POSTERS

Theme: CLINICAL TRIALS METHODOLOGY

P001- UNDERREPRESENTED ELDERS IN THE BRAIN HEALTH REGISTRY: US REPRESENTATIVENESS AND REGISTRY BEHAVIOR.

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Backgrounds: The Many dementia-related registries and clinical trials are limited by a lack of representative samples, especially underserved groups (e.g. racial or ethnic groups, low socio-economic status). Reduced participation of unrepresented groups in dementia-related research has serious scientific and ethical ramifications. Online research registries offer the possibility to facilitate the recruitment of traditionally underrepresented groups into clinical research by remotely prescreening and referring to relevant clinical trials. However, little is currently known about the degree to which online research registries are representative of the US population, and what factors are associated with participation. **Objectives:** The Brain Health Registry (BHR) is an online research registry for recruitment, assessment, and longitudinal monitoring of currently over 66,000 participants, focusing on cognitive aging. The first objective was to assess the extent to which older BHR participants are representative of the US population of older adults. The second objective was to assess associations between race, ethnicity, and education and registry behaviors (task completion and retention) in BHR. **Methods:** BHR participants complete a series of online, unsupervised self-report questionnaires and neuropsychological tests (e.g. the Cogstate Brief Battery (CBB)) every 6 months. This analysis focused on US BHR participants aged 65 years or older and the following demographics: gender, race, ethnicity, and education. The US Census data from the 2017 American Community Survey was used to determine nationally representative percentage estimates for the US population 65 years or older. First, to assess overall differences in the BHR and the US Census in terms of demographic variables of participants, the percentages of individuals in our demographic categories were compared using Pearson's Chi-squared test with Yates' continuity correction, and Cramer's V was calculated as a measure of strength of associations. Second, to determine registry participation, withdrawal and task completion rates for BHR online questionnaires and CBB were calculated. Participants who communicated a desire to no longer participate in BHR were considered as withdrawn. The core battery of self-report questionnaires we considered included three questionnaires most commonly used for analysis (demographics, medical history, and initial). The CBB included four subtests that assess cognition across the domains of processing speed, attention, and memory. Third, we determined associations between demographic variables (gender, race, ethnicity, and education) and registry participation (withdrawal and task completion) using logistic regression methods. **Results:** Of the 17,073 BHR participants age 65+, 65% were female, 85% identified as Caucasian, 91% identified as non-Hispanic/Latino, and 68% had a bachelor's degree or higher. Compared to the Census data, the BHR underrepresented males (Δ=-9.39%, p<.0001, V=0.003) and Hispanic/Latino participants (Δ=-5.81%, p<.0001, V=0.005). Non-Caucasians were also underrepresented (p<.0001, V=0.005), specifically Black/African American participants (Δ=-6.06%), Asian participants (Δ=-2.35%), Native American and Alaska Native participants (-0.31%), and participants from some other race (Δ=-0.26%). Participants with lower education levels were also underrepresented (p<.0001, V=0.02), including those with a community college degree or associate's degree (Δ=-1.37%), a high school degree (Δ=-25.27%), or lower (Δ=-15.26%). Only Native Hawaiian/Other Pacific Islander participants matched the US Census percentage. Rates of withdrawal from the BHR online study were the highest for Non-Hispanics/Latino (16.5%) and the lowest for Black/African American participants (3.4%). Non-Caucasian participants had lower withdrawal rates from the BHR study (OR=0.8, CI=0.64,0.99, p=.04). However, regarding task completion, Black/African American participants (Core:45.3%, CBB:32.8%) and participants with less than a high school education (Core:42.9%, CBB:27.0%) had the lowest rates for completion of BHR self-report questionnaires and CBB, compared to those with a bachelor's degree or higher (Core:77.0%, CBB:59.9%) and Caucasian participants (Core:74.5%, CBB:74.6%). Identifying as non-Hispanic/Latino and a higher education level was significantly associated with completion of all four CBB tests (OR=1.23, CI=1.01,1.51, p=.04; OR=1.12, CI=1.1,1.13, p<.001), as well as completion of all core questionnaires (OR=1.33, CI=1.11,1.14, p<.001; OR=1.12, CI=1.11,1.14, p<.001) at least once, respectively. The same significant associations were found for completing CBB and core questionnaires at least twice. Identifying as non-Caucasian was associated with lower completion of core questionnaires (OR=0.47, CI=0.42,0.52, p<.001) and CBB (OR=0.61, CI=0.55,0.68, p<.001). Being female was significantly associated with completion of the core questionnaires (OR=1.2, CI=1.12,1.3, p<.001). **Conclusion:** Older adult males, Hispanic/Latino, Black/African American, Asian participants and especially those with a lower educational status were underrepresented in BHR compared to the US Census. This indicates that the BHR reflects general participation biases present in most scientific research. Thus, there is a clear need to develop and evaluate improved recruitment and engagement strategies to make BHR more attractive to underrepresented groups (e.g. targeted online advertising and tailoring the BHR website). Increasing registry diversity is important to increase the generalizability of results and applicability of findings to underserved and underrepresented groups. Non-Caucasian race, non-Hispanic/Latino ethnicity, and lower education were associated with decreased BHR task completion. However, being non-Caucasian was also associated with lower withdrawal rates. Future analyses need to determine whether covariates such as, for example, age and subjective memory concern might account for any of these differences.

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P002- A PHASE 3- EFFICACY AND SAFETY STUDY PROTOCOL OF TRANEUROCIN (NA-831) IN PARTICIPANTS WHO ARE ASYMPTOMATIC AT RISK FOR DEVELOPING ALZHEIMER'S DEMENTIA (PREVENTION). L. Tran, F. Vu, S. Neave, B. Tran *(NeuroActiva, Inc. - Moffett Filed, CA, (United States))*

Background: Approximately The purpose of this study is to evaluate whether treatment with Traneurocin (NA-831) slows cognitive decline compared with placebo treatment, as measured by a composite cognitive measure, the Preclinical Alzheimer Cognitive Composite (PACC), in participants who are asymptomatic at risk for developing Alzheimer's dementia. Traneurocin (NA-831) is an endogenous small molecule that exhibits neuroprotection, neurogenesis, and cognitive protective properties across a range of disease models. Phase 2 studies demonstrated that NA-831 was effective for improving cognitive and global functioning in patients with MCI and mild and moderate Alzheimer's disease over 24 weeks. The drug was well-tolerated taken orally at 30 mg per day. No adverse effects were observed. This is a randomized, double-blind, multi-center, placebo-controlled, parallel-group study in 575 participants who are asymptomatic and at risk for developing Alzheimer's dementia. The study will consist of a Screening Phase (approximately 90 days), treatment Phase (48 months) and follow-up Phase (60 days). In treatment Phase eligible Participants will be randomized to receive study drug or placebo once daily for up to 4 years. The maximum study duration for a participant will be 48 months. Participants' safety will be monitored throughout the study. **Outcome Measures:** Primary Outcome Measures : Change from Baseline in Preclinical Alzheimer Cognitive Composite (PACC) up to Month 48.The PACC is composed of 4 measures [Free and Cued Selective Reminding Test, Delayed Paragraph Recall, Wechsler Adult Intelligence Scale (WAIS)-IV Coding and Mini Mental State Examination (MMSE) Total Score] that are weighted towards episodic memory and includes a timed executive function test and a global cognitive screening test. Higher scores indicate better performance. Secondary Outcome Measures : 1. Change from Baseline in Cognitive Function Index (CFI) to up to Month 48. Cognitive Function Index (CFI) is a 15 point rating scale that assesses the Participants perceived ability to perform high-level functional tasks in daily-life and sense of overall cognitive functional ability. The higher scores indicate greater impairment. 2. Change from Baseline in Alzheimer's Disease Cooperative Study - Activities of Daily Living - Prevention Instrument (ADCS-ADLPI) Total Score up to Month 48. The Alzheimer's Disease Cooperative Study - Activities of Daily Living -Prevention Instrument (ADCS-ADLPI) is a functional measure composed of 18 items that includes 15 activities of daily living rated on a 4 point scale and 3 high level function items. The scores range from 0 to 45 with higher scores indicating less impairment. 3. Change from Baseline in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Total Scale Score to up to Month 48. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) rating scale is used to assess the cognitive assessment, detection, and characterization of dementia. The scores range from 40 to 160, and are normalized to a mean of 100 and standard deviation of 15. Higher scores indicate less impairment. 4. Change from Baseline in Clinical Dementia Rating - Sum of Boxes (CDR-SB) Score up to Month 48. The Clinical Dementia Rating - Sum of Boxes (CDR-SB) scores ranging from 0 to 18. The CDR assesses 3 domains of cognition (memory, orientation, judgment/problem solving) and 3 domains of function (community affairs, home/hobbies, personal care) using semi-structured interviews of both the study participant and an informant carried out by a trained rater. The Higher CDR-SB scores indicate greater impairment. 5. Number of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs) up to Month 48. An AE was any untoward medical event that occurs in a participant administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. **Eligibility Criteria:** Ages Eligible for Study: 60 Years to 85 Years (Adult, Older Adult), Sexes Eligible for Study: All. Accepts Healthy Volunteers: Yes. Inclusion Criteria: · Participant must have a global Clinical Dementia Rating Scale- (CDR) score of '0' at Screening; · Participants 60 to 64 years of age must also have either (a) a positive family history for dementia (minimum of 1 first degree relative), or (b) a previously known apolipoprotein E, ε4 allele (APOE ε4) genotype, · Participant must be able to read and write and must have adequate hearing and visual acuity to complete the psychometric tests. The legally acceptable representative must also be able to read and write; · Participant must be otherwise healthy for their age group or medically stable with or without medication on the basis of physical examination, medical history, vital signs, and 12-lead electrocardiogram (ECG) performed at Screening or at Baseline. Details of the Inclusion and Exclusion Criteria and other methodology will be presented and discussed.

P003- USING NETWORK ANALYSIS AND MACHINE LEARNING METHODS TO EVALUATE THE EFFICACY OF LEMBOREXANT IN PATIENTS WITH IRREGULAR SLEEP WAKE RHYTHM DISORDER AND ALZHEIMER'S DISEASE DEMENTIA. N. Rabbee[1], M. Moline[1], S. Dhadda[1], M. Kemethofer[2], N. Kubota[3] *((1) Eisai, Inc. - Woodcliff Lake (United States), (2)The Siesta Group - Vienna (Austria), (3) The Siesta Group - Tokyo (Japan))*

Background: Disturbances in sleep-wake regulation appear early in the course of Alzheimer's disease dementia (AD-D) and are associated with impaired cognition and patient/caregiver burden. One such manifestation of this disturbance is the circadian rhythm sleep disorder, Irregular Sleep-Wake Rhythm Disorder (ISWRD). There are currently no treatments approved for ISWRD. The controlled treatment period of a Phase 2 proof-of-concept and dose-finding clinical trial has been completed, which included endpoints related to the effect of lemborexant on nighttime sleep, daytime wakefulness, circadian rhythm parameters, and other clinical measures of ISWRD in patients with mild to moderate AD-D. **Methods:** Subjects 60 to 90 years who met criteria for both AD and ISWRD were recruited from sites in the United States, Japan and the UK. Eligible subjects had Mini-Mental State Examination (MMSE) scores between 10 and 26 and were not clinically depressed. Patients with moderate to severe sleep

apnea were excluded based on polysomnography. Subjects wore actigraphy devices (MotionWatch 8, CamNtech; MW8) continuously on the non-dominant wrist for approximately 14 days, and were eligible for randomization after meeting criteria indicating both disrupted nighttime sleep and daytime wakefulness. Subjects were randomized to placebo or to 1 of 4 treatment arms of lemborexant (2.5, 5, 10, or 15 mg), and provided instructions to take the study medication before the time the subject intended to try to sleep. Efficacy variables were derived from the actigraphy data at screening, baseline, and over 1 month of treatment, and included but were not limited to actigraphy-based sleep and wake efficiency, sleep and wake fragmentation indices, duration of sleep bouts during the day and wake bouts at night, timing and activity within the least 5 active hours, relative amplitude, intradaily variability, and interdaily stability. In addition, scored epochs (30 sec) from each patient were obtained for further analysis. The raw actigraphs from each patient for each data was available and utilized for functional analysis as well. To assist in the analysis of data, informants maintained a log each day of the study to indicate when the subjects went to bed for the night and when they got out of bed in the morning as well as times when the actigraph was not recording data, e.g. if the device had been removed for some reason. Following the 4-week treatment period, there was a 2-week follow-up period without study medication to assess for possible rebound ISWRD symptoms (using actigraphy) and for safety. **Results:** Since ISWRD is a relatively new therapeutic area, there is limited knowledge about the utility of numerous efficacy measures obtained from the patients' actigraphy data for evaluating efficacy. To this end, Multivariate Network Analysis of key efficacy variables related to circadian rhythms was conducted to identify the primary variables impacted by treatment, as well as inter-relationships among them. Special methods were used, since the number of variables was large compared to the small sample size of 61 randomized subjects. In particular, machine learning methods were applied to perform variable selection, assuming a sparse multivariate network topology. The algorithm selected a few night-time and day-time efficacy variables for each patient. The selected variables were compared across treatment groups in univariate regression models. In addition, functional data analysis summary measures were obtained using a novel algorithm to process the patients' actigraphy data. Differences between treatment groups using these functional measures were evaluated as well. The key findings were that lemborexant 5 mg showed benefit over placebo between baseline and week 4 of treatment as follows, (a) larger decrease in average duration of sleep bouts during the day; (b) larger decrease in average activity during the least active 5 hours of the day; (c) earlier onset of the least 5 hours of activity of the day (but still during the night); and (d) larger decrease in the average number of wake bouts at night. The actigraph functional analysis showed that lemborexant 5mg was associated with a higher increase in amplitude (1/2 peak to nadir difference) and circadian quotient (ratio of amplitude and mesor (the average activity over the 24-hr period) when compared with placebo from baseline to week 4 of treatment. **Conclusions:** This randomized clinical trial provides important new information regarding the potential utility of this investigational medication to address both nighttime and daytime symptoms that impact the quality of life of ISWRD/AD-D patients and their caregivers and families through the use of novel analytic methodology.

P004- MEDICARE ADVANTAGE – IMPACT OF NEW MEMORY FITNESS BENEFIT AND REIMBURSEMENT STRUCTURE TO INCREASE REFERRALS TO ALZHEIMER'S DISEASE CLINICAL TRIALS. J. Dwyer, C. Cordell *(The Global Alzheimer's Platform (GAP) Foundation - Washington, DC (United States))*

Background: Potential clinical trial participants with mild cognitive impairment (MCI) or dementia due to mild Alzheimer's disease (AD) are often not aware of their condition or are fearful "nothing can be done." Healthcare professionals (HCPs) often have a similar attitude. If HCPs could be encouraged to treat MCI or mild AD similar to other chronic conditions, this would likely prompt more referrals to specialists and to AD trials. Fortunately, US Medicare Advantage (MA) insurance plans now have a financial incentive beginning in 2020 to detect and diagnosis dementia among their beneficiaries (~22M) with new risk adjustment payments (HCC 51 and HCC 52), and in 2019 the Centers for Medicare and Medicaid Services (CMS) permitted MA plans at their discretion to offer Memory Fitness Activities in their supplemental benefits. **Objectives:** To determine whether the new MA risk adjustment payments for beneficiaries with dementia (with and without complications) and allowance of Memory Fitness Activities in MA plans could provide a pool of 'better characterized' AD trial participants. **Methods:** The Global Alzheimer's Platform (GAP) Foundation initiated a review of 2019 MA plans to determine the prevalence of benefits for Memory Fitness. GAP, along with other experts, calculated an estimate for the number of MA beneficiaries that could serve as possible 'better characterized' AD trial participants and the value of risk adjustment payments for HCC 51 and HCC 52. Due to the negligible number of MA brain health programs being offered, GAP initiated in September 2019 a targeted Facebook survey of residents in Rhode Island >60 years of age to determine interest in Memory Fitness Activities and MA plans. Survey will be open until 300 responses are acquired. **Results:** Up to 4.4 million beneficiaries could be newly characterized in 2020 as interested in brain health or diagnosed with MCI or mild AD creating a new pool of possible trial participants. The estimated value of payments to MA plans for beneficiaries with diagnosis of dementia ranges from ~$6,000/member/year for dementia with complications to $1,500/member/year without complications (~$3 to $4 billion in total). GAP found that only 1 plan offered a Memory Fitness benefit in 2019 and no plan offered a comprehensive set of brain health activities. A few other plans offered some form of Memory Fitness Activities in their "wellness" programs ranging from brain stimulating activities, such as discounted access to online BrainHQ or walking activities. Survey results as of September 9, 2019 (N=74) show that 74% would likely enroll in an MA plan with memory fitness vs one without. Furthermore, 50% of these respondents also self-reported 5 or more health brain activities (out of 8) that they already embrace. Fewer than 14% stated the were not likely or weren't interested in any MA plan with brain health benefits. **Conclusion:** Providing US research centers in the GAP network (GAP-Net) a better characterized potential trial participant is central to GAP's mission to increase the speed of AD trials. With potential risk adjustment payments to MA plans reaching >$3 billion, GAP is committed to working with HCPs, MA insurance plans, and health systems to reach the 4.4 million MA beneficiaries that have interest or knowledge about their brain health and connect them with clinical trial opportunities. Survey results support MA plans that offer

brain health benefits will attract those who are currently living a healthy lifestyle and want more options for brain health and not adversely select only potential participants with serious memory issues.

P005- SUITABILITY OF EPAD LONGITUDINAL COHORT STUDY (EPAD LCS) POPULATION FROM MEMORY CLINICS FOR PREVENTIVE CLINICAL TRIALS. I. Carrie[1], P.J. Ousset[1,2,3], D. Pennetier[1], J. Delrieu[1,2,3], N. Sastre Hengan[1], F. Lala[1], B. Vellas[1,2,3] *((1) Gerontopole, Toulouse University Hospital - Toulouse (France), (2) INSERM Unit 1027 - Toulouse (France), (3) Toulouse University III - Toulouse (France))*

Background: The European Prevention of Alzheimer's Dementia Longitudinal Cohort Study (EPAD LCS) is an ongoing prospective, multicentre, pan-European longitudinal cohort study (Solomon et al.2018). One of the key objectives for building the EPAD-LCS is to provide a well-phenotyped population (readiness population) for the EPAD Proof of Concept (EPAD-PoC) trial to minimize trial screening failures. Research participants can only enter the EPAD LCS if they have been selected from the EPAD Registry (Vermunt et al. 2018). The EPAD registry was designed in order to facilitate recruitment by preselecting subjects from either existing parent cohorts or registers. In France, EPAD LCS participants were selected from the French Alzheimer research registry constituted by patients seen in memory clinics. **Objectives:** Based on the baseline cognitive and biomarker measures collected from EPAD LCS participants recruited in France, we were interested in checking if our population would be suitable in terms of readiness for preventive clinical trials. **Methods:** The EPAD LCS V500.0 dataset includes the baseline data from volunteers aged ≥ 50 years from 13 sites. Participants undergo detailed phenotyping including, MMSE, CDR and CSF measures. We first analyzed these data for the EPAD LCS participants recruited in France (3 sites) in comparison to the other sites (10 sites). Then, we evaluated the proportion of participants meeting the following main inclusion criteria usually used for clinical trials targeting (1) prodromal AD population [CDR=0.5 + MMSE≥24+ CSF Ab positivity (Ab42 < 1000pg/ml) (2) preclinical AD population [CDR=0 + MMSE≥27 + CSF Ab positivity (Ab42 < 1000pg/ml)]; and (3) asymptomatic population [CDR=0 + MMSE≥24]. **Results:** Respectively, among the 106 French participants and the 394 participants from the other recruiting sites: the mean (SD) age was 69.4 (7.7) and 65.5 (6.1) years; the mean (SD) MMSE score was 28.4 (2.0) and 28.7 (1,5); the number of participants with a CDR of 0.5 was 55 (52.9%) and 32 (8.3%); 33 (34.7%) and 124 (35.2%) participants had a positive amyloid status based on CSF. The number of participants presenting: (1) main prodromal inclusion criteria was 22 (20.8%) for France and 16 (4.1%) for the other sites (2) main preclinical inclusion criteria was 10 (9.4 %) for France and 102 (25.9%) for the other sites; (3) main asymptomatic inclusion criteria was 48 (45.3%) for France and 348 (88.3%) for the other sites. **Conclusion:** The French EPAD LCS participants recruited from memory clinics appeared to be somewhat different to those recruited from parent cohorts, notably in terms of age and CDR status. There was a high percentage of participants with a CDR of 0.5, corresponding to a potential prodromal population. These findings suggest that recruitment from memory clinics is suitable for prodromal AD trials while recruitment from parent cohorts may be more adequate for trials involving asymptomatic subjects. Solomon A et al. European Prevention of Alzheimer's Dementia Longitudinal Cohort Study (EPAD LCS): study protocol. BMJ Open. 2018; 8; Vermunt Let al. European Prevention of Alzheimer's Dementia Registry: Recruitment and prescreening approach for a longitudinal cohort and prevention trials. Alzheimers Dement. 2018 ;14(6):837-842.

P006- A 48-WEEK PHASE 3 CLINICAL TRIAL METHOD TO EVALUATE THE EFFICACY AND SAFETY OF NA-831) IN SUBJECTS WITH EARLY ALZHEIMER'S DISEASE. L. Tran, F. Vu, B. Tran, S. Neave *(NeuroActiva, Inc. - Moffett Field, CA(United States))*

NA-831 is an endogenous small molecule that exhibits neuroprotection, neurogenesis, and cognitive protective properties across a range of disease models. Phase 2 studies demonstrated NA-831 was effective for improving cognitive and global functioning in patients with MCI and mild and moderate Alzheimer's disease over 24 weeks. The drug was well-tolerated taken orally at 30 mg per day. No adverse effects were observed. This phase 3 study method consists of a Core and Open Label Extension (OLE) Phase in 465 participants with Early Alzheimer's Disease (EAD), and will be conducted to evaluate the efficacy and safety of NA-831. The Core is a 48-week treatment, multicenters, double blind, placebo controlled parallel group study. The OLE is a 48-week treatment, one group study. **Experimental:** Core Study: Participants will receive one capsule of 30 milligram (mg) NA-831 orally once a day in the morning. The core study will be double blinded. Placebo Comparator: Core Study: Participants will receive one matching capsule of 30 mg placebo orally once a day in the morning. The core study will be double blinded. **Experimental:** Open Label Extension Phase: Participants completing the core study will receive one 30 milligram (mg) NA-31 capsule orally once a day in the morning. Key Outcome Measures: Key Primary Outcome Measures: 1. Core Study: Change From Baseline in the Clinical Dementia Rating - Sum of Boxes (CDR-SB) Score at 48 Weeks [Time Frame: Baseline, Week 48]; 2. Open-Label Extension Phase: Number of Participants With Treatment-Emergent Adverse Events (AEs) [Time Frame: Up to Week 48 of Extension Phase]. Key Secondary Outcome Measures : 1. Core Study: Change From Core Study Baseline in Alzheimer's Disease Assessment Scale-Cognition-13 (ADAS-Cog-13) at Weeks 24, 48 [Time Frame: Baseline, Week 24, Week 48 of Extension Phase]; 2. Open-Label Extension Phase: Change From Core Study Baseline in Mini Mental State Examination (MMSE) at Weeks 8, 16, 24, 32, 40, and 48 Time Frame: Baseline, Weeks 8, 16, 24, 32, 40 and 48 of Extension Phase]; 3. Open-Label Extension Phase: Time to Conversion to Dementia for Participants who were not Clinically Staged as Dementia at Core Study Baseline Based on Clinical Diagnosis [Time Frame: Up to 96 weeks of Extension Phase]. **Eligibility Criteria:** Ages Eligible for Study: 50 Years to 85 Years (Adult, Older Adult). Sexes Eligible for Study: All. Accepts Healthy Volunteers: No. Core Study: Mild cognitive impairment due to AD or mild AD dementia including. 1. MMSE score equal to or greater than 24; 2 CDR global score of 0.5; 3. CDR Memory Box score of 0.5 or greater: · Impaired episodic memory confirmed by a list learning task;· Positive biomarker for brain amyloid pathology as indicated by either amyloid PET or cerebrospinal fluid AD assessment or both. Extension Phase: Participants who complete the Core Study. **Locations:** The Phase 3 clinical trial will be conducted on 465 subjects in more than 25 sites in the US, UK, Canada, Australia, New Zealand, France, Germany, Vietnam

and China. The details of the Phase 3 methodology and protocol will be presented and discussed.

P007- DIVERSITY & INCLUSION IN ALZHEIMER'S DISEASE CLINICAL TRIALS WORKFORCE: A SURVEY TO ASSESS BASELINE MEMBERSHIP AND CLIMATE IN THE ALZHEIMER'S CLINICAL TRIALS CONSORTIUM (ACTC). R. Raman[1], A. Smith[2], G. Jimenez-Maggiora[1], K. Ernstrom[1], J.S. So[1], M. Wong[1], P. Aisen[1], R. Sperling[3], N. Aggarwal[4] *((1) Alzheimer's Therapeutic Research Institute, University of Southern California - San Diego (United States), (2) USF Health Byrd Alzheimer's Institute & Department of Psychiatry and Behavioral Neurosciences, University of South Florida Morsani College of Medicine - Tampa (United States), (3) Department of Neurology, Massachusetts General Hospital, Harvard Medical School - Boston (United States), (4) Rush Alzheimer Disease Center & Department of Neurological Sciences - Chicago (United States))*

Background: Alzheimer's disease (AD) clinical trials in the Unites States face a major problem with lack of diversity, both among study participants and research teams conducting the studies. However, recently, there have been several national initiatives to identify and eliminate barriers to enrolling underrepresented communities in AD clinical trials. Key to the success of these initiatives is the establishment of a diverse and inclusive workforce. **Objectives:** The Alzheimer's Clinical Trials Consortium (ACTC) is a national clinical trials consortium, funded by the National Institute on Aging, established to conduct clinical trials in AD and related dementias. A key aim of this consortium is to implement cutting-edge participant recruitment and retention strategies, especially in diverse populations. The ACTC's Inclusion, Diversity and Education in Alzheimer's disease Clinical Trials (IDEA-CT) committee was established to identify and train a diverse group of research staff, junior investigators and future leaders interested in and committed to optimizing the design and conduct clinical trials in AD and related disorders. As a first effort, the committee developed a survey to establish a baseline assessment of the membership of the Consortium as well as to better understand the current experience and perceptions of the members as it relates to inclusion. **Methods:** The IDEA-CT survey working group developed and administered a national, anonymized, non-incentivized, electronic diversity and inclusion survey to all active members of the consortium, including study sites, units, committees, coordinating center, and key collaborators. The survey consisted of two parts: the first part (21 questions) was designed to collect information about the individual to permit an overview of current diversity within the consortium, and the second part (40 questions) was to determine and assess members experience and perceptions regarding inclusion in their professional and personal lives. **Results:** Two hundred and eighteen ACTC members completed the survey, representing an overall response rate of 48%. Similar response rates were observed across all categories of respondents, namely, site personnel, leadership team members and coordinating center staff. The snapshot of respondents represented a diverse community with respect to sex, race, ethnicity, religion, socioeconomic status and age. Respondents indicated general satisfaction regarding workplace respect, purpose and appreciation with the greatest concerns expressed being about access to opportunity. The most common types of past discrimination reported by the respondents were related to sex, gender, race, and age, with a third also reporting never having experienced any discrimination. Surprisingly, over two thirds of the respondents had never had training in clinical trial diversity and inclusion. **Conclusions:** This survey provides a first look at the diversity of the AD clinical trials research community within this large, national consortium. The higher than expected response rate to the inaugural survey and low (less than 5%) percentage of non-informative data even for the most sensitive questions illustrates the feasibility of conducting such surveys and demonstrates the commitment of consortium members to diversity and inclusion issues. Study results provide us with baseline data needed to develop goals and formulate a strategic plan to support the ACTC's core values of inclusion, diversity and training in the field of AD clinical trials.

P008- THE IMPACT OF PATIENT SELECTION STRATEGIES ON CLINICAL TRIAL POWER. M. Donohue[1], J. Cara[2], L. Schneider[1], T. Beach[2], J. Collens[2], K. Shah[2,3] *((1) University of Southern California - Los Angeles (United States), (2) Vivid Genomics - San Diego (United States), (3) Banner Sun Health Research Institute - Phoenix (United States))*

Background: Protein aggregation in the brain underlies much of neurodegenerative diseases. For example, amyloid and tau protein aggregates in Alzheimer's disease. However, in individuals that present with dementia, there are frequently multiple underlying pathologies that can be difficult to distinguish clinically. As many as 40% of patients with Alzheimer's disease also have some burden of Lewy Bodies, TDP-43 proteinopathy, or show vascular brain injury. The variations in brain pathology and severity can lead to differences in rates of cognitive decline. While some protein aggregations can be detected via PET or CSF (i.e amyloid), others have no detection methods until autopsy (for example, Lewy Bodies, microinfarcts and TDP-43). numbers of patients. The difficulty in assessing the underlying pathology causing a patient's dementia means that, in general, the patient populations being recruited into clinical trials are heterogeneous and this can impact the apparent efficacy of potential drugs. **Objectives:** In this study, our goal is to evaluate the impact of a heterogeneous patient population on the power of a clinical trial to detect a difference in cognitive decline between a drug and placebo arm. The heterogeneity in a patient population could be due to comorbid pathologies, clinical misdiagnosis, or other underlying disease mechanisms. The type and severity of protein aggregation in the brain can also lead to differences in the rate of cognitive decline of a patient. We estimated the power of a clinical trial to detect a change in clinical dementia rating - sum of boxes (CDR-SB) score (a commonly used metric of drug response in dementia) as a function of the degree of patient heterogeneity. Even with existing tools, tests can be expensive and burdensome when screening large. **Methods:** Using simulations, we show the power of a clinical trial to detect a meaningful change of 0.25 in CDR-SB score due to drug response. We demonstrate the improvement in power if the underlying study population can be made more homogeneous by removing individuals with slow cognitive decline or non-response due to comorbid disease a priori. The standard deviation of CDR-SB change was assumed to be 1.0, based on the estimated standard deviation of CDR-SB change from baseline to 18 months in ADNI MCI participants (SD=0.93). The mean decline in the placebo group was assumed to be 1.0, except for non-decliners who were assumed to have mean change 0, regardless of

treatment assignment. The mean decline in the active group was assumed to be 0.75 (a benefit of 0.25 points), except for non-declincers (mean change 0) and non-responders (mean change of 1.0 points). We allowed the proportion of non-responders and non-decliners to vary, and considered the effect on the power to detect the simulate treatment effect assuming 15% attrition. **Results:** Our simulations suggest that the power of a study could be improved by identifying and excluding non-responders or slow decliners from the trial. For example, if the proportion of non-decliners (p) within a trial is reduced from 25% to 0% of the cohort, the power to detect a change in CDR-SB improves from 50% to 80% with a trial size of 300 individuals per group. Even reducing p by half, from 25% to 12.5%, provides a significant boost in power (50% versus 63%). Put another way, a trial targeting 80% power to detect a 0.25 change of CDR-SB score would require 300 patient participants per group if all are expected to show some response/cognitive change. If, however, 25% of the trial population is either non-responsive or slow to decline, then the trial size would need to be over 500 individuals to detect the same true effect of 0.25 change in CDR-SB. **Conclusion:** Our simulations show a marked improvement in power to detect a change in CDR-SB within a clinical trial if non-responders or slow-decliners can be excluded during recruitment or analysis. While it is widely recognized that there is a need for improved recruiting criteria for AD and dementia clinical trials, identifying appropriate participates remains a challenge. We are developing a suite of tools to predict patients with likely comorbidities or slow cognitive decline. These tools could help improve the likelihood of detecting drug response and getting drug approved for use in a subset of AD patients when employed as part of a recruiting and/or stratification strategy within a clinical trial.

P009- PHYSICAL ACTIVITY AND ALZHEIMER'S DISEASE - 2: CLINICAL TRIAL PROTOCOL. J.L. Etnier[1], L. Wideman[1], W.B. Karper[1], J.D. Labban[1], C.N. Wahlheim[1], T.M. Williams[2], Y.P. Mobley[1], A.B. Slutsky[1,3], K.S. Park[1], N.T. Berry[1] *((1) University of North Carolina at Greensboro - Greensboro (United States), (2) East Carolina University - Greenville (United States), (3) UNC Greensboro Gateway MRI Center - Greensboro (United States))*

Objective: The global prevalence of Alzheimer's disease (AD) is expected to reach 131.5 million by the year 2050. Although scientists are exploring disease-modifying pharmacological interventions, there is currently no known cure. For this reason, researchers are also focusing on behavioral interventions with the potential to delay the onset of the disease. Evidence from observational studies shows that physical activity (PA) is associated with a reduced risk of AD. Cross-sectional and prospective studies show cognitive benefits of PA for persons with a family history of AD (FH+), with most studies reporting larger benefits for those with a greater genetic risk of AD (i.e., the carriers of the apolipoprotein e-4 allele (APOE4+) as compared to non-carriers (APOE4-)). **Objectives:** The purpose of this Phase II clinical trial is to (a) confirm the causal relationship between PA and cognitive performance for persons with FH+, (b) further our understanding of neurological and biological mechanisms that underlie observed benefits, and (c) test the moderating role of APOE4 status on outcomes and mechanisms. **Methods:** We will recruit cognitively normal, middle aged (40-65 years) adults with FH+ who do not meet PA recommendations. Participants will be randomly assigned to a treatment group that participates in a 1-year PA program consisting of walking and strength training performed for 1 hour, 3 days/week or to a control group that is asked to maintain their normal lifestyle. At a pre-test, mid-test, and post-test, participants will complete a cognitive testing battery and perform a submaximal fitness test. The cognitive testing battery will consist of measures of information-processing speed, verbal and visual episodic memory, constructional praxis, mnemonic discrimination, and executive functions such as selective attention, set-switching, inhibition, working memory, planning, cognitive flexibility, and fluid intelligence. At the pre-test, participants will provide saliva samples to determine APOE genotype. At the pre-test and post-test, they will also complete a series of magnetic resonance imaging (MRI) scans and provide blood samples. The images will be reduced to assess brain structure volume (e.g. hippocampus), brain function, white matter microstructure, and white matter hyperintensities. From the blood samples, we will assess brain-derived neurotrophic factor (BDNF), glucose, insulin, irisin, insulin-like growth factor 1 (IGF-1), tumor necrosis factor alpha (TNF-α), serum amyloid protein (SAP), albumin, apolipoprotein E, and α-2 macroglobulin. **Results:** We hypothesize that (1) the PA group will demonstrate improved cognition compared with the control group; (2) PA will positively affect brain structures and function as well as various biomarkers relative to controls; and (3) the effects of PA on cognition and putative mechanisms will be moderated by APOE4 status such that larger benefits are evident for those who are APOE4+. **Conclusions:** Results will provide important insights into the potential of PA to preserve cognitive function in people with a heightened risk of AD. Because there is no known cure for AD, the identification of behavioral interventions that can reduce a person's progression toward AD has important implications for persons who are FH+ and APOE4+. Furthermore, because delaying the onset of AD by one year can reduce its incidence by 11% and delaying by 5 years could reduce its prevalence by 29-43%, this research has important public health implications in terms of the concomitant reductions in health care costs..

P010- REPRODUCIBILITY AND REPLICABILITY OF DIGITAL BIOMARKERS FOR REDUCING SAMPLE SIZES IN PRECLINICAL ALZHEIMER TRIALS. C.Y. Wu[1,2], H. Dodge[1,2,3], Z. Beattie[1,2], N. Mattek[1,2], J. Kaye[1,2] *((1) Department of Neurology, Oregon Health & Science University - Portland, Oregon (United States), (2) Oregon Center for Aging and Technology (ORCATECH), Oregon Health & Science University - Portland, Oregon (United States), (3) Michigan Alzheimer's Disease Center, Department of Neurology, University of Michigan - Ann Arbor, Michigan (United States))*

Background: Despite billions of dollars spent on preclinical or early-phase Alzheimer drug development, and hundreds of clinical trials, no meaningful treatment has been approved. In this climate, the prospect of advancing new trials at tremendous additional cost is daunting. Much of this expense in Alzheimer trials lies in their inefficiency, i.e., the requirement for lengthy follow-up and large sample sizes to detect treatment effects with sufficient statistical power. Digital biomarkers offer a solution to improve the efficiency of Alzheimer trials. Using an in-home sensor platform continuously measuring digital biomarkers with high temporal resolution (e.g., walking speed, computer usage), our previous study demonstrated that these biomarkers could differentiate older community-dwelling

adults with normal cognitive function versus progression before mild cognitive impairment (MCI) incidence.1 Importantly, based on this digital biomarker data, markedly lower sample sizes (compared to conventional cognitive tests) were projected to be needed in preclinical Alzheimer trials. Aligning with the National Institute of Health (NIH) calls to enhance the robustness of research, we examined the reproducibility and replicability of this original study. The ability of researchers to duplicate the results of the original study using the same data (reproducibility) and new data (replicability) would support the reliability of findings in moving this platform and methodology forward. **Objectives:** The purposes of the study were to reproduce and replicate the study conducted by Dodge and colleagues1 by estimating the sample sizes needed for a typical 4-year preclinical Alzheimer trial with two measurement outcomes: 1) in-home digital biomarkers and 2) conventional neuropsychological tests. **Methods:** We reproduced the study conducted by Dodge et al. using the same dataset and approach.1 We then replicated the study by collecting new sensor data in 114 older persons living in their own residence with data spanning over 3.7 years from the Oregon Center for Aging and Technology (ORCATECH) Life Laboratory. The in-home sensor platform included passive infrared sensors placed on the ceiling to estimate walking speed and commercial software installed on participants' computers to collect daily computer usage time. Data were automatically sent to and stored on encrypted servers. Digital biomarker outcomes included weekly walking speed, weekly walking speed variability, and weekly computer usage time. Weekly walking speed variability was estimated by the weekly standard deviation divided by the weekly mean. The likelihood of having low performance on walking speed and computer usage time was defined based on the comparison with baseline (individual-specific distributions of walking speed and computer usage in the first 3 months of data collection). Seven neuropsychological tests were collected from annual home visits for 4 years, including: Category Fluency (animal + vegetable), Trail Making Test A and B, Digit Symbol, Logical Memory Immediate and Delayed Recall, and Boston Naming. Data collected after MCI incidence were excluded from analysis. Linear and generalized linear mixed models were used to estimate time slopes on digital biomarker and neuropsychological test outcomes between normal cognition and MCI incidence before transition. Sample sizes were estimated using Monte Carlo simulation. We selected four features to examine replicability between original and replicated results: concordance in significant p-value using Cohen's Kappa, concordance in coefficient estimates using Spearman's correlation, % of estimates where original coefficient estimates lay within the 95% confidence interval (CI) of replicated estimates, and sample sizes. **Results:** Eighteen subjects developed MCI. The original study was reproducible; the same p-values and coefficient estimates were found. A high agreement of the significance of p-value was found between original and replicated results (Cohen's Kappa = 0.85). A strong correlation was found between original and replicated coefficient estimates (Spearman's r = 0.88, p <.001). Ninety-three percent (15/16) of original coefficient estimates were within the 95% CI of replicated estimates, except for the Logical Memory Immediate Recall Test outcome. When the outcome was the likelihood of having low computer usage time, defined using person-specific computer usage time at baseline, the sample sizes needed to achieve a 30% effect size with 80% statistical power in original and replicated studies were 26 and 38 subjects respectively. Similarly, for the likelihood of having high walking speed variability, 86 and 56 subjects were needed in the original and replicated studies respectively. By comparison, for the Logical Memory Delayed Recall task, 1912 and 915 subjects were needed in the original and replicated studies respectively. **Conclusion:** The sample sizes needed with outcomes generated with continuous, in-home digital biomarkers are reproducible and replicable, while this is not always the case for traditional neuropsychological tests. The latter could be due to practice effects and other factors which modify its variabilities. Features collected by an in-home sensor platform are viable complements to future Alzheimer trials to reduce cost and increase the efficiency of trials. **Reference:** 1. Dodge HH, Zhu J, Mattek NC, Austin D, Kornfeld J, Kaye JA. Use of high-frequency in-home monitoring data may reduce sample sizes needed in clinical trials. PLoS One. 2015;10(9):e0138095.

P011- NOVEL ANALYTICS FRAMEWORK FOR AUGMENTING SINGLE-ARM PHASE 2A OPEN LABEL TRIALS WITH REAL-WORLD EXTERNAL CONTROL DATA: APPLICATION TO THE BLARCAMESINE (ANAVEX®2-73) STUDY IN ALZHEIMER'S DISEASE MATCHED WITH PROPENSITY CORRECTED PATIENTS FROM ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE (ADNI) CONFIRMING TREATMENT EFFICACY IN COGNITIVE DECLINE AT INTERIM TWO-YEAR (104-WEEK) ANALYSIS.

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Background: Employing a real-world (RW) external control arm to obtain registration and accelerate reimbursement is gaining momentum. Recent examples have been described in Oncology where a RW external control arm cohort of 77 ceritinib-treated patients was compared to the Phase II single-arm alectinib patients and successfully submitted to regulatory authorities, and with the FDA's Framework for Real World Evidence document released in December 2018 showing how Real World Evidence can be incorporated into regulatory decision making. This framework was applied to the study of Blarcamesine (ANAVEX®2-73), a selective sigma-1 receptor (SIGMAR1) agonist that was investigated in an open-label 57-week Phase 2a study of Alzheimer's Disease (AD) patients (N=32) showing a favorable safety profile (NCT02244541) and was further extended by 208 weeks (NCT02756858). A hypothesis free data-driven analysis using Formal Concept Analysis Machine Learning as implemented in Knowledge Extraction and Management (KEM) software platform was used to identify patient selection biomarkers including SIGMAR1-Q2P (rs1800866). Individual patient-level data (IPD) was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI). ADNI is a longitudinal multicenter study designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of AD. A total of 1891 patients were followed in this study including 345 patients with AD having Mini Mental State Examination (MMSE) scores available over a 104-week period. **Objectives:** The overall goal of developing external control arms that is to enable single-arm registration trials to be executed with reduced time and costs. An additional goal of this study is to evaluate the efficacy of Blarcamesineas measured by MMSE between treated patients and an external control AD cohort of

patients from ADNI database over a 104-week period. **Methods:** A matching on propensity scores (PS) was applied to balance baseline characteristics and any confounding factors between AD patients in the Phase 2a Blarcamesine cohort and AD patients from the control ADNI cohort. The logit propensity score was estimated by regressing treatment assignment on previously identified and similarly defined key prognostic factors and baseline characteristics within the population (i.e. age, sex, SIGMAR1_p.Q2P, APOE ε4 and MMSE at baseline). Evolution of change in MMSE from baseline (DeltaMMSE) was modeled using Mixed Model Repeated Measures (MMRM), with a linear time effect hypothesis, and Linear Mixed Effect (LME). DeltaMMSE was compared between the treated cohort having high concentration and treated cohort with low concentration with the external control cohort of AD patients from ADNI. DeltaMMSE scores were adjusted for age, sex, carrier status of the APOE ε4 allele, the interaction between the APOE ε4 allele and the time. The variant SIGMAR1-Q2P (rs1800866) was also included in the model. **Results:** Blacarmesine treated cohort showed a significantly higher adjusted DeltaMMSE (-0.7) compared to the control cohort (-5.2) at week 104 ($p = 0.05$). Furthermore, the treated cohort with a higher Blacarmesine plasma concentration showed a significantly higher adjusted Delta MMSE (-1.1) compared to the control cohort (-4.4) at week 104 ($p = 0.02$). The treated cohort with a low concentration showed a non-significant smaller DeltaMMSE trend at week 104 (-3.9) compared to the control cohort (-4.4) ($p= 0.71$). **Conclusions:** The exploratory efficacy analysis at interim 104-week shows that the cohort of patients with the highest concentration of Blarcamesine (ANAVEX®2-73) had improved DeltaMMSE scores throughout the duration of the trial, compared to the matched external AD control patient cohort. In parallel, the patients with a low concentration presented a smaller decline of the MMSE score compared to the control cohort. APOE ε4 carrier status was significantly associated with DeltaMMSE. Robust analytics and quality data are required to avoid issues of selection bias, confounding factors and misclassification leading to biased interpretation. This new approach of precision medicine, which incorporates RWD such as IPD could become a template for efficacy analysis of small cohort single-arm open label studies in AD.However, this approach has certain limitations such as a small number of patients treated, variables and timepoints in common between the two cohorts.

