether there was a significant difference in the findings for CN vs MCI, MCI vs AD, and CN vs AD for all possible data combinations. The most significant findings were observed in comparisons of MCI vs AD statuses for all three modalities (p-val=0.0002), compared to SNP for CN vs MCI (p-val=0.0720), and FDG-PET (p-val=0.0159) and sMRI (p-val=0.0633) findings for CN vs AD. **Conclusions:** Combining FDG-PET with sMRI and

SNP data achieved higher statistical reliability and more easily identified significant differences of the MCI vs AD disease statuses using data driven methods then single or pair-wise data fusions. Data-driven techniques showed improvement upon group comparisons made among disease statuses by considering the inter- and intra-relationships of the modalities. These findings showcase the ability of decomposition methods to permit hypothesis-driven, disease-specific questions when multiple modalities are used.

CLINICAL TRIALS: RESULTS

P41- SINGLE AND MULTIPLE ASCENDING DOSE STUDIES IN HEALTHY VOLUNTEERS TO ASSESS THE SAFETY AND PK OF LY3372689, AN INHIBITOR OF THE O-GLCNACASE (OGA) ENZYME. Paul Goldsmith, Stephen Lowe, Krista Phipps, Kevin Donnelly, Kevin Biglan, Michele Mancini, Hugh Nuthall, Dustin J. Mergott, William Kielbasa *(Eli Lilly And Company, Lilly Corporate Center - Indianapolis (United States))*

Background: LY3372689, a centrally penetrant OGA enzyme inhibitor, is being developed as a potential treatment for tauopathies, including Alzheimer's disease. OGA inhibition is proposed to delay the progression of tau-related diseases by slowing the accumulation of hyper-phosphorylated, insoluble tau filaments. **Objective:** To report the safety and pharmacokinetics (PK) of LY3372689 after single and multiple oral doses in healthy volunteers (HV). **Methods:** The single ascending dose (SAD) and multiple ascending dose (MAD) studies were single center, subject- and investigator-blind, placebo-controlled and randomized. In the SAD study [NCT03819270], 6 LY3372689 dose levels from 0.15 mg up to 16 mg and placebo were evaluated. In the MAD study [NCT04106206], LY3372689 (1, 3 and 7 mg) or placebo was given once daily (QD) for 14 days; non-Japanese and Japanese HV were enrolled in the MAD study. Safety was assessed by adverse events (AE), safety laboratories, electrocardiograms, vital signs, physical examinations, and neurological examinations. Plasma pharmacokinetics (PK) was assessed up to 48 hours and 24 hours post-dose in the SAD and MAD studies, respectively. **Results:** In the SAD, 23 HV (15 males, 8 females; 22 – 63 years) participated, of which 18 HV completed. In the MAD, 40 HV (5 males, 35 females; 29 – 65 years) participated in the study, of which 39 HV completed. LY3372689 was generally well tolerated up to the highest dose in each study, and no deaths or other serious AE were reported. In the SAD, 40 treatment-emergent AE (TEAE) were reported, which were mostly mild in severity. The most common TEAE were headache, nausea, pain in extremity, pain of skin, vessel puncture site pain, and limb discomfort. There were no subject withdrawals from the study due to AEs, and a maximum tolerated dose was not achieved. In the MAD, 42 TEAE were reported, all of which were mild in severity. The most reported TEAE were headache, abdominal pain, diarrhea, back pain, nausea, constipation, dizziness, medical device site irritation, and feeling cold. One participant discontinued due to an AE of mild influenza, which was judged unrelated to LY3372689. In the SAD and MAD studies, there were no clinically significant changes in safety laboratories, including markers of inflammation, muscle injury, hormones and hepatoxicity. Furthermore, there were no clinically significant changes in ECGs, including QTc and PR prolongation, vital signs and neurological examinations. The safety profile in the MAD was similar in Japanese and non-Japanese HV. Following single and multiple doses, the tmax and t1/2 were approximately 1 hour and 6 hours, respectively. LY3372689 exposure based on AUC and Cmax increased in a generally dose-proportional manner in the SAD and MAD studies. At the highest dose of 7 mg QD in the MAD, the ratio of LY3372689 AUC on day 14 to day 1 was approximately 1.1 indicating exposure accumulation was minimal after repeated LY3372689 administration. At 3 mg QD, food intake had a minimal effect on AUC, decreased Cmax by 43% and increased tmax by 5 hours, compared to a fasted state. Renal clearance was not a major contributor of LY3372689 elimination after single or multiple dosing of LY3372689. The PK parameters in Japanese and non-Japanese HV in the MAD study were similar. **Conclusions:** LY3372689 demonstrated an acceptable safety and PK profile following single and multiple doses of LY3372689 in HV. These results support investigation of LY3372689 in efficacy trials for tauopathies and help support dose selection for those trials.

P42- CPAD: ACCELERATING ALZHEIMER'S DISEASE DRUG DEVELOPMENT THROUGH PRE-COMPETITIVE DATA SHARING AND GENERATION OF DATA-DRIVEN QUANTITATIVE DRUG DEVELOPMENT TOOLS. Sudhir Sivakumaran[1], Jackson Burton[1], Yashmin Karten[1], Zihan Cui[1], Bob Stafford[1], Corissa Lau[1], Eileen Priest[1], Hazel White[1], Michael Irizarry[2], Klaus Romero[1] *(1. Critical Path Institute - Tucson (United States), 2. Eisai Inc. - Woodcliff Lake (United States))*

Background: The Critical Path for Alzheimer's Disease (CPAD) consortium aims to create new tools and methods that can be applied to increase the efficiency of the medical product development process, leading to treatments for neurodegenerative diseases that progress to dementia with shared characteristics of Alzheimer's disease (AD), the most common and devastating form of dementia globally. CPAD has acquired contemporary high-quality AD clinical trial datasets focused on early stages of the disease, as part of the Industry Data Sharing Initiative, and the aggregated patient-level data are utilized to address unmet needs in AD drug development through novel regulatory-grade modeling and simulation tools built from these datasets. **Methods:** Through formal data contribution agreements, contemporary Phase2/Phase3 AD clinical trials and observational studies are acquired; which are then curated, mapped to the Clinical Data Interchange Standards Consortium (CDISC) AD therapeutic area data standard, and integrated for analysis. From the integrated data, analysis ready subsets are created for development of a comprehensive set of disease progression models across the continuum of the disease. Models characterize the time course of clinically relevant measures (ADAS-Cog, CDR-SB, other clinical assessment scales and biomarkers). Models include demographics, time from and to diagnosis, genetic status (APOE4), and are assessed using non-linear mixed effects methods. Monte Carlo simulations are performed to compare the statistical power by sample size in trials with and without enrichment using relevant covariates. **Results:** As of May 2021, CPAD's clinical trial repository contains 42 studies with 21,078 individual anonymized patient records. CPAD has acquired contemporary AD clinical trial datasets focused on early stages of the disease, providing a rich source of key amyloid, tau, and neurodegeneration biomarkers, assessed through magnetic resonance and positron emission tomography neuroimaging and through analysis of biofluids (plasma and cerebrospinal fluid). Analysis subsets generated from 4 key datasets rich in fluid and imaging biomarkers were used to inform statistical

analysis plans for disease progression models incorporating amyloid-β and tau (biofluid and neuroimaging) as key covariates, linked to predicting timing of clinically relevant progression and disease states, mild cognitive impairment and/or AD diagnosis. Base models were developed using parametric mixed-effects approaches with selection based on goodness-of-fit plots. Covariate analyses are being performed to identify variables that constitute relevant predictors of baseline severity and disease progression rates. The models will serve as the basis for clinical trial simulation tools to facilitate informed decision making in the drug development process and optimize patient selection, endpoints and design of efficacy studies. **Conclusions:** The precompetitive and neutral forum provided by CPAD enables acquisition and analysis of high-quality datasets from relevant AD clinical trials and provides sponsors with regulatory grade tools to optimize AD trial design. Such tools are intended to provide confidence for the industry drug development teams in advancing their respective research and drug development efforts.

P43- INTERIM RESULTS OF AN OPEN-LABEL STUDY OF SIMUFILAM IN MILD-TO-MODERATE ALZHEIMER'S DISEASE. Lindsay Burns[1], Tamara Doehner[2], John Puente[2], Brian Beck[3], Yaneicy Gonzalez Rojas[4], Evelyn Lopez-Brignoni[5], Boris Nikolov[5], Ben Murray[1], Antonio Hernandez[1], Carrie Crowley[1], Nadav Friedmann[1] *(1. Cassava Sciences - Austin (United States), 2. Cognitive Clinical Trials - Omaha (United States), 3. Cognitive Clinical Trials - Phoenix (United States), 4. Optimus U - Miami (United States), 5Imic Research - Palmetto Bay (United States))*

Background: Simufilam is a small molecule drug candidate for Alzheimer's disease (AD). Simufilam reverses an altered conformation of filamin A in the AD brain, reducing tau hyperphosphorylation and neuroinflammation initiated by Aβ42. In a prior randomized, placebo-controlled trial in 64 patients with mild-to-moderate AD, oral simufilam significantly improved eleven CSF biomarkers of AD pathology, neurodegeneration, neuroinflammation and blood-brain barrier integrity over 28 days, with no safety issues. In this open-label study, CSF biomarkers showed profound improvements from baseline in 25 study subjects after 6 months of treatment. **Objectives:** To assess long-term safety and changes in cognition and neuropsychiatric symptoms in a 12-month, open-label clinical trial of sumifilam in mild-to-moderate AD. **Methods:** This open-label study is enrolling up to 200 patients with mild-to-moderate AD, MMSE 16 to 26, across 16 sites in the US and Canada. Study participants receive 100 mg twice-daily oral simufilam for one year. In addition to safety, patients are assessed on the 11-item Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog11) and the Neuropsychiatric Inventory (NPI). **Interim Results:** Interim results summarize data from the first 50 patients to complete 12 months of open-label treatment. Simufilam was safe and well-tolerated, consistent with prior clinical studies of simufilam. Adverse events were mild and transient, with no drug-related serious adverse events. Subjects were 69.6 ± 6.4 years of age with mean baseline MMSE 22.7 ± 2.8. For the first 50 subjects to complete 12 months of open-label treatment with simufilam, the mean change from baseline to Month 12 in ADAS-Cog11 scores was -3.23 ± 6.25 points (negative change indicates improvement). The median change was -4.0 points. ADAS-Cog11 scores improved from baseline to Month 12 in 68% of these 50 subjects. ADAS-Cog11 scores on Day 1 (mean 16.73 ± 7.86) were significantly different ($p<0.001$ by paired t test) from ADAS-Cog11 scores on Month 12 (mean 13.51 ± 9.20). This interim analysis also assessed behavior and neuropsychiatric symptoms of dementia by the Neuropsychiatric Inventory (NPI). At baseline, 34% of the 50 subjects had no neuropsychiatric symptoms. At 12 months, over 50% of subjects had no neuropsychiatric symptoms. **Conclusions:** Simufilam 100 mg twice-daily continues to be safe and well-tolerated. In a patient population that is expected to decline over 12 months, ADAS-Cog11 scores improved -3.23 points from baseline to Month 12 in the first 50 subjects to complete 12 months of open-label treatment, with 68% of subjects showing an improved ADAS-Cog11 scores. This work was supported by NIA grant AG065152.

P43BIS- BRAIN TARGET OCCUPANCY OF LY3372689, AN INHIBITOR OF THE O-GLCNACASE (OGA) ENZYME, FOLLOWING ADMINISTRATION OF SINGLE AND MULTIPLE DOSES TO HEALTHY VOLUNTEERS. William Kielbasa[1], Sergey Shcherbinin[1], Paul Goldsmith[1], Krista M. Phipps[1], Kevin Biglan[1], Michele Mancini[1], David Russell[2], Cristian Constantinescu[2], Roger N. Gunn[3], Hugh N. Nuthall[1], Dustin J. Mergott[1], Stephen Lowe[1], Emily C. Collins[1] *(1. Eli Lilly And Company, Lilly Corporate Center - Indianapolis (United States), 2. Invicro, A Konica Minolta Company New Haven - Connecticut (United States), 3. Invicro, A Konica Minolta Company, Burlington Danes Building, Imperial College London, Hammersmith Hospital, Du Cane Road - London (United Kingdom))*

Background: LY3372689, a centrally penetrant O-GlcNAcase (OGA) enzyme inhibitor, is being developed as a potential treatment of tauopathies, including Alzheimer's disease. OGA inhibition is proposed to delay the progression of tau-related diseases by slowing the accumulation of hyper-phosphorylated, insoluble tau filaments. Understanding the relationship between LY3372689 dose/exposure and brain target engagement, measured by OGA enzyme occupancy (EO), is critical for optimizing dose selection in efficacy trials. **Objective:** To evaluate the effect of single and multiple doses of LY3372689 on brain OGA EO as measured by PET imaging. Based on the potential for enzyme up-regulation, maintenance of brain OGA EO after multiple dosing of LY3372689 was assessed to provide additional evidence for target engagement in longer term efficacy trials. **Methods:** A positron emission tomography (PET) radioligand, 18F-LY3316612, was used to assess brain OGA EO in healthy volunteers (HV). In the single dose study [NCT03944031], 0.25, 1 and 5 mg LY3372689 were evaluated across 4 cohorts (N = 4 HV per cohort). Each HV had brain PET scans at baseline and two post-dose intervals. Post-dose scans occurred at 2 and 24 hours at 0.25, 1, and 5 mg, with additional PET scans for 1 mg at 30 hours and 54 hours. The multiple dose study [NCT04392271] consisted of 1 cohort (N = 4 HV) given 1 mg LY3372689 once daily for 14 days. Each HV had brain PET scans at baseline, and at 24 hours post-dose after the 1st and 14th administration of LY3372689. Plasma concentrations of LY3372689 were assessed up to 54 hours post-dose in the single dose study, and up to 24 hours post-dose in the multiple dose study. The pharmacodynamic relationship between plasma LY3372689 concentrations and brain EO was evaluated using nonlinear regression. **Results:** In the single dose study, the mean [standard deviation] for brain OGA EO at 5 mg was 98% [2] at 2 hours and 93% [3] at 24 hours. At 1 mg, the EO was 97% [3] at 2 hours, 81% [6] at 24 hours, 68% [12] at 30 hours, and 30% [19] at 54 hours. The EO at 0.25 mg was 26% [13] at 2 hours and 46% [16] at 24 hours. The plasma LY3372689 concentrations and

brain OGA EO data were characterized by a sigmoidal Emax model. Model parameters Emax, EC50, and Hill slope were estimated to be 97%, 0.1 ng/mL, and 1.1, respectively. In the multiple dose study at 1 mg LY3372689, the brain OGA EO at 24 hours after the 1st administration and 14th administration was 84.1% [1] and 83.7% [5], respectively. **Conclusions:** PET studies using the radioligand 18F-LY3316612 demonstrated that LY3372689 can achieve high brain OGA EO in HV. LY3372689 target engagement as measured by OGA EO was maintained following repeated dosing, thus supporting its use in longer duration clinical trials. The pharmacodynamic data from the PET studies will support LY3372869 dose selection for efficacy trials in tauopathies.

P44- ACI-24, AN ANTI-BETA AMYLOID VACCINE, IN PATIENTS WITH MILD ALZHEIMER'S DISEASE: RESULTS OF A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY. Olivier Sol[1], Saskia Delpretti[1], Marija Vukicevic[1], Merja Hallikainen[2], Roy Jones[3], Anne Börjesson-Hanson[4], Aliya Asher[5], Alex Thompson[6], Christopher Kipps[7], Emer Mcsweeney[8], Tanja Touilloux[1], Julian Gray[1], Nicolas Fournier[1], Valérie Hliva[1], Antonio Melo Dos Santos[1], Mika Scheinin[9,10], Marie Kosco-Vilbois[1], Johannes Streffer[1,11], Andrea Pfeifer[1], Juha Rinne[9,10] *(1. Ac Immune Sa - Lausanne (Switzerland), 2. University Of Eastern Finland - Kuopio (Finland), 3. University Of Bath - Bath (United Kingdom), 4. Karolinska University Hospital - Stockholm (Sweden), 5. Mac Clinical Research - Manchester (United Kingdom), 6. Mac Clinical Research - Cannock (United Kingdom), 7. Southampton General Hospital - Southampton (United Kingdom), 8. Cognition Health Ltd. - Guildford (United Kingdom), 9. University Of Turku - Turku (Finland), 10. CRST Oy - Turku (Finland), 11. Department of Biomedical Sciences, University of Antwerp - Antwerp (Belgium))*

Background: Alzheimer's Disease (AD) is a progressive degenerative disorder of insidious onset characterized by loss of memory and other cognitive function, loss of ability to perform daily living activities and behavioral disturbances. One of the key pathological hallmarks of AD is the progressive accumulation of beta-amyloid (Aβ) plaques in the brain. ACI-24 is a liposomal, T-cell independent, anti-Aβ vaccine comprising the human sequence 1-15 of Aβ as the antigen. The Aβ1-15 sequence contains the B-cell epitopes but not the T-cell reactive sites of full-length Aβ1-42, thus avoiding potential unwanted T-cell related inflammatory reactions. ACI-24 was tested in a phase 2, randomized, double-blinded, placebo-controlled study in mild AD patients. **Objectives:** The primary objectives of the study were to assess the effect of ACI-24 on safety, tolerability, induction of anti-Aβ antibody response, and brain amyloid load. The secondary objectives were to explore several parameters including AD-related fluid biomarkers, cognition (COWAT, TMT parts A and B, Category Fluency Test, ADAS-cog 13 and MMSE), global function (CDR-SB), daily living activities (ADCS-ADL-MCI), and behavior (NPI) tests. **Methods:** This phase 2, double-blind, randomized, placebo-controlled study was performed in patients with mild AD. The study was conducted in several European countries. Study participants were randomly allocated to receive either ACI-24 at the dose of 1,000μg given by intramuscular injection or placebo at 8 occasions (active:placebo ratio = 2:1) during the 18-month treatment period, which was followed by a 6-month safety follow-up period. Main study population criteria were male or female subjects with probable AD dementia according to NIA-AA core clinical criteria, Florbetaben-PET scan at screening consistent with the presence of amyloid pathology, MMSE total score 20-28 and age-range 50-85 years old. **Results:** Twenty-one subjects were randomized in the study. Baseline demographics were as follows: mean age 71.2 (min-max: 58-85), sex-ratio: 11F/10M, race: White 95%, Asian 5%, mean MMSE score 24.2 (min-max: 20-28). Overall, the safety and tolerability were good. No episodes of ARIA-E/H or CNS inflammation were reported by MRI. Local tolerability was good, mild injection site pain was reported on two occasions in one subject. Additionally, results on immunogenicity and pharmacodynamic effects of target engagement will be presented. **Conclusions:** Treatment with the anti-Aβ vaccine ACI-24 was safe and well tolerated in mild AD patients in the phase 2 study. Initial evidence of a pharmacodynamic effect of ACI-24 suggesting target engagement was observed. Overall, these results support the ongoing development of optimized vaccine formulation of ACI-24 in patients with AD.

P45- A PHASE 1 STUDY OF AL003 IN HEALTHY VOLUNTEERS AND PARTICIPANTS WITH ALZHEIMER'S DISEASE. Mike Ward, Felix Yeh, Hua Long, Tina Schwabe, Herve Rhinn, Ilaria Tassi, Daniel Maslyar, Madeline Spencer, Candace Hagey, Glenn Morrison, Robert Paul *(Alector, Inc. - South San Francisco (United States))*

Background: AL003 is a human anti-CD33 monoclonal antibody in development for the treatment of Alzheimer's Disease (AD). Evidence indicates that CD33 regulates uptake of the amyloid β1-42 (Aβ42) peptide by myeloid cells, and that effective phagocytosis of Aβ42 in the brain correlates with low functional expression of CD33. AL003 specifically binds to CD33 leading to down-regulation observed in preclinical models and provides an immunologically mediated mechanism to treat AD. **Objectives:** This is a Phase 1 study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of AL003 in healthy volunteers (HV) and patients with mild to moderate AD. **Methods:** The single ascending dose (SAD) part of this study is a blinded, randomized, placebo-controlled, study of single dose intravenous (IV) AL003 in HV in doses ranging from 0.05 mg/kg up to 60 mg/kg. The second part of the study assesses a fixed dose of AL003 administered every two weeks for three doses in a blinded, randomized, placebo-controlled manner in patients with a diagnosis of probable AD, aged 50-85 years, with a MMSE score of 16-28, a CDR global score of 0.5, 1, or 2, and a positive amyloid-PET scan based on visual read. In both parts of the study, assessments included standard clinical safety measures as well as pharmacokinetic (PK) and pharmacodynamic (PD) markers in plasma as well as CSF. **Results:** The SAD part of the study completed assessment of all dose levels in the healthy volunteers. Across all dose levels, the most frequently reported adverse events reported in the subjects receiving AL003 were headache (20.7%), post-lumbar puncture syndrome (i.e., headache after lumbar puncture; 17.2%), nausea (13.8%), upper respiratory tract infection (13.8%), and puncture site pain (10.3%). Dose levels up to 15 mg/kg were well tolerated in healthy volunteers with immune-related adverse events seen at higher dose levels. Peripheral PK and PD data in HV appears dose-dependent and CSF PD data established evidence of target engagement. **Conclusions:** To date AL003 has been seen to be generally safe and well tolerated and the Phase 1 HV data demonstrated target engagement in both peripheral and central nervous system compartments up to 60 mg/kg. AL003 is being considered for investigation in a proof-of-concept Phase 2 study.

P46- A FIRST-IN-HUMAN STUDY OF THE ANTI-SORTILIN ANTIBODY AL101. Mike Ward, Daniel Maslyar, Felix Yeh, Hua Long, Michael Kurnellas, Emmanuel Ang, Amber Silva, Robert Paul *(Alector Inc. - South San Francisco (United States))*

Background: Mutations in GRN, the coding gene for Progranulin (PGRN), have been implicated in a number of neurodegenerative disorders, including Frontotemporal dementia (FTD), Alzheimer's Disease (AD) and Parkinson's Disease (PD). The Sortilin receptor, expressed on neurons and microglia, is a key regulator of PGRN levels through Sortilin-mediated degradation. AL101 is a human monoclonal IgG1 antibody that downregulates Sortilin and increases PGRN in pre-clinical models and is being developed by Alector for the treatment of neurodegenerative disorders. Restoring PGRN levels may be an effective therapeutic approach, potentially reducing the rate of neuron loss and clinical decline in individuals with neurodegenerative disease. **Objectives:** This first-in-human Phase 1 study is designed to investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of AL101, administered intravenously (IV) and subcutaneously (SC). **Methods:** Healthy volunteers received a single dose of AL101 in ascending IV dose cohorts of 6, 15, 30 and 60 mg/kg (randomized 8:3 AL101:placebo) and a single 600 mg SC dose of AL101 in an open-label cohort (n=9) to assess bioavailability. Assessments included standard clinical safety measures as well as pharmacokinetic (PK) and pharmacodynamic (PD) markers in plasma as well as CSF. Depending on dose cohort, CSF profiles of AL101 and PGRN were measured up through 85 days after AL101 administration. Safety follow-up was conducted for up to 16 weeks in the 60 mg/kg IV cohort or 12 weeks for all other cohorts. **Results:** AEs were generally mild to moderate and self-limiting, with the most frequent treatment emergent AEs being headache (19%), anemia (9%), and procedural pain (9%). One subject experienced a moderate infusion reaction at the 60 mg/kg dose level requiring discontinuation of study treatment. AL101 exhibited dose-proportional serum PK, with some increase in clearance seen at the lowest doses. AL101 increased the levels of PGRN in the CNS of healthy volunteers to approximately twice baseline levels, with prolonged durations of CSF PGRN elevations with increasing dose. **Conclusion:** AL101 has been generally safe and well tolerated with single-dose IV or SC administration in healthy volunteers. AL101 is a potent modulator of PGRN levels in the CSF, with a PK/PD profile that supports development of SC AL101 in chronic conditions.

LP13- POSITIVE CLINICAL OUTCOMES OF POSIPHEN IN TWO PHASE2A STUDIES-- ALZHEIMER' DISEASE AND PARKINSON'S DISEASE. Maria Maccecchini[1], Cheng Fang[1], Henrik Zetterberg[2], Michael Chen[3] *(1. Annovis Bio - Berwyn (United States), 2. University Of Gothenburg - göteborg (Sweden), 3. Tcm - New Jersey (United States))*

Overexpression of neurotoxic proteins drives downstream events that dysregulate axonal transport, lead to inflammation, nerve cell death, and loss of function. By inhibiting the translation of amyloid precursor protein, tau and alpha-synuclein, our drug Posiphen has been shown in animal models to restore axonal transport, lower inflammation and protect nerve cells from dying; it reversed the toxic cascade leading to nerve cell death. By reversing the toxic cascade, Posiphen preserved and restored full function in 7 animal models including Alzheimer's disease (AD) [Teich et al 2018], Parkinson's disease (PD) [Kuo et al 2019], Down Syndrome [Chen et al 2020], stroke [Turcato et al 2018], traumatic brain injury [Chesselet M-F Lab], frontotemporal dementia [Davies P lab], and blindness in acute glaucoma [Sundstrom J lab]. Posiphen showed safety in over 130 healthy and sick people [Maccecchini et al 2012].vTo show that Posiphen reverses the toxic cascade and potentially shows efficacy in humans, we started two double-blind, placebo- controlled clinical phase 2a studies in AD and PD patients.vIn the first part of the study, we enrolled 14 AD and 14 PD patients (4 placebo and 10 treated with 80 mg posiphen QD for 25 +/- 2 days. Before and after we took blood, CSF, conducted safety evaluation and psychometric tests and in plasma and CSF we measured markers of the toxic cascade leading to nerve cell death: AD and PD specific biomarkers, markers of axonal transport, inflammation, neurodegeneration and synapse health. The second part of the study enrolled an additional 40 PD patients with the same study design to test the result on markers as well as on efficacy at different concentrations of posiphen. From the first part of the study, we are reporting statistically significant improvements in ADAS-Cog 11 and WAIS coding in treated AD patients comparing to baseline. Posiphen reduced sAPPα, sAPPβ, Tau, p-Tau and improved the Aβ42/40 ratio. Posiphen also improved axonal health as measured by NfL. In PD patients, we also see statistically significant improvements in the WAIS coding test and strong trends in all 4 UPDRS parts. Inflammation in treated patients is statistically significantly lowered whether to baseline or to placebo. Before the end of September, we are expecting to finish analyzing all the remaining biomarkers and show reversal of the toxic cascade leading to nerve cell death of part 1 for AD and PD patients. We also expect to show safety and efficacy of part 2 in the additional 40 PD patients. We will be able to report on Posiphen's safety, efficacy and dosage curve. In conclusion, our data from the first 28 patients shows that Posiphen improves cognition in AD and motor function in PD as well as reverses of the toxic cascade leading to nerve cell death. The expected additional markers of the toxic cascade and the new part 2 data will solidify and confirm that Posiphen works in AD and PD patients.

LP14- IMPACT OF ALZHEIMER'S DISEASE (AD) RELATED CO-PATHOLOGY ON TREATMENT EFFECTS OF THE ORAL P38A KINASE INHIBITOR NEFLAMAPIMOD IN MILD-TO-MODERATE DEMENTIA WITH LEWY BODIES (DLB). John Alam[1], Stephen Gomperts[2,3], Afina Lemstra[4,5], Inge Verberk[4], Sherif Bayoumi[4], Hui-May Chu[6], Amanda Gardner[1], Kelly Blackburn[1], Niels Prins[4,5], Charlotte Teunissen[4] *(1. Eip Pharma - Boston (United States), 2. Massachusetts Alzheimer's Disease Research Center - Boston (United States) - Boston (United States), 3. Massachusetts General Hospital - Boston (United States), 4. Amsterdam Umc - Amsterdam (Netherlands), 5. Brain Research Center - Amsterdam (Netherlands), 6. Anoixis Corporation - Natick (United States))*

Background: Neflamapimod (NFMD) targets pathogenic mechanisms underlying basal forebrain cholinergic (BFC) neurodegeneration (Pensalfini et al, 2020), considered to be a major driver of dementia in DLB. In preclinical studies NFMD rescues cholinergic neurodegeneration in the basal forebrain in Ts2 transgenic mice (Jiang et al, 2019). At last year's CTAD, positive clinical results from a 91-patient, 16-week placebo-controlled phase 2 study ("AscenD-LB Study") in mild-to-moderate DLB were reported. In that study, 40mg three-times-daily (TID) NFMD demonstrated significant improvement, relative to placebo, in cognition [assessed by

DLB-specific Neuropsychological Test Battery (NTB], motor function [assessed by the Timed-Up-and-Go (TUG) Test], and cognition and function [assessed by Clinical Dementia Rating Scale (CDR-SB)]. Because up to half of patients with DLB have "AD co-pathology" (amyloid and/or medial temporal lobe tau pathology; van der Lee et al, 2021) and literature evidence indicates that such co-pathology may impact response to cholinesterase inhibitors (Graff-Radford et al, 2012), we had obtained plasma samples during the screening phase of AscenD-LB to analyze when a test that predicted AD co-pathology became available. With a recent report that in patients with DLB plasma phospho-tau (either ptau217 or ptau181) correlated with tau-PET signal in the temporal cortex and predicted abnormal tau-PET status and CSF β-amyloid status (Hall et al, 2021), plasma ptau181 levels were assessed in those stored plasma samples and we herein report on the association of AD co-pathology to treatment outcome in AscenD-LB. **Objectives:** To evaluate the impact of AD co-pathology on the treatment effects of neflamapimod in mild-to-moderate DLB patients receiving cholinesterase inhibitor therapy. **Methods & Patients:** Mild-to-moderate (MMSE 15-28) probable DLB by consensus criteria (McKeith et al, 2017), including a positive DaTscan™, and currently receiving cholinesterase inhibitor therapy; randomized to 40 mg NFMD capsules or matching placebo capsules for 16 weeks, with the dosing regimen being based on weight: subjects weighing <80 kg received capsules twice-daily (BID) and those weighing ≥80 kg received capsules TID. To evaluate treatment effects, linear mixed effects model for repeated measures (LMMRM) was utilized to compare outcomes in NFMD40mg TID, the dose group that achieved therapeutic plasma drug levels and demonstrated efficacy in the main analyses reported previously, to (1) all placebo recipients, and (2) the matched higher weight placebo-recipients (placebo TID). Plasma ptau181 levels were determined by Simoa® pTau181 Assay (Quanterix) at the VU Medical Center, where the in-house defined cut-off for AD pathology had been set at 2.2 pg/mL. **Results:** At baseline, 22 of 41 (53%) of placebo and 22 of 42 (54%) of neflamapimod participants in the efficacy analysis population (baseline and on-treatment data on at least one efficacy endpoint) had plasma ptau181 < 2.2 pg/mL (i.e., those predicted to not have AD co-pathology). For all four endpoints that had shown significant treatment effects in the main analysis (NTB z-sore, attention z-score, TUG, CDR-SB), descriptive evaluation of the results by baseline ptau181 status revealed that positive treatment effects were primarily seen in the patients who were below the threshold (2.2 pg/mL) for having AD co-pathology, with no discernible treatment effect (positive or negative) with baseline plasma ptau181 levels above the threshold, i.e., those with mixed AD-DLB. When LMMRM analysis was confined to patients who had ptau181<2.2 ng/mL at baseline, for both comparisons significant positive treatment favoring NFMD 40mg TID were seen for the attention composite z-score (p=0.021 vs. placebo, difference=0.42 95%CI 0.07, 0.78; p=0.034 vs. placebo TID, difference=0.46 z-score, 95%CI 0.04, 0.88), TUG (p<0.001 vs. placebo, difference=¬ 3.1 , 95%CI 4.7, 1.6; p=0.010 vs. placebo TID, difference= 3.5 seconds, 95%CI 6.1, 0.9), and the CDR-SB (p=0.031 vs. placebo, difference= 0.60, 95%CI-1.14, 0.06; p=0.009 vs. placebo TID, difference= 0.93 points, 95%CI, 1.61, 0.25). For the NTB z-score, though numerically favoring NFMD 40mg TID treatment (difference=0.21 vs. placebo, 95% CI 0.07,0.49; difference=0.25 vs. placebo TID, 95% CI -0.07, 0.57), with the limited sample size the differences were not significant (p=0.13 vs. placebo, p=0.12 vs. placebo TID). However, for the NTB, a significant PK-PD relationship (p=0.035, r=0.46, for estimated trough plasma neflamapimod drug concentration vs. NTB z-score score) was evident. Compared to the results in the overall population, the magnitude of the neflamapimod treatment effect relative to placebo for the individual endpoints was 1.5 to 2.0-fold greater in the population with plasma ptau181<2.2 ng/mL at baseline. **Conclusion:** Neflamapimod demonstrates very good efficacy in DLB patients without co-existing AD pathology, defined by plasma ptau181<2.2 ng/mL. The finding of a specific effect in DLB without prominent AD co-pathology (i.e., DLB, rather than mixed AD-DLB), a disease considered to be disease of the basal forebrain cholinergic system, is consistent with the mechanism of action of neflamapimod and the preclinical results. Taken together, these results further demonstrate that neflamapimod has robust and specific pharmacological and clinical activity against DLB. The results also add to the literature evidence that AD co-pathology impacts the clinical course of DLB.

LP15- SAFETY AND BIOLOGICAL ACTIVITY OF A FIXED-DOSE COFORMULATION OF SODIUM PHENYLBUTYRATE AND TAURURSODIOL (PB/TURSO) FOR THE TREATMENT OF ALZHEIMER'S DISEASE: RESULTS FROM THE PHASE 2A PEGASUS STUDY.

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Background: An oral, fixed-dose coformulation of sodium phenylbutyrate (PB) and taurursodiol (TURSO) was designed to reduce neuronal death by simultaneously mitigating endoplasmic reticulum and mitochondrial dysfunction. Coformulated PB/TURSO was shown to significantly slow functional decline and prolong survival in a placebo-controlled trial in amyotrophic lateral sclerosis (CENTAUR). Preclinical evidence suggests potential activity of PB and TURSO individually in Alzheimer's disease (AD). PB has been shown to reduce hippocampal neurodegeneration and amyloid plaque burden in murine AD models, with concordant improvements in spatial memory tasks. TURSO ameliorated amyloid deposition, reduced glial activation, and prevented cognitive decline in a double-transgenic murine model expressing chimeric mouse/human amyloid precursor protein and mutant human presenilin 1 (APP/PS1). PEGASUS (NCT03533257) is the first clinical trial to evaluate PB/TURSO in AD. **Objective:** Assess the safety, tolerability, neurobiological activity, and

preliminary clinical effects of PB/TURSO in a broad range of patients with dementia or mild cognitive impairment (MCI) due to AD over 24 weeks. **Methods:** PEGASUS was an early phase 2, multicenter, randomized, double-blind, placebo-controlled trial enrolling adults aged 55–89 years with AD or MCI accompanied by biomarkers supporting AD pathology (amyloid positron emission tomography [PET], cerebrospinal fluid [CSF] AD biomarkers, fluorodeoxyglucose PET, or volumetric magnetic resonance imaging [vMRI]) and baseline Montreal Cognitive Assessment (MoCA) score ≥8. Participants were randomized to receive PB/TURSO or matching placebo for 24 weeks. Use of standard-of-care AD medications was permitted in participants on stable dosing regimens. MRI scans and lumbar punctures were performed on each participant at baseline and week 24. The primary objective was safety and tolerability of PB/TURSO compared with placebo. The primary efficacy outcome was a global test statistic for change from baseline to week 24 in 3 end points: Mild/Moderate Alzheimer's Disease Composite Scale (MADCOMS), Functional Activities Questionnaire (FAQ), and hippocampal vMRI. Secondary efficacy outcomes included changes from baseline in clinical assessments, including MADCOMS, the 14-item Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog14), MoCA, the Dementia Severity Rating Scale (DSRS), FAQ, and the Neuropsychiatric Inventory Questionnaire, and in neuroimaging assessments, including regional brain volumes, white matter, and functional connectivity. Biomarker outcomes included changes in core AD biomarkers (amyloid beta species [Aβ1-42 and Aβ1-40], total tau [t-tau], and phospho-tau 181 [p-tau]) in CSF, as well as other biomarkers of neuronal injury, oxidative damage, and inflammation. Mean changes from baseline to week 24 were compared between active and placebo arms for all efficacy outcomes and declared significant at the $P<0.05$ level. No hypothesis testing was performed for safety variables. **Results:** A total of 95 participants were randomized (PB/TURSO, n=51; placebo, n=44). The average participant age was 70.7 years; approximately 80% of participants were receiving concomitant acetylcholinesterase inhibitors and 42%, concomitant memantine. Mean (SD) cognitive assessment scores indicated a significantly greater baseline level of cognitive impairment among those randomized to PB/TURSO versus placebo (ADAS-Cog14 total score, MOCA, and MADCOMS, all $P<0.01$). The PB/TURSO group had a numerically higher percentage of apolipoprotein E ε4 carriers compared with the placebo group (77.1% vs 61.4%, respectively; $P=0.12$). Baseline values for all other measures were similar between groups. Treatment-emergent adverse events (TEAEs) were reported in 34 (67%) participants in the PB/TURSO group and 26 (59%) participants in the placebo group, with gastrointestinal events (primarily diarrhea) accounting for the greatest proportion of TEAEs in the PB/TURSO group (39% vs 14% in the placebo group). Ten of 51 (20%) participants in the PB/TURSO group and 2 of 44 (5%) participants in the placebo group discontinued study. No significant between-group differences were observed for the primary or secondary end points. Changes in core AD biomarkers were found to be significant, with reductions in CSF t-tau ($P=0.0005$) and p-tau ($P=0.0008$) over the 24 weeks in the PB/TURSO versus placebo group and an increase in Aβ1-42/Aβ1-40 ($P=0.017$). **Conclusions:** PB/TURSO was associated with a greater incidence of primarily gastrointestinal events compared with placebo, in line with previous clinical trial experience. While the study was not powered to test differences between groups in efficacy outcomes, no differences were found. There was suggestion of PB/TURSO activity on biomarkers of AD pathology (t-tau, p-tau, and Aβ1-42/Aβ1-40). Analyses of additional CSF biomarkers and imaging sequences are planned to further understand the effects of PB/TURSO in patients with AD. **Disclosures:** Conflicts of interest will be listed in the presentation at CTAD.