P012- USING DIRECT-TO-CONSUMER GENETIC TESTING RESULTS IN ALZHEIMER'S DISEASE CLINICAL TRIAL RECRUITMENT. M. Ryan[1,2], C. Cox[3], J. Grill[3,4,5], D. Gillen[1]
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Background: The apolipoprotein E (APOE) gene is the best described genetic risk factor for Alzheimer's disease (AD). Carriage of one or two copies of the ε4 allele of APOE indicates increased risk for AD. Given that APOE ε4 carriage is associated with preclinical AD in older populations, APOE genotype can be used to enrich preclinical AD trials. Other trials are underway that exclusively enroll specific APOE genotypes. In 2017, the Food and Drug Administration granted 23andMe permission to market 10 disease-risk genetic tests direct-to-consumers (DTC), including APOE. With DTC genetic testing available to the public, participants may enter studies with personal knowledge of their APOE genotype. Researchers could use this personal knowledge to pre-enrich preclinical AD trials, were participants willing to share this knowledge with investigators. Little is known, however, about potential study participants' willingness to disclose their personal genetic information gained though DTC testing. Improved understanding of participant attitudes could instruct intervention to improve trial recruitment, including recruitment of underserved populations. **Objectives:** We sought to quantify the relationship between participant characteristics and whether a participant has used DTC genetic testing. We hypothesized that non-White participants would be less likely to have used DTC testing than their non-Hispanic White counterparts. We also sought to assess the relationship between participants' use or non-use of DTC genetic services and their willingness to use DTC results to be matched to clinical studies. Finally, we sought to assess differences in reasons for reluctance to share genetic results, comparing DTC users and non-users. **Methods:** Links to a survey were emailed to 2,306 members of the University of California, Irvine Consent-to-Contact (C2C) Registry who were at least 50 years of age or older. The age restriction for this analysis was implemented to reflect inclusion criteria for AD trials. In total, 1,313 valid responses were recorded. Branching logic was used to examine participants' awareness and previous use of DTC services, willingness to learn their APOE status, and willingness to share genetic information with researchers. Specific questions queried participants' desires for researchers to use genetic test results to match them to studies and reasons for reluctance to permit this. Survey responses were linked to demographic information available in the C2C Registry. We used logistic regression models to assess the relationship between previous use of DTC testing and race/ethnicity, as well as the relationship between previous use of DTC testing and willingness to use the results of DTC testing for invitation to clinical studies. We also used a logistic regression model to assess the relationship between previous use of DTC testing and reasons for reluctance to share genetic results. Participant age, years of education, and sex were adjusted for in all models as potential confounding variables. In addition, race/ethnicity and APOE carrier status were adjusted for in the latter two models. **Results:** Most survey participants were aware of DTC genetic testing (N=1,016, 77.44%), while few had used such a test prior to the survey (N=91, 6.93%). Among those undergoing testing, 27 (29.67%) identified themselves as APOE ε4 carriers. Most participants who knew their APOE status from DTC tests were willing to share those results in their C2C Registry profile (N=77, 84.61%). Participants who identified as American Indian/Alaska Native (OR: 0.13; 95% CI: 0.01, 2.93) or Asian (OR: 0.08; 95% CI: 0.01, 0.71) were less likely to be users of DTC genetic tests, compared to non-Hispanic Whites. Participants who had used DTC genetic tests were more likely to be willing to include their APOE status in their registry profile, compared to non-users (OR: 1.28; 95% CI:0.11, 14.68). DTC users who were APOE ε4 carriers were more likely to be willing to include their APOE status than DTC users who were non-carriers (OR: 3.45; 95% CI:0.37, 32.34). Finally, out of the 37 participants who indicated they would be unwilling to share their APOE

genotyping results in the registry, most were concerned about implications to their insurance (N=16; 43.24%) and implications to their healthcare (N=13; 35.14%). **Conclusions:** Previous DTC users are more willing to share their results for clinical trial matching, compared to non-users. This may indicate that hypothetical responses about willingness to share genetic information with investigators may be underestimates. Alternatively, those most willing to share their results may also be those most likely to use DTC testing.

P013- DIFFERENCES IN WILLINGNESS TO PARTICIPATE IN CLINICAL RESEARCH ACCORDING TO DIAGNOSTIC GROUPS. L. Park, S. Semenova, G. Alarcon, Z. Mendoza, L. Morris, L. Gertsik, S. Lee, S. Jhee *(Parexel International - Glendale (United States))*

Introduction: Patient recruitment in AD related clinical trials continues to be a significant hinderance to the progress of clinical research. The recruitment rates are even lower for early phase clinical trials, where there is no expectation of benefit as a result of participation. The Memory Clinic at the Los Angeles Early Phase Clinical Unit is a community based service that provides comprehensive neuropsychological evaluations for patients and their families. The Memory Clinic serves as a consultation service to patients and their treating physicians, while also serving as a vehicle for recruitment, education about clinical trials, and research participation to members of the community. Although the Memory Clinic was initially designed to facilitate recruitment of patients and their loved ones into Alzheimer's disease research, another aspect of the Memory Clinic was to create a dataset so that we could understand the patient populations, motivations for participating in clinical research, and to monitor longitudinal decline. For the purposes of this particular study, we were interested in evaluating if there were differences among different diagnostic groups in their willingness to participate in early phase clinical research. **Methods:** Patients were referred from a variety of sources to evaluate memory and cognitive function. They were given a comprehensive neuropsychological evaluation, using a flexible battery approach depending on the nature of the referral question. A differential diagnosis was done via a multidisciplinary team evaluation and the results were shared with the patients and their treating physicians. Patients and their caregivers were asked if they could be contacted by a member of the clinical research team regarding potential early phase clinical trials. Willingness to participate was assessed during patient consent to the evaluation and included in the analyses if they agreed. **Results:** Overall, 191 patients were included in the analyses. The mean age was 65.58 with 15 years of education. The results showed that those with AD, MCI, and other neurologic conditions such as PD, TBI, and Stroke were more likely to agree to clinical research than those who were diagnosed with primary psychiatric disorders ($p<.05$). Follow-up analyses showed that those who had higher levels of depression on a symptom rating scale, were less likely to participate in clinical research. Those who scored higher on the GDS ($p<.01$) were less willing to learn about opportunities for research participation. Cognitive performance only accounted for 2% of the variability on willingness to participate. **Conclusion:** Results show that various diagnostic groups may have differing underlying reasons for choosing to participate in research, that are independent of the protocol requirements and expectations during trial participation. Researchers can use this information to tailor their conversations about clinical research when they speak to older adults with differing clinical profiles. Moreover, addressing mood related factors during the clinical evaluation may help facilitate willngness to participate in future trials.

P014- GENE- AND AGE-INFORMED SCREENING FOR PRECLINICAL ALZHEIMER'S DISEASE TRIALS. B. Spencer, L. Digma, R. Jennings, J. Brewer *(UC San Diego - La Jolla (United States))*

Background: Clinical trials of preclinical Alzheimer's disease (AD) require the efficient identification of clinically unimpaired, amyloid positive individuals. Achieving greater efficiency of enrollment, in terms of both cost and time, requires novel enrichment methods. A recently-developed polygenic hazard score (PHS) is associated with neuritic plaques, neurofibrillary tangles, and hippocampal volume loss, and predicts age of AD onset better than APOE alone. We hypothesized that, when combined with age, PHS could be used to efficiently enrich a cognitively normal cohort for amyloid positivity. **Objective:** To test the efficiency of age- and polygenic risk-informed amyloid screening for preclinical AD trials. **Methods:** For the development cohort, data were obtained from the Alzheimer's Disease Neuroimaging Initiative database (adni.loni.usc.edu). Inclusion was limited to subjects who had available amyloid positron emission tomography (PET) imaging and PHS data. For the validation cohort, an independent sample of subjects were selected from the Shiley-Marcos Alzheimer's Disease Research Center (ADRC) of the University of California, San Diego. Inclusion was limited to cognitively normal subjects who had undergone a lumbar puncture and been genotyped. In both the discovery and validation cohorts, subjects were genotyped using a commercially available illumina BeadChip array. PHS was calculated as described in Desikan et al. (2017) for the validation cohort. Briefly, AD-associated single nucleotide polymorphisms (SNPs) were identified in the International Genomics of Alzheimer's Project cohort at $p < 10\text{-}5$. These SNPs were then integrated into a stepwise Cox proportional hazards model using Alzheimer's Disease Genetics Consortium phase 1 genetic data, which identified 31 SNPs. A PHS was calculated for each participant based on their genotype for each of these 31 variants and APOE. When combined with the population baseline incidence rate, the PHS can be used to calculate an individualized genetic assessment of age-associated AD risk in the form of a predicted annualized incidence rate. For a given rate, the age at which there is equivalent risk in the baseline population is the AD–Age. Amyloid status was determined with Florbetapir summary data in the development cohort and cerebrospinal fluid quantification by liquid chromatography-tandem mass spectrometry in the validation cohort. We used Meng's test for comparing two or more correlated correlations to test whether the ADAge was more predictive of amyloid positivity than chronological age in the discovery cohort. An ADAge cutpoint was chosen to maximize the Youden index for predicting Florbetapir PET positivity in cognitively normal controls. To validate our findings, we generated 1000 bootstrap samples of the ADRC cohort where the differences in means between the unenriched and ADAge-enriched samples were calculated to determine the efficiency of age- and polygenic risk-informed amyloid screening for preclinical AD trials as well as to compare demographic differences between such cohorts. **Results:** Compared to chronological age, ADAge was more

correlated with Florbetapir SUVR (p<.01) in the development cohort. In 1000 bootstrapped samples, the ADAge-enriched cohort had a higher proportion of amyloid positive individuals (mean [95% CI] 0.39[0.21 - 0.57]) than the unenriched cohort (.27 [0.18 - 0.36]). When comparing the theoretically-enrolled amyloid positive subjects from each cohort, the ADAge-enriched cohort was older (mean difference in chronological age [95% CI] [3.45–8.43]), however the proportion of ε4 carriers did not differ. **Conclusion:** Given a theoretical target enrollment for a preclinical AD trial, ADAge enrichment can reach that target 1.4 times faster, saving both cost and time. Importantly, the ultimate cohort does not differ from the unenriched cohort apart from age.

P015- ECT-AD STUDY DESIGN: A RANDOMIZED CONTROLLED TRIAL OF ELECTROCONVULSIVE THERAPY PLUS USUAL CARE VERSUS SIMULATED-ECT PLUS USUAL CARE FOR THE MANAGEMENT OF TREATMENT-REFRACTORY AGITATION IN ALZHEIMER'S DEMENTIA. M. Lapid[1], B. Forester[2], A. Hermida[3], L. Nykamp[4], M. Mueller[5], R. Knapp[5], B. Sutor[1], E. Johnson[1], M. Walton[1], S. Seiner[2], D. Harper[2], E. Kilpatrick[2], H. Heintz[2], W. Mcdonald[3], P. Riva Posse[3], R. Seidemann[3], A. Dhingra[3], J. Mahdasian[4], S. Sanghani[6], G. Petrides[6] *((1) Mayo Clinic - Rochester (United States), (2) McLean Hospital - Belmont (United States), (3) Emory University - Atlanta (United States), (4) Pine Rest Christian Mental Health Center - Grand Rapids (United States), (5) Medical University of South Carolina - Charleston (United States), (6) Zucker Hillside Hospital/Northwell Health - Glen Oaks (United States))*

Introduction: Over 90% of individuals with Alzheimer's disease (AD) experience neuropsychiatric symptoms such as agitation, depression and apathy, which increase morbidity and mortality and contribute to caregiver burden. There are no FDA-approved treatments for severe agitation in people with advanced dementia. Psychotropic medications, especially antipsychotics, are widely used off-label to treat agitation in AD even with documented limitations in efficacy and safety concerns. Behavioral management strategies are recommended as first-line treatments for agitation in AD; however, they may be less efficacious for the most severely agitated patients. Therefore, new management strategies for severe agitation in AD refractory to psychopharmacologic and behavioral interventions are timely and warranted. Preliminary open-label data from the ECT-AD group suggests acute electroconvulsive therapy (ECT) treatment is safe and effective in reducing agitation in this population. Based on this prior work, the aim of the present randomized controlled trial is to determine the efficacy and safety of ECT for severe agitation in advanced AD, and examine the durability of the acute treatment effect in an exploratory maintenance naturalistic design. The hypothesis is that ECT with usual care will be more efficacious in reducing severe agitation in AD subjects than simulated ECT (S-ECT) with usual care, and that there will be no difference in tolerability or safety outcomes. **Methods:** We describe an NIA-funded multi-site, single blind, randomized trial of ECT with usual care (ECT+UC) versus S-ECT with usual care (S-ECT+UC). We plan to enroll 200 inpatients with AD who have severe agitation who have not responded well to prior trials of psychotropic medications. The primary efficacy outcome measure is the Cohen Mansfield Agitation Inventory (CMAI), and the secondary efficacy outcome measures are the Neuropsychiatric Inventory – Clinician Version (NPI-C), Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change Scale (ADCS-CGIC), and Pittsburgh Agitation Scale (PAS). Safety and tolerability will be assessed with the Severe Impairment Battery – 8 item (SIB-8) for cognitive decline, the Confusion Assessment Method (CAM) for development of delirium, and adverse event monitoring. **Conclusion:** This innovative study will fill a gap in the current clinical practice of treating severe agitation in AD using a rigorous methodological approach thus providing evidence for a new therapeutic application (severe agitation in AD) of a well-studied, established, and safe treatment (ECT). Study findings may demonstrate support for a new therapeutic use of ECT for severe agitation in AD. Successful management of neuropsychiatric symptoms reduces long-term care placement, decreases the risk of mortality, and enhances patient and caregiver quality-of-life. Such an approach has the potential to offer enormous relief to the substantial socioeconomic burden of AD-related behavioral disturbances.

P016- GENERATING SYNTHETIC CONTROL SUBJECTS USING MACHINE LEARNING FOR ALZHEIMER'S DISEASE CLINICAL TRIALS. C. Fisher, J. Walsh, A. Smith *(Unlearn.Health - San Francisco (United States))*

Background: Recently, there has been a flurry of attention focused on the benefits of synthetic control patients in clinical trials. However, most of the interest has concerned the simpler problem of supplementing rare disease and cancer trials with observational data. The ability to replace control subjects with synthetic subjects in clinical trials for complex diseases like Alzheimer's Disease is more difficult. But if successfully achieved, this capability would drastically improve the search for beneficial therapies. **Objectives:** Simulating the disease progression of individual synthetic control subjects (SCSs) as assessed by several metrics in order to diminish reliance on actual control subjects in Alzheimer's Disease clinical trials. **Methods:** We developed a machine learning model of Alzheimer's Disease progression trained with data from 1,335 subjects from 24 clinical trial control arms involving early or moderate Alzheimer's Disease. The model is an example of a Conditional Restricted Boltzmann Machine (CRBM), a kind of undirected neural network whose properties are well suited to the task of modeling clinical data progression. The model generates values for 44 variables for each SCS at three-month intervals over 18 months. **Results:** We validated our model by comparing predicted ADAS-Cog scores with the scores of subjects from a diverse set of clinical trials that were not involved in training the model. Predicted scores were statistically indistinguishable from the test scores. We further compared the mean ADAS-Cog scores of SCSs generated by our unsupervised model with those generated by several supervised machine learning algorithms of different types, trained on the same data. All algorithms exhibited a similar error profile over time, with CRBM uniquely capable of predicting both means and standard deviations of the data distributions. These comparisons demonstrate that our model is capable of making accurate and precise simulations based on unsupervised learning from extant trials. **Conclusions:** Recently, increased attention has been focused on the benefits of using SCSs in clinical trials as a mechanism to accelerate trials and reduce their cost. Machine learning models are one approach for comprehensively simulate the evolution of multiple metrics

simultaneously for individual SCSs, thus diminishing reliance on actual control patients. Our work demonstrates the potential for the unsupervised Conditional Restricted Boltzmann Machine algorithm used here to generate SCSs indistinguishable from actual control patients.

P017- A PARADIGM SHIFT IN AD CLINICAL TRIAL DESIGN: SEQUENTIAL, TEMPORAL, OVERLAPPING COMBINATION THERAPY FROM THE COGNITIVELY NORMAL AT RISK POPULATION TO PRECLINICAL DISEASE STAGE AND BEYOND. C. Brisard[1], J. Murphy[2], J. Bell[3] *((1) Syneoshealth.com - Paris (France), (2) Syneoshealth.com - San Francisco (United States), (3) Syneoshealth.com - Wilmington (United States))*

These recommendations arise from our 25+ years of designing and analyzing AD clinical drug trials from positions in academia, the pharmaceutical industry and the CRO sector. The successive failures in recent AD clinical trials underlies the need to reexamine our predominant models of both AD etiology and evaluation. The EU/US CTAD Task Force wisely argues for adopting combination therapy for a disease that involves multiple pathogenic pathways with polygenic origins. Salient is their observation that amyloid targeted therapies should still be considered for inclusion as amyloid pathology is, at least, part of that degenerative cascade which initiates in the at-risk brain. The combination approach will require validated biomarkers for each of its current contributors: but amyloid and tau are only two of anticipated multiple biomarkers that will be needed. Under development are perhaps more prescient, initial biomarkers of impending disease: susceptibility locus genotyping, proteomic and metabolomics shift, neuroinflammatory markers, microglial activation targets, synapse degradation markers (both imaging and plasma), and neurodegenerative biomarkers. But what has not yet been considered is the staging of such combination interventions or possibly a series of interventions beginning at the foremost alterations in brain function. Additionally, while FDA now considers prevention a potential therapeutic approach, the targeted 'normal' population has to be well defined in terms of risks. Thus, how can one (or more) intervention(s) be effective if the pathologic process it targets has not yet initiated? Similarly, targeted interventions may not necessarily be needed long term, or there may be successive windows of intervention with overlap, dependent upon the time for marker stabilization. When is it optimal to start these series of interventions: what are the earliest, first markers or signals of a patient who is "destined to AD diagnosis"? How do these sequential biomarkers appear in those destined to be cognitively stable until end of life? Emerging would be a longitudinal map or timeline of biomarker/cognitive stability for a lifetime in comparison to a path of sequential and multiplying insults leading to an ultimate dementia diagnosis. Clinical sequalae need to be considered: three marker categories can be effectively measured via patient smart phone application: the cognitive, psychiatric and behavioral-health domains. From the earliest stages, cognitive health could be measured via sensitive computerized tests of attention, executive functioning, and memory. Psychiatric health could be measured via self-reported measures of depression and stress, and behavioral health indicators known to contribute to AD (HTN, blood glucose level, hypercholesterolemia, BMI, exercise frequency, gait and balance, diet type) could use a methodology similar to the CAIDE dementia risk App. As our ability to detect even the most subtle of cognitive, psychiatric, and behavioral-health shifts improve, even earlier discovery becomes possible. Further exploration of this integrated and longitudinal intervention concept will be further elaborated in the poster presentation.

P018- DEVELOPMENT OF A MACHINE LEARNING ALGORITHM TO CLASSIFY DEMENTIA STAGE BASED ON SYMPTOMS REPORTED ONLINE. K. Rockwood[1,2], A. Shehzad[2], J. Stanley[2], T. Dunn[2], S. Howlett [1,2], A. Mitnitski[1,2], C. Chapman[2] *((1) Dalhousie University - Halifax (Canada), (2) DGI Clinical - Halifax (Canada))*

Background: Our group has shown that data on people living with dementia and their care partners can be acquired with a web-based tool called the SymptomGuide® Dementia. This symptom tracking software provides a dementia symptom menu from which users can identify and track dementia symptoms that are important to them. The value of these data would be enhanced if the dementia stage could be identified based on each user's symptom and demographic profile. Here, we used individual symptom profiles from a memory clinic and two dementia clinical trials as inputs to train an algorithm that can classify the stage of dementia, using machine learning methods. The performance of this algorithm was cross-validated against two well established clinical measures of dementia stage, the Functional Assessment Staging Test (FAST; Reisberg 1988) or the Global Deterioration Scale (GDS; Reisberg 1982). **Objective:** To automate staging of dementia based on symptom data by applying supervised machine learning methods, validated against well-established clinical dementia staging tools. **Methods:** Symptom data were obtained from a memory clinic, a study on admissions to assisted living/nursing home care facilities (Rockwood et al., 2013a) and from two clinical trials: the vascular and mixed dementia (VASPECT) trial (Rockwood et al., 2013b) and the Atlantic Canadian Alzheimer Disease Investigation of Expectations (ACADIE) trial (Rockwood et al., 2002) The data consisted of basic demographic information and symptom profiles of patients with dementia (N=688). Data from the memory clinic and VASPECT were captured and stored using a web-based tool SymptomGuide® (Rockwood 2010). Symptom profiles in ACADIE were derived from symptom goals set by individual patients. The patient profiles also included FAST or GDS scores. These data were used to predict four stages: Mild Cognitive Impairment (MCI), and mild, moderate, and severe dementia. Only symptom data collected at baseline (first visit) were used to train the algorithm. To keep the number of variables low, the 67 symptoms, weighted by number of descriptors and frequency, were pruned to yield only the variables that most accurately distinguished the four stages of dementia from each other. This resulted in a final data matrix of 48 symptom-based variables and patient age. Missing data were imputed from group means stratified by dementia stage. Data were randomized and split into training (80%) and testing (20%) datasets. Metrics used to validate and select the optimal algorithm were accuracy, Cohen's Kappa for stage differences, Positive Predicted Value (PPV), recall (sensitivity), and area under the receiver operating characteristic curve (AUC), in the test dataset. Multiple supervised machine learning algorithms were trained and compared based on the above metrics to select the most performant. **Results:** Users were mostly female (60%), and older (77; range – 72.6-81.5 years). The validation

sample included mostly women (62%), age (77.2 ± 11 years) and people with mild dementia (34% Mild, 25% MCI, 20% Moderate, 20% Severe). The optimal algorithm selected, based on test metrics, was Support Vector Machine (SVM). Cross validation (5-fold) was repeated 200 times, with the algorithm scored on sensitivity, specificity and accuracy for each fold and iteration. The mean ± standard deviation accuracy of the algorithm was 83% ± 6% [95% Confidence interval (CI) 77.2% - 88.3%] and the mean Cohen's Kappa statistic was 0.77 ± 0.08 [CI 0.69 – 0.84]. The mean weighted PPV was 0.83 ± 0.06 [CI 0.77 - 0.88] and mean weighted recall score (sensitivity) was 0.83 ± 0.06 [CI 0.76- 0.88]. The averaged AUC was 0.95 and average precision score was 0.88. The algorithm successfully identified the correct dementia stage between 83 and 89% of the time. The algorithm performed best when classifying individuals with severe dementia (PPV=0.85, Sensitivity=0.93). The weakest precision and recall scores occurred when classifying moderate dementia (PPV=0.85, Sensitivity=0.77). Most misclassifications (97%) were within one stage of the true dementia stage. **Conclusion:** A supervised machine learning algorithm exhibited excellent performance in identifying dementia stage based on dementia symptoms reported by caregivers. This novel dementia staging algorithm can be used in SymptomGuide® or other similar databases to identify dementia stage based on users' symptom profiles. **References:** Reisberg B. Functional assessment staging (FAST). Psychopharmacol Bull. 1988;24(4):653-9. Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry. 1982;139(9):1136-9. Rockwood JKH, Richard M, Garden K, Hominick K, Mitnitski A, Rockwood K. Precipitating and predisposing events and symptoms for admission to assisted living or nursing home care. Can Geriatr J. 2013a Mar 5;17(1):16-21. Rockwood K, Mitnitski A, Black SE, Richard M, Defoy I, VASPECT study investigators. Cognitive change in donepezil treated patients with vascular or mixed dementia. Can J Neurol Sci. 2013b;40(4):564-71. Rockwood K, Graham JE, Fay S; ACADIE Investigators. Goal setting and attainment in Alzheimer's disease patients treated with donepezil. J Neurol Neurosurg Psychiatry. 2002 Nov;73(5):500-7. Rockwood K. An individualized approach to tracking and treating Alzheimer's disease. Clin Pharmacol Ther. 2010 Oct;88(4):446-9.

P019- A FRAILTY INDEX BASED ON ROUTINELY COLLECTED LABORATORY SAFETY DATA IS ASSOCIATED WITH COGNITIVE DECLINE IN CLINICAL TRIALS FOR ANTI-DEMENTIA DRUGS. K. Rockwood[1, 2], T. Dunn[2], S. Howlett[1,2], J. Stanley[2], A. Mitnitski[1,2], C. Chapman[2] *((1) Dalhousie University - Halifax (Canada), (2) DGI Clinical - Halifax (Canada))*

Background: Most clinical drug trials, including those for anti-dementia drugs, effectively aim to exclude frail older adults. Still, it is possible that frail individuals are included in these trials and may impact on trial outcomes. Our group has shown that the degree of frailty can be quantified with a frailty index based on the accumulation of deficits in routine blood work and vital signs (FI-Lab). Here, we investigated whether an FI-Lab could be constructed using lab safety data from the Coalition Against Major Disease (CAMD) database, and explored links between frailty and longitudinal cognitive function performance as assessed by the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog). **Objective:** To determine whether an FI-Lab can be constructed from CAMD clinical trial laboratory safety data and to evaluate the relationship between frailty and ADAS-Cog progression in dementia clinical trials. **Methods:** Of the 6500 subjects (from control arms of 24 trials), 2079 (from seven trials) were included in the analyses. Inclusion criteria were: 1) sufficient lab data to construct an FI-Lab with ≥ 20 items; 2) baseline and at least one longitudinal ADAS-Cog 11 measurement; 3) baseline dementia severity (as measured by MMSE scores); and 4) ApoE ε4 genotype information. To construct the frailty index, measurements which fell within the trial reference normal ranges were scored as 0; values outside were scored as 1. Individual deficits were summed and divided by the total number measured to yield and FI score between 0-1. A Bayesian mixed-effect beta regression model was used to investigate factors affecting ADAS-Cog 11 progression. The beta regression model accounted for the floor and ceiling effects typical of ADAS-Cog progression, and necessitated rescaling the 0-70 ADAS-Cog range to 0-1. Fixed effects included time from baseline, FI-Lab, baseline MMSE score, age, sex, number of ApoE ε4 alleles, and the use of background dementia medication (cholinesterase inhibitors and/or memantine), as well as their interactions with time. Subject and study ID were included as random effects. **Results:** Subjects were 73.4 ± 8.5 years old and 55.0% were female. The mean baseline MMSE score was 21.1 ± 5.3 and the mean baseline ADAS-Cog 11 was 23.2 ± 9.5. Most subjects (70.6%) used background AD medication during the trial. Results showed that it was possible to create an FI-Lab score from safety data in the CAMD database. Here, we constructed FI-Lab scores from between 20 to 50 laboratory test results in seven trials lasting between 12 and 78 weeks. The mean FI-Lab score for all trials was was 0.07 ± 0.05. The FI-Lab showed a modest effect on ADAS-Cog progression: the posterior mean of the time by FI-Lab interaction was 0.33 [95% CI = -0.05, 0.72]. For an average CAMD subject – a 73-year-old female with a single ApoE4 allele, on AD medication, and with a baseline MMSE of 21 – this corresponded to a one-year increase of 0.73 [-0.51, 2.01] points on the ADAS-Cog, if entering the trial with no deficits (FI-Lab = 0). By contrast, for a high-frailty individual (FI-Lab = 0.3), the model-predicted increase in ADAS-Cog was 2.38 [0.144, 4.71] points in one year. The strongest predictors of ADAS-Cog progression over the year were baseline MMSE (-0.87 [-1.02, -0.72]) and the use of background dementia medication (0.20 [0.15, 0.26]). **Conclusion:** An FI-Lab based on the results of common laboratory tests can be developed from clinical trial safety data available in the CAMD database. Results showed that individuals with higher FI-Lab scores exhibited a higher rate of worsening in their ADAS-Cog 11 scores. This work is motivating further study into how frailty affects dementia progression.

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P020- COMPARISON OF THE FCSRT AND RBANS IN SCREENING EARLY ALZHEIMER'S DISEASE PATIENTS FOR CLINICAL TRIALS. E. Teng, S. Djakovic, P. Manser, N. Hu, H. Swendsen, K. Sink *(Genentech - South San Francisco (United States))*

Background: As treatment trials for Alzheimer's disease (AD) have increasingly focused on early (i.e., prodromal-to-mild) AD, screening procedures have been implemented to more efficiently identify potential participants that: a) fulfill applicable clinical diagnostic criteria, b) have biomarker data consistent with underlying AD, and c) are most likely to exhibit

clinical progression over the course of the clinical trial. Since episodic memory deficits represent a key predictor for each of these screening objectives, assessments of episodic memory have been incorporated into the initial stages of screening to optimize this process. However, the relative impacts of the different tests used across different trials on optimizing screening efficiency and/or rates of clinical progression remain uncertain. **Objectives:** We sought to compare the impacts of using the Free and Cued Selective Reminding Test-Immediate Recall (FCSRT-IR) and the Repeatable Battery for the Assessment of Neuropsychological Status Delayed Memory Index (RBANS-DMI) on screen-failure rates due to episodic memory performance and evidence of significant cerebral β-amyloid (Aβ) accumulation between two clinical trials in early AD. **Methods:** We analyzed screening data from the CREAD2 (NCT03114657) and Tauriel (NCT03289143) trials, which sought to enroll similar cohorts of participants who fulfilled National Institute on Aging-Alzheimer's Association criteria for probable AD dementia or mild cognitive impairment (MCI) due to AD and had Clinical Dementia Rating-Global Scores (CDR-GS) of 0.5 or 1, evidence of significant cerebral Aβ pathology per positron emission tomography (PET) or cerebrospinal fluid (CSF) analyses, and significant episodic memory impairment. The inclusion criterion for memory impairment differed between the CREAD2 (FCSRT-IR; free recall ≤ 27, cueing index ≤ 0.67) and Tauriel (RBANS-DMI ≤ 85) studies. In both studies, episodic memory assessments occurred early in screening, while confirmation of Aβ pathology occurred near the end of screening, after other inclusion/exclusion criteria had been met. Across studies, for patients with screening Mini-Mental State Examination (MMSE) scores of 22-30, we compared proportions of potential participants that scored below specified cut-points on the FCSRT-IR or RBANS-DMI. For potential participants who subsequently fulfilled all other inclusion/exclusion criteria, we compared the rate of positive Aβ PET scans (per visual read) at screening across studies. **Results:** Preliminary analyses of neuropsychological data from individuals with MMSE scores of 22-30 indicate that potential CREAD2 participants fulfilled the FCSRT-IR inclusion criterion (~54%) at a significantly lower rate than potential Tauriel participants fulfilled the RBANS-DMI inclusion criterion (~76%). As expected, potential participants with lower screening MMSE scores were more likely to exhibit significant impairment on these memory tests. Preliminary analyses of Aβ PET data for potential participants fulfilling the respective episodic memory impairment criteria and all other inclusion/exclusion criteria indicate that similar proportions of positive Aβ PET scans were seen across studies. **Conclusion:** The proportion of scores meeting the FCSRT-IR inclusion criterion in CREAD2 was lower than the proportion of scores meeting the RBANS-DMI inclusion criterion in Tauriel. This result is consistent with the implementation of a more stringent cut-point (relative to normative data) on the FCSRT-IR than on the RBANS-DMI. However, the requirement for relatively more severe episodic memory impairments in CREAD2 did not further increase the rates of positive Aβ PET scans; these rates were similar at screening across the two studies. As subsequent longitudinal data from placebo arms of these studies become available upon their completion, the relative impacts of these FCSRT-IR and RBANS-DMI inclusion criteria on rates of clinical progression will be further assessed.

P021- PRIMARY ANALYSIS MODEL FOR SPORADIC ALZHEIMER DISEASE: UNIVARIATE MODEL FOR THE COMPOSITE SCORE OR MULTIVARIATE MODEL FOR ALL THE COMPONENT SCORES? Y. Li[1], G. Wang[1], A. Aschenbrenne[1], J. Hassenstab[1], E. Mcdade[1], J. Llibre-Guerra[1], S. Berry[2], R. Bateman[1], C. Xiong[1] *((1) Washington University in St. Louis - St. Louis (United States), (2) Berry Consultants, LLC - Austin (United States))*

Background: Composite scores have been used as the primary outcome in multiple clinical trials for Alzheimer disease (AD) because of their superior sensitivity to the individual component scores which form the composite. The primary analysis model for the composite score is typically the mixed effects model for repeated measures (MMRM) with time as categorical variable or the linear mixed effects (LME) model with time as continuous variable. A composite score is usually an average of the individual components. This clinical trial framework is henceforth referred to as the univariate composite score method. Some major shortcomings of the composite score method include that it requires all the components to be available to form the composite and a large change in one component can be masked by small changes in other component scores. An alternative method to overcome these shortcomings is the multivariate model where the multiple component scores are analyzed simultaneously using a multivariate MMRM (mMMRM) or multivariate LME (mLME) with a single treatment effect parameter. This clinical trial framework is henceforth referred to as the multivariate component scores method. Both the univariate composite score method and the multivariate component scores method assume the treatment leads to the same treatment effect (e.g. a 20% reduction in the composite score corresponds to a 20% reduction in each of its component score); **Objectives:** Comprehensively compare the power advantage of the multivariate component scores method over the univariate composite score method considering different degree of correlations among the component scores. Develop a SAS Macro for implementation of the mMMRM in clinical trials. **Methods:** We compare the power of the multivariate component scores methods (mMMRM and mLME) and the univariate composite score methods (MMRM and LME) in the case of four component scores. The mMMRM and mLME employ a single treatment effect parameter for the four components so that all the components are analyzed simultaneously in a single run of the model. For mMMRM, the single treatment effect parameter is the percentage reduction in the change from baseline to the end of study; and for mLME, the single treatment effect parameter is the percentage reduction in the rate of change. Various variance-covariance matrices for the four components were investigated. **Results:** Regardless the correlations among the component scores (large, small, or no correlation at all), the mMMRM leads to as much as 8% power increase over the univariate MMRM and similar results were observed for mLME over the univariate LME. As the missing data increase in the individual components unequally meaning one component misses more than another, the power discrepancy increases as well, but moderately. On the other hand, the correlations among the component scores significantly affect the power within each method. For example, a moderate correlation (ranging from 0.3 to 0.5) leads to around 20% decrease in power compared with the case where all the four components are independent for the univariate composite method, and leads to a similar percentage decrease

in power for the multivariate component scores method as well. Our procedure can handle multivariate models with up to five component scores and allows the variance-covariance matrix to be various structure such as the unstructured and ARH(1). **Conclusion:** Both the multivariate component scores method and the univariate composite method have equivalent assumptions such as the equal treatment effect on each component score and the normal distribution of the outcome. The former leads to slightly increase in power when the missing patterns are the same among the components, but can lead to more power gain when the missing patterns are different. The multivariate component scores model can more efficiently utilize the information from multiple scores which can help reduce sample size needed for AD clinical trials and should be considered as the primary analysis method for AD clinical trials with multiple continuous outcomes available.

P022- STUDY PARTNER TYPE AND DROPOUT IN ALZHEIMER'S DISEASE REGISTRATION CLINICAL TRIALS. O.M. Bernstein[1], J.D. Grill[2], D.L. Gillen[1] *((1) Department of Statistics, Institute for Memory Impairments and Neurological Disorders, University of California, Irvine - Irvine (United States), (2) Departments of Psychiatry & Human Behavior and Neurobiology & Behavior, Institute for Memory Impairments and Neurological Disorders, University of California, Irvine - Irvine (United States))*

Background: Missing data in clinical trials can lead to bias in estimated treatment effects if, for example, dropout occurs non-differentially by treatment arm. The National Academy of Science's first recommendation for handling missing data is to prevent its occurrence, which may be facilitated by understanding predictors of loss to follow-up (1). Clinical trials of potential disease-modifying therapies for Alzheimer's disease (AD) require participants to enroll with a study partner—someone who attends visits and reports on the participant's health and functional performance. In a sample of Phase 2 NIH-funded AD trials, risk of drop out was lower for participants with a spouse study partner, compared to participants with other study partner relationships (2). **Objectives:** We sought to quantify the relationship between participant characteristics, including study partner type, and trial retention in multisite, industry-sponsored registrational trials. **Methods:** We assessed missing data patterns in a dataset that combined two industry-sponsored multinational 76-week Phase 3 trials of an oral therapy being developed as a disease modifying treatment for mild-to-moderate AD dementia that employed essentially identical inclusion criteria and protocols. Based on the recommendation from a Data Safety Monitoring Board (DSMB), the trials were stopped prior to completion. We considered participants lost to follow-up if they failed to complete the primary endpoint or died. We censored participants if they were unable to complete the trial due to sponsor decision stemming from the DSMB recommendation. We categorized participants based on their study partner type (spouse, adult child, or other) and used proportional hazards regression to look at the association between participant characteristics and time to dropout. We used generalized estimating equations to quantify associations between participant characteristics and the binary outcome of trial completion. **Results:** The two trials had a combined 2648 participants with 1729 (65%), 663 (25%), and 245 (9%) spousal, adult child, and other study partner types at baseline, respectively. Study partner information was missing for 11 participants. The complete case analysis included 2603 participants of which 883 were lost to follow-up, 45 died, 634 completed the primary endpoint, and 1041 were unable to complete due to sponsor decision. The mean (standard deviation) baseline age of participants was 71.81 (7.9), 75.78 (7.8), and 74.89 (8.4) years for those with spousal, adult child, and other study partners. More participants in a spousal dyad (n = 722, 42%) attended a study site in North America compared to adult child (n = 172, 26%) and other dyads (n = 90, 37%). In unadjusted proportional hazards models, risk of dropout was estimated to be 23% higher (Hazard Ratio [HR]: 1.23, 95% Confidence Interval [CI]: 1.06-1.42) for participants with an adult child study partner and 8% higher (HR: 1.08, 95% CI: 0.86-1.36) for participants with an other study partner, respectively, compared to those with a spousal partner. The association between study partner type and dropout was no longer significant when adjusting for potential confounding variables. Risk of dropout was 6% higher (HR: 1.06, 95% CI: 0.79-1.43) for adult child dyads and 2% higher (HR: 1.02, 95% CI: 0.74-1.39) for other study partner dyads, respectively, compared to spousal dyads, when controlling for differences in apolipoprotein E genetic status, sex, race, ethnicity, study site region, age, education level, baseline cognition (Mini-Mental State Exam), baseline Hachinski Ischemic Score, baseline Geriatric Depression Scale score, study partner sex, study partner age, and study partner education level. When exploring contributors to the unadjusted study partner type effects, we found that when we accounted only for age, the relative risk of dropout was only 6% higher (HR: 1.06, 95% CI: 0.91, 1.24) for adult child dyads and 2% lower (HR: 0.98, 95% CI: 0.78, 1.24) for other dyads, compared to spousal dyads. For every one-year increase in baseline participant age there was a 3% increased risk of dropout (HR: 1.03, 95% CI: 1.03, 1.04; p-value: <.001) for participants with similar demographics, cognition, and study partner demographics. The effect of age remained significant when adjusting for other variables. No other covariates explained the study partner relationship on its own as effectively as age. To check the sensitivity of our model, we subset the primary analyses to participants from North America. Additionally, we ran the primary analysis and censored death. Neither meaningfully altered the observed results. **Conclusions:** In two industry sponsored registration trials, dropout was more frequent among non-spousal dyads, but this relationship was primarily explained by participant age. Increased participant age had a robust association with dropout after accounting for other participant characteristics. **References:** (1) National Research Council (US) Panel on Handling Missing Data in Clinical Trials. The Prevention and Treatment of Missing Data in Clinical Trials. Washington (DC): National Academies Press (US). 2010. (2) Grill JD et al. Effect of study partner on the conduct of Alzheimer disease clinical trials. Neurology. 2013;80(3):282–288.

P023- A PHASE II STUDY EVALUATING EFFICACY AND SAFETY OF ORAL BI 425809 IN PATIENTS WITH COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S DISEASE DEMENTIA. G. Wunderlich[1], F. Jessen[2], M. Garcia Jr.[3], Z. Blahova[4] *((1) Boehringer Ingelheim - Burlington (Canada), (2) Klinik und Poliklinik für Psychiatrie und Psychotherapie, Uniklinik Köln - Koln (Germany), (3) Boehringer Ingelheim Pharmaceuticals Inc - Ridgefield (United States), (4) Boehringer Ingelheim RCV GmbH & Co KG - Vienna (Austria))*

Background: Acetylcholinesterase inhibitors are the current gold standard treatment for mild-to-moderate Alzheimer's disease (AD) dementia. However, there is an unmet need for additional symptomatic therapies. Glutamate is the major excitatory neurotransmitter in the brain, with the post-synaptic N-methyl-D-aspartate (NMDA) receptor playing an essential role in its transmission. It has been hypothesized that NMDA receptor hypofunction is associated with cognitive impairment in AD dementia; therefore, improving post-synaptic signaling by inhibiting glycine transporter 1 (GlyT1) may improve cognitive function. **Objectives:** This proof of clinical concept study aims to investigate the efficacy and safety of BI 425809, a GlyT1 inhibitor, in patients with mild-to-moderate AD dementia. This study will also provide dose-ranging data to define a suitable dose of BI 425809 in this population. **Methods:** This study is an ongoing Phase II, multicenter, double-blind, parallel-group study for which recruitment was completed in May 2019. Inclusion criteria were patients aged ≥55 years with mild-to-moderate AD dementia, according to the recommendations from the National Institute on Aging Alzheimer's Association workgroups on diagnostic guidelines for AD dementia. Additional inclusion criteria were a mini mental state exam (MMSE) score of 15–26 and the presence of a reliable study partner who is in close contact with the patient and can contribute to the neurophysiological rating scales. The concomitant use of acetylcholinesterase inhibitors was permitted but not required. Eligible patients are being randomized (1:1:1:1:1) to receive BI 425809 2, 5, 10, 25 mg, or placebo once daily in the morning for 12 weeks. Randomization is planned for completion in June 2019. The primary endpoint of the study is change from baseline in Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog11) total score at Week 12. Secondary endpoints include change from baseline in the Alzheimer's Disease Cooperative Study/Activities of Daily Living score and clinician's interview-based impression of change score at Week 12. Further endpoints include the Neuropsychiatric Inventory Questionnaire and change from baseline in the derived composite endpoint of selected tests from ADAS-Cog11 and additional cognitive tests (Controlled Oral Word Association Test, Verbal Fluency Test, Digit Span Backwards, and Coding) at Week 12. This will allow for the cognitive composite of the cognitive-functional composite, a novel outcome measure for patients with early AD, to be derived. Pharmacokinetic parameters are being investigated, and safety is being evaluated throughout the study. A multiple comparison procedure with modeling (MCPmod) approach for mixed model repeated measures will be used to evaluate proof of concept and dose finding for the primary endpoint. This approach allows for the simultaneous assessment of various dose response models, while protecting the overall probability of Type I error. The MCPmod procedure will also be applied to the secondary endpoints, if deemed necessary. The further efficacy endpoints will be evaluated using descriptive statistics. **Results:** To date, approximately 599 patients have been randomized. The last patient visit is estimated to be in October 2019 and the study completion is planned for March 2020. The study population thus far has an approximate mean age of 70 years, with a 1:1 male to female ratio. An estimated 33%, 61% and 6% of patients were recruited from North America, Europe, and Japan, respectively. The mean MMSE score at screening is currently ~21. **Conclusions:** The results of this study will be used to test for a positive proof of clinical concept and to define a suitable dose of BI 425809 with regards to efficacy and safety for future studies.

P024- THE COGNITIVE TASK FORCE; A NOVEL APPROACH TO IMPROVING THE EFFICIENCY OF COGNITIVE SCREENING FOR THE ELENBECESTAT MISSIONAD GLOBAL PHASE 3 STUDIES IN EARLY ALZHEIMER'S DISEASE. T. Doherty[1], J. Murphy[2], R. Smith[3], J. Marsh[4], L. Koschalka, M. Martinez[6], M. Gee[7], B. Albala[8] *((1) Universtiy of Westminster - London (United Kingdom), (2) Syneos Health - San Francisco (United States), (3) Worldwide Clinical Trials - Narbonne (France), (4) Medavante - Miami (United States), (5) Syneos Health - Valencia (Spain), (6) Syneos Health - Miami (United States), (7) Eisai Ltd - Hatfield (United Kingdom), (8) Eisai Inc. - Woodcliffe Lake (United States))*

Background: MissionAD 1 & 2 are two large global Phase 3 studies in Early Alzheimer's disease, testing the BACE inhibitor, elenbecestat. Diagnosis of MCI due to AD or mild AD dementia was made according to the National Institute of Aging – Alzheimer's Association core clinical criteria and required an MMSE score ≥24, a CDR Global score of 0.5 and a CDR Memory Box score of ≥0.5. Cognitive impairment of at least 1 SD from age-adjusted norms was also required and the objective test of episodic memory that was used in these studies was the International Shopping List Test (ISLT). Confirmation of brain amyloid pathology by either amyloid PET or CSF assessment or both was also required. A tiered approach to screening for the studies was implemented with the quicker, less invasive assessments performed in the earlier tiers and the more invasive assessments scheduled for the later tiers. As with any clinical trial, it was important to keep the screen failure (SF) rate as low as possible and therefore screen failure numbers and reasons were monitored very closely. A low screen failure rate on the initial tier of screening (Tier 1: including MMSE, ISLT and CDR) was also targeted. During the early stages of recruitment into the studies (August 2017) there was a 53% SF rate at Tier 1. **Objectives**: In August 2017, a Cognitive Task Force (CTF) of post-doctorally trained neuropsychologists was established for the MissionAD program with the aim of reducing the SF rate to ≤20% on the ISLT and ~30% on Tier 1 (ISLT, MMSE, & CDR combined). The CTF strategy and outcome metrics are presented here, to illustrate an innovative approach to successfully and efficiently recruit early AD subjects. **Method:** The CTF implemented: 1) monitoring ISLT, MMSE and CDR data at the site level with pre-determined thresholds set to identify sites that could benefit from a 1:1 discussion with a member of the CTF, 2) holding a telephone discussion with appropriate site staff to learn their pre-screening efforts/methods, patient population, recruitment strategy and site characteristics and 3) advising sites on which objective episodic memory pre-screening tests could be employed in order to reduce their Tier 1 SF rates, including details of appropriate cut-off scores that would better predict subject performance on the

ISLT and MMSE during screening for the studies. **Results:** To effectively reduce SF rates on Tier 1 cognitive tests, a regional, flexible approach was required, allowing sites to pre-screen with episodic memory tests which were normed in their countries, validated in their language, and were easily accessible. For the pre-screening test to best predict ISLT outcome, this flexibility had to be balanced with the requirement that the test was measuring the same list-learning episodic memory construct as the ISLT, was published in a peer-reviewed journal and had age-based norms. The MMSE pre-screening tool had to have score-adjustments made when global cognitive screening tools like the MOCA were used, but had varying level of difficulty. Among sites contacted by the CTF, Tier 1 total SF rates were reduced from 67% pre-contact (n=1583 screened; 1067 SF) to 43% post-contact (n=907 screened; 387 SF) yielding a 24% decline in Tier 1 SF rate. Amongst these, MMSE-related SF rates were reduced from an average of 21% pre-contact to 12% post-contact. ISLT-related SF rates were reduced from 47% pre-contact to 31% post-contact. Overall study metrics revealed that the Tier 1 SF rate started at 53% upon the inception of the CTF (Aug2017) and at the end of screening into the studies it had been reduced to 41% (Feb 2019). **Conclusion:** The primary role of the CTF was to reduce Tier 1 SF rates in the MissionAD studies, and thereby reduce unnecessary subject burden, site burden and excess trial costs. The CTF significantly improved cognitive screening efficiency in the MissionAD program, with a 24% decline in Tier 1 SF rate for the sites that the CTF contacted. The global 11.5% reduction in Tier 1 SF rates were likely further driven by wider country-level initiatives in which CTF members held CTF-specific Investigator meetings with the recruitment staff, speaking to all sites on a country level regardless of their recruitment performance. Additional benefits included improved site relationships, increased engagement in MissionAD and access to a group of cognitive experts for consulting, with a focus on achieving more efficient trial recruitment. The establishment of a CTF to support efficient cognitive screening for future studies in Alzheimer's Disease and indications with a neuropsychological component to eligibility criteria is highly recommended.