LP16- RETISPEC'S HYPERSPECTRAL IMAGING SYSTEM: RESULTS OF A VALIDATION STUDY IN PRECLINICAL AD AND MCI. Sharon Cohen[1], Arthur Plante[2,3,4], Alon Hazan[5], Adam Gribble[5], Yi Ping Lin[5], Justin Digregorio[5], Westreich Jared[5], Ian Cohen[1], Andriy Strilchuk[1], Julie Soehner[1], Fred Leblond[6,7], Michal Schnaider-Beeri[8] *(1. Toronto Memory Program - Toronto (Canada), 2. Retispec Inc. - Montréal (Canada), 3. Department of Engineering Physics, Polytechnique Montreal - Montréal (Canada), 4. Centre de recherche du Centre hospitalier de l'Universite de Montréal - Montréal (Canada), 5. Retispec Inc - Toronto (Canada), 6. Department Of Engineering Physics, Polytechnique Montreal, Montreal, Quebec, Canada; Centre De Recherche Du Centre Hospitalier De L'universite De Montréal, - Montréal (Canada), 7. Centre De Recherche Du Centre Hospitalier De L'universite De Montréal, - Montréal (Canada), 8. The Joseph Sagol Neuroscience Center, Sheba Medical Center, Israel; Professor, Icahn School Of Medicine At Mount Sinai - Tel Hashomer (Israel))*

Background: Current technologies to detect the pathobiology of Alzheimer's disease (AD) are often invasive, expensive, and not widely available. The retina, a protrusion of the central nervous system, is a promising candidate for the non-invasive identification of various AD biomarkers. The retina shares developmental and biological similarities to the brain. High-resolution imaging of the retina enables quantification of many biophysical and biochemical properties. By harnessing hyperspectral imaging technology and proprietary machine learning, RetiSpec's patented technology allows for the rapid, simple and cost-effective identification of AD at early stages of the disease. **Objectives:** The primary objective of this study was to evaluate the accuracy of RetiSpec's hyperspectral retinal imaging system in predicting individual brain amyloid beta (Aβ) status (Aβ+ or Aβ-), as compared to clinical gold standards of Aβ PET and/or CSF assessment. A secondary goal of the study was to examine participant perceptions of RetiSpec's system in terms of comfort, duration, and acceptability. **Methods:** This study employed a cross-sectional study design. Participants were drawn from two study sites -- Toronto Memory Program, Canada and the Joseph Sagol Neuroscience Center at Sheba Medical Center, Israel. Eligible individuals were adults between ages 50 and 90 years who were at risk for or who had preclinical AD or who had mild cognitive impairment (MCI), according to the National Institute on Aging and Alzheimer's Association 2011 criteria. Aβ assessment via CSF and/or PET scan occurred within 12 months of retinal imaging. Those with a known history of advanced or severe ocular diseases were excluded. Individuals with mild-to-moderate conditions (e.g., cataract) were not excluded. Participants were divided into two groups based on their PET or CSF amyloid results: (1) participants who were brain Aβ+, and (2) participants who were brain Aβ-. For objective 1, the retinal recording system was based on a Topcon fundus camera in conjunction with a commercially available hyperspectral camera. Transpupillary recordings were conducted using this proprietary spatial-spectral system. The system captured high resolution hyperspectral images of the retina in the wavelength range of 450nm-1000nm. Conventional and spectral images for each of the retinal targets were located in recordings from each eye. Image quality was reviewed to make sure no stray light from iris reflection was present. The data were then classified

with a Multiple Instance Learning (MIL) algorithm based on mapped bag space methods to detect spatial-spectral-patterns in hyperspectral-retinal-images (HRI), that are common to brain Aβ+ patients and do not appear in HRI of brain Aβ patients. Additionally, participants from Toronto Memory Program completed a survey to report on their experience with the RetiSpec imaging procedure relative to comfort, duration, and acceptability. **Results:** The study included 108 participants who had a mean age of 70 years (range=51-89), 53% females. Most participants were well-educated with 70% (n=76) having completed post-secondary education. About a quarter of participants had undergone lens replacement surgery (n=26; 24%). The sample consisted of mostly individuals at risk for or with preclinical AD (n=74; 69%) versus those with MCI or prodromal AD (n=33; 31%). Most participants were drawn from Toronto Memory Program (n=84; 78%) while 22% (n=24) were from Sheba Medical Center. Diagnostic performance of RetiSpec's technology to detect Aβ status was evaluated as compared to clinical gold standards of Aβ PET (n=48; 44%) or CSF assessment (n=57; 53%); a small number of participants had both PET and CSF comparators available (n=3; 3%). For objective one, diagnostic performance of our approach to predicting brain Aβ status was demonstrated by an area under the curve (AUC) reaching 0.88, which corresponded with 86% sensitivity and 80% specificity when the cutoff was applied, and with no other data (e.g., age, APOE status) added to improve the model. Regarding the secondary goal of the study, on a scale from 1 (strongly disagree) to 5 (strongly agree), 85 participants strongly agreed that: the scan was comfortable for their eyes (mean=4.1) and the duration of the RetiSpec scan was reasonable (mean=4.3). Further, on a scale from 1 (very unlikely) to 5 (very likely), participants reported being very likely to undergo RetiSpec scan in the future (mean=4.8). **Conclusion:** Results indicate that hyperspectral retinal imaging technology is effective in predicting brain Aβ status in individuals at risk for or with preclinical AD or who had MCI when compared to the clinical gold standards of Aβ PET and CSF assessment. Additionally, participants reported an easy and comfortable experience of undergoing the RetiSpec scan and reported high willingness to undergo the scan in the future. Our results suggest that if replicated in larger and diverse samples, retinal amyloid imaging may serve as a non-invasive, inexpensive, sensitive and specific biomarker for Alzheimer's disease in its earlier stages.

LP17- MAPPING THE COHEN-MANSFIELD AGITATION INVENTORY TO THE CLINICAL GLOBAL OF SEVERITY OF AGITATION: DATA FROM THE BREXPIPRAZOLE PHASE 3 PROGRAM FOR THE TREATMENT OF AGITATION IN ALZHEIMER'S DEMENTIA. Anne De Jong-Laird[1], Pedro Such[2], Dalei Chen[3], Ross Baker[3] *(1. Otsuka - The Hague (Netherlands), 2. Lundbeck - Copenhagen (Denmark), 3. Otsuka - Princeton (United States))*

Learning Objective: Understand how the Cohen Mansfield Agitation Inventory, an objective scale for measurement of agitation, relates categorically to the clinical global impression of severity (CGI-S) for agitation both in terms of baseline severity as well as change after treatment with Brexpiprazole. **Background:** There is a need to relate changes measured by the CMAI in clinical trials to changes in the CGI-S in order to better understand the clinical relevance of the CMAI scale. We compared CMAI scores with CGI-S scores based on pooled data from two Phase 3 studies of brexpiprazole 2 mg/day for the treatment of agitation in Alzheimer's dementia (AAD). **Method:** Two 12-week, randomized, double-blind, placebo-controlled, parallel-arm studies (NCT01862640, study 1; NCT01922258, study 2; Grossberg et al., 2019 AJGP). **Intervention:** Pooled trial subjects receiving 2 mg/day of brexpiprazole vs. placebo were analyzed post-hoc. Mean baseline CGI-S and CMAI scores were calculated using descriptive statistics, and changes in both scales in brexpiprazole subjects vs. placebo were compared using a likelihood ratio chi-square test. **Results:** Patients with a mean baseline CGI-S score of 4 (N=301), moderately ill, had a mean CMAI score of 66.2, +/- 14.1 sd, and mean baseline CGI-S score of 5 (N= 224), markedly ill, had a mean CMAI score of 76.8 +/- 15.5 sd. Results at the week 12 study endpoint showed 1: 59.1% (140/237) of brexpiprazole patients had a CGI-S score of 1 or 2 (normal or minimally ill) vs 45.6% of placebo patients (108/237), a significant difference of 13.5% (4.6% to 22.4%, p = 0.0033). Also, 79.3% (188/237) of brexpiprazole patients showed an improvement on the CGI-S of at least 1 point from baseline vs. 67.9% (161/237) for placebo, a significant difference of 11.4% (3.5% to 19.3%, p=0.0048). Finally, 74.7% (177/237) of brexpiprazole patients showed an improvement in the CMAI scale of at least 10 points from baseline vs. 66.7% (158/237) for placebo patients, a numerical difference of 8.0% (-0.2% to 16.2%, p = 0.0550). **Conclusions:** The results show a score of 66.2 on the CMAI represents moderately severe agitation, while a score of 76.8 represents markedly severe agitation. The proportion of patients with an improvement of 1 point from baseline in CGI-S was similar to that of patients with an improvement of 10 points on the CMAI, suggesting an improvement of 1 point on the CGI-S represents a 10 point improvement on the CMAI.

LP18- FINAL DATA FROM A PHASE 1 SINGLE-ASCENDING-DOSE TRIAL OF PNT001, A MONOCLONAL ANTIBODY UNIQUELY RECOGNIZING CIS-PT231 TAU FOR TREATMENT OF TAUOPATHIES. Wendy Luca, Kelly Foster, Kim Mc Clure, Martin Jefson, Michael Ahlijanian, Larry Altstiel *(Pinteon Therapeutics - Newton Centre (United States))*

Background: Pinteon Therapeutics has generated a humanized monoclonal antibody, PNT001, that uniquely recognizes cis-pT231 tau. Cis-pT231 tau is present selectively in the brains of tauopathy patients and is a potent driver of tau-related neurodegeneration. PNT001 has high affinity and selectivity for cis-pT231 tau. In preclinical models, the murine form of PNT001 reduces the spread of tau pathology, neuroinflammation, acute and chronic neurodegeneration, as shown by reduction in serum NfL. It improves synaptic and functional endpoints, and depletes aggregation-competent tau from AD and PSP brains. There were no test article related findings in toxicity studies and all regulatory safety studies are complete. **Objectives:** The objective of the Phase 1, randomized, double-blind, placebo-controlled, single-ascending-dose trial was to evaluate the safety, tolerability, immunogenicity, and pharmacokinetics of intravenous PNT001 in healthy volunteers. Drug concentrations were measured in both CSF and serum. **Methods:** The trial was a single-dose, double-blind, placebo-controlled dose cohort escalation design employing dose levels of 33mg, 100mg, 300mg, 900mg, 2700mg and 4000mg delivered as a single intravenous infusion. Each cohort included 8 subjects, 6 randomized to receive active drug and 2 randomized to receive placebo. Safety, tolerability, CSF and serum pharmacokinetic (PK), serum anti-drug antibodies, and biomarker samples were collected over the 16 week course of the trial. An external, independent data safety monitoring board reviewed safety data twice for each dose cohort; first

for continued enrollment at a dose level when the sentinel group reached Day 7 and again for dose escalation when the complete cohort reached Day 14. In each instance, the DSMB authorized continued dosing. **Results:** A total of fifty (50) subjects enrolled in the trial. One subject did not receive study drug and one subject was replaced. Of the 49 subjects who received study drug, 73.5% were male, 65.3% were White, 30.6% were Black and 4.1% were Asian. Of the 48 subjects who received study drug and were not replaced, 41 (85.4%) completed the study. Thirty-six (36) subjects dosed received PNT001. Three related non-serious Grade 1 adverse events occurred at the lowest doses of 33mg and 100mg. Each event resolved without sequelae. No maximum tolerated dose was identified and there were no premature discontinuations, dose reductions, or dose interruptions due to treatment related adverse events. One unrelated serious adverse event occurred in a subject randomized to placebo. Non-compliance with concomitant medication for an undisclosed seizure disorder resulted in seizure and hospitalization. Symptoms resolved with resumption of prescribed seizure medication. Well-tolerated doses (900 mg – 4000 mg) produced CSF concentrations well in excess of the binding affinity constant of PNT001 for cis-pT231 tau thereby indicating safe, well-tolerated doses of PNT001 can provide CSF concentrations sufficient for target engagement. Serum and CSF PK were as expected for a monoclonal antibody. The terminal half-life ranged from 23.8 – 33.8 days and CSF exposures were dose proportional. **Conclusion:** PNT001 was well tolerated in human volunteers at CSF drug concentrations expected to produce target engagement supporting multiple ascending dose studies in patients with neurodegenerative tauopathies like Alzheimer's disease.

RP18- FORTASYN CONNECT'S LONG-TERM INTERVENTION EFFECTS ON CLINICAL DEMENTIA RATING – SUM OF BOXES AND ON MEMORY IN THE LIPIDIDIET RCT. Tobias Hartmann[1,2], Alina Solomon[3,4,5], Pieter Visser[6,7], Suzanne Hendrix[8], Kaj Blennow[9,10], Miia Kivipleto[3,4,5], Hilkka Soininen[3,11] *(1. Deutsches Institut Für Demenz Prävention (didp), Medical Faculty, Saarland University - Homburg (Germany), 2. Department of Experimental Neurology, Saarland University - Homburg (Germany), 3. Department Of Neurology, Institute Of Clinical Medicine, University Of Eastern Finland - Kuopio (Finland), 4. Department of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet - Huddinge (Sweden), 5. Clinical Trials Unit, Theme Aging, Karolinska University Hospital - Huddinge (Sweden), 6. Department Of Psychiatry And Neuropsychology, Alzheimer Centre Limburg, University Of Maastricht - Maastricht (Netherlands), 7. Department of Neurology, Alzheimer Centre, Amsterdam Neuroscience, VU University Medical Center - Amsterdam (Netherlands), 8. Pentara Corporation - Millcreek (United States), 9. Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy At University Of Gothenburg - Mölndal (Sweden), 10. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital - Mölndal (Sweden), 11. Neurocentre, Department of Neurology, Kuopio University Hospital - Kuopio (Finland))*

Background: Lifestyle factors such as nutrition and diet are increasingly recognized as modifiable risk factors for the progression of mild cognitive impairment (MCI) to Alzheimer's disease (AD). They may contribute to improved cognitive performance in individuals at risk of progression to dementia (1,2). Fortasyn Connect is a multinutrient combination that has been shown in preclinical studies to reduce AD-linked brain pathology (3). Benefits on memory and functional connectivity were demonstrated in patients with mild AD (4,5). In prodromal AD Fortasyn Connect slowed cognitive decline and reduced brain atrophy (6, 7). The LipiDiDiet study is designed to investigate the effects of Fortasyn Connect on cognition and related measures in individuals with prodromal AD. Significant intervention effects compared to the placebo group were observed as early as in the first 12 months of intervention on the clinical dementia rating-sum of boxes (CDR-SB). **Objectives:** Here we report on the long-term intervention effects of Fortasyn Connect on the cognitive-functional CDR-SB outcome and on memory as assessed by the 3-item neuropsychological test battery (NTB) memory outcome. **Methods:** The LipiDiDiet trial (NTR1705) was a double-blind, parallel-group, multi-center randomized controlled clinical trial (11 sites in Finland, Germany, the Netherlands, and Sweden). Following initial 24-month intervention, participants could continue in the trial for a maximum total of 72 months of randomized, controlled, double-blind, parallel-group intervention, and another 24 months of open-label extension. Here we report analyses over a total of 36 months of intervention following the initial randomization. A total of 311 participants with prodromal AD, defined according to the International Working Group (IWG)-1 criteria, were enrolled. Participants were randomly assigned (1:1) to active product (125 mL drink containing the multinutrient combination Fortasyn Connect) or an iso-caloric placebo control drink once daily. Primary outcome was the 24-month change in an NTB 5-item cognitive function composite z-score. Secondary outcomes reported here are CDR-SB and NTB memory. Statistical analyses were performed using a linear mixed model for repeated measures in a modified intention-to-treat (mITT) population, excluding (i.e. censoring) data collected after the start of open-label medication (defined as use of active product and/or AD medication after dementia diagnosis). **Results:** Of the 382 participants assessed for eligibility, 311 were randomized, and of those 162 participants completed 36 months of intervention, including 81 with 36-month data eligible for efficacy analysis (mITT). Over 36 months, significant reductions in decline were observed for the NTB 5-item composite (-60%; between-group difference 0.212 [95% CI 0.044 to 0.380], p=0.014), CDR-SB (-45%; -0.90 [-1.62 to -0.19], p=0.014), and NTB memory (-76%; 0.274 [0.071 to 0.477], p=0.008); with small to medium Cohen's d effect size (0.25-0.31) similar to established clinically relevant AD dementia treatment, and larger than the standardized effect sizes for primary endpoints in clinical studies with Fortasyn Connect in mild AD7. When assessing those individuals who consistently used the study product over time, i.e. the per-protocol population, similar or slightly larger reductions in decline were observed for the NTB 5-item composite (-74%; 0.269 [95%CI 0.081 to 0.457], p=0.005), CDR-SB (-55%; -1.15 [-1.90 to -0.41], p=0.003), and NTB memory (-91%; 0.352 [0.125 to 0.579], p=0.003). Sensitivity joint model analyses, supportive analyses including censored data points, and analyses investigating potential confounder effects gave comparable results. **Conclusions:** Over 36 months of intervention with Fortasyn Connect, we observed significantly slower decline on prespecified outcomes measuring cognition including memory, cognition, and function. In addition to clinically detectable benefits, the intervention had a good safety profile and high compliance throughout this study. For the clinically relevant CDR-SB, results were strongest for those participants with high baseline MMSE scores and separation from the control group was observed already over the first 12 months of intervention. Similar to the results on CDR-SB as reported over the first two years, a 45% reduction in decline in

active compared to the placebo control was observed over the 3 years studies, suggesting that the cognitive-functional benefit as assessed by CDR-SB is sustainable long-term. A memory benefit was first observed in the per-protocol group over 24 months of intervention. However, for the mITT group the intervention effect on memory reached statistical significance only after the longer intervention period of 36 months with a 76% benefit over the placebo control group. The trajectories of CDR-SB and NTB memory suggest that these outcomes have reached a stable benefit as compared to the placebo control group, that the intervention benefit became more pronounced with long-term use and that the initial principal point of separation was within the first treatment year. The results indicate that the intervention triggers multiple cognitive-functional benefits which may appear at different paces, and those responses might differ for sub-populations. Funding EU FP7 LipiDiDiet, EU JPND EU-FINGERS; Dutch Trial Register: NTR1705. **References:** 1. Anastasiou CA, et al. Nutrients. 2018;10. 2. Lehtisalo J, et al. Br J Nutr. 2017;118:291-302. 3, van Wijk N, et al. J Alzheimers Dis. 2014;38:459-479. 4. Scheltens P, et al. Alzheimers Dement. 2010;6:1-10 e1. 5. Scheltens P, et al. J Alzheimers Dis. 2012;31:225-236. 6. Soininen H, et al. Lancet Neurol. 2017;16:965-975. 7. Soininen H, et al. Alz Dementia. 2021;17 :29-40

RP19- VALIDATION OF EXPOSURE-DEPENDENT ACTIVITY ON COGNITIVE AND FUNCTIONAL DECLINE CONFIRMS HYDROMETHYLTHIONINE AS A POTENTIAL NEAR-TERM ORAL TREATMENT FOR ALZHEIMER'S DISEASE (AD). Claude Wischik[1, 2], Helen Shiells[1], Bjoern Schelter[1, 2] *(1. Taurx Therapeutics Ltd - Aberdeen (United Kingdom), 2. University of Aberdeen - Aberdeen (United Kingdom))*

Background: Recruitment to a 12-month Phase 3 trial (Lucidity) in mild/moderate AD testing oral hydromethylthionine mesylate (leuco-methylthionine dihydromesylate, LMTM) at a dose of 16mg/day as monotherapy against placebo has been completed and is due to report in 2022. Amyloid related imaging abnormalities (ARIA) were one of three classes of Adverse Events of Special Interest that were monitored closely. LMTM was found to be free of ARIA risk of at any of the doses tested (8, 150, 200, 250mg/day) in 1,686 patients participating in two completed Phase 3 trials in which MRI scans were conducted every 3 months over 15-18 months (Gauthier et al., Lancet 2016,388:2873-2884; Wilcock et al., JAlzDis 2018,61:435-457). A post-hoc population PK analysis conducted in 1,162 of the patients (70%) revealed a steep exposure-response relationship at the 8mg/day dose (Schelter et al., JAlzDis 2019,72:931-946). At 8mg/day, the majority of patients (875, 72%) were found to have steady-state plasma levels above a threshold (0.378ng/ml) defined on the basis of the lower calibration limit of the assay and a minority (342, 28%) had below-threshold exposure. Those with high exposure had significantly less cognitive and functional decline and progression of brain atrophy compared to those with low exposure. The 16 mg/day dose was identified as the minimum at which 95% of subjects would have above-threshold plasma levels. There was no additional benefit at doses in the range 150-250mg/day. **Objective:** The main objective of the present study was to compare cognitive and functional decline according to level of exposure against a meta-analysis of historical placebo/natural history data available from approximately 10,000 patients with mild or mild/moderate AD with a view to validating the rationale and design assumptions of the Lucidity trial. If LMTM lacks relevant clinical pharmacological activity, it would be expected that patients receiving LMTM at the 8mg/day dose would have declined similarly to historical placebo on cognitive and functional outcomes irrespective of steady-state plasma levels of the drug. **Methods:** Patients receiving LMTM 8mg/day in the completed trials were divided into two exposure groups according to the 0.378ng/ml steady-state plasma level threshold. Cognitive decline over 12 months was compared with historical data available from 5,534 patients in 12 data studies conducted since 2000 with mild AD. In patients with mild/moderate AD, cognitive decline was compared with data available from 4,357 patients in 17 studies conducted since 1996 and functional decline was compared with data available from 1,296 patients in 5 studies reported between 2012 – 2019. **Results:** Mild AD. The expected weighted mean placebo/historical cognitive decline in mild AD over 12 months is 4.15 (95%CI 3.35–4.95) ADAS-cog11 units. Decline in patients with below-threshold exposure to LMTM 8mg/day was comparable (4.74±0.60, p=0.4169). Those with above-threshold plasma levels at the same dose declined by 1.58±0.46 units (difference -2.57±0.616, p<0.0001). Patients with high exposure at the 8mg/day dose were further subdivided according to co-medication status with cholinesterase inhibitors or memantine. Those with high exposure declined significantly less than expected both for LMTM as add-on therapy (difference -2.04±0.65, p=0.0016) and as monotherapy (difference -4.66±1.02, p<0.0001). Mild/moderate AD. In mild/moderate AD, the expected weighted mean placebo decline on the ADAS-cog11 scale is 5.26 (95%CI 4.45–6.06) units and -7.59 (95%CI -8.90 – -6.29) units on the ADCS-ADL23 scale. Patients with sub-threshold exposure at 8mg/day declined as expected on both cognitive and functional scales (p-values with respect to meta-analysis weighted means: 0.4312 and 0.4766 respectively). Those with high exposure at the same dose differed significantly from expected historical decline (ADAS-cog11 difference -2.68±0.566, p<0.0001; ADCS-ADL23 difference 2.22±0.84, p=0.0084). When subdivided according to co-medication status with standard AD drugs, patients with high exposure at 8mg/day as add-on declined significantly less than expected on the ADAS-cog11 scale (difference -2.14±0.587, p=0.0003), but not on the ADCS-ADL23 scale (difference 1.56±0.87, p=0.0719). For patients with high exposure as monotherapy, the differences relative to expected decline were significant on both scales (ADAS-cog11 difference -5.23±0.953, p<0.0001; ADCS-ADL23 difference 5.33±1.288, p<0.0001). **Conclusion:** In the completed LMTM Phase 3 trials, patients with subthreshold plasma levels at the 8mg/day dose declined as expected on standard cognitive and functional scales relative to comparable external populations. Decline in those with high exposure at the same dose differed significantly. Therefore, LMTM produces exposure-dependent differences in clinical outcomes relative to those expected in similar populations with treatment effects for monotherapy approximately double those for LMTM as add-on. These results validate the rationale and design assumptions underlying the Lucidity trial and provide an indication of the magnitude of the treatment effects of LMTM 16mg/day as monotherapy that might be expected relative to co-temporaneous placebo. Hydromethylthionine offers the potential of an oral near-term tau-based alternative to intravenous amyloid-based approaches that is free of ARIA risk.

LRP10- BENEFICIAL EFFECTS OF MASUPIRDINE ON AGITATION IN PATIENTS WITH ALZHEIMER'S DISEASE: A NOVEL NON-SEDATING MECHANISM. Ramakrishna Nirogi, Anil Shinde, Abdul Rasheed Mohammed, Vinod Kumar Goyal, Santosh Kumar Pandey, Vijay Benade, Veera Raghava Chowdary Palacharla, Ramkumar Subramanian, Renny Abraham, Pradeep Jayarajan, Jyothsna Ravula, Satish Jetta *(Suven Life Sciences Ltd - Hyderabad (India))*

Background: Neuropsychiatric symptoms (NPS), a core feature of Alzheimer's disease (AD) is associated with increased caregiver burden, decreased functioning, and accelerated progression to severe dementia. Among the NPS, agitation is rated as one of the most distressing symptoms. Currently there are no approved treatments for agitation in AD. Though off-label use of antipsychotics and SSRIs offer short term benefits, they are associated with risks of accelerated cognitive decline, stroke, and death. Therapies in active clinical development involve sedatives and do not have positive effects on cognition. These limitations warrant newer, safer and non-sedating treatment options with procognitive potential. **Objective:** To evaluate the effect of masupirdine, a serotonin 6 receptor antagonist on agitation symptom assessed using the 12-item neuropsychiatric inventory (NPI-12) scale. **Methods:** Masupirdine was evaluated in a multicenter, randomized, double-blind, parallel group, 26-week, placebo-controlled proof of concept phase-2 clinical trial in subjects with moderate AD (NCT02580305). Subgroup analyses were carried out on the agitation/aggression domain of the NPI-12 scale. Analyses were based on the independent patient subgroups with baseline symptoms. A mixed-effects model for repeated measures was used to determine the effect of masupirdine on agitation/aggression symptoms in modified intention to treat population. **Results:** A statistically significant ($p<0.01$) reduction in agitation/aggression scores was observed in the masupirdine treatment (50 & 100 mg) arms at Week 13. The effect was sustained for the entire study duration of 26 weeks in the masupirdine 50 mg treatment arm ($p<0.01$). Effect size (Cohen's d) observed in masupirdine 50 mg treatment at the end of 26 weeks was 0.66, suggesting clinically meaningful effects. **Conclusions:** Further exploration is warranted to confirm the beneficial effects of masupirdine on agitation. Currently, a phase-3 study to evaluate the effects of masupirdine on agitation in patients with dementia of the Alzheimer's type has been initiated.

COGNITIVE ASSESSMENT AND CLINICAL TRIALS

P48- CULTURAL INFLUENCE ON CDR SCORES: COMPARISON ACROSS SEVEN GEO-CULTURAL GROUPS. Sayaka Machizawa, Todd Feaster, Jessica Stenclik, Zinan Chen, Danielle Digregorio *(Signant Health - Blue Bell (United States))*

Background: In an attempt to successfully recruit Alzheimer's disease (AD) subjects, trials are becoming increasingly global. Given this geographic expansion, identifying regions and countries that are able to provide high quality data is paramount. One challenge in using dementia rating scales in global studies is a potential cultural bias embedded in these scales. These scales are often derived from majority Caucasian populations in North America and tend to assume familiarity with Western culture. While the Clinical Dementia Rating scale (CDR) has been successfully employed in dementia studies across the globe and has been validated locally, it is not free from cultural bias. One may suspect cultural factors affect raters' perceptions and ratings, as well as caregivers and subjects' perceived ability levels. This study aims to examine whether differences exist on the CDR domain and Sum of Box (SOB) scores across seven geo-cultural regions. **Objectives:** To compare the CDR domain and Sum of Box (SOB) scores across seven geo-cultural regions among the older adults enrolled in multi-national AD clinical trials. **Methods:** This study included eCDR (electronic CDR) data from four multi-national AD clinical trials of subjects with Prodromal to Mild AD. Data included eCDR assessments at screening visits from seven geo-cultural regions: East Asia (n = 1121); Eastern Europe (n = 15,979); Latin America (n = 10,017); Middle East/Africa (n = 2,198); North America (n = 65,989); Oceania (n = 2,636) and Western Europe (n = 47,334). All raters were uniformly trained and certified on the administration and scoring of the CDR, and all studies utilized an enhanced eCDR scale to help facilitate a quality interview and mitigate rater error. Each of the four trials also included a data quality surveillance program with a central audio review of scale administration and scoring to assess for errors and provide rater remediation when necessary. The Kruskal–Wallis test was conducted to determine if there was significant variance in the CDR domain and SOB scores across the seven geo-cultural regions. Additionally, the Dunn's test was used for post-hoc analyses to understand between-group differences. **Results:** The Kruskal–Wallis test revealed a statistically significant variance on all six CDR domains and SOB scores across geo-cultural regions ($p<.0001$). Results of the Dunn's test revealed scores for East Asia are significantly lower than those for other geo-cultural regions across all six CDR domains and the SOB ($p<.0001$). **Conclusion:** Our study found the elderly subjects in East Asia had lower CDR scores on all six domains in comparison to their counterparts in other regions. It is unclear, however, what caused the differences in their scores. One potential explanation is psychometric and/or rating bias due to cultural factors. Considering the CDR is a clinician-rated outcome that relies on subjective information from the caregiver, it is possible such factors as cultural norms, beliefs and values, as well as education and socioeconomic status affect the perceptions of rater and caregiver. Raters and caregivers in East Asia may have lower expectations for the elderly to function independently due to the cultural value of interdependence, and this may affect their subjective report and ratings. Another potential interpretation of the finding is that East Asian subjects' lower CDR scores actually reflect their higher global functioning. Due to the collectivist, community-oriented culture in East Asia, the elderly receive extended support from their family and community members that may help them maintain relatively high functioning levels. Additional studies are needed to determine whether the relatively low CDR scores among the elderly subjects in East Asian reflect psychometric and/or rating bias versus higher functioning in comparison to their counterparts in other geo-cultural regions.

P49- GEO-CULTURAL INFLUENCES ON MMSE TOTAL SCORE IN ALZHEIMER'S DISEASE TRIALS. Jessica Stenclik, Sayaka Machizawa, Zinan Chen, Todd Feaster *(Signant Health - Blue Bell (United States))*

Background: Clinical trials in Alzheimer's disease are becoming increasingly global. The effort to recruit diverse subjects from various geo-cultural regions can assist with not only subject representation, but also increased sample sizes and treatment generalizability. Often, assessments that were initially

created, validated, and normed in Western culture, most frequently with Caucasian populations in North America, are translated directly for administration cross-culturally without considering the cultural nuances of local trial participants. This can lead challenges to the attainment of valid and reliable data. The Mini Mental State Examination (MMSE) is an extensively, globally utilized measure of cognitive impairment in dementia clinical trials. The MMSE has been found to be sensitive to education, age, and ethnicity in prior studies. In addition, some studies have revealed variations in translation, administration, and scoring in country specific MMSE versions, particularly for Asian countries. Thus, as the use of multinational studies increases, the impact of cultural and linguistic differences on this measure should be examined further to ensure reliable and valid data while prioritizing consistency and cultural differences. In this analysis, we evaluated the cross-cultural variance of the MMSE Total Score across geo-cultural regions. **Objectives:** To compare the MMSE Total Score across seven geo-cultural regions in multi-national Alzheimer's Disease clinical trials. **Methods:** This study included eMMSE (electronic MMSE) data from four multi-national AD clinical trials of subjects with Prodromal to Mild AD. Data included eMMSE assessments at screening visits from seven geo-cultural regions: East Asia (n = 1916); Eastern Europe (n = 1882); South America (n = 1601); Middle East/Africa (n = 188); North America (n = 9311); Oceania (n = 363) and Western Europe (n = 5174). All raters were uniformly trained and certified on the administration and scoring of the MMSE, and all studies utilized an enhanced eMMSE scale to help facilitate a quality interview and mitigate rater error. Each of the four trials also included a data quality surveillance program with a central audio review of scale administration and scoring to assess for errors and provide rater remediation when necessary. The Kruskal–Wallis test was conducted to determine if there was significant variance in the MMSE Total Score across the seven geo-cultural regions. Additionally, the Dunn's test was used for post-hoc analyses to examine between-group differences. **Results:** The Kruskal-Wallis test revealed a statistically significant difference in MMSE Total Score across the seven geo-cultural regions ($p<.0001$). The Dunn's test indicated that scores in North American were significantly higher than those in the six other geo-cultural regions. In addition, scores in East Asia were significantly higher than those in Western and Eastern Europe, and scores in South America were higher than those in Western Europe ($p<.05$). **Conclusion:** Findings indicate that North American elderly subjects have higher Total Scores on the MMSE in comparison to subjects in other regions of the world. This is not surprising given that the MMSE was normed and validated in North America. Thus, other geo-cultural regions may experience lower due to translation issues associated with cultural variations and nuances. As this is a standardized measure designed to reduce rater subjectivity, the impact of rater bias is less likely. It is also possible that subjects recruited in other geo-cultural regions are experiencing greater cognitive impairment compared to those in North America. The significant difference between Total Score for East Asia and Europe and South America and Western Europe is unclear but further elucidates the impact of cultural influences on the MMSE. Future research is needed to examine the cause of discrepancy in Total Score on the MMSE between subjects in North America and those in other geo-cultural regions, as well as those in East Asia compared to Europe and South America compared to Western Europe. Item analysis may prove useful in identifying specific items on the MMSE, rather than Total Score, that are measuring abilities differently in various subgroups.

P50- DIFFERENT METHODS OF IDENTIFYING RAPID COGNITIVE DECLINERS FOR ALZHEIMER'S DISEASE.

Haiyang Zhang[1], Jason Goode[1], Michael Donahue[2], Ali Torkamani[3], Jared Cara[1], Julie Collens[1] *(1. Vivid Genomics - San Diego (United States), 2. University Of Southern California - Los Angeles (United States), 3. Scripps Research Institute - San Diego (United States))*

Background: Heterogeneity in the progression of cognitive impairment in Alzheimer's disease (AD) populations can negatively impact the efficiency and statistical power of clinical trials, and in fact was recognized as a key confounder leading to discordant results in the recent aducanumab trials. While the progressive cognitive decline over the development of the disease is a commonly used characteristic of Alzheimer's disease, the definition standard of fast/slow decliners is still obscure. The rate of progression is usually merely defined by the annual point change of the Mini-Mental State Examination (MMSE) rather than a data-driven approach to tackle this problem. Patients with an average decline of 2-3 MMSE points/year, are usually characterized as slow decliners and those with a MMSE decline slope greater than this are considered fast decliners. This arbitrary definition, without considering other factors such as genetic and phenotypic features, will cause inaccurate target labeling and exaggerate errors for any downstream analysis on the same cohort. In this study, we introduced the polygenic risk scores (PRS) calculated based on multiple common genetic variants identified in large genome-wide association studies (GWAS) as the genetic factor for each individual. PRS allows us to take the comprehensive genetic effect into consideration beyond APOE genotype. Here we applied three different data-driven approaches to identify rapid decliners and provided a comprehensive comparison of these different methods, which allowed us to characterize PRS-predicted fast decliners and explore the efficiency of AD clinical trials with PRS-based inclusion criteria. **Methods:** We studied 3,790 National Alzheimer's Coordinating Center (NACC) patients with longitudinal cognitive measures. A PRS was calculated using GWAS summary statistics for clinical AD diagnosis for each sample. Individuals who have only a single visit history were excluded. Three different methodologies were applied for rapid decliner identification: Firstly, the 10th percentile of the individuals with the sharpest slopes of MMSE point change over their clinical trial period was selected and characterized as rapid decliners. Secondly, a linear mixed-effect regression model and gaussian mixture model were used for fast decliner identification based on the slope of MMSE. Lastly, an unsupervised learning model k-means was performed after determining the best cluster number to apply. Both genetic and phenotypic features including age, sex, education, APOE-ε2, APOE-ε4, baseline MMSE score, and PRS were used in the algorithm. Post-analysis was performed to confirm the fast decliner MMSE change slope and evaluate the homogeneity in each cluster. **Results:** The 10th percentile of the patients with the fastest MMSE slope decreased by ≥ 4 MMSE points per year over their longitudinal follow-up. The Gaussian mixture model and k-means algorithms identified rapid decliner subpopulations with annual MMSE point change 3.2 and 2.7 respectively. In addition, the majority of the rapid decliners identified by k-means (n=320) were also selected by using the Gaussian mixture model. There were 97 individuals identified by all three methods as the rapid decliners. All three methods were able to partition homogenous clusters of NACC subjects with significantly different cognitive trajectories evaluated on the features age, sex, education, APOE-ε2, APOE-ε4, baseline

MMSE score, and PRS. **Conclusions:** The proposed methods provide a novel perspective of fast decliner identification for AD clinical trials. Instead of using an arbitrary threshold of MMSE score change over a given clinical trial period, our analysis strategies not only utilized the slope of MMSE but also considered both the genetic and phenotypic factors, which provided statistical evidence and support for the fast decliner characterization. The post-analysis on the determined fast decliners showed that a more homogenous fast decliner cluster can be identified by using k-means algorithms and the Gaussian mixture model than selecting the 10th percentile of individuals with the fastest annual MMSE slope. While the top percentile method only considers the MMSE change, it is still a data-driven approach and can be used together with the k-means and the Gaussian mixture model to select the most compelling and convincing identification of the rapid decliners.

P51- QUICK DEMENTIA RATING SYSTEM AND ITS RELATIONSHIP TO NEUROPSYCHOLOGICAL SCORES AND BIOMARKERS. Kevin Duff[1], Deborah Levine[2], Bruno Giordani[2], Angie Fagerlin[1], Nicole Fowler[3], John Hoffman[1] *(1. University Of Utah - Salt Lake City, UT (United States), 2. University Of Michigan - Ann Arbor, MI (United States), 3Indiana University - Bloomington, IN (United States))*

Background: Although the Clinical Dementia Rating (CDR) scale is the gold standard for assessing dementia severity in trials in Alzheimer's disease (AD), briefer options are needed to make screening for trials more feasible. The Quick Dementia Rating System (QDRS) is an informant-rated 10-item questionnaire that approximates CDR scores (i.e., higher scores indicate greater dementia severity). Although this rapid dementia screening tool has demonstrated initial reliability and validity, its relationship to neuropsychological test scores and AD biomarkers has not been examined. **Objectives:** Examine the relationship between the QDRS and neuropsychological test scores and AD biomarkers in those classified as cognitively intact, Mild Cognitive Impairment (MCI), and mild AD. **Methods:** One hundred twenty-one older adult participants (54 intact, 35 MCI, 32 AD) completed a battery of neuropsychological tests, amyloid PET imaging, MRI, and APOE testing. An informant also completed the QDRS on each participant. Correlations examined relationships between the QDRS Total and Cognitive subtotal with neuropsychological test scores, global amyloid burden, hippocampal volumes, and APOE e4 status. **Results:** The QDRS Total did not correlate with a measure of premorbid intellect, but it did significantly correlate with measures of global cognition ($r=-0.64$, $p=<0.001$), immediate ($r=-0.62$, $p=<0.001$) and delayed ($r=-0.71$, $p=<0.001$) memory, language ($r=-0.49$, $p=<0.001$), attention ($r=-0.37$, $p=<0.001$), and visuospatial construction ($r=-0.34$, $p=<0.001$), with more severe dementia being associated with lower cognitive scores. The QDRS Total also significantly correlated with amyloid deposition ($r=0.48$, $p=<0.001$), hippocampal volumes ($r=-0.42$, $p=<0.001$), and APOE e4 status ($r=0.25$, $p=0.005$), with more severe dementia being associated with greater amyloid deposition, smaller hippocampal volumes, and the presence of APOE e4. All relationships were similar or greater for the Cognitive subscale of the QDRS. **Conclusion:** Although the QDRS provides a brief screening of dementia severity (like the CDR), it has not been formally validated against neuropsychological tests or AD biomarkers, which potentially limits its application in clinical trials. The current results support preliminary use of this rapid tool in these trials, pending additional validation in larger and more diverse samples. There are no conflicts of interest related to this abstract.

P52- CAN SCORES ON THE REPEATABLE BATTERY FOR THE ASSESSMENT OF NEUROPSYCHOLOGICAL STATUS PREDICT AMYLOID DEPOSITION? Kevin Duff[1], Kayla Suhrie[1], Dustin Hammers[2], Ava Dixon[1], John Hoffman[1] *(1. University Of Utah (United States), 2. Indiana University (United States))*

Background: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a widely-used cognitive screening battery in clinical settings, which has recently been introduced into clinical trials in Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD). However, there is limited information about the relationship between various scores on the RBANS and amyloid deposition in these older adults. **Objective:** Use scores on the RBANS to predict amyloid deposition in those classified as cognitively intact, Mild Cognitive Impairment (MCI), and mild AD. **Methods:** One hundred twenty-one older adult participants (54 intact, 35 MCI, 32 AD) completed the RBANS and an F18-Flutemetamol PET scan. A software program generated a composite standardized uptake value ratio (SUVR) normalized to the pons. Three stepwise multiple regressions were calculated, with the composite SUVR as the dependent variable and demographic variables (age, education, sex) and RBANS scores as the predictor variables. In these three regression models, the RBANS scores were: 1) Total Scale score, 2) five Index scores, and 3) four subtests of the Delayed Memory Index (DMI). **Results:** In the first model, the RBANS Total Scale score significantly predicted the SUVR ($F[1,119]=59.9$, $p<0.001$, $R2=0.34$), In the second model, the RBANS DMI significantly predicted the SUVR ($F[1,119]=94.8$, $p<0.001$, $R2=0.44$). In the final model, only the Story Recall subtest significantly predicted the SUVR ($F[1,119]=100.1$, $p<0.001$, $R2=0.46$). In all three models, demographic variables did not significantly add to the prediction of SUVR. With these models, one can predict an SUVR based on the relevant RBANS scores. For example, a predicted SUVR can be obtained via: 1.098 – (Total Scale*0.005); 1.001 – (DMI*0.004); 0.823 – (Story Recall*0.028). When these prediction equations were applied back to the original sample, they yielded predicted scores that were within -0.01 to 0.02 SUVR points of the observed SUVR (e.g., predicted and observed SUVRs significantly correlated at $ps<0.001$; paired t-tests were non-significant with $ps>0.05$). **Conclusion:** Although these predicted SUVRs from the RBANS need to be validated in external samples, the current work supports a proof of concept. These results suggest that neuropsychological tests, like the RBANS, can be used as initial screening instruments to estimate amyloid deposition in those being considered for clinical trials in MCI and AD. These findings, if validated, could have tremendous cost and time savings for these studies and reduce burden of patients, their families, and site personnel. There are no conflicts of interest related to this abstract.

P53- DETECTION OF PRE-CLINICAL ALZHEIMER'S DISEASE WITH SIMULTANEOUS MODELING OF UNDERLYING COGNITIVE PROCESSES IN RECALL AND RECOGNITION TESTS. Jason Bock[1], Michael Lee[2], William Shankle[1, 2, 3], Junko Hara[1, 3], Dennis Fortier[1], Tushar Mangrola[1] *(1. Embic - Newport Beach (United States), 2. Dept. Of Cognitive Sciences, University Of California At Irvine - Irvine (United States), 3. Pickup Family Neuroscience Institute, Hoag Memorial Hospital - Newport Beach (United States))*

Background: Wordlist memory (WLM) tests are commonly used to detect and monitor cognitive impairment due to Alzheimer's disease (AD). While traditional scoring methods and analyses of WLM tests (e.g., summary scores) are effective at identifying dementia, they are insufficient for detecting earlier stages of progressive decline, such as pre-clinical AD. This is partly due to the fact that summary scores of WLM test tasks (e.g., immediate and delayed free recall and delayed recognition tasks) do not contain sufficient information to make these more subtle distinctions in cognition. Our previous work demonstrated that using item response data from immediate and delayed free recall tasks, along with a hierarchical Bayesian cognitive processing (HBCP) model, enables greater information extraction from WLM tests, sufficient to characterize differences among subjects in varying stages of severity across the progression of AD. This was achieved by quantifying unobservable (latent) cognitive processes that underlie learning and recall, including encoding, storage, and retrieval of WLM test items. In further work, the HBCP model was applied to immediate and delayed free recall task data from Alzheimer's Disease Neuroimaging Initiative (ADNI) subjects who were cognitively normal at baseline, a subgroup of which would remain normal, and another which would progress to impairment during follow-up. Using only baseline assessment data, the model successfully characterized and demonstrated statistically significant differences between these two subgroups. **Objective:** To expand our HBCP model to incorporate delayed recognition task data in addition to immediate and delayed free recall data, and to identify meaningful differences or similarity in individual cognitive processes between healthy, normal subjects and pre-clinical AD subjects. **Methods:** Nine hundred fifteen (915) cognitive assessments, performed on 254 subjects from a community memory clinic between 2002 and 2019, were included in this study. All subjects were cognitively normal by clinical diagnosis, and were given the MCI Screen (MCIS), a battery of cognitive tasks, including multi-trial free recall of a wordlist (with three immediate and one delayed free recall tasks) and a delayed recognition task of the same wordlist (with the addition of foil words). Subjects were classified into two groups: a decliner group (subject n = 92; assessment n = 234), if the subject declined to amnestic mild cognitive impairment or dementia within 2 years; and a non-decliner group (subject n = 162, assessment n = 681), if the subject remained cognitively normal or only subjectively cognitively impaired for at least 2 years. The HBCP model was expanded to include signal detection theory (SDT) parameters, discriminability and criterion, for measurement of recognition task data. This was done in such a way that the existing cognitive processing parameters benefit from both the free recall and recognition task information. We examined cognitive processing parameter posterior samples to characterize patterns in cognitive performance, and we performed Bayes factor analyses of parameter mean differences between decliner and non-decliner groups. **Results:** Despite diagnosis as cognitively normal at time of assessment, numerous significant differences were identified between decliner and non-decliner groups. Subjects in the decliner group demonstrated significantly lower encoding parameters for WLM task items in both early- and late-list positions, with unique patterns across specific encoding parameters. However, moderate evidence for statistical similarity between decliner and non-decliner groups was found for the SDT parameters of criterion and discriminability. **Discussion:** This preliminary evaluation of a mathematical model expansion validates previous findings on the ability to detect pre-clinical AD with WLM test item response data, and the additional SDT parameters enable further characterization of cognitive processes. Lower encoding processes in the decliner group corroborates our previous findings, and similar levels in subject criterion and discriminability between groups aligns with existing literature pertaining to recognition task performance resilience to cognitive decline. Identifying specific cognitive processes which change before observable cognitive decline occurs, and differentiating them from processes that do not change until later in the progression timeline, is of great value in clinical and research trial settings, both for early detection of AD and ongoing monitoring of cognition during treatment.

P54- AN EXPLORATION OF MINIMAL CLINICALLY IMPORTANT DIFFERENCES FOR COGNITIVE OUTCOMES IN PRECLINICAL AND PRODROMAL STAGES – IMPLICATIONS FOR CLINICAL AD TRIALS. Emma Borland[1], Chris Edgar[2], Erik Stomrud[1], Nicholas Cullen[1], Oskar Hansson[1], Sebastian Palmqvist[1] *(1. Lund University - Lund (Sweden), 2. Cogstate - London (United Kingdom))*

Background: Identifying a clinically meaningful change in cognitive test score is essential when using cognition as an outcome in clinical trials. This is especially relevant as clinical trials increasingly feature novel composites of cognitive tests. We wished to explore estimates of minimal clinically important differences (MCID) for cognitive tests of relevance to clinical trials in preclinical and prodromal AD. **Objectives:** This study has two purposes: 1) to explore different estimates for minimal clinically important differences (MCID) for commonly used cognitive tests, using anchor and distribution-based approaches and 2) to investigate an optimal composite cognitive measure that best predicts a change in Clinical Dementia Rating Sum of Boxes (CDR-SB). **Methods:** We performed statistical analyses (descriptive statistics, ROC analyses, and logistic regression, using CDR-SB as an anchor) on two groups of people: 1) 451 cognitively unimpaired individuals, (90 people with subjective cognitive decline and 361 people without symptoms of cognitive decline) and 2) 292 people with mild cognitive impairment (MCI). We calculated MCID associated with a change of 0.5-1.0 on CDR-SB for MMSE, ADAS-cog delayed recall 10-word list, A Quick Test of Cognitive Speed (AQT) Color and Form, Stroop, Letter S Fluency, Animal Fluency, Symbol Digit Modalities Test and Trailmaking Test A and B. For investigating cognitive measures that predict a change in CDR-SB we conducted ROC-analyses and AUC-curves. **Results:** By investigating different anchor and distribution-based estimates we identified potential MCIDs for individuals with and without cognitive impairment on a range of cognitive test outcomes. AUC values were typically low to moderate for individual tests (range 0.54-0.75) for the prediction of change in CDR-SB. We found the best predicting composite cognitive measure for cognitively unimpaired individuals was a combination of ADAS-cog delayed recall 10-word list, MMSE and Trailmaking B, which produced an AUC of 0.79 (95% CI

0.73-0.86) for identifying a MCID (defined as a progression of CDR SB of ≥0.5) and for MCI AQT, MMSE and Stroop, with an AUC of 0.81 (CI 0.75-0.87) (CDR SB≥1). **Conclusion:** We have estimated MCIDs for outcome measures investigating cognitive decline, which may be applied in clinical practice or to identify treatment benefit in clinical trials of therapies for early AD, and we have explored predicting composite cognitive measures for progression of cognitive disease.

P55- EVALUATION RELATIONSHIPS BETWEEN SUBJECTIVE WELLBEING, PERSONALITY TRAITS, AND ALZHEIMER'S DISEASE: A TWO-SAMPLE MENDELIAN RANDOMIZATION STUDY. Ya-Hui Ma[1], Yu-Xiang Yang[2], Qiang Dong[2], Lan Tan[3], Jin-Tai Yu[2] *(1. Qingdao Municipal Hospital, College Of Clinical Medicine, Qingdao University - Qingdao (China), 2. Fudan University - Shanghai (China), 3. Qingdao Municipal Hospital, College Of Clinical Medicine, Qingdao University - Shanghai (China))*

Background: Observational studies have suggested that subjective wellbeing and personality traits link to the risk of Alzheimer's disease (AD). Crucially, the evidence for these relationships remains inconsistent because results may be biased due to differences in sample size, analytic models with specific covariates, population demography, and risk factors assessments. Besides, it is unclear if these associations are causal. **Objectives:** To investigate whether subjective wellbeing and personality traits causally affect the incidence of AD. **Methods:** We performed two-sample Mendelian randomization (MR) to assess potential causality. Genetic associations were obtained from the largest genome-wide association studies in Social Science Genetic Association Consortium (N = 298,420), Genetics of Personality Consortium (N = 81,036), and four independent consortia of AD (N = 455,258). Finally, 77 single nucleotide polymorphisms (SNPs) of subjective wellbeing, 33 SNPs of agreeableness, 31 SNPs of conscientiousness, 31 SNPs of openness, 73 SNPs of neuroticism, and 65 SNPs of extraversion were instruments of traits. The causal effects were estimated using the inverse variance weighted method (IVW) as principal MR analysis. For sensitivity analyses, the MR Egger method, weighted mode based estimation, and weighted median method were run to assess the robustness of the findings. A Bonferroni-corrected threshold of $p < 8.33 \times 10{-}3$ was considered significant, and p values between $8.33 \times 10{-}3$ and 0.05 were considered to be suggestive of an association. **Results:** The suggestive association with decreased risk of AD was noted for a genetically predicted 1-SD increase in subjective wellbeing (odds ratio = 0.963, 95% confidence interval = 0.930–0.997; p = 0.032) without substantial heterogeneity across the instrumental variables for this association (Q = 78.24, p > 0.05). Given possible causality between personalities and subjective wellbeing inferred by meta-analyses of observational evidence, the MR approach additionally evaluated causal effect estimates in two independent sample consortiums. Genetically predicted greater neuroticism was significantly associated with lower subjective wellbeing (β = −0.077; p = 0.004). However, no putative personality traits were significantly associated with AD risk after correction for multiple tests, including agreeableness (β = −0.0010; p = 0.477), conscientiousness (β = 0.0018; p = 0.270), openness (β = 0.0004; p = 0.738), neuroticism (β = −0.0098; p = 0.262), or extraversion (β = 0.0120; p = 0.262). **Conclusion:** Subjective wellbeing may independently reduce the risk of AD. Residual confounding is likely to be responsible for the previous observational relationships between personality traits and AD.

P56- SERUM URIC ACID MAY AGGRAVATE ALZHEIMER'S DISEASE RISK BY AFFECTING AMYLOIDOSIS IN COGNITIVELY INTACT OLDER ADULTS: THE CABLE STUDY. Lin-Lin Li[1], Ya-Hui Ma[2], Jin-Tai Yu[3] *(1. Dalian Medical University - Dalian (China), 2. Qingdao Municipal Hospital, College Of Clinical Medicine, Qingdao University - Qingdao (China), 3. Fudan University - Shanghai (China))*

Background: Serum uric acid (SUA) affects the reaction of oxidative stress and free radicals in the neurodegenerative processes. However, whether SUA impacts Alzheimer's disease (AD) pathology remains unclear. **Objectives:** To investigate whether the changes of SUA levels linked with the preclinical AD and influenced CSF indicators of AD pathology. **Methods:** We analyzed cognitively intact participants (n=839, age 62.16 years) who received SUA and CSF biomarkers (β-amyloid [Aβ], total tau [t-Tau], and phosphorylated tau [p-Tau]) measurements from the Chinese Alzheimer's Biomarker and LifestylE (CABLE) database using multivariable-adjusted linear models. **Results:** Levels of SUA in the preclinical AD elevated compared with the healthy controls (p=0.007) and subjects with amyloid pathology had higher concentration of SUA than controls (p=0.017). Roughly, equivalent levels of SUA displayed among cognitively intact individuals with or without tau pathology and neurodegeneration. CSF Aβ1-42 (p = 0.019) and Aβ1-42/Aβ1-40 (p = 0.027) were decreased and CSF p-Tau/Aβ1-42 (p = 0.009) and t-Tau/Aβ1-42 (p = 0.043) were increased with the highest (≥ 75th percentile) SUA when compared to lowest SUA, implying a high burden of cerebral amyloidosis in individuals with high SUA. Sensitivity analyses using the usual threshold to define hyperuricemia and precluding drug effects yielded robust associations. Besides, heavier amyloidosis, reflected by CSF indicators, were observed in APOE-ε4 non-carriers with high SUA but not in APOE-ε4 carriers. Nevertheless, the quadratic model did not show any U-shaped relationships between them. **Conclusion:** SUA may aggravate brain amyloid deposition in preclinical AD and produce severe AD pathological changes for the low-risk population (i.e., APOE-ε4 non-carriers), which corroborated the detrimental role of SUA.

P57- THE AMSTERDAM INSTRUMENTAL ACTIVITIES OF DAILY LIVING QUESTIONNAIRE: VALIDATION OF A CLINICALLY MEANINGFUL OUTCOME MEASURE IN ASYMPTOMATIC AND EARLY SYMPTOMATIC ALZHEIMER'S DISEASE. Mark Dubbelman[1], Merel Postema[1], Philip Scheltens[1], Wiesje Van Der Flier[1,2], Sietske Sikkes[1,3] *(1. Alzheimer Center Amsterdam, Department Of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam Umc - Amsterdam (Netherlands), 2. Department of Epidemiology and Biostatistics, Amsterdam UMC - Amsterdam (Netherlands), 3. Department of Clinical, Neuro- & Developmental Psychology, Vrije Universiteit Amsterdam - Amsterdam (Netherlands)*

Background: People in the early stages of Alzheimer's disease (AD) are most likely to benefit from disease-modifying medication trials, hence there is an urgent need for clinical outcome measures that are sensitive to detect subtle changes in cognition and function in these early stages. According to the National Institute on Aging–Alzheimer's Association (NIA-AA) research framework, cognitively healthy individuals with amyloid pathology are in clinical stage 1 of the AD continuum, and cognitively healthy individuals with accompanying subjective cognitive decline (SCD) in stage 2. The clinical staging

scheme ends at stage 6 (advanced AD dementia), with each stage being characterized by increasingly severe cognitive and functional impairment. The Amsterdam Instrumental Activities of Daily Living Questionnaire (A-IADL-Q) was developed to detect functional changes in the context of early dementia and was previously extensively internationally validated. The short version contains 30 cognitively complex everyday activities rated by a study partner on a five-point scale. Total scores are calculated using item response theory, and range from approximately 20 to 75, with higher scores representing better functioning. More information about this instrument's quality as an outcome measure in the early stages of AD is necessary. **Objectives:** To validate the A-IADL-Q in a sample of biomarker-confirmed AD patients in the NIA-AA clinical stages 1 and 2, by investigating three different aspects of validity: factor structure, construct validity, and sensitivity to change over time. Based on prior studies, we expect a single factor structure, low correlations with sociodemographic characteristics, and moderate correlations with cognitive screening measures, thus demonstrating a good construct validity. With regards to sensitivity to change, we expect a decrease in both stage 1 and stage 2 individuals. **Methods:** In this international multicenter study, we combined data from multiple studies aimed at understanding the early stages of AD, including the population-based European Prevention of Alzheimer's Disease Longitudinal Cohort Study and the memory clinic-based Amsterdam Dementia Cohort. From these studies, we selected stage 1 and 2 AD individuals, based on the presence of amyloid pathology (as measured in cerebrospinal fluid or using positron emission tomography), subjective cognitive decline, and cognitive performance. Confirmatory factor analysis with a one-factor structure was performed to test the factor structure of A-IADL-Q. Then, we correlated A-IADL-Q scores with demographic characteristics (age, sex, education years) and cognitive screeners, including Mini-Mental State Examination (MMSE) and Clinical Dementia Rating Sum of Boxes (CDR-SB), and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), using Pearson's r correlation coefficient. Last, we used linear mixed effects random intercept models to investigate the sensitivity of the A-IADL-Q to change over time in everyday functioning. **Results:** We included 799 individuals (67.2±7.8 years old, 49% female, median 15 years of education). At baseline, stage 2 individuals (N = 372, A-IADL-Q total score: 62.0±9.0) scored significantly lower than those in stage 1 (N = 427, A-IADL-Q total score: 72.9±3.2, $p < .001$). Confirmatory factor analysis results supported the single-factor model, showing a good model fit ($\chi2(405) = 574.3$, $p < .001$; comparative fit index = .99). A-IADL-Q scores showed low correlations with sociodemographic characteristics (age: Pearson's r = -.17, 95% confidence interval (CI) = [-.23, -.10], sex: r = .10, 95%CI = [.03, .17], education years: r = .11, 95%CI = [.04, .19]). Additionally, scores were moderately correlated with cognitive screeners (MMSE: r = .35, 95%CI = [.28, .41], CDR: r = -.55, 95%CI = [-.60, -.49], RBANS r = .39, 95%CI = [.33, .46]). Score distributions showed a ceiling effect in the whole sample. Separate distributions for stages 1 and 2 revealed that the ceiling effect was more outspoken in stage 1, whereas scores were more normally distributed in stage 2. Regarding sensitivity to change over time, we observed no apparent change in IADL (yearly change B = -.12, SE = .12, p = .322) in the whole sample, after adjustment for age, sex, and education. Further analysis revealed that there was a subtle but significant decline in stage 2 (B = -.76, SE = .22, $p < .001$), whereas there was no change in stage 1 (B = .05, SE = .14, p = .735). **Conclusion:** These results suggest that the A-IADL-Q retains its proven quality when administered to stage 1 and 2 AD individuals specifically. Moreover, the A-IADL-Q seems to be sensitive to very subtle changes in IADL functioning in early symptomatic individuals and can thus be a useful instrument to monitor functional changes and evaluate potential treatment effects. Taken together, our findings advocate the use of the A-IADL-Q as a potentially valuable outcome measure in studies targeting early-stage AD.

P58- MONTHLY AT-HOME COMPUTERIZED COGNITIVE TESTING TO DETECT DIMINISHED PRACTICE EFFECTS IN PRECLINICAL ALZHEIMER'S DISEASE.

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Background: A major challenge for Alzheimer's disease (AD) secondary prevention trials is the long and subtle course of cognitive decline observed in individuals with preclinical AD. Computerized cognitive testing has the potential to capture cognitive change more rapidly, by enabling standardized administration and data analyses allowing for remote, unsupervised, and more frequent assessments. Furthermore, the higher frequency assessments afforded through use of computerized tests enable the study of practice effects (PE) that can occur with repeated assessments in older adults, and which previously has been shown to provide a meaningful cognitive marker in preclinical AD (1, 2). **Objectives:** We aimed to investigate whether changes in performance over three months assessments using a computerized cognitive composite (C3) could aid in the detection of early AD-related cognitive changes in cognitively unimpaired (CU) individuals. We first investigated whether PE on computerized testing were observed over 3 months. Next, we determined whether diminished PE were associated with AD biomarkers and/or change on the Preclinical Alzheimer's Cognitive Composite (PACC) over one year. We then examined whether diminished PE over 3 months could identify individuals who would show more than 0.10 standard deviation (SD) decline on the PACC (3). **Methods:** N=117 CU individuals (age=77.1±4.9, 61% female, MMSE 29±1.3) from the Harvard Aging Brain Study (HABS) completed the self-administered C3 monthly, at-home on an iPad, over 3 months. C3 includes two well-validated episodic memory tests: the Face Name Associative Memory Exam (FNAME) and the Behavioral Pattern Separation Task-Object version (BPSO), and the Cogstate Brief Battery including the One Card Learning Task (OCL) (4). The BPSO, FNAME and OCL scores can be combined into a primary C3 memory outcome (5). At the start of the at-home study, participants underwent standard in-clinic PACC testing, and a subsample (n=75, age=78.1±5.2, 59% female, MMSE 29±1.3) also had one year follow-up in-clinic PACC testing available. Most participants had PIB-PET imaging (n=116, 1.25±1.05 years

within at-home baseline) and Flortaucipir PET (n=109, 0.56±0.4 years within at-home baseline) available. Linear mixed models (LMM) were used to investigate C3 performance over 3 months adjusting for age, sex, and years of education. Based on those LMM, individual covariate-adjusted slopes were extracted for the C3 memory composite. Correlations were used to investigate the association between monthly C3 slopes and 1) global amyloid burden (DVR) and tau deposition in the entorhinal and inferior-temporal cortex (SUVr, partial-volume corrected), as well as 2) change on the PACC (adjusted for age, sex, and education) after one year. Receiver Operating Curve (ROC) analyses were conducted to examine how accurately monthly C3 slopes could identify individuals who would show more than 0.10 SD decline on the PACC over one year. Results: Overall, individuals' performance on the C3 primary memory outcome improved over 3 months (β=0.65, 95% CI [0.56-0.75], p<.001). However, less improvement over 3 months was associated with more global amyloid burden (r =-.21 95%CI= [-.38 – -.04], p=.02) and tau deposition in the entorhinal (r =-.35 95%CI= [-0.54 – -0.12], p<.001) and inferior-temporal cortex (r =-.20, 95%CI= [.38-.02], p=.04). Additionally, less improvement on the C3 over 3 months was associated with decline on the PACC5 over one year (r =.63, 95%CI= [.47 - .75], p<.001). ROC analyses showed good discriminative ability for 3-month C3 slopes to identify PACC decline over one year (optimal cut-off C3 slope: 0.7, area under the curve (AUC)= 87.8%, 95%CI= [79.9% - 95.9%]), which was found to perform better than baseline C3 performance (AUC=72.3%, p=.003) and baseline PACC performance (AUC=73.3%, p=.01). **Conclusion:** While PE commonly occur in CU adults, we showed that diminished PE over monthly repeated testing are associated with AD biomarkers and future cognitive decline. Our findings imply that unsupervised computerized testing using monthly retest paradigms may provide an examination of lack of practice as a more nuanced way of exploring cognitive change. This could aid in more rapid detection of individuals at risk for cognitive decline due to AD, which has important implications for clinical trial design and recruitment strategies. **References:** 1. Samaroo et al. Diminished Learning Over Repeated Exposures (LORE) in preclinical Alzheimer's disease. Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring 12, (2020); 2. Hassenstab et al. Absence of practice effects in preclinical Alzheimer's disease. Neuropsychology 29, 940–948 (2015); 3. Petersen et al. Association of Elevated Amyloid Levels With Cognition and Biomarkers in Cognitively Normal People From the Community. JAMA Neurology 73, 85–92 (2016); 4. Rentz et al. The Feasibility of At-Home iPad Cognitive Testing For Use in Clinical Trials. The journal of prevention of Alzheimer's disease 3, 8–12 (2016); 5. Papp et al. The computerized cognitive composite (c3) in a4, an alzheimer's disease secondary prevention trial. The journal of prevention of Alzheimer's disease 8, 59–67 (2021).

P59- USE OF APP-BASED COGNITIVE ASSESSMENTS DURING THE COVID-19 PANDEMIC: ADHERENCE AND ACCEPTABILITY AMONG COGNITIVELY NORMAL OLDER ADULTS. Louisa Thompson[1], Karra Harrington[2], Nelson Roque[3], Jennifer Strenger[1], Stephen Correia[1], Richard Jones[1], Stephen Salloway[1], Martin Sliwinski[2] *(1. Brown University Medical School - Providence (United States), 2. Penn State University - University Park (United States), 3. University Of Central Florida - Orlando (United States))*

Background: The early detection of cognitive impairment is one of the most important current challenges in Alzheimer's disease (AD) research as reflected in the National Plan to Address Alzheimer's Disease. Digital cognitive assessment measures could help meet this demand. The COVID-19 pandemic has highlighted potential advantages of remote methods of cognitive assessment. App-based cognitive tests that can be deployed remotely on mobile devices are rapidly becoming more feasible and acceptable. The use of brief, short-term repeated assessment sessions via smartphone app has thus far demonstrated similar or better reliability and validity compared to standard in-clinic assessments in adult samples. **Objective:** The present study examined adherence and acceptability for a remote app-based cognitive screening protocol in healthy older adults with and without AD risk biomarkers. **Methods:** Participants were 52 cognitively unimpaired adults aged 61-80 years (71% female, 86% White) recruited for an ongoing pilot study. We recruited from the Butler Hospital Alzheimer's Prevention Registry (BAPR), an online database of older adults who are interested in participating in AD research at our Memory and Aging Program (MAP). A portion of BAPR registrants had previously disclosed and recorded biomarker data. Available amyloid PET imaging status (n = 36) and apolipoprotein E (APOE) genotyping results (n = 44) were pulled for these analyses. Screening was conducted by telephone and online survey. A modified Telephone Interview for Cognitive Status (TICSm) cutoff score of ≥34 was used to establish unimpaired cognition. Participants completed 8 consecutive days of digital cognitive tasks using Mobile Monitoring of Cognitive Change (M2C2), a mobile app-based testing platform developed as part of the National Institute of Aging's Mobile Toolbox initiative. Brief (i.e., 3-4 minute) M2C2 sessions were assigned daily within morning, mid-day, and evening time windows. The first day was treated as a practice day. Extra sessions (optional/make up) could be completed on day 9. The tasks included measures of visual working memory, processing speed, and episodic memory with prior theoretical and empirical support. **Results:** Participants completed an average of 93% (SD = 10.2) of the 24 assigned sessions within 8-9 days. While only 44% of participants completed all 24 sessions, the majority (46/52) completed at least 20 of the 24 assigned testing sessions (83% adherence rate). There were no significant differences in adherence on the basis of age, education, sex, or race/ethnicity. There was a significant effect of session time on adherence between the morning and afternoon sessions, $F(1, 51) = 9.15$, $p = .004$. There were no significant differences in adherence on the basis of APOE e4 carrier status. Individuals with Aß (-) status completed significantly fewer morning sessions, on average, relative to the rest of the sample, $F(2, 49) = 3.7$, $p = .03$. Post hoc comparisons indicated that the mean percentage of morning sessions completed for the Aß (-) participants (n = 23; M = 90.8, SD = 15.6) was significantly lower than the mean percentage for the those without Aß PET data (n = 16; M = 100, SD = 0), but not from those with Aß (+) positive status (n = 13; M = 97.8, SD = 97.1). In an exit survey, 65% of participants reported that they were definitely open to completing the sessions again, while only 4% said that they definitely were not. Interestingly, 80% of participants reported that they would at least somewhat consider using this app as part of an annual cognitive screening for their primary care doctor. About 80% reported that they would like to know how they performed on the tasks. About 17% reported some degree of difficulty motivating themselves to complete the sessions. Most participants (89%) reported that it was very easy to use the app and navigate the digital interface on their own. On average, participants ranked the episodic memory task as the most challenging task and also as

their least favorite. **Conclusions:** Adherence to this 8-day, fully remote, app-based cognitive assessment protocol was very good, with an average session completion rate of 93 percent. Adherence was lower for afternoon sessions relative to morning and evening sessions. Afternoon schedules and routines may be more variable relative to the morning and evening, making it harder to remember sessions or increasing the chance of a time conflict. Participants with previously disclosed negative cerebral amyloid status had lower adherence for the morning sessions relative the rest of the sample. This was not due to any discernable differences in motivation or engagement assessed in the exit survey. The protocol was largely well-tolerated by participants based on exit survey data, with a majority reporting that they would consider completing the again as part of their own clinical care. Overall, our results so far support the feasibility of remote mobile-based cognitive testing. Limitations include restricted generalizability due to this being a largely white, college educated, and motivated sample (self-selected for AD research).

P60- METABOLICALLY HEALTHY OBESITY AND LIPIDS MAY BE PROTECTIVE FACTORS FOR PATHOLOGICAL CHANGES OF ALZHEIMER'S DISEASE IN COGNITIVELY NORMAL ADULTS. Shu-Juan Huang[1], Ya-Hui Ma[1], Lan Tan[1], Jin-Tai Yu[2] *(1. Qingdao Municipal Hospital, Qingdao University - Qingdao (China), 2. Fudan University - Shanghai (China))*

Background: The associations between obesity and Alzheimer's disease (AD) at different ages have been debated. Recent evidence implied the protective effects of metabolically healthy obesity on AD. **Objectives:** To exam whether obesity and lipids could mitigate the detrimental impacts of AD pathological changes among metabolically healthy individuals in late life. **Methods:** A total of 604 metabolically healthy participants with normal cognition were included from the Chinese Alzheimer's Biomarker and LifestylE (CABLE) database. Multiple linear regression models were used to test the associations of body mass index (BMI) or lipids with cerebrospinal fluid (CSF) biomarkers after adjustment for age, gender, education, and Apolipoprotein E-ε4 (APOE-ε4). **Results:** The results showed the lower CSF levels of total tau protein (t-tau: $p = .0048$) and phosphorylated tau protein (p-tau: $p = .0035$) in obese participants than in non-obese participants, even after correcting for covariates. Moreover, in late life, higher BMI was associated with decreased CSF t-tau (β: -0.15, $p = .0145$) and p-tau (β: -0.17, $p = .0052$). As for lipids, higher levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) were associated with decreased CSF t-tau (TC: β: -0.16, $p = .0115$; LDL-C: β: -0.16, $p = .0082$) and p-tau (TC: β: -0.15, $p = .0177$; LDL-C: β: -0.14, $p = .0225$) in obese participants. Furthermore, these associations were only significant in participants with late-life obesity and APOE-ε4 non-carriers. **Conclusion:** In a cognitively normal population, we found metabolically healthy obesity and lipids in late life might be protective factors for neurodegenerative changes

LP19- BOSTON COGNITIVE ASSESSMENT (BOCA) — A COMPREHENSIVE SELF-ADMINISTERED SMARTPHONE- AND COMPUTER-BASED AT-HOME TEST FOR LONGITUDINAL TRACKING OF COGNITIVE PERFORMANCE. Andrey Vyshedskiy *(Pinteon Therapeutics - Newton Centre (United States))*

Background: Longitudinal cognitive testing is essential for developing novel preventive interventions for dementia and Alzheimer's disease; however, the few available tools have significant practice effect and depend on an external evaluator. We developed a self-administered 10-minute at-home test intended for longitudinal cognitive monitoring, Boston Cognitive Assessment or BOCA. **Objectives:** The goal of this project was to validate BOCA. **Methods:** The BOCA test uses randomly selected non-repeating tasks to minimize practice effects. BOCA evaluates eight cognitive domains: 1) Memory/Immediate Recall, 2) Language Comprehension/Prefrontal Synthesis, 3) Visuospatial Reasoning / Mental rotation, 4) Executive function / Clock Test, 5) Attention, 6) Mental math, 7) Orientation, and 8) Memory/Delayed Recall. BOCA was administered to patients with cognitive impairment ($n = 50$) and age- and education-matched controls ($n = 50$). **Results:** Test scores were significantly different between patients and controls ($p < 0.001$) suggesting good discriminative ability. The Cronbach's alpha was 0.87 implying good internal consistency. BOCA demonstrated strong correlation with Montreal Cognitive Assessment (MOCA) ($R = 0.90$, $p < 0.001$). The study revealed strong ($R = 0.94$, $p < 0.001$) test-retest reliability of the total BOCA score one week after participants' initial administration. The practice effect tested by daily BOCA administration over 10 days was insignificant ($\beta = 0.03$, $p = 0.74$). **Conclusion:** The BOCA test has the potential to reduce the cost and improve the quality of longitudinal cognitive tracking essential for testing novel interventions designed to reduce or reverse cognitive aging. BOCA is available online gratis at www.bocatest.org.

LP20- DAILY BOSTON REMOTE ASSESSMENT FOR NEUROCOGNITIVE HEALTH (BRANCH): GENERATING SHORT-TERM LEARNING CURVES FROM FULLY REMOTE, WEB-BASED MEMORY ASSESSMENTS. Daniel Soberanes[1], Stephanie Hsieh[2], Olivia Schneider[1], Rachel Buckley[3], Michael Properzi[2], Emma Weizenbaum[2], Dorene Rentz[3], Keith Johnson[3], Reisa Sperling[3], Rebecca Amariglio[3], Kathryn Papp[3] *(1. Brigham And Women's Hospital - Boston (United States), 2. Massachusetts General Hospital - Boston (United States), 3. Harvard Medical School - Boston (United States))*

Background: Repeated cognitive assessments over short periods of time can help capture multiple levels of information about an individual's memory performance, including their short-term learning curve (STLC). Previously, this type of assessment presented logistical difficulties, but digital assessments completed on a participant's own device remotely offer a unique opportunity to capture high frequency data. As the need for detection of subtle, early cognitive changes in the preclinical stages of Alzheimer's disease (AD) becomes more prevalent, developing digital assessments that can track an individual's performance over days to generate STLCs becomes increasingly useful. **Objectives:** Our aim was to determine the feasibility and validity of examining STLCs generated from the daily version of the Boston Remote Assessment for Neurocognitive Health (BRANCH), a web-based assessment previously validated at a single timepoint (Papp et al., in press). **Methods:** To determine the feasibility of older adults completing 7 daily BRANCH assessments, we examined the completion rates for the daily assessments and tracked adherence to a scheduling window. To determine the validity of the assessments, we explored associations between Day 1 performance and STLCs (change in performance from Day 1 to Day 7), and in-clinic paper and pencil testing and demographics (e.g., age). 101 clinically normal individuals

(mean age=73.9; 61.4% female; 89.1% Caucasian) were assigned the 7-day series of daily BRANCH, to be completed at home on their own smartphones/devices. Prior to engaging in the tasks, participants attested that they would not use any kind of aid to boost their performance. If a participant were to miss a day of the series, they would continue with the missed test the following day until completing the entire series. Each day's assignment consisted of two paired associate learning tasks with the identical version administered daily: a modified Face-Name Associative Memory Exam (FNAME), and a groceries and prices task. Mixed-effects models and correlations were used to observe the associations between Day 1 performance, STLCs and age, and performance on the Preclinical Alzheimer's Cognitive Composite (PACC), a composite of standardized neuropsychological measures administered in clinic. **Results:** A total of 100 out of the 101 individuals completed the full series of tests without difficulties. 74% of the participants completed the series perfectly within the scheduled original 7-day timeframe, and 93% of the participants completed it within 2 extra days. Participants exhibited STLCs (i.e., improved performance) on each task: more specifically, they improved by 0.065 z-score per day on FNAME (95% CI [0.0615, 0.0691]) and 0.03 z-score per day on groceries-prices (95% CI [0.0277, 0.0326]). Correlations between Day 1 performance and STLCS were r=0.73 (p<0.001) for FNAME and r=0.59 (p<0.001) for groceries, suggesting that Day 1 performance only explained 53% of the variance in STLC for FNAME and 35% of the variance in STLC for groceries-prices. Better Day 1 performance on both BRANCH tasks was associated with better PACC performance and with younger age for FNAME only. STLCs were not associated with PACC performance on either BRANCH task. However, a better STLC was associated with younger age for groceries-prices. **Conclusions:** Remote daily memory assessments completed on individuals' own devices are feasible for older populations when using automated notifications to ensure timely completion. The significant associations between Day 1 BRANCH performance and PACC suggest that remote, memory assessments capture valid information regarding cognition. Further work is needed to examine the unique cognitive information captured by STLCs, particularly in relation to AD biomarkers. Fully remote repeated memory assessments that can generate STLCs are a valid and promising way of evaluating and detecting subtle early changes in cognition in preclinical AD.

LP21- AMYLOID PATHOLOGY BUT NOT APOE4 STATUS IS PERMISSIVE FOR TAU-RELATED HIPPOCAMPAL DYSFUNCTION. Emrah Duzel[1], Gabriel Ziegler[1], Hartmut Schutze[1], David Berron[1], Anne Maass[1], Glanz Wenzel[1], Michael Buryn[1], Martin Reuter[2], Annika Spottke[2], Anja Schneider[2], Frederic Brosseron[2], Michael Heneka[2], Christoph Laske[3], Oliver Peters[4], Josef Priller[4], Stefan Teipel[5], Ingo Kiliman[5], Jens Wiltfang[6], Michael Wagner[2], Frank Jessen[7] *(1. Dzne, Magdeburg - Magdeburg (Germany), 2. Dzne, Bonn - Bonn (Germany), 3. Dzne, Tübingen - Tübingen (Germany), 4. Dzne, Berlin - Berlin (Germany), 5. Dzne, Rostock - Rostock (Germany), 6. Dzne, Göttingen - Göttingen (Germany), 7. Dzne, Bonn/cologne - Cologne (Germany))*

We investigated whether the impact of tau-pathology on memory performance and on hippocampal/medial temporal memory function in non-demented individuals depends on the presence of amyloid pathology, irrespective of diagnostic clinical stage. We conducted a cross-sectional analysis of the observational, multi-centric DZNE-Longitudinal Cognitive Impairment and Dementia Study (DELCODE) study. 235 participants completed task fMRI and provided cerebrospinal fluid (CSF) (92 cognitively unimpaired, 100 experiencing subjective cognitive decline and 43 with mild cognitive impairment). Presence (A+) and absence (A-) of amyloid pathology was defined by CSF Aβ42 levels. Free recall performance in the Free and Cued Selective Reminding Test (FCSRT), scene recognition memory accuracy and hippocampal/medial temporal fMRI novelty responses to scene images were related to CSF total-tau and phospho-tau181 levels separately for A+ and A- individuals. We found that total-tau and phospho-tau levels were negatively associated with memory performance in both tasks and with novelty responses in the hippocampus and amygdala, in interaction with Aβ42 levels. Subgroup analyses showed that these relationships were only present in A+ and remained stable when very high levels of tau (>700 pg/ml) and phospho-tau (>100 pg/ml) were excluded. These relationships were significant with diagnosis, age, education, sex, assessment site and Aβ42 levels as covariates. They also remained significant after propensity score based matching of phospho-tau levels across A+ and A- groups. After classifying this matched sample for phospho-tau pathology (T-/T+), individuals with A+/T+ were significantly more memory impaired and showed significantly reduced hippocampal/medial temporal novelty responses than A-/T+ despite the fact that both groups had the same amount of phospho-tau pathology. ApoE status (presence of the E4 allele), a known genetic risk factor for Alzheimer's disease, did not mediate the relationship between tau pathology and hippocampal function and memory performance. Thus, our data show that the presence of amyloid-pathology is associated with a linear relationship between tau pathology, hippocampal dysfunction and memory impairment although the actual severity of amyloid-pathology is uncorrelated. Our data therefore indicate that the presence of amyloid pathology provides a permissive state for tau-related hippocampal dysfunction and hippocampus-dependent recognition and recall impairment. They raise the possibility that in the predementia stage of Alzheimer's disease, removing the negative impact of amyloid-pathology could improve memory and hippocampal function even if the amount of tau-pathology in CSF is not changed, whereas reducing increased CSF tau-pathology in amyloid-negative individuals may not proportionally improve memory function.

RP20- ASSOCIATION BETWEEN A COMPUTERISED, SELF ADMINISTERED COGNITIVE ASSESSMENT AND FLUID BIOMARKERS OF NEURODEGENERATION. Mina Aghaei[1], Mohammad Hadi Modarres[2], Zahra Vahabi[3,4], Chris Kalafatis[5,6,7], Haniye Marefat[8], Mahdie Khanbagi[1], Hamed Karimi[1,9], Seyed-Mahdi Khaligh-Razavi[1,2] *(1. Royan Institute For Stem Cell Biology And Technology, Acecr - Tehran (Iran, Islamic Republic of), 2. Cognetivity Ltd - London (United Kingdom), 3. Department Of Geriatric Medicine, Ziaeian Hospital, Tehran University Of Medical Sciences - Tehran (Iran, Islamic Republic of), 4. Memory and Behavioral Neurology Division, Roozbeh Hospital, Tehran University of Medical Sciences - Tehran (Iran, Islamic Republic of), 5. South London & Maudsley Nhs Foundation Trust - London (United Kingdom), 6. Department of Old Age Psychiatry, King's College London - London (United Kingdom), 7. Cognetivity ltd - London (United Kingdom), 8. School Of Cognitive Sciences, Institute For Research In Fundamental Sciences (ipm) - Tehran (Iran, Islamic Republic of), 9. Department Of Mathematics And Computer Science, Amirkabir University Of Technology - Tehran (Iran, Islamic Republic of))*

Background: Biomarkers such as amyloid β (Aβ), and tau play a vital role in informing the diagnosis and clinical management of Alzheimer's Disease (AD). Accurate assessment of patients' Aβ, and tau levels requires positron emission tomography (PET) or cerebrospinal fluid (CSF) sampling. However, these methods are time-consuming, expensive, invasive, and lack scalability, making them unsuitable for large-scale population-wide screening. Recently blood-based biomarkers of AD, such as 42 and 40 amino acid-long amyloid β and their ratio, as well as phosphorylated tau (P-tau181), have been of great interest. However, in light of disease-modifying therapies becoming available for AD, the provision of a scalable digital tool to streamline the process of identifying candidates with specific neurodegenerative disorders is promising and beneficial. We developed the Integrated Cognitive Assessment (ICA), a 5-minute self-administered computerised cognitive assessment tool based on a rapid categorisation task. ICA presents a series of rapidly changing images on a mobile device to measure cognitive impairment via a person's accuracy and response time in categorising those images. **Objectives:** The aim of this study was to investigate the relationship between the ICA as a digital biomarker of cognition and blood biomarkers associated with AD. **Methods:** This study was performed on three groups of healthy controls (HC), people with mild cognitive impairment (MCI) and people in the early stages of AD (Mild-AD). Plasma samples were analyzed using sandwich Elisa assays from 22 HC, 23 MCI, and 15 Mild-AD participants. The ICA test was conducted for all participants. **Results:** We found significant correlations between the ICA and the fluid biomarkers: phosphorylated-tau181 (Pearson r= -0.33, p-value= 0.010), Aβ-42 (Pearson r = -0.34, p-value= 0.010), Aβ-40 (Pearson r = -0.52, p-value=2.02e-05), and Aβ ratio(Aβ-42/Aβ40) (Pearson r = 0.21, p-value=0.010). Furthermore, we used a combination of ICA, demographic data and APOE4 to predict the level of biomarker in serum using linear regression models which were tested by cross-validation. As an example, the model achieved a coefficient of determination of 0.2 in predicting the level of the Aβ-40 biomarker (F-statistic of 2.64, $p<0.05$). **Conclusion:** A digital cognitive biomarker such as the ICA has the potential to be used for screening of a wide population of at-risk individuals, rapidly identifying those for whom additional testing would be beneficial. It can further be used to monitor disease progression and treatment efficacy, both in clinical care and the earlier process of drug development.