P025- QUANTIFYING IMPACT OF ENRICHMENT IN ALZHEIMER'S DISEASE TRIALS WHEN PRE-POST MODELS ARE UTILIZED. N. Hakhu[1], D. Gillen[1,2], J. Grill[1,3] *((1) Institute for Memory Impairments and Neurological Disorders, University of California, Irvine - Irvine (United States), (2) Department of Statistics, University of California, Irvine - Irvine (United States), (3) Department of Psychiatry and Human Behavior, University of California, Irvine - Irvine (United States))*

Background: Randomized clinical trials (RCTs) represent the gold standard to assess whether an intervention is causally associated with a clinically favorable benefit to risk ratio. In a RCT, the analysis of covariance (ANCOVA), also called a pre-post model, is a common statistical analysis that uses the within subject correlation between baseline (``pre») and final (``post») measurements to increase efficiency. Enrichment of ``high risk» subjects according to their baseline measurement(s) prior to randomization is common in Alzheimer's disease (AD) trials. In these cases regression to the mean (RTM) may arise and a consequence of this may be reduced within subject correlation, which will affect power in the ANCOVA design. **Objectives:** In this talk we present results quantifying the impact of enrichment in AD trials on statistical operating characteristics (scientific estimand, bias, precision, power) when pre-post models are utilized. **Methods:** ANCOVA is a common method to analyze data from a typical pre-post RCT design. The two-sample t-test and paired t-test are two additional methods that can be employed in such settings. Without enrichment, these three analytic methods yield consistent and unbiased estimates and valid inference after using a robust standard error estimate to account for possibility of heteroscedasticity (unequal variances between treatment groups). When enriching the sample to be randomized, however, we expect the observed correlation between baseline and final assessments to be reduced after enrichment compared to no enrichment. Owing to this reduction in the correlation, we consider three candidate analysis methods: two-sample t-test; ANCOVA; and paired t-test. A simulation study is performed under a variety of scenarios to estimate the correlation between baseline and final assessments after enrichment, the mean estimated treatment effect and corresponding 95% confidence interval, and statistical power under different assumed values of true treatment effect. We generate data under constant, proportional, and inversely proportional mean-variance relationships (MVRs), correlation prior to enrichment (0.60, 0.90), and enrichment type (none, top 50%, top 25%, top 10%). We consider two forms of enrichment according to patient inclusion criteria based on: (1) the true mean assessment value for each subject, and (2) a single baseline assessment (typically resulting in RTM). These two forms will allow us to assess the sensitivity of using (1) multiple pre-randomization assessments for enrichment vs. (2) a single pre-randomization assessment. **Results:** Simulation results are based on 1000 simulations. Each generated data set comprises 100 subjects randomized in a 1:1 fashion to treatment or placebo. Enrichment is based on the top 10% from 1300 screened subjects assuming correlation of 0.90 before enrichment. Enrichment based on True Mean: Observed correlation between baseline and final assessments after enrichment dropped to approximately 0.60 within a given treatment arm and specified MVR when multiple assessments were available prior to randomization. Two-sample t-test produces unbiased estimates of treatment effect only under a constant MVR or assumed values of true treatment effect close to the null hypothesis of zero. For large assumed treatment effects (negative values further from zero), the two-sample t-test produces overestimates under a proportional MVR and underestimates under an inversely proportional MVR. Similar findings of bias occur when using ANCOVA, but to a lesser, yet meaningful, degree. The paired t-test, however, produces unbiased estimates under constant, proportional, and inversely proportional MVRs with up to an approximate 2% increase, 4% decrease, and 3.4% increase in power, respectively, compared to no enrichment settings. Enrichment based on Single Pre-Randomization Assessment: Observed correlation between baseline and final assessments after enrichment dropped to approximately 0.64 within a given treatment arm and specified MVR. None of these candidate analysis methods yield unbiased estimates under all three MVRs. **Conclusion:** Enrichment has an impact on statistical operating characteristics for a pre-post RCT design. Simply relying on using robust standard error estimates in an enrichment setting does not mitigate the effects of RTM from enrichment. Unlike the no enrichment setting where the three analysis methods yield consistent and unbiased estimates, we find only the paired t-test provides unbiased estimates when enrichment is based on the true mean. However, caution is advised if using the paired t-test when enrichment

is based on a single pre-randomization assessment or using either the two-sample t-test or ANCOVA for either enrichment type. Proportional MVR yields overestimates and inversely proportional MVR yields underestimates. An overestimate of treatment effect in the enriched population can be problematic if the experimental therapy is approved for AD because the treatment effect in the non-enriched population could be attenuated to the null, a lower effect that may not be clinically meaningful. An underestimate of treatment effect may lead to lower power. Overall, it appears an enrichment period with multiple pre-randomization assessments will reduce the impact of RTM compared to a single assessment, especially when using the paired t-test.

P026- VALIDATION OF ALZHEIMER'S BIOMARKERS: AMYLOID BETA 1-40 AND PHOSPHORYLATED TAU IN CEREBROSPINAL FLUID (CSF) BY AUTOMATED CLEIA ON FUJIREBIO'S LUMIPULSE PLATFORM. S. Narla[1], A. Dider[1], F. Florent[2] *((1) Covance - Indianapolis (United States), (2) Covance - Geneva (Switzerland))*

Background: Guidelines for Alzheimer's disease diagnosis (AD) suggests using AD biomarkers for the pre-symptomatic and symptomatic phases. Cerebrospinal fluid (CSF) level of β-amyloid 1-42 (Aβ-42), β-amyloid 1-40 (Aβ-40), Total Tau (TTau) and Phosphorylated Tau (PTau) proteins have been increasingly included in the diagnostic process of Alzheimer's disease. Aβ-40 peptide is a major component of amyloid deposits. Aβ-40 is used in conjunction with Aβ-42 to determine the amyloid ratio (Aβ-42/ Aβ-40) to aid in diagnosis of AD in patients with cognitive impairment. The combination of decreased concentrations of β-amyloid and increased CSF concentrations of Total Tau and PTau are considered to be pathological CSF biomarker signatures that are used for prognosis of AD. Fujirebio (Fujirebio Inc., Japan) has developed fully automated chemiluminescence enzyme immunoassays (CLEIA) for analysis of Aβ-40 and PTau-181 in CSF along with the existing Aβ-42 and TTau assays. The purpose of this study is to evaluate the performance of the new Aβ-40 and PTau assays as per CLSI guidelines. **Method:** CSF Aβ-40 and PTau are measured quantitatively by chemiluminescence enzyme immunoassay technology by a two-step immunoassay method on the LUMIPULSE G 1200 (Fujirebio Inc., Japan) using respective immunoreaction cartridges. **Results:** Precision: Intra precision: 3 levels of controls tested in replicates of 20 over 1 day, average CV is 1.63 % for Aβ-40 and 2.03 % for PTau; Inter precision: 3 levels of controls tested in replicates of 1 over 10 day, average CV is 2.03 % for Aβ-40 and 2.43 % for PTau; Analytical Measuring Range (AMR): 5 levels of CSF spiked with recombinant protein covering the target AMR were tested in replicates of 4, AMR of Aβ-40 is 5 to 30,000 pg/mL with slope of 0.986 and AMR of PTau is 1.1 to 400.0 pg/mL with slope of 1.043; Sensitivity (Lower limit of quantification, LLOQ): 5 levels of diluent spiked with recombinant protein were tested in replicates of 5 per day over 5 days, LLOQ of Aβ-40 is 5 pg/mL with achieved % CV of 10.7% and 1.1 pg/mL for PTau with % CV of 7.4%; Dilution Verification: Two samples diluted with diluent with 2 fold dilution up to X20, tested in duplicate, dilution acceptable up to X20 for both Aβ-40 and PTau with ULOQ respectively at 600.000 pg/mL and 8.000 pg/mL. Length of Run: 3 levels of QC tested over 3 days at three time points during the day (morning, afternoon and evening), No significant change observed throughout the day. **Conclusion:**Lumipulse G Aβ-40 and PTau are robust quantitative assays and meet the Clinical and Laboratory Standards Institute (CLSI) requirements. CSF Aβ-40 and PTau could be proposed in clinical or drug trials as markers for AD according to the guideline. **References:** 1. Alzheimer's Dement. 2011, 7(3): 257–262, 2. Alzheimer's and Dementia, 2011, 7, 3, 280–292; 2. Alzheimer's and Dementia, 2011, 7(3): 270–279, 4. Alzheimer's and Dementia, 2011, 7, 3, 263–269

P027- A COHORT STUDY TO IDENTIFY PREDICTORS FOR THE CLINICAL PROGRESSION TO MILD COGNITIVE IMPAIRMENT OR DEMENTIA FROM SUBJECTIVE COGNITIVE DECLINE. S. Ho, D.W. Yang *(The Catholic University of Korea, Seoul St. Mary's Hospital - Seoul (Korea, Republic of))*

Background: There are many reports that subjective cognitive decline had a significantly higher risk of a progression to Alzheimer's disease and had a faster rate of neurodegeneration or cognitive decline than that of the control group. In addition, subjective cognitive decline showed more positive results in the biomarker tests of Alzheimer's disease. Therefore, it is necessary to find out the natural course of subjective cognitive decline and risk factors for converting to Alzheimer's disease. The purpose of this study is to identify which risk factors that can predict the progression to mild cognitive impairment or dementia by constructing a cohort of elderly people who have normal cognitive function but have subjective cognitive decline. **Methods:** This cohort study is a prospective study aimed to enroll 120 people who aged 60 years or older presenting with a complaint of persistent cognitive decline in five different centers. In the neuropsychological test, subjects who are in the range of 7% to 50% of the memory domain and over 7% of the rest domains are included. All patients have graduated from elementary school or higher and agree to the participation of study in writing. Subjects who diagnosed dementia or mild cognitive impairment are not included. Those who have brain lesions and blood test abnormalities which affect a cognitive function are excluded in this study. Subjects who have severe uncontrolled depression, schizophrenia, alcoholism, and drug dependence are not included. Cross-sectional and longitudinal analysis of risk factors, protective factors, and initial clinical findings affecting cognitive decline including memory and cerebral neurodegeneration in brain magnetic resonance imaging (MRI), and cerebral amyloid deposition in brain amyloid-beta Positron Emission Tomography (PET) will be performed. We plan to investigate a basic demographic information such as age, sex, education level, comorbid underlying disease, medication and family history through surveys. Apolipoprotein E genotype test and blood test which can affect in cognition will be done. Brain atrophy will be analyzed by visual rating and MRI volumetry using brain MRI. Blood-based amyloid quantification, a quantitative analysis of Electroencephalography (EEG), neuropsychological tests, subjective perception questionnaire surveys, and measuring physical activities using a wearable device are used to predict the possibility of a progression to mild cognitive impairment or Alzheimer's dementia. Balance test and gait analysis, pure tone test will be performed to evaluate the association with cognitive function. All tests are scheduled for baseline, one year and two years from baseline. Primary outcome is a progression to mild cognitive impairment and secondary outcome is a progression to Alzheimer's

dementia. **Discussion:** The purpose of this study is to identify which risk factors that could be used to predict the progression to mild cognitive impairment or dementia by constructing a prospective cohort of elderly people who have subjective cognitive decline. It can be expected that dementia or mild cognitive impairment can be prevented from the advance by controlling these risk factors.

P028- CONSISTENCE IN ASSAYING PLASMA AMYLOID AND TAU PROTEIN USING TWO DIFFERENT PROTOCOLS OF PREPARING PLASMA SAMPLES VIA IMMUNOMAGNETIC REDUCTION. S.Y. Yang[1,2], W.P. Chen[2], M.J. Chiu[3] *((1) MagQu Co., Ltd. - New Taipei City (Taiwan, China), (2) MagQu LLC - City Of Surprise (United States), (3) National Taiwan University Hospital - Taipei (Taiwan, China))*

For assaying ultra-concentration biomarkers such as amyloid and Tau protein in human plasma, the preparations of plasma samples are so critical to the results. In this work, two typical protocols of plasma preparation are used. One is that used in AIBL study, the other is suggested by MagQu. The clear differences in these two protocols of plasma preparation are the speed and the period of time of centrifugation. AIBL's protocol suggests cascading steps of centrifugation. The highest speed of centrifugation in AIBL's protocol is 3200g. There is only one step of centrifugation with the speed approximately 2000g. Immunomagnetic reduction (IMR) is utilized to quantitatively detect amyloid b 1-40 (Aβ1-40), Aβ1-42 and total Tau protein (T-Tau) in human plasma prepared by the two different protocols. Eight normal controls (NC) and five patients with Alzheimer's disease (AD) were enrolled for assays of plasma AD biomarkers. Significant differences in the levels of detected Aβ1-40, Aβ1-42, and T-Tau are found between NC and AD ($p < 0.001$). However, the detected levels of plasma Aβ1-40 and Aβ1-42 using AIBL's protocol are approximately 85%-90% of that using MagQu's protocol. The detected T-Tau level in AD using AIBL's protocol is 65% of that using MagQu's protocol. The results show that both AIBL's and MagQu's protocols of plasma preparation are suitable for preparing plasma samples for assaying AD biomarkers using IMR. But, the cut-off values in terms of plasma Aβ1-40, Aβ1-42 or T-Tau concentration to discriminate AD from NC would be different with various protocols of plasma preparation. Therefore, the protocol of plasmas preparation has to be standardized for clinical studies or trials.

P029- DENSE LONGITUDINAL MOLECULAR DATA FOR TURBOCHARGING CLINICAL TRIALS. J. Roach[1], J. Hara[2], J. Lovejoy[1], D. Fridman[2], L. Heim[2], M. Rapozo[1], L. Heath[1], C. Funk[1], M. Fischer[1], L. Hood[1], N. Price[1], M. Brant Zawadski[2], W. Shankle[2] *((1) Institute for Systems Biology - Seattle (United States), (2) Hoag Memorial Hospital Presbyterian - Newport Beach (United States))*

Background: Background: The design goal of most prospective randomized clinical trials (RCTs) is to maximize statistical power to test a null hypothesis. The design goal of most longitudinal studies is to gather data to enable further exploration and understanding of human phenomena and phenotypes. We recommend that an increasing number of RCTs should combine these goals and be designed to maximize at least two objectives: (1) test a null hypothesis and (2) explore molecular underpinnings of human biology. Three concurrent forces drive this recommendation. First, the cost of molecular assays – "omics" – is plummeting and has begun to make the cost of longitudinal molecular assays palatable. Second, the diseases and interventions that are now the focus of major biomedical efforts are increasingly complex, and outcomes are decreasingly predictable, so the need to gather data to understand unexpected outcomes increases. Third, an increasing amount of scientific value now stems from meta-analyses of large diverse molecular datasets, so research studies have an ethical obligation to support future studies that will rely on rich data gathered from many individual studies. We have designed the Coaching for Cognition in Alzheimer's (COCOA) trial for Alzheimer's disease (AD) as a prototype for this new concept in clinical trials. The premise of COCOA is that comprehensive treatment of AD requires management of medical conditions and personalized lifestyle modifications. Furthermore, adherence to medical and lifestyle interventions varies widely, increasing the diversity and complexity of the biological systems responses to intended interventions. Thus, for the COCOA trial, both the intervention and the and the underlying pathology of the disease studied are complex, making COCOA an ideal prototype for this new trial methodology. **Objective:** Our overall objective is to enable clinical trials to advance science in myriad ways driven by comprehensive molecular and phenotype data beyond classic statistical tests focused solely on testing to accept or reject a null hypothesis. Our two specific objectives with COCOA are (1) to use classical methods to test the hypothesis that data-driven health coaching enhances compliance with lifestyle interventions (including diet, cognitive training, physical activity, sleep, and stress management), enhances adherence to medical treatment, and improves cognitive outcomes compared to routine care alone, and (2) to create dense dynamic data with rich potential to explain observed results and to inform the design of future hypotheses and trials. **Methods:** In the COCOA trial, inclusion criteria encompass persons over 50 years old, with the FAST Staging 2-4, and 65 or below on the Memory Performance Index (MPI) component of the Mild Cognitive Impairment Screen (Medical Care Corporation, Newport Beach, California). Persons with an existing diagnosis of a non-AD neurodegenerative disorder (e.g., Lewy Body Disease, Frontal-Temporal Disease) are excluded. Once consented, enrollees are randomly assigned to routine care alone or routine care plus data-driven health coaching. All participants receive comprehensive health data collection several times per year and the coaching group also receives telephonic health coaching from licensed dietitians/nutritionists monthly (or more frequently) to address lifestyle behaviors that may influence cognitive decline or dementia. In particular participants in the coaching arm are coached to increase exercise, improve diet, and complete online cognitive training – primarily BrainHQ (Posit Science, San Francisco, CA) – several times per week. The primary outcome measure is the MPI. In addition, COCOA evaluates "personal dense, dynamic data clouds" (Price et al., Nature Biotechnology, 2017) consisting of clinical labs, lifestyle, genomic, proteomic, metabolomic and gut microbiome data for each participant – in an effort to explain potential causal underpinnings of any observed differences between the two arms and to guide future study designs. We monitor each participant for two years. **Results:** COCOA recruitment began in January 2018. As of June 2019, 53 participants are enrolled in the COCOA trial. Participant retention rate is high. Substantial dense molecular and cognitive assessment data has been

acquired, in some cases for over a year. **Conclusion:** Enrollment and engagement of participants with prodromal or very early stage AD in an intensive telephone based coaching trial with online cognitive training is feasible. Acquisition of dense data clouds permits interpretation of mechanisms underlying compliance and responses to interventions. We recommend that other trials use this methodology. These trials should use many of the same basic longitudinal measurements across all trials – including clinical labs, blood proteomics, and metabolomics – plus assays specific to each particular trial design. For trials focused on neurodegeneration, these additional assays might include brain imaging and cognitive testing.

P030- STUDY DESIGN FOR PREVENTING ALZHEIMER'S WITH COGNITIVE TRAINING: THE PACT TRIAL. D. Morgan[1], A. Harrison-Bush[2], A. Houseknecht[2], J. O'brien[2], J. Edwards[2] *((1) Michigan State University - Grand Rapids (United States), (2) University of South Florida - Tampa (United States))*

Background: The ACTIVE trial compared randomization to reasoning-, memory-, or speed of processing- cognitive training (SPT) to a no-contact control group on operationally defined dementia across 10 years. Results indicated 29% reduced risk of dementia (inferred among those randomized to SPT (Edwards et al, 2017 Alz & Dement 3:603-11). However, the ACTIVE trial was not designed to use conversion to dementia as an endpoint, and the criteria for identifying those with dementia did not include medical diagnoses in all instances. **Objectives:** The PACT trial was specifically designed to test the ability of SPT to prevent or delay conversion to mild cognitive impairment (MCI) or dementia using medical diagnosis as the primary end point. The PACT study will directly compare SPT trained participants with an active control group performing computer games. After 3 years, the number of participants in each group that develop MCI or dementia will be determined to see if SPT can reduce the incidence of conversion. **Methods:** The PACT Study, a collaboration between the University of South Florida and Michigan State University, has received pilot funding to demonstrate the feasibility and rate of enrollment for the study. For the pilot phase, there are 4 sites in the Tampa Bay region and 2 sites in the Grand Rapids metropolitan area enrolling participants. The study is designed to minimize personnel effort during recruitment, enrollment, and training, yet plans an intensive neuropsychological and medical diagnosis on those who appear to decline. The study will include cognitively normal older adults 65 years and older with no history of serious neurological disorders. After being consented, participants are administered the Montreal Cognitive Assessment (MoCA) and the Geriatric Depression Scale (GDS). Participants scoring 26 or greater on the MoCA and 5 or less on the GDS are enrolled. Participants are randomized to SPT training or computer games and instructed how to perform the assigned activities across three study visits. Participants then complete 22 more sessions on their home computer or a loaned tablet computer. At 1 year after the initial training, participants will be contacted and asked to complete 10 additional booster sessions. Again, 2 years after the initial training, another 10 booster sessions will be performed. Three years after enrollment, participants will visit the study site and receive a second MoCA. Those individuals whose MoCA score drops below 26 will receive a more detailed neuropsychological evaluation and provided a free medical evaluation to ascertain if they have developed mild cognitive impairment or dementia. This will include MRI, amyloid PET, blood tests, neuropsychological testing, genetic analysis and evaluation by a physician specializing in memory impairment. The number of cases considered to have developed MCI or dementia will be tallied for each treatment condition. Power calculations indicate that with a .05 level of significance and 20% attrition rate, a total sample size of 7600 participants are required to have 82% power to detect a 20% reduction with an estimated 3-year incidence rate of 10.5%. **Results:** As of June, 2019, 4 sites are open in the Tampa Bay area and 2 sites are preparing to launch in Grand Rapids. After the first 3 months, we are enrolling participants at a rate of 24 per month per site. Thus, over 3 years the existing sites should enroll 5000 participants. **Conclusions:** To reach the 7600 sample required, we will include 4 additional sites that will enroll for a 2-year period randomizing another 2600 participants. These additional sites will be outside the Tampa and Grand Rapids metropolitan areas. Supported by R56 AG-058234 from the NIA/NIH to JDE and DM.

P031- FEASIBILITY OF REMOTE COLLECTION OF GENETIC MATERIAL FROM PARTICIPANTS ENROLLED IN AN INTERNET-BASED REGISTRY. W. Kwang[1,2], J. Fockler[1,2], D. Flenniken[1,2], J. Hwang[1,2], D. Truran[1], R.S. Mackin[1,3], R. O'hara[4], J. Hallmayer[4], J. Yesavage[4], M. Weiner[1,2], R. Nosheny[1] *((1) Center for Imaging of Neurodegenerative Diseases, San Francisco Veteran's Administration Medical Center - San Francisco (United States), (2) University of California, San Francisco Department of Radiology and Biomedical Imaging - San Francisco (United States), (3) University of California, San Francisco Department of Psychiatry - San Francisco (United States), (4) Stanford University Department of Psychiatry and Behavioral Sciences - Stanford (United States))*

Background: There is an ongoing need to identify those who are at higher genetic risk for Alzheimer's disease in order to facilitate clinical research recruitment and identify older at-risk adults in the general population. The collection of biological samples in-clinic can be costly and resource intensive. Saliva-based collection kits offer the possibility for the remote collection of genetics and are resource- and cost-efficient. Previously, a number of studies (e.g., Alzheimer's Prevention Initiative) and companies (e.g., 23andMe) have collected saliva samples from individuals at home using an internet-based platform. Brain Health Registry (BHR) is an online website and registry of over 62,000 participants with the goal of recruitment, assessment, and longitudinal monitoring of participants for neuroscience research. The BHR platform includes a comprehensive battery of self- and study partner (SP)-report questionnaires and online neuropsychological tests. The Brain Health Registry-GenePool Study (BHR-GPS) was launched as a pilot study to test the feasibility and acceptance of remote saliva collection by participants already engaged in longitudinal online evaluation. **Objective:** The objective is to assess the feasibility of remote biological sample collection in older adults enrolled in BHR-GPS. **Methods:** BHR participants were recruited into BHR-GPS by email invitation. Prior to the launch of BHR-GPS, all BHR participants were invited to complete an online Genetic Study Interest questionnaire to gage general interest. Inclusion criteria for BHR-GPS included: age 60+, has completed three online cognitive tests, has completed online Medical History questionnaire and Everyday Cognition Scale within the past two years, has a SP enrolled in BHR, and their SP has completed one Everyday Cognition Scale. Those interested in joining the

study provided consent online. They were then mailed salivary DNA self-collection kits with detailed saliva collection and mailing instructions. The participants completed the kits by collecting their saliva samples and mailing them back to the study team. Saliva samples were processed to determine APOE ε4 genotype. Saliva kit tracking and participant communication were automated using a novel BHR Biofluid Collection Management Portal. This infrastructure allows study team members to collect, store, maintain, and organize data related to remote biofluids collection. Once samples were processed, APOE results were uploaded into the portal and APOE data was linked to BHR data collected online. After completing saliva collection, participants completed an online feedback questionnaire about their experience in BHR-GPS. **Results:** Of the 20,891 BHR participants who completed the Genetic Study Interest questionnaire, 96% expressed willingness to participate in a genetics study in which they remotely provide a saliva sample, 93% said they would be interested in knowing if they are a carrier of a gene that affects their risk of developing Alzheimer's disease, and 69% said their interest in participating in a genetics study would not depend on disclosure of results. Since March 2018, 834 BHR participants, selected by using the above stated inclusion criteria, have been invited to join BHR-GPS. Of those, 50% have consented to enroll in the study. Out of the 399 saliva kits sent to participants so far, 90% have been completed and sent back to the study team. In the post-study feedback questionnaire, 91% respondents rated the difficulty of using the DNA saliva collection kit as 1 or 2 based on a scale of 1-5 (1 = least difficult and 5 = most difficult). Similarly, 91% reported the instructions included in the kit were either "extremely clear" or "very clear". 99% reported that if given the opportunity, they would agree to participate in another study similar to BHR-GPS. So far, a total of 245 saliva samples have been processed for APOE genotyping and all samples have been successfully processed. Of those, 29% had at least one APOE ε4 allele, which included 27% that had APOE ε3/ε4, 1% that had APOE ε4/ε4, and 1% that had APOE ε2/ε4. 71% had no APOE ε4 alleles, which included 13% that had APOE ε2/ε3 and 58% that had APOE ε3/ε3. Participants had an average age of 71.3 ± 6.8 (range 59-94). As for the demographic and cognitive profile of these participants, 64% were female, 96% were Caucasian, 35% reported subjective memory concerns, and 5% self-reported a diagnosis of mild cognitive impairment. **Conclusion:** A high percentage of BHR participants were willing to participate in genetics research. The high enrollment and completion rate in BHR-GPS supports the feasibility of remote collection of genetic material from a large cohort of older adult participants enrolled in an Internet-based registry. The novel BHR data infrastructure developed to execute BHR-GPS, which provides a more streamlined and automated approach to biological sample collection compared to in-clinic collection, can be used to successfully enroll participants in a genetics study. In the future, the infrastructure can be further automated and used to greatly expand efforts to collect biofluids data from a larger cohort of BHR participants.

P032- PROPOSED METHODS FOR DISCLOSING BETA-AMYLOID STATUS TO COGNITIVELY UNIMPAIRED LATE-MIDDLE AGED ADULTS. C. Erickson, N. Chin, L. Clark, S. Johnson *(University of Wisconsin-Madison - Madison (United States))*

Background: Beta-amyloid signal observed in midlife or early late-life via amyloid positron emission tomography (PET) imaging is associated with subsequent cognitive and functional decline. Because this key Alzheimer's disease (AD) biomarker appears years before clinical manifestation of AD, there may be a temporal window for which secondary prevention trials may be most effective. With the 2018 NIA-AA guidelines defining AD by pathophysiological changes, preclinical AD criteria of elevated markers of amyloid and tau proteins have become paramount. To initiate experimental prevention approaches, disclosure of biomarker status is a prerequisite step. Recently, studies disclosed amyloid status to cognitively unimpaired participants as part of prevention and clinical drug trials. Despite initial rises in distress measures among amyloid elevated individuals, negative effects of amyloid disclosure are mild and subside after a few months. Thus far, disclosing amyloid status to research participants as part of clinical trials has been a safe and well-tolerated process. However, studies have yet to assess if disclosure of amyloid status is associated with additional and potentially positive outcomes, such as motivation to engage in healthy lifestyle practices which could promote overall brain health. **Objectives:** This study will be conducted with participants enriched for AD risk due to parental family history of AD enrolled in the Wisconsin Registry for Alzheimer's Prevention (WRAP), a longitudinal biomarker research program. Using a carefully planned protocol, we will determine if amyloid disclosure accompanied with a personalized lifestyle risk-reduction care plan results in increased willingness to engage and actual engagement in addressing modifiable risk factors for brain heath. We hypothesize amyloid disclosure combined with a personalized care plan to reduce dementia risk factors will result in increased willingness to engage in addressing modifiable risk factors and future planning activities as well as reduced anticipated negative outcomes. We hypothesize that these results will vary by amyloid status, age, education level, and perceived AD risk. **Methods:** Using a single group non-randomly selected design, approximately 150 cognitively unimpaired middle-aged and older adult volunteers undergoing amyloid PET scans as part of the larger WRAP or WRAP-affiliated studies will be recruited into this study. The proposed disclosure method involves three in-person and three telephone visits. At the first in-person visit, we will conduct informed consent, eligibility screening, and a biomarker education session. We will collect baseline participant information on current engagement in lifestyle behaviors and willingness to change behavior. Here, utilizing the teach back method, we will educate participants on AD biomarkers and assess their understanding of biomarker information and the possible results of an amyloid PET scan. The disclosure of amyloid status will occur during the second in-person visit using graphics and standardized language. Amyloid status is determined using a visual rating of [11] C-Pittsburgh Compound B elevation rated on a 0 to 3 point scale. Only a rating of unambiguous amyloid binding in the cortex will be considered amyloid elevated. After answering participant questions, the clinician will reassess participant's understanding of the result. One to three days following the

disclosure visit, participants will be called to assess mood, anxiety, suicidality, the impact of the result, and satisfaction with the disclosure process. At the third in-person visit, the study physician will conduct a personalized risk-reduction care plan by providing an overview of scientifically studied potential modifiable risk factors and creating specific personalized health goals. We will follow-up via telephone with participants at one and six months to assess psychological factors, willingness and actual engagement in healthy lifestyle behaviors, impact of disclosure, change in time perception, and process satisfaction. At each in-person and telephone visit, participants will be screened for existing or elevated levels of depression, anxiety, and suicidality. Follow-up by a study clinician or exclusion from the study will occur if participants exhibit significant baseline or changes in mood, anxiety, and suicidality symptoms. **Conclusion:** This study builds on prior studies of amyloid disclosure in cognitively healthy at-risk adults and is novel in its personalized risk-reduction care plan visit and follow-up to assess behavioral changes following amyloid disclosure. Our expected outcomes are an infrastructure that further supports a careful approach to AD biomarker disclosure in a clinical research setting with ample medical support and relevant resources to support participants; and an understanding of factors associated with increased willingness to reduce modifiable risk factors following amyloid disclosure. These data will be used to launch a program of research focused on developing, implementing, and testing evidence-based biomarker disclosure procedures in a diverse population of cognitively unimpaired adults. Ultimately, disclosing amyloid status to these participants will provide information that may lead to future planning and healthy lifestyle changes to enhance brain health.

P033- DON'T FORGET THIS! THE PATIENT IN YOUR STUDY MAY BE IN ANOTHER. T. Shiovitz, B. Steinmiller, C. Steinmetz, S. Perez *(CTSdatabase, LLC - Sherman Oaks (United States))*

Background: As Alzheimer's Disease (AD) investigators we develop close relationships with patients and their families/caregivers. Does this mean that our studies are the only ones that our patients participate in? Duplicate (and professional) subjects are a significant issue in CNS studies, although they have been better characterized in indications such as schizophrenia or depression. Duplicate subjects in AD studies, however, are not often considered. When you take into account the large number of clinical trials enrolling in Early AD, exploring varied mechanisms of action (MOA), the many investigative sites in geographic proximity and enrollment pressures, there may be incentives for subjects and caregivers to participate in multiple studies. CTSdatabase is a subject registry that specializes in the detection of duplicate subjects in clinical trials. These subjects affect safety and efficacy signals and may adversely affect study outcomes. **Objectives:** Of the over 60,000 subjects in CTSdatabase, we reviewed subjects screening for memory loss studies (Alzheimer's Disease/Prodromal AD/AD with Agitation) that were entered into the registry between Jan 1, 2017 and May 30, 2019, n=1087. We then examined how many attempted to screen at more than one site, either for a memory study or for a different indication within a two-year timeframe (i.e. this includes Jan 1, 2015 to May 30, 2019.) A case history of a duplicate subject in an AD study is also presented. **Results:** 117 of 1087 Memory Loss subjects, 10.8%, went to at least one other site (i.e. a unique site) within two years. This was significantly smaller compared with the overall population of potential research subjects, where 40.0 % of potential research participants visited a unique site. When potential memory study subjects went to a second site, it was more often for a non-memory indication (most commonly MDD or schizophrenia) than for a memory indication. In addition, a substantial number of the subjects who tried to enroll at different sites for a memory study were duplicate enrollers (enrolling for the same study or for a different study within an exclusionary timeframe). **Conclusions:** A small but significant number of AD patients and their caregivers may try to enroll at multiple sites, confounding efficacy and safety signals in clinical trials. This may be for money (i.e. a professional subject who participates in an Early AD study while in a schizophrenia study), or a duplicate subject (and caregiver) who may wish to take advantage of multiple studies with similar or different MOA in order to find something that can slow the progression of their disease. Either way, the use of an available subject registry (such as CTSdatabase) at screen is a simple and cost-effective way to detect these subjects and mitigate their effects on data integrity and safety. When designing and executing studies in Early AD space, it is important to consider the motivation (treatment, money) of the subjects you intend to enroll.

P034- DATA-DRIVEN PARTICIPANT RECRUITMENT: FINDINGS FROM THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE 3. C. Barger[1], J. Fockler[2], W. Kwang[2], S. Moore[1], D. Flenniken[2], A. Ulbricht[2], P. Aisen[1], M. Weiner[2] *((1) USC Alzheimer's Therapeutic Research Institute - San Diego, Ca (United States), (2) UCSF Department of Radiology and Biomedical Imaging & Center for Imaging of Neurodegenerative Diseases, San Francisco Veteran's Administration Medical Center - San Francisco, Ca (United States))*

Background: A major obstacle in developing new Alzheimer's disease treatments is the identification and enrollment of participants in multi-center clinical research. Although participant recruitment has been primarily conducted at the site-level, as studies become more competitive for participants, there is an increasing need to expand efforts and provide referrals to sites through central activities. To address this need, the Alzheimer's Disease Neuroimaging Initiative 3 (ADNI3) study utilized a range of centralized recruitment activities implemented in a manner that would permit a link to measurable outcomes. Using technology and tracking tools, we were able to collect recruitment metrics which provided preliminary but valuable insights on which methods were most effective at reaching potential participants. **Objectives:** ADNI3 can serve as an example of how a data-driven approach to centralized participant recruitment can be utilized to facilitate clinical research. **Methods:** Central recruitment activities employed in ADNI3 include: national newspaper and radio coverage; local TV and newspaper coverage; search engine, website, social media and newspaper advertisements; and registry referrals and e-blasts. All digital activities funneled visitors to the ADNI3 recruitment website, which was developed as a collaboration between the Clinical Core at the Alzheimer's Therapeutic Research Institute at University of Southern California and the Brain Health Registry (BHR) at University of California, San Francisco. The website captures data using the methods listed below to track visitors during the screening process. Additional information is collected at the

in-person screening visit to determine where the participant heard about the study. This data is reported visually through an active dashboard, allowing recruitment metrics to be seen in real-time. Trackable Links: Custom URLs are used to identify how web visitors arrived at the recruitment website. These are placed in all digital communication, advertisements, emails, articles and social media posts. Pre-screener: This web-based questionnaire asks study-specific questions to determine eligibility for the study and connect eligible referrals to a research site. Sign Up Form: This web-based form collects contact information and zip codes from visitors to determine if there is a research site enrolling in their area. They are then provided with a referral code and the research sites' contact information. Phone Numbers: Unique phone numbers are used to track phone calls to research sites from recruitment campaigns and the recruitment website. Contact Us Form: This web-based form allows visitors to provide their contact information for a specific research site. This is provided to the site along with a referral code to track them into enrollment. **Results:** Central recruitment activities accounted for 48% of new participant enrollment into ADNI3. There have been 62,378 visitors to ADNI3.org and 2,843 phone calls with sites attributable to central recruitment efforts. Of the visitors to the website, 26.6% completed the pre-screener, contact us form, sign up form, or called a site directly. The most popular action was to complete the pre-screener form (12.6%) and the least popular action was calling a site directly (1.6%). Of those that completed the pre-screener, 58% passed the initial pre-screening questions and were referred to a site. This minimized site burden by eliminating approximately 56 ineligible individuals per site. In total, approximately 7,663 referrals were provided to research sites through the recruitment website. The recruitment sources that produced most referrals include: Facebook and Google advertisements targeted by age and location; radio interviews in local markets with the Principal Investigator; articles and press releases in local newspapers; e-blasts from Caring.com and the Alzheimer's Prevention Registry (APR); and direct referrals from BHR. These activities resulted in 65% of the total website traffic, 46% of the total completed website pre-screeners, and 26% of the total calls. **Conclusion:** We found that central recruitment efforts using a multi-faceted approach that includes targeted advertising, media coverage and partnership outreach can be effective. Additionally, the use of an online pre-screening questionnaire is an effective entry method for referrals and saves sites time by eliminating referrals that do not meet the basic study criteria. Since most web sessions are brief, it is important to have a clear message on the homepage of the website with a call-to-action that encourages visitors to take the pre-screener. Using recruitment metrics, we were able to obtain an assessment of central recruitment efforts in real-time, using this information to inform recruitment planning and use resources wisely. With this data-driven approach to centralized recruitment, along with site-driven local activities, investigators can effectively and efficiently pursue enrollment goals.

P035- LEARNING FROM FAILED TRIALS : VIRTUAL PATIENT ANALYSIS OF ADUCANUMAB TRIAL USING A QUANTITATIVE SYSTEMS PHARMACOLOGY APPROACH. H. Geerts, A. Spiros *(In Silico Biosciences - BERWYN (United States))*

Objectives: Clinical trials with amyloid modulating interventions, such as Aducanumab (ADU) - an antibody with high affinity for aggregated forms of b-amyloid- in Alzheimer's Disease (AD) have failed to show cognitive benefit despite substantial target engagement. We use a Quantitative Systems Pharmacology (QSP) model to understand the pharmacodynamic interactions with comedications and genotypes at the individual patient level. **Methods:** We implemented clinical data on amyloid synthesis, preclinical data on b-amyloid aggregation [1] and the dose-dependent neurostimulatory effects of short b-amyloid peptides (Ab1-40) together with the neuro-inhibitory effects of longer amyloid peptides (Ab1-42) on glutamate and nicotinic cholinergic neurotransmission (nAChR) [2] in a mechanism-based and ADAS-Cog calibrated QSP model of cortical microcircuit [3]. We showed previously that after 52 weeks treatment, the cognitive readout worsens after BACE-inhibition, solanezumab and g-secretase inhibition in subjects with low baseline amyloid but improves in those with high baseline amyloid [4]. ADU's effect on oligomer and aggregates is implemented using Michaelis-Menten kinetics affecting amyloid aggregation dynamics. We simulated the pharmacodynamic effect of COMT, APOE and 5-HTTLPR genotypes and of donepezil and memantine. **Results:** We reproduced the observation that immediate dosing of 10mpk of ADU after 52 weeks treatment is able to provide a cognitive benefit [5] in a responder population with high amyloid baseline and modulated by the 5HTT-LPR genotype. We then simulated a virtual patient trial according to the design of the ENGAGE and EMERGE aducanumab Phase III clinical trial for 3055 patients (40 months after enrollment), using the same distributions of common genotype variants and comedications as the Ph1b trials and with random distribution of amyloid load above the threshold for positivity. The reduction in oligomers was calculated from the observation that the highest dose eliminated all the amyloid plaques. Simulated group average outcomes did not differ significantly from placebo outcome at 104 weeks, as the variability was substantially greater than the effect size (ranging from 0.5-1 points worsening at lower amyloid baseline to 1-1.5 points improvement at high amyloid baseline). Different scenarios of switching APOE4/4 subjects to lower doses also lead to a lower efficacy. **Discussion:** An advanced QSP cognition model in AD can identify different hypotheses to explain clinical trial outcomes of b-amyloid modulation and illustrates the numerous non-linear pharmacodynamic interactions that affect clinical response. Application of this approach early on during clinical trial design can help mitigate negative PD-PD interactions and increase the probability of success. **References:** 1. Garai, K. and C. Frieden, Quantitative analysis of the time course of Abeta oligomerization and subsequent growth steps using tetramethylrhodamine-labeled Abeta. Proceedings of the National Academy of Sciences of the United States of America, 2013. 110(9): p. 3321-6. 2. Wang, Y., et al., Multiple effects of beta-amyloid on single excitatory synaptic connections in the PFC. Frontiers in Cellular Neuroscience, 2013. 7: p. 129. 3. Roberts, P.D., A. Spiros, and H. Geerts, Simulations of symptomatic treatments for Alzheimer's disease: computational analysis of pathology and mechanisms of drug action. Alzheimer's research & therapy, 2012. 4(6): p. 50. 4. Geerts, H., A. Spiros, and P. Roberts, Impact of amyloid-beta changes on cognitive outcomes in Alzheimer's disease: analysis of clinical trials using a quantitative systems pharmacology model. Alzheimer's research & therapy, 2018. 10(1): p. 14. 5. Sevigny, J., et al., The antibody aducanumab reduces Abeta plaques in Alzheimer's disease. Nature, 2016. 537(7618): p. 50-6.

P036- A SEAMLESS PHASE 2A-2B RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF PQ912 IN PATIENTS WITH EARLY ALZHEIMER'S DISEASE: DESIGN AND METHODS. H. Feldman[1], K. Messer[1], F. Weber[2], K. Erickson[1], B. Huisa[1], T. Oltersdorf[1], D. Jacobs[1], D. Salmon[1], C. Revta[1], S. Bruins[2], D. Galasko[1], O. Lopez[3], M. Quiceno[4], M. Raskind[5], M. Sabbag[6], R.S. Turner[7] *((1) Alzheimer's Disease Cooperative Study, University of California at San Diego - La Jolla (United States), (2) Probiodrug AG - Halle (Saale) (Germany), (3) University of Pittsburgh Medical Center - Pittsburgh (United States), (4) University of North Texas Health Science Center - Fort Worth (United States), (5) University of Washington - Seattle (United States), (6) Cleveland Clinic Lou Ruvo Center for Brain Health - Las Vegas (United States), (7) Georgetown University - Washington DC (United States))*

Background: PQ912 is an inhibitor of the enzyme glutaminyl cyclase (QC) and its isoenzyme (isoQC). In preclinical models, PQ912 effectively reduces levels of post-translationally modified forms of pyroglutamated Aβ (pGlu-Aβ) and cytokine monocyte chemoattractant protein 1, pGlu CCL2. pGlu-Aβ is neuro and synaptotoxic, proinflammatory, promotes its self-aggregation into oligomers, and resists degradation, while pGlu-CCL2 is a proinflammatory cytokine linked to negative neuroinflammation in AD. In preclinical models 50% inhibition of QC reduces pathology and improves behavioral measures. In the phase 1 program (n=163), a wide dose range was explored while in a phase 2A clinical trial (SAPHIR) PK/PD results were consistent with the preclinical and phase 1 predictive models. SAPHIR provides preliminary evidence efficacy on disease-relevant CSF biomarkers, favorable EEG findings, and a potentially early cognitive signal while demonstrating predictable and measurable target engagement. We are undertaking a phase 2a-b seamless double-blind RCT to evaluate safety and efficacy of PQ 912 in early AD. **Design:** Multicenter (55 sites in North America), double-blind placebo-controlled trial of PQ912 with seamless phase 2A and 2B. Phase 2A includes adaptive dosing of three dose levels with exposure at full dose for 8 weeks, to determine the highest tolerated dose for phase 2B which will evaluate efficacy and longer-term safety through 72 weeks of treatment. **Study Population:** Early AD with MMSE 20-30, MoCA <26, and CDR global score of 0.5 or 1 with memory score of >0.5. CSF findings of AD confirmed by levels of Abeta, total tau/Abeta ratio. **Outcome Measures:** Primary CDR, and target occupancy of QC, key secondary CFC2 a cognitive functional composite, and other secondary measures including composite sum of Z scores from ADNI neuropsychological test measures, quantitative EEG, Functional Assessment Questionnaire, ADAS cog 13 and the Neuropsychiatric Inventory. **Sample Size and Statistical Power:** The sample size of 462 participants randomized 1:1 with no more than 25% drop out will have 80% power to detect an effect size of 0.7 in CDR-SoB. This corresponds to about 37% of the expected 1.9 point mean change in CDR SoB in the placebo arm with an enrolled sample of 40% MCI and 60% mild AD. An interim futility analysis will be performed when the first 230 participants have either completed week 48 or dropped out with data available from participants who have been on study drug for at least 6 months. **Trial Funding:** NIA R01 AG061146-01 and Probiodrug. **References:** Lues, I., et al., A phase 1 study to evaluate the safety and pharmacokinetics of PQ912, a glutaminyl cyclase inhibitor, in healthy subjects. Alzheimer's & Dementia: Translational Research & Clinical Interventions, 2015. 1(3): p. 182-195. Scheltens, P., Safety, tolerability and efficacy of the glutaminyl-cyclase inhibitor PQ912 in Alzheimer's disease: results of a randomized, double-blind, placebo-controlled phase 2a study. Alzheimer Research and Therapy, 2018.