RP21- THE DEVELOPMENT OF OBSRVR: AN OBSERVATIONAL INSTRUMENT TO MEASURE REACTIONS OF PEOPLE WITH DEMENTIA EXPERIENCING VIRTUAL REALITY. Lora Appel[1], Erika Kisonas[2], Eva Appel[2] *(1. York University - Toronto (Canada), 2. University Health Network - Toronto (Canada))*

Background: Virtual reality (VR) technologies have increasingly been considered as valuable tools in dementia-related research, assessment, and care. More recently it has been suggested that VR could serve as a non-pharmacological therapy to improve the quality of life (QoL) and wellbeing for people with dementia (PwD). VR is a computer-simulated environment which enables users to experience the sensation of being present in a different physical space by stimulating multiple senses (e.g., sight, sound) simultaneously. Most commercial VR systems consist of head-mounted-display (HMD) that covers the user's eyes and includes built-in sensors that update what an individual experiences in the artificial "virtual" environment to correspond with their orientation and physical movement in the real world. While the use of VR as an assessment tool (e.g., for measuring recall) or as a means to impact clinical outcomes (e.g., ability to conduct iADLs), can be evaluated with existing validated instruments that quantitatively measure corresponding outcomes (e.g. Lawton–Brody Scale), estimating the VR impact on the more subjective outcomes (like wellbeing, level of enjoyment, engagement), remain difficult to quantify for several reasons. PwD experience significant declines in communication abilities as their condition progresses, and with it, their ability to share opinions and feedback becomes impaired, making it difficult for researchers to determine PwD reactions to experiences. VR evaluation presents unique challenges when compared to other non-pharmacological interventions; for instance, in music-therapy, one can see the participant's entire face, and rely on gestures and observing their eyes. For VR-therapy the same is not easily achievable, with the HMD covering part of the face and, most importantly, the eyes of the person experiencing VR. As growing evidence mounts on the potential benefits of VR-therapy, along with more funding dedicated to evaluating this non-pharmacological therapy, there is a need to develop a psychometrically validated, observational measurement tool that provides a holistic image of the positive and negative reactions displayed by the PwD while experiencing VR. **Objective:** To design and prototype an observational instrument for researchers to measure the reactions of PwDs during VR-therapy sessions. **Methods:** The design was informed by expert opinion, results of a scoping review performed in 2021 examining VR as a means to promote wellbeing in people with dementia, and in consultation with individuals with lived experience. The first iteration of the instrument was field-tested by researchers and clinicians in three different studies across several settings, including hospitals, long-term care, rehabilitation facilities, and out-patient clinics. Feedback from stakeholders was incorporated and a refined measurement was generated. **Results:** Of the 18 articles that met the scoping review inclusion criteria, only the Observed Emotion Rating Scale (OERS), was used more than once (in four studies). We also identified the Music in Dementia Assessment Scale (MiDAS) as a relevant tool, given it captures observable engagement in PwD, "who may have limited verbal skills to directly communicate their experiences". These two scales were compared and contrasted, identifying common elements: alertness/interest, enjoyment/pleasure and anger/aggression, and unique elements: MiDAS captured

reminiscence and relaxation, OERS had more detailed focus on sadness, anger, and anxiety/fear. The two measures differed in their rating methods (MiDAS uses 100-point visual analog scale while OERS uses 6-point Likert frequency scale), and administration methods (such as observer(s) and timeframes). Based on the researchers' experiences conducting studies with PwD, the appropriate features were selected from each instrument and included into the initial version of ObsRVR, resulting in the refined measurement tool. This tool evaluates both potential positive and negative reactions to VR and places a distinct focus on reminiscence. Reminiscence VR-therapy is a frequently used intervention for PwD and their caregivers. The refined ObsRVR measure is suggested below: Three positive (engagement, enjoyment, relaxation) and three negative (apprehension/anxiety, aggression, sadness) reactions are rated on a four-point frequency scale: 0 indicating "never", 1 indicating "rarely", 2 indicating "sometimes", and 3 indicating "often". Ratings are to be selected by the observer considering frequency and severity of the reaction within the time frame of exposure to VR-therapy. Each reaction includes suggested physical and/or verbal signs which the observer can identify. For example, Engagement includes the description "reaching out for an object in VR"; Relaxation includes the description "grip loosening, sighing and/or slow breathing"; Apprehension/Anxiety includes the description "recoiling from their surroundings, expressed concerns for their safety"; Sadness includes the description '"crying, expressing longing or regret". Reminiscence is captured distinctly. Finally, each category has an open-ended field where the observer can record relevant notes. **Conclusion:** With input from a number of informed sources and our extensive expertise in research evaluating outcomes of VR-therapy for PwD, we demonstrate the robust development procedure for the prototype ObsRVR tool, a dementia-specific observational measurement. We expect this tool to be effective in evaluating similar technologies, such as augmented and mixed reality. As technology continues to progress, the tool will be expanded to incorporate other quantitative metrics, like eye-movement tracking (already available in some commercial HMDs) and bio-tracking.

RP22- PSYCHOMETRIC VALIDATION OF THE BRIEF AND SIMPLE INDEX OF COGNITION (BASIC) AND SENSITIVITY TO COGNITIVE IMPAIRMENT IN INDIVIDUALS LIVING WITH MCI AND ALZHEIMER'S DISEASE.

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Background: A variety of digital and 'paper-and-pencil' (P&P) measures are available for assessing cognitive change in individuals living with Alzheimer's disease (AD). The measurement of attention and episodic visual memory are both facilitated by digital technology. However, the assessment of executive function, episodic verbal memory and working memory can be readily achieved using P&P paradigms commonly employed in clinical psychology. A caveat to this latter statement is that exemplars of these paradigms are often employed in their standard clinical formats. In the case of verbal fluency measures this includes prohibitions against the mention of proper nouns, numbers, mythological and imaginary animals, etc. The retention of these rules adds to the length of test instructions and complicates test scoring. In the case of assessing episodic verbal memory, measures such as the Rey Auditory Verbal Learning Test (RAVLT) are commonly employed in their full clinical formats, which in the case of the RAVLT includes seven trials of immediate recall, the imposition of an interference list, and a 30-minute delay period between immediate and delayed recall. The impact of these test characteristics often yields floor performance at delayed recall in individuals living with AD. This is a helpful test characteristic when using tests to detect AD caseness. However, range restrictions are unhelpful when testing for treatment effects. In response to the need for a brief and easy to administer P&P assessment of cognition, an international group has developed the Brief and Simple Index of Cognition (BASIC). The primary intended purpose of BASIC is to detect treatment effects of experimental and established therapeutic interventions. In service of this ambition, we have constructed new versions of episodic memory, working memory and executive function paradigms that have all previously demonstrated assay sensitivity to pharmacological interventions employed in AD clinical trials. In this abstract we report details of the psychometric validation of BASIC in typical controls, as well as details of cognitive impairment sensitivity and AD caseness detection in confirmed cases of AD. **Methods**: For the psychometric validation N=30 typical control study participants were assessed on the entire BASIC assessment on two occasions separated by an average of two weeks. All study participants were assessed using BASIC in a fixed order on the following measures: 'Boxfiller' is a 1-minute version of the symbol matching paradigm. 'Alphabet' is a simplified version of the phonological verbal fluency paradigm. To facilitate the test's use in clinical trials we have reducedthe task to fluency for a single letter and simplified the scoring rules. 'Sequence' is an adaptation of the digit span paradigm. Study participants are read a string of numbers and required to order them in anascending sequence. 'Inventory' is an auditory verbal learning task in which study participants must repeat each of 12 words after they are spoken by the test administrator. The word list is presented twice and after each presentation recall for the 12 words is assessed. BASIC begins with the immediate recall element of this test and ends with the delayed recall component. 'Category' is a simplified version of a semantic fluency test. To facilitate use in clinical trials we have simplified the scoring rules to allow mythical and imaginary animals as correct responses. To assess the sensitivity to impairment and AD caseness detection, the BASIC assessment was administered to a cohort of individuals with confirmed dementia diagnoses, of which N=21 had a diagnosis of AD or MCI. **Results:** The mean age of the typical control cohort was 21.3 (SD=3.97) years, with 15 (SD=0.53) years of education. The cohort was comprised of 14 males and 16 females. Baseline performance yielded scores free of range restrictions with the following mean (SD) values: Inventory Trial 1 = 6.3 (1.62); Inventory Trial 2 = 8.2 (1.4); Alphabet = 11.8 (4.5); Boxfiller = 30.7 (6); Category = 22.9 (4.4); Sequence = 48.6 (3.1) and Inventory (delayed) 6.9 (1.8) Calculation of Test-Retest Reliability scores yielded values between 0.73 for the Category test to 0.96 for the Alphabet test. With respect to the AD/MCI cohort, the mean age was 72.2 (SD=7.0) years, with 13.9 (SD=2.9) years of education. The cohort contained 14 females and 7 males. As expected, Inventory Delayed Recall yielded poor performance with only one confirmed AD case recalling any words from the list and in the MCI cases between 2-4 words. Comparison of performance on this measure with the typical control cohort yielded sensitivity and specificity of 100% for the AD cohort. **Conclusions:** BASIC meets required

levels of psychometric integrity with respect to reliability and test composition meets content validity requirements specified by expert groups. Components of the assessment are sensitive and specific to AD and given past use of the paradigms are likely to demonstrate assay sensitivity. **Disclosures:** Dr. Harrison reports receipt of personal fees in the past 2 years from AlzeCure, Aptinyx, Astra Zeneca, Athira Therapeutics, Axon Neuroscience, Axovant, Bial Biotech, Biogen Idec, BlackThornRx, Boehringer Ingelheim, Brands2life, Cerecin, Cognition Therapeutics, Compass Pathways, Corlieve, Curasen, EIP Pharma, Eisai, FSV7, G4X Discovery, GfHEU, Heptares, Ki Elements, Lundbeck, Lysosome Therapeutics, MyCognition, Neurocentria, Neurocog, Neurodyn Inc, Neurotrack, the NHS, Novartis, Nutricia, Probiodrug, Prothena, Regeneron, ReMynd, Rodin Therapeutics, Samumed, Sanofi, Signant, Syndesi Therapeutics, Takeda, Vivoryon Therapeutics and Winterlight Labs. Additionally, he holds stock options in Neurotrack Inc. and is a joint holder of patents with MyCognition Ltd.

RP23- TAU PATHOLOGIES MEDIATE THE ASSOCIATION OF BLOOD PRESSURE WITH COGNITIVE IMPAIRMENT IN ADULTS WITHOUT DEMENTIA: THE CABLE STUDY. Hu Hao[1], Tan Lan[1], Yu Jin-Tai[2] *(1. Qingdao University - Qingdao (China), 2. Fudan University - Shanghai (China))*

Background: Dementia is one of the fastest growing public health problems affecting an estimated 30 to 40 million people worldwide. Hypertension, the leading cause of global disease burden affecting 1 billion individuals worldwide, has been identified as a potentially modifiable factor of dementia. However, the relationships of blood pressure (BP) with dementia or cognitive impairment seem to be more complex, and several key questions remain to be explored before the formulation of specific regulations for BP. First of all, although long-term follow-up studies showed that mid-life hypertension was associated with an increased risk of dementia, there were ambiguous results for the association of hypertension in late life. Because the diagnosis of hypertension alone cannot fully reflect the pathophysiological changes of BP, more BP indicators should be explored in one large sample study. More importantly, few studies have investigated the biological mechanisms underlying the relationship of BP and cognitive impairment. The the roles of Alzheimer's disease (AD) core pathologies on the associations of BP with cognition were still unclear. **Objectives:** This study aimed to delineate the interrelationships among blood pressure (BP), cerebrospinal fluid (CSF) core biomarkers of AD, and cognition. **Methods:** The linear regression analyses were conducted in 1546 non-demented participants (mean age of 61.58 years, range 40 to 89 years; 40% female; average days of BP measurement, 9.10 days). The BP variables included three aspects: the diagnosis of hypertension, major BP indicators (continuous: systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse pressure [PP], and mean arterial pressure [MAP]) and BP variability (continuous: BPV). The the CSF core biomarkers of AD included Aβ42, Aβ40, the ratio of Aβ42 to Aβ40 (Aβ42/40), phosphorylated tau protein (p-tau), and total tau protein (t-tau). Mediation analyses with 10,000 bootstrapped iterations were used to explore the mediation effects. **Results:** A clear age-related pattern of BP was delineated. As for the diagnosis of hypertension, we found that hypertension was associated with decreased cognitive scores ($P = 0.0002$) and increased levels of tau-related biomarkers (p-tau, $P = 4.90 \times 10–6$; t-tau, $P = 2.91 \times 10–6$), which remained significant only in midlife. A post hoc analysis on grade diagnosis of hypertension got a similar result. Compared with the non-hypertension group, individuals with more severe hypertension (especially the Grade 3: SBP ≥180 mmHg or DBP ≥110 mmHg) had more significant cognitive impairment and tau pathologies. And this trend existed only in mid-life. As for four major BP indicators (SBP, DBP, PP and MAP), consistent with the results of hypertension, higher SBP was associated with decreased cognitive function ($P = 0.0005$) and increased tau-related biomarkers (p-tau, $P = 0.0030$; t-tau, $P = 5.23 \times 10–5$), which existed only in mid-life. However, unlike SBP, we got inverse results on DBP. Lower DBP was associated with increased CSF tau-related biomarkers (p-tau, $P = 0.0004$; t-tau, $P = 0.0042$), which existed only in late life. Furthermore, we also found that higher PP was strongly associated with decreased cognitive function and increased tau pathologies in total participants (MoCA, $P = 1.26 \times 10–5$, p-tau, $P = 2.43 \times 10–11$; t-tau, $P = 1.33 \times 10–13$), mid-life (MoCA, $P = 0.0043$; p-tau, $P = 1.77 \times 10–7$; t-tau, $P = 5.72 \times 10–8$) and late-life groups (MoCA, $P = 0.0011$; p-tau, $P = 3.38 \times 10–5$; t-tau, $P = 6.87 \times 10–7$). In post hoc analyses, MAP exhibited the same pattern of association with biomarkers found in the systolic analysis among participants in mid-life but showed a statistically significant pattern among participants in late life similar to the diastolic analysis. These age-related influences of SBP, DBP, and PP on tau-related biomarkers were also supported by interactive analyses (interaction terms for age: SBP and DBP, $P < 0.05$; PP, $P > 0.05$). Overall, Mediation analyses showed that the associations between BP and cognition were partially mediated (proportion: 11% to 30%) by tau pathologies, independently of amyloid pathology. In addition to above BP indicators, higher BPVs (including SBP-BPV and DBP-BPV) were also found associated with cognitive impairment in both midlife and late life. However, we did not found any association between BPVs and CSF AD core biomarkers, which indicated that BPV might aggravate cognitive impairment via more complex mechanisms instead of direct effects on AD pathologies. **Conclusion:** Tau pathologies might play important roles in the relationship between BP and cognition, with significant age- and BP-type dependences. This provided a key supplement to reveal the pathological mechanisms of BP involved in dementia or AD.

RP24- IDENTIFICATION OF NOVEL DRUG TARGETS FOR ALZHEIMER'S DISEASE BY INTEGRATING GENETICS AND PROTEOMES FROM BRAIN AND BLOOD. Jin-Tai Yu *(Department Of Neurology And Institute Of Neurology, Huashan Hospital, State Key Laboratory Of Medical Neurobiology And Moe Frontier Center For Brain Science, Shanghai Medical College, Fudan University - Shanghai (China))*

Background: Over the last decade, the widespread application of large-scale genome-wide association studies (GWASs) has drastically advanced the discovery of genetic variants associated with AD. Nevertheless, it is still challenging to decipher the underlying biological mechanisms which has hindered translating these genetic findings to drug development of AD by targeting these candidate genes. **Objectives:** Accordingly, we sought to discover promising drug targets for AD by combining high-throughput proteomics in brain and blood with genetic data to determine the genomic architecture associated protein levels in AD. **Methods:** We systematically link protein biomarkers to AD by taking a five-step approach. First, we leveraged pQTL data derived from brain tissue and findings from two large-scale AD GWASs to conduct a PWAS analysis aimed at identifying the candidate protein biomarkers. Second, we integrated these data using a MR framework which harnesses genetic colocalization to

highlight genes and AD are influenced by a shared causal variant. Third, by leveraging gene-expression data, we identified the significant genes driving GWAS signals at the transcriptional level. Fourth, a specificity analysis was conducted to detect the cell type that targeted genes express on the highest levels. Last, we verified the findings by applying them to the proteomic data derived from blood serum to assess the consistency between the two tissues. **Results:** The PWAS conducted in the Schwartzentruber AD GWAS identified 10 genes (ACE, EPHX2, ICA1L, MADD, PAFAH1B2, PLEKHA1,PVR, SNX1, STX4 and TOM1L2) whose brain protein levels were associated with AD at a Bonferroni-corrected P-value threshold of 3.41×10-5 (0.05/1468). Six of these 10 proteins (ACE, EPHX2, ICA1L, PLEKHA1, PVR and STX4) were replicated in another PWAS using Jansen AD GWAS. After corrections for multiple testing of MR analysis, we identified 6 protein biomarkers that provided strong evidence of an association [P<8.18×10-5 (0.05/611)] in the first AD GWAS. Associations between lower ACE, ICA1L, and SLC20A2 levels and higher AD risk (P=5.76×10-5 for ACE; P=1.57×10-5 for ICA1L; P=4.17×10-5 for SLC20A2) were also identified, as well as associations between higher MAP1S, TOM1L2, and EPHX2 levels and higher AD risk (P=3.17×10-5 for MAP1S; P=1.53×10-5 for TOM1L2; P=2.72×10-13 for EPHX2). We then evaluated 609 protein biomarkers with AD risk in the Jansen GWAS dataset. Consistent positive associations were observed for EPHX2 level with AD risk (P=1.09×10-8). In addition, genetically determined increased levels of CTSH and RTFDC1 increased the risk of AD (P=6.29×10-6 for CTSH; P=1.76×10-5 for RTFDC1), whereas SNX32 (P=2.26×10-6) decreased the risk of AD. The statistical colocalization analysis identified 5 of the 6 genes which provided evidence of genetic colocalization based on a PPH4>80%. Results indicated that ACE, ICA1L, MAP1S, SLC20A2, and TOM1L2 play a role in AD risk (PPH4=96.9%, 97.2%, 93.2%, 89.9%, and 87.6%, respectively). All of the 4 genes (CTSH, EPHX2, RTFDC1, and SNX32) also passed the PPH4>80% criterion in the analysis of the Jansen GWAS dataset. We then asked whether genes with evidence for being causal in AD at the protein level had similar evidence at the transcriptional level by conducting MR and colocalization analyses. ACE was associated with a negative Wald ratio (P=8.85×10-8). ACE gene was also associated with AD in the shared genetic effect between gene expression (eQTL) and AD risk (PPH4=99.2%). Furthermore, the expression of SNX32 in brain was associated with reduced AD risk in the Jansen GWAS dataset (P=3.12×10-6, PPH4=99.2%). Then applying our MR framework using serum proteomes data, 6 genetically predicted effects in the blood proteomics survived corrections for multiple testing (P<7.80×10-5, based on 641 genes). Of these, the concentrations of 2 proteins were positively associated with AD risk (APOE, P=4.00×10-123; CD33, P=4.88×10-6), while the other 4 were inversely associated with AD risk (ACE, P=1.92×10-6; CKM, P=1.98×10-7; TMEM106B, P=1.34×10-5; TREM2, P=1.05×10-12]. We next repeated the analysis using the Jansen GWAS meta-analysis, which verified 3 AD risk genes: ACE, APOE, and CD33. A total of 26 and 15 Wald ratio effects showed evidence of MR at the multiple comparison corrected threshold of P<7.84×10-6 in the two AD GWASs, respectively. When colocalization method was applied to these genes, 6 showed strong evidence for colocalization (PPH4>80%). Analysis in the Jansen GWAS found that the SNX32 gene passed the MR P-threshold with a value of 4.22×10-6. **Conclusion:** In the present study, we proposed a pipeline of analytical techniques that investigate the functional associations between multiple protein biomarkers in brain and blood with AD risk. Collectively, we identified seven genes (ACE, ICA1L, TOM1L2, SNX32, EPHX2, CTSH, and RTFDC1) from a comprehensive analyses including brain PWAS, MR and colocalization, as well as 2 genes (ACE and SNX32) with their protein abundance in significant association with AD on the blood-based studies. Our current study results on genetic, proteomic and transcriptomic approaches has identified compelling genes, which may provide important leads to design future functional studies and potential drug targets for AD.

RP25- SIGMOID METHODOLOGY ALLOWS EARLY PREDICTION OF COGNITIVE DECLINE TOWARDS ALZHEIMER'S DISEASE ACROSS SEVERAL COGNITIVE DOMAINS. Marcela Cespedes[1], Cai Gillis[2], Paul Maruff[3,4], Nancy Maserejian[2], Chris Fowler[5], Stephanie Rainey-Smith[6,7], Victor Villemagne[8,9], Christopher Rowe[5,10], Ralph Martins[7,9,11], Colin Masters[5], James Doecke[1] *(1. Australian E-Health Research Centre, Csiro - Herston, Qld (Australia), 2. Biogen - Cambridge, Ma (United States), 3. Cogstate Pty. Ltd - New Haven, Ct (United States), 4. University of Melbourne - Parkville, Vic (Australia), 5. The Florey Institute Of Neuroscience And Mental Health, University Of Melbourne - Parkville, Vic (Australia), 6. Centre For Healthy Ageing, Health Futures Institute, Murdoch University - Murdoch, Western Australia (Australia), 7. Centre of Excellence for Alzheimer's Disease Research and Care, School of Medical and Health Sciences, Edith Cowan University - Joondalup, Western Australia (Australia), 8. Department Of Molecular Imaging And Therapy, Austin Health - Heidelberg, Victoria (Australia), 9. Department of Psychiatry, The University of Pittsburgh - Pittsburgh, Pa (United States), 10. Department of Biomedical Sciences, Faculty of Medicine, Health and Human Sciences, Macquarie University - Sydney, New South Wales (Australia), 11. Sir James McCusker Alzheimer's Disease Research Unit (Hollywood Private Hospital) - Perth, Western Australia (Australia))*

Background: Clinical trials in Alzheimer's disease (AD) depend on clinical endpoints that may lack sensitivity to the cognitive changes that characterize the disease prior to dementia diagnosis. Consequently, trials designed to determine whether new drugs can forestall dementia or prevent cognitive decline prior to onset of AD dementia will require outcomes measures that are sensitive to cognitive changes earlier in the disease. **Objectives:** The objective of this work was to identify individuals whose cognitive scores progress more rapidly ("accelerators") from those whose cognition does not reach this same level over the same time period ("non-accelerators"). The specific aim was to assess the MMSE, CDR-SB and seven different cognitive composite scores to examine 1) their ability to cluster accelerators and non- accelerators, 2) which cognitive scores can be used as strong predictors of cognitive change, and 3) the proportion agreement of progression classification within specific subgroups of AD pathology. This process was entirely data driven in that it was performed without using the formal AIBL clinical classification to inform disease stage. **Methods:** Using longitudinal data from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of ageing, seven cognitive composite scores (the AIBL PACC score (CVLT-II, LMII, DSC & MMSE), attention and processing speed (DSC & total digit span), episodic memory (delayed recall, LMII & RCFT30), executive function (verbal fluency & category switching), language (BNT & verbal fluency [D-KEFS]), recognition (recognition CVLT-II & RCFT), visuospatial function (RCFT copy & clock along) along with MMSE and CDR-SB from 144 months of AIBL were selected from all participants with at least three time points (at baseline: total

N=1269; 973 Cognitively Normal (CN), 143 with Mild Cognitive Impairment (MCI), 153 with AD). Using the mathematical properties of a proposed sigmoidal function, "cognitive turning points" are defined to allocate accelerator/non-accelerator groups for each of the nine cognitive scores. Proportions of AIBL participants groups are assessed in the complete cohort, and in groups stratified to include Ab-/Tau unknown (N=523), Ab+/Tau unknown (N=420), Ab-/Tau- (N=218), Ab+/Tau- (N=200), Ab+/Tau+ (N=75) and lastly in those without Ab or Tau information (N=325). Using the mathematical properties of the sigmoid function, we identified turning points (thresholds) for each score whereby a participant would be allocated to an "accelerator" or "non-accelerator" group. Group classifications were compared across all nine cognitive scores and then between stratified participant groups. **Results:** In the full cohort, visuospatial function identified accelerators with the highest proportion of accelerators among all of the measures explored, with a total of 68% of the cohort progressing past the derived "cognitive turning point" for accelerated decline. The cognitive test with the next highest classification of accelerators was 2) language (64%); 3) the AIBL PACC (61%); 4) attention and processing (59%); 5) executive function (42%); 6) recognition (38%); 7) episodic recall (26%); 8) MMSE (22%); and 9) CDR-SB (20%). In contrast to CDR-SB and MMSE, all of the cognitive composite scores, except episodic memory, classified a higher proportion of AIBL participants as accelerators as compared with non-accelerators. Of the top ranked cognitive measures, the highest proportions of agreement in identifying accelerators were observed for visuospatial function, language, the AIBL PACC, and attention and processing, with proportions of cross-classification ranging between 59 to 69%. Reducing the sample to those with known pathology provided the strongest classification rates. Amongst Ab+/Tau+ participants, the AIBL PACC had the highest proportion of classified accelerators (85%), followed by language (80%), visuospatial functioning (73%) and attention and processing speed (71%). For Ab+ participants where Tau levels were unknown, the AIBL PACC and language both identified 75% of participants as accelerators, while visuospatial function identified 73% as accelerators. Among Ab+/Tau- participants, visuospatial function (76%), language (66%), attention and processing speed (66%) and the AIBL PACC (56%) ranked the highest to classify accelerators. Among Ab- participants where Tau was unknown, proportions to classify accelerators were reduced (visuospatial function [62%], language [55%], attention and processing speed [55%] and the AIBL PACC [52%]). Lowest accelerator classification rates were seen for the Ab-/Tau- subgroup, with only visuospatial function (57%) and attention and processing speed (51%) reaching 50%. When considering the group where both Ab and Tau pathology were unknown, proportions were ranked similarly, however proportions were lower when compared to results in known pathological groups (visuospatial function [73%], language [64%], attention and processing speed [53%] and the AIBL PACC [58%]) when compared to results in known pathological groups. **Conclusion:** This is the first representation of data derived accelerator groups and group comparisons using a sigmoid function to determine "cognitive turning points" across multiple common cognitive measures. Our results suggest that the cognitive composite scores including the AIBL PACC, language, visuospatial function and attention and processing are well suited to detect change in cognitive function. Such scores continued their high classification proportions across all subgroups of baseline cognition and AD pathology. **Disclosures:** CG and NM are employees and stockholders of Biogen. This work was sponsored by Biogen Global Analytics and Data Sciences, Epidemiology in Collaboration with the Australian Imaging, Biomarkers and Lifestyle study (AIBL)

EPIDEMIOLOGY AND CLINICAL TRIALS

P61- ESTIMATES OF FRONTOTEMPORAL DEMENTIA BY GEOGRAPHIC REGIONS. Cai Gillis[1], Flavia Nery[1], Ellen Huang[1], Elena Ratti[1], Dana Flanders[2], Cathy Lally[3] *(1. Biogen - Cambridge, Ma (United States), 2. Emory University, Rollins School Of Public Health, - Atlanta, Ga (United States), 3. Epidemiologic Research & Methods, Llc - Atlanta, Ga (United States))*

Background: Frontotemporal Dementia (FTD) is a heterogeneous neurodegenerative disease that present with alterations in behavior, language, and/or motor function. Estimates of the prevalence of FTD are highly heterogeneous in the literature due to diagnostic criteria differences, the insidious course of the disease, geographic differences in genetic risk, and differences in methodology among studies. **Objectives:** Objectives for this work were to examine and synthesize the literature on FTD prevalence and provide pooled estimates of cases in selected North American, Central American, South American, Asian, and European countries. Our work focused on estimating the projected FTD prevalent cases by country for the years 2020 through 2040. **Methods:** A comprehensive literature review based on a broad search of PubMed and EMBASE databases was conducted using the terms "frontotemporal dementia", "frontotemporal lobar degeneration" and "prevalence". Studies for inclusion were required to be in English, methodologically rigorous, and with study populations from one or more of the regions of interest. Studies were considered methodologically rigorous if methods for case identification and inclusion were clear and reasonably sensitive and specific, the study data came from a population-based national or large regional registry that was considered representative of the country population, and case determination criteria were clear. Since FTD prevalence differs by age, we stratified by age groups (<45, 45-64, and ≥65 years). Studies included had to report the number of cases, population size, or a derived population case prevalence estimate. Age-group estimates were pooled using a weighted average to obtain estimates by global region and applied to the underlying population of the country of interest. **Results:** Population-based and registry-based studies meeting our inclusion criteria were from Italy, UK, Finland, Greece, South Korea, Japan, Brazil, and Peru. Few studies meeting our inclusion criteria provided age-stratified estimates and not all countries of interest were represented. A total of 6 studies were included for the European estimate among for those 45-64 years and 3 studies for 65 and older. No studies were found meeting inclusion criteria for Europe for the under 45 years age group. For Europe, the weighted average of prevalence for 45 to 64 years was approximately 23.4 per 100,000 persons and for 65 and older was approximately 75.1 cases/100,000 persons. An inadequate number of studies were found to allow for pooling of North American estimates and therefore the European estimates were applied since it was assumed the genetic lineage was most similar to the European pooled population estimates. In 2020, we estimated approximately 7500 cases of prevalent FTD in Canada, 14400 in France, 19300 in Germany, 14800 in Italy, 7500 in Poland, 26100 in Russia, 10200 in Spain, 13400 in the UK, and 62100 in the US. For Asian countries, a total of 1 study was included for estimates in those under 45 years, 2 studies were

included for those 45-64 years, and 2 studies for those 65 years of age and older. Asian countries provided our only estimate of those under 45 years of age at 0.11 per 100,000 persons. The estimated prevalence in Asian countries tended to be lower than other regions of similar age ranges with 2.5 cases/100,000 persons among those 45 to 64 and 38.0 cases/100,000 persons among those 65 and older In 2020, we estimated that there were approximately 76700 cases of prevalent FTD in China, 41900 cases in India, 14500 in Japan, 350 in Singapore, and 3500 in South Korea. For Central and South American estimate, a total of 2 studies, both in age groups of 65+ years, were included. We used a South American estimate for the 65+ age range, and due to lack of studies reporting estimates for those under 65 years of age, the European estimate was used for the 45-64 group. The estimate for those 65+ was preferred over the European estimate for these countries as they are substantially higher and support some evidence for higher prevalence of dementia in Latin American regions. Among those 65+, the estimated prevalence in South America of FTD was 156.8 per 100,000 persons. Using these results, we estimated that in 2020 there were approximately 10200 prevalent cases of FTD in Argentina, 43200 in Brazil, 4700 in Chile, 9700 in Columbia, 6100 in Peru, and 4900 in Venezuela. **Conclusion:** Studies on the prevalence of FTD by age using rigorous methodology in representative populations are currently limited. Further work should be done to explore prevalence of FTD within countries using similar methodology and diagnostic criteria to help reduce heterogeneity in estimates. In our work, Asian countries tended to have the lowest estimates of prevalence compared to European and South American countries. Literature was limited among South American countries for those under the age of 65 years, but among those over 65 years there was indication of higher prevalence of FTD compared to Asian and European countries.

P62- SOCIAL NETWORKS AND CEREBROSPINAL FLUID BIOMARKERS OF ALZHEIMER'S DISEASE PATHOLOGY IN COGNITIVELY INTACT OLDER ADULTS: THE CABLE STUDY. Ya-Hui Ma[1], Ya-Yu Wang[2], Lan Tan[3], Jin-Tai Yu[4] *(1. Qingdao Municipal Hospital, College Of Clinical Medicine, Qingdao University - Qingdao (China), 2. Qingdao Municipal Hospital, College Of Clinical Medicine, Dalian Medical University - Dalian (China), 3. Qingdao Municipal Hospital, College Of Clinical Medicine, Dalian Medical University - Qingdao (China), 4. Fudan University - Shanghai (China))*

Background: Concerning research has attached the utmost importance to the determination of modifiable risk factors to delay the symptomatic onset and especially the occurrence of Alzheimer's disease (AD) pathology. Social networks are deemed as moderators of incident AD, but few data are available on the mechanism relevant to AD pathology. **Objectives:** We aimed to investigate whether social networks affect metabolisms of cerebrospinal fluid (CSF) AD biomarkers during the early stage and identify modification effects of genetic factor and subjective cognitive decline (SCD). **Methods:** We studied participants from the Chinese Alzheimer's disease Biomarker and Lifestyle (CABLE) database who received cognition assessments and CSF amyloid-β (Aβ1–42 and Aβ1–40) and tau proteins (total-tau [T-tau] and phosphorylated-tau [P-tau]) measurements. The social networks were measured using self-reported questionnaires about social ties. Linear regression models were used. **Results:** Data were analyzed from 886 cognitively intact individuals aged 61.91 years (SD = 10.51), including 295 preclinical AD participants and 591 healthy controls. Social networks were mostly associated with CSF indicators of AD multi-pathologies (low P-tau/Aβ1–42 and T-tau/Aβ1–42 and high Aβ1–42/Aβ1–40). Significant differences of genetic and cognitive status were observed for CSF indicators, in which associations of social network scores with CSF P-tau and indicators of multi-pathologies appeared stronger in APOE-4 carriers (versus non-carriers) and participants with SCD (versus controls), respectively. Alternatively, more pronounced associations for CSF T-tau ($\beta = -0.005$, $p < 0.001$), Aβ1–42/Aβ1–40 ($\beta = 0.481$, $p = 0.001$), and T-tau/Aβ1–42 ($\beta = -0.047$, $p < 0.001$) were noted in preclinical AD stage than controls. **Conclusion:** These findings consolidated strong links between social networks and AD risks. Social networks as a modifiable lifestyle probably affected metabolisms of multiple AD pathologies, especially among at-risk populations.

P63- DISTRIBUTION AND BASELINE CHARACTERISTICS OF PARTICIPANTS WITH RAPID PROGRESSING ALZHEIMER'S DISEASE AS MEASURED BY CDR-SB OVER 78 WEEKS IN THE NATIONAL ALZHEIMER'S COORDINATING CENTER (NACC). Cai Gillis, Nancy Maserejian, Ryan Miller *(Biogen - Cambridge, Ma (United States))*

Background: Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) display considerable heterogeneity in disease progression across subjects in clinical studies. Different progression patterns may differentiate underlying disease pathology and clinical phenotypes; however, there is no consensus on a definition of what constitutes rapid clinical progression. Most work to date has utilized the Mini-Mental State Exam (MMSE) change from baseline scores to monitor clinical progression, but few studies have explored rapid progression using CDR-SB and even fewer have explored the effect of varying thresholds of change, which may distinguish underlying differences in clinical syndromes. Better understanding of the distribution of rapid progressors and how baseline characteristics may distinguish between those with and without subsequent rapid progression may provide insight into the natural history of these groups and heterogeneity within AD. **Objectives:** The objective of this analysis was to characterize rapid and non-rapid progressing participants using change in CDR-SB from baseline to approximately 78-weeks and explore baseline demographic and clinical characteristics between these groups. **Methods:** Participants from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set, a database of Alzheimer's Disease Centers across the United States, with MCI or Mild AD aged 50-85 years were eligible for inclusion. Included participants were required to have a baseline CDR global score of 0.5, baseline MMSE score ≥ 24, ≥ 6 years education, and follow-up within 48-90 weeks after baseline visit. Additionally, to limit to those most likely to have MCI due to AD, we required either a positive amyloid CSF/PET test or if amyloid information was unavailable (majority of sample) to be classified as amnestic MCI, given that those with amnestic vs non-amnestic MCI are more likely to be of AD etiology. We classified rapid and non-rapid progressors using three thresholds of substantial change in the CDR-SB score over follow-up standardized to 78-weeks after baseline. The three selected thresholds were a gain ≥ 5, ≥ 7, and ≥ 8 points on the CDR-SB from baseline to a standardized follow-up of 78-weeks. The same analysis sample was used for each of the three threshold analyses to allow comparisons across thresholds. Linear mixed effect models to estimate change in CDR-SB from

baseline standardized to 78-weeks of follow-up were used with person-specific random effects for baseline score and rate of change. Histograms were created for change between baseline and follow-up for CDR-SB. We compared means and frequencies between rapid and non-rapid progressors using the three thresholds of interest. Power for statistical comparisons was limited given the relatively small number of participants classified as rapid, particularly at the higher thresholds. Means between rapid and non-rapid progressors were tested for statistical significance using t-tests. Frequencies between groups were tested using chi-square tests or fisher's exact tests depending on sample size. **Results:** A total of 2680 individuals meeting our inclusion criteria were included in the analyses. Of these, 1764 were MCI due to Alzheimer's disease and 916 were of the Mild AD type. Among the MCI participants, N=101 had amyloid information and the remainder were classified based on having amnestic MCI. A total of 56 (2.1%) individuals were classified as rapid progressors using the ≥5 threshold on the CDR-SB delta, 14 (0.5%) using the ≥7 threshold, and 8 (0.3%) using the ≥8 threshold. Examination of histograms of the change scores on the CDR-SB indicated a right-skewed distribution. No significant differences across cut points between rapidly and non-rapidly progressing participants were identified for age, sex, race/ethnicity, ApoE ε4 allele carrier status, medical history, nor medication use. Rapid progressors had higher mean baseline CDR-SB scores (ranging from approximately 0.5-1 point depending on threshold), lower baseline MMSE scores (approximately 1-1.5 points depending on threshold), higher baseline FAQ scores, higher educational attainment, and higher prevalence of atrial fibrillation at baseline. Rapid progressors had slightly higher frequencies of neuropsychological symptoms present at baseline as measured by the NPI, although the magnitude of these differences was not consistent across thresholds and sample sizes were notably small in the rapid progression group. **Conclusion:** Over 78-weeks of follow-up, approximately 2.1% of MCI and Mild AD participants had a change in CDR-SB ≥5 points, 0.5% had a change in CDR-SB ≥7 points, and 0.3% had a change in CDR-SB ≥8 points. Despite strict baseline MMSE and CDR-Global criteria, those classified as rapid progressors had worse baseline values on both MMSE and CDR-SB. Additionally, rapid progressors had higher baseline functional impairment and the suggestion of increased neuropsychiatric symptoms at baseline. Generally, subjects with rapidly progressing AD in the NACC show considerable heterogeneity across clinical measures and baseline characteristics and are difficult to identify in early symptomatic stages. Our work provides information on the distribution of rapid progressors using inclusion criteria often applied in clinical trials. Future work should continue to examine characteristics that differentiate rapid progressors sooner, with particular attention on baseline differences in function, cognition, and neuropsychiatric symptoms. **Disclosures:** CG, NM, and RM are employees and share holders of Biogen.

LP22- UPDATED U.S. PREVALENCE ESTIMATES ACCOUNTING FOR RACIAL AND ETHNIC DIVERSITY FOR TRIALS AND THERAPIES TARGETING MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S DISEASE (AD) AND MILD AD DEMENTIA. Cai Gillis, Mattia Gianinazzi, Mina Nejati, Nancy Maserejian *(Biogen - Cambridge (United States))*

Background: Recently, new data on the underlying prevalence of all-cause mild cognitive impairment (MCI) and Alzheimer's dementia clinical syndrome in three racial/ethnic groups in the U.S. (Rajan et al. 2021), and on the percentage of cases with confirmed amyloid positivity (Janssen et al. 2021), have been published. Considering these new epidemiological data, updated estimates of the number of individuals living with MCI due to AD and mild AD dementia are needed for drug development, including clinical trial design and recruitment. **Objectives:** To update estimates of the number of people in the U.S. living with MCI due to AD and mild AD dementia and account for differences across Hispanic, non-Hispanic black, and non-Hispanic white ethnoracial groups. **Methods:** A funnel approach for calculating estimates was developed, using age-stratified and peer-reviewed published data as available in each step. We applied the funnel approach using data published in 2021 in comparison to data from previously published studies. First, general population age-stratified estimates were obtained from the CDC Wonder 2021 database. Second, for the update, new epidemiological data on the age-stratified U.S. prevalence of all-cause MCI and clinical Alzheimer's dementia syndrome were applied for ages ≥65y in 10-year age categories and 3 racial/ethnic groups (Rajan et al. 2021). This was compared to the previous method of using epidemiological data from a global systematic literature review and meta-analysis for MCI prevalence (Petersen et al. 2018) and from an earlier analysis of the Chicago Health and Aging Project for AD prevalence (Hebert et al. 2013; Alzheimer's Association 2020). MCI and AD prevalence estimates for people <65y were limited; therefore, for both the original and updated method, the same references were used for MCI ages 60-64y (Petersen et al. 2018), for MCI ages 50-59y (Lopez-Anton et al. 2015, extrapolating from 55-59y to 50-54y), and for AD ages 50-65y (Alzheimer's Association 2019). In the third step, the funnel restricts to the portion of AD dementia that is mild (Hebert et al. 2003 for age groups ≥65y; Yuan et al. 2021 for ages 50-64y), and in parallel, the portion of MCI that clinically is attributed to AD (Knopman et al. 2016). In the fourth step, data on the amyloid-beta positive percentage among mild AD dementia clinical syndrome or MCI was applied, using updated age-stratified data from the Amyloid Biomarker Study (Janssen et al. 2021). This was compared to the previous method using the IDEAS study for dementia across all ages and MCI ages ≥65y (Rabinovici et al. 2019), and a prior publication from the Amyloid Biomarker Study for MCI ages 50-65y (Jansen et al. 2015). We further explore scenarios for health care seeking and likelihood of receiving a diagnosis from other peer-reviewed studies. **Results:** Using the 2021 data inputs and accounting for age and racial/ethnic strata, the estimated number of U.S. individuals with MCI due to AD (i.e., MCI with amyloid-beta confirmed) is 6.9 million (M) for ages ≥50y (5.7% of the entire ≥50y population), and 5.7M for ages ≥65y (9.8% of the entire ≥65y population); the estimated number of U.S. individuals with mild AD dementia is 2.51M for ages ≥50y (2.1%), and 2.46M for ages ≥65y (4.2%); and the total number of individuals with AD with MCI or AD with mild dementia is estimated as 9.4M for ages ≥50y (7.7%), and 8.2M for ages ≥65y (14.0%). These estimates are higher than those derived using references prior to 2021 or collapsing on race/ethnicity: MCI due to AD was previously estimated as 4.7M for ages ≥50y (3.8%), and 3.7M for ages ≥65y (6.4%); mild AD dementia was 2.13M for ages ≥50y (1.8%), and 2.08 for ages ≥65y (3.6%); and total AD with MCI or mild AD dementia was estimated as 6.8M for ages ≥50y (5.6%), and 5.8M for ages ≥65y (9.9%). Of importance, estimates from both the update and the original method do not take into account that a large portion of the prevalent population, ranging in the literature from 52% of non-Hispanic

white dementia cases (Chen et al. 2019) upwards to 98% of non-Hispanic black MCI cases (Qian et al. 2021), remain undetected or undiagnosed. **Conclusion:** Using 2021 published data and accounting for differences in clinical disease prevalence across age and Hispanic, non-Hispanic black and non-Hispanic white populations, the estimated U.S. prevalence of MCI due to AD and mild AD dementia increased, likely owing to the higher prevalence among the Hispanic and non-Hispanic black populations, which were typically under-represented in prior studies. Given high rates of underdiagnosis, particularly among Hispanic and black individuals (Chen et al. 2019; Qian et al. 2021), these prevalence estimates presumably over-estimate the actual number of patients detected, diagnosed, seeking treatment, or readily accessible for clinical trial recruitment. Future studies should be designed to include sufficient numbers of under-represented populations, including Asian, Native American, and mixed race/ethnicity and provide results stratified by both age and race/ethnicity.

LP23- URGENCY TO TREAT BEFORE IT'S TOO LATE: DAILY TRANSITIONS TO MILD OR MODERATE AD DEMENTIA IN THE US AND EUROPE. Cai Gillis, Mina Nejati, Robin Thompson, Nancy Maserejian *(Biogen - Cambridge (United States))*

Background: Many individuals with mild cognitive impairment (MCI) due to Alzheimer's Disease (AD) remain undiagnosed since activities of daily living may not be impaired (Galvin 2021). Early diagnosis and treatment of AD become more critical as the elderly population rapidly increases worldwide. Aducanumab has been approved in the U.S. as the first therapy for MCI and mild AD dementia patients to reduce a defining pathophysiological feature of the disease, brain amyloid plaques, and has been predicted to delay progression to moderate dementia for 2.6 years compared to standard of care (Herring 2021). **Objectives:** In this work, we use data from multiple published sources to estimate the daily numbers of people in the US and EU-27 progressing from MCI due to AD to mild AD dementia, or from mild to moderate AD dementia. **Methods:** For the US estimates, we began with the 2021 Alzheimer's Association estimate of approximately 5 million Americans aged 65+ y with biomarker-confirmed MCI due to AD and 4 million with biomarker-confirmed AD dementia. For the EU AD estimates, we began with the Alzheimer Europe estimate of 7.4 million individuals 65+ y with dementia (Dementia in Europe Yearbook 2019) and that approximately 68% of these were assumed to be due to AD (Tognoni 2005), thereby arriving at an estimate of approximately 5.0 million individuals with AD in the EU 65+ y population. We calculated the number of patients with mild AD dementia (~2 million in US and ~2.5 million in the EU) by applying estimates from the distribution of AD severity as determined by consensus review in the Framingham Heart Study (Yuan 2021). For the EU MCI estimates, we applied age-stratified MCI prevalence estimates from a meta-analysis (Petersen et al. 2018) to the underlying population structure of the EU-27 countries using EUROSTAT 2021 age-stratified data. This resulted in an estimated 15.6 million individuals 65+ y with MCI due to any cause. We then used the method of the Alzheimer's Association (2021) that approximately half of MCI cases are biomarker confirmed to arrive at 7.8 million individuals with MCI due to AD in the EU 65+ y population. We then applied transition probabilities from a recent paper that examined transition among prevalent amyloid-beta positive (Aβ+) individuals in the National Alzheimer's Coordinating Center (NACC), showing estimated annual probabilities of 0.307 for MCI due to AD individuals and 0.336 among mild AD dementia patients transitioning to the next severity classification (Potashman 2021).We selected the transition probabilities from the Aβ+ NACC based, peer-reviewed publication because it was focused on biomarker-confirmed individuals. Finally, we divided these transition counts by 365 days to approximate the number of MCI due to AD and mild AD cases transitioning daily to the next stage of disease severity. **Results:** Of the approximately 5 million Americans 65+ years with MCI due to AD in 2021, approximately 1,535,000 could transition to mild AD within the year – an estimated 4,205 people per day. Of the approximately 2 million Americans 65+ years living with biomarker-confirmed mild AD dementia in 2021, approximately 672,000 could transition to moderate AD dementia over the next year - an estimated 1,841 people per day. Of the approximately 7.8 million Europeans 65+ living with biomarker-confirmed MCI due to AD, approximately 2,387,649 could convert to mild AD dementia – an estimated 6,541 per day. Of the approximately 2.5 million Europeans 65+ living with biomarker-confirmed mild AD dementia, approximately 846,297 could convert to moderate AD in the next year – an estimated 2,319 people per day. These results do not account for the annual transition of individuals who progress through more than one severity classification within a year (i.e., mild AD dementia to severe). Thus, the number of individuals transitioning per day in these stages of disease may be higher when including those who transition to one or more stages annually. **Conclusions:** An estimated 4,200 Americans and 6,500 Europeans could transition from MCI due to AD to mild AD dementia each day. An estimated 1,800 Americans and 2,300 Europeans could progress from mild to moderate AD dementia per day. Thus, for many individuals, there remains a narrow opportunity to treat at the early stages of AD. With treatment that may slow disease progression in these earlier stages of the AD disease continuum, the numbers transitioning daily could be reduced, and more of these individuals would be able to maintain their independence for longer periods of time.

RP34- ASSOCIATION OF BODY MASS INDEX WITH RISK OF COGNITIVE IMPAIRMENT AND DEMENTIA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF PROSPECTIVE STUDIES. Yi Qu[1], Lan Tan[1], Jintai Yu[2] *(1. Department Of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao, China - Qingdao (China), 2. Department Of Neurology And Institute Of Neurology, Huashan hospital, Shanghai Medical College, Fudan University, Shanghai, China - Shanghai (China))*

A growing number of meta-analyses demonstrates the adverse and protective effects of BMI on cognition in midlife and late-life. However, due to the lack of research, a different conclusion is reached. Moreover, these meta-analyses don't specifically examine the association of BMI with risk of cognitive impairment and dementia subtypes. Given the controversial results and ignored aspects, the effect of BMI on cognition remains to be further explored. Therefore, this systematic review and meta-analysis is performed for better qualification and quantification to ascertain the association of BMI with risk of cognitive impairment and dementia, in which Embase, PubMed and Cochrane databases were searched to identify prospective studies up to May 2019. Random-effects meta-analyses and dose-response meta-analysis were conducted, involving twenty-nine of 20,083 identified literatures. Meta-analysis showed that midlife underweight,

obesity and late-life underweight conferred 1.39-, 1.31- and 1.64-fold excess risk for cognitive impairment and dementia, while late-life overweight and obesity conferred 21% and 25% reduced risk. In dose-response meta-analysis, all cause dementia (ACD), Alzheimer's disease (AD) and vascular dementia (VaD) risk in midlife was significantly elevated when BMI surpassed 29, 30 and 32 kg/m2. AD risk in late-life was decreased when BMI was under 27 kg/m2, while this protection for VaD was absent when BMI surpassed 39 kg/m2.It is confirmed in this study that overweight and obesity were positively associated with dementia in mid-age people, while negatively associated with dementia in old-age people and cognitive impairment among the mid- and old-aged. Besides, on the one hand, our results indicated that underweight were harmful to dementia among mid- and old-age population, On the other hand, our dose-response analysis demonstrated that excessive body mass would possibly advance the risk of dementia among mid-aged, paralleled with qualitative analysis. In terms of the elder, our results revealed that increasing body mass was associated with lower risk of dementia, suggesting that the elderly could properly increase their body weight to combat dementia. In summary, our data suggests that the association of BMI with risk of cognitive impairment and dementia is different in that in mid- and late-age population. Firstly, the dose-response relationship between BMI and the risk of cognitive impairment and dementia is reported, thus indicating that the ACD risk is significantly increased when BMI surpassed 31.5 kg/m2 in midlife, while the AD risk is decreased when BMI surpassed 27 kg/m2 in late-life. These cutoffs provide a novel prevention strategy to reduce the dementia risk.

RP35- MODIFIABLE RISK FACTORS FOR INCIDENT DEMENTIA AND COGNITIVE IMPAIRMENT: AN UMBRELLA REVIEW OF EVIDENCE. Jin-Tai Yu *(Department Of Neurology And Institute Of Neurology, Huashan Hospital, State Key Laboratory Of Medical Neurobiology And Moe Frontiers Center For Brain Science, Shanghai Medical College, Fudan University - Shanghai (China))*

Background: Backgrounds: Dementia and cognitive impairment can be attributed to both genetic and modifiable risk factors. Recently, considerable evidence emerged in modifiable factors and urgently require further standardized evaluation. **Objectives:** To fully evaluate the strength and validity of current evidence for the associations of dementia and cognitive impairment with various modifiable risk factors. **Methods:** We conducted an umbrella review of available systematic reviews and meta-analyses of prospective studies. Evidence was graded into convincing, highly suggestive, suggestive, or weak based on random-effects p value, number of cases, heterogeneity, 95% prediction interval, small study effect and excess significance bias. Mendelian randomization studies were descriptively reviewed to explore the causality for these associations. **Results:** Altogether, 12015 articles were identified and 118 were eligible for umbrella review, of which 70 systematic reviews and meta-analyses yielded 243 unique associations. Convincing evidence was found for associations of dementia and cognitive impairment with early-life education, midlife to late-life plasma glucose, BMI, atrial fibrillation, benzodiazepine use, and gait speed. Suggestive to highly suggestive evidence was found for associations of dementia and cognitive impairment with midlife to late-life blood pressure, homocysteine, cerebrovascular diseases, hearing impairment, respiratory illness, anemia, smoking, alcohol consumption, diet, sleep, physical activity and social engagement. Among convincing evidence, Mendelian randomization studies further verified genetic predicted causal relationships for education and plasma glucose with Alzheimer's disease. **Conclusion:** Modifiable risk factors identified in this umbrella review, especially those with high levels of evidence, should be considered in dementia prevention. Further studies are needed to improve the strength and credibility of the biased evidence base.

RP36- GLOBAL PREVALENCE OF ALZHEIMER'S DISEASE ACROSS DISEASE STAGES. Anders Gustavsson[1], Nicholas Norton[2], Thomas Fast[2], Lutz Frölich[3], Drew Holzapfel[4], Tunahan Kirabali[5], Pierre Krolak-Salmon[6], Paolo Maria Rossini[7], Lydia Lanman[8], Antonella Santuccione Chadha[5], Wiesje M. Van Der Flier[9] *(1. Quantify Research; Department Of Neurobiology, Care Sciences And Society, Karolinska Institute - Stockholm (Sweden), 2. Quantify Research - Stockholm (Sweden), 3. Department Of Geriatric Psychiatry, Central Institute Of Mental Health Medical Faculty Mannheim, University Of Heidelberg - Mannheim (Germany), 4. Ceo Initiative On Alzheimer's Disease - Philadelphia (United States), 5. Biogen - Baar (Switzerland), 6. Lyon Institute For Elderly, Clinical & Research Memory Center Of Lyon - Lyon (France), 7. Faculty Of Medicine Of The Catholic University Of The Sacred Heart; Neuroscience Area Of Policlinico Foundation A. Gemelli. - Rome (Italy), 8. F. Hoffmann-La Roche - Basel (Switzerland), 9. Alzheimer Center Amsterdam, Department Of Neurology, Department Of Epidemiology And Data Science, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam Umc - Amsterdam (Netherlands))*

Background: The large social and economic burden of Alzheimer's disease (AD) and dementia is well established. Evidence of effective preventive measures, e.g. life-style changes in asymptomatic at-risk populations, and recent developments of candidate therapies targeting AD pathology, in early symptomatic stages of AD such as mild cognitive impairment (MCI) and early stages of dementia due to AD, offer hope for the future. However, the size of the predementia AD population, and specific target populations that may benefit from future therapies, is partly unknown. **Objectives:** To describe the evidence on the prevalence of AD across all stages of disease, and to synthesize this evidence into estimates on the global number of persons with AD, and in potential target populations for preventive measures and future therapies. **Methods:** We reviewed published literature on epidemiological evidence with well-defined populations across Alzheimer disease stages, prioritizing meta-analyses that drew from multiple cohorts. Relevant stages included AD dementia, MCI due to AD (henceforth prodromal AD) and cognitively normal populations with Alzheimer pathology who are at risk of developing symptomatic AD (henceforth preclinical AD). Patients with prodromal AD or mild AD dementia were additionally considered in a separate combined subgroup because this is a common target population for candidate therapies targeting AD pathology. We considered both data on cohorts with confirmed Alzheimer pathology with a positive amyloid-beta biomarker (Aβ+), as well as clinically diagnosed cohorts without biomarker data (clinical AD). The available prevalence estimates were synthesized for selected subgroups defined by sex, age, stage of disease and Alzheimer pathology. We then designed a simple model that derived global estimates on the number of persons with AD, based on prevalence estimates of Aβ+ AD and global 2020 census data. **Results:** We found evidence on the prevalence of AD across disease stages, often stratified by sex and age, and

sometimes including biomarker data. Studies on differences across countries/regions were limited to the dementia stage of AD. Sex differences are apparent across stages, yet not fully considered in meta-analyses of the predementia stages of AD. Other determinants include education, ethnicity and genetic profile. We found evidence for clinical AD dementia, although more detailed data for all-cause dementia across geographic regions. The prevalence increases with age and is higher for women. The prevalence of amyloid-positivity in clinical AD dementia decreases with age, from 93% at age 50 to 79% at age 90. Combining data on all-cause dementia (assuming 70% have clinical AD) and amyloid-positivity, resulted in global average prevalence estimates of Aβ+ AD dementia increasing from 1% at age 60 to 25% at age 90+ for women, and 0.8% to 17% for men. The regional variation is large: up to 85% higher and 61% lower in certain age groups. We estimated 32 million persons with Aβ+ AD dementia in 2020, world-wide, or 1.7% of all aged 50+, with the majority (65%) being female. For prodromal AD, separate meta-analyses on the prevalence of clinical MCI and biomarker-positivity in clinical MCI populations were found. Combining these data resulted in an increasing prevalence of Aβ+ prodromal AD with age, from 3% at age 60 to 27% at age 90+. We estimated 69 million persons with prodromal AD in 2020, world-wide (3.7% of all 50+). In preclinical AD, two meta-analyses found an increasing prevalence with age from about 10% at age 50 to 40% at age 80+. We estimated 315 million persons with Aβ+ preclinical AD in 2020, world-wide (17% of all 50+). Assuming a proportion of mild cases of dementia at 60% at age 60, decreasing to 45% at age 90+, the size of the combined Aβ+ prodromal and mild AD dementia subgroup was estimated at 86 million in 2020, world-wide (4.6% of all 50+ and 59% female). The uncertainty and variation across individual studies were relatively high. The published confidence intervals, where available, suggest that the true population sizes for the groups presented here may be between 39% lower to 61% higher than our estimates. **Conclusion:** We estimated the global number of persons with Aβ+ AD at 416 million, including asymptomatic, preclinical, at-risk stages of AD. This corresponds to 22% of the population aged 50+, the majority female, which emphasizes the staggering number of those that may benefit from future preventive and disease-modifying measures towards AD. With these potential patient numbers, a major challenge will be to accurately, efficiently and equitably both identify and treat the right patients if/when therapies targeting AD pathology become available for prodromal AD, and subsequently also for preclinical AD. Our estimates are based on the best available evidence at present, but a lot of uncertainty remains. Data gaps include evidence on biomarker-confirmed populations, sex differences in preclinical and prodromal AD and differences across geographic regions. Future researchers should pay attention to the choice of methods, especially on case ascertainment and recruitment, which likely have great impact on prevalence estimates. **Conflict of interest:** Presenting author Anders Gustavsson is a partner of Quantify Research, providing consultancy services to pharmaceutical companies and other private and public organisations and institutions.

RP37- ASSOCIATION BETWEEN WIDESPREAD PAIN AND DEMENTIA, ALZHEIMER'S DISEASE AND STROKE: A COHORT STUDY FROM THE FRAMINGHAM HEART STUDY. Kanran Wang *(The First Affiliated Hospital Of Chongqing Medical University - Chongqing (China))*

Background and objective: Chronic pain may be an early indicator of cognitive decline, but prior studies have not systematically examined the population-level associations between widespread pain (WSP) and adverse cognitive outcomes and stroke. This study was designed to determine the association between WSP, a common subtype of chronic pain, and subsequent dementia, Alzheimer disease (AD) dementia and stroke. **Methods:** This retrospective cohort study used data from the US community-based Framingham Heart Study (FHS). Pain status was assessed uniquely between 1990 and 1994. And WSP was determined based on the FHS pain homunculus. Dementia follow-up occurred across a median of 10 years (interquartile range, 6-13years) for persons who were dementia free at baseline. Proportional hazards models examined associations between WSP and incident dementia, AD dementia and stroke. **Results:** A total of 347 (14.1%) subjects fulfilled the criteria for WSP, whereas 2117 (85.9%) subjects did not. Of 188 cases of incident all dementia, 128 were AD dementia. And 139 patients suffered stroke during the follow-up. After multivariate adjustment including age and sex, WSP was associated with 43% increase in all dementia risk(HR, 1.43;95% CI, 1.06-1.92), 47% in AD dementia risk(HR, 1.47;95% CI, 1.13-2.20) and 29% in stroke(HR,1.32;95% CI, 1.08-2.54).The comparable results were shown in the subgroup for individuals over 65 years old. **Conclusion:** WSP was associated with increased incidence of all dementia, AD dementia and stroke. **Conflicts of interest:** None.

RP38- GENETICALLY DETERMINED BLOOD PRESSURE, ANTIHYPERTENSIVE MEDICATIONS, AND RISK OF ALZHEIMER'S DISEASE: A MENDELIAN RANDOMIZATION STUDY. Ya-Nan Ou[1], Lan Tan[1], Jin-Tai Yu[2] *(1. Department Of Neurology, Qingdao Municipal Hospital, Qingdao University - Qingdao (China), 2. Department Of Neurology And Institute Of Neurology, Who Collaborating Center For Research And Training In Neurosciences, Huashan Hospital, Shanghai Medical College, Fudan University - Shanghai (China))*

Background: Observational studies indicated that hypertension might be a potential risk factor for Alzheimer's disease (AD), and antihypertensive medications (AHMs) was highlighted as priority repurposing candidates for AD prevention. However, inference from observational studies is limited by residual confounding, reverse causation and detection bias. Difficulties in implementing large-scale randomized clinical trials also restrict the exploration of this association. **Objectives:** A novel method for estimating causal effects of risk factors in observational studies using genetic variants is Mendelian randomization (MR). Due to the random assortment of genes at conception, MR overcomes the core shortcomings of observational studies and assesses lifelong exposures to risk factors, and thus it can clarify potential causal associations. Herein, we aimed to explore the effects of blood pressure (BP) and lowering systolic BP (SBP) via the protein targets of different AHMs on AD through a two-sample MR approach. **Methods:** Significant SNPs ($P<5\times10-8$) for BP were identified from a genome wide association study (GWAS) meta-analysis that included 757601 individuals of European ancestry drawn from UK Biobank and the International Consortium of Blood Pressure database. We selected genetic variants as proxies

for the SBP lowering effects of common antihypertensive drug classes: angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), β-blockers (BB), calcium channel blockers (CCB) and thiazide diuretic agents. We identified the genes encoding pharmacologic targets related to BP-lowering for common antihypertensive drug classes in DrugBank (https://www.drugbank.ca/) and screened the genomic SNPs corresponding to these genes in GeneCards (https://www.genecards.org/). Variants that are significantly associated with the exposure ($P<5 \times 10-8$) and clumped to a linkage disequilibrium (LD) threshold using the 1000G European reference panel were considered as candidate proxies. AD data were from a large famous GWAS dataset from International Genomics of Alzheimer's Project (IGAP) GWAS Stage 1 result (N=21982 cases, 41944 controls). Causal effects were estimated with the random-effects maximum likelihood estimation method. We applied five complementary methods [inverse variance weighted (IVW), MR-Egger, weighted median, Simple mode and Weighted mode], which provided different assumptions about horizontal pleiotropy. The IVW method was performed as our primary method. The intercept of MR-Egger regression, which represented the average horizontal pleiotropy was conducted. Leave-one-SNP-out analysis in which we systematically removed one SNP at a time to assess the influence of potentially pleiotropic SNPs on the causal estimates was performed. **Results:** A total of 400/398/343 independent genetic variants were found to be associated with SBP/DBP/PP, respectively. There was no evidence of an association between either genetically predicted SBP or PP with AD, with P values> 0.05 in all of the analyses. However, the results were suggestive of an association between DBP and AD using IVW method with an OR of 0.990 (95% CI=0.979-1.000, P=0.055). There was evidence of heterogeneity in the causal effect estimates from all of the MR analyses (all P values<0.05). Nonetheless, horizontal pleiotropic effects were absent in MR Egger regression (P=0.935 for SBP; P=0.182 for DBP; P=0.897 for PP). We did not find a single genetic variant of BP that had an influence on the association in the leave-one-out analysis. Next, we examined the effects of BP-lowering variants in genes encoding drug targets on AD. We identified a total of 52 variants for AHMs, including 1 for ARB, 1 for BB, 45 for CCB, and 5 for thiazides. However, we failed to explore the casual effects of ACEI on AD risk because no proxy was identified. All SNPs had F values >10, suggesting that they were unlikely to introduce marked weak instrument bias. The MR analyses showed an association of the overall use of AHMs with lower risk of AD (OR=0.961, 95% CI=0.944-0.978, P=5.74E-6). The associations were confirmed using sensitivity analyses including the methods of weighted median (OR=0.961, 95% CI=0.937-0.985, P=0.001), simple mode (OR=0.949, 95% CI=0.903-0.996, P=0.032) and weighted mode (OR=0.958, 95% CI=0.921-0.996, P=0.031). The Cochran Q statistic of IVW method (Q=26.130; P=0.985) indicated no notable heterogeneity across instrument SNP effects. Egger analyses did not show evidence of directional pleiotropy (P>0.05). There was no distortion in the leave-one-out plots. Reduction in SBP through variants in genes encoding targets of CCB was associated with a lower risk of AD (OR=0.959, 95% CI=0.941-0.977, P=3.92E-6). The association was confirmed by sensitivity analyses using weighted median method (OR=0.960, 95% CI=0.935-0.985, P=0.001). No evidence of heterogeneity and pleiotropy in the causal effect estimates was found (all P>0.05). Leave-one-out analysis didn't change the overall direction. However, we didn't find evidence of causal effects of ARB, BB and thiazides on the risk of AD. **Conclusion:** This two-sample MR study, in which we used genetic variants as proxies associated with BP in a very large cohort of well-characterized research participants, provided suggestive evidence for associations between genetically exposure to BP-lowering through AHMs and a reduced risk of AD, and further identified CCB as a promising strategy for AD prevention. **Conflict of interests:** The authors declare that they have no competing interests.

DIGITAL HEALTH / E-TRIALS

P64- PROSPECT-AD- POPULATION-BASED SCREENING OVER SPEECH FOR CLINICAL TRIALS IN AD.

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Background: Language and speech impairments are an early feature of neurodegenerative dementias. Consequently, digital biomarkers of language and speech performance may be promising tools for early diagnosis. The current "new era of Alzheimer's disease (AD) clinical trials" suggests a shift to very early identification of people at risk. Hence, digital markers of language and speech may serve the screening of at-risk populations that are at a prodromal stage of AD, eventually in combination with advanced machine learning longitudinal modelling. Here, we conceived a pre-screening battery consisting of speech-based neurocognitive tests, enabling automated first-line pre-screening to be performed remotely using a telephone. **Objectives:** PROSPECT-AD aims to build and validate speech-based machine learning models for the detection of the relevant phenotype through access to gold-standard phenotyped cohorts. Further, the predictive potential (sensitivity/specificity) for differential/prognostic diagnosis based on information extracted from the participant's speech in cognitive vocal and narrative speech tasks and its usefulness for remote pre-screening and monitoring will be examined. **Methods:** PROSPECT-AD collaborates with already ongoing cohorts such as EPAD (UK), DELCODE (Germany), INSIGHT-preAD II (France) or BIOFINDER (Sweden) by adding the collection of speech data to existing protocols or as follow-up assessments over the telephone. Participants at preclinical stages are mainly recruited from existing parent cohorts across Europe to form a 'probability-spectrum' population covering the entire continuum of anticipated probability for Alzheimer's dementia development. This characterization of cognitive, biomarker and risk factor (genetic and environmental) status of each research participants over time combined with audio recordings of speech samples will provide the necessary well-phenotyped population for developing predictive longitudinal models for Alzheimer's disease covering the entire disease course and concurrently create a pool of highly characterized individuals for the validation analysis. 300 participants aged 50 or older will be included per cohort, with a clinical dementia

rating scale (CDR) score of 0 or 0.5. The study protocol is planned to run over 18 months. The speech protocol includes the following tests which will be administered remotely: Word List, Story Retelling [Learning & Memory]; Digit Span, Phonemic Verbal Fluency, Semantic Verbal Fluency [Executive Functions], Spontaneous free speech [Psychological and/or behavioral symptoms]. The spoken features extracted from the recordings will be compared to data from the neuropsychological evaluations, genetic profiles, biomarkers, neuroimaging, family history. Based on the analysis of vocal performances, models will be trained to predict participant's risk to convert to AD dementia; employing advanced machine learning and different computational techniques to identify the most significant speech markers that could represent an early indicator for a pre-screening scenario. **Results:** The overall study protocol is being developed and will be presented at the conference in addition to previous research findings and its resulting new hypotheses. **Conclusion:** The outcome of PROSPECT-AD may have a major impact on the improvement of drug development research methodology by providing a validated telemedical solution for neurocognitive pre-screening and monitoring of participants of early AD clinical trials.

P65- OPTIMIZING PATHS FOR EFFICIENT USE OF DIGITAL HEALTH TECHNOLOGIES IN PD CLINICAL TRIALS: THE CRITICAL PATH FOR PARKINSON'S 3DT INITIATIVE. Derek Hill[1], Martijn Müller[2], Jesse Cedarbaum[3], Josh Cosman[4], Lauren Oliva[5], Mark Frasier[6], Marissa Dockendorf[7], Ariel Dowling[8], Kirsten Taylor[9], Emily Kunka[10], Caldeira Caldeira[11], Ray Dorsey[12], Diane Stephenson[2] *(1. University College Of London - London (France), 2. Critical Path Institute - Tucson (United States), 3. Coeruleus Clinical Sciences - Woodbridge (United States), 4. Abbvie - Cambridge (United States), 5. Biogen - Cambridge (United States), 6. The Michael J. Fox Foundation - New York (United States), 7. Merck - Philadelphia (United States), 8. Takeda - Social Circle (United States), 9. Roche - Basel (Switzerland), 10. Ucb - San Francisco (United States), 11. Lundbeck - Copenhagan (Denmark), 12. University Of Rochester - Rochester (United States))*

Background: Assessment of disease progression in the early manifest stages of neurodegenerative disorders such as Alzheimer's disease (AD) or Parkinson's disease (PD) remains a challenge with current endpoints. PD clinical research is at the forefront of using Digital Health Technologies (DHT), including wearable devices and smartphones, to detect early changes in many symptoms of importance to patients. To achieve regulatory acceptance to use DHT in clinical drug trials, several gaps and challenges are yet to be addressed. Regulatory agencies have recommended that public private partnerships (PPP) play a key role in advancing the field while including regulators in the process. Existing PPP in the PD space may provide a template for achieving regulatory maturity for DHT in the AD space. **Objectives:** To describe the Critical Path for Parkinson's (CPP) consortium's Digital Drug Development Tools (3DT) initiative, aimed at advancing the regulatory maturity of DHT as drug development tools for PD, and discuss relevance to AD drug development. **Methods:** CPP consists of pharmaceutical companies, academic advisors, non-profit research organizations, and regulatory agency representatives. The Digital Drug Development Tools (3DT) group has been created under the auspices of the CPP consortium as a dedicated team that is sharing knowledge and data in the precompetitive space. A staged plan has been initiated which aims to advance a data driven collaboration framework to collectively advance the DHT field in a device agnostic way. Critical Path Institute receives generous funding from the FDA, and both FDA and EMA are actively engaged in the consortium. Critically, the 3DT group also works directly with people living with PD. **Results:** CPP is leveraging the ongoing, prospective study called WATCH-PD (Wearable Assessments in The Clinic and Home in PD, NCT03681015), a multicentre, prospective, longitudinal, digital assessment study of PD progression in subjects with early, untreated PD, as an exemplar pilot study to facilitate discussion and alignment with regulatory agencies on evidentiary considerations for DHT for drug development. WATCH-PD has an emphasis on changes in motor symptoms, but cognition, sleep, psychiatric status, quality of life, and activity patterns are also assessed, and many of these are relevant to multiple neurodegenerative diseases. Regulatory feedback from the FDA's Critical Path Innovation Meeting and EMA's Innovative Task Force briefing meeting provided input on key topics including technical, acquisition and analytical recommendations, including controlling sources of variability in the data, determining clinical meaningfulness of both motor and non-motor the relevance of DHT outcome to patients' perception of function, and importance of evaluating DHT performance in normative controls. In response, a normative sub study has been added to the WATCH-PD study, co-funded by the 3DT members. Moreover, the 3DT group has developed consensus recommendations on security best practices and for sponsors conducting DHT studies to align with patient needs to enhance compliance. Two workstreams have aligned on outlining case studies for documenting metadata standards for studies employing DHT and identifying sources of variability that are key to design of ongoing and future studies. **Conclusions:** Many of the learnings of CPP's 3DT team are relevant in AD drug development. CPP's progress to date has provided a framework for multiple sponsors who have agreed to collaborate on optimizing the use of DHT in future PD clinical trials. Regulatory agencies have encouraged CPP to continue to have iterative, data-driven, disease-specific discussions, including strategies for establishing meaningful clinical endpoints, controlling sources of variability, and evaluating DHT performance in normative as well as diseased cohorts. Many of the issues being addressed in CPP 3DT apply also to the use of DHT in other neurodegenerative diseases including AD. We therefore propose that similar frameworks and strategies could accelerate development of DHT for AD and beyond. Reference: Stephenson D, Alexander R, Aggarwal V et al., Precompetitive consensus building to facilitate the use of digital health technologies to support Parkinson disease drug development through regulatory science. Digit Biomark 2020;4(suppl 1):28–49.

P66- REDUCING SOURCES OF VARIABILITY OF DIGITAL HEALTH TECHNOLOGIES IN CLINICAL TRIALS BY ADDING ENVIRONMENTAL CONTEXT. Derek Hill, Tri Thanh Tam Tran, Nicolas Defranoux, Alizee Devaux, Souleymen Sahnoun *(Panoramic Digital Health - Grenoble (France))*

Background: Digital Health Technologies (DHT) including wearable sensors have the potential to provide continuous quantification of patient activities, behaviours and symptoms in a home setting. Such measures could be a valuable tool in clinical trials, providing "real world" assessments that may be more realistic and higher frequency than traditional in-clinic assessments. However, variability caused by the home environment, eg room size and temperature, location within the

home, presence of family members, can mask changes due to disease progression and treatment. Regulatory concerns about the impact of these sources of variability are slowing down the regulatory acceptance of these technologies as clinical trial endpoints. **Objective:** To present an automatic means of adding environment context to wearable sensor data an to demonstrate how this may reduce variability in home based wearable sensor measures of mobiltiy. **Methods:** We have developed an approach in which environmental context is provided by placing environmental beacons around the home. These beacons contain temperature, noise and light sensors, plus an accelerometer and magnetometer to determine the orientation of the beacon. They use an in-built blue tooth low energy (BLE) module to periodically broadcast a signal that includes values of these beacon sensor measures including the orientation information. These broadcasts are picked up by a wearable bracelet "Context Wearable" (CW), with built in accelerometer, magnetometer, gyroscope and pressure MEMS sensors (STMicroelectronics). The wearable bracelet also has an in-built BLE module which receives the beacon broadcasts, from which it can estimates the distance to each beacon within range using the received signal strength and relative orientations of the antennae of the beacon and bracelet. In this way, the wearable sensor data is labelled with context data comprising the place of data location (from the closest beacon) and the environmental parameters in that location (ambient temperature, luminosity and noise). Beacons may also be worn by family members or carers to determine who the patient is with. The impact of the addition of context was demonstrated in an experiment in which three normal subjects, wearing the PC, moved around a two-room test environment. Room 1 was smaller, with a 45cm chair. Room 2 has a 55cm chair. The subjects walk around the rooms, sitting down and getting up from the chairs under two conditions. Baseline, and Intervention carrying a 5kg load. The CW automatically associates each sensor measure with the room and ambient temperature, noise and luminosity by means of identifying the closest beacon at 1 second intervals. The raw data was processed to quantify step time (cadence) and sit-to-stand transition time. **Results** Results were obtained for (a) cadence and (b) sit-to-stand time for the subjects in the baseline and intervention condition (i) without and (ii) with context information from the beacon to identify the room in which the subject was present while the sensor measurement was collected. Compared to baseline, when carrying a load, the median cadence and median sit-to-stand time are increased. The mean and variance of the cadence and sit-to-stand time was measured calculated pre and post intervention, with and without the use of the context information from the beacon. By using the beacon context information to identify which room the measures were made, it was possible to select cadence and sit-to-stand times from just room 2. In this case, the variability is reduced and the benefit can be quantified by calculating the sample size needed to provide 95% power for detecting the impact of the intervention. The effect size (Cohen's D) was found to increase from 1.33 to 1.77 for sit-to-stand transition time and from 0.23 to 0.37 for cadence time when the context was used to select data only from room 2, and the sample size reduces by 45% for sit-to-stand transition time and 57% for cadence time. In further work we will investigate the benefit of also including the ambient temperature, luminosity and noise data to determine whether this, along with room location information, can reduce variability in home data collection. **Conclusions:** The impact of Digital Health Technologies on the design of AD clinical trials has so far been limited. One of the major barriers to uptake of this technology and its acceptance by regulators is variability caused by the home environment. Such variability is not random noise. For example there may be a seasonal change in room temperature during the study period, or a change in a patient's symptoms may mean that they spend their time within different rooms in their home, and thus environmental variability introduces a bias rather than random noise into measurements. Incorporation of automatic environment context into wearable sensor measures can reduce variability and reduce sample size required to quantify disease progression or treatment response.

P67- REMOTE SELF-ADMINISTRATION OF COGNITIVE TESTS IN OLDER ADULTS WITH AND WITHOUT SUBJECTIVE COGNITIVE DECLINE USING THE BAC TABLET-BASED EPRO PLATFORM. Alexandra Atkins[1], Mike Kraus[1], William Horan[2], Matthew Welch[1], Joshua Yuan[1], Heather Stevens[1], Philip Harvey[3], Kathleen Welsh-Bohmer[4,5], Richard Keefe[2,5] *(1. Verasci - Durham (United States), 2. Verasci - Durham (United States) - Durham (United States), 3. University Of Miami Miller School Of Medicine - Miami (United States), 4. Verasci - Durham (United States minor outlying islands) - Durham (United States), 5. Duke University Medical Center - Durham (United States))*

Introduction: The COVID-19 pandemic required a rapid and agile response by industry sponsors, CROs, vendors, sites and study participants engaged in ongoing clinical trials. When enrollment was slowed or paused at clinical sites beginning March of 2020, the question of if, how and when to support remote collection of cognitive endpoints became salient, increasing widespread interest in leveraging existing validated technologies to support reliable in-home testing. For clinical trials in Stage 1 -3 Alzheimer's disease, straightforward and reliable self-administered cognitive testing platforms have strong potential to facilitate efficient monitoring of cognitive performance to assess both treatment efficacy and clinical progression. The BAC is a brief, fully validated, tablet-based cognitive battery that has demonstrated equivalency to the original pen-and-paper Brief Assessment of Cognition (BACS) that has been used in hundreds of research studies and clinical trials. The BAC includes voice-over instructions, automated stimulus presentation, integrated scoring, automatic data upload and cloud-based data storage in compliance with FDA 21CRF Part 11. Although it was originally developed for face-to-face administration, remote rater administration guidelines were developed in response to needs of ongoing studies during the COVID-19 pandemic. Self-administered versions of select BAC subtests were developed to allow remote self-administration from home using a Pathway ePRO tablet. **Objective:** The present work describes an ongoing investigation examining the feasibility of at-home self-administration of cognitive tests within the BAC platform. Preliminary data provides within-subject comparisons of site-based and in-home cognitive testing in a sample of older adults with and without subjective cognitive decline (SCD). **Methods:** At the time of submission, the sample included 30 older adults (mean age=66, SD=6.7, 17 female) who participated as a part of a larger investigation of remote and wearable technologies. Of these, 9 participants endorsed moderate subjective cognitive decline (SCD) over the past year, based on a score of greater than or equal to 4 on the self-reported Cognitive Function Instrument (CFI). Participants completed self-administered versions of the following BAC assessments: Symbol Coding, 3-trial Verbal Memory with delayed free recall, and Verbal Fluency (semantic and phonemic). To allow comparison between remote and site-

based testing scenarios, all participants completed two BAC testing sessions. The order of site-based and remote testing was counterbalanced, with half of all participants completing remote testing first. Alternate forms of Symbol Coding and Verbal Memory were completed at each timepoint. Additional assessments, including the MMSE and performance-based measures of functioning (not reported) were completed in-person. **Results:** Participants with SCD performed somewhat worse and more variably on the MMSE than the remaining healthy older adult (hOA) sample (M=27.11, SD=4.3 for SCD; M=28.23, SD=2.4 for hOA group). Due to limitations in sample size at the time of submission, comparisons between remote and in-person testing were completed using the combined sample. Differences between remote and in-person assessments were examined using a linear mixed effects model controlling for age and education. No differences were observed based on testing order on any endpoint (p>.5 for all). Mean Symbol Coding total correct was 34.84 (SD=14.0) for in-person testing and 34.36 (SD=12.3) for remote testing, with no reliable difference observed (p>.7). Similarly, Verbal Fluency did not differ based on testing modality (p>.2). In contrast, Verbal Memory was significantly higher for remote versus in person testing: mean total learning was 17.27 (SD=4.3) for in-person and 19.80 (SD=7.23) for remote testing (p<.05). This difference persisted on Delayed Free Recall: mean recall was 5 (SD=2.70) for in person and 6.33 (SD=3.6) for remote testing (p.05). **Conclusions:** Preliminary results suggest that the reliability of in-home unmonitored cognitive testing may differ by assessment type, and potentially by cognitive domain. For the non-memory-based tests examined (Symbol Coding and Verbal Fluency), no differences between site-based and in-home testing were observed, suggesting these data may be reliably collected in an at-home environment. For the memory-based endpoints, at-home unmonitored testing could result in inflated test scores. Potential explanations and solutions will be discussed.