Theme: CLINICAL TRIALS RESULTS

P037- MASUPIRDINE (SUVN-502) IN COMBINATION WITH DONEPEZIL AND MEMANTINE IN PATIENTS WITH MODERATE ALZHEIMER'S DISEASE: EXPLORATORY SUBGROUP ANALYSES OF MEMANTINE REGIMEN, CONCENTRATIONS AND DURATION OF TREATMENT. A. Atri[1], J. Cummings[2], R. Nirogi[3], V. Goyal[3], G. Bhyrapuneni[3], P. Jayarajan[3], V. Jasti[3] *((1) Banner Sun Health Research Institute, Banner Alzheimer's Instiitue, Banner Health; Department of Neurology, Brigham and Women's Hospital and Harvard Medical School, Boston - Sun City And Phoenix (United States), (2) Department of Brain Health, School of Integrated Health Sciences, University of Navada, Las Vegas; Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas - Las Vegas (United States), (3) Suven Life Sciences - Hyderabad (India))*

Background: Masupirdine (SUVN-502) is a 5-hydroxytryptamine-6 (5-HT6) receptor antagonist being evaluated for the treatment of moderate Alzheimer's disease (AD). Preclinical experiments have supported a rationale for the study of masupirdine to treat AD. A randomized, double-blind, placebo controlled 26-week phase-2 proof-of concept study assessed the effects of triple therapy with masupirdine added to background treatments with donepezil and memantine in patients with moderate AD. **Objectives:** To perform an exploratory analysis of the potential effects of memantine regimen, plasma memantine concentration, and memantine treatment duration on study primary and secondary outcome measures (ADASCog11, CDR-SB, ADCS-ADL, NPI, C-SDD and MMSE) in moderate AD patients who are on stable treatment with donepezil and memantine assigned to placebo versus masupirdine. **Methods:** A total of 564 subjects were randomized. Subjects received placebo or masupirdine (50 or 100 mg) in combination with donepezil and memantine for 26 weeks. Different regimens of donepezil and memantine were allowed (donepezil 10 mg QD + memantine 10 mg BID or Namenda XR 28 mg QD; or Namzaric QD (28 mg memantine + 10 mg donepezil). Exploratory subgroup analyses using mixed models with repeated measures (MMRM) methodology was used to assess the potential effects of different memantine regimens(memantine IR vs memantine XR – by itself or in a combination formulation with donepezil as Namzaric), memantine plasma concentrations, and memantine background treatment duration on primary and secondary study outcomes in patients assigned to placebo, masupirdine 50 mg daily and masupirdine 100 mg daily. **Results:** In the mITT population, 65.7% of subjects were on donepezil 10 mg QD +memantine 10 mg BID; 17.9% were on donepezil 10 mg daily+Namenda XR 28 mg daily; and 16.4% were on Namzaric – there are no significant differences in assignment across the three treatment arms. Masupirdine improved cognitive functions in subjects on memantine 10 mg, BID than subjects on Namenda XR or Namzaric. Masupirdine demonstrated significant improvement in cognitive endpoints in subset of subjects with memantine plasma concentrations of ≤ 100 ng/mL. It also demonstrated

significant improvement in cognitive endpoints in subset of subjects with memantine treatment duration above 3 years. **Conclusions:** Masupirdine is safe and well tolerated. The results of these exploratory subgroup analyses suggests potential differential effects of memantine regimen, memantine plasma concentrations and memantine treatment duration on outcome measures of masupridine triple therapy.

P038- POTENTIAL BENEFITS OF MASUPIRDINE (SUVN-502) ON BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS IN PATIENTS WITH MODERATE ALZHEIMER'S DISEASE. J. Cummings[1], R. Nirogi[2], P. Jayarajan[2], A. Shinde[2], V. Jasti[2] *((1) Department of Brain Health, School of Integrated Health Sciences, University of Nevada; Cleveland Clinic, Lou Ruvo Center for Brain Health - Las Vegas (United States), (2) Suven Life Sciences - Hyderabad (India))*

Background: Neuropsychiatric symptoms (NPS) are core features of Alzheimer's disease (AD) and are distressing for patients and their caregivers. NPS are generally associated with risk and negative outcomes including early institutionalization. Apathy, depression, hallucinations, delusions, aggression, agitation, wandering and sundowning are hallmark behavioral and psychotic symptoms manifest in moderate-to-severe stages of the disease. Currently there are no FDA approved medications for the treatment of behavioral and psychotic symptoms. Masupirdine (SUVN-502) is a selective 5-hydroxytryptamine-6 (5-HT6) receptor antagonist being investigated for the treatment of moderate AD. Masupirdine added to background treatment with donepezil and memantine was evaluated in moderate AD subjects in a double-blind placebo controlled, randomized 26-week treatment phase-2 study. Behavioral outcomes were monitored with the Neuropsychiatric Inventory (NPI). **Objectives:** To evaluate the effect of masupirdine on Behavioral and Psychological Symptoms of Dementia (BPSD) in moderate AD patients. **Methods:** Masupirdine was studied in a phase-2, multicenter, randomized, double-blind, parallel group, 26-week, placebo-controlled proof-of-concept study in subjects with moderate AD, receiving stable doses of donepezil and memantine. A total of 564 participants were randomized. Participants received placebo or masupirdine (50 or 100 mg) with donepezil and memantine for 26 weeks. The efficacy and safety assessments included are the NPI-12 and C-SDD. The effects of masupirdine on BPSD were analyzed using MMRM. **Results:** Out of 564 randomized patients, 183 patients in the placebo group, 184 on 50 mg masupirdine and 176 on 100 mg masupirdine were included in the final analysis. The mean (SD) NPI baseline score was 9.9 (10.2) consistent with the other studies not enriched for the neuropsychiatric symptoms. Treatment groups with masupirdine achieved better outcomes than placebo in the NPI scores. Masupirdine showed statistically significant reduction in the NPI agitation/aggression scores in the modified intent to treat population. In the subgroup of population who had baseline agitation/aggression, masupirdine showed statistically significant reduction in the agitation/aggression scores with respect to placebo at the end of 26 weeks. The treatment difference was above the minimum clinically important difference (0.4 SD). Similar outcome was also observed in the subgroup of population who had severe baseline agitation/aggression score (treatment difference was above the minimum clinically important difference). The effect observed with masupirdine on aggression/agitation sustained for the entire study duration of 26 weeks. In addition, masupirdine showed better outcome in the delusions score with respect to placebo. Effect sizes on delusions score was estimated to be closer or more than 0.35 at the end of 26 weeks. **Conclusions:** Masupirdine is generally well tolerated. With regard to behavioral symptoms, masupirdine therapy compared with placebo, improved behavioral symptoms as measured by NPI scores, individual domains of agitation/aggression and delusions. Masupirdine may have a potential utility in the management of behavioral and psychotic symptoms in AD.

P039- PHASE 1 SINGLE ASCENDING DOSE STUDY OF THE MUSCARINIC POSITIVE ALLOSTERIC MODULATOR VU319. P. Newhouse, A. Conley, A. Key, J. Blackford, J. Rook, P.J. Conn, C. Lindsley, C. Jones *(Vanderbilt - Nashville (United States))*

Background: Background: M1 is the primary muscarinic acetylcholine receptor (mAChR) subtype involved in domains of cognitive function impaired in Alzheimer's disease. The failure of previous orthosteric and allosteric agonists of the M1 mAChRs has been the result of a lack of specificity, resulting in off target mAChR activation and dose-limiting adverse effects. In contrast we have focused on allosteric modulation of less highly conserved binding sites to avoid peripheral muscarinic activation. Our clinical lead compound VU319 appears to have robust M1-mediated effects on hippocampal synaptic plasticity, excitatory drive to the prefrontal cortex, and had positive effects on cognitive function in animal models. VU319 is an investigational new drug and has not been approved for any use by the US FDA. This presentation describes both the Phase 1 Single Ascending Dose (SAD) study, as well as a Food Effect (FE) substudy. **Objectives:** The main objectives of the SAD study were to assess the safety and tolerability of VU319 in healthy adults. The FE substudy objective was to examine whether the pharmacokinetics of VU319 changed when administered in a fed compared to a fasted state. An additional exploratory objective of both studies was to identify early markers of functional engagement which would offer information on how VU319 may enhance cognition in patient sample in future studies. **Method:** A double-blind Phase 1 human SAD tolerability and dose ranging study in both sexes (n = 40) was conducted. The SAD consisted of five cohorts of eight participants, in which six participants received oral VU319 and two participants received placebo. The FE substudy consisted of 12 participants, in which ten received oral VU319 and two received placebo. The five doses for the SAD study were 60, 120, 240, 400 and 600 mg. Participants in the FE substudy received VU319 at a single dose of 120 mg. For the five cohorts of the SAD study, all participants were dosed in a fasted stated. In contrast, all 12 participants in the Food Effect substudy completed were dosed twice; once fasted, and once following breakfast. All six cohorts combined typical safety and PK assessment with behavioral and brain-based measures that targeted cognitive processes and was sensitive to cholinergic drug effects including the effects of cholinergic stimulation on electrophysiologic measures of memory using event-related potentials (ERP). These tests of functional engagement were performed pre-dose and 5-7 hours post-dose. **Results:** The SAD and the FE studies showed good tolerability with no observed dose limiting side effects and no observed significant adverse events consistent with off target mAChR stimulation throughout the full range of the first five cohorts. PK evaluation showed

good oral absorption and bioavailability that is improved with food and a half-life consistent with once daily dosing. VU319 appears to induce effects consistent with the potentiation of M1 activity in the CNS by altering cortical ERP amplitudes to novel vs repeated stimuli and changes in cognitive performance at doses that do not seem to produce typical muscarinic side effects. **Conclusion:** Single dose VU319 across five ascending cohorts appeared to have a favorable safety profile, had a PK profile consistent with once daily dosing, and appeared to alter cognitive performance and brain activity at doses that do not appear to produce peripheral muscarinic side effects. Planned further studies include a multiple ascending dose study, and a Phase 2a POC study to assess VU319 effects on cognition and modulation of the functional integrity of cortical networks in MCI by assessing resting and task-based connectivity of the default mode and cognitive control networks. This will help in selecting measures for larger Phase 2 and 3 trials.

P040- REVERSAL OF ALZHEIMER'S MEMORY IMPAIRMENT BY TRANSCRANIAL ELECTROMAGNETIC TREATMENT: ASSOCIATED A-BETA AND TAU CHANGES IN CSF/BLOOD AND BRAIN IMAGING BENEFITS.

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Background: Recent studies indicate small aggregates (oligomers) of the toxic proteins Aβ and p-tau inside neurons as the primary cause of Alzheimer's Disease (AD). We have pioneered a new bioengineering technology (Transcranial Electromagnetic Treatment; TEMT) that penetrates neurons in the human forebrain globally. In human/mouse AD brains, TEMT disaggregates both Aβ and p-tau oligomers, apparently due to targeted destabilization of H-bonds between oligomer monomers through dipole-dipole interactions/vibration. In addition, TEMT also induces mitochondrial enhancement within neurons via Complex IV activation. These probable "disease-modifying" mechanisms of TEMT both prevented and reversed memory impairment in our AD transgenic mouse studies. **Objectives:** To evaluate the safety and initial clinical efficacy of TEMT against AD, a comprehensive clinical trial was performed in AD patients utilizing essentially the same TEMT parameters as in our pre-clinical studies. **Methods:** Eight mild/moderate AD patients were treated with TEMT in-home by their caregivers for two months in an open-label study, utilizing NeuroEM's first-in-class MemorEM head devices. The device provides full brain TEMT through a constellation of eight specialized emitters embedded within a head cap, with emitters activated sequential at 217 Hz/second. When active, any given emitter projects EMF (radiofrequency) waves into the brain at 915 MHz and 1.6 W/kg average power. The MemorEM allows for near complete mobility to do daily tasks during treatment. TEMT was given for two 1-hour periods each day (120 treatments total). At baseline, end-of-treatment (2M), and/or 2-weeks following treatment completion, a battery of cognitive tests was administered, as well as FDG-PET scans, anatomic/DTI MRI scans, and both CSF and blood samples taken. **Results:** No deleterious behavioral effects, discomfort, or physiologic changes resulted from 2M of TEMT, as well as no evidence of tumor or micro-hemorrhage induction. Two-months of daily TEMT resulted in clinically-important (effective size; ES) and statistically significant improvements in ADAS-cog13, as well in multiple measures of the Rey AVLT. With a single non-responder removed, ADAS-cog13 scores were improved overall by 4.1 points after 2-month of treatment compared to baseline (ES= 1.21; $p<0.02$), as was ADAS-cog13 immediate recall (ES=1.15; $p<0.025$). For all eight subjects collectively in the "5-trial recall" measure of Rey AVLT, TEMT induced a robust and clinically-important increase in word recall vs. baseline (ES=1.55; $p<0.005$). For some measures, significant cognitive benefits at completion of TEMT became even stronger during testing two-weeks thereafter. At this time point, the "percent forgetting" component of Rey AVLT showed patients having 50%+ less forgetting compared to baseline (ES=1.27; $p<0.01$) and digit forward length was increased appreciably by TEMT vs. baseline (ES=1.32; $p<0.01$). Parenthetically, all cognitive testing was done hours following in-home treatment, underscoring the daily extended nature of TEMT's cognitive benefits. Compared to baseline, 2-months of TEMT also produced increases in CSF levels of soluble/monomeric Aβ1-40 and Ab1-42, cognition-related changes in CSF oligomeric Aβ, decreases in CSF p-tau/Aβ1-42 and CSF t-tau/Aβ1-42 ratios, and reduced levels of oligomeric Aβ in plasma. All of these CSF/blood effects are consistent with a disaggregation of Aβ oligomers in the brain. Post-treatment FDG-PET brain scans revealed stable or enhanced (>6%) glucose utilization in at least 102 of 109 brain regions for seven of the eight subjects - several subjects exhibited visually-enhanced glucose utilization comparing pre- vs. post-treatment scans. Additionally, Diffusion Tensor Imaging (Fractional Anisotropy) provided evidence of region-specific increases in functional connectivity within the cingulate cortex/cingulum - a brain region critical for cognitive integration. Because of the enthusiasm of all patients to continue treatment after study completion, an "extension" study (4-months treatment) was initiated, with the non-treatment period between studies being 6-16 months. Interim results from this ongoing extension study have revealed stable and/or improved cognitive performance in patients wherein there was no more than an 8-month period between the initial and extension studies. Conclusion: This is the first clinical study to administer electromagnetic (radiofrequency) waves to the entire human brain, and over an extended two-month period involving 120 in-home treatments. TEMT administration to AD subjects appears to be safe, while providing clinically-important cognitive improvement, beneficial changes to AD markers, and enhanced brain functionality. Although a controlled pivotal trial is needed to confirm the actions of TEMT against AD, these results suggest that TEMT can stabilize and reverse AD cognitive impairment. As such, TEMT may be an entirely new bioengineered intervention against AD - an intervention that appears to be "disease-modifying», non-invasive without side effects, and easily administered in-home.

P041- A 48-WEEK, OBSERVATIONAL, LONGITUDINAL MULTICENTER STUDY ON THE EFFECTIVENESS OF 9.5 MG/24 H (10 CM2) RIVASTIGMINE IN PATIENTS WITH MILD TO MODERATE DEMENTIA OF THE ALZHEIMER'S TYPE. Chang Chiung-Chih[1], Chan Lung[2], Chou Hsi-Hsien[3], Yang Yu-Wan[4], Chen Ta-Fu[5], Chen Ting-Bin[6], Chen Chin-I[7], Hu Chaur-Jong[8] *((1) Kaohsiung Chang Gung Memorial Hospital, (2) Taipei Medical University-Shung Ho Hospital, (3) Chung Shan Medical University Hospital, (4) China Medical University Hospital, (5) National Taiwan University Hospital, (6) Taichung Veteran's General Hospital, (7) Wan Fan Hospital, (8) Taipei Medical University-Shung Ho Hospital)*

Background: Rivastigmine patch 9.5 mg/24 h(10 cm2) was approved in 2013 in Taiwan, yet its real-world treatment efficacy in Alzheimer's disease (AD) patients is stillunclear or limited. Thus, the current study aimed to provide additional data to investigate the effectiveness of rivastigmine patch 10 cm2in real-worldsetting. **Objectives:** The objective of the study was to evaluate the effectiveness of rivastigmine patch in the management of cognitive and global functionsin patients with AD in a real-world clinical setting. **Methods:** Investigators were asked to enroll patients initiating rivastigmine patch 10 cm2 treatment based on the physician's judgment and the drug label. The primary endpoint was to observe the changes in the Cognitive Assessment Screening Instrument (CASI) scores at week 48 versus baseline. The change from baseline in Clinical Dementia Rating (CDR), treatment persistence and safety profile were also observed. **Results:** A total of 285 subjects were enrolled from 7 sites. Of the 285 subjects, 63.5% of patients titrated from rivastigmine patch 5 cm2, and the rest were switched/titrated from various doses of rivastigmine capsule. Among the total population, 216(75.8%) subjects completed the study (patients were not considered as dropped out if they switched to another form/dose of rivastigmine after rivastigmine patch 10 cm2) and 180(63.2%) subjects remained on rivastigmine patch 10 cm2for 48 weeks. The majority (89.1%) of the patients wasmild in severity (CDR 0.5 or 1) at baseline. CASI had a 2.1 point reduction from baseline (64.1 to 62.5) in the overall population. The majority of the subjects (81.8%) had no change or improved in stage in CDR score at week 48. The most common drug related adverse events (AE)were pruritus (11.2%), nausea (3.5%), rash (3.2%) and vomiting (2.8%). Forty-eight (16.8%) patients discontinued rivastigmine patch 10 due to AE, and was most commonly (>2%) caused by pruritus (4.9%) and rash (2.1%). **Conclusion:** The results of this multicenter, open-label study demonstrate that the use of rivastigmine patch 10 cm2in a real-world setting provides clinical benefit in patients with AD across the spectrum of mild to moderate dementia. Rivastigmine patch 10 cm2enables patients to maintain a stable cognitive statusand prevent them from the progression of AD over 48 weeks of treatment. The application of patch formulation also provided acceptable drug persistence. Thus, rivastigmine patch 10 cm2represents an efficacious, tolerable, and convenient treatment option for the management of mild-to-moderate AD in Taiwan.

P042- TAU AGGREGATION INHIBITOR DOSE-SELECTION FOR FURTHER PHASE 3 TRIAL DETERMINED FROM POPULATION PHARMACOKINETIC ANALYSIS IN COMPLETED STUDIES SHOWING EXPOSURE-DEPENDENT ACTIVITY OF HYDROMETHYLTHIONINE ON COGNITIVE DECLINE AND BRAIN ATROPHY IN MILD-MODERATE ALZHEIMER'S DISEASE. C. Wischik[1,2], S. Gauthier[3] *((1) TauRx Therapeutics Ltd - Aberdeen (United Kingdom), (2) University of Aberdeen - Aberdeen (United Kingdom), 3McGill Centre for Studies in Aging - Montreal (Canada))*

Background: There is increasing interest in disease modifying approaches to Alzheimer's disease (AD) targeting pathological aggregation of tau protein. The only completed tau-based Phase 3 trials to date tested the small molecule protein aggregation inhibitor hydromethylthionine. One interpretation of the lack of dose-response comparing a low dose of 8 mg/day (assumed to be inactive) and higher doses (150 – 250 mg/day) in the completed trials is that hydromethylthionine is not pharmacologically active. However, hydromethylthionine is a potent inhibitor of tau aggregation in vitro with activity at a tau:hydromethylthionine molar ratio of 1:0.1. It reverses tau aggregation pathology and associated behavioural deficits in tau transgenic mouse models, increasing acetylcholine levels in hippocampus, reversing impairment of glutamate release from brain synaptosomal preparations, increasing synaptic proteins of the SNARE complex and increasing mitochondrial Complex IV activity. An oxidised variant (methylthioninium chloride, MTC) was found to reduce cognitive decline and impairment on functional neuroimaging outcomes at a dose of 138 mg/day in a dose-finding Phase 2 trial in mild-moderate AD. The MTC findings provided the rationale for dose-selection in the completed hydromethylthionine trials since total methylthioninium levels in blood were similar. A new assay for plasma has been developed which discriminates between the active form of the drug and the predominant inactive conjugate. A preclinical study in minipig using this assay revealed that plasma levels are 3-fold higher and the brain:plasma ratio is 20-fold higher for hydromethylthionine compared with MTC. These findings raise the possibility that an alternative explanation for the lack of dose-response in the completed hydromethylthionine trials is that the 8 mg/day dose of hydromethylthionine is pharmacologically active, that higher doses provide no additional benefit, and that the MTC results provided an inappropriate basis for dose-selection using hydromethylthionine. **Objectives:** We undertook a population pharmacokinetic and pharmacokinetic-pharmacodynamic study in patients participating in the completed hydromethylthionine Phase 3 trials to determine whether there is an exposure-response relationship at the 8 mg/day dose, and if so to use this as a more appropriate basis for dose-selection in a further trial. **Methods:** A two-compartment pharmacokinetic (PK) model was first constructed and qualified from subjects enrolled in Phase 1 studies using the discriminatory plasma assay. This was applied post hoc to first-dose plasma concentration data obtained from 1,162 of 1,686 patients participating in the completed trials for whom plasma concentration and efficacy outcome data at 65 weeks were available. The validated lower limit of quantification of the assay was 0.20 ng/mL, corresponding to an estimated steady state peak plasma concentration of 0.37 ng/ml. Concentrations below these levels were imputed by extrapolation below the validated calibration standards. **Results:** There is a steep exposure-response relationship for

cognitive decline and brain atrophy outcomes over 65 weeks at peak steady-state plasma levels in the range 0.3 – 0.8 ng/ml in patients receiving the 8 mg/day dose, with 0.29 ng/ml as the apparent zero-effect level. Patients with plasma levels below 0.2 ng/ml following their first dose provided a basis for defining a group of 193 patients with minimal drug exposure at the 8 mg/day dose. Compared with these, the 373 patients with higher plasma levels at the same dose had less cognitive decline (-3.41 ± 0.76 ADAS-cog units [mean ± SEM], $p < 0.0001$) and less whole brain volume loss (-4.39 ± 1.18 cm3, $p < 0.0001$) over 65 weeks. Although patients receiving hydromethylthionine alone or in combination with standard symptomatic treatments for AD had similar exposure-response profiles, the maximum predicted activity was reduced by half in the add-on group. There was an implied response plateau in the range 0.9 – 4.1 ng/ml in both groups (corresponding to theoretical doses of 16 – 80 mg/day), and plasma concentrations in the range 4 – 21 ng/ml (produced by the 150-250 mg/day doses) were not associated with additional benefit. The main determinant of drug exposure at the 8 mg/day dose was found to be creatinine clearance, consistent with urinary excretion as the known main elimination route. **Conclusions:** Hydromethylthionine has exposure-dependent pharmacological activity on brain structure and function at peak steady state plasma concentrations in the range 0.4 – 0.8 ng/ml in the majority of patients receiving the 8 mg/day dose. These results are consistent with the substantial difference in brain bioavailability of hydromethylthionine compared with MTC. Hydromethylthionine retains exposure-dependent pharmacological activity when added to symptomatic treatments, but at a reduced level, consistent with similar results in tau transgenic mice showing that chronic pretreatment with symptomatic drugs reduces multiple hydromethylthionine effects in the brain. The minimum dose required for all patients to have therapeutic exposure irrespective of renal function is 16 mg/day. A confirmatory Phase 3 trial in mild-moderate AD is now ongoing in US, Canada and EU comparing hydromethylthionine at 16 mg/day against placebo.

P043- ALZHEIMER'S DISEASE DRUG DEVELOPMENT PIPELINE 2019. A. Ritter, K. Zhong, G. Lee, J. Cummings, M. Sabbagh *(Cleveland Clinic - Las Vegas (United States))*

Background: Background: Alzheimer's disease (AD) has few symptomatic treatments and no disease modifying therapies. Failure rates have been unacceptably high over the past 20 years. Analyzing the current drug development pipeline can provide insights into the evolution of drug development and can inform best practices regarding optimizing development practices. **Objectives:** To survey the current AD drug development pipeline to understand trends in the field and compare to last year's pipeline. **Methods:** We queried Clinicaltrials.gov collecting data on all trials of AD agents in Phase 1, 2, and 3, using a lock date of February 12, 2019. We collected data on trial title, beginning date, duration, subjects needed, biomarkers, and sponsorship. **Results:** There are 132 agents in clinical trials for the treatment of AD. Twenty-eight are in 42 Phase 3 trials, 74 agents are in 83 Phase 2 trials, and 30 agents are in 31 Phase 1 trials. This represents an increase in the number of agents in each Phase compared to last year. Agents that target amyloid are the most common mechanism of action (40%) while 18% of agents target tau. There is a trend in the field toward testing agents in earlier populations and several trials have adopted new trial designs. **Discussion:** The AD drug development pipeline continues to evolve. There are more agents in the pipeline from previous years and new approaches to drug development have been implemented. Several recent high profile failures of anti-amyloid therapies will likely have a lasting impact on future drug development programs and may lead to a greater diversity in agents selected for development. There continues to be an urgent need to recruit large numbers of participants for AD trials as well as a need for new and more sophisticated biomarkers/clinical trial designs.

P044- ALLOPREGNANOLONE SHOWS SIGNIFICANT EFFECT ON THE LIPID PATHWAYS FROM PLASMA METABOLOMIC ANALYSIS OF ALZHEIMER'S CLINICAL TRIAL. Y. Shang[1], G. Hernandez[1], C. Lopez[1], F. Yin[1], L. Schneide[2], R. Brinton[1] *((1) the University of Arizona - Tucson (United States), (2) University of Southern California - Los Angeles (United States))*

Background: Age, apolipoprotein E ε4 (APOE4) and chromosomal sex are top risk factors for Late-Onset Alzheimer's disease (LOAD). We previously demonstrated that Allopregnanolone (Allo), a naturally occurring brain steroid, could stimulate neurogenesis, oligodendrogenesis, white matter generation, and cholesterol homeostasis while simultaneously reducing β-amyloid and neuroinflammatory burden in Alzheimer's animal models. For human studies, plasma is an easily accessible biofluid suitable for recurrent measures. Multiple studies of the metabolites in the plasma of AD patients has established metabolic changes of the disease progression. **Objectives:** The present study investigated metabolomic, lipidomic and pathway-centric bioinformatics in women and men APOE 3/3 and 3/4 carriers diagnosed with LOAD before and after Allo treatment. **Methods:** Phase 1 (NCT02221622) randomized double-blind, placebo-controlled, multiple ascending dose clinical trial was conducted in participants with mild cognitive impairment due to AD or mild AD. Participants were age ≥ 55 years, MMSE score ≥ 20 and clinical dementia rating of 0.5-1. Plasma samples were analyzed by Metabolon, MetaboAnalyst and R. **Results:** PCA analysis indicated separation between females and males in metabolomic profiles at baseline. Sex differences were apparent in triglyceride species. Female APOE4 carriers had significantly higher TAG-B compared to APOE3 carriers whereas male APOE4 carriers exhibited lower TAG-B. PCA indicated a uni-directional shift between baseline and end of study. Allo treated participants exhibited less of a shift compared to placebo, which is consistent with a delay in dysregulation. Pathway-based analysis indicated that Allo significantly impacted amino acid and lipid related metabolic pathways. Allo treatment increased amino acid metabolites which was most evident in males. In APOE3 carriers, Allo reversed the trend of TAG-B accumulation in the plasma whereas in APOE4 carriers, Allo treatment resulted in significant higher levels of select fatty acids. **Conclusion:** These exploratory findings from an early stage clinical trial of Allo suggest the potential of sex and APOE genotype specific outcomes on metabolic and lipid pathways following Allo treatment. Further analyses to confirm and extend these findings are underway. **Acknowledgements:** This work was supported by National Institute on Aging U01AG031115, U01AG047222, UF1AG046148, R01AG057931, P01AG026572, and Alzheimer's Association SAGA-17-419459 to RDB. **Keyword:** APOE, lipid, metabolism.

P045- ASSOCIATION BETWEEN A CHOLINESTERASE INHIBITOR AND CHOLINE ALPHOSCERATE IN ALZHEIMER'S DISEASE: THE RESULTS AT THE END OF THE TRIAL. F. Amenta[1], A. Carotenuto[1,2], A. Fasanaro[2], V. Manzo[2], E. Traini[3] *((1) Clinical Research, Telemedicine and Telepharmacy Centre, University of Camerino, - Camerino (Italy), (2) Neurology Unit, National Hospital, "A. Cardarelli", - Naples (Italy), (3) Clinical Research, Telemedicine and Telepharmacy Centre, University of Camerino - Camerino (Italy))*

Background: Cholinesterase inhibitors (ChE-Is) are used for symptomatic treatment of mild-to-moderate Alzheimer's disease (AD), but long-term effects of these compounds are mild and not always obvious. Preclinical studies have shown that combination of ChE-Is and the cholinergic precursor choline alphoscerate increases brain acetylcholine levels more effectively than single compounds alone. **Objective:** ASCOMALVA (Effect of association between a ChE-I and choline alphoscerate on cognitive deficits in AD associated with cerebrovascular injury) is a double-blind trial investigating if treatment with the ChE-I donepezil and choline alphoscerate in combination are more effective that donepezil alone. **Methods:** The trial lasting 4 years has recruited 210 AD patients with associated ischemic brain damage documented by neuroimaging. Patients were randomly assigned to an active treatment group [donepezil (10 mg/day) + choline alphoscerate (1,200 mg/day)] or to a reference group [donepezil (10 mg/day) + placebo]. 102 patients (48.6 %) have completed 4 years of observation. Cognitive functions were assessed by the Mini-Mental State Evaluation and Alzheimer's Disease Assessment Scale Cognitive subscale. Daily activity was evaluated by the basic and instrumental activities of daily living tests. Behavioral symptoms were assessed by the Neuropsychiatric Inventory. **Results:** After 4 years of observation, patients of the reference group showed a time-dependent worsening in all the parameters investigated. Treatment with donepezil plus choline alphoscerate significantly slowed changes of the different items analyzed. **Conclusions:** These findings suggest that the combination of choline alphoscerate with a ChE-I may prolong/increase the effectiveness of cholinergic therapies in AD with concomitant ischemic cerebrovascular injury.

P046- AMYLOID POSITIVE SUBJECT CHARACTERISTICS IN THE ELENBECESTAT MISSIONAD PHASE 3 PROGRAM. C. Roberts[1], M. Kanekiyo[2], J. Kaplow[2], B. Albala[2] *((1) Eisai Ltd - Hatfield (United Kingdom), (2) Eisai Inc - Woodcliff Lake (United States))*

Background: Eisai's elenbecestat is currently being investigated in two Phase 3 studies, collectively known as MissionAD, in early Alzheimer's disease (AD). These studies have screened a cohort of more than 8,000 subjects, establishing eligibility through cognitive assessments, laboratory assessments, MRI safety and amyloid status. **Objectives:** The objective of this presentation is to compare the characteristics of amyloid positive versus amyloid negative subjects in this large cohort of subjects from MissionAD. **Method:** The screening process was performed in 5 sequential tiers over a maximum of 80 days, of which amyloid status was determined in those subjects that reached tier 5. Cognitive assessments, medical history and clinical diagnosis were determined in tier 1. Questionnaires were administered in tier 2 to establish baseline quality of life and to assess any suicidality risk. Laboratory assessments, including APOE4 status, were conducted in tier 3. A MRI scan was done at tier 4 and finally an amyloid PET scan or a CSF sample was taken to determine amyloid status in tier 5. The subjects were categorized into amyloid positive and negative groups and age, gender, disease staging, country, and APOE4 status evaluated based on a data cut of 06Dec2018. **Results**: 2707 subjects screened in MissionAD reached tier 5 of the screening cascade and had a known amyloid status. All of these subjects had a measurable cognitive deficit with a MMSE score ≥24, CDR Global score of 0.5, and a cognitive impairment of ≥1 standard deviation from age-adjusted norms in the International Shopping List Task, as required for study eligibility. 1486 (55%) out of the 2707 subjects were amyloid positive and 1221 (45%) amyloid negative. The mean age and gender distribution was similar in both amyloid positive and negative cohorts. The mean age was 72 years (range 50-85) for amyloid positive and 69 years (range 50-85) for amyloid negative subjects. 51% of the amyloid positive cohort and 53% of the amyloid negative cohort were female. Frequency of Mild Cognitive Impaired (MCI) compared to early mild AD dementia tended to be higher in the amyloid negative cohort. Among amyloid negative subjects, 89% were MCI and 9% early mild AD. In amyloid positive subjects, 83% were MCI and 16% early mild AD. In contrast, the frequency of APOE4 positive subjects was greater in the amyloid positive cohort (65%) compared to the amyloid negative group (21%). **Conclusion:** In this large cohort of cognitively impaired subjects, roughly half were amyloid positive when assessed at the end of the screening cascade. Demographics were comparable regardless of amyloid status. However frequency of MCI was greater in the amyloid negative cohort while the frequency of APOE4 positive subjects was greater in amyloid positive subjects. This data confirms that APOE4 positivity is a high risk factor of amyloid burden in the early AD population.

P047- CONCENTRATION-DEPENDENT REDUCTION IN CLINICAL DECLINE AND BRAIN ATROPHY IN A PHASE 3 TRIAL OF LEUCO-METHYLTHIONINIUM BIS(HYDROMETHANESULPHONATE) (LMTM) IN BEHAVIOURAL VARIANT FRONTOTEMPORAL DEMENTIA. C.M. Kipps[1], H.C. Shiells[2], B.O. Schelter[2,3], S. Gauthier[4], C.M. Wischik[2,3] *((1) University Hospital - Southampton (United Kingdom), (2) TauRx Therapeutics Ltd - Aberdeen (United Kingdom), (3) University of Aberdeen - Aberdeen (United Kingdom), (4) McGill Centre for Studies in Aging - Montreal (Canada))*

Background: LMTM (hydromethylthionine) is a potent inhibitor of aggregation of Tau and TDP-43, proteins which are responsible for neurodegeneration in the majority of patients with behavioural variant frontotemporal dementia (bvFTD). Population pharmacokinetic (PK) analyses in two AD trials of LMTM showed consistent concentration-response relationships between plasma levels of the drug and treatment effects on clinical outcomes and magnetic resonance imaging (MRI) measures of atrophy at the 8 mg/day dose and an inverse concentration-response at high doses in the range 150 – 250 mg/day. **Objectives:** The initial objectives were to determine whether LMTM is effective and safe in bvFTD in a Phase 3, randomised, controlled, double-blind, parallel-group trial designed to compare LMTM doses of 200 and 8 mg/day. A population PK analysis was also undertaken to determine whether the concentration-response relationships were similar

in bvFTD to those seen in AD. **Methods:** We undertook a 52-week Phase 3 study in 220 patients with bvFTD randomised to compare LMTM doses of 200 and 8 mg/day (100 mg bid and 4 mg bid respectively), assuming that the lower dose was inactive and could be used as a mask for urinary discoloration. The trial was conducted at 70 sites in Canada, United States, Australia, Asia and Europe. Eligible patients had to be younger than 80 years of age with a diagnosis of probable bvFTD according to the International Consensus Criteria for bvFTD, with MMSE score greater than or equal to 20 at screening and having definite evidence of brain atrophy in frontal and/or temporal lobes on the baseline MRI scan. The primary outcomes were change on the Addenbrookes Cognitive Examination – Revised (ACE-R) and the Functional Activities Questionnaire (FAQ) or whole brain volume (WBV) with a Bonferroni-Holm correction. A population pharmacokinetic (PK) model, validated in Phase 1 studies, was applied post hoc to plasma concentration data available from 176 of the patients to determine exposure-dependence of treatment effects. Blood samples for assessment of drug levels were collected from each patient on the first treatment visit (two samples: pre-dose and approximately 3.5 hours after the dose) and at each subsequent on-treatment visit. Drug levels in plasma were measured blind to treatment using liquid chromatography-tandem mass spectrometry assay. The method was validated for use in the Phase 3 studies over the range of 0.2 to 10 ng/mL. Extrapolated concentration values were available below the lower limit of quantitation (but above the lower limit of detection) in approximately 35% of the Day 1 patients randomised to the 8 mg/day dose. The group with minimal exposure to the drug was used as a proxy for placebo for statistical comparisons of concentration-dependent treatment effects. Model development and pharmacodynamic analyses were undertaken independent of the sponsor by the Institute of Clinical Pharmacodynamics (ICPD, NY). Statistical parametric mapping of baseline scans was used to compare patients at baseline with a parallel study in mild AD. **Results:** Patients in this study had significantly more atrophy in frontal cortex and anterior temporal cortex, and significantly less atrophy in hippocampus, middle temporal gyrus, cuneus and insula compared with mild AD patients. As randomised, there were no significant differences between the two doses tested on any of the primary or secondary outcomes. However, the population PK analysis revealed consistent concentration-response relationships for all outcomes. Compared against the 35% of patients with plasma levels below the validated limit of quantitation of the assay on Day 1 (steady state plasma levels below 0.346 ng/ml), the treatment differences for patients with therapeutic levels at the 8 mg/day dose were 5.1 units ($p = 0.0536$, 45% reduction) on the ACE-R scale, -3.3 units ($p = 0.0131$, 46% reduction) on the FAQ scale, and 11.7 cm3 ($p = 0.0006$, 42% reduction) in whole brain atrophy. Outcomes were worse at 200 mg/day, consistent with a biphasic concentration-response profile. Decline on the ACE-R and FAQ scales in patients with subtherapeutic exposure was comparable to historical studies. The withdrawal rate over 12 months was lower at 8 mg/day (15%) than at 200 mg/day (38%). **Conclusions:** The treatment effects of LMTM in bvFTD may be determined by plasma concentration. The minimum effective dose is 8 mg/day for most patients and doses in the range 20 – 40 mg/day are predicted to provide maximal benefit. LMTM has an acceptable safety profile and is well tolerated. The results are essentially identical to those obtained in the AD studies conducted in parallel, implying that shared underlying protein aggregation pathophysiology can be modified in both diseases by LMTM. Although these post hoc results come from non-randomised population PK analyses, they support the potential use of LMTM for treatment of bvFTD. A further placebo-controlled study is now planned to confirm the efficacy of LMTM at a dose of 20 mg/day.

P048- REDUCTION OF CLINICAL DECLINE AND BRAIN ATROPHY IN MILD TO MODERATE ALZHEIMER'S DISEASE IS CONCENTRATION-DEPENDENT FOR LEUCO-METHYLTHIONINIUM BIS(HYDROMETHANESULPHONATE) (LMTM) AS MONOTHERAPY AND AS ADD-ON THERAPY IN TWO PHASE 3 CLINICAL TRIALS. B.O. Schelter[1,2], H.C. Shiells[1], S. Gauthier[3], C.M. Rubino[4], C.M. Wischik[1,2] *((1) TauRx Therapeutics Ltd - Aberdeen (United Kingdom), (2) University of Aberdeen - Aberdeen (United Kingdom), (3) McGill Centre for Studies in Aging - Montréal (Canada), (4) Institute of Clinical Pharmacodynamics - Schenectady (United States))*

Background: LMTM (hydromethylthionine) is a potent tau aggregation inhibitor. We have previously reported that there was no overall difference in any outcome comparing doses in the range 150-250mg/day with 8mg/day in two Phase 3 trials in mild to moderate Alzheimer's disease (AD). However, in non-randomised cohort comparisons undertaken as modified primary analyses in the second trial, there were significant differences between patients receiving LMTM as monotherapy and those receiving LMTM as add-on to approved symptomatic treatments for AD (acetylcholine-esterase inhibitors (AChEI) and/or memantine) on all clinical and magnetic resonance imaging (MRI) endpoints. We have also reported recently that many of the treatment effects of LMTM are attenuated or eliminated entirely when it is administered to tau transgenic mice receiving chronic pretreatment with either an AChEI or memantine, although effects on tau aggregation persist. This suggests that symptomatic treatments interfere with a range of responses to LMTM which result from reduction in the tau oligomer load in the brain. Therefore, differences seen clinically may be due to differences in neuropharmacological response to drug rather than to cohort differences between patients receiving or not receiving symptomatic treatments at trial entry. **Objectives:** In order to determine whether treatment response to LMTM is determined by drug exposure, and whether the treatment effects differ according to co-medication status with symptomatic treatments in patients with similar plasma levels of drug, we undertook a population pharmacokinetic (PK) analysis in patients participating in either of the two Phase 3 trials in AD with available data. **Methods:** A two-compartment PK model was first validated in Phase 1 studies across a range of doses of LMTM and in elderly volunteers in a repeat-dose study. This was applied post hoc to plasma concentration data obtained from 1,296 of the patients participating in either of the two Phase 3 studies in AD. Blood samples for assessment of parent methylthionine (MT), N-desmethyl MT and total MT (sum of parent MT and a labile LMT conjugate), were collected from each patient on the first treatment visit (two samples: pre-dose and approximately 3.5 hours after the dose) and at each subsequent on-treatment visit. MT levels in plasma were measured blind to treatment using liquid chromatography-tandem mass spectrometry assay. The method was validated for use in the Phase 3 studies over the range of 0.2 to 10 ng/mL. Extrapolated MT concentrations were available below

the lower limit of quantitation (but above the lower limit of detection) in approximately 35% of the Day 1 patients randomised to the 8 mg/day dose. The group with minimal exposure to the drug was used as a proxy for placebo for statistical comparisons of concentration-dependent treatment effects. Model development and pharmacodynamic analyses were undertaken independent of the sponsor by the Institute of Clinical Pharmacodynamics (ICPD, NY). **Results:** Plasma concentration determines treatment effects on cognitive decline and brain atrophy measured by MRI at the 8 mg/day dose, with significantly better outcomes for patients with plasma levels within the validated assay range on Day 1 (steady state levels above a 0.373 ng/ml threshold) than those with subthreshold levels, both as monotherapy and as add-on therapy. The concentration-dependent treatment difference at this dose in patients receiving LMTM as monotherapy was -2.60 (CI -4.88 –– -0.33, p=0.0251) units on the ADAS-cog11 scale and -1.73 (-2.33 –– -0.58, p=0.0011) cm3 reduction in expansion of lateral ventricular volume (LVV). In patients receiving LMTM in combination with AChEI and/or memantine the differences were -3.52 (CI -5.05 –– -2,00, p<0.0001) units on the ADAS-cog11 scale and -1.35 (CI -2.08 –– -0.62, p=0.0003) cm3 on LVV expansion. A standard concentration-response analysis (using the Hill equation) produced robust fits to the data for both monotherapy and add-on therapy, consistent with a lower concentration limit for treatment being 0.29 ng/ml in both groups. The estimated maximum treatment effect for LMTM as add-on therapy is about half that for monotherapy. The inhibitory effect of symptomatic treatments is not competitive and hence cannot be overcome by increasing the dose. Indeed treatment responses are generally worse at high doses than in patients with plasma levels in the therapeutic range at the 8 mg/day dose, consistent with a biphasic concentration-response. *Conclusions:* Treatment effects of LMTM are determined by plasma concentration of the drug both as monotherapy and as add-on to approved symptomatic treatments for AD. The principal determinant of plasma concentration at a given dose is renal function, consistent with 70% of excretion known to be via the urine. Given the observed population variability in plasma levels, it possible to predict that a dose of at least 16 mg/day is required for all patients to have exposure in the therapeutic range. A placebo-controlled study is currently ongoing to confirm the efficacy of LMTM at 8 and 16 mg/day in mild to moderate AD.