LP24- EVALUATION OF A REMOTE SPEECH-BASED AI SYSTEM FOR DETECTION OF AMYLOID-CONFIRMED PRODROMAL ALZHEIMER'S DISEASE. Emil Fristed, Caroline Skirrow, Marton Meszaros, Lenain Raphael, Udeepa Meepegama, Jack Weston *(Novoic - London (United Kingdom))*

Background: Disease modifying treatments are often trialled in individuals with Mild Cognitive Impairment (MCI) or Mild Alzheimer's disease (AD), and confirmed Amyloid beta (Aß) positivity, and it is in these individuals that treatment response and risk profiles are established. MCI is typically identified through clinical interview and cognitive testing, while Aß positivity usually is established using higher cost, more invasive measures, which are ill-suited for broader screening in clinical care. Screening methods that are accessible, well tolerated, cost-effective, and simple to administer are urgently needed to improve screening for trials and treatment suitability. Subtle cognitive changes early in the AD continuum are seen in episodic and semantic memory, typically measured during verbal cognitive assessments. However the simple response indices used for scoring the verbal responses have uniformly small effect sizes for detecting Aß positivity. In recent years AI models have surpassed humans in understanding natural language, and such models could be leveraged to extract sensitive biomarkers from spoken responses. Further, speech-testing can be rapidly implemented at scale via mobile devices. To date, no studies have combined deep speech phenotyping with an early-stage biomarker-confirmed AD population. **Objectives:** To develop speech-based AI algorithms to detect amyloid-confirmed prodromal Alzheimer's disease. **Methods:** We present initial results from the AMYPRED study (NCT04828122). Subjects were approached if they had undergone a prior Aß PET scan or CSF test (confirmed Aß- within 30 months, or Aß+ within 60 months), and were cognitively unimpaired (CU; Mini mental state exam (MMSE) 26-30) or were diagnosed with MCI or Mild AD (MMSE 23-30). Participants underwent a clinical assessment via telemedicine, followed by optional remote assessments daily using their personal digital devices for 7-8 days. Assessments included the Automatic Story Recall Test (ASRT), using 18 'short' and 18 'long' parallel story variants, administered in triplets (three stories administered for immediate and delayed recall). Short story ASRTs at immediate recall were selected for onward analysis. A random triplet was picked uniformly for all participants, provided they had fully completed the three stories. Responses were transcribed using an out-of-the-box Automatic Speech Recognition (ASR) technology. Responses were analysed with ParaBLEU, a paraphrase representation learning model and evaluation metric. Static representations were obtained from ParaBLEU by inputting pairs of story target and response, and fed into a logistic regression model trained with the sklearn package in Python. Classifiers were trained using tournament leave-pair-out cross-validation analyses, where logistic regression models were trained to predict pairs of labels (MCI/Mild AD vs. CU; or Aß+ vs. Aß-). Participant level probabilities were ensembled across the stories to create a ranking for each participant for Receiver Operating Curve (ROC) analysis. 95% confidence intervals for Area Under the Curve (AUC) were computed using DeLong's method. The AI system was compared to a demographic baseline (age, gender and years in education). Real-world implementation was simulated using an age 50+ sample in eight 5-year buckets with proportional representation of each age group representative of the US population, and prevalence estimates of MCI vs. CU, and Aß+ vs. Aß- from prior meta-analysis. The AI system's confusion matrix within the sample was determined, using a conservative ROC cutoff value of 0.7. Prescreening simulation followed established methods. **Results:** One hundred and six participants (mean age=69.6, range 54-80, 54 Female/52 Male; 60 CU and 46 MCI/Mild AD (20 Aß+ and 26 Aß-)) completed at least one full set of remote short ASRTs. Groups did not differ on demographic variables, except in the MCI subanalysis, where a significantly higher proportion of men were in the amyloid positive group (75% Aß+ vs. 42% Aß-). The AI system used an average of 2.7 minutes of automatically transcribed speech as its only input. MCI classification using the AI system had an AUC of 0.85+/-0.07. The demographic baseline (AUC = 0.50+/-0.12) was not statistically better than random. For amyloid classification within the MCI group the AI system had an AUC of 0.74+/-0.14. The demographic baseline had an AUC of 0.64+/-0.16, again not reaching statistical significance. For population wide screening for MCI in the simulated population sample the AI system had a Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of 43.2% and 95.4% at age 50+, and 54.7% and 92.8% at age 65+ (US Medicare population). For Aß pre-screening in the simulated population sample the AI system had a PPV and NPV of 61.8% and 68.0% at age 50+, and 71.2% and 58.2% at age 65+. Such prescreening would reduce the cost of a molecular screening programme at age 50+ and 65+ by 33.8% and 27.9%. **Conclusion:** Speech-based testing offers scalable screening to identify suitable patients for clinical trials and approved treatments.

LP25- AI-DRIVEN PHYSICIAN REFERRAL NETWORK RECRUITMENT INITIATIVE TO DRIVE VOLUME, SPEED AND EFFICIENCY FOR CLARITY AD, A PHASE 3 TRIAL IN EARLY AD (CLARITYAD). Michael Stalder[1], Seth Goodman[1], Erin Beck[1], Russel Harris[2], Kate Tranotti[2], Chad Swanson[2] *(1. SiteRx Inc. - New York, NY (United States), 2. Eisai Inc. - Woodcliff Lake, NJ (United States))*

Aims: Recruitment to Alzheimer's disease (AD) trials is a critical challenge in clinical development. The objective of the SiteRx platform is to use electronic health records (EHR) to identify trial participants for increasing physician engagement and clinical referrals. **Methods:** SiteRx has a nationwide network of community physicians and an AI-driven process for analyzing structured and unstructured EHR data against trial inclusion/exclusion criteria, which is validated by a human reviewer. The physician introduces the trial opportunity to the trial match and initiates the referral if the patient is interested. Support services are provided to referring physicians, patients and sites to enhance patient centricity and reduce site burden. Key performance indicators included speed and conversion from referral to screening to randomization. **Results:** SiteRx provided recruitment services on a late stage early AD trial during the last 3 months of enrollment. A total of 200 patients were referred, of which 90% were contacted by the site, 69% pre-screened, 64% screened, and 15-38% randomized (range due to key protocol changes). Screen fail rates were comparable to study average. Eighty-one percent of referrals signed informed consent within 30 days and patients randomized 53 days from referral on average. Over 10% of referrals were Latinx. Results were achieved despite COVID-19 challenges. **Conclusions:** Platforms that allow physicians to seamlessly identify and refer patients to clinical trials can improve recruitment. Bridging clinical care and clinical research has the potential to improve protocol design, site selection, enrollment timelines and diversity/inclusion in clinical trial research across various therapeutic areas.

LP26- A FIRST LOOK AT TELEMEDICINE USE FOR PRE-SCREENING IN ALZHEIMER'S DISEASE CLINICAL TRIALS DURING A GLOBAL PANDEMIC. Jennifer Mitolo, Elly Lee, Razyya Abdulmumin, Catherine Eng, Ralph Lee, Brenda Martinez *(Irvine Clinical Research - Irvine (United States))*

Background: Alzheimer's Disease (AD) researchers often experience difficulty pre-screening candidates for clinical trials. Identifying quality candidates and actively engaging them in order to ensure continued participation after the initial pre-screen visit are typical barriers to participant enrollment. The Covid-19 pandemic and its associated "lockdowns" added yet another layer of complexity to an already challenging aspect of clinical trials. (Zisko et al, 2020) Historically, potential research candidates came into our research center to meet the team and participate in a short assessment to determine if they may qualify for a particular clinical trial. This proved to be an effective method for identifying eligible research subjects, but was suddenly unavailable as of March 2020. Researchers were quickly required to pivot their strategies. Our site turned to telemedicine (video conference and telephone calls) as a replacement for in-person pre-screen appointments. **Objective:** Our goal was to determine if there is a qualitative and quantitative difference in the population of subjects whose pre-screen visits are conducted virtually versus in-person. We sought to determine if telemedicine would provide the same number of qualified research subjects as the historically used in-person appointment method of engagement and assessment. **Methods:** We gathered data from our pre-screen database from May to August 2021. The data addressed the number of pre-screens conducted via traditional in-person appointments versus the number of pre-screens conducted via telemedicine and the outcomes of each of these modalities. Outcomes were classified as (1) the number of subjects who qualified for screening from each modality, (2) the number of subjects who then enrolled in any clinical trial and (3) how many subjects were lost to contact between pre-screen and screen appointments. **Results:** We analyzed 641 individuals who were prescreened between May and August 2021. Of those, 80% (515 subjects) did not qualify for any current AD trial at our site. Of the remaining 126 individuals who qualified for screening, 78 were seen via videoconference, 17 were conducted via telephone and 31 were seen for in-person appointments. Of these 126 individuals, 79 screened for an AD study. Of these 79, 63.3% screen-failed (50 subjects), 15.2% (12 subjects) randomized into a study, and 21.5% (17 subjects) are still in the screening process. The other 47 subjects did not show up to their screening appointment or were otherwise lost to contact. Additionally, 16% of in-person pre-screens referred for an industry screen were randomized into a study versus only 7% of telemedicine pre-screen referrals. While this isn't statistically significant in the traditional sense, the p value is low enough that it is very unlikely modality has no impact on randomization success ((estimate) 1.0296 (SE) 0.5638 (Z-value) 1.826 p = 6.78%). We intend to continue this data analysis as our sample size increases. Preliminary data analysis did reveal a difference in pre-screen disqualification rate between in-person vs. telemedicine pre-screening. In other words, we found that participants who were pre-screened in-person were more likely to convert to screening than those who were pre-screened through telemedicine (X^2 (1, N= 471) =14.29, p = 0.01). **Conclusions:** Telemedicine may be a favorable solution to some common impediments to clinical trial enrollment. However, after analyzing our preliminary data, we found that we did not have a large enough sample size to detect a statistically significant effect of prescreen modality on subject randomization at this time. In follow-up studies, we will analyze a larger sample size to expand upon these findings. Additionally, we intend to include analysis of the statistical effects potentially introduced by varying raters in future studies. While the data set is still immature these preliminary results indicate there might be differences in identifying quality research subjects when using telemedicine versus in person pre-screening methods. **Reference:** Zisko L, Cordell C, Smith J, Trotter J, Thurman L, Sipchen S. Reinventing Alzheimer's Disease Prescreening:The Global Alzheimer's Platform Foundation® (GAP) Remote Recruitment and Prescreening Program. Poster presented at Clinical Trials on Alzheimer's Disease (CTAD) 2020; November 4-7, 2020; Digital.

RP26- EVALUATION OF EFFICACY AND COST-EFFECTIVENESS OF PROMOTIONS FOR RECRUITING ONLINE PARTICIPANTS TO JAPANESE TRIAL-READY COHORT (J-TRC) STUDY. Kenichiro Sato[1], Yoshiki Niimi[2], Ryoko Ihara[3], Kazushi Suzuki[4], Atsushi Iwata[3], Takeshi Iwatsubo[1] *(1. University Of Tokyo - Bunkyo City (Japan), 2. University Of Tokyo Hospital - Bunkyo City (Japan), 3. Tokyo Metropolitan Geriatric Medical Center Hospital - Itabashi City (Japan), 4. National Defense Medical College - Tokorozawa City (Japan))*

Background: "Preclinical Alzheimer's disease (AD)", where patients exhibit the earliest pathological changes of AD in their brain but have no significant cognitive decline, has now been focused on as primary targets of AD clinical trials for the development of disease-modifying therapies of AD. Web-based registry is considered as suitable for identifying preclinical AD individuals who are eligible for the clinical trials, because they seldom visit hospitals for their cognitive status. For the success of such online registry studies, effective public relations through advertising might be critical; however, while there are many kinds of promotion methods available for clinical trial recruitment, it remains uncertain about which of these promotions may be appropriate in the field of preclinical AD. **Objectives:** The Japanese Trial-Ready Cohort (J-TRC) webstudy (https://www.j-trc.org/) is our ongoing web-based screening registry to identify pre-symptomatic Alzheimer's disease (AD) individuals in Japan, which was adopted its basic system from 'APT Webstudy' being run in the United States. In the first year since its launch in 2019 the J-TRC webstudy had recruited more than thousands of online participants via multiple methods of promotions, including press release, advertisements on newspaper or websites, or e-mail invitations to another cognitive registry. The purpose of this study is to measure the efficacy and cost-effectiveness of these promotion methods quantitatively. **Methods:** Vector-autoregression (VAR) model was applied to the time-series data of daily visits and registrants to the J-TRC webstudy website, in order to evaluate whether or to what extent the advertisement by each promotion method will contribute to increase the daily visitors or registrants to the J-TRC website on the next days. The averaged cost-effectiveness (in JP¥) of each promotion method was calculated using the total cost required and the effectiveness obtained as the coefficients in the VAR model, and converted to the cost-effectiveness in US$ (1 US$ = 109.7 JP¥ on June 13, 2021). **Results:** We reviewed the first 9 months of period from October 2019 to June 2020, and there were approximately 50,000 website visitors and 3,000 eligible registrations in total. Press release at the timing of study launch and successive newspaper advertisements markedly increased the number of daily visitors and daily registrants on the next day of advertisement. The calculated average cost-effectiveness for the initial press release was US$ 24.2 /visitor and US$ 94.6 /registrant, while the calculated average cost-effectiveness for the newspaper advertisements was US$ 28.2 /visitor and US$ 224.3 /registrant, respectively. In February-March 2021 we again performed newspaper advertisement, confirming the similar level of cost-effectiveness of newspaper advertisements: US$ 47.6 /visitor and US$ 329.6 /registrant. Web listing advertisements significantly contributed to increase the daily visitors continuously during the advertising period, but not contributed to the daily registrants. The calculated average cost-effectiveness for the web listing advertisement was US$ 1.8 / visitor. We observed no significant contribution of web banner advertisement to increase the daily visitors or registrants in the current VAR model-based approach. Direct invitation e-mail to other cognitive registry (IROOPTM) also showed no significant effect to increase the daily visitors or registrants, but the website visitors via this approach were more likely to register to the J-TRC webstudy. **Conclusions:** Our multivariate time-series analysis revealed that each promotion method has different features in their effect of recruiting participants to the J-TRC webstudy. Under the advertisement condition settings so far, newspaper advertisements were the most effective promotion method, with fairly-equivalent cost-effectiveness as of earlier studies to recruit participants for clinical trials of other disease domains. Web-based advertisement may have a great potential due to its attractive cost-effectiveness, although we could not confirm its effectiveness sufficiently here, so that improvement of online advertisement to reach to the target individuals (e.g., 60-70 years old people) might be crucial. These results provide important suggestions for the future recruitment of participants for preclinical AD trials in Japan.

RP27- DECISION-MAKING AND REACTIONS ON GENETIC TESTING IN ALZHEIMER'S DISEASE AMONG PATIENTS, CAREGIVERS, AND HEALTHCARE PROFESSIONALS. Amir Tahami[1], Stephen Doogan[2], Nardin Farid[2], Margaret Bray[1], Esra Karahan[1], Quanwu Zhang[1] *(1. Eisai - Woodcliff Lake, Nj (United States), 2. Real Life Sciences - King Of Prussia, Pa (United States))*

Background: Apolipoprotein E- ε4 (APOE-4) is a gene variation known to increase the risk for Alzheimer's disease (AD). Increasingly, patients are opting for APOE-4 genotyping in AD of pre-symptomatic or symptomatic stage. This study was to describe concerns, barriers, planning, and rationale of decisions for testing among stakeholders. **Objective:** To gain insights about the genetic testing in AD from social media narratives posted by patients, caregivers, healthcare providers. **Methods:** We used the RLytics Natural Language Processing (NLP) platform to aggregate and analyze online narratives from over 100 social media portals. The posts were extracted from AD-specific social media using the search terms of "APOE" or "Genetic Testing". Additionally, we extracted posts from non-AD-specific social media sites using only the "APOE" as a search term to exclude posts referring to non-AD-specific genetic tests. RLytics uses syntactic/relational concept models to classify the ways in which medical conditions and functions are reported in raw text. These terms and their relationships, e.g. diagnostic relations, functional impairment relations, etc., were analyzed using RLytics. A total of 2,558 narrative posts were analyzed. These posts were classified into 21 mid-level themes and made by 261 unique online participants. Individuals who potentially posted online narratives using different web usernames would be counted as different participants. Of all participants, 95 were identified as patients, 130 caregivers, and 36 healthcare professionals (HCP). The narrative posts were classified into 21 mid-level themes and 8 high-level themes based on a 'bag of words approach'. Each post might contain more than one theme hence they were classified accordingly.**Results:** Of the 1,132 posts from patients, 393 (34.7%) posts contain contents about unmet needs for information, education, and peer support, 370 (32.7%) about financial concerns such as testing costs and insurance coverage, 377 (33.3%) about logistical challenges, 150 (13.3%) about a need for genetic counseling, 70 (6.2%) about (potential) emotional impact, 16 (1.4%) about family planning, 186 (16.4%) about data privacy and security, and 411 (36.3%) expressed psychological uncertainty with testing accuracy. Of the 1,355 posts from

caregivers, 478 (35.3%) posts contain contents about unmet needs for information, education, and peer support; 492 (36.3%) about financial concerns, 442 (32.6%) about logistical challenges, 166 (12.3%) about genetic counseling, 87 (6.4%) about (potential) emotional impact, 20 (1.5%) about family planning, 216 (15.9%) about data privacy and security, and 502 (37.0%) expressed uncertainty. Of the 71 posts from HCPs, 15 (21.1%) posts contain contents about the need for patient education on genetic testing, 8 (11.3%) about the testing cost for patients, 7 (10%) about logistical challenges, 4 (5.6%) about the need for patient genetic counseling, and 15 (21.1%) expressed uncertainty about tests. The eight high-level categorical themes may be illustrated with sample statements by stakeholders as follows: 1) Unmet needs for information, education, and peer support: e.g. Has anyone been tested? Any ideas about cost? Would genetic testing help confirm a diagnosis of early onset AD? 2) Financial concerns: e.g. "It was going to cost about $8000 … which was more than I could afford". 3) Logistical challenges - challenges with finding affordable or available channels for testing: e.g., "I was suggesting there might be university studies or clinical trials which would involve genetic testing." 4) Need for genetic counseling: e.g., "Genetic counseling is very important and should be included if you go for genetic testing". 5) Emotional impact: e.g. "This finding on 23andMe has me spinning and questioning every little thing I forget. It does feel like a ticking time bomb, and it's really scary." 6) Family planning: e.g., "I'm interested in genetic testing because I'm trying to decide if I want to have children." 7) Data privacy and security: e.g., "There is so much bias out there regarding potential risk… as well as future employers who would not want this to be an issue for themselves". 8) Uncertainty about accuracy or value of testing: e.g., "I think genetic testing for AZ is still in its infancy and there is a long way to go before a test would be able to categorically state to a high level of accuracy whether you would get the disease." **Conclusion:** This study of online narratives over social media sites presents a variety of barriers for APOE-4 genotyping in AD and unmet educational needs to aid the decision making on the genetic testing. It also suggests potential benefits of timely APOE-4 testing for proactive AD disease management and personal/family planning, perceived by patients, caregivers and healthcare professionals.

RP28- AMYLOID PREDICTION IN EARLY-STAGE ALZHEIMER'S. Emil Fristed, Marton Meszaros, Caroline Skirro1, Jack Weston *(Novoic - London (United Kingdom))*

Background: Recent research has identified subtle cognitive changes during the preclinical stages of Alzheimer's disease (AD), in domains including episodic memory, potentially due to amyloid accumulation in the hippocampus, and in semantic memory, potentially due to accumulation of tau in the entorhinal and perirhinal cortex. At the prodromal stage, a similar but more pronounced impairment is observed. Other retrospective studies have identified changes in linguistic patterns decades before disease onset. These cognitive changes can be reflected in how someone speaks, for example in more vague retellings (episodic memory), less semantic diversity (semantic memory), or more improbable sentences (linguistic patterns). Today, speech can easily be collected remotely via mobile devices, and audio- and text-based machine learning models can be used to extract sensitive biomarkers. To date, there are no studies combining deep speech phenotyping with an early-stage biomarker-confirmed Alzheimer's disease population. **Objectives:** To describe the study design for the AMYPRED and AMYPRED-US studies, two sister studies to evaluate the ability of speech-based algorithms to detect amyloid-confirmed prodromal and preclinical Alzheimer's disease. **Methods:** AMYPRED and AMYPRED-US are observational, cross-sectional, case-control sister studies in the UK (multi-site) and US (single-site). The studies have been designed to allow for out-of-sample validation of the tested algorithms across geographies. AMYPRED and AMYPRED-US will enroll approximately 140 and 80 participants respectively, across four arms: Mild Cognitive Impairment (MCI) amyloid positive (Arm 1), MCI amyloid negative (Arm 2), Cognitively Normal (CN) amyloid positive (Arm 3), and CN amyloid negative (Arm 4). Inclusion required confirmation of amyloid status, either through PET or CSF sampling; with test results at most 30 months old for negatives, and 60 months for positives. Enrolled participants are aged 50-85, with MMSE scores of 23-30 for the MCI, and 26-30 for CN cohorts. Additional inclusion criteria includes English as a first language, availability of a caregiver, and an eligible smartphone device for the remote self-assessments. Key exclusion criteria include current or recent history of general anxiety disorder, major depressive disorder, unstable psychiatric illnesses, stroke or transient ischaemic attack. Participants treated with medications for symptoms related to AD are required to be on stable doses for a minimum of 8 weeks prior to participation. Visits are performed remotely through video-conference in AMYPRED and in-person in AMYPRED-US. Eligibility is evaluated at a combined screening/baseline visit, where demographic, medication and medical history information is recorded, and the Mini Mental State Examination (MMSE) is administered. Eligible participants complete the rest of the screening/baseline visit, where neuropsychological testing, including the Preclinical Alzheimer's Clinical Composite with semantic processing (PACC5), CDR and a subjective memory decline questionnaire are administered, together with a set of audio-verbal assessments, designed to elicit open-ended, connected speech. Audio-verbal assessments are recorded via Novoic's mobile application using the participant's own smartphone and, in AMYPRED-US, high-definition recording equipment. In both studies, the screening/baseline visit is followed by a week of remote, self-administered testing. Here fully automated audio-verbal assessments are self-administered daily through Novoic's mobile application, and the elicited speech automatically recorded. Participants of all four cohorts complete the same assessments, with minor differences in the assessment schedule between AMYPRED and AMYPRED-US. Audio-verbal tasks most notably include a novel story recall task, the Automated Story Recall Task (ASRT), designed for repeated remote administration, where both the administration and analysis can be fully automated. Other tasks included multiple variations of describing pictures, describing how to carry out everyday tasks, reading a scripted passage, and semantic and phonemic category fluency tests – administered both in the visit and as remote self-assessments. **Results:** The primary objective of both studies is to evaluate whether speech-based algorithms can detect amyloid-specific cognitive impairment in early stage Alzheimer's disease, as measured by the Area Under the Curve (AUC) of the receiver operating characteristic curve of the binary classifier distinguishing amyloid positive (Arm 1 and 3) from amyloid negative (Arm 2 and 4) arms. Secondary objectives are to evaluate these algorithms as measured by binary classifier performance (AUC, sensitivity, specificity, Cohen's kappa) for detecting (1) amyloid in prodromal (Arm 1 vs 2) and preclinical AD (Arm 3 vs 4) separately; and (2) cognitive impairment (Arm 1+2 vs Arm 3+4). Additionally, agreement between the PACC5 composite and

the corresponding regression model predicting PACC5 from speech in all arms pooled (Wilcoxon signed-rank test, coefficient of individual agreement). Participants that enroll in either AMYPRED and AMYPRED-US are offered to enroll into two extension studies: FUTURE(-US) and PAST(-US). FUTURE extension studies are three year longitudinal studies with yearly visits for neuropsychological testing and ongoing remote self-assessment. PAST extension studies are retrospective, collecting past spoken and written material. **Conclusion:** AMYPRED and AMYPRED-US will evaluate the ability of speech-based algorithms to detect amyloid-confirmed prodromal and preclinical Alzheimer's disease.

RP29- A MULTI-MODAL CURRICULUM ON DEMENTIA-RELATED PSYCHOSIS FOR THE PUBLIC: A RANDOMIZED TRIAL. Nabeel Saif, Kellyann Niotis, Ciara Gaglio, Richard Isaacson *(Weill Cornell Medicine - New York (United States))*

Background: There are several symptoms of Alzheimer's disease and related dementias (ADRD) that are commonly understood by the general public, including loss of memory, global confusion, and problems with language, to name a few. However, other debilitating symptoms, such as psychosis, delusions, hallucinations, and paranoia are commonly misunderstood by people with dementia, their caregivers, and their family members. Considering this, there is an unmet need to educate the public on these lesser-known symptoms, which are commonly referred to as dementia-related psychosis (DRP). Alzheimer's Universe (www.AlzU.org) is an online tool created to raise awareness about ADRD among patients, family members, caregivers, and clinicians. AlzU.org provides evidence-based content to educate users about AD risk reduction and management. Tailored courses are provided to six target audiences, including the general public, healthcare providers, neurology resident trainees, medical students, college and high school students. Advantages to internet-based tools such as AlzU.org include large audience reach and access where local support may not be insufficient. **Objectives:** The purpose of this randomized study was to evaluate the effectiveness of different digital mediums to teach the general public about DRP management. We developed a two-lesson e-learning curriculum with learning objectives including: (1) Understand changes in the brain that lead to DRP; (2) Understand DRP symptoms, such as hallucinations, delusions, paranoia; (3) Learn the roles of healthcare providers, patients, family, and caregivers in the supervision of people with DRP; and (4) Learn caregiving tips and non-pharmacologic interventions that are useful for coping with alterations in behavior. Lessons were offered across three distinct digital mediums: (1) interactive webinar lesson which contain intra-periodic questions, (2) video lessons that do not require user interaction, and (3) audio-only lessons that do not contain any visuals, similar to a podcast. **Methods:** Participants were recruited via social media advertisements (e.g., Facebook, Instagram) to join AlzU.org and participate in the online study. After informed consent was obtained, users were randomized to one of the three lesson formats listed above. Users were required to complete a quiz that contained three multiple choice questions before and after each lesson. Surveys were administered at baseline to collect user demographics, as well as after each lesson to assess users' self-reported attitudes towards lesson content and format using 1-5 Likert scales (5 being the best rating). **Results:** From November 2020 to May 2021, 14,675 users were recruited to participate in the study. Users predominantly listed their gender as women (87.39%) and their ethnicity as White or Caucasian (83.50%). The average user age was 58.36 years old. Users most commonly described themselves as either "having no personal connection to dementia, but I want to learn more" (25.43%), being "a child of a person with dementia" (24.18%), or being "a person with memory loss" (10.83%). At baseline, the highest percentage of users preferred the video lesson format for education about brain health (48.00%), followed by interactive webinar lessons (27.47%), and audio-only lessons (24.53%). The mean score on the pre-lesson multiple choice quizzes was 2.51 correct (out of 6 questions) for all three groups. All three groups scored higher on the post-lesson quizzes (all $p<0.0001$). Quiz score improvements were significantly greater for the interactive webinar users (mean score improvement of 2.81) compared to video lesson users (difference 0.67, $p<0.0001$) and audio-only lesson users (difference 1.46, $p<0.0001$). When comparing post-lesson survey responses, Video lesson users strongly valued the information in the lesson (mean 4.50, SD 0.39) significantly greater than the interactive webinar (difference 0.44, $p<0.0001$) and audio-only lesson users (difference 0.82, $p<0.0001$). Video lesson users reported learning from this style of teaching (mean 4.51, SD 0.41) significantly greater than the interactive webinar (difference 0.43, $p<0.0001$) and audio-only lesson users (difference 1.11, $p<0.0001$). Video lesson users reported finding the lesson easier to navigate (mean 4.47, SD 0.41) significantly greater than the interactive webinar (difference 0.57, $p<0.0001$) and audio-only lesson users (difference 0.25, $p<0.0001$). Video lesson users reported wanting more lessons in this format (mean 4.55, SD 0.39) significantly greater than the interactive webinar (difference 0.54, $p<0.0001$) and audio-only lesson users (difference 1.26, $p<0.0001$). **Conclusion:** While self-reported survey measures demonstrated that users preferred the video lessons and believed that they learn more compared to users with other lesson formats, users who completed the interactive webinar lessons actually saw the greatest improvement in quiz scores. Further research is warranted to better understand why there exists this discrepancy between self-assessed knowledge transfer and objective knowledge assessments. Additionally, the low mean in pre-lesson quiz scores highlights the importance of educating the general public about DRP and DRP management. As such, it is essential that future efforts are made to address this unmet need in public health education.

RP30- COMPARISON OF THE ACCURACY OF COGNICITI'S SELF-ADMINISTERED, ONLINE, BRAIN HEALTH ASSESSMENT TO THE MONTREAL COGNITIVE ASSESSMENT IN DETECTING AMNESTIC MILD COGNITIVE IMPAIRMENT. Theone Paterson[1,2], Brintha Sivajohan[3], Sandra Gardner[4], Malcolm Binns[5], Kathryn Stokes[2], Morris Freedman[6,5,7], Brian Levine[5,8], Angela Troyer[2] *(1. University Of Victoria - Victoria (Canada), 2. Baycrest Health Sciences Centre - Toronto (Canada) - Toronto (Canada), 3. Western University - London (Canada), 4. Baycrest Health Sciences Centre - Toronto (Canada), 5. Rotman Research Institute - Toronto (Canada), 6. Baycrest Health Sciences Centre-Toronto (canada) - Toronto (Canada), 7. Toronto Dementia Research Alliance - Toronto (Canada), 8University of Toronto - Toronto (Canada))*

Background: As the population ages, there is an increasing need for easily administered online assessments sensitive to mild cognitive difficulties not only for clinical practice but also to support research trial initiatives. There are currently few digital cognitive assessments readily available for self-administration online. Cogniciti's Brain Health Assessment

(BHA) provides statistically normed results for those aged 20-94, allowing for its use across the adult lifespan. The BHA is, therefore, uniquely positioned to provide self-administered clinical screening for cognitive impairment. **Objectives:** Our team has recently presented data indicating the accuracy of the BHA. The aim of the present study was to further examine the utility of the BHA compared to that of the Montreal Cognitive Assessment (MoCA) in detecting amnestic mild cognitive impairment (aMCI) in a sample of community dwelling older adults, and to provide indication of convergent validity between tasks on the BHA and standard clinical neurocognitive assessment tasks measuring similar constructs. **Method:** Using a cross-sectional design, community-dwelling older adults aged 60-89 completed a gold standard neuropsychological assessment to determine a diagnosis of normal cognition (NC) or aMCI (by consensus of 3 staff neuropsychologists). Each participant also completed the BHA and MoCA. Penalized logistic regression (PLR) analyses were used to examine which specific BHA tasks and measured demographic variables contributed to this test's predictive utility in detecting aMCI; MoCA variables were similarly modeled along with demographics, in a separate PLR analysis. Diagnostic accuracy of the PLR models for the BHA and MoCA were compared using area under the receiver operating characteristic curve (ROC-AUC) analyses. Pearson correlations were examined between traditional neuropsychological measures and BHA tasks to assess convergent validity. **Result:** 91 participants met inclusion criteria (51 aMCI, 40 NC). PLR modelling for the BHA indicated Face-Name Association, Spatial Working Memory, and age predicted aMCI (ROC-AUC = 0.76; 95%CI: 0.66, 0.86). Optimal cut-points resulted in 21% classified as aMCI (positive), 23% negative, and 56% inconclusive. For the MoCA, digits, abstraction, delayed recall, orientation, and age predicted aMCI (ROC-AUC = 0.71; 95%CI: 0.61, 0.82). Optimal cut-points resulted in 22% classified positive, 8% negative, and 70% inconclusive (standard logistic regression [LR] results will also be presented). The BHA model classified fewer participants into the inconclusive category and more as negative for aMCI, compared to the MoCA model (Stuart-Maxwell p = 0.004). Convergent validity of the BHA tasks was supported by moderate to large effect correlations between BHA and standard clinical tasks. **Conclusion:** There is a need for brief cognitive assessment tools that can detect early signs of cognitive decline in clinical practice and aid in appropriate participant selection into research trials. Online, self-administered measures provide potential for broad reach of cognitive screening to individuals who may otherwise not be easily reached to receive clinical or research assessments. The self-administered BHA showed similar detection of aMCI as compared to the clinician-administered screener (MoCA), with fewer participants classified inconclusively. Given the BHA is an online, self-administered task, this measure has the potential to save practitioners and researchers time, decrease unnecessary referrals for comprehensive assessment to determine presence of aMCI, and improve selection into trials of potentially efficacious early interventions.

RP31- "COMUNICHIAMO": AN E-HEALTH PILOT STUDY FOR THE DEVELOPMENT OF A COMUNITY SUPPORT NETWORK FOR CARERS OF PEOPLE WITH DEMENTIA.

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Background: Most people with dementia (PwD) are supported by unpaid informal caregivers, usually spouses or children. Caregivers often experience poor physical and psychological health, an impaired immune response, and work and financial difficulties. Although established psychoeducation programs are known to benefit caregivers, attending in-person programs is challenging since this requires time, arrangement for transportation and support for care, all of which entail more financial burden. **Objectives:** The project aimed at creating a community network of social and long-term care support for informal caregivers of PwD based on a close collaboration among dementia professionals, social workers and local non-profit associations. The expert network developed a psycho-educational program to provide caregivers with detailed pieces of information on neurocognitive disorders, their management, and municipal or national services addressed to PwD and their family members. In other words, all the skills and perspectives needed to undertake and succeed in the caregiver role. **Methods:** The Internet-based psycho-educational programme was delivered to groups of 8-12 caregivers in eight weekly sessions lasting two hours and led by a skilled psychotherapist. Each meeting addressed an a priori topic defined and presented by a professional expert in the care of PwD (i.e., a geriatrician, a neuropsychologist, an educator, a psychologist, or a social worker). Caregivers of PwD in mild-to-moderate stage and home residents were recruited by social workers from two towns in the province of Brescia (Italy) or by advertisements in local newspapers. A pre-test–post-test design was used. The content was partially adapted from the "Savvy Caregiver program", a well-known caregiver training program (Hepburn et al. 2008). Before and after intervention, participants completed the following self-administered scales, the State-Trait Anxiety Inventory [STAI-Y]), the Zarit Burden Interview [ZBI], and the Short Form 12 Health survey [SF12]. They were also asked to complete an anonymous form regarding their satisfaction with the course. **Results:** The intervention was repeated 4 times from October 2020 and march 2021, during the Covid-19 Health Emergency. A total of 42 caregivers (mean age: 57; range 31-82; female: 78%; sons: 61%) were involved. PwD had neurodegenerative disease of different aetiology at mild to moderate stage (mean MMSE: mean±SD=19±5), and with a significant frequency and severity rate of behavioural symptoms (NPI:18±11). Almost all (97%) enjoyed the online mode. The project had high participation and high adherence rate (88% attended at least 7 meetings), with a final attrition rate of only 2.4%. All topics covered were perceived to be useful by at least 81% of participants, with an average satisfaction index of 3.3 on a scale of 1 (not satisfied) to 4 (very satisfied). At the end of the course, 72% of the caregivers reported mental benefit

and 44% even an improvement in their relationships. The benefit stems primarily from increased knowledge on dementia symptoms and their management. A statistically significant change in the anxiety and burden scales was observed (STAI-Y1: deltapre-post = 4.6, t(40) = 3.17, p = 0.003; STAI-Y2: deltapre-post=2.49, t(40) = 2.33, p = 0.025);ZBI (deltapre-post= 4.3, t(40) = 2.29, p = 0.027). Almost half (47%) reported of being more aware of the right and the need to carve out their own private space, involving other family members/friends or turning to the social and health services. As proof of this, the SF-12 revealed an improved personal physical well-being, with increased vitality (Physical Component Summary deltapre-post= -2.4, t(40) = 2.56, p = 0.014). **Conclusion:** Results point to the feasibility of achieving significant results in caregivers' well-being with a fully online program. Participants found the program educational, practical, useful and interesting. They endorsed feeling more confident in caregiving skills and communication with their family members. The intervention has been an important support for caregivers, both in overcoming isolation during periods of closure and in establishing lasting relationships with neighbours with similar problems and with experts working in the area. The combination of technology and community approach appears to meet psychoeducational needs for knowledge of disease management and avoiding caregivers' social isolation. Prospective, randomized studies are needed to better evaluate the long-term effect of this type of intervention.

RP32- VRCT: RANDOMIZED CONTROLLED TRIAL EVALUATING THE IMPACT OF VIRTUAL REALITY-THERAPY ON BPSD AND QOL OF ACUTE CARE IN-PATIENTS WITH DEMENTIA Lora Appel[1], Eva Appel[2], Erika Kisonas[2], Jarred Rosenberg[3], Julian Appel[4], Christopher Smith[3] *(1. York University - Toronto (Canada), 2. University Health Network - Toronto (Canada), 3. Michael Garron Hospital - Toronto (Canada), 4. Ryerson University - Toronto (Canada))*

Background: Virtual reality (VR) technologies have increasingly been considered as valuable tools in dementia-related assessments (cognitive and physical) and treatments (to manage Behavioural and Psychological Symptoms of Dementia (BPSDs) and improve quality of life (QoL)). Prior studies in community-care settings have shown that it is feasible for frail older adults with varying degrees of cognitive impairment to wear VR head-mounted displays (HMDs) and engage with VR environments. To our knowledge, no studies have rigorously evaluated the impact of VR-therapy on people with severe cognitive impairment admitted to acute-care hospitals. The present Randomized Controlled Trial (RCT) was informed by a pilot study at the same institution, as well as outcomes from a multi-site feasibility study including an outpatient clinic, a rehabilitation hospital, a long-term care home, and a day program centre for people with dementia. **Objectives:** The primary objectives of this RCT were to evaluate the impact of VR-therapy on reducing BPSDs, number of falls, length of stay (LoS), and improving QoL for inpatients with dementia admitted to an acute care hospital. **Methods:** This was an open longitudinal interventional RCT conducted at an acute-care community teaching hospital in Toronto, Canada (ClinicalTrials.gov, ID:NCT03941119) between April 29, 2019 and March 13, 2020. The research was temporarily stopped due to the first wave of COVID-19, and recruitment was later permanently closed due to the ongoing pandemic and restrictions on research, particularly with this vulnerable population. **Participants:** Electronic Medical Records (EMR) were screened daily to determine if newly admitted inpatients met the study eligibility (aged ≥65, diagnosis of dementia, and did not meet exclusion criteria). A total of 77 patients were consented, enrolled in the study and randomized into one of two arms: the control arm (following current standard of care) (n = 39) and the treatment arm (receiving VR-therapy once every 1-3 days) (n = 38). In the intervention arm 29 participants completed at least one session of VR-therapy. A CONSORT diagram describes the participant flow. **Protocol:** During their hospital stay, consented patients participated in one or more study sessions (treatment or control) every 24-72h during their stay. In the first study session, the Research Coordinator (RC) conducted a baseline demographic survey with the participant and their caregiver (if present). At the beginning of each study session, the RC conducted a short survey with the participant and filled out the modified QUALID after at least 5 minutes of conversation. If assigned to the control arm, the participant continued per current standard of care (i.e., no exposure to VR-therapy). If assigned to the intervention arm, the RC obtained verbal and/or physical assent from the participant before applying the VR HMD (Oculus Go) to the participant's head. Participants watched 360-degree VR films for up to 20 minutes. The RC used a standardized tool "ObsRVR" to observe and record the participant's reactions while experiencing VR, and conducted a semi-structured interview asking the participant's feedback on various aspects of the VR-therapy session, including their willingness to participate in additional sessions. Once discharged from the study, factors related to participants' hospital care experience (e.g., falls with/out injury, LoS) and instances of daily BPSDs recorded in nursing documentation were collected from the hospital's EMR. **Results:** VR-therapy had a statistically significant effect (p=0.015) on reducing the cluster of aggressive BPSDs (including Aggression, Screaming/Loud Vocalization, Restraints Applied, Security Intervened, Bedside Sitter). All other BPSD clusters as categorized by the NPI-10 (Wandering, Delusions, Hallucinations, Agitation, Depression, Anxiety, Apathy, Irritability, Euphoria, Disinhibition and Aberrant Motor Behaviour) as well as the number of falls while in hospital, had changes that were not statistically significant. There was a small (-0.122) correlation between receiving VR-therapy and LoS (p=0.16). This may represent a clinically significant decrease in LoS (17%) and warrants further research on the impact of VR-therapy on LoS. Changes in QoL were not observed between study arms or participants in the same arm over time, but it was noted that QoL scores were very high at baseline, leaving little room for possible increases. **Conclusion:** Immersive VR-therapy appears to have a positive effect on some behaviours (i.e., cluster of "aggressive" BPSDs) and might reduce the LoS for inpatients with all stages of dementia in acute-care settings. Due to the COVID-19 pandemic, this RCT was interrupted prematurely, before reaching the required sample size to allow for statistical significance in most outcomes; however, trends in the results were promising. The study's partial results support conducting further research, particularly in acute-care settings which present special challenges but may produce considerable benefits for the target patient population and the hospital staff as well. The protocol and outcome measurement instruments may need revising; for example, the QUALID tool was not sensitive enough to capture changes in QoL over the typical short acute-care hospitalization, as was the case with other selected instruments used in this RCT.