P049- THE ANTI-AMYLOID TREATMENT IN ASYMPTOMATIC ALZHEIMER'S DISEASE (A4) STUDY IN JAPAN: REPORT OF SCREENING DATA RESULTS. T. Iwatsubo[1], K. Suzuki[1], R. Ihara[1], C. Sakanaka[1], Y. Umeda-Kameyama [1], S. Ishii[1], K. Kirihara[1], A. Iwata[1], C.K. Sun[2], M. Donohue[2], P. Aisen [2], R. Sperling[3] *((1) The University of Tokyo Hospital - Tokyo (Japan), (2) Alzheimer's Therapeutic Research Institute - San Diego (United States), (3) Brigham and Women's Hospital - Boston (United States))*

Background: The Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) Study is a phase 3 randomized, double-blind, placebo-controlled secondary prevention trial of solanezumab vs. placebo in clinically normal older individuals with evidence of elevated amyloid-β on screening PET being conducted at 67 sites in the U.S., Canada, Australia and Japan. **Objectives:** To report and analyze the screening data results of A4 study conducted at the University of Tokyo Hospital as the single participating site from Japan. **Methods:** Clinically normal Japanese elderly individuals (age 65-85 y) were screened for cognitive and functional status using the inclusion criteria of CDR 0, MMSE 25-30 and logical memory delayed recall 6-18, as well as medical conditions, and eligible participants underwent 18F-florbetapir-PET imaging. Demographics, APOE genotype, cognitive testing results of Preclinical Alzheimer Cognitive Composite (PACC) and report of Cognitive Function Index (CFI) obtained at the screening visit were compared between the amyloid-elevated (Aβ+) and amyloid-not elevated (Aβ-) individuals, as well as the Japanese and total participants. Fisher's Exact test and t Test/ANOVA with unequal variances for two/three groups were used for the statistical analysis of categorical and continuous variables, respectively, using nominal p-values. **Results:** 161 volunteers were screened at the University of Tokyo Hospital site between Sep 2016 and Dec 2017, 100 underwent 18F-florbetapir-amyloid PET, and 20 were characterized as Aβ+ and 80 were Aβ-. The age at consent (mean: 75.5 y in Aβ+, 71.4 y in Aβ-, p=0.0026) and APOE4 positivity (45% in Aβ+, 18% in Aβ-, p=0.016) were significantly higher in Aβ+ than in Aβ-, whereas no significant differences were found in education, sex and family history. Single-point PACC at screening showed a trend of worsening in Aβ+ (mean: -1.06) compared with Aβ- (mean: -0.10; p=0.15). CFI-Participant (Pt) was significantly higher in Aβ+ (mean: 4.14) than in Aβ- (mean: 3.10; p=0.042), whereas CFI-Study Partner (SP) was not significantly different (1.79 vs 1.51; p=0.50), and the total CFI showed a trend of increase in Aβ+ (5.93 vs. 4.61, p=0.068). The percentage of individuals with CFI-Pt >2 was significantly higher in Aβ+ (90%) than in Aβ- (64%; p=0.029). These results were consistent with those from the cohort of all sites including North America and Australia. **Conclusion:** The present results showed that the Aβ+ cognitively normal individuals performed less well on PACC and reported higher concerns about recent changes in cognitive function on CFI in the Japanese population, similarly to the western countries, and demonstrated the feasibility of enrolling the preclinical AD population for prevention trials in Japan, using similar procedures to those established by the A4 Study.

P050- EFFECT OF INTENSIVE COGNITIVE INTERVENTION IN MID ALZHEIMER'S DISEASE: A PILOT STUDY. S.H. Joo, C.U. Lee, D.W. Kang *(Seoul St. Mary's hospital - Seoul (Korea, Republic of))*

Background: Increasing number of studies suggested that cognitive intervention is beneficial in treatment of patients with Alzheimer's disease. However, the effect of frequency and intensity of cognitive intervention on cognitive function has not been proven. We hypothesized that the people who participate in cognitive intervention intensively every day will experience slower cognitive decline compared to those who do not. **Objectives:** To determine whether intensive cognitive intervention can slowing down cognitive decline for people with mild Alzheimer's disease. **Methods:** This is community setting study. Forty mild Alzheimer's disease patients entered the study for 6 months. All participants were taking more than one acetylcholine esterase inhibitor. We compared three groups: intensive cognitive intervention group (n=14), usual cognitive intervention group (n=16), and non-cognitive intervention group (n=10). Our cognitive intervention includes group programs consisting of memory training, computerized cognitive training, recreational activities (games, crafts, and

learning to play musical instruments), and physical training implemented by trained therapist in the Seocho Center for Dementia in Soeul, Republic of Korea. Participants in intensive cognitive group attended five times a week for three hours on scheduled programs during the week. Participants in unsual cognitive intervention group attended an hour twice a week in the programs. Participants in the non-cognitive intervention group did not participate in any cognitive intervention program. Each participant underwent a detailed clinical interview and standardized neuropsychological battery, namely the Korean version of the Consortium to Establish a Registry for Alzheimer's disease (CERAD-K) at baseline, and 6 months. **Results:** At 6 months, we observed improvement usual cognitive intervention group (47.8±48.1) and intensive cognitive intervention group (49.3±52.0) in CERAD-K total score. The score improved more in intensive cognitive intervention group compare to usual cognitive intervention group. However, the score declined in the non-cognitive intervention group 6 month later (48.2±45.0). **Conclusion:** Engaging in the intensive cognitive intervention may be more beneficial in slowing down cognitive decline in early stage dementia than participating in the usual cognitive intervention or not participating any cognitive intervention.

P051- IS AMYLOID STILL A VALID TARGET FOR AD DRUG DEVELOPMENT? A META-ANALYSIS OF SOLANEZUMAB MILD AD DEMENTIA STUDIES. K. Holdridge, R. Yaari, S. Andersen, J. Sims *(Eli Lilly and Company - Indianapolis (United States))*

Background: Solanezumab is a monoclonal antibody that binds to the mid-domain of soluble amyloid-β (Aβ) and is in development for the treatment of Alzheimer's disease (AD). Three Phase 3 clinical studies in patients with AD dementia were completed at the 400-mg every-4-week dose. EXPEDITION (NCT00905372) and EXPEDITION2 (NCT00904683) were completed in 2012 in mild to moderate AD dementia, and EXPEDITION3 (NCT01900665) was completed in 2017 in mild AD dementia patients who were amyloid positive. None of the studies met its primary endpoint. A meta-analysis of the mild AD dementia populations from all 3 EXPEDITION studies are described herein. **Objectives:** Evaluate the effect of solanezumab on the progression of cognition and function in a mild AD dementia study population from the EXPEDITION studies. **Methods:** The EXPEDITION studies were double-blind, placebo-controlled, Phase 3, global studies. The analysis population for this meta-analysis comprises patients ≥55 years of age with mild AD, defined as a Mini Mental-State Evaluation (MMSE) score of 20 through 26. Additionally, EXPEDITION3 patients had confirmed amyloid pathology based on F18 florbetapir positron emission tomography (PET) or cerebrospinal fluid (CSF) Aβ1-42. Patients were randomized to 400 mg solanezumab or placebo administered intravenously every 4 weeks for 80 weeks. The 14-item Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog14) and the Alzheimer's Disease Cooperative Study Activities of Daily Living inventory, instrumental items (ADCS-iADL) were collected approximately every 3 months, and the MMSE was collected approximately every 6 months. Mixed-model repeated-measures (MMRM) analyses included independent variables for study, baseline age, baseline use of symptomatic medications, and baseline scale results. Additionally, the European Prevention of Alzheimer's Dementia Consortium (EPAD) Bayesian longitudinal model was fit. The EPAD model includes a subject-specific random effect and assumes a constant rate of percent slowing of disease progression relative to placebo by the active treatment over time. **Results:** Results of MMRM analyses and summaries of the posterior distributions of the disease rate ratio from the Bayesian longitudinal model for the ADAS-Cog14, ADCS-iADL, and MMSE will be presented. **Conclusion:** These analyses will integrate potential treatment effects of solanezumab and may provide insight into amyloid as a target for AD drug development. Ongoing solanezumab studies with participants earlier in the continuum of AD and a higher dose will help determine whether solanezumab has a clinically meaningful effect.

P052- LOWER SERUM CALCIUM AS A POTENTIALLY ASSOCIATED FACTOR FOR CONVERSION OF MILD COGNITIVE IMPAIRMENT TO EARLY ALZHEIMER'S DISEASE IN JAPANESE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVES. A. Iwata, S. Kenichiro, I. Ryoko, S. Kazushi, I. Takeshi *(The University of Tokyo - Tokyo (Japan))*

Background: The aim of this study was to investigate the effect of baseline serum calcium level for the incidence of mild cognitive impairment (MCI) conversion to early Alzheimer's disease (AD) in the Japanese Alzheimer's disease Neuroimaging Initiatives (J-ADNI) study cohort. **Methods:** In this sub-analysis within the J-ADNI study, we reviewed data from MCI participants at baseline regarding their conversion to early AD during the 3 years of observation period and assessed the associated factors including serum calcium level. In addition, we compared our results from the J-ADNI study with the corresponding results from the North American (NA) - ADNI. **Results:** Of 234 eligible MCI participants from the J-ADNI cohort, 121 (51.7%) converted to AD during the first 36 months of observation. Using univariate analysis, being female, having a lower number of years of education, and lower serum calcium level were correlated with increased risk of MCI-to-AD conversion exclusively in J-ADNI cohort. The lower corrected serum calcium level remained as one of conversion-associated factors in the J-ADNI cohort even after adjustment for multiple confounding variables, although this was not observed in the NA-ADNI cohort. **Conclusions:** Our findings suggest that lower serum calcium may be associated with an increased risk of MCI conversion to AD in Japanese cohorts. The reason for this correlation remains unclear and further external validation using other Asian cohorts is needed. It would be interesting for future AD studies to obtain serum calcium levels and other related factors, such as vitamin D levels, culture-specific dietary or medication information.

Theme: CLINICAL TRIALS IMAGING

P053- ENTORHINAL CORTICAL TAU ACCUMULATION IS INVERSELY ASSOCIATED WITH HIPPOCAMPAL SYNAPTIC DENSITY IN OLDER INDIVIDUALS WITH NORMAL COGNITION AND EARLY ALZHEIMER'S DISEASE. A. Mecca, M.K. Chen, M. Naganawa, T. Toyonaga, T. Godek, J. Harris, H. Bartlett, J.D. Gallezot, N. Nabulsi, Y. Huang, A. Arnsten, R. Carson, C. Van Dyck *(Yale School of Medicine - New Haven (United States))*

Background: Synaptic loss is an early and robust pathology in Alzheimer disease (AD) and the major structural correlate of cognitive impairment. Using [^{11}C]UCB-J and positron

emission tomography (PET) we have previously shown significant reductions in hippocampal synaptic vesicle glycoprotein 2A (SV2A) binding as a marker of synaptic density in participants with AD (Chen M, et al. Assessing synaptic density in Alzheimer disease with synaptic vesicle glycoprotein 2A positron emission tomographic imaging. JAMA Neurol. 2018;75:1215), consistent with the early degeneration of entorhinal cortical (ERC) cells that project to the hippocampus via the perforant path. To assess the relationship between tau deposition and synaptic density, we performed PET imaging with [^{18}F]flortaucipir and [^{11}C]UCB-J and hypothesized that tau deposition in ERC would be inversely associated with synaptic density in the hippocampus. **Methods:** [^{11}C]UCB-J binding to SV2A and [^{18}F]flortaucipir binding to tau were measured in 10 AD and 10 cognitively normal (CN) participants. [^{11}C]UCB-J distribution volume ratios (DVRs) were calculated using SRTM2 and a whole cerebellum reference region. [^{18}F]Flortaucipir standardized uptake value ratios (SUVRs) were calculated using an inferior cerebellum reference region. **Results:** AD participants (68.8±6.6 years, CDR = 0.5-1.0) were all Aβ+ by [^{11}C]Pittsburgh Compound B ([11C]PiB) PET and spanned the disease stages from amnestic Mild Cognitive Impairment (aMCI, n = 5) to mild dementia (n = 5). CN participants (72.1±7.9 years) were free of clinical symptoms (CDR = 0); 8 were found to be Aβ– by [^{11}C]PiB PET, but 2 were Aβ+. AD compared to CN participants demonstrated significant reductions in hippocampal [^{11}C]UCB-J binding (AD DVR = 0.88±0.13, CN DVR = 1.06±0.08, P = 0.002) and significant increases in ERC [^{18}F]flortaucipir binding (CN SUVR = 1.11±0.12, AD SUVR = 1.68±0.16, P < 0.00001). In the overall sample, higher ERC tau was significantly inversely associated with lower hippocampal synaptic density (r = –0.63, P = 0.005). **Conclusions:** As predicted, these preliminary imaging results revealed higher ERC tau and lower hippocampal synaptic density in AD compared to CN participants. Consistent with our hypothesis, in the overall sample ERC tau accumulation was associated with lower hippocampal synaptic density. This inverse association may reflect synaptic failure due to tau pathology in ERC neurons projecting to the hippocampus. Further studies are needed to elucidate the relationship between tau accumulation and synaptic loss in AD.

P054- DISTINGUISHING ALZHEIMER'S DISEASE WITH VENTRICULOMEGALY FROM NORMAL PRESSURE HYDROCEPHALUS USING MRI BIOMARKERS. M. Kim, J.H. Lee, S.H. Lee *(Seoul National University, Medical College - Seoul (Korea, Republic of))*

Background: Few studies have been performed to clinically differentiate between Normal Pressure Hydrocephalus(NPH) and Alzheimer's disease(AD) for proper treatment. Although NPH symptoms could be dramatically improved by a shunt surgery, AD patients with ventriculomegaly showed poor response to the surgery. The purpose of this study was to evaluate radiological parameters as a clinically useful tool to discriminate NPH from AD with ventriculomegaly. **Methods:** This study is a retrospective review of randomly selected medical records. A total of 56 patients (iNPH:25, AD:31) were diagnosed under the criteria of international guidelines of idiopathic NPH (iNPH) and the NINCDR-ADRDA of Alzheimer's disease. Nine radiological parameters—Evans' index, callosal angle, Sylvian fissure dilation, Sylvian fissure height, temporal horns, periventricular high signal intensity, narrow sulci, focally enlarged sulci—were measured on MRI. **Results:** Among nine radiological parameters, callosal angle, Evans' index, narrow sulci, Sylvian fissure dilation (Kappa value: 0.256), Sylvian fissure height (Intraclass correlation coefficient: 0.722), and perihippocampal fissure showed statistically significant difference between the AD group and the iNPH group ($p<0.05$). ROC analysis was performed to define cut-off values for maximized sensitivity and specificity. The cut-off value of Evans' index, Sylvian fissure height, and callosal angle was 0.37 (sensitivity: 0.64, specificity: 0.81), 25.49 (sensitivity: 0.80, specificity: 0.55), 97.35 (sensitivity: 0.84, specificity: 0.68), respectively. **Conclusions:** Small callosal angle, high Evans' index, narrow sulci, dilation of Sylvian fissure, narrow sulci, and unexpanded perihippocampal fissure are characteristic features of NPH patients compared with AD patients. These radiological indices may be useful as non-invasive and comprehensive tools for the differential diagnosis of AD and NPH, which are difficult to classify clinically.

P055- DIAGNOSTIC ACCURACY OF WHOLE BRAIN CORTICAL DTI CHANGES MEASURED IN ALZHEIMER'S DISEASE. S. Chance[1], M. Torso[1], M. Bozzali[2], O. Ehsan[1], G. Zamboni[3], M. Jenkinson[4] *((1) Oxford Brain Diagnostics - Oxford (United Kingdom), (2) Santa Lucia Foundation - Rome (Italy), (3) Universita` di Modena e Reggio Emilia, - Modena (Italy), (4) University of Oxford - Oxford (United Kingdom))*

Background: Alzheimer's Disease (AD) is the most common age-related cause of dementia in occidental countries, characterized pathologically by important neural architecture changes like extracellular plaques and intracellular neurofibrillary tangles associated with synapse loss and neurodegeneration leading to memory impairment and other cognitive problems. The recent ATN framework proposed by the National Institute on Aging-Alzheimer's Association (NIA-AA) suggests a descriptive classification based on the patient's biomarker profile (Jack et al. 2018). In this framework the "A" biomarkers refer to the amyloid deposition detected through amyloid positron emission tomography (PET) imaging or β-amyloid (Aβ) concentration in the cerebrospinal fluid (CSF); the "T" biomarkers refer to tau levels investigated through cortical tau PET and CSF phosphorylated tau (P-tau); "N" includes biomarkers of neurodegeneration or neural injury as shown by atrophic brain structures in magnetic resonance image (MRI), reduced 18F-fluorodeoxyglucose (FDG)-PET or higher CSF total tau (T-tau). The ATN framework considers AD as a continuum in which the extreme points are represented by A-T-N- cognitively unimpaired subjects and A+T+N+ subjects with dementia. This study focused on change in the underlying neural architecture that is responsible for cognitive function and can play a role as a biomarker within the "N" group of markers. In addition to the well-known features of cell loss and synapse loss, previous observations have found that the vertical cellular micro-circuits, known as minicolumns, which constitute the fundamental structure throughout the cerebral cortex, are altered in a graded manner during ageing, Mild Cognitive Impairment (MCI), and through the transition to AD (Chance et al. 2011). The microscopic disruption of columnar architecture correlates with plaque load and cognitive decline (van Veluw et al. 2012). This disruption is detectable independently of gross variation in brain size, and the relationship to cognitive measures is regionally specific (Chance et al 2011; Van Veluw et al 2012).

A careful validation of a method used to detect correlates of these cortical microstructural changes was conducted previously using novel ex-vivo MRI comparisons with post-mortem dissection (McKavanagh et al. 2019). The method used Diffusion Tensor Imaging which is a technique sensitive to microstructural changes in brain tissues. The rationale of the present study was to provide a preliminary in-vivo validation of those neuroimaging measurements that have been shown to correlate with elements of the microstructure of the cerebral cortex (McKavanagh et al 2019), and to demonstrate that they are sensitive to dementia-related pathology. Based on non-invasive MRI, this analysis method is complementary to existing methods for extracting other forms of "neurodegenerative" biomarkers and requires only conventional MRI scanners, without requiring contrast agents, and with standard diffusion imaging protocols. It is, therefore, potentially useful for exploring markers of disease, monitoring the evolution across AD stages by virtue of its simplicity and wide applicability to a large variety of acquisition protocols, especially those common in the clinical realm. It could be also useful to address phenotypic characteristics crucial for the development of precise and effective therapeutics in AD and quantifying the response to therapies in clinical trials. **Objectives:** The main goal of this research was to test a newly developed in-vivo brain MRI analysis method, which is sensitive to the cytoarchitecture of the cerebral cortex and correlates with the minicolumnar microcircuit organization of the brain, in order to investigate neural architecture in patients with Alzheimer Disease. **Methods:** Three cohorts of patients with probable AD (respectively 20, 40 and 25 individuals comprising a total of 85 patients) and 75 healthy elderly volunteers (respectively 20, 30 and 25 controls) were used, to assess the accuracy of our novel method for detection of AD. The first group was used as the "Discovery" cohort (to refine the analysis), the second as the "Test" cohort (to validate our method), and the last "ATN" cohort was used in order to address the increasing use of the ATN framework. We therefore made comparison of CDM to existing data on protein levels where it was available in the datasets, acquired through PET scan or other methods. Receiver Operating Characteristics (ROC) curve analysis was used to assess the group discrimination capability of our method. **Results:** The results showed that the new DTI derived measures can detect altered quality of cortical grey matter in AD patients, distinguishing between these and healthy controls with an accuracy range between good and excellent. **Conclusion:** These new measurements could be used within the "ATN" framework and as an index of cortical microstructure quality. Further development may aid early diagnosis, patient selection, and quantification of the "Neurodegeneration" component in response to therapies in clinical trials. **References:** Jack Jr, C. R., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., ... & Liu, E. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's & Dementia, 14(4), 535-562. Chance, S. A., Clover, L., Cousijn, H., Currah, L., Pettingill, R., & Esiri, M. M. (2011). Microanatomical correlates of cognitive ability and decline: normal ageing, MCI, and Alzheimer's disease. Cerebral Cortex, 21(8), 1870-1878. van Veluw, S. J., Sawyer, E. K., Clover, L., Cousijn, H., De Jager, C., Esiri, M. M., & Chance, S. A. (2012). Prefrontal cortex cytoarchitecture in normal aging and Alzheimer's disease: a relationship with IQ. Brain structure and function, 217(4), 797-808. McKavanagh R., Torso M., Jenkinson M., Kolasinski, J., Stagg,C.J., Esiri M.M., McNab J.A., Johansen-Berg H., Miller K.L. and Chance S.A. (2019) Relating Diffusion Tensor Imaging measurements to microstructural quantities in the cerebral cortex in Multiple Sclerosis. Human Brain Mapping; DOI:10.1002/hbm.24711

P056- ONE-YEAR LONGITUDINAL CHANGE OF 18F-RO948 PET AMONG COGNITIVELY UNIMPAIRED AND PATIENTS WITH MCI OR DEMENTIA IN THE BIOFINDER2 STUDY. G. Klein[1], A. Leuzy[2], R. Smith[2], S. Palmqvist[2], N. Mattsson[2], D. Van Westen[2], O. Strandberg[2], J. Jögi[2], T. Ohlsson[2], E. Borroni[1], P. Coloma[3], E. Stromrud[2], O. Hansson[2] *((1) Roche Pharma Research and Early Development - Basel (Switzerland), (2) Clinical Memory Research Unit, Department of Clinical Sciences - Lund (Sweden), (3) Roche Pharma Development Personalized Health Care - Basel (Switzerland))*

Background: The Swedish BioFINDER2 (Biomarkers For Identifying Neurodegenerative Disorders Early and Reliably) Study is a prospective study driven by researchers at Skåne University Hospital that focuses on identifying key mechanisms and improved diagnosis of Alzheimer's Disease (AD) and other neurodegenerative disorders. The study started in May 2017 and aims to recruit more than 1500 subjects across the AD spectrum, including cognitively unimpaired (CU), and patients with subjective cognitive decline, mild cognitive impairment (MCI) or different types of dementia. Here we report the preliminary longitudinal tau PET data seen for the first 51 patients scanned with 18F-RO948 at two time points. **Objectives:** Describe the longitudinal change in tau pathology after one year using 18F-RO948 PET in a population of cognitively normal individuals, patients with MCI, and clinically diagnosed AD, recruited to date in the BioFINDER2 study. **Methods:** All study participants in the longitudinal substudy are scanned at baseline and a targeted first follow-up scan at 12 months with 18F-RO948 tau PET on one of four identically configured GE Discovery MI PET cameras. PET scans are obtained during 20 minutes, 70-90 min after an injection targeting 370 MBq. Patients are also scanned with an extensive MRI protocol using a MAGNETOM Prisma 3T scanner (Siemens), including a high-resolution MPRAGE sequence used in PET processing. FreeSurfer v6.0 is used to obtain SUVR images using an inferior cerebellar grey reference region. A regional analysis of the PET data is carried out using a Braak staging model, which defines ROIs approximating the anatomical definitions of entorhinal/hippocampal (Braak stage I/II), temporal/limbic (III/IV), and neocortical (V/VI) Braak stages [1], as well as a Braak I-IV temporal meta-ROI [2]. Potential reference regions including whole cerebellum, brainstem and white matter were also investigated. Subjects were analysed separately based on baseline clinical diagnosis: cognitively unimpaired (CU), MCI and dementia due to AD. Subjects were further stratified via amyloid status (Aβ+ or Aβ-) based on the CSF Aβ42/Aβ40 ratio (cutoff<0.089), as defined in clinical practice by the neurochemistry laboratory at the Sahlgrenska University Hospital. **Results:** As of July, 2018, 51 patients have undergone longitudinal 18F-RO948 tau PET imaging with baseline diagnosis along the AD spectrum: CU_Aβ- (N=9), MCI_Aβ- (N=3), CU_Aβ+ (N=14), MCI_Aβ+ (N=18), and AD_Aβ+ (N=7). The Aβ- groups were combined in the analysis because of the small sample size. Mean (SD) follow-up intervals for the different cohorts were obtained at 393 (80), 335 (44), 439 (81), 410 (19) days for the Aβ-, CU_Aβ+, MCI_Aβ+, and AD_Aβ+ groups, respectively. Baseline tau burden for all four composite ROIs was significantly lower for

the Aβ- group (p<0.001). Mean longitudinal percent change and effect size were slightly negative for this group (< 1% change). Largest longitudinal change and effect size for the CU_Aβ+ were in the Braak I-II region (2.45% change, 0.69 effect size). Largest change and effect size for the MCI_Aβ+ were in the Braak III-IV regions (4.2% change, 0.69 effect size) and for the AD_Aβ+ group were in the Braak V-VI regions (2.7% change, 0.55 effect size). Overall the inferior cerebellar grey matter reference region resulted in the largest longitudinal effect size for the HC_Aβ+ and MCI_Aβ+ groups, while the brainstem and corpus callosum showed higher effect size for the AD group. **Conclusions:** Tau burden change seen via the second-generation tau PET tracer 18F-RO948 replicates the post-mortem spreading pattern of tau, with the highest effect size and percent change seen in Braak regions I/II for Aβ+ CU subjects, and Braak regions III/IV and V/VI for Aβ+ MCI and AD subjects, respectively. The low off-target binding characteristics adjacent to Braak I/II regions may offer this tracer superior ability to detect change for pre-clinical/early AD subjects compared with other tau PET tracers. Amyloid negative subjects showed low baseline tau burden levels and no elevation of tau over the one-year observation period. The inferior cerebellar grey matter reference region resulted in highest longitudinal effect size for early AD, but not for late AD subjects, indicating that tau accumulation likely takes place in the cerebellum late in the disease. **References:** [1] Cho et al., Ann Neurol ; 2016 ; 80 :247-258; [2] Jack et al., Brain ; 2018 ; 141 :1517-1528

P057- SIGNIFICANT CHANGE OF EEG BIOMARKER IN PARKINSON'S DISEASE WITH MCI AFTER 1YEAR OF DONEPEZIL INTAKE. S.M. Kim[1], S.W. Kang[1,2], S.M. Kim[1], D.W. Kang[1], H. Lee[1], U. Park[1], S.Y. Kang[3], Y.H. Sohn[4], P.H. Lee[4], K.W. Baik[4] *((1) iMediSync Inc - Seoul (Korea, Republic of), (2) Data Center for Korean EEG, College of Nursing, Seoul National University (Korea, Republic of), (3) Department of Neurology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine - Gyeonggi-Do (Korea, Republic of), (4) Department of Neurology, Yonsei University College of Medicine - Seoul (Korea, Republic of))*

Background: Patients with Parkinson's disease (PD) often have mild cognitive impairment (MCI), and it is reported that PD with MCI (PD-MCI) patients more progress to dementia than non PD-MCI patients. Donepezil, FDA-approved memory enhancing drug by inhibiting AchE, showed effective for Parkinson's disease with dementia (PDD), but it is unknown to work for PD-MCI. **Objectives:** To explore the clinical effectiveness of donepezil on the neurophysiological function of the PD-MCI, and evaluate the feasibility of EEG biomarker as clinical endpoint of effectiveness. **Methods:** Open-label, double arm study was done for 54 PD-MCI participants for 12 months. The patients were randomized to donepezil (5 or 10mg/day) or nootropic drug. 21 patients (67.6 ± 7.3 years) were administered with donepezil, and the other patients (69.1 ± 7.1 years) were not. 19 channel electroencephalography (EEG) was measured under the resting state for three minutes before and after intervention for all participants as well as neurocognitive functional battery. Among lots of EEG features, spectral power ratio of theta (4~8Hz) to Beta2 band (15~20Hz) or TB2R was analyzed as main endpoint and compared between each group either at each electrode and at estimated source activity by sLORETA, which is mathematical assumption of EEG current activity at cerebral cortex. Complex network analysis was also tried. **Results:** Donepezil group showed significant decrease of TB2R (overall post/pre ratio: 0.9±0.5) at bilateral frontotemporoparietal channels (left side: F7, T3, C3, P3, T5. Right side: Fp2, F8, T4, C4, P4) after intervention compared to non-donepezil group (overall post/pre ratio: 1.4±0.99). Among the source ROI activity by sLORETA, significant decrease of TB2R was observed at isthmus of posterior cingulate cortex (PCC) only in donepezil group after intervention (overall post/pre ratio in donepezil: 0.9±0.42, overall post/pre ratio in nootropics: 1.2±0.64, p<0.05). TB2R of Entorhinal and parahippocampal area in both hemispheres also showed decreasing patterns, which were not statistically significant. According to the network analysis, donepezil group showed significant increase of node degree at right temporal pole, entorhinal and parahippocampal, and left superior temporal in beta2 band as opposed to control group. There were no significant changes of neurocognitive functional test score in both groups. **Conclusion:** Relative increase of theta wave has been observed in many cases of neurodegeneration. Enhancement of beta2 could be a neural compensation against it. In this trial, theta wave in donepezil group decreased relatively to the baseline condition as well as to that of placebo group. Main node of default mode network (DMN) such as PCC, entorhinal and parahippocampal cortex which also play important role in memory retrieval and consolidation were activated in beta2 band. Although we could not find any significant improvement of neurocognitive functional test, it could be assumed that progression of neurodegeneration was delayed, and neural compensation or memory-related circuit was activated in donepezil group of PD-MCI from the point of EEG biomarkers.

P058- QEEG CHANGES IN MILD COGNITIVE IMPAIRMENT WITH CHOLINE ALPHOSCERATE. Y.C. Youn[1], S.W. Kang[2] *((1) Dept. of Neurology, Chung-Ang Univ. Hospital - Seoul (Korea, Republic of), (2) Data Center for Korean EEG, College of Nursing, Seoul National University - Seoul (Korea, Republic of))*

Choline alphoscerate has limited evidence of the effects in mild cognitive impairment (MCI). Object of this study is to evaluate the spectral change at a source level of EEG as a biomarker for cognitive function after taking choline alphoscerate in patients with MCI. Resting-state EEG studies were done in baseline (n = 18) and 2 months after taking choline alphoscerate (n = 18). We analyzed qEEG. When compared to control (n=12), MCI showed decreased delta and theta in bilateral parietal and occipital lobes, and decrease alpha 1 in whole cerebral cortex. However beta 1, 2 and 3 were posterior dominantly increased in MCI group. Follow-up qEEG after taking choline alphoscerate showed the significant change in delta, theta and alpha waves. The delta and theta were posterior dominantly decreased and alpha was increase. Even though there are some limitations, choline alphoscerate could improve the electrophysiological markers in MCI patients.

P059- APOE4/4 SUBJECTS WITH EARLY ALZHEIMER'S DISEASE SHOW ACCELERATED LOSS OF CORTICAL THICKNESS AND COGNITIVE DECLINE COMPARED TO APOE3/3 SUBJECTS. Susan Abushakra[1], Anton Porsteinsson[2], Marwan Sabbagh[3], Luc Bracoud[4], Joël Schaerer[5], Aidan Power[1], John A. Hey[1], David Scott[5], Joyce Suhy[4,5], Martin Tolar[1]
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Background: Prognosis The apolipoprotein ε4 allele (APOE4) is the strongest genetic risk factor for late onset Alzheimer's disease (AD), is associated with accelerated appearance of brain amyloid (Aβ) pathology in APOE4 carriers. Compared to noncarriers, APOE4/4 homozygotes APOE4 alleles have a higher burden of neurotoxic Aβ oligomers, thought to be an early driver of AD. The increased burden of soluble Aβ oligomers in APOE4/4 homozygotes is likely due to increased production and decreased clearance of Aβ monomers. We previously showed that APOE4/4 subjects with Mild Cognitive Impairment (MCI) or Mild AD, have significantly smaller hippocampal volume (HV) and faster rates of hippocampus atrophy over 12 - 24 months, compared to APOE3/3 subjects at the same clinical stage (Abushakra et al., CTAD 2018). APOE4/4 subjects are thus an optimal clinical trial population for candidate drugs that are directed at inhibition of Aβ oligomer formation, such as tramiprosate or its oral pro-drug ALZ-801 (Abushakra 2017, Kocis 2017, Hey 2018). In the APOE4/4 AD population, use of HV as an imaging biomarker of drug efficacy is attractive. It is unclear whether other volumetric MRI measures, such as cortical thickness, are equally useful as biomarkers in the APOE4/4 AD population. **Objectives:** To further optimize selection of imaging biomarkers for a planned ALZ-801 trial in APOE4/4 subjects with Early AD (MCI and Mild AD), by evaluating the rate of cortical thickness loss in APOE4/4 versus APOE3/3 subjects, and assessing its correlation with cognitive decline. **Methods:** We analyzed ADNI-1 study data which enrolled 722 subjects, and included 255 Cognitively Normal (CN), 301 Late MCI and 166 Mild AD individuals. The MCI group had 228 APOE3/3 non-carriers and 73 APOE4/4, while the Mild AD group had 101 APOE3/3 and 65 APOE4/4 subjects. We analyzed the subgroup with volumetric MRIs (vMRI) at baseline, 12 and 24 months (http://adni.loni.ucla.edu), that included: MCI (93 APOE3/3, 29 APOE4/4) and Mild AD (29 APOE3/3, 21 APOE4/4). Clinical scores (MMSE, ADAScog13, CDR-SB) were collected at Baseline and Months 3, 6, 9, 12, 18 and 24. The 3D T1-weighted MRI collection consisted of MP RAGE (Siemens), 3D TFE (Philips) and 3D Fast SPGR (General Electric) pulse sequences, with 1.25×1.25×1.2 mm3 voxel resolution in sagittal orientation. Total hippocampus volumes (HV= L+R) were derived. HV changes at follow-up timepoints were assessed using Boundary Shift Integral. Cortical thickness was measured using FreeSurfer, and the Mayo AD signature ROI (Mayo Index, Jack 2017) was calculated at baseline. Changes in cortical thickness were analyzed by a Jacobian-based method. Baseline vMRI measures were adjusted for age, years of education, and head size. Clinical score changes were estimated by fitting a linear model for each subject. Correlations between vMRI changes at M24 and clinical decline were analyzed by Pearson's correlations. Comparative analyses were focused on APOE3/3 versus APOE4/4 subjects in LMCI and Mild AD groups. **Results:** In this ADNI-1 MRI dataset, demographics and baseline scores in the MCI and Mild AD groups were similar except APOE4/4 subjects being significantly younger than APOE3/3 with smaller HV ($p<0.001$). APOE4/4 subjects with MCI had significantly worse ADAS-cog scores than APOE3/3 subjects ($p=0.016$). Across the groups, cortical thickness at baseline was numerically smaller in Mild AD than MCI, with no significant differences between APOE3/3 and APOE4/4 subjects. In contrast, differences in baseline HV were significant between the two genotypes in both MCI and Mild AD subjects, with the smallest baseline HV observed in APOE4/4 Mild AD, followed by APOE4/4 MCI. APOE4/4 MCI and Mild AD subjects showed significantly more loss of cortical thickness at 12 and 24 months, compared to APOE3/3. In APOE4/4 subjects with MCI, the rate of cortical thickness loss was 0.09 mm (SD 0.03) at 12 months, and 0.17 mm (SD 0.06) at 24 months, compared to 0.05 mm (SD 0.04) at 12 months, and 0.09 mm (SD 0.07) at 24 months in APOE3/3. In APOE4/4 subjects with Mild AD, the rate of cortical thickness loss was 0.12 mm (SD 0.06) at 12 months, and 0.22 mm (SD 0.08) at 24 months, compared to rates of 0.09 mm (SD 0.04) and 0.17 mm (SD 0.08) in APOE3/3, respectively. In the APOE4/4 MCI group, cortical thickness loss at 24 months was significantly correlated with changes in ADAS-cog ($r = -0.59$, $P < .001$), and MMSE ($r = 0.38$, $P = .041$). In the APOE4/4 Mild AD group, cortical thickness loss was not significantly correlated with changes in clinical scores. Cortical thickness loss was not correlated with CDR-SB changes in APOE4/4 at either MCI or Mild AD stages. **Conclusions:** Our analyses suggest that APOE4/4 subjects with Early AD (MCI and Mild AD) show accelerated loss of cortical thickness, compared to APOE3/3. In APOE4/4 MCI subjects, the loss of cortical thickness is significantly correlated with cognitive decline over 24 months. These findings suggest that cortical thickness can be a valuable imaging biomarker of disease progression and drug efficacy in APOE4/4 subjects with Early AD. Considering the reported accelerated hippocampus atrophy in APOE4/4 subjects, cortical thickness may complement HV as a biomarker in Early AD, by providing a comprehensive picture of a drug's effect on disease modification. If drug effect on slowing atrophy on these imaging measures correlate with cognitive efficacy in prospective trials, this could allow the use of HV, cortical thickness, or both as surrogate outcomes in prevention trials of APOE4 carriers with presymptomatic AD. Surrogate imaging endpoints in prevention trials can accelerate drug approvals by allowing shorter and more efficient clinical trials in AD.

P060- ATN CHARACTERISTICS OF IMAGING BIOMARKERS OF THE CURRENT LEADS SAMPLE. B. Dickerson[1], J. Collins[1], P. Vemuri[2], B. Borowski[2], L. Iaccarino[3], R. La Joie[3], O. Lesman-Segev[3], A. Eloyan[4], P. Aisen[5], A. Fagan[6], T. Faroud[7], C. Gatsonis[4], C. Jack[8], J. Kramer[3], R. Koeppe[9], A. Toga[10], M. Carillo[11], L. Apostolova[7], G. Rabinovici[3], L. Leads Co-Investigators And Staff[7] *((1) MGH/Harvard - Boston, MA (United States), (2) Mayo Clinic - Rochester, MN (United States), (3) UCSF - San Francisco, CA (United States), (4) Brown - Providence, RI (United States), (5) USC - San Diego, CA (United States), (6) Washington U - St. Louis, MO (United States), (7) Indiana U - Indianapolis, IN (United States), (8) Mayo - Rochester, MN (United States), (9) U Michigan - Ann Arbor, MI (United States), (10) USC - Los Angeles, CA (United States), (11) Alzheimer's Assoc - Chicago, IL (United States))*

Background: Approximately 5% of the 5.6 million (~280,000) Americans with Alzheimer's disease (AD) develop symptoms at age 65 or younger and are classified as having early-onset AD (EOAD). Although EOAD and late-onset AD (LOAD) share the same pathologic substrate, there are notable differences in their clinical and biological phenotypes. Compared to LOAD, patients with sporadic EOAD show more rapid cognitive decline and lower prevalence of amnestic versus non-amnestic clinical presentations. EOAD is associated with greater baseline cortical atrophy/hypometabolism, less medial temporal lobe involvement and more severe AD pathology than LOAD. EOAD patients present with a relatively "pure" form of AD because of lower rates of age-related brain co-pathologies. EOAD patients often face a significant delay to diagnosis, access to AD treatments, and social and financial support services. Despite being highly motivated and having few comorbidities, EOAD patients are commonly excluded from large scale observational biomarker studies (e.g. ADNI) and therapeutic trials due to their young age or non-amnestic deficits. **Objective:** Our over-arching goals of are to 1) advance our knowledge about AD diagnosis, 2) develop sensitive composite clinical and biomarker tools that capture disease progression in this unique cohort for implementation in clinical trials, 3) to establish a network of EOAD sites ready to launch interventional studies in this population; and 4) explore possible genetic susceptibility factors through GWAS. The goals of this preliminary presentation are to summarize the clinical and ATN imaging biomarker characteristics of our current sample. **Methods:** Leveraging existing infrastructure and processes applied in ADNI and DIAN, we have launched the Longitudinal Early-onset AD study (LEADS) -a multi-site, observational clinical and biomarker study of EOAD. We plan to recruit and longitudinally follow 400 amyloid PET-positive EOAD subjects meeting NIA-AA criteria for MCI due to AD or probable AD dementia (including primary amnestic, dysexecutive, language or visuospatial presentations), 100 amyloid-negative cognitively impaired participants, and 100 age-matched controls. LEADS participants are undergoing clinical assessments, psychometric testing, MRI, amyloid ([18F]Florbetaben) and tau ([18F]AV1451) PET, CSF and blood draw for collection of DNA, RNA, plasma, serum and peripheral blood mononuclear cells. Cognitively impaired participants are being assessed at three timepoints. Methods are harmonized with ADNI and DIAN. We are comprehensively characterizing cognitive, imaging and biofluid changes over time in EOAD, and planning to compare to a matched sample of LOAD participants identified in ADNI. An exploratory aim will apply next generation sequencing to assess for novel genetic risk factors for disease. In this analysis we will examine amyloid and tau PET characteristics of participants using a visual read and quantification, and we will compare several methods for defining neurodegeneration from MRI scans, including whole brain volume, hippocampal volume, average cortical thickness, and AD-signature cortical thickness. **Results:** At the time of abstract submission, complete imaging data (MRI & amyloid and tau PET) were available for 29 EOADs (mean age 58.8, MMSE 22.3, 2 non-white race), 10 cognitively impaired individuals who were amyloid-negative (mean age 58, MMSE 25.2, 0 non-white race), and 28 controls (mean age 54.1, MMSE 29.2, 3 non-white race). Clinical phenotypes for most participants are amnesic or non-amnesic multi-domain cognitive impairment; 3 subjects have PPA and 3 subjects have PCA. We will present a summary of ATN and additional clinical characteristics of the current sample. Conclusions: Successful completion of this project will address several substantial gaps in our understanding of EOAD and AD research in general. Importantly, patients with EOAD are outstanding clinical trial candidates, as they present a "pure" form of AD, tend to be otherwise healthy, and show more rapid progression on cognitive and imaging measures, allowing for the detection of a potential disease modifying drug effect in a short amount of time. This project will facilitate these trials by developing a publicly available natural history dataset of biomarker and clinical inclusion and outcome measures suited for the EOAD population and will establish a network of EOAD sites that will enable future planning and implementation of clinical trials in EOAD.

P061- CHANGES IN [18F]GTP1 SUVR CORRELATE WITH COGNITIVE DECLINE OVER 18 MONTHS AND DEPEND ON BASELINE SUVR INTENSITY AND SPATIAL DISTRIBUTION. A CROSS-SECTIONAL STUDY. R. Weimer, S. Sanabria Bohórquez, E. Teng, S. Baker, J. Marik, P. Manser *(Genentech - South San Francisco (United States))*

Background: Molecular imaging biomarkers have the potential to play key diagnostic roles in tauopathies. Aggregated tau protein has been identified as one of the key pathological features of Alzheimer's disease (AD). [18F]GTP1 has been developed as a positron emitting radiopharmaceutical for in vivo imaging of tau protein aggregates. **Objective:** To characterize the longitudinal change in tau pathology as measured by [18F]GTP1 over an 18 month observation period and its relationship with longitudinal cognitive decline and baseline tau pathology in a cohort of AD patients and cognitively normal controls (CNs). **Methods:** [18F]GTP1 scans were performed in amyloid negative and positive cognitive normal subjects (CN; n=2 and 8, respectively), and amyloid positive prodromal (Prod; n=27;MMSE 24-30, CDR = 0.5), mild (Mild; n=19; MMSE 22-30, CDR = 0.5 or 1), and moderate (Mod; n=16; MMSE 22-30, CDR = 0.5-2) AD subjects. Quantification was performed using the cerebellar gray as reference to calculate SUVR. Measurements were made within a whole cortical gray matter (WCG) ROI, within in vivo Braak ROIs (Schöll et al., Neuron 2016), and within a temporal meta-ROI (Jack et al., Brain 2017). Relationships between longitudinal change in [18F]GTP1 SUVR and longitudinal change in ADAS-Cog13 and CDR-SB scores at 6, 12, and 18 months post-baseline were summarized with Spearman correlations. To assess the relationship of longitudinal [18F]GTP1 SUVR changes with baseline SUVR, annualized rates of SUVR change were

calculated on a per-patient basis using simple linear regression. The slopes from these regression models were then compared with baseline SUVR using Spearman correlations. **Results:** At 18 months, change in [18F]GTP1 WCG SUVR correlated with change in ADAS-Cog13 and CDR-SB cognitive scores (rs= 0.43, p=0.009; rs= 0.45, p=0.005). Changes in temporal meta-ROI SUVR more modestly correlated with change in ADAS-Cog13 and CDR-SB cognitive scores (rs= 0.26, p=0.122; rs= 0.27, p=0.118) indicating that, for many of these patients, changes in tau pathology leading to subsequent cognitive decline are also likely occurring outside of the temporal lobe. For both ROIs, correlations of [18F]GTP1 SUVR changes with changes in cognitive indices became progressively stronger with longer follow-up after baseline. Baseline [18F]GTP1 was prognostic of annualized rate of SUVR change, with strength and direction of association differing by Braak ROIs. Baseline SUVR in Braak 1 had a negative correlation with annualized rate of SUVR change within the same Braak 1 ROI (rs= -0.31, p=0.017) suggesting a possible saturation of tau pathology in this region for patients with higher baseline SUVRs. However, later Braak stages (4, 5, and 6) had numerically stronger and positive correlations between baseline SUVR and annualized rate of change (rs= 0.37, p=0.027; rs= 0.47, p=0.003, rs= 0.50, p=0.002), which may indicate earlier stages of spreading/seeding of pathology in these regions leading to faster rates of accumulation over the subsequent 18 months. **Conclusions:** We observed correlations between changes in [18F]GTP1 SUVR and two cognitive indices commonly used as primary endpoints in AD clinical trials: ADAS-Cog13 and CDR-SB. These results support the clinical use of [18F]GTP1 as a disease progression biomarker that correlates with cognitive decline in addition to [18F]GTP1 having the potential to demonstrate a pharmacodynamic effect of an anti-tau therapy. We also observed that baseline [18F]GTP1 SUVR was prognostic of 18 month SUVR change in an in vivo Braak ROI-dependent manner suggesting that [18F]GTP1 may be used for staging AD severity of patients and identifying specific brain regions where tau pathology may subsequently accumulate over 12 to 18 months.

P062- TAU-IQ: AN ANALYTICAL ALGORITHM WITH GREATER POWER THAN SUVR FOR QUANTIFICATION OF TAU PET TRACERS ILLUSTRATED WITH [18F] FLORTAUCIPIR AND [18F]GTP1. A. Whittingto[1], J. Hesterman[2], S. Sanabria[3], R. Weimer[3], J. Seibyl[4], R. Gunn[1]
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Background: Tau PET scans are used in clinical trials of AD to image pathological tau in the brain. To date, Braak region SUVR or global cortical SUVR have been used as outcome measures to quantify amplitude and extent of brain tau. **Objectives:** We introduce a novel algorithm, TauIQ for quantifying tau PET radiotracer data. The power of TauIQ is tested on both cross-sectional and longitudinal data from [18F] Flortaucipir and [18F]GTP-1. **Methods:** Two phases are required for the TauIQ algorithm. In phase one, tracer specific canonical images of the non-specific binding and tau carrying capacity are created. The second phase uses these canonical images in the TauIQ algorithm to calculate Tau Load. Canonical images were created for [18F]Flortaucipir and [18F]GTP-1. The dataset used to create the canonical images for [18F]Flortaucipir was obtained from ADNI and consisted of 234 subjects (88 healthy controls (HC), 40 significant memory concern(SMC), 58 early mild cognitive impairment (EMCI), 16 mild cognitive impairment (MCI), 30 late mild cognitive impairment (LMCI)) all of whom received [18F]Flortaucipir PET, [18F]Florbetapir PET and a structural MRI. The dataset used to create the canonical images for [18F]GTP-1 consisted of 61 subjects (9 HC, 22 Prodromal AD, 16 Mild AD, 14 Moderate AD) all of whom received [18F] GTP-1 PET, [18F]Florbetapir PET and a structural MRI. To create the canonical images, amyloid scans were analysed with AmyloidIQ to derive a subject-specific time in the disease trajectory. These times were subsequently used to perform parametric spatiotemporal modelling of the associated tau data with a regression model. The gradient and intercept provided canonical images for the tau carrying capacity (K), and non-specific binding (NS) respectively. The TauIQ algorithm models spatially normalised tau PET images as the linear combination of the K and NS in an image based regression. Tau Load is obtained as the co-efficient of K. TauIQ was applied to cross-sectional [18F]Flortaucipir data (675 Subjects: 365 HC, 49 SMC, 82 EMCI, 113 MCI, 37 LMCI, 29 AD), cross-sectional [18F] GTP-1 data (same dataset as was used to generate the canonical images), longitudinal [18F]Flortaucipir data (97 Subjects with between 2 and 4 timepoints: 43 HC, 19 SMC, 17 EMCI, 6 MCI, 12 LMCI) and longitudinal [18F]GTP-1 data (61 Subjects with between 2 and 4 timepoints: 9 HC, 22 Prodromal AD, 6 Mild AD, 14 Moderate AD) to obtain Tau Load for each scan. In addition, for each scan, cortical SUVR and Braak regional SUVRs were calculated for comparison. The power of SUVR and Tau Load were compared in the cross-sectional data by calculating effect sizes (Hedges' g) between disease groups and healthy controls. In the longitudinal data, the mean annual percent per year increase along with a confidence interval was calculated for both SUVR and Tau Load. **Results:** Tracer specific canonical images were successfully created for both [18F]Flortaucipir and [18F]GTP-1. The derived canonical images successfully partitioned background (NS: non-specific and off target binding) and tau (K: stereotypical tau distribution in AD) signals. The [18F]Flortaucipir and [18F]GTP-1 carrying capacity images were similar in the their spatial distribution whereas clear differences were observed in the non-specific images. The highest tau carrying capacities were seen in the temporal and parietal regions. Cortical SUVR demonstrated increased power over Braak regional SUVR outcome measures for both cross-sectional and longitudinal data sets. In the cross-sectional [18F] Flortaucipir data, there was a 4% increase in the average effect size between disease groups and healthy controls when using Tau Load instead of cortical SUVR. The greatest increase of 16% was seen between in the AD to HC comparison (SUVR effect size: 2.14, Tau Load effect size: 2.5). An average increase in effect size of 35% with Tau Load relative to cortical SUVR was seen in the cross-sectional [18F]GTP-1 data. The largest effect sizes for both Tau Load and cortical SUVR were seen between the moderate AD and HC groups where the effect size for SUVR was 1.66 and the effect size for Tau Load was 2.06 (24% increase with Tau Load). The average annual percentage change in Tau Load was statistically greater than zero for all groups other than EMCI for Tau Load in the [18F]Flortaucipir longitudinal data whereas an annual percentage increase was only observed in HC for cortical SUVR. The greatest rate of increase for Tau Load was found in LMCI subjects where the average annual percent increase was estimated to be 15.1% per year (C.I. [8.6 21.7]). In the longitudinal [18F]GTP-1 data the mean percent per year increase of the Tau Load was significantly

different from zero in all patient groups other than in healthy controls. The percent per year increase in moderate AD for Tau Load was greatest (mean 8.1%, C.I. [4.5, 11.7]). **Conclusion:** TauIQ is a novel methodology which for quantifying tau PET radiotracers. For [18F]Flortaucipir and [18F]GTP-1 TauIQ has demonstrated increased power over SUVR for both cross-sectional and longitudinal data and offers the prospect of more efficient clinical trials with fewer subjects needed to adequately power a tau imaging biomarker outcome measure.

P063-RELATIONSHIPS BETWEEN GLUCOSE METABOLISM, VOLUME, TAU BURDEN, AND CLINICAL ENDPOINTS IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE. D. Matthews[1], A. Ritter[2], R. Thomas[3], R. Andrews[1], A. Lukic[1], C. Revta[3], B. Tousi[4], J. Leverenz[4], H. Fillit[5], K. Zhong[2], H. Feldman[3], J. Cummings[3] *((1) ADM Diagnostics Inc - Northbrook (United States), (2) Cleveland Clinic - Lou Ruvo Center for Brain Health - Las Vegas (United States), (3) Alzheimer's Disease Cooperative Study, University of California San Diego - La Jolla (United States), (4) Cleveland Clinic - Lou Ruvo Center for Brain Health - Cleveland (United States), (5) Alzheimer's Drug Discovery Foundation - New York (United States))*

Background: Clinical trials in AD have been challenged by patient variability in clinical status and trajectory, and uncertainty regarding relationships between clinical outcomes and AD pathology. Imaging biomarkers of glucose metabolism, brain atrophy, and tau burden may help to characterize patients to improve diagnosis, therapeutic targeting, and treatment effect detection in clinical trials. A Phase II study of rasagiline in mild to moderate AD patients provided an opportunity to explore relationships between FDG PET, flortaucipir, volumetric MRI, and clinical endpoints acquired at the same time points. **Objectives:** To characterize the interrelationships of glucose metabolism, tau burden, and brain atrophy with clinical outcomes in a mild to moderate AD population. Aims included determining the relationship of hypometabolism and atrophy to tau pathology, and establishing which imaging biomarkers were most closely associated with cognitive status and subsequent rate of clinical decline. **Methods:** FDG PET, flortaucipir PET, volumetric MRI, and clinical endpoints including MMSE and ADAS-cog11 were acquired from fifty patients with a clinical diagnosis of mild to moderate AD, age 57-90, MMSE 11-26, having evidence of an AD-like pattern evaluated using previously developed FDG PET disease and AD Progression classifiers. PET scans were coregistered to MRIs, which were segmented using Freesurfer 6.0 and spatially transformed using SPM12. Scans were evaluated using prespecified and exploratory regions of interest and right/left asymmetry measures. Voxel-based classifiers were developed using tau burden, MMSE, and ADAS-cog separately as the criteria for training class definitions. Correlation and linear mixed effects models were used to compare measures within and between modalities, adjusting for covariates. **Results:** The study group (age 74(7.2), education 14(2.5), MMSE 20(4.2), ADAS-cog 26(8.8), 44%F/56%M), was diverse in tau accumulation, extent of brain atrophy and glucose hypometabolism. Tau distribution generally followed Braak staging with SUVRs highly correlated across stages, but varied in total burden, asymmetry, occipital deposition, and hippocampal sparing. Tau was associated with age, with greatest fronto-parietal burden in younger subjects in their 50s and 60s, lower/primarily temporal burden in participants in their 80s, and wide variability in subjects in their 70s. Significant relationships were found across imaging modalities and between imaging biomarkers and clinical endpoints. Glucose metabolism, tau burden, and volumetric measures were correlated in regions including posterior cingulate-precuneus, inferior/middle temporal, inferior parietal, and middle frontal cortices (p-values all< 0.001), with slopes influenced by age. Right/left hemisphere asymmetries in tau SUVR correlated negatively with asymmetry in glucose metabolism and atrophy, particularly in middle temporal, inferior parietal, and middle frontal cortices (FDG-to-tau: R = -0.77, -0.75, -0.72; MRI-to-tau: R = -0.80, -0.63, -0.61; p-values <0.00001). Voxel-based canonical variate analysis trained with classes having increasing tau SUVRs produced a flortaucipir pattern characterized by posterior cingulate, precuneus, inferior parietal, middle frontal and superior frontal accumulation against which all subjects were quantitatively scored for pattern expression. Analysis of FDG and MRI scans using the same class definitions produced spatial patterns of hypometabolism and atrophy for which subject pattern expression scores correlated with tau pattern expression (FDG-to-tau: R= 0.61, MRI-to-tau: R= 0.60, p-values<0.00001). In MRI analysis, subjects exhibiting a medial/lateral temporal atrophy profile corresponded to a low, primarily temporal, tau burden while those having a parietal dominant profile corresponded to greater tau burden in those regions. Frontal atrophy corresponded to tau burden particularly in younger subjects with high tau burden, but was also found in some older subjects in the absence of tau. Females had more hypometabolism than males in middle frontal cortex (p<0.004) and total cortex (trend), and greater tau in inferior temporal, left caudal middle frontal, AD composite region (all p<0.04), and most Braak stage regions (trend). Baseline FDG scans correlated with baseline MMSE and ADAS-cog11 scores with strongest associations found with the AD Progression classifier pattern scores and left posterior cingulate-precuneus and inferior parietal SUVRs (p-values<0.0001). Tau correlated with baseline MMSE across numerous regions including Braak Stage 5, left frontal cortex, and total cortical burden (p-values<0.001), whereas correlations with ADAS-cog were seen primarily in frontal cortex (p<0.001). Baseline volumetric measures correlated with MMSE and ADAS-cog in left temporal, inferior and middle frontal, and parietal regions (p<0.001). In a comparison between imaging values, age, and cognitive scores at baseline as predictors of subsequent cognitive decline in the placebo group, FDG left middle frontal SUVR and AD Progression classifier score were the strongest predictors of subsequent ADAS-cog worsening (R=-0.64, 0.62, p<0.005, N=19), while greater tau burden and lower volume in a temporal composite region were the strongest predictors of decline in MMSE (tau p<0.008, volume p<0.004). **Conclusion:** Patients with a clinical diagnosis of mild to moderate AD exhibit a wide range of tau burden, hypometabolism, and atrophy, which correlate with one another, baseline clinical endpoints, and subsequent clinical progression. These relationships provide insight into differences observed in rates of decline and suggest that imaging biomarkers can be valuable in patient stratification to aid in detection of therapeutic effect.

P064- DIFFUSION TENSOR IMAGING INFORMS THE DETECTION AND PREDICTION OF WHITE MATTER HYPERINTENSITY LOAD. D. Scott[1], L. Bracoud[2], C. Conklin[3], J. Suhy[1] *((1) Bioclinica - Newark (United States), (2) Bioclinica - Lyon (France), (3) Bioclinica - Philadelphia (United States))*

Background: White matter hyperintensities (WMH) as detected on T2-weighted or FLAIR MRI are presumed to have vascular origin, and represent evidence of small vessel cerebrovascular disease, axonal loss and demyelination. Their appearance is common and increases with normal aging, but WMH load is also a prominent marker of many neuropsychiatric diseases including mild cognitive impairment (MCI) and Alzheimer's Disease (AD). Asymptomatic cerebrovascular disease combined with amyloid and tau pathology may significantly accelerate the trajectory of cognitive decline and disease progression. Subjects at risk for worsening vascular features thus become a relevant sub-population for therapeutic intervention along the dementia cascade. Diffusion tensor imaging (DTI) permits examination of microstructural tissue alterations in white matter tracts beyond the resolution of clinical MRI sequences used to detect WMH. **Objectives:** We sought to assess whether DTI could provide evidence of the likelihood of increasing WMH load in MCI and AD patients from the Alzheiemer's Disease Neuroimaging Initiative (ADNI). **Methods:** From the ADNI website, we identified 166 subjects (45 normal controls, 87 MCI patients, and 34 AD patients) who had 2 visits with WMH load, and had DTI on or near the time of their WMH baseline scan. WMH load was calculated as part of a four-tissue segmentation method by the DeCarli lab at UCD and was subsequently normalized by intracranial volume. For each subject, we identified the earliest and latest visits for which WMH load was available; visits were separated by an average of 2.2 years. The difference in WMH load for each subject was calculated as the percent change in normalized WMH from baseline, then annualized by dividing by the time between visits. DTI summary measures provided by the Thompson lab at UCLA include fractional anisotropy (FA), and mean, axial and radial diffusivity from a set of 57 white matter atlas labels. DTI and WMH baseline visits were the same for most subjects (screening visit) and differed by an average of 29 days across all subjects. Baseline DTI and annualized change in WMH were entered as coefficients into a non-linear regularized regression model using the lassoglm routine in MATLAB. The lasso is a sparse implementation of ridge regression where coefficient estimates minimizing model RSS plus the shrinkage penalty are tuned by a parameter lambda. The effect of lambda is to control the impact of RSS and the penalty term, which if sufficiently large leads to some coefficients being set to zero and effectively dropped from the model. The value of lambda was selected through 5-fold cross-validation and the final model was fit using all predictors and the cross-validated lambda value. **Results:** WMH load at baseline was significantly greater in MCI ($t = 2.3$, two-tailed $p = 0.02$) and AD patients ($t = 3.8$, $p = 0.0002$) than normal controls. Change in WMH load was not significantly different at the group level for any patient group, though roughly 50% of subjects demonstrated increasing load in each group. At baseline, the lasso model revealed DTI features which strongly correlated with WMH load, including an index of anisotropy ($t = -8.4$, $r = -0.55$, two-tailed $p < 3 \times 10\text{-}14$), and a radial diffusivity feature ($t = 8.8$, $r = 0.57$, $p < 2 \times 10\text{-}15$). Baseline DTI was also strongly correlated with change in WMH load, where the model revealed an axial diffusivity feature ($t = -4.5$, $r = -0.39$, $p < 2 \times 10\text{-}5$). All features remained significant following Bonferroni correction for multiple comparisons (corrected threshold $p < 0.0002$). **Conclusion:** These results extend findings suggesting that DTI can reveal microstructural tissue damage underlying the appearance and future development of WMH. Axonal damage is associated with lower anisotropy and higher radial diffusivity, reflecting greater diffusion of water perpendicular to white matter tracts. Subjects with higher WMH load at baseline prominently demonstrated these effects in several brain regions. In contrast, axial diffusivity reflects diffusion of water parallel to white matter tracts, and is expected to decrease where white matter is disrupted. We observed reduced axial diffusivity at baseline was associated with worse WMH load outcomes over the next two years. Machine learning was instrumental in performing dimensionality reduction necessary to identify DTI features linked to WMH load. These features indicate diffusivity within a distributed set of white matter tracts may inform the diagnosis and prognosis of WMH appearance, and could help identify subjects at risk for worsening vascular contribution to disease progression.

P065- CLASSIFYING COGNITIVELY HEALTHY SUBJECTS FROM MILD COGNITIVE IMPAIRED AND ALZHEIMER'S DISEASE PATIENTS USING TAU-PET: THE ROLE OF SPATIAL RESOLUTION AND PET PRE-PROCESSING. A. Palombit[1], R. Manber[1], R. Joules[1], R. Parker[1], R. Wolz[1,2] *((1) IXICO Plc - London (United Kingdom), (2) Imperial College London (United Kingdom))*

Background: A fundamental hallmark of Alzheimer's Disease (AD) has been established in the spatial bio-distribution of misfolded phosphorylated Tau protein [1]. The availability of in-vivo methods to assess such distribution based on Positron Emission Tomography (PET) scans with [18F]-AV-1451 (Tau-PET) paved the way for its clinical implementation. To achieve sufficient motion-robustness in a range of imaging protocols, Tau-PET assessments are often based on composite regions for example derived from Braak staging [1]. Beyond the relatively coarse Braak regions, it is of interest to understand how Tau-PET uptake differs in more localised regions between Cognitively Normal (CN), Mild Cognitive Impaired (MCI) and AD. Furthermore, it is unclear how different PET pre-processing steps might impact group classification performance. **Objectives:** To compare the performance of classifiers trained on Tau-PET Standard uptake value ratio (SUVR) features defined over high-resolution whole-brain segmentations (FreeSurfer [2] and LEAP [3]) and low-resolution Braak composites. The impact of PET pre-processing on classification performance reproducibility will be investigated. **Methods:** Included is 610 (380 CN, 173 MCI, 57 AD) Tau-PET datasets from ADNI (http://adni.loni.ucla.edu). SUVR measures, available from ADNI as tabled results, were selected across 94 FreeSurfer (FS) [4] regions and 3 Braak composites (1+2, 3+4, 5+6) for all subjects. The cerebellum cortex was considered as reference region [5]. A random subset ("test set", 35 CN, 11 MCI, 17 AD) of this dataset was selected to simulate an independent study cohort and the remaining 547 subjects were used as a "modelling set" in the classification experiments described below. In the test set, LEAP segmentations were calculated on the associated T1w MRI, uptake was then measured in the motion-corrected Tau-PET scan in 142 regions of interest. The modelling set was randomly split into training

(80%) and validation set (20%). Based on this division, group classification (3-class) was separately performed with two random forest classifiers based on subject's SUVR measures across 1) low-resolution Braak composites (RF- Braak) or 2) high-resolution FS parcels (RF-HR), both including age, sex and education features. Performance of the trained classifiers was confirmed on the independent test set and associated LEAP processing. To assess RF-HR classification performance on the independent test set, LEAP ROI's were matched to the corresponding FS ROI's used to train the classifier, allowing a fair comparison with different pre-processing and segmentation pipelines. This setup allows for exploring the role of pre-processing on classifier performance. **Results:** The RF-Braak model showed significant test set performances with accuracy/recall/precision/F1 (A/R/P/F1) of 0.63/0.63/0.51/0.51. When ranked by feature importance, Braak 5-6 was ranked most discriminative, followed closely by Braak 1-2. Inspection of the confusion matrix revealed high misclassification rate between CN and MCI, reducing the overall accuracy. The RF-HR model reported superior group discrimination having significant A/R/P/F1 of 0.70/0.70/0.71/0.66 with similar misclassification rate between NC and MCI as RF-Braak. Relevant imaging regions were highlighted as amygdala, hippocampus along with entorhinal, parahippocampal, inferior-temporal, insular, frontal and temporal poles, fusiform and lingual cortices, also relevant Braak sub-regions [1]. The RF-HR model performed similarly in validation and test sets considering SUVR features from ADNI FS regions: A/R/P/F1 of 0.65/0.65/0.62/0.62. Similar performances were observed when classifying test subjects based on the feature set obtained with by means of in-house pre-processed data: A/R/P/F1 of 0.65/0.65/0.62/0.61 showing that unbiased classification can be obtained using consistent Tau-PET pre-processing pipelines. **Conclusion:** In this work, we demonstrated the usage of [18-F]-AV-1451 Tau-PET data to provide biomarkers that effectively discriminate AD vs HC vs MCI providing classification performance robust to differences in pre-processing. SUVR in Braak composites was less discriminative for MCI and HC than SUVR features from whole-brain segmentations. Many classification-relevant regions were nonetheless part of such composites, suggesting their aggregation might mask relevant in-vivo Tau-PET patterns. Making use of a different Tau-PET pre-processing to that employed for the training set data, did not affect the classification performances on an independent test set. Note that pre-processing differences in this work included the usage of a different atlas while PET pre-processing did operate in native PET reconstruction space without additional smoothing or resampling steps (unlike standard ADNI PET pre-processing [4]) before the regional LEAP sampling step to preserve maximal Tau-PET sensitivity. These results suggest the feasibility of using classification models trained on comparable datasets to support cross-sectional stratification over novel Tau-PET studies and trials. **References:** [1] Braak H, et al.Acta Neuropathol. 2006;112(4):389–404. [2] Fischl, B., et al. Neuron 33, 341-355. [3] Wolz R, et al. Neuroimage. 2010;49(2):1316–1325. [4] Jagust WJ, et al. Alzheimers Dement. 2015;11(7):757–771. [5] Baker SL, et al. J Nucl Med. 2017; 58(2):332–338.

P066- COMBINED THERAPY BETWEEN THE CHOLINESTERASE INHIBITOR DONEPEZIL AND THE CHOLINERGIC PRECURSOR, CHOLINE ALPHOSCERATE IN ALZHEIMER'S DISEASE: EFFECT ON BRAIN ATROPHY.

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Background: Cerebral atrophy is a common feature of several neurodegenerative disorders, including Alzheimer's disease (AD). In AD brain atrophy is associated with loss of gyri and sulci in the temporal and parietal lobes, in parts of the frontal cortex and cingulate gyrus as well as in the hippocampus. **Methods:** ASCOMALVA [Effect of association between a cholinesterase inhibitor (ChE-I) and choline alphoscerate on cognitive deficits in AD associated with cerebrovascular injury] is a multicenter, randomized, placebo-controlled, double-blind clinical trial that was designed spontaneously by the investigators. The trial recruited AD patients with concurrent cerebrovascular damage (n = 210; 78 males and 132 females). The reason of the choice is that these patients represent a population with major cholinergic hypofunction. Patients were treated with donepezil + choline alphoscerate [donepezil (D,10 mg/day) + choline alphoscerate (CA 1,200 mg/day)] or donepezil + placebo [reference group, D (10 mg/day) + placebo]. Patients were examined by cognitive, functional and behavioral tests. Among patients who underwent annual MRIs, 56 patients were selected (27 treated with D+P; 29 treated with D+CA). These subjects had resonances obtained with similar and new generation equipment to ensure data comparability. Data from magnetic resonance were used for the cerebral volume analysis. **Results:** Patients in the D group showed a statistically significant reduction in gray matter from baseline after the second year of observation. The reduction of the volumes of grey and white matter was compensated by a significant increase in cerebrospinal fluid volume. D+CA treatment resulted in a significant difference from baseline only after the third year of observation. The volume analysis of hippocampus and amygdala grey matter has shown, a progressive reduction in the volume of these two areas noticeable along the course of the study. These reductions were more pronounced in the D group than in the D+CA group. The trend of cerebral atrophy was similar for the limbic areas (hippocampus, amygdala and parahippocampal gyrus) and cerebrocortical and striatal areas (frontal cortex, caudate nucleus, putamen and globus pallidus) considered. Morphometric findings were confirmed by neuropsychological tests. **Conclusions:** Our findings indicate that cholinergic precursor loading strategy consisting in the addition of choline alphoscerate to standard treatment with the ChE-I donepezil counters to some extent the loss in volume occurring in some brain areas of AD patients. The observation of results in cognitive, functional and behavioral tests suggests that morphological changes observed may have clinical relevance.

P067- A FULLY AUTOMATIC PIPELINE FOR ESTIMATION OF REGIONAL BRAIN VOLUME CHANGE USING JACOBIAN INTEGRATION. R. Joules[1], R. Wolz[1,2], R. Parker[1] *((1) IXICO Plc - London (United Kingdom), (2) Imperial College London - London (United Kingdom))*

Background: Regional brain volume change is a commonly employed endpoint in clinical trials assessing Alzheimer's disease (AD) progression and potential treatment effects. Several methods have been used to estimate volume change from T1 weighted MR images, the commonly employed gold-standard for volume change is the boundary shift integration (BSI) method (Freborough; IEEE; 1997). This however, often requires a manual intervention, increasing resource cost and may be susceptible to inter and intra-rater variability. An alternative method, with potentially increased sensitivity compared to BSI is an automated Jacobian Integration (JI) approach (Nakamura; Neuroimage Clin; 2014) which permits the elimination of manual intervention and its associated errors. **Objectives:** Here we integrate a multi-atlas whole-brain segmentation pipeline, LEAP (Ledig; Proc ISBI; 2012) to a fully automatic pipeline for estimation of volume change over time for a range of brain regions. In this work we validate the JI pipeline against the BSI method in the lateral ventricles for an AD cohort. **Method:** We have developed a fully automatic pipeline to estimate regional volume change between T1 weighted images using a Jacobian integration based approach. In brief, longitudinal images are brain extracted using a multi-atlas approach Pincram (Heckermann; PLOS ONE; 2015) , inhomogeneity corrected using the N4 pipeline from ANTs. Once prepared, images are affinely registered and transformed to a "half-way" space between the image pair to reduce registration bias. Once aligned, a diffeomorphic, symmetric non-linear registration is performed using SyN (Avants; Med Image Anal; 2008) and the Jacobian determinant image computed from the nonlinear warping fields. This Jacobian determinant image encodes volume changes between images at a voxel level which can then integrated within a region of interest to estimate regional percentage volume change. This method was applied to 190 subjects enrolled in a clinical trial with a baseline and 1 year follow-up acquisition. All subjects have independently computed BSI values derived from a manually defined lateral ventricle region of interest (ROI) at baseline. All baseline images were brain extracted and a whole-brain segmentation estimated with the LEAP pipeline. The lateral ventricles from these segmentations were employed as the region of interest in the JI analysis pipeline. The JI approach was applied to subject-wise image pairs of baseline and 1-year follow-up T1 scans with ROIs defined by the LEAP segmentation transformed to the "halfway space" between image pairs. The agreement in volume change for the lateral ventricles was computed between JI and BSI methods using correlation and bland-Altman plots. **Results:** Automatic quality control was applied to identify image subjects failing the JI pipeline by assessment of image agreement after the non-linear registration. Four subjects (2%) were found to have failed and were excluded from analysis. For the remaining 186 we observe a significant correlation in percentage volume changes over 1year between the JI and BSI approach ($r=0.91$, $p<<0.001$). A mean difference in percentage volume of -0.12% (SD: 2.4%) indicating a negligible offset between method volumes. No notable bias was observed in Bland-Altman plots indicating methods report comparable changes in volumes across the range of input volumes. **Conclusions:** We have presented a fully automatic pipeline for estimation of volume change over time in which we have demonstrated comparability to a commonly accepted standard method, BSI, for the lateral ventricles in an AD cohort. The JI method has the advantage of being fully automated thus can offer efficiency savings and improved consistency when compared to BSI and can be integrated easily with any atlas in an automated approach. Furthermore quality control measures can be integrated to automatically identify cases of algorithm failure thus reducing manual rater burden and improving dataset quality. Moreover, the JI pipeline, when integrated with a whole brain parcellation, provides a flexible approach to compute regional volume change for a range of regions of interest in an operationally efficient manner without the resource burden of additional segmentations.

P068- IMAGING MARKERS OF CEREBRAL SMALL VESSEL DISEASE AND AMBULATORY BLOOD PRESSURE MONITORING PROFILE IN OLDER ADULTS WITH COGNITIVE COMPLAINTS. Y.S. Shim *(The Catholic University of Korea - Seoul (Korea, Republic of))*

Background & Objective: Hypertension is a well-known major risk factor for cerebral small vessel disease (cSVD), and 24-hour ambulatory blood pressure monitoring (ABPM) is used to study blood pressure (BP) under normal living conditions as it provides a reliable estimate of the habitual diurnal BP rhythm, which may be used to independently predict hypertension-related complications. We investigated the clinical differences including magnetic resonance imaging (MRI) findings and cognitive function between vascular risk groups, according to the ABPM results. Additionally, we examined which ABPM profiles have influences on the individual imaging findings of cSVD, such as white matter hyperintensities (WMHs), lacunae, and cerebral microbleeds (CMBs), respectively. **Methods:** A total of 186 subjects with memory complaints, including 60 mild cognitive impairment and 185 Alzheimer's dementia, were recruited. Visual severity of WMHs and numbers of lacunae and CMBs were assessed using brain MRI. Through the ABPM, ambulatory hypertension (AMHBP) was defined as over 135/80 mmHg. High risk group was classified with nocturnal BP dipping <10%, night time systolic BP variability of standard deviation >10.8, and pulse pressure >53 mmHg. Group comparisons and logistic regression analysis was performed. **Results:** There was no differences of clinical and imaging findings between groups with and without AMHBP. However, among 3 groups (No AMHBP, intermediate risky with AMHBP, and high risky with AMHBP), age (76.02±7.80, 72.84±7.17, and 76.80±6.73, p=0.008), MMSE score (20.92±5.82, 21.40±5.70, and 18.69±7.19, p=0.037), and the severity of WMHs, especially deep WMHs (1.27±0.80, 0.93±0.84, and 1.35±0.83, p=0.017) were different. Nocturnal dipping and variability of BP showed associations with the severity of WMHs and the number of CMBs and lacunae. Especially, logistic regression analysis showed association of nocturnal dipping with moderate to severe WMHs (Exp(B)=1.072, 95% confidence interval (CI) 1.02~1.126, p-0.006), CMB (Exp(B)=1.093, 95% CI 1.018~1.173, p=0.014) and lacune (Exp(B)=1.056, 95% CI 1.003~1.173, p=0.036). **Conclusions:** We found that loss of nocturnal dipping, high night-time systolic BP variability, and increased pulse pressure had harmful effects on cognition and cSVD, in addition to AMHBP. Especially, loss of nocturnal dipping associated with severe WMHs, and numbers of CMB and lacune. Further

research is needed to fully establish the causal and therapeutic effects of ABPM profile and clinical and MRI findings of cSVD.

P069- A PIPELINE FOR AUTOMATED DIFFUSION MRI ANALYSIS: OVERVIEW AND APPLICATION TO THE STUDY OF ALZHEIMER'S DISEASE. R. Parker[1], R. Joules[1], R. Wolz[1,2] *((1) IXICO plc - London (United Kingdom), (2) Imperial College London - London (United Kingdom))*

Background: Diffusion MRI (D-MRI) has proved invaluable for the study of Alzheimer's Disease, probing tissue structural properties at scales beyond the reach of more rudimentary MR sequences and allowing for advanced 3D modelling of nerve bundle trajectories. Here, we introduce a pipeline for the analysis of D-MRI brain scan data, incorporating steps for the minimisation of common artefacts (subject motion, EPI distortion, eddy currents), calculation of diffusion tensor and NODDI (Zhang, et al., 2012) metrics for 200+ gray and white matter regions, and exploration of structural connectivity properties via the combination of streamline tractography and graph analytics. 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 of processed data. **Objectives:** to demonstrate pipeline validity via i) comparison with ExploreDTI (Leemans, et al., 2009): a software package widely used in academic research (but which requires significant manual intervention), and ii) by application to a cohort of older adults with and without Alzheimer's Disease. **Methods:** D-MRI and T1-weighted MRI for 14 cognitively-normal older adults (CN, average age=71.74, no. males=7) and 14 adults with Alzheimer's Disease (AD, n=14, average age=73.26, no. males=8) was downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (Petersen, et al., 2010). T1-weighted images were segmented into anatomical subregions, using IXICO's LEAP algorithm (Wolz, et al., 2010). Processed T1 images and raw D-MRI images were then processed using the pipeline presented here. Image analysis was also repeated using ExploreDTI, and Spearman's correlation was used to assess the similarity of several endpoints common to both pipelines: measures of tissue structural integrity - fractional anisotropy (FA) and mean diffusivity (MD) - averaged over anatomical regions-of-interest, as well two measures of brain structural network configuration: node degree and local efficiency. To identify AD-related changes in brain structural properties, plugin endpoints (FA, MD and 5 network measures) were collated and contrasted across disease groups using the permutation test. **Results:** In comparing our pipeline with ExploreDTI, strong correlations were found for regionally-averaged FA ($r=.94$, $p<.001$) and MD endpoints ($r=.96$, $p<.001$). Concerning network measures, node degree was similar between pipelines ($r=.79$, $p<.001$), but network local efficiency yielded a weaker (but still significant) relationship ($r=.31$, $p<.001$). This discrepancy may stem from the use of the Anatomically-constrained tractography (Smith, et al., 2012) modifier within our pipeline, which employs biologically-realistic tissue priors in order to reduce false positive connections between regions (leading to sparser, but more accurate networks). Visual inspection of structural connectomes corroborates this interpretation. Differences between AD and CN groups in FA and MD were found in regions including the hippocampus, fornix and splenium of the corpus callosum, but not in the corticospinal tract, brainstem (medulla) or the cerebellar white matter, consistent with previous reports. Exploratory analysis of whole-brain network properties revealed AD-related connectivity alterations in regions including the medial orbital gyrus (reduced centrality), precuneus (reduced node degree) and the anterior cingulate gyrus (reduced clustering) ($p<.01$, uncorrected), regions previously implicated in the pathogenesis of the disease. **Conclusions:** We present a pipeline for diffusion MRI analysis and demonstrate its potential for analysis in Alzheimer's Disease. 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:** Leemans, A.J.B.S.J.J.D.K., Jeurissen, B., Sijbers, J. and Jones, D.K., 2009, April. ExploreDTI: a graphical toolbox for processing, analyzing, and visualizing diffusion MR data. In Proc Intl Soc Mag Reson Med (Vol. 17, p. 3537). 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P070- PREDICTION OF CLINICAL PROGRESSION USING AMYLOID BIOMARKERS IN SUBJECTIVE COGNITIVE DECLINE: A LONGITUDINAL OBSERVATIONAL STUDY. Y.J. Hong[1], Y.B. Kim[1], S.H. Kim[1], H.E. Shin[2], S.B. Lee[1], D.W. Ryu[1], J.W. Park[1], K.W. Park[3] *((1) Department of Neurology, Uijeongbu St. Mary's Hospital - Uijeongbu (Korea, Republic of), (2) Department of Neurology, Bucheon St. Mary's Hospital - Bucheon (Korea, Republic of), (3) Department of Neurology, Dong-A University Medical Center - Busan (Korea, Republic of))*

Backgrounds: Subjective cognitive decline (SCD) represents self-reported cognitive decline occurring in the absence of objective cognitive impairment. It is regarded as the first symptomatic stage of Alzheimer's disease (AD) and known to have an increased risk of clinical progression. However, due to its heterogeneity, using sensitive biomarkers at baseline to predict clinical progression would be clinically important. Prospective longitudinal studies whether the baseline characteristics and biomarkers would predict cognitive decline have not yet been clearly explored in this population. We conducted an observational cohort study and investigated the relevance between the baseline amyloid biomarkers and progressions. **Objectives:** The objective of this study was to investigate clinical characteristics of SCD with amyloid pathologies and confirm whether SCD subjects with amyloidosis would show faster cognitive decline than those without amyloidosis. **Methods:** Data from a longitudinal observational cohort study between February 2016 and January 2019. Individuals aged 50 and above with consistent cognitive

complaints without any objective cognitive impairment were eligible for the study. All the subjects underwent baseline physical and neurologic examinations, blood samplings, detailed neuropsychological tests, a self-report questionnaire, brain MRIs, and florbetaben Positron Emission Tomography (PET) scans. Baseline vascular lesions and hippocampal atrophies in the MRIs were assessed. PET findings were interpreted using a visual rating scale named brain amyloid plaque load (BAPL) and rated as positive amyloidosis with a BAPL score of 2/3. Subjects underwent annual follow-up evaluations to assess clinical progression during the study period. Group comparisons were performed using SPSS (version 18.0). **Results:** A total of 47 participants with SCD (mean age: 69.9±6.7) were enrolled at baseline and 31 SCDs completed at least one annual follow-up evaluation. Twelve among the 47 (25.6%) showed positive amyloid depositions. Mean follow up durations were 24.7±7.5 months (range, 10-36 months). The other 16 refused the follow-up evaluations and dropped out from the study. Study completers were not different from dropped-out subjects in terms of clinical characteristics except the age. Amyloid-positive group were similar in the baseline characteristics and cognitive scores compared to the amyloid-negative group except the frontal executive function. Mean durations from the baseline to the last follow-up visit were not different between amyloid-positive and amyloid-negative groups. None progressed to mild cognitive impairment or dementia during the study period. Mini-Mental State Examination scores decreased 1.2 point in the amyloid-positive group, while, 0.6 point in the amyloid-negative group although those differences did not reach statistical significance ($p>0.05$). Instead, amyloid-positive SCDs progressed more in the verbal memory function compared to the amyloid-negative SCDs after adjustment for age. **Conclusion:** In this study, 25.6% among the SCDs were preclinical AD and they showed faster memory decline compared to the SCDs without amyloid pathologies during 24 months.

P071- VALIDATION OF RESTING STATE NEUROVASCULAR COUPLING IN THE OASIS-BRAINS DATASET TO DIFFERENTIATE NORMAL ELDERLY BRAINS FROM ALZHEIMER'S DISEASE. T. Kuhn[1], F.S. Pereles[2], M. Whitney[2], S. Becerra[3], S. Jordan[4], H. Kachhia[2]
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Background: Neurovascular coupling (NVC) refers to the dependence of neuronal activity on the supply of oxygen and nutrients delivered by blood vessels. Studies have suggested that the disruption of cerebrovascular regulation is present in many diseases, including neurodegenerative ones (Alzheimer's). Previous attempts have been made to measure and/or visualize this phenomenon using EEG, optical imaging and task-based fMRI. However, these techniques all relied on comparing recordings of the brain at rest to recordings of the brain while it performs a task (e.g. visual task, breath hold, or cognitively engaging task). Here, we describe a method of measuring and visualizing NVC using resting state fMRI data only. **Objectives:** While our group has demonstrated the feasibility that resting state fMRI based NVC analysis could successfully differentiate subjects with Alzheimer's disease and Parkinson's disease from age matched healthy controls in our own clinical practice and imaging centers, we sought to validate our techniques are generalizable by applying NVC on independently acquired data sets to prove that our clinical findings were not biased. **Methods:** Resting BOLD imaging data was used from an external data set: Open Access Series of Imaging Studies (OASIS). Cross-sectional cohort: Participants selected received a rating assessing degree of cognitive impairment using the Clinical Dementia Rating scale. CDR level 0 corresponded to "no cognitive impairment" (N= 1310, mean age = 68.9, sd = 9.32, 58.9% female); CDR level 0.5 corresponded to "mild cognitive impairment" (N= 277, mean age = 75.1, sd = 7.38, 43.4% female); CDR level 1 corresponded to "mild dementia" (N= 95, mean age = 74.8, sd = 8.37, 44.0% female). Measuring neurovascular coupling (NVC): Using resting BOLD fMRI images only, our NVC method measures the voxelwise range of BOLD signal and compares that against an anatomically plausible variability range using signal strength from an identified anatomical arterial structure. This important step, controlling for the subject arterial signal, normalizes differences between people and across different scanners, allowing for comparison of separate subjects. This analysis results in a voxel-wise ratio of range of signal strength over arterial signal. Differentiation of Cognitive Levels: Discriminant ability as well as sensitivity, specificity, positive and negative predictive value were computed from iterative discriminant function analyses to determine the ability of NVC to differentiate participants based on CDR value (0, 0.5 and 1). **Results:** Based on NVC data, patients with CDR level 0 were accurately classified as CDR level 0 with 96.7% sensitivity, 100% specificity, 100% PPV and 97.1% NPV. Patients with CDR level 0.5 were accurately classified as CDR level 0.5 with 94.1% sensitivity, 97% specificity, 86.5% PPV and 98.8% NPV. Patients with CDR level 1 were accurately classified as CDR level 1 with 97.1% sensitivity, 98.5% specificity, 97.1% PPV and 98.5% NPV. **Conclusions:** Neurovascular coupling (NVC) analysis successfully differentiated dementia and mild cognitive impairment patients from controls as well as from one another. Neurovascular coupling was also successfully cross-validated in its ability to differentiate patients based on CDR value with high accuracy. Results from application of our new NVC method to differentiate healthy subjects from cognitive decline in an independently acquired dataset validates that our technique is generalizable to populations outside our own practice and therefore applicable to patient populations for pharmaceutical studies. A benefit of our new NVC method is that NVC does not require any special fMRI add on beyond the standard BOLD acquisition. Further analyses will involve investigating potential improvements in diagnostic accuracy using regional neurovascular coupling metrics and more clearly delineated patient samples (e.g. amyloid and tau PET negative).

P072- PREDICTION OF TREATMENT RESPONSE TO DONEPEZIL USING AUTOMATED HIPPOCAMPAL SUBFIELDS VOLUMES SEGMENTATION IN PATIENTS WITH MILD ALZHEIMER'S DISEASE. H.R. Na *(Catholic medical center - Seoul (Korea, Republic of))*

Previous studies reported some relationships between donepezil treatment and hippocampus in Alzheimer's disease (AD). However, due to methodological limitations, their close relationships remain unclear. The aim of this study is to predict treatment response to donepezil by utilizing the automated segmentation of hippocampal subfields volumes (ASHS) in AD. Sixty four AD patients were prescribed with donepezil

and were followed up for 24 weeks. Cognitive function was measured to assess whether there was a response from the donepezil treatment. ASHS was implemented on non-responder (NR) and responder (TR) groups, and receiver operator characteristic (ROC) analysis was conducted to evaluate the sensitivity, specificity, and accuracy of hippocampal subfields in predicting response to donepezil. The left total hippocampus and the CA1 area of the NR were significantly smaller than those of the TR group. The ROC curve analysis showed the left CA1 volumes showed highest area under curve (AUC) of 0.85 with a sensitivity of 88.0%, a specificity of 74.0% in predicting treatment response to donepezil treatment. We expect that hippocampal subfields volume measurements that predict treatment responses to current AD drugs will enable more evidence-based, individualized prescription of medications that will lead to more favorable treatment outcomes.

Theme: CLINICAL TRIALS: BIOMARKERS INCLUDING PLASMA

P073- LOW TESTOSTERONE LEVELS RELATE TO HIGHER CEREBROSPINAL P-TAU LEVELS: IMPLICATIONS FOR SEX DIFFERENCES IN PATHOLOGICAL TAU.

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Background: Throughout the developmental states of Alzheimer's disease (AD), women have higher levels of pathological tau than men; however, the reason for this sex difference in unknown. Sex differences often indicate an underlying role of sex hormones. Evidence for a protective role of testosterone against the hyperphosphorylation of tau in animal models suggests that the lower testosterone levels in women versus man may be a contributing mechanism to their greater tau levels although the effects of testosterone on AD-related outcomes in women have been minimally examined. Neuroinflammation is also known to play a role in mechanisms related to tau and, given a known relationship between inflammation and tau and a typically heightened inflammatory response in women versus men, neuroinflammation is another potential mechanism underlying sex differences in tau. **Objective:** In this preliminary analysis, we examined the relationship between plasma testosterone levels and cerebrospinal fluid (CSF) levels of p-tau in men versus women at-risk for AD by way of a mild cognitive impairment (MCI) diagnosis. Secondarily, we examined whether testosterone moderates the effect of neuroinflammation on CSF p-tau in women and men. **Methods:** The sample included 97 participants from the Alzheimer's Disease Neuroimaging Initiative who were diagnosed as MCI and had baseline measures of CSF p-tau and plasma testosterone levels measured using the Rules Based Medicine Human DiscoveryMAP Panel. Participants included 68 men and 29 women aged 55-90 years, and 96% White. We used linear regressions to examine the separate and interactive effects of sex and testosterone on CSF p-tau levels. In subsamples with CSF neuroinflammatory markers, we examined whether testosterone moderates the effect of continuous levels of neuroinflammatory markers sTREM2 (n=82), IL-6, TNFα, TNFR1 and TNFR2 (n=65), and YKL-40 (n=42) on p-tau. Analyses adjusted for age, education, and APOE ε4 genotype. **Results:** As expected, women had significantly lower testosterone levels ($p<.001$) and higher CSF p-tau levels ($p=.01$) compared to men. We found that lower testosterone levels were significantly associated with higher CSF p-tau regardless of sex ($p=.001$) although this was mostly driven by the low testosterone levels in women. In fact, we found that the higher p-tau levels in women versus men was eliminated ($p=.81$) when comparing men to women in the higher range of female testosterone levels (i.e., above the median in women). Across sex, testosterone levels significantly interacted with the neuroinflammatory markers of TNFR1, TNFR2 and YKL levels (p's$<.05$). When dichotomizing the overall sample into low testosterone (35% men) versus high (100% men) testosterone groups based on a median split, relationships between higher neuroinflammatory markers and higher CSF p-tau were either stronger in or specific to those with lower testosterone versus those with higher testosterone. **Conclusions:** Low testosterone levels relate to greater CSF p-tau across sex and provide a context in which neuroinflammation relates more strongly to CSF p-tau. Results suggest that the low testosterone levels commonly seen in women may predispose them to greater pathological tau. Although the effect of testosterone supplements on cognitive outcomes has been considerably examined in men, our results raise the possibility that testosterone supplements may have benefit in women and warrants consideration for intervention studies in women with symptomatic AD.