LRP12- REMOTE ACTIGRAPHY MEASUREMENT WITH A SIMPLE-TO-USE WEARABLE DEVICE: FEASIBILITY AND COMPLIANCE IN OLDER ADULTS WITH AND WITHOUT SUBJECTIVE COGNITIVE DECLINE. Michael Kraus, Alexandra Atkins, William Horan, Heather Stevens, Erica Walton, Joshua Yuan, Matthew Welch, Haley Evans, Richard Keefe *(Verasci - Durham (United States))*

Background: Low physical activity has been identified as a potentially modifiable risk factor for Alzheimer's disease, and increasing physical activity may improve memory and delay cognitive decline among individuals with mild cognitive impairment. Wearable actigraphy monitors present an opportunity to directly measure real world physical activity while patients are engaged in their daily lives. However, the utility of remotely gathered wearable data is dependent on adequate compliance from study participants. A wide variety of actigraphy monitors have been employed in clinical trials and monitors differ in several ways, including the number and types of sensors, sampling rate, and form factor. Monitors also differ substantially in how burdensome they are for participants, with many requiring frequent battery recharging and data offloading. In older individuals, more burdensome devices can lead to higher levels of non-compliance, and may do so differentially based on cognitive status. We previously observed higher rates of noncompliance in individuals with subjective cognitive decline (SCD) compared to healthy controls (HC) when using an actigraphy device with typical maintenance requirements, including daily recharging and Bluetooth pairing with a study phone to upload data. **Objectives:** Here we report compliance rates when using a wrist-worn actigraphy wrist monitor with low maintenance requirements for the real-time capture of actigraphy measures in older adults with and without subjective cognitive decline. **Methods:** Participants included 61 older adults (age 55 or greater), including 41 HC and 20 individuals with SCD. Individuals were categorized as endorsing SCD based on total scores of ≥ 4 on the Cognitive Functional Instrument (CFI). Participants completed 2 office visits approximately 1 week apart. During Visit 1, participants completed a standard test battery that included the Mini-Mental State Examination (MMSE) to assess cognition, the Virtual Reality Functional Capacity Assessment Test (VRFCAT) to assess functional capacity, and the ADCS-ADL-PI Self-Report to assess Activities of Daily Living. Participants were then fitted with an Actigraph CentrePoint Insight Watch that provides continuous measurement of compliance, motor activity (i.e., actigraphy), and sleep. The Insight watch features battery life and on-board memory sufficient for up to 1 month data collection without the need to recharge or transfer data off the device. Participants were trained on using the Actigraph watch at home and instructed to wear the device as much as possible during the following week. Participant compliance was not monitored remotely, but participants were given a study help number to call if they experienced any issues with the Actigraph watch. After 1 week of continuous at-home data collection, subjects returned for a second visit. Participant data was transferred from the activity monitor to Actigraph's cloud based CentrePoint platform. An a priori compliance threshold was set at 10 hours of wear time data per day for that day to be considered a valid day of data collection. **Results:** Participants with SCD performed significantly worse than HC on the MMSE , ($p=.02$, Cohen's $d=.64$) and VRFCAT Adjusted Total Time ($p=.01$, Cohen's $d=.76$), indicating objective cognitive and functional capacity impairments in the SCD sample. Participant's with SCD also reported worse activities of daily living on the ADCS-ADL-PI than HC ($p<.01$, Cohen's $d=1.38$). Participants in both the HC and SCD groups exhibited high levels of compliance with the Actigraph Insight watch. On days 2 through 7 (first through last full days in the study), HC wore the watch 23.77 hours per day on average, while individuals with SCD exhibited a mean compliance of 23.71 hours per day, which did not significantly differ, $t(59)=.58$, $p=.57$. Of the 366 total days of actigraphy monitoring (61 participants x 6 days), the worst single day of compliance was 17.13 hours of wear, easily exceeding the a priori 10 hour wear compliance threshold. Thus, there was no missing data in the actigraphy dataset for this study. **Conclusion:** These findings suggest that assessment of actigraphy in older individuals is feasible, even in those that endorse subjective cognitive decline. The very high compliance rates observed in this study are likely attributable to the relatively simple-to-use wearable device. We previously found substantially lower compliance rates in older individuals both with and without SCD using an actigraphy watch with more complex maintenance requirements, including frequent charging and the need to maintain a Bluetooth connection to transfer data to free up memory on the watch. Individuals with SCD particularly struggled with these more demanding maintenance requirements and demonstrated even lower compliance than HC. Taken together, our findings suggest that ease of use of an actigraphy device is a crucial determinant of compliance rates in older individuals, particularly those with SCD. **Conflict of Interest:** Michael Kraus, Alexandra Atkins, William Horan, Heather Stevens, Erica Walton, Joshua Yuan, Matthew Welch and Haley Evans are full-time employees of VeraSci. Richard Keefe is co-founder and CEO of VeraSci and receives royalties from the Virtual Reality Functional Capacity Assessment Tool (VRFCAT).

LRP13- A MACHINE LEARNING BASED MULTI-MODAL IMAGING GENETIC STUDY TO PREDICT FUTURE PROGRESSION AND CONVERSION TO ALZHEIMER'S DISEASE. Ghazal Mirabnahrazam[1], Da Ma[1], Sieun Lee[1,2], Karteek Popuri[1], Hyunwoo Lee[3], Jiguo Cao[1], Lei Wang[4], James E Galvin[5], Mirza Faisal Beg[1] *(1. Simon Fraser University - Burnaby (Canada), 2. University Of Nottingham - Nottingham (United Kingdom), 3. University Of British Columbia - Vancouver (Canada), 4. Ohio State University Wexner Medical Center - Columbus (United States), 5. University Of Miami Miller School Of Medicine - Miami (United States))*

Background: Alzheimer's Disease (AD), or Dementia of Alzheimer's type (DAT), is a progressive neurodegenerative condition that accounts for 60% to 80% of all dementia cases. As there is no currently available cure, it is critical to invest in developing biomarkers that can detect those at risk at an early stage of the disease and before the symptomatic onset. The increasing availability of databases containing both magnetic resonance imaging (MRI) and genetic data allows researchers to utilize multimodal data to better understand the characteristics of DAT. However, due to the high dimensionality of genetic data, existing image/genotype studies of DAT mainly focused on Single Nucleotide Polymorphisms (SNPs) from previously known DAT-related genes. Such approaches rely on existing knowledge, which may reduce the likelihood of discovering novel genetic risk factors that can be useful in the drug discovery procedures. **Objectives:** The goal of this study is to develop and analyze novel biomarkers that can help predict the development and progression of DAT using multimodal MRI and genetic data. In addition, we address the above-mentioned potential limitations by using all available SNPs

in the Alzheimer's Disease Neuroimaging Initiative (ADNI) database to uncover potentially new genetic risk factors of DAT. **Methods:** The data in our study is from the ADNI database. A total of 543 subjects, who had both MRI and genetic data available, are included in the study. We employ a database stratification method that focuses on the subjects' past, present, and future clinical diagnoses. This method divides the subjects into seven novel subgroups which are as follows: 1) stable Normal Control (sNC), 2) unstable Normal Control (uNC), 3) progressive Normal Control (pNC), 4) stable Mild Cognitive Impairment (sMCI), 5) progressive Mild Cognitive Impairment (pMCI), 6) early Dementia of Alzheimer's Type (eDAT), and 7) stable Dementia of Alzheimer's Type (sDAT). If a subgroup includes a follow-up diagnosis of DAT, it's categorized as DAT+. Otherwise, it belongs to the DAT- category. We utilize a 2-stage probabilistic multi-kernel classifier. The first stage focuses on the feature selection using 10-fold cross-validation: in each fold, we select the most discriminative features by applying Fisher's Exact test on SNP data and Welch's t-test on MRI data using subjects in the subgroups with the most certain clinical diagnoses at their baseline test (sNC in DAT- and sDAT in DAT+). In the second stage, using only the most frequently selected features above, we retrain on 80% of sNC and sDAT, validate on the remaining 20%, and test on subjects in the remaining subgroups with milder clinical diagnoses (uNC and sMCI in DAT- and pNC, pMCI, and eDAT in DAT+). Three experiments were carried out using: 1) MRI-only, 2) genetic-only and 3) MRI+genetic features. The DAT score is the output of our model, and it indicates the probability p Є [0 1] that the input data belongs to the DAT+ class, and 1−p denotes the probability of DAT- membership. We use a threshold of 0.5 to create a diagnostic label of DAT- or DAT+ from the DAT score. Finally, we compare the effects of using MRI, genetic, and their combination on the predictive power of our model. **Results:** Our study showed that although genetic features have a lower prediction power than MRI features, combining both modalities can improve the prediction accuracy of future conversion to DAT. For subjects in the pNC subgroup, dementia scores based on genetic data could better predict future DAT progression (Accuracy=0.857) compared to MRI (Accuracy=0.143), while MRI could better characterize subjects in the sMCI subgroup (Accuracy=0.614) compared to genetics (Accuracy=0.356). Our feature selection method has successfully identified SNPs that overlap with significant genetic risk factors already mentioned in the literature as well as some novel risk factors that could advance clinical diagnostics in the future. **Conclusion:** Our study showed that MRI and genetic data can contribute to DAT prediction in different ways. Specifically, MRI data can reflect anatomical changes in the brain at early stages of AD-related symptomatic onset, while genetic data is more sensitive to detecting the risk of DAT progression prior to the symptomatic onset. An effective combination of information from both modalities can improve prediction performance. Our results showed that using effective feature selection methods alleviate the constraint of relying only on prior knowledge about known AD-related genes to achieve optimal results. Having biomarkers that can accurately predict a patient's likelihood of developing AD will lead to an accurate prediction of time to conversion to AD, which can be beneficial in clinical trials and can speed up the search for the best treatment option at the right time.

HEALTH ECONOMICS AND CLINICAL TRIALS

P68- STAYING SHARP BEYOND THE AGE OF 65 YEARS: A SOCIAL MARKETING APPROACH TO THE PROMOTION OF COGNITIVE HEALTH IN LUXEMBOURG.

Mathilde Barbier[1], Anna Elena Kornadt[1], Carine Federspiel[2], Jean-Paul Steinmetz[2], Claus Vögele[1] *(1. University Of Luxembourg - Esch-Sur-Alzette (Luxembourg), 2. Zitha - Luxembourg (Luxembourg))*

Background: Offerings for active ageing in developed economies have been increasing. The WHO report on ageing and health has made recommendations to align health systems to the needs of older people. Yet during the time since this report was issued, no one has yet described these specific needs and how the WHO's recommendations can be properly followed. There is little scientific evidence on how participation in activities designed for the promotion of cognitive health can be increased. **Objectives:** Using the Behaviour Change Wheel, this study aims to identify, for the first time, how elderly people perceive their capability, opportunity, and motivation to adopt cognitive health promoting behaviours. **Methods:** Semi-structured interviews with older people aged 65+ years without cognitive impairment (n = 20), and physicians (n = 10; general practitioners and geriatricians), in Luxembourg are used to assess elderly people's perceptions. The data from the interviews transcripts are analysed using content analysis. **Results:** The findings emphasise the importance of the social role one which must be preserved past State retirement age. **Conclusion:** From a social marketing perspective, we will discuss clear strategies to ensure the adequacy of pension systems in responding to the older people's needs. The results of this qualitative study will provide information to be integrated into a large questionnaire survey. In due course, it hopes to empower older people and ultimately enable them to remain both active, healthy and well-being beyond the age of 65 years. The authors declare no conflict of interest.

P69- UNDERSTANDING TREATMENT GOALS FOR PATIENTS AND CAREGIVERS WITH ALZHEIMER'S DISEASE ALONG THE CONTINUUM OF THE DISEASE CONSIDERATION IN CLINICAL TRIAL DESIGN.

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Background: Regulators, like the Food and Drug Administration (FDA), recommend global scores, including functional and cognitive components, as primary endpoints in Alzheimer's disease (AD) clinical trials (FDA, 2018). However, patients and caregivers may have wider views toward relevant outcome measures in AD (Reynolds et al., 2017). Initiatives such as "What Matters Most" have attempted to quantify the importance of symptoms, impacts and outcomes of AD for patients and caregivers, showing a multi-dimensional pattern of meaningful items (Hauber et al., 2020). **Objective:** To evaluate what are the most important treatment goals to AD patients and caregivers, for consideration in the design of AD clinical trials. **Methods:** Web-based surveys (one completed by AD patients and one completed by AD caregivers) were conducted in five European (Germany, Italy, Spain, Sweden, UK) and two North American (Canada and USA) countries. Patients and caregivers were recruited from existing online AD panels in

each country. Eligible participants were 18 years of age or older, and had to either be diagnosed with Mild Cognitive Impairment (MCI) or mild-to-moderate AD (patient-reported group), or be involved in the care of a patient with MCI or mild-to-moderate AD (caregiver-reported group). Participants were requested to provide patient socio-demographic and disease-related (time since diagnosis, staging, medications, and symptoms) details and their preferences in AD treatment goals. Logistic regression models were applied to compare results between relevant groups. Statistical significance was set at $p<0.05$. **Results:** A total of 322 patients and 614 caregivers completed the survey. Mean (SD) patient age was 62.3 (9.9) and 76.0 (16.9) years in the patient-reported and the caregiver-reported group, respectively. Females comprised 40.4% of the patient-reported group, and 51.1% of patients in the caregiver-reported group. Among the patient-reported group, 196 (60.8%) patients had been diagnosed in the previous 2 years, with current AD staging being 24.2% MCI, 28.9% mild AD and 46.9% moderate AD, according to the latest HCP-patient/caregiver communication. Among the caregiver-reported group, 265 (43.2%) patients had been diagnosed in the previous 2 years, and 6.0%, 21.8% and 72.1% were reported as MCI, mild AD, and moderate AD, respectively. Galantamine was the most frequently reported current AD medication in the patient-reported group (37.0%), followed by memantine (33.5%). Conversely, in the caregiver-reported group, the most common current medications were donepezil (33.2%) and memantine (21.3%). For the patient-reported group, the most reported symptoms were memory loss not disrupting daily life (50.6%), getting lost and misplacing things (46.6%), and memory loss disrupting daily life (46.0%). Memory loss that disrupts daily life, and getting lost and misplacing things were the most frequently reported symptoms (59.3% and 55.4%, respectively) among the caregiver-reported group, while memory loss that does not disrupt daily life was reported for fewer patients (30.6%). When forced to pick the primary treatment goal, maintenance of quality of life (QoL) was reported as the single most important AD treatment goal for both the patient-reported (31.1%) and the caregiver-reported (38.8%) groups ($p=0.01$ for the comparison), followed by slowing the progression of memory loss (15.4% and 20.1% in the patient-reported and the caregiver-reported groups, respectively, $p=0.055$). The preference of maintenance of QoL as the main AD treatment goal was consistent across disease stages, both in the patient-reported group (MCI: 34.7%, mild AD: 27.8%, moderate AD: 31.3%) and the caregiver-reported group (MCI: 24.3%, mild AD: 35.1%, moderate AD: 41.1%), with the exception of the caregiver-reported MCI subgroup, in which slowing the progression of memory loss was identified as the main reason by 27.0% of participants. **Conclusion:** The results from our survey suggest that maintenance of QoL is consistently considered the most relevant treatment goal for both AD patients and caregivers along the different stages of the disease. There is a discrepancy between the primary outcomes recommended by regulators and what is a relevant outcome to AD patients and caregivers. When considering the design of an AD clinical trial, patient-relevant outcomes, specifically Quality of Life should be given more relevance in response to AD patients and caregivers' needs and demands. **References:** U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation Early Alzheimer's Disease: Developing Drugs For Treatment, Guidelines for Industry https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM596728.pdf (2018); Reynish E, Burns A, Roberts C. Defining a standard set of patient-centered outcomes for patients with dementia. Innov Aging. 2017;1(Suppl 1):290; Hauber B, Paulsen R, Callahan LF, et al. Quantifying what matters most to patients and care partners in Alzheimer's disease. Alzheimer's Dement. 2020;16(Suppl. 6):e040095.

LP27- ESTIMATION OF LONG-TERM CARE UTILIZATION AND LIFETIME DISTRIBUTION OF MEDICAL COST FOR DEMENTIA IN KOREA. Jun Hong Lee *(National Health Insurance Service Ilsan Hospital - Goyang-Si (Korea, Republic of))*

Background & Objective: To investigate the current status of long-term care services for patients with dementia and lifetime medical costs for dementia in South Korea. **Methods:** This study utilized the National Health Insurance Service-National Health Information Database (NHIS-NHID) from January 2013 to December 2017. The prevalence and incidence of dementia was estimated by extracting people who were diagnosed and treated with dementia (age ?45 years) from the database. The use of long-term care services for the elderly with newly diagnosed dementia was also investigated. Additionally, the lifetime medical expenses for dementia were estimated using data on single year's medical costs, population data, and a life table from Statistics Korea. **Results:** The prevalence of dementia increased over three years from 2015 to 2017, while the incidence of dementia gradually decreased. Among the patients with newly diagnosed dementia, approximately 30% used the long-term care services, while 4th graders accounted for the highest proportion every year. The older the age and the lower the income quartile, the shorter the time it took to apply for long-term care services after diagnosis of dementia. The total medical expenses per capita increased steadily every year, and the lifetime medical expenses were higher for females than males. Half of the lifetime medical costs of dementia occurred after 67 years of age for males and 83 years for females. **Conclusions:** This study suggests that medical, social, and political measures are needed to effectively manage long-term care service recipients and prepare for rising medical costs for dementia.

RP33- USING ARIA TO DETECT COGNITIVE NORMAL SUBJECTS WITH HIGH BURDEN WMH FOR EARLY PREVENTION CLINICAL TRIALS OF DEMENTIA – SUGGESTIONS BASED ON A SIMULATION TRIAL Jianlin Liang *(Chinese University of Hong Kong - Hong Kong (China))*

Background: White matter hyperintensities (WMHs) are lesions commonly seen on brain magnetic resonance imaging (MRI) and associated with dementia risk in observational studies. Nowadays, early prevention of dementia is still the key measure. High burden WMH may be observed by automatic retinal image analysis (ARIA) before the occurrence of dementia. Using ARIA as the screening tool to detect cognitive normal subjects with high burden WMH for designing the early prevention trial of dementia is not discussed yet. **Methods:** A double-blind randomized controlled early prevention clinical trial was simulated. Participants were set to be 65-70 years old, 12-18 education years and at least 26 Montreal Cognitive Assessment (MoCA) score. We randomly assigned participants in a 1:1 ratio to a 5-year treatment group (potential positive intervention) or a control group (general health advice). The primary outcome was the change in cognition as measured through MoCA score. The secondary outcome was the proportion of participants developing mild cognitive impairment (MCI) and dementia. **Results:** By

simulation, 320 individuals were screened by ARIA and 22 of them were excluded after confirmed by MRI. 298 participants were randomly assigned to the treatment group (n=149) or control group (n=149). 284 participants (95.3%) had at least one post-baseline test. 231 (77.5%) participants completed the 5-year assessments. 67 (22.4%) participants dropped out overall. Between-group difference in the change of MoCA score was statistically significant started from year 3 and it was -1.3 (95% CI [-2.01, -0.59]) at year 5. The proportions of developing MCI/dementia per year were 41 (27.5%)/4 (2.7%) in the treatment group and 52 (34.9%)/10 (6.7%) in the control group. The treatment group showed a better protective effect of cognitive with a relative short time and low cost in the simulation study. **Conclusion:** Based on existed evidences, it is potential that using ARIA as the screening tool to detect cognitive normal subjects with high burden WMH for early prevention clinical trials of dementia could be economical of cost and time. Next would make the simulation study true in the real world to confirm our suggestions.

LRP11- IMPACT OF PHYSICAL ACTIVITY ON COGNITIVE DECLINE IN ADULTS: A FLAME ANALYSIS IN THE PROTECT COHORT. Helen Brooker[1], Vincent Hayman[1], Dag Aarsland[2], Byron Creese[1], Clive Ballard[1], Anne Corbett[1] *(1. Exeter University Medical School - Exeter (United Kingdom), 2. Department Of Old Age Psychiatry, Institute Of Psychiatry, Psychology & Neuroscience, Maurice Wohl Clinical Neuroscience Institute, King's College London, London, Uk - London (United Kingdom))*

Background: Evidence continues to build to support the value of regular physical activity as an affordable dementia risk reduction intervention for cognitively healthy older adults. However, the types and intensities of activity that yield the greatest benefits are yet to be established. This study uses the recently published FLAME cognitive analysis measure to explore the impact of physical activity on cognition in older adults in an online cohort. This approach provides greater sensitivity to change and granularity of detail with regards to changes in cognitive domains and global cognitive trajectory. **Objectives:** To understand the relationship between exercise and cognitive health. To better understand the role of physical activity as a modifiable risk factor for cognitive trajecotries. **Methods:** PROTECT is an innovative online study (www.protect.org.uk) in adults aged 50 and over in the UK, Participants complete annual cognitive assessment in addition to lifestyle and health measures. Participants (n=7199) in these groups who completed the CHAMPS Physical Activity Questionnaire for Older Adults (CHAMPS) on two consecutive timepoints and within four weeks of the cognitive assessment were included in this analysis. The analysis compared change in cognition from baseline using a one-way ANOVA with physical activity composite as a fixed factor and gender, age and education fitted as covariates. **Results:** Composite measures of Speed of Attention [p<0.0001, d=0.19], Accuracy of Attention [p=0.0002, d=0.08], Memory [p<0.0001, d=0.17] and Executive Function [p=0.0008, d=0.22], as well as the composite FLAME measure [p=0.004, d=0.06] all showed significant benefits in participants with who had a higher composite physical activity score compared to indiviudals with lower activity scores. **Conclusions:** These findings add further evidence to the gorwing body of work that shows that regular physical activity offers benefits to major aspects of cognitive function. It is increasingly clear that there is a need to invest in effective interventions to promote physical activity in older adults as a priority affordable modifiable risk factor. **Conflict of interest:** Helen Brooker has worked as an employee for a company supplying some of the cognitive tests used in this research and has also developed some of the cogntive tests used in this research.

NEW THERAPIES AND CLINICAL TRIALS

P70- PHASE I SINGLE (SAD) AND MULTIPLE ASCENDING DOSE (MAD) STUDIES EVALUATING THE SAFETY, TOLERABILITY PHARMACOKINETICS (PK) AND PHARMACODYNAMICS (PD) OF YTX-7739, A NOVEL BRAIN PENETRANT SMALL MOLECULE SCD INHIBITOR, IN HEALTHY SUBJECTS. Ajay Verma, Brigitte Robertson *(Yumanity Therapeutics - Boston (United States))*

Background: Recent advances in our understanding of the pathological processes underlying neurodegenerative diseases indicate that misfolded proteins may play a critical role in neurodegeneration. Multiple lines of research suggest inhibiting the enzyme stearoyl-CoA desaturase (SCD) can overcome toxicity from misfolded proteins in neurodegenerative diseases, including Alzheimer's, Parkinson's disease, and Amyotrophic Lateral Sclerosis. SCD is an enzyme that catalyzes fatty acid desaturation, the products of which are incorporated into phospholipids, triglycerides, or cholesterol esters. These lipid-related molecules regulate multiple diverse cellular properties and processes, including membrane structure and function, vesicle trafficking, intracellular signaling and inflammation. In preclinical models, SCD inhibition appears to normalize the dynamic interaction of pathological alpha-synuclein with membranes, which improves neuronal function and reduces toxicity, leading to enhanced neuronal survival. Inhibition of stearyl-CoA desaturase (SCD) reduces levels of mono-unsaturated C16 and C18 fatty acids, which are involved in neurotoxicity in vitro1,2 and in vivo3,4. Preclinically, the ratio of unsaturated to saturated fatty acids (fatty acid desaturase index, FA-DI) in plasma after SCD inhibition correlates with effects on the FA-DI in brain, such that the plasma FA-DI may be used as a surrogate for drug-induced changes in brain FA-DI4. FA-DI activity may serve as a relevant biomarker for the effects of SCD inhibition. **Objective:** The key objectives of these first-in-human, Phase I, randomized, double-blind, placebo-controlled single (SAD) and (MAD) studies* are to identify a safe and pharmacodynamically active dose range for YTX-7739 to be used in subsequent clinical studies in patients with neurodegeneration. **Methods:** In the Phase 1 SAD study, single oral doses of YTX-7739 or placebo (5 mg to 400 mg) were administered to 72 healthy male and female (non-childbearing potential) volunteers (aged 19-39 years old) in the fed and or fasted state. Each cohort contained 8 subjects (6 YTX-7739, 2 Placebo). In the MAD study, once daily oral administration of 2 doses of YTX-7739 (15 mg and 25 mg) were administered to 16 healthy male and female (non-childbearing potential) volunteers for 14 to 28 days. The study included 2 cohorts of 8 subjects each, (6 YTX-7739, 2 Placebo). In both studies, safety assessments included adverse events (AEs), vital signs, ECG and clinical laboratory parameters. Serial blood samples were drawn for assessment of PK and PD parameters (FA-DI) pre-dose and at regular intervals thereafter at multiple doses in both the SAD and MAD studies. Analyses of CSF drug concentrations and other exploratory biomarkers were also included. Preliminary results are reported here; results will be available at the time of presentation. **Results:** YTX-7739 was found to be well tolerated in the SAD and MAD study in healthy volunteers. All AEs were mild or moderate. Headache, fatigue, and abdominal discomfort were among

the most frequently reported AEs in both studies. There were no serious AEs, or dose-limiting toxicities identified. The maximum tolerated dose was not reached in the SAD, however concentrations for target engagement were achieved. Frequency of AEs by treatment group will be presented. In the fed state, dose proportionality in the pharmacokinetic profile was observed following single and multiple dose administration in plasma and CSF (Dose normalized Cmax and Dose normalized AUC24h). Expected changes were observed in the target engagement biomarker with dose dependent decreases in the FA-DI, consistent with a drug effect and will be presented in greater detail. **Conclusion:** YTX-7739 was well tolerated and demonstrated a favorable safety profile in healthy subjects receiving single oral doses up to 400 mg or multiple doses of 15 mg or 25 mg for up to 28 days. YTX-7739 demonstrated a dose proportional PK profile in the fed state in plasma and CSF. Proof of biology and target engagement was achieved, with dose dependent decreases observed on the target engagement biomarker (FA-DI) that were consistent with a drug effect. *Two low dose cohorts were conducted open label in the SAD study. Bibliography. 1. Vincent BM, Tardiff DF, Piotrowski JS, et al. Inhibiting Stearoyl-CoA Desaturase Ameliorates α-Synuclein Cytotoxicity. Cell Rep. 2018;25(10):2742-2754.e31. doi:10.1016/j.celrep.2018.11.028; 2. Fanning S, Haque A, Imberdis T, et al. Lipidomic Analysis of α-Synuclein Neurotoxicity Identifies Stearoyl CoA Desaturase as a Target for Parkinson Treatment. Mol Cell. 2019;73(5):1001-1014.e8. doi:10.1016/j.molcel.2018.11.028; 3. Nuber S et al., A Stearoyl-Coenzyme A Desaturase Inhibitor Prevents Multiple Parkinson Disease Phenotypes in a-Synuclein Mice. Ann Neurol. 2021; 89(1):74-90; 4. Tardiff D. (2021, March X). A Clinical Stage Stearoyl-CoA Desaturase Inhibitor for Parkinson's Disease Improves Behavioral and Pathological Features in an a-Synuclein Mouse Model [Conference presentation abstract]. The 15th Annual International Conference on Alzheimer's and Parkinson's Diseases (AD/PD™ 2021) Virtual Conference, March 9 to 14, 2021; 5. Mazzulli JR, Xu Y-H, Sun Y, et al. Gaucher disease glucocerebrosidase and α-synuclein form a bidirectional pathogenic loop in synucleinopathies. Cell. 2011;146(1):37-52. doi:10.1016/j.cell.2011.06.001; 6. Gündner AL, Duran-Pacheco G, Zimmermann S, et al. Path mediation analysis reveals GBA impacts Lewy body disease status by increasing α-synuclein levels. Neurobiol Dis. 2019;121:205-213. doi:10.1016/j.nbd.2018.09.015

P71- DESIGN OF INFRONT-3: A PHASE 3 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF AL001 IN FTD-GRN. Sam Jackson, Michael Ward, Yijie Liao, Brian Mangal, Felix Yeh, Whedy Wang, Robert Paul *(Alector - South San Francisco, Ca (United States))*

Background: Frontotemporal dementia (FTD) is a rare, early-onset form of dementia, and loss-of-function mutations in the progranulin gene (GRN) are a common cause of familial FTD. In the brain, progranulin (PGRN) is a key regulator of microglia activity and lysosomal function. AL001 is a human monoclonal IgG1 antibody that blocks and downregulates Sortilin, a receptor in the most important degradation pathway of PGRN. Restoring PGRN levels by interfering with degradation may be an effective therapeutic approach in FTD-GRN. In a Phase 2 study, repeat administration of AL001 was shown to normalize CSF PGRN levels and impact biomarkers representing key nodes of the pathophysiological disease cascade of FTD in GRN mutation carriers. **Methods:** INFRONT-3 is intended as a single pivotal, registration-enabling study that assesses the efficacy and safety of AL001 in carriers of heterozygous GRN mutations that are either at risk of developing FTD symptoms as evidenced by a biomarker or, have symptomatic FTD. The primary objective is to demonstrate slowing of disease progression as measured by change in the CDR® plus NACC FTLD sum of boxes (CDR-FTLD-SB). **Results:** This is a global study that will enroll approximately 180 participants in North America, Australia, and Europe (NCT04374136). All participants must have a heterozygous GRN mutation causative for FTD. It is estimated that the study will enroll ~35% at-risk participants and 65% symptomatic participants. Participants will be randomized to receive 60 mg/kg AL001 or placebo (3:2 ratio), administered via IV infusion every 4 weeks, for 96 weeks. Randomization will be stratified based on CDR® plus NACC FTLD scores at baseline. In addition, clinical efficacy will be assessed by the CGI-I, CGI-S and RBANS. To account for heterogeneity of the broad patient population enrolled, the population will be stratified by disease severity in the statistical analysis of efficacy endpoints. Pharmacodynamic endpoints including MRI measures and fluid biomarkers (both serum and optional CSF) will also be assessed. PK in serum will be assessed. Safety will be assessed through routine monitoring of AEs, changes in laboratory and vital signs, ECG and MRI, and assessment of suicidality. In addition, an independent Data Monitoring Committee will review the progress of the study and perform ongoing safety reviews. **Conclusions:** INFRONT-3 is designed to provide confirmatory evidence of efficacy and safety as a single pivotal study for AL001, a novel, first-in-class neuro-immunological approach for treating FTD-GRN, which has received Orphan Designation in the US. Enrollment is ongoing.

P72- EXTERNAL COUNTERPULSATION (RENEW™ NCP-5 DEVICE) FOR THE TREATMENT OF MCI DUE TO ALZHEIMER'S DISEASE OR MILD DEMENTIA OF THE ALZHEIMER'S TYPE: A PIVOTAL TRIAL. Patrick Moriarty[1], Lauryn Gorby[1], David Salat[2], Jeffrey Burns[3], Tom Moreno[4], Jonathan Helfgott[4] *(1. University Of Kansas Medical Center - Kansas City (United States), 2. Harvard Medical School - Boston (United States), 3. Kansas University Alzheimer's Disease Center - Kansas City (United States), 4. Renew Research - Farmington Hills (United States))*

Background: Vascular impairment may play a role in the pathophysiology of Alzheimer's dementia, highlighting a potential target for therapeutic intervention. Renew NCP-5 is an FDA-cleared, external counterpulsation (ECP) device used clinically for refractory angina and heart failure to improve coronary and peripheral vascular hemodynamics. The device sequentially compresses and decompresses the vasculature of extremities in synchrony with the cardiac cycle to increase cardiac output, angiogenesis, and improved endothelial function. If approved by the FDA for the treatment of mild cognitive impairment (MCI) due to Alzheimer's disease (AD) and mild dementia of the Alzheimer's type, NCP-5 would be the first device added to the treatment armamentarium for this increasingly prevalent disorder. **Objectives:** To evaluate efficacy and safety of the Renew NCP-5 device as an adjunctive therapeutic option for patients with MCI due to AD or mild dementia of the Alzheimer's type. **Methods:** This randomized, single-blind, sham-controlled pivotal trial was conducted in 10 sites across the US and 1 site in Europe. Subjects aged 55-85 years, with a clinical diagnosis consistent with 2011 NIA-AA core clinical criteria guidelines for dementia due to AD or MCI due to AD, and a MOCA score ≥11 were randomized to NCP-5 (n=95) or active sham (n=95), stratified by disease severity (MCI

due to AD or mild AD) and cardiovascular risk score (low/medium or high/very high). Following screening and baseline assessment, subjects entered the 7 to 12 week treatment period consisting of 35 sessions 60-minutes in duration from 3 to 5 times/week. The subsequent maintenance period of up to 24 weeks consisted of 60-minute sessions, twice a week, with at least 2 days between sessions. Cognitive assessment occurred at weeks 6, 12, 18, 24, and months 9 and 12. The primary endpoint was mean change from baseline in VADAS-Cog at 12, 18, and 24 weeks. Secondary endpoints included mean change from baseline at 12, 18, and 24 weeks in: ADCS-ADL, ADCS-CGIC, ADAS-Cog14, and Trail Making Test B. Magnetic resonance imaging was performed at screening, week 24, and month 12. Neuroimaging measures included T1-weighted hippocampal volume and arterial spin labeling (ASL)-based measures of cerebral blood flow (CBF). Other exploratory analyses included hippocampal and white matter lesion volume, and Neuropsychiatric Inventory-Questionnaire and subscales. Safety of Renew NCP-5 was also evaluated based on adverse events, laboratory tests, and vital signs. **Results:** NCP-5 treatment was statistically superior to active sham on the primary endpoint of change from baseline in VADAS-Cog, averaged across 12, 18, and 24 weeks, with a posterior probability of superiority of 0.988 (exceeding posterior probability of superiority of 0.979 selected to control overall Type I error rate of the trial design at the 2.5% level), using a prespecified Bayesian model for the difference between treatment and active sham. NCP-5 treatment was also superior to active sham on secondary endpoints: ADCS-ADL (posterior probability of superiority = 0.995); ADAS-Cog14 (posterior probability of superiority = 0.983); and CGI-C ($p<0.05$ for the prespecified logistic regression model for the common proportional odds ratio at weeks 12 and 24). No significant superiority was observed at 24 weeks on the Trail Making Test B. At week 24, separation between NCP-5 treatment and active sham on VADAS-Cog was particularly large in subjects with comorbid diabetes ($p<0.001$), and all subjects with diabetes improved with treatment across all sites. Notably, NCP-5 treatment was superior to active sham in reducing severity scores on the Neuropsychiatric Inventory-Questionnaire scale and subscales: NPI-Q ($p<0.01$), NPI-Q-4 Agitation/Aggression ($p<0.05$), NPI-Q-Mood ($p<0.01$), and NPI-Q-4 Frontal ($p<0.05$). Although there was no effect of treatment on global CBF in simple group comparisons, there was an increase in regional CBF normalized to global CBF in the insula and lateral frontal areas across sites using Siemens and GE scanners. The effect of NCP-5 treatment on absolute CBF was significant in subjects across the Siemens sites only. There was no evidence of a protective effect of treatment on hippocampal volume or white matter lesion volume. At 24 weeks, 10.5% of subjects in the NCP-5 group discontinued vs 18.9% of subjects in the active sham group, but there were no withdrawals due to treatment. Skin abrasions/irritations were the most common adverse event (AE), and the only one to occur at >5%. The rate of AEs judged to be device-related was 0.3% per session (36/10,658). **Conclusions:** This randomized, controlled, pivotal trial is the first demonstration of efficacy by a device on cognitive and neuroimaging measures of MCI due to AD or mild dementia of the Alzheimer's type in a clinical trial. In addition to positive findings on primary and secondary endpoints, the Renew NCP-5 device was exceptionally safe and well tolerated, consistent with its extensive use in angina and long-term safety profile. These findings resonate with increased interest in the role of the vascular system in the pathophysiology of AD and other dementias, and support vascular health as a viable therapeutic strategy. **Disclosures:** Funded by Renew Research, LLC. Dr. Patrick M. Moriarty is an advisory board member for Novartis; a consultant for Amgen, Esperion, Kaneka, Regeneron, and Stage II Innovations/Renew; a member of the executive committee for Esperion; participates in research for Aegerion, Amgen, Esperion, FH Foundation, GB Life Sciences, Ionis, Novartis, Regeneron, and Stage II Innovations/Renew; and is a speaker for Amarin, Amgen, and Regeneron.

LP28- A PHASE 1A, RANDOMIZED, PLACEBO-CONTROLLED, SINGLE AND MULTIPLE DOSE, DOSE-ESCALATION STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF NOVEL REGENERATIVE THERAPEUTIC NNI-362. Judith Kelleher-Andersson[1], Esther Yoon[2], Carol Green[3], Claire Mcfarlane[3], Raymond Turner[4] *(1. Neuronascent, Inc. - Mountain View (United States), 2. California Clinical Trials Medical Grp - Glendale (United States), 3. Sri - Menlo Park (United States), 4. Georgetown University - Washington, D.c. (United States))*

Background: NNI-362 is a new chemical entity discovered through a phenotypic assay to identify small molecules that promote new neurons from human neural progenitor cells. Preclinical efficacy and safety studies supported a first-in-human testing in a healthy aged population. A placebo-controlled study allowed the determination of safety and tolerability, as well as secondary pharmacokinetics of two distinct NNI-362 formulations. **Objectives:** The aim of this study was to determine the safety and tolerability of NNI-362 in a first-in-human study and compare two formulations. **Methods:** NNI-362 was formulated by Parexel (Glendale, CA) as an aqueous suspension or lipid suspension. Individuals were enrolled in a placebo-controlled study with a 1:3 ratio of placebo:drug. The dosing in SAD cohorts was 10, 20, 60, and 120 mg and MAD cohort at 20 mg and a SAD/MAD at 120 and 240 mg under fasted conditions. Direct SAD and MAD pharmacokinetics were assessed at the two highest doses. A total of 56 subjects ages 50 to 72 were randomized to drug or placebo, with the sponsor, PI, and subjects all blinded. **Results:** Of the 34 total adverse events (AEs) noted, all were mild, temporary, and with no treatment required. No subjects were discontinued prior to end of study. Of the 23 total AEs reported at the two highest lipid-formulated doses, 13 were in the placebo group and 10 in the intervention group. There were no apparent drug-related or dose-dependent AEs (6 AEs were deemed unrelated or unlikely related to study drug). No serious adverse events were reported. The lipid suspension of oral NNI-362 revealed a slower overall absorption profile and increased Cmax and AUClast compared to the aqueous suspension. **Conclusion:** Oral NNI-362 is safe and well tolerated at oral doses up to 240 mg. A maximum tolerated dose was not achieved in a healthy aged population. The lipid formulation of NNI-362 at 120 and 240 mg revealed an increased Cmax and AUClast but no increase in AEs. These data support a proof-of-concept trial of oral NNI-362 in individuals with Alzheimer's disease (AD) and other neurodegenerative disorders of aging associated with neuronal loss. A planned randomized, double-blind, placebo-controlled phase 2 trial will enroll a diverse population of individuals with amyloid-positive AD (MMSE 16-26). Three groups of 30 will be treated with ether placebo,120 mg, or 240 mg NNI-362 by mouth daily for 9 months. To measure neurogenesis, the primary outcome will be change in hippocampal volume (vMRI). Secondary outcomes include quantitative EEG, proteomic biomarkers of AD in cerebrospinal fluid and plasma, and standard measures of cognition, function,

and behavior. Stable use of all FDA-approved medications, including aducanumab, will be permitted. Evidence of safety/tolerability and efficacy will support a subsequent phase 3 study of NNI-362. **COI statement:** Georgetown University receives research funding from Lilly, Biogen, Eisai, Novartis, Roche, Genentech, Janssen, and Alector. RST is a consultant for Neuronascent, Inc. and Re:Cognition Health.