P074- ASSOCIATION BETWEEN SERUM MARKERS OF INTESTINAL PERMEABILITY AND CSF BIOMARKERS OF ALZHEIMER'S DISEASE AND NEURODEGENERATION

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Background: Evidence has shown that increased gut membrane permeability associates with a range of immune and metabolic diseases, as well as neurological disorders. For instance, higher intestinal permeability has been observed in autism, multiple sclerosis and Parkinson's disease. Gut microbial dysbiosis has been associated with decreased intestinal membrane integrity, and we have previously demonstrated that patients with Alzheimer's disease (AD) dementia harbor altered gut microbial communities compared to cognitively unimpaired (CU) individuals. However, the extent to which intestinal permeability is altered in AD is unknown. **Objectives:** We performed exploratory analysis to determine whether patients with AD dementia and biomarker evidence of AD pathology exhibit increased intestinal membrane permeability compared with CU individuals.

Additionally, we tested whether permeability associates with AD pathology measured via cerebrospinal fluid biomarkers, as well as with hippocampal volume measured via MRI. **Methods:** Participants were enrolled in the Wisconsin Alzheimer's Disease Research Center and the Wisconsin Registry for Alzheimer's Prevention. Twenty-nine participants (10 CU amyloid-negative (CU-), 9 CU amyloid-positive (CU+), and 10 amyloid-positive with AD dementia diagnosis) were selected for intestinal permeability analysis, matching on age and sex. Blood serum samples were assayed by Cyrex Laboratories, LCC, using ELISA to capture levels of antibodies associated with both gut epithelial tight junction proteins (including actomyosin IgA, occludin/zonulin (O/Z) IgG, O/Z IgA, and O/Z IgM), and bacterial products (including lipopolysaccharide (LPS) IgG, LPS IgA, and LPS IgM). AD biomarkers (N = 24) in CSF included Aβ42, A 40, pTau, Aβ42/Aβ40, pTau/A 42, total tau, NfL, neurogranin, YKL-40, and MCP-1. Hippocampal volumes were determined via T1-weighted MRI (N = 28) and averaged across hemispheres. Antibody levels were compared across all three groups via Kruskal-Wallis and pairwise via Wilcoxon rank-sum test. Additionally, Spearman's partial correlations controlling for age, sex and CSF biomarker assay batch were performed to test for associations between serum antibodies and CSF biomarkers, as well as serum antibodies and hippocampal volume. **Results:** There were no significant differences in permeability antibody levels between groups. LPS IgA, LPS IgM and O/Z IgM antibodies were negatively correlated with CSF biomarkers, while LPS IgG antibodies showed moderate positive correlations. Specifically, in the full participant cohort LPS IgM negatively correlated with Ptau/A 42, pTau, and total tau (rs={-.45, -.47, -.47}, P={.04, .03, .03}), O/Z IgM negatively correlated with pTau and total tau (rs={-.54, -.48}, P={.01, .03}), and LPS IgG positively correlated with NfL (rs=.47, P =.04). Among CU- participants, LPS IgM correlated negatively with pTau and MCP-1 (rs={-.76, -.84}, P={.045, .02}), and O/Z IgG correlated positively with Aβ42 (rs=.81, P=.03). Actomyosin IgA antibody was also negatively correlated with hippocampal volume (rs=-.77, P=.04) in CU- participants. Within the AD cohort O/Z IgM, O/Z IgA, and LPS IgA correlated significantly with neurogranin (rs={-.98, -.96, -.97}, P={.02, .04, .03}), and LPS IgM correlated with neurogranin and total tau (rs={-1, -.93}, P={.02, .003}) . No partial correlation significance testing survived FDR correction for multiple comparisons. **Conclusion:** In this small exploratory study, intestinal permeability did not differ by cognitive status or CSF amyloid status. Correlation analysis performed across participants suggested relationships between LPS IgM, LPS IgG, LPS IgA and CSF biomarkers of AD and neurodegeneration, but did not survive adjustment for multiple comparisons. Larger studies are needed to interrogate these preliminarily observed relationships.

P075- PREDICTION OF AMYLOID PATHOLOGY BY THE PLASMA AB(1-42)/AB(1-40) RATIO MEASURED WITH FULLY AUTOMATED IMMUNOASSAY SYSTEM (HISCL™ SERIES). K. Yamashita[1], T. Hasegawa[1], T. Iino[1], M. Miura[1], T. Watanabe[1], S. Watanabe[1], S. Iwanaga[1], A. Harada[1], D. Verbel[2], S. Dhadda[2], H. Amino[3], M. Ino[3], A. Koyama[2], T. Miyagawa[4], T. Yoshida[1] *((1) Sysmex Corporation - Kobe (Japan), (2) Eisai Inc. - Woodcliff Lake (United States), (3) Eisai Co., Ltd. - Tsukuba (Japan), (4) Eisai Co., Ltd. - Tokyo (Japan))*

Background: Alzheimer's disease (AD) is the most prevalent form of dementia with significant global public health impact. Confirmation of amyloid pathology in the brain can impact diagnosis and facilitate recruitment of patients into AD clinical trials. Amyloid PET is often used to detect amyloid pathology, but its use may be limited by cost and accessibility. Plasma amyloid beta (Aβ) is a candidate biomarker for early detection of amyloid pathology. There are several reports that suggest plasma Aβ measurement, which is a simple and cost-effective method, has a potential to predict amyloid pathology. Recently we reported the development of fully automated Aβ1-40 and Aβ1-42 immunoassay system (HISCLTM series) which showed good correlation between the plasma Aβ1-42/Aβ1-40 ratio and the CSF Aβ1-42/Aβ1-40 ratio. Here, we report the evaluation of the performance of this assay capable of distinguishing between amyloid positive and negative subjects using clinical trial samples with PET information. **Objectives:** To assess the performance of HISCLTM series using screening plasma samples from the Eisai Elenbecestat Phase 3 program to distinguish amyloid positive from amyloid negative subjects based on visual read of amyloid PET. **Methods:** We used our fully automated immunoassay system (HISCLTM series) to measure plasma Aβ1-40 and Aβ1-42. The dynamic range of Aβ1-40 and Aβ1-42 were 8.6 – 975 pg/ml and 0.7 – 895 pg/ml, respectively. Samples were from clinical trial subjects in screening with a clinical diagnosis of MCI and mild AD who underwent amyloid PET to confirm amyloid status for enrollment. Samples and data from a subject's screening/baseline visit were collected. Amyloid status was established using the visual read of a subject's PET scan. Half of the samples were from subjects considered as amyloid positive based on visual read; the other half from amyloid negative subjects. To evaluate the overall performance of these analytes as measured by HISCLTM series, as measured by area under the curve (AUC), receiver operating characteristic (ROC) analysis was performed using logistic regression. The plasma Aβ1-42/Aβ1-40 ratio, as well as a model incorporating plasma Aβ1-42 and Aβ1-40 (treated independently), subject age and APOE4 status, were also evaluated in separate analyses. The plasma Aβ1-42/Aβ1-40 ratio cutpoint that best distinguished these samples overall was also determined. **Results:** An initial cohort of 192 subjects was selected for this study. The mean (SD) age of the cohort was 73.3 (6.28) years; 92.7% of subjects were White and 51% were Male. APOE4 status was positive in 42.2% of subjects. 84.9% of subjects were considered as having MCI due to AD; 10.4% were diagnosed as having mild AD dementia. Plasma Aβ1-42/Aβ1-40 ratio predicted Aβ PET positivity with an AUC of 0.74. The plasma Aβ1-42/Aβ1-40 ratio cutpoint that best distinguished amyloid status was 0.097 (determined using the Youden Index) resulting in sensitivity of 73% and specificity of 71%. Including age and APOE4 status, in addition to the plasma Aβ1-42/Aβ1-40 ratio, as predictors in the model increased the overall performance (AUC = 0.80). **Conclusion:** We have observed that plasma Aβ1-42/Aβ1-40 ratio measured by our fully automated immunoassay system can predict amyloid pathology. This preliminary result is consistent with several other reports and indicates this fully automated immunoassay system could be a prescreening method for amyloid PET.

P076- ASSESSING AB CLEARANCE AIDED BY MASS SPECTROMETRY. S. Torsetnes[1,2], M. Wettergreen[1,2], E. Christensen[3], T. Fladby[1,4] *((1) Department of Neurology, Akershus University Hospital - Lørenskog (Norway), (2) Clinical Molecular Biology (EpiGen), Medical Devision, Akershus University Hospital and University of Oslo - Oslo (Norway), (3) PreDiagnostics AS - Oslo (Norway), (4) nstitute of Clinical Medicine, Campus Ahus, University of Oslo - Oslo (Norway))*

Background: Amyloid beta (Aβ) is derived from processing of amyloid precursor protein and is the main component in amyloid plaques in Alzheimer's disease (AD). Catabolism in brain innate immune cells (microglia) contribute to Aβ clearance, however, Aβ is catabolized also in peripheral blood (pb) monocytes1. This likely is an enzymatically driven process that may be differentially up- or downregulated and therapeutically influenced. Measurements of catabolized and cleared Aβ fragments in monocytes, other blood derived samples and cerebrospinal fluid (CSF) may thus be of pathological relevance. Our investigation of Aβ degradation products in pb monocytes enabled identification of peptides that predominantly derive from cleavage at the following peptide bonds (pbs); 13-23, 33-34 and 37-40 (data not shown here). These peptides were compared to Aβ42 degradation peptides from in vitro experiments2, suggesting that cleavage close to pbs 20-23, and 33-34 is particularly relevant for intracellular clearance. **Objectives:** Our objective was to compliment the immunoassay technique by use of IP LCMS to map the affinity and selectivity of these targeted antibodies, and simultaneously map the CSF peptides derived from Aβ catabolism. In an accompanying abstract we present results from a Simoa (Quanterix, MA, USA) immunoassay technique showing levels of target peptides in pb monocytes and CSF. **Methods:** A panel of sheep antibodies (by Bioventix Ltd, UK) were raised against an Aβ20-34 peptide, and epitope-mapping was using both standard immunoassay and ELISA was performed to select a preferred monoclonal antibody (mAb, 2A9) to be used for capture. Next, the comprehensive HuCAL library (BioRad, CA, USA), containing 45 billion synthetic antibodies, was screened. The H3 antibody was selected by its capacity to form a complex only when an AβX-34 ligand was bound to mAb 2A9, to form a highly selective anti-complex sandwich. Immunoprecipitation and reversed phase liquid chromatography mass spectrometry (IP LCMS) was performed on CSF with the purpose to test which Aβ peptides and potentially other proteins participating in the HuCAL H3-mAb 2A9 complex. Excess CSF from patients was pooled and used for these affinity and selectivity studies. The IP beads were coated with either the mAb 2A9 alone or the BioRad antibody H3 alone. The IP procedure was then performed in CSF for both types coated beads. However, in addition, a parallel sample, where 2A9 was added CSF, was also used for the H3 beads IP, as only mid-domain Aβ peptides bound to 2A9 should condition H3 binding. **Results:** The output for 2A9 IP in CSF was a total number of 164 unique Aβ peptides extracted, where AβX-40 made up most of the total peptide signal (>20 %), and AβX-34 peptides made up <11 % of the signal from n=6 peptides. The output from H3 IP in CSF with added 2A9 was a total number of 39 unique Aβ peptides, where AβX-40 contributed sparsely to the peptide signal (<3 %), AβX-34 peptides made up more than one third of the signal from n=11 peptides, while all mid–domain peptides (ending from AA32-38) made up almost all signal (>95 %). In addition, when making a rough comparison of the identified peptides in this IP with that of the one with 2A9 (above) the number of AβX-34 peptides doubles when using the 2A9-H3 complex, while the numbers are roughly halved for the non-AβX-34 peptides. These results imply a preferential binding of AβX-34 > AβX-40 when using 2A9 and H3 in a sandwich. The output from H3 alone gave, as predicted, no Aβ peptides; proving that 2A9 bound to a mid-domain peptide is needed for complex formation with H3. **Conclusion:** IP LCMS is a useful tool for the process of designing an immunoassay method with added information on affinity and selectivity in biologically relevant samples. We present an antibody pair that is highly selective for Aβ mid-domain, with highest affinity for AβX-34 peptides, which may be relevant for studies on Aβ clearance and catabolism. The immunoassay application of these on a Simoa instrument is shown an accompanying CTAD contribution. **References:** 1 Simard, A. R. & Rivest, S. Neuroprotective properties of the innate immune system and bone marrow stem cells in Alzheimer's disease. Mol Psychiatry 11, 327-335, doi:10.1038/sj.mp.4001809 (2006). 2 Rogeberg, M., Furlund, C. B., Moe, M. K. & Fladby, T. Identification of peptide products from enzymatic degradation of amyloid beta. Biochimie 105, 216-220, doi:10.1016/j.biochi.2014.06.023 (2014).

P077- A NEW BLOOD-BASED BIOMARKER OF AB CLEARANCE – THE MONOCYTE AB MID-DOMAIN ASSAY. M. Wettergreen[1,2], S.B. Torsetnes[1], B. Gisladottir[1], E. Christensen[3], T. Fladby[1,4] *((1) Department of Neurology, Akershus University Hospital - Lorenskog (Norway), (2) Clinical Molecular Biology (EpiGen), Medical Division, Akershus University Hospital and University of Oslo - Oslo (Norway), (3) Pre Diagnostics AS - Oslo (Norway), (4) Institute of Clinical Medicine, Campus Ahus, University of Oslo - Oslo (Norway))*

Background: Deficiency in cerebral Amyloid beta (Aβ) clearance is implicated in the pathogenesis of Alzheimer's disease (AD), and Aβ clearance systems are potential therapeutic targets in AD. Clearance of Aβ is a complex process were phagocytosis and degradation of Aβ are two important components. Innate immune-linked genetic risk factors contribute to AD, and innate immune cells; microglia in the brain and monocytes/macrophages in the peripheral blood (PB), phagocytose Aβ and contribute to clearance. Several proteases degrade Aβ both in vitro (Rogeberg et al, 2014) and in vivo (accompanying CTAD poster), and at intracellular, cell-membrane and extracellular locations. Activity of these proteases may reflect cellular activation states, and may be manipulated for therapeutic purposes. A number of the reported Aβ cleavage sites give rise to Aβ mid-domain peptides. (Rogeberg et al, 2015). Two common cleavage sites are between amino acid residue 19 (Phe) and 20 (Phe), and between amino acid residue 34 (Leu) and 35 (Met) in the Aβ 1-42 nomenclature, generating the Aβ 20-34 peptide which we produced to raise antibodies. **Objectives:** Our objective was to develop an assay measuring Aβ mid-domain peptides in relevant biological specimens. The intracellular concentration of peptides containing mid-domain fragments may reflect phagocytic activity or Aβ degradation efficiency, and may be measured in microglia/monocytes/macrophages. **Methods:** An immunoassay on the Quanterix Single Molecule Array (Simoa) platform was developed using a proprietary anti-mid-domain sheep monoclonal antibody as capture antibody ("2A9", Bioventix Ltd, UK). The detector reagent consists of an anticomplex antibody, ("H3", Bio-Rad HuCAL technology)

ensuring the optimal Aβ mid-domain peptide specificity and assay sensitivity (CTAD poster ref). CSF pool: Cerebrospinal fluid (CSF) were centrifuged at 2000 g for 10 min and frozen in polypropylene tubes. A CSF pool were made by thawing, pooling and aliquoting excessive CSF from 15 patients. Monocyte samples: Monocytes were isolated from 8 ml blood samples using a combination of BD CPT blood sampling tubes and RosetteSep antibodies from StemCell. Monocyte pool: Monocytes from voluntary blood donors were isolated from the leukocyte unit using a combination of density gradient centrifugation and RosetteSep antibodies. Monocytes from 16 blood donors were pooled and aliquoted. Monocytes were lysed before analysis. **Results:** The anti- Aβ mid-domain antibodies run on the Simoa platform gave a sensitive immunoassay detecting Aβ mid-domain containing peptides with a lower limit of quantification (LLOQ) of approximately 1 pg/ml resulting in measurable levels of the peptides in both CSF and monocyte lysates. The CSF pool had an average conc. of 317 pg/ml, individual monocyte lysate samples ranged from 2-21 pg/ml and the monocyte lysate pool had a concentration of 11 pg/ml. **Conclusion:** Aβ clearance is a key mechanistic determinator in Alzheimer disease progression, and decreased Aβ clearance precedes the clinical AD symptoms by a decade or more. As we show in the accompanying CTAD abstract, the 2A9/H3 combination has a high specificity for mid-domain restricted peptides. Here we show that as used in a sensitive Simoa-assay, this assay detects Aβ mid-domain containing peptides both in CSF and monocyte lysates, and may serve as a tool for PB measurement of Aβ catabolism in both disease progression studies and intervention studies. **References:** Rogeberg M, Furlund CB, Moe MK, Fladby T. Identification of peptide products from enzymatic degradation of amyloid beta. Biochimie. 2014 Oct;105:216-20. Rogeberg M, Wettergreen M, Nilsson LN, Fladby T. Identification of amyloid beta mid-domain fragments in human cerebrospinal fluid. Biochimie. 2015 Jun;113:86-92.

P078- DESIGN OF AN ALZHEIMER'S DISEASE SPECIFIC SNP ARRAY FOR DRIVING POLYGENIC RISK SCORING ALGORITHMS. A. Gibson[1], R. Pither[1], P. Daunt[2], G. Davidson[3], O. Oshota[2], J. Williams[4], V. Escott-Price[4], R. Sims[4], E. Bellou[4], J. Hardy[5], M. Shoai[5], Z. Nagy[6] *((1) Cytox Ltd - Oxford (United Kingdom), (2) Cytox Ltd - Manchester (United Kingdom), (3) Ledcourt Associates - Cambridge (United Kingdom), (4) University of Cardiff - Cardiff (United Kingdom), (5) University College London - London (United Kingdom), (6) University of Birmingham - Birmingham (United Kingdom))*

Background: Stratification and subsequent selection of suitable subjects for clinical trials remains a challenge for Alzheimer's Disease studies and though more tests are becoming available many of them are not feasible for large scale use. Over recent years genetics, beyond ApoE genotyping, has emerged as a potential useful tool for assessing risk of disease and as such is now being considered as part of trial participant screening. In addition to the identification of further risk associated variants, polygenic risk scores have been developed by a number of groups to improve upon the assessment of underlying genetic risk for onset of Alzheimer's Disease. Current methods for collecting genetic data through whole genome sequencing or commercially available SNP arrays are not necessarily optimal for capturing all the relevant genetic information ideally required. Cytox has been working in partnership with leading academic teams in Cardiff University, The University of Birmingham and UCL to implement different PRS algorithms into our SNPfitRTM software to validate the performance of these PRS algorithms and to facilitate global access these tools by drug developers and researchers on a global basis. In addition, we have designed a SNP array in conjunction with Thermo Fisher Scientific that will not only allow generation of genotyping data to drive these PRS algorithms, but also report specifically on key variants in Alzheimer's Disease and other dementias. **Objectives:** To design, build and test a high-density SNP array to provide optimal coverage for Alzheimer's Disease (and other dementias) genetic profiling, specifically to be able to run multiple PRS algorithms from a single genotype. **Methods:** Cytox, working in partnership with Thermo Fisher Scientific, has developed a next generation dementia specific SNP genotyping arrays from which multiple PRS algorithms can be run, named variaTECT IITM (Affymetrix Axiom™) plates and processed on an Affymetrix GeneTitan® scanner. The content of the array was designed to include approximately 800,000 SNPs that have been selected either as a) SNPs that have been identified in very large GWAS studies (including those at sub-threshold significance) b) SNPs of common interest such as ApoE c) rare variants derived from published and unpublished data d) variants important in early-onset AD e) SNPs associated with the mTOR pathway f) SNPs more specifically associated with non-Caucasian populations g) other dementias and neurological disorders h) a pharmacogenetics/ADME panel i) specific content to ensure technical performance such as Quality Control and a GWAS tagging backbone. **Results:** Observed performance metrics show >99% sample pass rate and >99% average call rate. In reproducibility studies using DNA extracted from blood samples from the same donor, a >99% concordance in SNP calls was observed. Equivalence was observed in studies comparing DNA extracted from blood and saliva from the same donor. SNP call concordance was >99%. **Conclusion:** The variaTECT IITM array is believed to be the most comprehensive SNP array suitable for understanding the genetic profile of individuals and specifically their risk of future onset of Alzheimer's Disease. It allows for genotyping of DNA extracted from either whole blood or saliva and will provide all the genetic-related information from an ApoE genotyping to the ability to derive multiple polygenic risk scores from several algorithms.

P079- PERFORMANCE OF A HIGH-THROUGHPUT PLASMA AMYLOID ASSAY FOR DIAGNOSIS OF ALZHEIMER'S DISEASE. I. Feinkohl[1], C. Schipke[2], J. Kruppa[3], G. Winterer[3], T. Pischon[1], I. Heuser[3], O. Peters[3] *((1) MDC - Berlin (Germany), (2) Predemtec - Berlin (Germany), (3) Charité - Berlin (Germany))*

Background: Today, the screening procedure for recruitment into clinical trials in Alzheimer's disease (AD) comprises the measurement of Amyloid beta (Aβ) species in the cerebrospinal fluid (CSF). To establish a highly sensitive and specific blood test is thus of outmost interest. **Objectives:** To evaluate the diagnostic accuracy of a novel assay for plasma Aβ. **Methods:** We examined CSF and plasma samples from AD patients (A+N+T+; n=44) and controls (A-N-T-, n=49). The Aβ42/40 ratio in CSF was determined by Mesoscale (MESO QuickPlex SQ 120). Aβ40 and Aβ42 in plasma were measured through enzyme-linked immunosorbent assay (ELISA) technology using ABtest40 and ABtest42 test kits (Araclon Biotech,

Zaragoza, Spain). Correlation analyzes of Aβ42/40 ratio in CSF and plasma were performed. **Results:** Plasma Aβ42/40 was positively correlated with CSF Aβ42/40 (Spearman's rho 0.22; p=0.037). Performing ROC analyzes, at the optimal cut-point of 0.076 plasma Aβ42/40 ratio had a sensitivity of 61.2% and a specificity 63.6% (Youden's index 0.25). Aβ42/40 in plasma at this cut-point correctly identified 28 out of 44 AD (64%) and 30 out of 49 controls (61%). Sixteen AD patients were misclassified as healthy (false negative) and 19 controls were wrongly assigned to AD (false positive). **Conclusion:** The here tested commercially available blood test may serve as a first step screening tool, but low sensitivity and specificity can be considered as a substantial limitation. CSF or Amyloid-PET continue to remain mandatory within the screening for clinical trials in AD.

P080- IDENTIFYING HEALTHY ELDERLY SUBJECTS WITH ALZHEIMER PATHOLOGY MORE EFFICIENTLY FOR CLINICAL TRIAL PARTICIPATION. S. Prins, A. Zhuparris, E. 't Hart, D. Ziagkos, G.J. Groeneveld *(Centre for Human Drug Research, Leiden, The Netherlands)*

Backgrounds: The current leading hypothesis regarding pathophysiology of AD is centered around the misfolding and aggregation of toxic amyloid beta (Abeta) species such as Abeta1-42, and drug research has therefore focused on this biomarker. Early identification of healthy elderly with CSF Abeta1-42 levels consistent with AD is therefore important for early phase drug development. When testing the cerebrospinal fluid (CSF) of 100 healthy elderly subjects above the age of 65, 19% are expected to have Abeta CSF levels consistent with AD. In the current study we aimed to develop an algorithm based on less-invasive biomarkers for AD pathology, to pre-select subjects who are suspected of lowered, abnormal, CSF Abeta levels consistent with the presence of AD pathology. This algorithm could be used to identify potential trial subjects with an expected higher risk of having CSF Abeta1-42 levels consistent with AD, resulting in a smaller group of subjects requiring lumbar punctures (LPs). **Objectives:** To define an algorithm based on plasma biomarkers, genetic status, a computerized cognitive test battery (NeuroCart), age, grip strength and level of education to discriminate between CSF Abeta positive and CSF Abeta negative healthy elderly subjects. **Methods:** We performed a single-centre, cross-sectional, correlational study in 200 healthy elderly (age 65+) with an MMSE >24. Blood plasma and CSF were collected from 189 subjects and all subjects performed measurements with the NeuroCart, an automated test battery for repetitive cognitive and neurophysiological testing. Tests included adaptive tracking, visual verbal learning test (VVLT), Milner maze test (MMT), facial encoding and recognition task, N-Back test, sustained attention to response test (SART), finger tapping, saccadic and smooth pursuit eye movements and 21 leads-EEG. Handgrip strength was measured using a digital grip strength dynamometer and self-reported level of independence was assessed by the clinical dementia rating scale and the instrumental activities of daily living scale. CSF Abeta1-42 concentrations were measured using the automated Roche Elecsys assay. Plasma Abeta1-40, Abeta1-42, Neurofilament Light and Total Tau concentrations were measured using the ultrasensitive Single Molecule (Simoa HD-1 analyzer) immunoassay technology. Plasma Abeta1-40 and Abeta1-42 were used to calculate the Abeta1-42/1-40 ratio. Also the neuroinflammation biomarker YKL-40 was tested in the plasma samples (Human CHI3L1 [YKL-40] ELISA Kit, ThermoFisher) and Apoe e4 status was determined (after isolating the DNA a sequential analyses was used according to the Sanger method). Data were analyzed using a 5-fold cross validation random forest and logistic regression model. The models were then evaluated based on their sensitivity, specificity and positive predictive value. **Results:** Two hundred healthy elderly subjects were enrolled in this study of which 189 were included in the analyses due to CSF availability (average age 72 +/-4 years). Of these 189 elderly, 55 (29.1%) were Abeta positive for AD (age 65-70: 27.3%, age >70: 72.7%). Results of the random forest algorithm analyses conclude that the best prediction of Abeta positivity/negativity in CSF in an elderly subject is by combining a number of 15 parameters. The algorithm included the following 7 tests and 2 blood analyses: MMT, VVLT, adaptive tracking, N-Back, SART, saccadic eye movements, EEG and the plasma biomarkers Abeta1-40/1-42 ratio and YKL-40. A sensitivity of 63.6% (±0.03) and a specificity of 66.6% (± 0.09) was reached. The receiver operating characteristic (ROC) curve showed a AUC of 66% (±0.02). Approximately 50 subjects is an acceptable number of subjects for a Proof-of-concept study. Based on the 29.1% Abeta positivity in our study we estimate that in a new group of 270 healthy elderly subjects, 79 (50/0.636) subjects will be Abeta positive. The algorithm will identify 113 subjects as having Abeta positive CSF. As the algorithm does not have 100% sensitivity, 28 Abeta positive subjects would not be identified as such. Also, 64 subjects would wrongfully be identified as Abeta positive to end up with 50 truly Abeta positive subjects. Using the algorithm would thereby reduce the number of unnecessary LPs in healthy elderly by 42% (±0.09, 113 instead of 270). **Conclusion:** Preselecting the right subjects to participate in clinical trials has become essential as new drugs treating AD continue to fail in phase 3 studies. Using the algorithm created in the current study can lower the number of LPs necessary to determine Abeta CSF levels by preselecting healthy elderly who are likely to have Abeta CSF levels consistent with AD. Using the algorithm can lower the costs of trials as less LPs have to be performed. The reduction of LPs in healthy elderly subjects and the additional benefits for clinical research have to be weighed against the ethical consequences of identifying healthy subjects with an elevated risk of developing AD, which still is an untreatable disease.

P081- CLINICAL UTILITY OF PLASMA AMYLOID BETA MEASUREMENTS BY IMMUNOAFFINITY ENRICHMENT AND LC-MS/MS. S. Watanabe[1], T. Iino[1], K. Yamashita[1], E. Tamada[1], T. Hasegawa[1], K. Matsumoto[1], S. Iwanaga[1], A. Harada[1], K. Suto[1], H. Amino[2], M. Ino[2], T. Miyagawa[3], T. Yoshida[1] *((1) Sysmex Corporation - Kobe (Japan), (2) Eisai Co. Ltd - Tsukuba (Japan), (3) Eisai Co. Ltd - Tokyo (Japan))*

Background: Alzheimer's Disease (AD) is the most common type of dementia which is a major public health problem worldwide, with significant socioeconomic implications. The efficacy of potential AD treatments would likely depend on an early treatment. So simple screening tests are urgently needed that can accurately detect the early stage of AD. Recent study showed that the amyloid beta (Aβ)1-42/Aβ1-40 ratio is negatively correlated with amyloid positron emission tomograghy (PET) imaging which can visualize amyloid burden in brain. However, since the collection of CSF is invasive, plasma-based biomarker would be highly

advantageous. To explore the diagnostics utility of plasma Aβ1-40 and Aβ1-42, this study aimed at developing a simple immunoaffinity enrichment and liquid chromatography-tandem mass spectrometry (IA-MS) system and analyzing the correlation between the plasma Aβ1-42/Aβ1-40 ratio and the CSF Aβ1-42/Aβ1-40 ratio. **Method:** We developed an IA-MS system involving the addition of isotope-labeled internal standards. Immunoaffinity purification of plasma Aβs was conducted by monoclonal antibody-labeled magnetic beads. Aβs were eluted from magnetic beads and analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) without enzymatic digestion which is used in previous reports. Assay performance such as the simultaneous reproducibility, the accuracy, the dynamic range, and the recovery, was evaluated using synthesized Aβ1-40 and Aβ1-42. Forty four commercially available plasma samples (two with Alzheimer's disease [AD], 33 with mild cognitive impairment [MCI], and nine cognitive normal [CN]) were measured by IA-MS system. CSF samples collected from the same patients were measured by our fully automated Aβ1-40 and Aβ1-42 immunoassay system (HISCLTM series). The correlation between the plasma Aβ1-42/Aβ1-40 ratio and the CSF Aβ1-42/Aβ1-40 ratio was also evaluated. **Result:** Developed IA-MS assay needs only 250 μL of plasma for measurement of Aβ1-40 and Aβ1-42 and turnaround time (TAT) is less than 2 hrs. The coefficient of variations of simultaneous reproducibility for Aβ1-40 and Aβ1-42 were ranged from 3 to 8% and from 3 to 11% respectively. The accuracies of Aβ1-40 and Aβ1-42 were ranged from 85 to 106% and from 93 to 107% respectively. The dynamic ranges of Aβ1-40 and Aβ1-42 were determined to be 10.8 to 692.8 pg/mL and 5.6 to 180.6 pg/mL respectively. The recovery rates of Aβ1-40 were 100% for 145 pg/mL spike sample, 106% for 276 pg/mL spike sample, and 103% for 571 pg/mL spike sample. The recovery rates of Aβ1-42 were 95% for 14 pg/mL spike sample, 91% for 25 pg/mL spike sample, and 89% for 50 pg/mL spike sample. The concentrations of Aβ1-40 and Aβ1-42 in plasma were successfully measured in all samples and we confirmed the good correlation between the plasma Aβ1-42/Aβ1-40 ratio and the CSF Aβ1-42/Aβ1-40 ratio. **Conclusion:** The plasma Aβ1-42/Aβ1-40 ratio measured by IA-MS correlates well with the CSF Aβ1-42/Aβ1-40 ratio. This result indicates a potential of plasma Aβs to reflect amyloid pathology. Further analysis should be conducted to elucidate the biological features of plasma Aβs. Our IA-MS can easily be modified to monitor multiple Aβs. Therefore, biology of Aβs such as the profile of plasma Aβ variants can be assessed with our system. Our IA-MS can provide an opportunity to open up new lines of biological and clinical discovery for amyloid pathology.

P082- RETISPEC TECHNOLOGY USED FOR PATIENT RECRUITMENT. S. Thein[1], J. Jirik[2] *((1) Medical Director - San Diego (United States), (2) Recruitment & Marketing Manager - San Diego (United States))*

Background: Patient recruitment is the single most cited reason for undermining clinical trial completion. Kadam, et.al. (s) states that "successful recruitment of patients is known to be one of the most challenging aspects in the conduct of randomized controlled trials." Alzheimer's disease (AD) trials have primarily focused on brain β-amyloid accumulation and the Tau pathology that subsequently collects. Currently, β-amyloid is only detected invasively via LP, or by an expensive PET scan. Consequently, identifying suitable candidates with pre-symptomatic AD is difficult. The need for more effective and less expensive biomarker detection is critical to research development. In addition, prospective subjects are asked to identify symptoms concerning the disease they do not know or are unwilling to disclose. RetiSpec has developed a non-invasive, label-free retinal imaging technology that detects AD biomarkers – namely signatures of Aβ aggregates. The non-invasive hyperspectral imaging is a quick, simple and cost-effective method used to identify AD retinal biomarkers years before clinical symptoms may appear. This system utilizes a RetiSpec spectral imaging camera and novel software, in combined with a commercially available fundus camera (routinely used by optometrists and ophthalmologists). **Objectives:** The RetiSpec eye-scan technology informs subjects about β-amyloid accumulation associated with aging and sometimes memory loss. Through this education process subjects may become more interested in clinical trial enrollment by identifying at-risk biomarkers before they become symptomatic using quick, non-invasive technology. **Methods:** A clinical trials site will run a print advertisement, up to three times, of similar size, color, and placement to ads run previously. It will include a brief description of the detection of age-related memory biomarkers. The number of responders to the ad will be compared to those who responded to former ads. Tabulation of appointments conducted will determine its success of "show" rates. During the appointment responders will have the opportunity to learn more about memory loss associated with aging, the role of β-amyloid presence in diagnosis, and receive a free eye scan aimed at β-amyloid detection. Afterwards, a questionnaire will assess physical and emotional comfort/distress as a result of the eye test. They will be asked to assign a dollar value to the test and a desire to repeat it, as an indicator of its worth. **Results/Conclusion:** TBD, study in progress. **Comments and/or Additional Thoughts:** TBD, study in progress. **References:** 1. Kadam et.al. Perspect Clin Res. 2016 Jul-Sep; 7(3): 137-143

P083- AMYLOID-TARGETING, BLOOD-BASED BIOMARKER OF ALZHEIMER'S DISEASE: STAGING AND CLASSIFICATION. Y.C. Youn[1], S.Y. Kim[2] *((1) ChungAng University Hospital - Seoul (Korea, Republic of), (2) Seoul National University Bundang H - Seongnam-Si (Korea, Republic of))*

Although CSF amyloid related proteins (Ab42, p-tau and t-tau) and amyloid PET are considered as current standard diagnostic biomarkers of Alzheimer's disease (AD). However, those are not enough to be an ideal biomarker of AD because they are too expensive to test, not simple to test, and it is not directly related to oligomeric beta-amyloid that is a real toxic species among many types of beta-amyloid. Many researches have been trying for a long time to find blood-based biomarkers that could simply detect AD related change. Plasma Aβ42 has long been proposed as a potential diagnostic biomarker of AD. However, the majority of past plasma Aβ studies have produced inconsistent and conflicting results. Recently new sensitive techniques have been developed to measure beta-amyloid and related peptides from plasma. They are showing a promising data with relatively high sensitivity and specificity. These methods were directly measuring the concentrations of Aβ peptides in plasma by using very sensitive machines. Moreover, a couple of new methods were trying to detect Aβ42 oligomerization related characteristic changes of plasma from patients with Alzheimer's disease. I tried to group amyloid-

targeting blood-based biomarker studies of AD based on their concepts and techniques. From the Stage I, Stage II-A, Stage II-B and Stage III. Stage I is for the studies directly measured Aβ in blood by routine ELISA and mass-spectroscopy. New high sensitive techniques measuring plasma Aβ were grouped as Stage II, amyloid-targeting blood-based biomarkers of AD. When this measuring are performed at plasma exosome using self-amplification techniques, I grouped them as Stage II-B. Finally measuring Aβ42 oligomerization dynamics or the secondary structure distribution of Aβ in plasma, especially α-helix and β-sheet, instead of measuring concentration of plasma Aβ peptides themselves were grouped as Stage III. In this presentation, I will discuss of the history of development of amyloid-targeting blood-based biomarker of AD and the rationale of staging using a diagram. The comparison of characteristic of each technique will also be included.

P084- GUT MICROBIOTA AND RESPONSE TO BLARCAMESINE (ANAVEX2- 73) IN ALZHEIMER'S DISEASE PATIENTS: ABUNDANCE OF LACHNOSPIRACEAE AND ENTEROBACTERIACEAE FAMILIES AS POTENTIAL BIOMARKER OF RESPONSE FROM A 2-YEAR STUDY INTERIM CLINICAL DATA ANALYSIS USING KEM ARTIFICIAL INTELLIGENCE. C. Williams[1], F. Parmentier[1], A. Etcheto[1], C. Missling[2], M. Afshar[1] *((1) Ariana Pharma - Paris (France), (2) Anavex - New York (United States))*

Introduction: Dysregulation of gut microbial communities (dysbiosis) has been described as a potential contributor to the development and maintenance neurological and behavioral disorders such as Autism, depression, Parkinson's and Alzheimer's disease (AD). Furthermore, recent studies have described the importance of the role of oxidative stress and inflammation as mediators of the pathological processes in which dysbiosis is involved, thus underlying the importance of the link between gut microbiota and neurodegenerative disease. Activation of sigma-1 receptor (SIGMAR1) is known to elicit potent neuroprotective effects and promote neuronal survival via multiple mechanisms, including regulating neuro-immunological functions and decreasing neuroinflammation and oxidative stress. Changes in diet, antibiotic exposure, aging and bacterial infection have been described as causes of alterations in gut microbial communities. Blarcamesine, a selective SIGMAR1 agonist, was investigated in a 57-week Phase 2a study with 32 mild-to- moderate AD dementia patients (ANAVEX2-73-002: NCT02244541). The study met its primary safety endpoint and was subsequently extended by an additional 208 weeks (ANAVEX2-73-003: NCT02756858). Patient stool samples were collected to perform gut microbiome analyses during this extension study and an initial analysis investigated microbiota abundance linked to improved response at week 148. **Objective:** Identifying potential microbiota as markers of response to blarcamesine as well as potential surrogate end points in SIGMAR1 therapy regulating inflammation and oxidative stress. Application of unsupervised Formal Concept Analysis as implemented in Knowledge Extraction and Management KEM Artificial Intelligence (AI) platform data-driven approach enabling the analysis of small well characterized cohorts of patients. **Methods:** During the extension study ANAVEX2-73-003, a total of 16 patients were consented to stool sample collection. After DNA extraction and amplification, 16s metagenomics sequencing was performed (Illumina® MiSeq). A custom bioinformatics pipeline was used for taxonomic classification of sequences; abundances measurement of 32,875 operational taxonomic units (OTU) were mapped to 11 phyla, 81 families and 230 genera. An initial subset of 12 genera and families associated to neurological disorders was defined using available literature. All microbiota descriptors, baseline descriptors, concomitant medication administration, study drug concentration, genomic data and outcome scores were integrated in a database consisting of 3,382 variables. A total search space of over 400 million relations was explored using Formal Concept Analysis (FCA) as implemented in Knowledge Extraction Management (KEM®) software. KEM® assumes no prior hypothesis. Associations towards response as measured by change from baseline in Mini Mental State Examination (MMSE) or Alzheimer's Disease Cooperative Study-Activities of Daily Living scale (ADCS-ADL) scores at weeks 57, weeks 83, 96, 109 (stool collection time) and week 148 (interim analysis) were identified. Combinations of gut microbiota abundance along with respectively concomitant medication, DNA variants and blacarmesine plasma concentration towards response were investigated. **Results:** KEM analysis identified relationship linking high levels of relative abundances of six genera from the Lachnospiraceaefamily with improved MMSE and ADCS-ADL response at weeks 57, 96 and 109 ($p<0.05$). Similarly, relative high abundance of a genera from the Enterobacteriaceaefamily was found to be associated with improved response to blarcamesine at week 109 (ADCS-ADL, $p<0.05$), and high abundance of two genera from the Prevotellaceaefamily at weeks 83 and 96 (ADCS-ADL and MMSE, $p<0.05$). A trend was identified associating lower abundance of Akkermansiagenera with improved response. **Conclusions:** Low levels of relative abundance ofLachnospiraceaefamily - known as fatty acid chain producers - as well as Enterobacteriaceaefamily have been previously described as associated with AD and Parkinson's disease. This study identifies that responders to blarcamesine display a higher relative abundance of the above families potentially identifying a biomarker of response to blarcamesine intervention. These results are consistent with blacarmesine's regulation of homeostasis including potential restoration of gut microbiota diversity and reduction of chronic and neuro-inflammation. Although this study is limited by the small number of participants, the use of data driven non-supervised data analytics enables identifying initial hypothesis that could be confirmed in follow-up studies. Moreover, on-going clinical studies of blacarmesine in AD and Parkinson's disease are expected to provide additional data of the effect of blacarmesine on gut microbiota. This analysis identifies potential clinically actionable microbiota-biomarkers of response in AD, and potential surrogate endpoints that may be linked to the patient's cognitive and functional response.

P085- PLASMA NEUROFILAMENT LIGHT IS A MARKER OF INCIDENT COGNITIVE DECLINE ASSOCIATED WITH MILD BEHAVIORAL IMPAIRMENT – LESSONS FOR CLINICAL TRIAL RECRUITMENT. Z. Ismail, J. Naude, S. Gill, S. Hu, A. Mcgirr, N. Forkert, O. Monchi, P. Stys, E. Smith *(University of Calgary - Calgary (Canada))*

Background: To a certain extent, failure of the Alzheimer's clinical trial program to discover a disease modifying drug has been attributed to poor recruitment and retention of early phase illness. Imprecise case ascertainment of prodromal

and especially preclinical AD, based on standard cognitive tests alone, necessitates further investigations. More in-depth neuropsychological testing, and/or biomarker confirmation with CSF or PET studies are required to confirm cases. Many of these investigations are negative, and result in screen failures with substantial financial expenditures to get to that point. This cost inflation may prove prohibitive for some drug developers, or render a trial infeasible. Simple, inexpensive, and scalable approaches to detect the at-risk population are required, in order to more efficiently recruit into trials. As neuropsychiatric symptoms (NPS) can occur early in the disease course, systematic incorporation of NPS, operationalized as Mild Behavioral Impairment (MBI) offers such an opportunity. MBI is an at-risk state for incident cognitive decline and dementia, characterized by later-life emergence of sustained NPS. For some, these new onset NPS are the initial manifestation of neurodegeneration, seen in advance of cognitive decline. MBI has a separate cognitive and functional trajectory from late life psychiatric illness, with a faster decline and higher incidence of dementia at 5 years. However, traditional clinical trial inclusion/exclusion criteria have not meaningfully differentiated between longstanding and/or recurrent psychiatric conditions in late life, versus those with new onset NPS. Rather, these separate clinical entities are conflated, and those above a predetermined severity level as measured by conventional psychiatric rating scales are excluded. Potentially, some excluded participants may indeed have preclinical or prodromal AD, with their exclusion undermining the generalizability of the enrolled sample, due to the exclusion of MBI participants who have in general a faster rate of cognitive decline. Despite the abundance of emerging data on MBI and incident cognitive decline, its utility as a proxy for neurodegeneration has not been demonstrated. Plasma neurofilament light (NfL) rate of change has been demonstrated as a marker of axonal loss and may serve as a vehicle to investigate the association of MBI and neurodegeneration. Here we prospectively link baseline MBI, and rate of change in NfL over 2 years, using participant data from the Alzheimer's Disease Neuroimaging Initiative dataset. **Objectives:** To link MBI with change in plasma NfL level over 2 years. To explore MBI as an approach to increase efficiency and precision of screening for potential clinical trial participants, to increase yield at the biomarker confirmation stage of trials. **Methods:** Non-demented ADNI participants with measurements of both NPS and NfL at baseline and 2 years were included. Modified MBI status (MBI+/-) was determined by transforming single time point Neuropsychiatric Inventory Questionnaire items using a published algorithm. The final sample of 584 included 190 MBI+ and 394 MBI- participants. Change in PNfL was calculated as the difference between 2 years and baseline. A full-factorial repeated measures ANOVA was then performed including significant demographic and clinical differences as covariates. MBI- participants were then reclassified as those who remained MBI- and those who developed MBI at 2 years. The latter group was then included with baseline MBI+ and the analysis was repeated. **Results:** The MBI+ group was significantly younger, had fewer years of education, more males, and was more likely to have a diagnosis of mild cognitive impairment than the MBI- group. Time*MBI status was the only significant interaction to predict change in PNfL concentrations ($F(1,578)=4.97$, $p<0.05$) and neither of age, gender, education nor baseline cognitive status (NC vs MCI) significantly modified the PNfL rate of change in this dataset. Analyses reclassifying 64 participants with new onset MBI over the follow-up period similarly demonstrated greater increases in PNfL ($F(1,578)=4.97$, $p<0.05$) without modification from clinicodemographic covariates. **Conclusion:** To our knowledge, the relationship between PNfL and MBI has never been longitudinally characterized in a pre-dementia sample. Our data support the hypothesis that MBI is a valid risk marker for neurodegeneration, as indicated by greater increase in PNfL over two years in individuals with MBI. These findings suggest that MBI is clinical proxy of early phase neurodegeneration with putative utility in identifying those at risk for dementia. MBI can thus be used as a case ascertainment approach to capture those at high risk for cognitive decline and dementia.Refining the approach to assessment of psychiatric symptomatology in older adults can result in identification of an enriched sample for biomarker positivity, and more efficient use of clinical trial participant screening dollars to find those with preclinical disease. As MBI also is associated with a steeper cognitive trajectory, with faster decline, incorporation of MBI into clinical trial samples can affect sample size calculations, study power, and duration of trials. Further investigation for these final points is required, as is research with the MBI checklist, the case ascertainment instrument that accurately reflects the MBI criteria.