LP29- BET-INHIBITION BY APABETALONE AND COGNITIVE EFFECTS: A PRESPECIFIED MOCA ANALYSIS NESTED IN THE BETONMACE RANDOMIZED CONTROLLED TRIAL. Jeffrey Cummings[1], Gregory Schwartz[2], Stephen Nicholls[3], Aziz Khan[4], Christopher Halliday[4], Peter Toth[5], Michael Sweeney[6], Jan Johansson[6], Norman Wong[4], Ewelina Kulikowski[4], Kamyar Kalantar-Zadeh[7], Kenneth Lebioda[4], Henry Ginsberg[8], Bengt Winblad[9], Henrik Zetterberg[10,11,12], Kausik Ray[13] *(1. Chambers-Grundy Center For Transformative Neuroscience, Department Of Brain Health, School Of Integrated Health Sciences, University Of Nevada Las Vegas (unlv) - Las Vegas (United States), 2. Division Of Cardiology, University Of Colorado School Of Medicine - Aurora (United States), 3. Victorian Heart Institute, Monash University - Melbourne (Australia), 4. Resverlogix Corp. - Calgary (Canada), 5. Cicarrone Center For The Prevention Of Cardiovascular Disease, Johns Hopkins University School Of Medicine - Baltimore (United States), 6. Resverlogix Corp. - California (United States), 7. Division Of Nephrology And Hypertension, University Of California Irvine - California (United States), 8. Department Of Medicine, Vagelos College Of Physicians And Surgeons, Columbia University, New York, Ny Department Of Neurobiology - New York (United States), 9. Care Sciences And Society, Center For Alzheimer Research, Division Of Neurogeriatrics, Karolinska Institutet, Solna, Sweden, And Karolinska University Hospital, Theme Inflammation And Aging, Huddinge - Stockholm (Sweden), 10. Department Of Psychiatry And Neurochemistry, Institute Of Neuroscience And Physiology, The Sahlgrenska Academy At The University Of Gothenburg - Mölndal (Sweden), 11. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital - Mölndal (Sweden), 12. UK Dementia Research Institute at UCL and Department of Neurodegenerative Disease, UCL Institute of Neurology - London (United Kingdom), 13. Imperial Centre For Cardiovascular Disease Prevention, Imperial College - London (United Kingdom))*

Background: Epigenetic changes may contribute importantly to cognitive decline in late life including Alzheimer's disease (AD) and vascular dementia (VaD). Bromodomain and extra-terminal (BET) proteins are epigenetic "readers" that may distort normal gene expression and contribute to chronic disorders. **Objectives:** To assess the effects of apabetalone, a small molecule BET protein inhibitor, on cognitive performance of patients 70 years or older participating in a randomized trial of patients at high risk for major cardiovascular events (MACE). **Methods:** The Montreal Cognitive Assessment (MoCA) was performed on all patients 70 years or older at the time of randomization. 464 participants were randomized to apabetalone or placebo in the cognition sub-study. In a prespecified analysis, participants were assigned to one of three groups: MoCA score ≥ 26 (normal performance), MoCA score 25 – 22 (mild cognitive impairment), and MoCA score ≤ 21 (dementia). Exposure to apabetalone was equivalent in the treatment groups in each MoCA-defined group. **Results:** Apabetalone was associated with an increased total MoCA score in participants with baseline MoCA score of ≤ 21 ($p = 0.02$) mostly contributed by the abstraction and recall domains (both $p<0.1$). There was no significant difference in change from baseline in the treatment groups with higher MoCA scores. Serum ALP was significantly and consistently reduced by apabetalone across the cohorts, regardless of MoCA baseline category. In the cognition study, more patients randomized to apabetalone discontinued study drug for adverse effects (11.3% vs 7.9%). **Conclusion:** In this randomized controlled study, apabetalone was associated with improved cognition as measured by MoCA scores in those with baseline scores of 21 or less. BET protein inhibitors warrant further investigation for late life cognitive disorders. **Key Words:** Montreal Cognitive Assessment, Alzheimer's disease, apabetalone, epigenetics, clinical trial, BET inhibitor

LP31- NOVEL THERAPEUTIC EFFICACY OF GALECTIN-3 ANTIBODY FOR TREATING ALZHEIMER'S DISEASE. Suhail Rasool, Pooja Patel, Jenny Johansson, Taufeeq Ahmed, Ludmila Volobouéva, Sangmi Lee, Catherine Gordon, Kyungjoon Lee, Dongxu Sun *(Truebinding Inc. - Foster City (United States))*

Background: Alzheimer's disease (AD) is a chronic progressive neurodegenerative disorder that is the leading cause of dementia among older adults. It is widely accepted that Aβ oligomers, rather than monomers and fibrils, are toxic and play a critical role in AD progression. Amyloid-β (Aβ) oligomers trigger microglial activation-mediated neuroinflammation and a series of toxic reactions in neurons, such as receptor disability, mitochondrial damage, Ca2+ homeostasis dysregulation, abnormal tau phosphorylation. It has been reported that Galectin-3 (Gal-3) is involved in Aβ oligomerization initiating the cascade underlying the pathology of AD. Gal-3 was also identified as a novel endogenous TREM2 ligand to detrimentally regulate the inflammatory response in AD. Here, we present TB006, a monoclonal antibody targeting Gal-3, as a possible treatment for AD by halting or even reversing AD pathology. **Objectives:** Gal-3 expression is increased in brains from AD patients, particularly in microglia associated with amyloid plaques. Our objectives were to examine the role of Gal-3 in Aβ aggregation (conformational oligomer formation) and to investigate the therapeutic efficacy of our novel Gal-3 antibody for treatment of AD. **Methods:** We used two anti-Gal-3 antibodies, our clinical candidate TB006 and a mouse cross-reactive surrogate mTB001, to establish the benefits of Gal-3 neutralization in AD. In vitro and in vivo studies were conducted to investigate the effect of TB006 and mTB001 antibodies on Aβ42 aggregation and AD pathology. Based on the pre-dose behavior, AD transgenic mice models (APPSwe, 5xFAD) and Aβ42 injected mice were randomized and distributed into two groups. Four doses of mTB001 and isotype control antibody (10mg/kg) were injected intraperitonially twice per week. After four doses, a spatial memory function test was conducted. Mice were then sacrificed and biochemical and immunohistochemical characterizations were conducted. **Results:** Truebinding Inc. has developed Gal-3 neutralizing monoclonal antibodies. TB001 and TB006 are human IgG4(S228P) isotypes and mTB001 is a mouse IgG2a-Leu234/235Ala (LALA) version of TB001. TB001 and TB006 potently bind human and cynomolgus Gal-3 with nanomolar affinity but only TB001 binds rodent Gal-3. mTB001 was used as a surrogate antibody for TB006 for in vivo studies while TB006 was used for safety studies in cynomolgus monkeys. In vitro, we found that Gal-3 intrinsically promotes oligomerization of Aβ42 and that TB001 and TB006 reduce/degrade Aβ42 oligomer formation. Additionally, human and mouse Gal-3 both bind to pre-formed Aβ oligomers; and TB006, TB001,

and mTB001 blocked this interaction. Functionally, microglia, the main cell type contributing to inflammation in AD brains, become activated to produce the pro-inflammatory cytokine TNFα when stimulated by Aβ42. Gal-3 enhanced Aβ42 induced microglia activation, while as mTB001 blocked the activation. Additionally, Aβ42 was toxic in vitro to HT-22 neuronal cells only when co-incubated with Gal-3, and treatment with mTB001 antibody reversed this effect with an IC50 of 1.5 mg/mL. Hence, anti-Gal-3 antibodies can prevent formation of oligomers, degrade conformational prefibrillar oligomers, and prevent Aβ-induced microglia activation and neuronal death. In three mouse models of AD (two familial transgenic mice models [APPSwe and 5xFAD] and one induced by Aβ42 aggregate injection), learning and memory cognitive deficits were either completely reversed or strongly attenuated after mTB001 treatment. Mechanistically, neutralizing Gal-3 blocked the initiating events in AD (Aβ aggregates and Tau hyperphosphorylation), reduced inflammation (microglia and astrocyte activation) and rescued neuronal damage. Furthermore, microhemorrhages, a potential safety liability seen in some clinical stage drugs, were significantly reduced. **Conclusion:** Taken together, our pre-clinical studies show that, attenuating Gal-3 is an immensely efficacious therapeutic entity by degrading toxic Aβ42 oligomers and blocking AD progression, which in turn reverses cognitive deficits that already occur. After extensive scrutiny by the FDA, our clinical candidate TB006 is under phase I/II trial and will possibly help AD patients to have a better quality of life. **Conflict of Interest:** All authors are paid employees of Truebinding Inc

RP39- ALPHA-1 ANTITRYPSIN VARIANTS AND OBSTRUCTIVE SLEEP APNEA: PRACTICAL TARGETS FOR MODULATING INFLAMMATION AND ALTERING TRAJECTORY OF MCI/DEMENTIA. Donald Schmechel *(Acrossalpha; Neurology Specialists Of Charleston - Burnsville)*

Background: Age-related cognitive decline is multifactorial and involves the chronic or intermittent failure of normal mechanisms that respond to injury and inflammation. Control of aging trajectory is a reasonable goal – whether stability or improvement – for persons presenting with clinically evident signs and symptoms. These may represent the result of years of 'silent' biological decline (e.g., APOE related cognitive decline, Parkinson Disease). **Objectives:** To examine the cognitive trajectory of persons presenting with MCI or dementia to an outpatient neurology clinic and treatment of two common pro-inflammatory respiratory factors -obstructive sleep apnea (OSA) and alpha-1 antitrypsin (A1AT) deficiency. **Methods:** Patients referred for MCI/dementia syndromes to an outpatient neurology clinic were consecutively typed for A1AT phenotype and carefully assessed for OSA or other sleep disorder. Consecutive patient base was 4409 patients with average age of 61 years at presentation (60:40 females to males). 1909 patients had cognitive diagnosis of MCI or dementia. OSA was diagnosed and treated in 30% of males (3% non-compliant) and 12% of females (2% non-compliant). A1AT polymorphisms were present in 15% of all patients presenting with MCI or dementia (expected prevalence of 4-7% in USA). A further random set of 104 patients with A1AT polymorphisms was assessed for childhood illnesses. Cognitive testing was done with Mini-Mental Status Exam (MMSE) every 6-12 months using alternative forms for registration, distraction task and naming. Persons with A1AT polymorphisms and history of respiratory symptoms received pulmonary function tests with volumes, high resolution chest tomography, and often abdominal ultrasound. Those patients satisfying ATS recommendations for A1AT augmentation therapy were offered weekly intravenous augmentation with purified human A1AT for A1AT deficiency. Patients with OSA were referred for CPAP evaluation and treatment. Treatment of B12 deficiency (ca. 25% of patients), homocysteinemia, mood disorder and other medical factors were emphasized in all persons. Most were on anticholinergic medications for MCI/dementia. Ancillary clinical support consisted of sleep medicine, pulmonary and primary care physicians. **Results:** OSA treatment effects: Results are reported for subsets: 604 patients with sleep studies (30% with OSA), interval of follow-up testing >= 1 year (average 2.8 yrs., range 1-12) and with APOE genetic testing. 62% of patients had 1 or 2 APOE4 alleles. Decline rate (MMSE points/year) was -2.3 (APOE4/4), -1.3 (E3/4 or E3/3). CPAP treated OSA patients had decline rate of -1.0 (E4/4, E3/4) and -0.6 (E3/3). Non-compliant OSA patients had steeper rate of decline greater patients without diagnosis of OSA. Results were significant for OSA factor (MANOVA, F ratio = 5.1, p=0.0065). Presence of OSA was associated with significant 3 yr earlier age of presentation for APOE4/4 patients (62 vs 65 years). A1AT background in MCI/dementia: A1AT polymorphisms are common in neurology patients (15% in APOE4/4, 18-19% in E3/4 and E3/3 and so far, 50% prevalence in rare E2/2 patients). Age of presentation is slightly less for A1AT carriers (2 years earlier than non-carriers, p=0.03, Logrank). A1AT Z polymorphism is associated with more subcortical white matter change. A1AT variants are significantly more common (>25%) in FTD-PD, PSP, and primary progressive aphasia. In 104 randomized A1AT patients presenting to neurology clinic, history of recurrent childhood otitis media was obtained in 18% with MCI/AD or neurological disease; age of onset for those presenting after age 45 was significantly earlier – 66 years compared to 71 years (Wilcoxon, chi-squared=4.6, p=0.03). In all, 40% had childhood or adult respiratory illness. A1AT augmentation effects: Persons with A1AT polymorphisms and MCI/dementia syndromes were screened for pulmonary illness by history, exam and if indicated high resolution chest CT and PFT's. Those with criteria for augmentation had significant pulmonary signs and symptoms, chest CT showing emphysematous changes particularly in base or bronchiectasis (orphan indication) and obstructive changes on PFT's without resolution with bronchodilators or mixed changes. A1AT augmentation was proposed for these persons. For those not eligible by ATS criteria or refused by insurance, yearly pulmonary follow-up was instituted. Results are reported for 906 patients with A1AT phenotype and sleep studies, but not all with APOE genetic testing. Testing interval was average of 1.7 years (range 1-12 years). 40 patients (27 male, 13 female) were placed on weekly A1AT infusions to increase A1AT levels. Average rate of MMSE change was +1.3 points per year compared to non-supplemented group rate of -1.4 points per year. Similar effects of OSA were observed on rates. A remarkable observation was that non-supplemented, non-treatable OSA patients declined at -1.8 points per year while three A1AT supplemented, non-compliant CPAP patients stabilized at +0.3 points per year. **Conclusions:** The goal of stabilization or improvement of MCI and dementia syndromes is still work in progress. Multifactorial disease may require multifactorial treatment programs. We present assiduous treatment of OSA and treatment where possible of A1AT related pulmonary and systemic inflammation. Both approaches result in apparent stabilization and or improvement of disease trajectory. OSA deserves detection and A1AT augmentation deserves attention.

RP40- A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, SINGLE ASCENDING DOSE STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF A SUBCOMMISSURAL ORGAN-SPONDIN-DERIVED PEPTIDE IN HEALTHY VOLUNTEERS. Valérie Bourdès[1], Peter Dogterom[2], Pierre Parmantier[3], Damien Colas[3], Sighild Lemarchant[1], Sébastien Marie[1], Khalid Abd-Elaziz[2], Yann Godfrin[4] *(1. Axoltis - Lyon (France), 2. QPS Netherlands B.V - Groningen (Netherlands), 3. Athena Bio Consulting - Lyon (France), 4. Godfrin Life Sciences - Caluire-et-Cuire (France))*

Background: NX210 is a chemically synthesized linear peptide of 12 natural amino acids derived from the subcommissural organ (SCO)-spondin, a large brain-specific glycoprotein that contributes to neurogenesis during embryogenesis. NX210 is a new compound that improves cognitive functions in acute and chronic CNS animal models in comparison to Donepezil (Le Douce et al., Front. Neurosci., 2021); NX210 also protects against glutamate neurotoxicity (Delétage et al.,Neuroscience, 2021). Due to its pleiotropic properties ensuring neuroprotection, neuroregeneration and cellular plasticity, NX210 represents an innovative drug candidate for neurodegenerative diseases, such as Alzheimer's Disease (AD). **Objectives:** The primary objective of this first-in-man study was to assess the safety and tolerability of single ascending doses of i.v. administered NX210. Pharmacokinetics (PK) was the secondary objective. The exploratory objectives aimed at assessing the effect of NX210 on blood and urine biomarkers, as well its effects on cerebral activity (EEG). **Methods:** This was a randomized, double-blind, placebo-controlled, single ascending dose Phase 1 study in healthy volunteers run in a single center in Netherlands. Five single ascending doses of NX210 (0.4, 1.25, 2.5, 5 and 10 mg/kg) were planned to be tested in 5 cohorts of 8 subjects each. In each cohort, subjects were randomized in a 3:1 ratio to either NX210 or placebo. On Day 1, subjects received a single i.v. (bolus injection or infusion) of study drug or placebo and were discharged from the clinic on Day 2 after completion of all protocol required study procedures. Pharmacodynamics (PD) assessments were performed for subjects in Cohorts 3, 4 and 5 (2.5, 5 and 10 mg/k) during an ambulatory visit on Day 3. Upon completion of the treatment, all subjects returned to the clinic 7 days (±1 day) after dosing of the study drug for a follow-up visit. Safety, tolerability and PK data from at least 6 evaluable subjects per cohort were assessed by a Safety Review Committee (SRC) between each cohort before ascending to the next dose level. SRC meetings occurred after the last subject of each cohort had at least completed Day 2. **Results:** A total of 39 subjects were randomized in 5 cohorts (0.4, 1.25, 2.5, 5, 10 mg/kg). All cohorts had 6 on active and 2 on placebo, except cohort 2 (5 active, 2 placebo). The mean age was 41.9 years (SD ±17.9), mean BMI was 24.1 kg/m2 (SD ±2.3), all men, at the exception of 4 female. A total of 17 TEAEs were recorded in 13 subjects all of them being of mild severity. Among the TEAEs, 12 out the 17 TEAEs (70.6%) were deemed drug related and 7 out of the 12 related AEs (58.3%) concerned nervous system disorders (dizziness, headache, somnolence). All TEAEs recovered (only one with an unknown outcome). Regarding the tolerability, 4 subjects reported 9 events of mild intensity (redness, swelling, pain). Only one subject reported a Grade 2 (moderate) pain 24 hours post-dose (catheter site related reaction). Due to an immediate cyclization of NX210 in blood compartment, the PK was assessed via its metabolite, NX210c (cyclic form). NX210c has a short half-life ranging from 6 to 20 minutes, meaning a short-term exposure. The apparent volume of distribution (Vz/F) ranged from 1870 L to 4120 L, and total clearance (CL/F) ranged from 7440 L/h to 16400 L/h, indicative of a fast clearance and high tissue diffusion. Although a large inter subject variability was observed among all investigated biomarkers, plasma levels of tryptophan and homocysteine (known as endogenous NMDA agonist) showed variations with a drug dose related effect. Trends in decrease of plasma glutamate while increase in glutamine suggested that the NX210 may play a role on glutamate-glutamine cycle. In urine, trends in increase were observed for serotonin, glutamate and GABA with no dose effect. The EEG activity showed trends in increase for Alpha bands in a dose depending manner, and decrease in Beta and Gamma bands, consistent with potential effects on cognition. PD effects were sustained (several hours in plasma, up to 48h in urine and EEGs). **Conclusion:** Five ascending doses (0.4mg/k up to 10mg/kg) of i.v administered NX210 were safe and well tolerated by 39 healthy subjects in this first-in-man study. PK and PD results suggested favorable, rapid and sustainable effects of NX210 via its metabolite, NX210c. Considering altogether the marked drug dose effect with plasma tryptophan and homocysteine, trends of plasma glutamate (decrease) and glutamine (increase), as well as the dose effect on EEG alpha bands, they provide preliminary and encouraging elements of NX210/NX210c effect on the CNS, in particular on cognitive functions improvement. The next steps of the development will be made with NX210c, a promising drug candidate that should be further tested in a clinical trial with AD patients.

RP41- MICRODOSE STUDY OF A NOVEL PSYCHOSTIMULANT PRODRUG, PRX-P4-003, WITH REDUCED ABUSE LIABILITY FOR APATHY IN AD. William Ziegler Potter[1], Valentino Stella[1,2], Sandeep Patil[1] *(1. Praxis Bioresearch - Sacramento (United States), 2. University of Kansas - Lawrence (United States))*

Background: Apathy is one of the most common symptoms of AD and leads to diminished motivation, rapid loss of function, and increased caregiver distress. Recent studies provide strong evidence that the dopamine and norepinephrine reuptake inhibitor, methylphenidate (MPH), improves apathy in AD. A compound with similar pharmacology but with reduced abuse liability would be desirable. PRX-P4-003 is a new chemical entity oral prodrug of fencamfamine (an older drug with similar properties to MPH) designed to be selectively metabolized to a pharmacologically active moiety, (-)-fencamfamine [(-)-FCF] only in the small intestine by pancreatic-lipase(s). Less than 1% of pancreatic lipase is found in the systemic circulation such that parenteral administration should not produce psychostimulant effects. Preclinical studies with PRX-P4-003 show that oral but not intravenous administration produce MPH-like effects. To date, however, it has not been established that pancreatic lipase dependent prodrug conversion demonstrated in preclinical studies occurs in humans. The rate at which peak levels are achieved are also believed to be relevant to abuse liability by the oral route. A microdose (Phase 0) study of PRX-P4-003 was therefore undertaken to learn whether it has properties in humans consistent with developing it as an effective psychostimulant treatment of apathy in AD with reduced abuse potential. **Objective:** To determine in a first in human single dose study whether oral administration of PRX-P4-003 was followed by the appearance of pharmacologically active (-)-FCF and whether there was a large effect on the rate of appearance in blood under fed vs fasting conditions. **Methods:** A two-part Phase

0 Open-Label study in healthy volunteers was designed. The first part "Study A" consisted of a 4 participant-crossover study (minimum of 4 days between treatments) to determine blood concentrations of (-)-FCF after oral administration of PRX-P4-003 (100 μg) and reference drug (-)-FCF hydrochloride (40 μg) in the fasted state. This was followed by "Study B" in a separate cohort of 4 volunteers following oral administration of a microdose of PRX-P4-003 in a fed state (Study B). The active phase of both studies required 2 inpatient nights. Subjects received an evening meal followed by at least 8-hour overnight fast before study drug dosing. On the morning of dosing, key inclusion/exclusion criteria were reconfirmed before administration of compound which was formulated at the site just prior to oral administration as a gel capsule or solution. Up to 12 post-dose PK blood samples over the following 24 hrs were collected along with periodic safety assessments. No food was allowed for 4 hrs post-dose. In Study B, a separate cohort of participants received a single oral microdose of 100 ug PRX-P4-003 within 30 min of a high-fat/high-calorie breakfast after an overnight fast. Plasma concentrations of (-)-FCF were quantified by a highly sensitive mass spectrometric assay specially developed to measure very low concentrations of FCF (up to 10 pg/level). **Results:** In Study A, 4 participants were dosed with PRX-P4-003 and 3 with (-)-FCF as one was lost to follow-up during the 4-day outpatient washout period. In Study B, 2 new participants were dosed with PRX-P4-003 under the fed condition (2 other participants were disqualified due to positive drug screen test on day of dosing). Findings were as follows: In the Study A (fasted), the average (-)-FCF plasma concentration after PRX-P4-003 administration peaked at 60 pg/ml at 12 h and was measurable from 4-24 hrs. In the Study B (fed), the average (-)-FCF concentration after PRX-P4-003 administration peaked at 140 pg/ml at 4 hrs with measurable levels from 2-24 hrs. In the Study A, the average (-)-FCF plasma levels after oral reference drug (-)-FCF peaked 60 ng/ml at 4-6 hrs with measurable levels from 2-24 hrs. No adverse events were reported. **Conclusions:** PRX-P4-003 is converted in humans to pharmacologically active (-)-FCF which is detected in plasma consistent with predictions from preclinical studies. The finding of a much earlier peak concentration in the fed state is consistent with the postulated dependence of release of pancreatic lipases into the gut following ingestion of food. The properties of PRX-P4-003 shown in this microdose study support its further development for the treatment of apathy in AD as a drug with at least equivalent efficacy to methylphenidate and a lower liability of abuse or diversion.

PROOF OF CONCEPT/TRANSLATIONAL RESEARCH FOR ALZHEIMER DRUG DEVELOPMENT INTERVENTIONS

P73- ALZHEIMER'S DISEASE PREVENTION WITHIN REACH BY 2025: TARGETED-RISK-AD-PREVENTION (TRAP) STRATEGY. Francesca Vitali[1,2,3], Gregory L. Branigan[1,4,5], Roberta D. Brinton[1,6,2] *(1. Center For Innovation In Brain Science, University Of Arizona - Tucson (United States), 2. Department of Neurology, University of Arizona - Tucson (United States), 3. Center for Biomedical Informatics and Biostatistics, University of Arizona - Tucson (United States), 4. Department of Pharmacology - Lawrence (United States), 5. MD-PhD training program, College of Medicine, University of Arizona - Tucson (United States), 6. Department of Pharmacology - Tucson (United States))*

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disease that results in cognitive decline, psychiatric symptoms and loss of independent living. Biological mechanisms driving AD progression can occur up to 20 years which provides an extended window for therapeutic intervention to alter the course of AD risk. In 2015, the National Plan to Address Alzheimer Disease as part of the National Alzheimer's Project Act was signed into law which proposed to effectively prevent AD by 2025. Timeline to achieve this goal is rapidly approaching. **Objectives:** AD prevention therapeutics target initiating mechanisms of AD not the full range of pathology present in AD. Therapeutics targeting AD-specific initiating risk factors can prevent or delay the cascade of mechanisms leading to AD. We aimed to analyze available publications with a bioinformatic approach to rank and select relevant and confident therapeutics to prevent AD. **Method:** We developed a targeted-risk-AD-prevention (TRAP) strategy based on a novel combination of text-mining and natural language processing strategies to identify (i) AD risk factors mining PubMed literature, (ii) FDA-approved therapeutics targeting risk factor pathways using drug-target databases, and (iii) studies supporting therapeutics in the currently published PubMed database. To classify the literature relevant to AD preventive strategies, we developed a relevance score based on STRING score for protein-protein interactions and a confidence score on Bayesian inference. This led to generation of a ranked list of significantly relevant and confident candidate therapeutics to reduce AD risk. We finally conducted network analysis of selected drug-target interactions. **Result:** Based on the TRAP strategy, 364 AD risk factors were identified based on mining 9,625 publications. Using drug databases, 629 FDA-approved drugs for identified AD risk factors were selected based on drug indications relevant to a given risk factor. These results were used to generate a pipeline to identify publications reporting a risk factor therapeutic with risk of AD, which resulted in 11,139 publications for 445 drugs. The computation of relevance and confidence scores enabled exclusion of publications that did not meet inclusion criteria and ranked 46 drugs associated with reduced risk. Within this list,16 drugs were reported in at least one clinical study of AD risk reduction, while the remaining 30 were in the in preclinical pipeline and not supported by clinical studies. Top therapeutics supported by clinical studies with reduced AD risk included five anti-inflammatories (e.g., ibuprofen, indomethacin), four lipid-lowering (e.g., pravastatin, simvastatin), two metabolic-related (pioglitazone and metformin), two hormone (estradiol and testosterone), one psychiatric (valproic acid), one cardiac (lisinopril) therapeutic, and vitamin A. Network analysis aimed at analyzing targets of these drugs resulted in 96 nodes (16 drugs and 80 target proteins) and 102 edges, where on average a drug was associated with six proteins. **Conclusion:** Outcomes of the TRAP strategy support therapeutic targeting of biological mechanisms and pathways underlying AD risk factors. Analysis of the drug-target interaction network revealed different biological networks of drug actions. On average, identified preventive therapeutics target six proteins, which indicates the efficacy multi-target profile required for AD prevention likely due to the multi-system biology contributing to AD. Because risk factor biology is linked to the pathophysiology of AD, combination therapy that targets the full preclinical risk factor profile could provide a combinatorial strategy to prevent AD. From this analysis, the most impactful risk factors that target biological mechanisms and pathways underlying AD risk include the immune, metabolic, cardiovascular, and endocrine systems. Based on our analyses, we propose that early interventions that target pathways associated with increased risk of AD has the potential to achieve the goal of

effectively preventing AD by 2025. **Acknowledgements:** This work was supported by the National Institute on Aging (grants P01AG026572 [Perimenopause in Brain Aging and Alzheimer's Disease], T32AG061897 [Translational Research in Alzheimer's Disease and Related Dementias (TRADD)], 5R01AG057931-02 [Sex Differences in Molecular Dementias of Alzheimer's Disease Risk: Prodromal Endophenotype], the Women's Alzheimer's Movement, and the Center for Innovation in Brain Science to Dr Brinton.

LP32- PROBING GUT-BRAIN LINKS IN ALZHEIMER'S DISEASE WITH RIFAXIMIN. Paul Suhocki, James Ronald, Anna Mae Diehl, David Murdoch, Murali Doraiswamy *(Duke University - Durham (United States))*

Background: Increasing evidence implicates gut-brain-microbiome links in Alzheimer's Disease (AD). Rifaximin is a minimally absorbed (<0.4%) antibiotic which modulates the gut microbiome by binding to the beta subunit of bacterial DNA-dependent RNA polymerase, inhibiting bacterial protein synthesis. **Objectives:** Evaluate the effect of rifaximin on neural and inflammatory markers as well as gut microbiome in AD dementia. **Methods:** Ten subjects with mild to moderate probable AD (MMSE 10-23) were treated with rifaxamin in this mechanistic 3-month study. Key exclusion criteria included a recent history of antibiotic use, cirrhosis or diarrhea and the presence of confounding active neuropsychiatric disorders. The change from baseline to 12 weeks (intent to treat) in serum NfL, total tau, GFAP, TNFα and cytokines was examined using ultrasensitive SIMOA and high sensitivity T-cell panel. Fecal samples underwent microbiome analysis with 16S rRNA gene sequencing and taxonomy. **Results:** Ten subjects (9 female, mean [SD] age 72.5 + 5.8 years, MMSE 17.3 + 3.3) were studied. Serum NfL levels were significantly reduced at week 12 following rifaximin treatment. Serum cytokine levels showed a trend to decrease for IL-6 and IL-13. There was a significant increase in several genera of bacteria and correlation between microbiome changes and p-tau, IL2 and IL5. **Conclusion:** To our knowledge, this is the first study to document the impact of microbiome modulation on serum markers of neurodegeneration and inflamation in AD, and supports pre-clinical evidence linking the microbiome with neurodegeneration. A larger study is planned to further elucidate mechanisms and therapeutic potential of the microbial changes identified.

RP42- INHIBITION OF THE EQUILIBRATIVE NUCLEOSIDE TRANSPORTER 1 (ENT1) RESCUES COGNITIVE IMPAIRMENT AND MISFOLDED PROTEIN ACCUMULATION IN TWO MOUSE MODELS WITH DISTINCT FEATURES OF ALZHEIMER'S DISEASE PATHOLOGY. Ching-Pang Chang[1,2], Chien-Yu Lin[1,2], Kuo-Chen Wu[2], Hsin-Hsien Yeh[3], Chun-Jung Lin[4], Yijuang Chern[1,2] *(1. Institute of Biomedical Sciences, Academia Sinica - Taipei (Taiwan, Province of China), 2. Biomedical Translation Research Center, Academia Sinica - Taipei (Taiwan, Province of China), 3. Brain Research Center, National Yang Ming Chiao Tung University - Taipei (Taiwan, Province of China), 4. School Of Pharmacy, National Taiwan University - Taipei (Taiwan, Province of China))*

Background: Alzheimer's disease (AD) is the most prominent neurodegenerative disease in aging societies. AD pathogenesis includes neuritic dystrophy, synapse loss, microgliosis, astrogliosis, and cognitive impairment. The major pathogenic hallmarks of AD include extracellular amyloid plaques, intracellular neurofibrillary tangles composed of hyperphosphorylated Tau protein, and neuroinflammation. In the past two decades, only drugs targeting neurotransmission pathways with limited therapeutic effects are available for the treatment of AD. The latest FDA-approved medicine for AD is Aduhelm, a human antibody that targets toxic beta-amyloid proteins. In addition to mAbs against amyloid or Tau, new targets are urgently needed. Another major pathological feature of AD is energy dysfunction associated with mitochondrial impairment and reduced ATP production. Consistent with this notion, overactivation of a homeostatic energy sensor (AMP kinase, AMPK) and abnormal purine metabolism have been observed in the brain of patients with AD. Targeting the purine metabolism and adenosine homeostasis thus become a new strategy for the development of AD treatment. **Objectives:** We set out to investigate whether modulating adenosine homeostasis through the suppression of equilibrative nucleoside transporter 1 (ENT1), a bidirectional transporter in the brain using an orally active small compound (J4), impacts AD pathology. **Methods:** Two AD mouse models (APP/PS1 and THY-Tau22) with onset of memory deficiency occurring at the age of 6 months were tested. For the purpose of disease prevention, animals were treated with J4 (3 mg/kg/day) in drinking water containing 1% HPβCD from the age of 3 months for 7 months. For the therapeutic treatment, mice were treated with J4 at the late disease stage (10-12 months old) as abovementioned for one month. The cognitive function of AD mice and their littermate controls were examined using the Morris water maze task, followed by biochemical and pathological analyses (including positron emission tomography, immunofluorescence staining, western blot analysis, RNAseq analysis and RT-qPCR). **Results:** Our results showed that treatment with J4 improved the impaired memory functions and the accumulation of extracellular amyloid plaques and hyperphosphorylated Tau protein in AD mice (APP/PS1 and THY-Tau22, respectively). In addition, defects of multiple pathways associated with AD pathogenesis (including mitochondrial dysfunction, synaptic loss, and elevated immune-related gene signatures) were also normalized by J4. **Conclusion:** Data of the present study showed that oral administration of J4 provided both preventive and therapeutic effects against AD pathology, supporting that targeting adenosine metabolism is a novel and effective strategy for AD. **Conflict of interest statement:** Yijuang Chern holds patents on J4 for the treatment of neurodegenerative diseases.

RP43- TARGETING MICRORNA-485-3P BLOCKS ALZHEIMER'S DISEASE PROGRESSION. Hanseok Koh[1], Sangjoon Lee[2], Hyojin Lee[1], Jaewoong Min[1], Takeshi Iwatsubo[3], Charlotte Teunissen[4], Hyunjeong Cho[5], Jinhyeob Ryu[6] *(1. Biorchestra Co., Ltd. - Daejeon (Korea, Republic of), 2. University Of Tsukuba - Ibaraki (Japan), 3. University Of Tokyo - Tokyo (Japan), 4. Amsterdam Umc, Vu University - Amsterdam (Netherlands), 5. College Of Medical Science, Konyang University - Daejeon (Korea, Republic of), 6. Biorchestra Co., Ltd. - Boston (United States))*

Background: Alzheimer's disease (AD) is a form of dementia characterized by progressive memory decline and cognitive dysfunction, which affects more than 44 million people worldwide. Currently, there is no effective therapy for AD despite its increasing global incidence; thus, effective treatment strategies for AD are urgently needed. While several drugs that decrease amyloid beta (Aβ) production or increase Aβ clearance in the brain have been identified, treatment with these

drugs is poorly correlated with improvements in AD severity and cognitive dysfunction. **Method:** Expression of miR-485-3p was analysed by real-time PCR in the human frontal cortex (8 healthy controls (HC), 7 AD patients), precentral gyrus (6 HC, 8 AD), cerebrospinal fluid (CSF) (6 HC, 7 AD), plasma exosomes (10 HC, 17 mild cognitive impairment (MCI), 12 AD). Aβ 1–42 plaque immunofluorescence and tau pathology were imaged in primary cultured mouse neurons after lentivirus-derived miR485-3p transduction. MiR-485-3p antisense oligonucleotide (ASO, 1.5 μg) or control oligonucleotide formulated with the in vivo jetPEI reagent was injected into 8-month-old 5XFAD mice by ICV injection once weekly for two weeks. Behavioral tests were performed at 8 months and their brain pathology was examined after 8-week-washout at 10 months. **Result:** We found that the miR-485-3p is overexpressed in brain tissues and CSF of AD patients, and its ASO reduces Aβ plaques, tau pathology, neuroinflammation, and cognitive decline in a transgenic mouse model of AD. Mechanistically, miR-485-3p ASO enhanced Aβ clearance via CD36-mediated phagocytosis of Aβ in vitro and in vivo. We found that miR-485-3p ASO reduces apoptosis, which effectively decreases truncated tau levels. Further, miR-485-3p ASO reduced secretion of pro-inflammatory cytokines, including IL-1β and TNF-α, and eventually relieved cognitive impairment. **Conclusion:** Collectively, our findings suggest that miR-485-3p is a useful biomarker as well as a causative factor of the inflammatory pathophysiology of AD; furthermore, miR-485-3p ASO represents a candidate therapy for AD pathology and cognitive decline, establishing a new paradigm in the AD field.

LRP14- INVESTIGATING POTENTIAL DRUGGABILITY OF LONG NON-CODING RNAS FOR NOVEL TREATMENT OF ALZHEIMER'S DISEASE. Yuji Zhang[1], Cui Tao[2]
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Background: As the sixth leading cause of death in the United States, Alzheimer's disease (AD) currently produces dementia in 5.8 million U.S. citizens and this number will increase to 13.8 million by 2050.1 However, clinical trials have not yielded therapies to prevent or slow disease progression with recent failures highlighting our incomplete knowledge of mechanisms.1-3 Accumulating evidence suggests that ADs are highly complex diseases involving dysregulation of not only protein-coding RNAs but also long non-coding RNAs (lncRNAs).4 Thousands of lncRNAs are expressed specifically in the brain with precisely regulated temporal and spatial expression patterns,5,6 although their specific influences in AD remain be largely unknown.4,7 Recently, we developed a comprehensive informatics approach to reannotate and characterize disease-associated novel lncRNAs in both melanoma8 and heart disease models.9 Furthermore, our recent studies and a few others10-13 suggested that in silico-based drug repositioning strategies can greatly expand our understanding of drug-drug target interaction and lead to novel opportunities for rational drug repositioning. **Objectives:** In this project, our objective is to investigate the potential roles of lncRNAs by examining their expression patterns across tissues in different brain regions. **Methods:** We developed a integrative informatics approach aiming to investigate the potential druggability of AD-altered lncRNAs (ADALs) by integrating three AD RNA sequencing (RNAseq) cohorts sponsored by the Accelerated Medicine Partnership (AMP) Program. First, we tailored our harmonization approach to reannotate 778 RNAseq samples across seven brain regions. Second, we employed our in-silico drug repositioning approach to identify and prioritize drug candidates targeting these ADALs though both network topology and weighted co-expression network analysis. **Results:** In total, we identified and characterize 2865 tissue-specific ADALs across seven brain regions. Based on their computationally inferred perturbational profiles using the Library of Integrated Network-based Cellular Signature (LINCS) dataset, these ADALs were then prioritized using our integrative weighted and co-expression network analyses. Finally, 142 ADALs were prioritized as potential drug targets for our future independent assessment by both registered clinical trial data and AD medical expert knowledge. **Conclusions:** Our integrative informatics approach for AD drug development will greatly accelerate the underpinning of AD by repositioning known perturbagens targeting ADALs for novel AD therapy. The outcome will benefit the biomedical community by guiding future targeted experimental designs and generating testable hypotheses. **Reference:** 1. Cummings, J., et al., Alzheimer's disease drug development pipeline: 2020. Alzheimers Dement (NY), 2020. 6(1): p. e12050. 2. Szeto, J.Y. and S.J. Lewis, Current Treatment Options for Alzheimer's Disease and Parkinson's Disease Dementia. Curr Neuropharmacol, 2016. 14(4): p. 326-38. 3. Cummings, J., et al., Alzheimer's disease drug development pipeline: 2019. Alzheimers Dement (NY), 2019. 5: p. 272-293. 4. Cortini, F., F. Roma, and C. Villa, Emerging roles of long non-coding RNAs in the pathogenesis of Alzheimer's disease. Ageing Res Rev, 2019. 50: p. 19-26. 5. Frankish, A., et al., GENCODE reference annotation for the human and mouse genomes. Nucleic Acids Res, 2019. 47(D1): p. D766-D773. 6. Zimmer-Bensch, G., Emerging Roles of Long Non-Coding RNAs as Drivers of Brain Evolution. Cells, 2019. 8(11). 7. Xu, J., et al., A comprehensive overview of lncRNA annotation resources. Brief Bioinform, 2017. 18(2): p. 236-249. 8. Wang, L., et al., Integrative Genome-Wide Analysis of Long Noncoding RNAs in Diverse Immune Cell Types of Melanoma Patients. Cancer Res, 2018. 78(15): p. 4411-4423. 9. Wang, L., et al., Systematic identification and characterization of cardiac long intergenic noncoding RNAs in zebrafish. Sci Rep, 2017. 7(1): p. 1250. 10. Zhang, Y., et al., Network-based analysis reveals distinct association patterns in a semantic MEDLINE-based drug-disease-gene network. J Biomed Semantics, 2014. 5: p. 33. 11. Tao, C., et al., Colorectal cancer drug target prediction using ontology-based inference and network analysis. Database (Oxford), 2015: bav015. 12. Liang, C., J. Sun, and C. Tao, Semantic Web Ontology and Data Integration: a Case Study in Aiding Psychiatric Drug Repurposing. AMIA Jt Summits Transl Sci Proc, 2016. 2016: p. 132-9. 13. Rastegar-Mojarad, M., et al., Opportunities for drug repositioning from phenome-wide association studies. Nat Biotechnol, 2015. 33(4): p. 342-5.