P086- APOE-E4 CARRIER IDENTIFICATION; RESULTS FROM THE GENERATION PROGRAM AT GLASGOW MEMORY CLINIC. K. Hendry, J. Lynch, S. Williamson, E. Lee, L. Wallace, A. Cranmer, L. Main, F. Inglis *(Glasgow Memory Clinic - Glasgow (United Kingdom))*

Background: The APOE gene is responsible for the transportation of fats in the body, including cholesterol. Most of the general population are APOE-ε3 homozygotes and have an "average" lifetime risk of developing AD after the age of 65. The APOE-ε2 variant is thought to be protective and slightly reduces an individual's risk of getting AD. On the other hand, the APOE-ε4 genotype is the strongest known genetic risk factor for accelerated cognitive ageing and Alzheimer's Disease (AD) with presence of the APOE-ε4 gene being a significant predictor of MCI and AD in older adults (>60 years old). (Bonham et al, 2016) Associations have been observed in subjects over the age of 60 between APOE genotype and cognitive test performance with poorer performance observed on domains of memory and processing speed in those with the ε4 allele (Marioni et al, 2016). **Objectives:** The Generation Program co-sponsored by Novartis, Amgen and the Banner Alzheimer Institute, investigated the use of novel pharmacological agents for the prevention of Alzheimer's Disease in 60-75-year-old subjects presenting with no memory impairment. We used a high-volume screening route utilising an effective process of pre-screening to identify subjects at higher risk of AD with either one or two copies of the APOE-ε4 gene. **Methods:** A hybrid approach to recruitment was used, with the majority of subjects responding to advertising campaigns and a minority of subjects obtained from the clinic database. Subjects initially completed a pre-screening telephone interview where-by they went through an exclusion criterion of key medications and medical conditions which would deem a subject ineligible for this clinical research. Eligible subjects were sent study information by post and invited to attend the clinic. Subjects met with a psychologist to discuss any study related questions and if willing to participate, consent to be genetically screened for APOE. Buccal swabs were obtained by a research nurse and analysed at an accredited laboratory. **Results:** 3673

swabs were obtained from subjects through-out Scotland over an 18-month period. 2515 subjects were non-carriers of the APOE-ε4 genotype (68.4%). Of these, 2057 were ε3/ε3 (56%), 443 were ε2/ε3 (12%) and 15 were ε2/ε2 (0.4%). 1056 were heterozygous for the APOE-ε4 genotype (28.8%) and 90 were homozygous for the APOE-ε4 genotype (2.5%). Buccal swabs were not able to be analysed in 12 subjects (0.3%) who declined to return for repeat sampling. **Conclusion:** A similar prevalence of homozygotes was found compared to the UK Biobank sample of 111,739 Caucasian volunteers; (2.5% vs 2.9% respectively). However, our sample revealed a lower APOE-ε4 non-carrier prevalence (68.4%), compared to the UK biobank (75.7%). We also revealed a higher rate of APOE-ε4 heterozygotes (28.8%) compared to the UK Biobank (21.6%). (Lyall et al, 2016). This may be due to an enriched population of subjects with an interest in AD due to family history volunteering for this AD prevention trial. Many volunteers and resources are required to identify subjects with the APOE-ε4 genotype, particularly when identifying the rare ε4 homozygous individuals. We have identified a total of 1146 subjects with a higher lifetime risk of AD than average based on having one or two copies of the APOE-ε4 genotype. It is currently not well understood why this genotype increases a person's risk of getting AD. We have identified a key cohort of subjects who can help us to better understand the association between AD and APOE-ε4 including how the presence of this gene interacts with the accumulation of amyloid- β deposits and tau proteins within the brain. **References:** Bonham L.W., Geier EG, Fan CC, Leong JK, Besser L, Kukull WA, et al. Age-dependent effects of APOE epsilon4 in preclinical Alzheimer's disease. Ann Clin Transl Neurol. 2016;3(9):668-77; Lyall, D. M. et al. (2016) Alzheimer disease genetic risk factor APOE e4, and cognitive abilities in 111,739 UK Biobank participants. Age and Ageing, 45(4), pp. 511-517. Marioni, R. E., Campbell, A., Generation Scotland., Hayward, C., Porteous, D.J., & Deary, I.J. (2016) Differential effects of the APOE e4 allele on different domains of cognitive ability across the life-course. European Journal of Human Genetics, 24, pp. 919-923.

P087- THE GENERATION PROGRAM ALZHEIMER'S DISEASE PREVENTION CLINICAL TRIALS - FINAL RESULTS OF RECRUITMENT STRATEGY FOR APOE4 CARRIERS AT GLASGOW MEMORY CLINIC. K. Hendry, J. Lynch, S. Williamson, E. Lee, L. Wallace, A. Cranmer, L. Main, F. Inglis *(Glasgow Memory Clinic - Glasgow (United Kingdom))*

Backgrounds: The Generation Program aimed to investigate the use of novel pharmacological agents for the prevention of Alzheimer's Disease in 60-75-year-old subjects presenting with no memory impairment. Subjects were tested for APOE genotype to determine Alzheimer's disease risk. The Generation program consisted of two trials based on APOE E4 genotype: homozygous (Generation Study 1) and heterozygous participants (Generation Study 2). APOE genotype is not tested for as a process of routine care in the United Kingdom. To identify subjects with APOE E4 genotype, a well-defined pre-screening process was required. **Objectives:** Here, we demonstrate the recruitment strategy implemented by Glasgow Memory Clinic and provide total recruitment figures for the 18-month duration of the Generation Program at this site. **Methods:** A multi-method advertising strategy was used to generate enquiries from subjects potentially eligible for the Generation program including television, social media, radio, AdWords and newspaper advertising. We also contacted subjects from our existing database of healthy volunteers. All enquiries were handled by our team of in-house patient liaison (PL) staff and overseen by the Clinic Development Director. The team responsible for processing enquiries consisted of 5 full-time/part-time PL administrators handling calls 5 days per week, 1 full time PL manager and 3 receptionists. The PL team completed telephone pre-screening by either answering direct calls from subjects enquiring about the Generation program or following-up subjects who had submitted enquiries either by telephone or internet. The PL team went, with each enquiring subject, through a series of medical conditions and medications which deemed subjects unsuitable for participation in the Generation program. Subjects who passed telephone pre-screening were then allocated an appointment by the PL team. PL administrators and receptionists handled all appointment rescheduling and cancellations. **Results:** A total of 3671 APOE genotyping swabs were conducted at Glasgow Memory Clinic between February 2018 and July 2019. To generate this level of genetic swabbing activity, the PL team had contact with a total of 7622 individuals (new enquiries as well as existing database subjects). Of which, 4528 appointments were booked following telephone pre-screening (59% of total enquiries). Of these appointments scheduled, 3671 subjects (81%) were consented and completed genetic swabbing for APOE genotype; 657 subjects (15%) cancelled or did not attend for booked appointments, 200 appointments (4%) were cancelled by the site due to early study termination. **Conclusion:** Our recruitment figures highlight the importance of a well-thought out recruitment strategy using a combination of advertisement methods to generate enquiries as well as making use of our existing database. Our advertising campaigns were tailored to the specific details of the Generation program, focusing on the role of genetics and Alzheimer's Disease prevention. Advertisement campaigns were revisited on a regular basis. Our recruitment success in the Generation Program is also attributable to the well-resourced and organised team of trained PL staff who completed telephone pre-screening and handled appointments. Successful pre-selection of the target population was important within our recruitment strategy to avoid unnecessary workload at later stages in the study process and to reduce subject burden.

P088- ASSOCIATION OF APOE E2 GENOTYPE WITH NEUROPROTECTION IN ALZHEIMER'S AND NON-ALZHEIMER'S NEUROPATHOLOGIES: A TRANSDIAGNOSTIC STUDY OF 1557 BRAINS IN THE NACC VERSION 10 DATABASE. T. Goldberg *(Columbia University Medical Center - Ny (United States))*

Objective: While Apolipoprotein E (APOE) e4 is the major common risk variant associated with clinically diagnosed late onset Alzheimer's disease (AD), e2 appears to be the major common neuroprotective variant. Here we examined the association of APOE e2 with multiple neurodegenerative pathologies including those related to AD, Lewy body disease (LBD), , and frontotemporal dementia (FTLD). **Methods:** The NACC v10 database of 1557 brains with uniformly measured neuropathologies included 130 e2/e2 or e2/e3 carriers and 679 e3/e4 and e4/e4 carriers. We examined the associations between APOE genotype and brain pathology in the complete dataset irrespective of NACC clinical diagnosis using chi-square and ordinal regressions. **Results:** For the AD-related pathologies

of amyloid plaques and neurofibrillary tangle Braak stage, e2 had large and highly significant protective effects contrasted with e3/e3 and e4 genotypic carriers with ORs of about .50 for e3 contrasts and .10 for e4 contrasts. Mediation analysis demonstrated that e2 had both direct and indirect effects (via amyloid) on Braak stage. When we examined e2/e4 carriers, we found that risk for AD pathologies was similar to that of e4 carriers, not e2 carriers. e4 increased the risk for spread of Lewy bodies to limbic and neocortical regions. For FTLD pathologies, e2 was associated with increased pathology for TDP-43, Pick's bodies, and progressive supranuclear palsy, but this effect did not survive Bonferroni correction. **Interpretation:** We demonstrated that e2 has robust effects in protecting against both amyloid and Braak stage pathology. In individuals with the e2/e4 genotype, the e4 effect predominated. We also found strong evidence that e4 promoted the spread of alpha-synuclein pathology beyond the midbrain in individuals with LBD neuropathology. In sum we found that e2 was associated with large protective effects on AD neuropathologies, but not on other neurodegenerative proteinopathies.

P089- SYNCHRONIZED CELL CYCLE GENE EXPRESSION TEST FOR ALZHEIMER'S DISEASE. F. Chirila, D. Alkon *(NeuroDiagnostics LLC - Rockville (United States))*

Backgrounds: The genetic aspect of late onset Alzheimer's disease (95% of cases) remained elusive despite intensive research. Most of the genetic studies used cells originating from dead tissue. Given the change of the gene expression with the cell cycle, these experiments measured genetic noise. In our novel approach live human skin fibroblasts were double synchronized, (AD cells showed differences of cell division, size, and protein levels), therefore elevating the gene expression from the genetic noise. 36 dysregulated genes found in the training study were confirmed in the validation study with autopsy confirmed blind samples. 12 known disorders are related with the 36 cross-validated genes, and 9 of the 12 disorders represent risk factors for Alzheimer's Disease. Cell synchronization offers a gateway for precision targeting and treatment.

P090- SOLUBLE TREM2 (TRIGGERING RECEPTOR EXPRESSED ON MYELOID CELLS 2) AS A NEW BLOOD BASED BIOMARKER IN ALZHEIMER'S DISEASE. J.H. Lee[1], E.H. Lee[2,3], H.J. Kim[1], S.H. Koh[2,3], S.H. Park[4] *((1) Depart of Neurology, University of Ulsan College of Medicine, Asan Medical Center - Seoul (Korea, Republic of), (2) Department of Neurology, Hanyang University College of Medicine - Guri (Korea, Republic of), (3) Department of Translational Medicine, Hanyang University Graduate School of Biomedical Science & Engineering - Guri (Korea, Republic of), (4) Seongnam Center of Senior Health - Seongnam (Korea, Republic of))*

Introduction and Objectives: Recent studies have shown that triggering receptor expressed on myeloid cells 2 (TREM2) in microglia is closely involved in the development of Alzheimer's disease (AD). However, the mechanistic link of TREM2 between microglial activation and Alzheimer's disease remains poorly understood. TREM2 is proteolytically processed to generate soluble TREM2 (sTREM2) fragments which can be measured in CSF and blood. Despite the potential use of sTREM2 as a new AD biomarker, very little is known about its role in neurodegeneration. We explore to find out whether sTREM2 in plasma well reflects that in CSF how it ties up with other AD key biomarkers such as amyloid beta and p-tau, and other neuroinflammation/degeneration markers in AD spectrum conditions. **Methods:** We plan to include total 100 patients of Alzheimer's spectrum disorder and control groups for 3 years comprising AD, prodromal AD, disease control and normal control who underwent baseline neuropsychological, laboratory, and neuroimaging assessments including brain MRI and 18-F florbetaben (FBB) PET scans. For the preliminary data, we investigated the serum/plasma and CSF samples of 21 subjects and used solid phase PLA method to measure sTREM2 from each of fluids. **Results:** sTREM2 in plasma showed a correlation with the sTREM2 in CSF. (Fig 1) Also it had a good correlation with the amyloid beta1-42 (p=0.019) and phosphorylated tau (p=0.0002), the classical biomarkers of the AD (Fig 2). Furthermore, there was also a tendency toward a positive correlation between sTREM2 levels and the those of other new candidate biomarkers such as neurogranin (NRGN, p=0.025) and neurofilament light chain (NFL, p=0.498). **Conclusion:** The functional significance of sTREM2 is not well known. However, we suggest the promising potential of sTREM2 as a new blood-based biomarker for AD through our preliminary data. With the increasing number of enrollment, we expect to gain new insights into the role of sTREM2 and have a better understanding of its relationship with other AD biomarkers.

P091- NEUROINFLAMMATION GENOMIC MARKERS IN GENOME-WIDE ASSOCIATION STUDY OF PARKINSON'S DISEASE. S.J. Chung[1], C. Nari[1], K. Juyeon[2], K. Kiju[1], K. Mi-Jung[3], R. Ho-Sung[4], J. Sungyang[1], P. Kye Won[1] *((1) Asan Medical Center - Seoul (Korea, Republic of), (2) Metro hospital - Anyang (United States), (3) Bobath Memorial Hospital - Seongnam (Korea, Republic of), (4) Kyungpook National University Hospital - Daegu (Korea, Republic of))*

Background: Neuroinflammation may contribute to the pathogenesis of neurodegeneration in Parkinson's disease (PD) because inflammation is a neuropathologic feature of patients with PD and it has been reported in experimental models of PD. However, the roles of genes related to inflammation in the development of PD has been unclear. **Objectives:** We aimed to investigate the association between genetic variants related to neuroinflammation and the risk of PD. **Methods:** Study subjects included patients with PD (N=1,070) and healthy controls (N=5,000) who were unrelated and ethnic Koreans. Genomic data was produced by the Korean Chip (K-CHIP), Affymetrix Axiom KORV1.1 (variants number of 827,400), which contains the imputation GWAS grid (505,000 Asian-based grid), functional variants of nonsynonymous exome content (84,000 Korean-based grid and 149,000 cSNPs and InDels selected from 2,000 whole-exome sequencing and 400 whole-genome sequencing data that are polymorphic in Korean), pharmacogenetics variants, variants in genes involved in absorption, distribution, metabolism and excretion (ADME) of drugs, and expression quantitative trait loci (eQTL). Genomic analysis was performed after stringent sample and SNP quality controls. Genetic variants related to neuroinflammation were selected and specifically analyzed in PD cases and controls. **Results:** The HLA-ASNP rs12665039 the most significant association with PD (OR=1.28, CI=1.15-1.44, P=1.89Í10-5). The HLA-DOBSNP rs2071469 was the second most significant loci (OR=0.83, CI=0.75-0.91, P=1.72Í10-4). Other variants in Chromosome 6 and 11 showed nominally significant

associations with PD, but those did not remain significant after Bonferroni correction. **Conclusions:** This GWAS suggests that genetic variants related to neuroinflammation may play potential roles in the development of PD.

P092- LEVELS OF GUT MICROBIOTA POTENTIALLY REGULATED THROUGH ANTI-INFLAMMATORY EFFECT IDENTIFIED AS ASSOCIATED TO RESPONSE TO BLARCAMESINE (ANAVEX2-73) IN ALZHEIMER'S DISEASE PATIENTS IN 2-YEAR INTERIM CLINICAL DATA USING KEM ARTIFICIAL INTELLIGENCE ANALYSIS. C. Williams[1], F. Parmentier[1], A. Etcheto[1], C. Missling[2], M. Afshar[1] *((1) Ariana Pharma - Paris (France), (2) ANAVEX - New York (United States))*

Introduction: Dysregulation of gut microbial communities (dysbiosis)has been described as a potential contributor to the development and maintenance neurological and behavioral disorders such as Autism, depression, Parkinson's and Alzheimer's disease. Furthermore, recent studies have described the importance of the role of oxidative stress and inflammation as mediators of the pathological processes in which dysbiosis is involved. The link between microbiota and neurodegenerative disease is believed to involve inflammation as well as oxidative stress. Activation of sigma-1 receptor (SIGMAR1) is known to elicit potent neuroprotective effects and promote neuronal survival via multiple mechanisms, including regulating neuroimmnological functions and decreasing neuroinflammation and oxidative stress. Blarcamesine, a selective SIGMAR1 agonist, was investigated in a 57-week Phase 2a study with 32 mild-to-moderate AD dementia patients (AV2-73-002: NCT02244541). The study met its primary safety endpoint and was subsequently extended by an additional 208 weeks (AV2-73-003: NCT02756858). Patient stool samples were collected to perform gut microbiome analyses during this extension study. **Objective:** Identifying potential microbiota as markers of response to Blarcamesine as well as potential surrogate end points in SIGMAR1 therapy regulating inflammation and oxidative stress. Application of unsupervised Formal Concept Analysis as implemented in Knowledge Extraction and Management KEM AI platform data-driven approach enabling the analysis of small well characterized cohorts of patients. **Methods:** During the extension study AV2-73-003, a total of 16 patients were consented to stool sample collection. After DNA extraction and amplification, 16s metagenomics sequencing was performed (Illumina® MiSeq). A custom, MOTHUR based, bioinformatics pipeline was used for taxonomic classification of sequences; abundances measurement of 32,875 operational taxonomic units (OTU) were mapped to 11 phylums, 81 families and 230 genera. A focused set of 11 gut microbiota families previously described in neurological disorders were used as an initial focus sub-group. An unsupervised, non-linear rules-based Formal Concept Analysis (FCA), as implemented in Ariana's KEM® software, investigated relationships between microbiota biomarkers from and efficacy outcome measures. A total of 8,143,928 relations between all available patient descriptors were explored. Filtering focused on relationships of gut microbiota genera and families previously described in neurological disorders. Associations towards response as measured by change from baseline in Mini Mental State Examination(MMSE) or Alzheimer's Disease Cooperative Study-Activities of Daily Living scale (ADCS-ADL)scores at weeks 57, weeks 83, 96, 109 (stool collection time) and week 148 (interim analysis) were identified. **Results:** KEM analysis identified relationship linking high levels of relative abundances of Lachnospiraceaefamily with improved response of MMSE and ADCS-ADL at weeks 57, 96 and 109 ($p<0.05$). Similarly, relative high abundance of Enterobacteriaceaefamily were found to be associated with improved response to Blarcamesine at week 109 ($p<0.05$). Other gut microbiota genus levels were found to be associated with improved response of MMSE and ADCS-ADL in AD patients treated with Blarcamesinehowever, these associations did not reach statistically significance. **Conclusions:** Low levels of relative abundance of Lachnospiraceae family - known as fatty chain producers - as well as Enterobacteriaceae family have been previously described as associated with AD and Parkinson's Disease. This study identifies that responders to Blarcamesine display a higher relative abundance of the above families potentially identifying a biomarker of response helping identify a population that may benefit from SIGMAR1 therapy. The relative abundance of Akkermansiahas been negatively correlated with amyloid beta in the brain of transgenic mice in a previous study. However, in a human study of AD vs healthy controls, higher levels of Akkermansiawere associated with AD patients. These apparently contradictory results illustrate the difficulty of gut microbiota data analysis and interpretation. Nevertheless, it has been hypothesized that depleted Akkermansiacould lead to a disrupted gut barrier increasing the impact of inflammation, as it was shown in mice and that the restoration of prebiotic-induced Akkermansiain the gut could reduce fat-mass gain and decrease systemic inflammation. This study is limited by the small number of patients. The gut microbiota is analyzed using ribosomal 16S rather than whole genome shut-gun analysis. Nevertheless, using data driven non-supervised data analytics enables identifying initial hypothesis that could be conformed in follow-up studies. This analysis identifies potential clinically actionable microbiota-biomarkers of response in AD, and potential surrogate endpoints that may be linked to the patient's cognitive function.

P093- USE OF TRANSLATIONAL ELECTROENCEPHALOGRAPHY BIOMARKER IN EARLY PHASE CLINICAL STUDIES FOR ALZHEIMER'S DISEASE. S. Semenova[1], L. Park[1], L. Gertsik[2], S. Jhee[1] *((1) PAREXEL International - Glendale (United States), (2) California Clinical Trials Medical Group - Glendale (United States))*

Background: The development of effective pharmacological treatment for Alzheimer's disease (AD) has been proven challenging and costly. Many compounds have failed late phase clinical trials. Many failures happen due to disease heterogeneity, lack of predictive animal models and biomarkers that can readily translate from animals to humans during early characterization of novel compounds for AD. The traditional focus of early phase clinical trials is evaluation of safety and tolerability of new compounds in healthy volunteers. However, an adaptive approach can be used to enhance clinical trial. Specifically, incorporation of translational methodology, such as electroencephalography (EEG), as well as inclusion of AD patient arm in early clinical trials, will provide critical information regarding new compound effects on pharmacodynamic endpoints in addition to drug pharmacokinetics, and facilitate go/no go decision making early on in drug development. This presentation aims to demonstrate recent progress regarding translational

aspects of EEG methodology as a biomarker in clinical trials with AD. **Methods:** Literature review was used to evaluate recent progress in EEG in both patients with AD and animal models. The electronic database has been used to evaluate EEG and cognitive endpoints in neurology and psychiatry in early phase clinical trials conducted in PAREXEL Los Angeles early phase clinical unit. **Results:** It is well-documented that patients with AD are characterized with dysfunction in brain function assessed by EEG methodology that correlate with disease progression and cognitive decline. Recent data in animal models related to AD showed similar changes in brain function. Thus, the contribution of EEG assessments in animal models of AD will have a valuable input into drug discovery and drug development by providing true translational assessments. The electronic database review indicates that in the last 7 years, none of clinical trials with new compounds for AD included EEG as a biomarker in ether healthy volunteers or patients with AD. These data are in contrast with clinical trials conducted in psychiatric population such as depression or schizophrenia where EEG are commonly used to assess brain connectivity, alterations in brain activity at resting state as well as event-related potentials as a surrogate biomarker for cognitive function. **Conclusion:** The full potential of EEG methodology applied into early phase clinical trials are yet to be demonstrated. Novel strategies should be employed in early phase clinical trials for AD. These strategies should incorporate translational methodology such as EEG that can provide valuable information regarding new compound brain penetration and target engagement as well as provide surrogate measures of cognitive enhancement that can be revealed after short treatment duration. It is believed that implementation of these approaches will increase efficiency of drug development in AD.

P094- NEUROPHYSIOLOGICAL BIOMARKERS PARALLEL GLUCOSE HYPOMETABOLISM IN ALZHEIMER'S DISEASE PATIENTS. S. Waninger[1], E. Angelopolous[1], C. Berka[1], A. Meghdadi[1], D. Salat[2], A. Verma[3] *((1) Advanced Brain Monitoring - Carlsbad (United States), (2) MGH/MIT/HMS Athinoula A. Martinos Center for Biomedical Imaging - Charlestown (United States), (3) Biogen - Cambridge (United States))*

The Neurophysiological biomarkers may provide robust, reliable, cost-effective tools for early diagnosis, tracking disease progression and assessing efficacy of interventions for Alzheimer's disease (AD), particularly treatments with purported "disease-modifying" effects. Resting state EEG with 5 minutes eyes open and 5 minutes eyes closed was acquired from a cohort of Alzheimer's disease (AD) subjects compared to age and gender matched healthy controls and benchmarked against 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), a measure of cerebral metabolic rates of glucose and a proxy for neuronal activity in clinical AD patients. The hallmark "slowing" of EEG was observed as an enhancement of slow bandwidths and a suppression of higher bands in the AD cohort compared to healthy controls. Significant correlations were identified between EEG metrics and regions of hypometabolism in AD patients including the cingulate gyrus and precuneus, two important structures to identify and analyze when reviewing brain FDG PET images obtained in patients with cognitive impairment. The data suggest that metrics from simple resting state EEG parallel hypometabolism associated with cognitive decline and Alzheimer's disease progression. The results support the use of a resting state EEG endpoint to evaluate efficacy of interventions in clinical studies focused on Alzheimer's disease.

P095- BLOOD-BASED BIOMARKERS FOR PREDICTING NEUROLOGICAL RESPONSE IN PATIENTS WITH ALZHEIMER'S DISEASE. A. Mishra[1], G. Hernandez[1], C. Lopez[1], B. Aydogan[2], Y. Shi[2], M. Law[2], L. Schneider[3], R. Brinton[1] *((1) Center for Innovation in Brain Science, University of Arizona - Tucson (United States), (2) Stevens Neuroimaging and Informatics Institute, Keck School of Medicine of USC - Los Angeles (United States), (3) Psychiatry, Keck School of Medicine of USC - Los Angeles (United States))*

Background: Allopregnanolone (Allo) is a first in class regenerative therapeutic for delaying progression and treating Alzheimer's disease (AD). Allo through its action on the GABA-A receptor modulates neuronal physiology and ameliorates glial induced inflammation. Activating the regenerative system of the brain while simultaneously reducing the inflammation is a novel therapeutic approach in treating AD. **Objectives:** In this study, we used Allo's modulation of the inflammatory response and neurogenesis to develop therapeutic blood-based biomarkers to identify potential regenerative responders for future clinical trials. **Methods:** Phase 1 (NCT02221622) randomized double-blind, placebo-controlled, multiple ascending dose clinical trial was conducted in patients with mild cognitive impairment due to AD or mild AD. Participants were age ≥ 55 years, MMSE score ≥ 20 and clinical dementia rating of 0.5-1. Participants were randomly assigned to receive weekly intravenous treatment of 2, 4 and 6mg of Allo or placebo. Magnetic resonance imaging was conducted to assess structural brain volume and microstructural changes. Plasma biomarker assessment was conducted to assess changes in inflammatory profile and neurofilament-light (NFL). **Results:** Structural analysis of gray matter volume was consistent with regeneration in select brain regions. Subfield analysis indicated a response to Allo in left hippocampal volume. Plasma biomarker assessment revealed Allo treatment associated reduction in levels of pro-inflammatory mediators: IL-2, IL-8, IFN-γ and IP-10. APOE genotype and sex impacted the therapeutic biomarker profile. Interestingly, the immune regulator Eotaxin-3 that attenuate inflammatory response and contribute to tissue remodeling and healing, were also modulated by Allo and showed significant positive correlation with increased hippocampal volume. Consistent with an improved neurological profile, NFL and IL-8 showed an inverse correlation with increased fractional anisotropy of the medial core of the fornix. **Conclusion:** These data suggest that a targeted profile of immune mediators could serve as a biomarker of therapeutic response to Allo which could be predictive of improved brain volume and myelin integrity. Further, these preliminary findings support a mechanistic based strategy for blood based biomarkers to identify potential responders to stratify and recruit patients for future trials. **Acknowledgements:** National Institute on Aging U01AG031115, U01AG047222, UF1AG046148 and Alzheimer's Drug Discovery Foundation (ADDF)

P096- INFLAMMATION MARKERS PREDICTING LONGITUDINAL CLINICAL PROGRESSION IN EARLY ALZHEIMER'S DISEASE. J. Pillai, J. Bena, L. Bekris, S. Rao, B. Lamb, J. Leverenz *(Cleveland Clinic - Cleveland (United States))*

Background: There is clear recognition for the role for inflammation in the pathophysiology of Alzheimer's disease (AD). We have shown earlier that inflammatory analytes from the Tumor necrosis factor signaling and the Complement and coagulation pathways are relevant in evaluating disease severity at the MCI stage of AD. **Objectives:** Here we address a key clinical question, which inflammation markers in the CSF and plasma best predict rate of longitudinal clinical progression in early AD. **Methods:** We addressed this question among a carefully characterized clinical population of 48 patients at the MCI stage of AD with positive AD biomarkers. We evaluated inflammatory analytes both in the CSF and plasma with the same validated RBM Multiplex panel. Patients had cognitive and biomarker evaluations at baseline and follow up cognitive evaluations at 9 and 15 months by Dementia Rating Scale (DRS) and MMSE (Mini Mental Status exam), and Clinical Dementia Rating: Sum of Boxes (CDR-SB). Results were further evaluated after adjusting for age, sex, APOE ε4 status, baseline cognitive score and corrected for false discovery rate (0.05). **Results:** None of cognitive measures related to baseline CSF and plasma inflammatory marker levels. The mean± SD MMSE change from baseline to 15 months was 2.3±3.7, CDR-SB was 2.4±2.0 and DRS was 9.6±10.4 points. Pearson correlations between the cognitive decline and inflammation markers were in the moderate range (0.3-0.5) for both CSF and plasma analytes. A common inflammatory analyte signature that correlated to clinical progression among all three cognitive scales was lacking. After adjusting for covariates noted above, baseline levels of CSF Monocyte chemoattractant protein-1 (CCL2) correlated to change in CDR-SB at 15 months, 0.54 (95% CI 0.25,0.73) and plasma α1-antitrypsin was inversely correlated to DRS change at 15months, -0.54 (95% CI -0.74,-0.23). **Conclusion:** Inflammatory analytes in MCI stage of AD track more closely with CSF neurodegeneration biomarkers than change in cognitive scores. Higher CSF levels of CCL2 a key regulator of migration and infiltration of monocytes/ macrophages and lower levels of plasma α1-antitrypsin, an acute phase reactant with anti-inflammatory, anti- leukocyte migratory activity significantly correlate with faster cognitive decline. Additional data from the ADNI study for the same markers will also be presented in tandem.

P097- PREDICTING COGNITIVE DECLINE IN LATE MIDDLE LIFE USING NEURONAL-DERIVED EXTRACELLULAR VESICLES. E. Eren[1], J. Hunt[2], N. Vogt[2], S. Johnson[2], B. Bendlin[2], D. Kapogiannis[1] *((1) Laboratory of Clinical Investigations, Intramural Research Program, National Institute on Aging - Baltimore (United States), (2) Wisconsin Alzheimer's Disease Research Center, University of Wisconsin - Madison (United States))*

Background: Neurodegeneration and clinical manifestations in Alzheimer's disease (AD) are most closely related to phosphorylated Tau pathology. AD is characterized by a long preclinical stage during which its core pathologies spread in the brain. Recent studies have demonstrated the spread of pathogenic Tau via Extracellular vesicles (EVs), membranous nanoparticles secreted and uptaken by all cells including neurons. We and others have isolated neuronal-derived EVs (NDEVs) from plasma and demonstrated that their Tau cargo serves as diagnostic and predictive biomarkers for AD depending on age, potentially reflecting clinical and preclinical tau AD pathology. **Objectives:** To use NDEVs to identify biomarkers that can predict cognitive decline in middle aged individuals by leveraging samples from participants in the Wisconsin Registry for Alzheimer's Prevention (WRAP) study. **Methods:** We blindly processed 292 repeated serum samples from 146 WRAP participants who were cognitively unimpaired at baseline (mean age 62.4±6.3 years old; 71.2% females; 42.5% APOE4 carriers). All participants had at least four time points of longitudinal cognitive testing (occurring approximately every 2 years), to facilitate the creation of two groups, 73 who were "cognitive decliners" and 73 who were cognitively stable. We isolated NDEVs using immunocapture for neuronal L1 cell adhesion molecule (L1CAM) and measured phosphorylated (p181 and p231) and total Tau using electrochemiluminescence assays. We fitted single measure and repeated measures mixed effects models for each biomarker including terms for cognitive status, sex, APOE4 status, age and the cognitive status*age interaction. **Results:** At baseline, there were significant cognitive status*age interactions for pTau231 ($p < 0.01$), total Tau ($p < 0.01$) and pTau181 ($p < 0.05$) with higher levels among older future decliners. Repeated measures analysis showed that longitudinally pTau231 and total Tau increased more over time in cognitive decliners compared to cognitively stable individuals ($p=0.04$ and $p=0.02$ respectively). **Conclusion:** NDEV Tau cargo can predict cognitive decline in cognitively normal middle-aged individuals at higher risk for AD, presumably due to subclinical spread of Tau pathology. Further NDEV biomarker development may allow preclinical AD diagnosis. This research was supported in part by the Intramural Research Program of the National Institute on Aging, NIH, and the WRAP grant R01AG027161.

P098- COMBINING SEX, APOE GENOTYPE, AND MITOCHONDRIAL GENETIC VARIANCE AS PREDICTIVE RESPONDER IDENTIFIER TO REGENERATIVE THERAPEUTIC ALLOPREGNANOLONE FOR ALZHEIMER'S DISEASE. Y. Wang[1], C. Solinsky[2], G. Hernandez[1], L. Schneider[2], R. Brinton[3] *((1) University of Arizona - Tucson (United States), (2) University of Southern California - Los Angeles (United States), (3) University of Southern California - Tucson (United States))*

Background: Late onset Alzheimer's disease (LOAD) is a systemic disease with multiple etiologies, and is associated with compromised brain metabolism and regenerative capacity. Allopregnanolone has been shown to promote brain mitochondrial function, neurogenesis, and memory in mouse models, and is currently being investigated as a regenerative therapeutic for AD (NCT02221622). While genetic markers such as APOE genotype may predict risk of AD, there is currently no genetic markers to predict therapeutic outcomes for AD. **Objective:** Because mitochondrial genetic variances and APOE genotype are known to be differentially associated with mitochondrial respiratory capacity and cell proliferation, we evaluated whether these genetic markers and functional indicators can predict responders for Alzheimer's disease therapeutics. **Method:** Induced pluripotent stem cells were derived from clinical trial participants and then differentiated into NSCs. Mitochondrial respiration was

determined by metabolic flux analysis in NSCs. To determine mitochondrial haplogroups, DNA was extracted from whole blood of the participants, and Hypervariable regions 1 and 2 of mitochondrial DNA were amplified, sequenced, and aligned to the Revised Cambridge Reference Sequence. Mitochondrial haplogroup was assigned using HaploGrep2 based on identified variants. RNA-Seq analysis was used to elucidate transcriptomic profiles and potential underlying mechanism of action of allopregnanolone. **Result:** Analysis revealed that allopregnanolone treatment preferentially increased maximum respiration in NSCs derived from females, APOE4 carriers, and participants of certain mitochondrial haplogroups (A, L, M, and N compared to those from haplogroups H, HV, and J). RNA-Seq analysis also supported a differential effect of allopregnanolone on differentiation and proliferation on the transcriptome level. **Conclusion:** Sex, APOE genotype, and mitochondrial genetic variation in combination could be a promising predictive genetic based biomarker to identify potential allopregnanolone responders. Predictive biomarkers will significantly contribute to a precision medicine strategy to identify responders to therapeutic agents for Alzheimer's disease. Research supported by NIA grants UF1-AG046148, U01-AG031115, U01-AG047222 and P01-AG026572 to RDB.

P099- SOLUBLE TREM2 AND OTHER IMMUNE FACTORS IN YOUNG ADULT DOWN SYNDROME. L. Bekris[1], K. Koenig[2], G. Weber[1], M. Khrestian[1], Y. Shao[1], J. Leverenz[3] *((1) Cleveland Clinic Lerner Research Institute - Cleveland (United States), (2) Cleveland Clinic Imaging Institute - Independence (United States), (3) Cleveland Clinic Neurological Institute - Cleveland (United States))*

Background: Individuals with Down Syndrome (DS) develop Alzheimer's disease (AD) related neuropathology characterized by amyloid β (Aβ)deposition in the brain as early as 10 years of age and by age 40 this is a universal finding at autopsy. Inflammatory disorders are frequent in DS individuals. Triggering receptor expressed in myeloid cells-2 (TREM2) genetic variants are risk factors for AD and other neurodegenerative diseases. A soluble cleavage product of TREM2 (sTREM2) has been described as elevated in AD cerebrospinal fluid and positively correlates with Aβ. There is relatively little information about TREM2 in young adult DS without dementia, but likely diffuse amyloid deposition in the brain. **Objective:** The objective of this investigation was to explore the relationship between sTREM2 and plasma Aβ or tau in a small exploratory cohort of DS. **Method:** Plasma from Down Syndrome (n=15) and age-matched cognitively normal controls (n=15) was analyzed for Aβ40, Aβ42, total-tau or phosphorylated-tau (Luminex: Millipore Multiplex) as well as other immune factors that included 38 cytokines and chemokines (Luminex: Millipore Multiplex). In addition, a custom designed sTREM2 assay (Luminex: Singleplex) was utilized to evaluate sTREM2 status in plasma from this cohort. **Results:** Similar to previous reports, we observed elevated plasma Aβ42 and Aβ40 as well as multiple immune factors in DS, compared to age-matched controls. Plasma sTREM2 was significantly elevated in DS. There was no relationship between other immune factors and Aβ42/Aβ40 or phosphorylated-tau, in DS, while there was a negative correlation between other immune factors and total-tau in DS. There was a positive correlation between plasma sTREM2 and Aβ42/Aβ40 in DS. **Conclusion:** The results of this exploratory study indicate that there is a relationship between plasma sTREM2 and Aβ42/Aβ40, but not total-tau or phosphorylated-tau, that is associated with a broad immune response in DS pre-dementia. Taken together, this information suggests a specific relationship between Aβ-related pathology and TREM2 in DS pre-dementia that warrants further study.

P100- IDENTIFYING SUBSETS OF PATIENTS WITH MILD COGNITIVE IMPAIRMENT AND CARDIOVASCULAR RISK FACTORS BASED ON DIFFERENTIAL EXPRESSION OF ANGIOGENIC AND INFLAMMATORY BIOMARKERS. Z. Winder[1], T.L. Sudduth[2], D. Fardo[3], Q. Cheng[4], L.B. Goldstein[5], P.T. Nelson[2], F.A. Schmitt[2], G.A. Jicha[2], D.M. Wilcock[2] *((1) University of Kentucky Physiology Department - Lexington (United States), (2) University of Kentucky Sanders-Brown Center on Aging - Lexington (United States), (3) University of Kentucky Biostatistics Department - Lexington (United States), (4) University of Kentucky Division of Biomedical Informatics - Lexington (United States), (5) University of Kentucky Neurology Department - Lexington (United States))*

Background: Vascular Cognitive Impairment and Dementia (VCID) is the current term to describe all cognitive disorders that are associated with cerebrovascular disease. The scope of VCID ranges from mild cognitive deficits to dementia with an increasing prevalence in the population as the diagnostic criteria becomes more sensitive in order to capture the full breadth of the disease. Patients with mild cognitive impairment due to cerebrovascular disease (MCI-CVD) are of particular interest in this disease spectrum because of their increased risk of developing dementia and their current stage of cognitive decline. Identifying subsets of patients under the MCI-CVD umbrella could allow for us to determine which patients have an increased likelihood of progressing to dementia. These subsets can be identified using an unsupervised machine learning technique called Hierarchical Clustering Analysis (HCA), where similar observations are clustered together using a pairwise dissimilarity matrix and linkage algorithm. **Objectives:** The aim of this study was to identify novel subsets of patients within a cohort of individuals with MCI-CVD using HCA and then compare each patient subset for fluid biomarker differences between groups. **Methods:** Plasma angiogenic (FGF, FLT, PLGF, Tie-2, VEGF, VEGF-D) and inflammatory (MMP1, MMP3, MMP9, IL8, TNFa) protein levels were measured using Meso Scale Discovery immunoassays in a cohort of individuals with a MoCA < 26 and at least one uncontrolled vascular risk factor. We compared two unique HCA techniques after applying them to this dataset with a novel HCA technique differing in two key aspects from one previously used in the literature: 1, use of consensus clustering to combine multiple HCA algorithms to create a dissimilarity matrix between observations determined by the percentage of models in which two observations are found within the same cluster; 2, creation of each HCA algorithm using the Minkowski distance to calculate dissimilarity between observations instead of the Euclidean distance. **Results:** The Euclidean distance HCA technique identified four subsets within the MCI-CVD cohort of patients, while the novel consensus clustering HCA technique was more conservative and found two subsets within the same cohort of patients. Both techniques identified one subset of patients with significantly increased levels of both angiogenic and inflammatory fluid biomarkers compared to the other subsets within the dataset. **Conclusion:** The application of

both HCA techniques onto our dataset provides a novel insight into the makeup of the MCI-CVD population. We were able to identify one subset of patients that exists within both HCA techniques with significantly increased levels of angiogenic and inflammatory fluid biomarkers, which potentially corresponds to an underlying angiogenic and inflammatory profile of disease that ultimately can progress from MCI to dementia.

P101-A CONFORMATION VARIANT OF P53 AS A PROMISING BLOOD-BIOMARKER FOR ALZHEIMER'S DIAGNOSIS AT PRE-CLINICAL AND PRODROMAL STAGES OF THE DISEASE. G. Abate[1], M. Vezzoli[1], A. Guaita[2], C. Fowler[3,4], M. Memo[1,5], D. Uberti[1,5] *((1) University of Brescia - Brescia (Italy), (2) Golgi Cenci Foundation - Abbiategrasso, (Italy), (3) The Florey Institute - Parkville (Australia), (4) The University of Melbourne - Parkville (Australia), (5) Diadem s.r.l. (Italy))*

Background: Historically, it was the onset of dementia symptoms that marked the beginning of Alzheimer's disease (AD), and diagnosis was confirmed by the presence of elevated levels of beta-amyloid and Tau in the brain upon autopsy. However, largely due to the development of imaging and CSF biomarkers, it is increasingly being recognized that the disease exists on a continuum that begins long before clinical symptoms appear. Between the beginning of Alzheimer's disease and the appearance of cognitive symptoms is a window of opportunity that may span 20 or more years. It is during this period that researchers believe therapies to prevent, slow, or stop the disease will be most effective. Recognizing this unprecedented window of opportunity, it's crucial that effective therapies and validated methods of early diagnosis are introduced as soon as possible. Blood-based biomarkers represent promising solutions for AD diagnosis and research, since they could yield an provide, non-invasive test to be used in the first steps of the diagnostic workflow, thus ruling out from further analyses those subjects who do not have underlying AD pathophysiology. **Objective:** In the research of blood-based signature for early diagnosis of Alzheimer Disease, p53 open isoform has been recently recognized as a promising candidate biomarker. p53 is a highly redox sensitive protein and redox posttranslational modifications can affect its tertiary structure. Thanks to specific conformational altered antibodies recognizing cryptic epitopes that becomes exposed following conformational changes, it is possible to easily measure in human plasma, p53 conformational variants. More recently, a new conformational specific antibody have been studied: 2D3A8. In particular, by using machine learning techniques 2D3A8 positive-p53 (Up532D3A8+) resulted the variable that impacted more on AD classification among ten different redox-related markers. The aim of this study was to validate Up532D3A8+ as specific for AD at the pre-clinical and prodromal stages of the disease, in two independent longitudinal cohorts and by using different techniques. **Methods:** 2D3A8 antibody, as the tool for identifying a specific p53 conformational variant was tested on a total of 491 plasma samples with two independent techniques. In details, 264 plasma samples (64 non-demented subjects (NDS) and 26 MCI at T_0, T_24 months and T_48 months) derived from a 4 years-longitudinal population study, InveCe.Ab (Milan, Italy), and 95 PD, 25 DLB and 19 OD, enrolled at the Cabueñes Hospital of Asturias (Spain) and at the Ospedali Civili di Brescia (Italy), were processed with indirect ELISA carried out with 2D3A8 antibody. While 36 NDS (17 out of them converted to AD in a total of 54 months), 42 MCI (20 out of them converted to AD in 18 months) and 10 diagnosed AD, all derived from AIBL cohort, were subjected to 2D3A8 immunoprecipitation-selected SRM-MS (selected reaction monitoring mass spectrometry), for selected p53-quantotypic peptides identification. **Statistical analysis:** Data mining and machine learning techniques were used for calculating the accuracy of Up532D3A8+ in a diagnostic and prognostic context of use (CoU). **Results:** Plasma Up532D3A8+ tested on samples derived from InveCe.Ab cohort, showed a high diagnostic accuracy in identifying NDS and MCI converted to AD when compared to whose remained stable NDS (AUC=0.98) and stable MCI (AUC=0.91). Its predictive performance, achieved with a Regression Tree algorithm based on two-step rolling window procedure, was 86.67% according to the clinical diagnosis. The relevance of 2D3A8 in detecting Up53 conformational variant exquisitely detected in AD was also confirmed by SRM-MS experiments preceded by 2D3A8 immunoprecipitation on AIBL plasma. With this technique, we identified two peptides, P1 and P2, with a sensitivity of 88.1% and 95.2% and specificity of 90.5% and 92.9% for predicting Amyloid status respectively. In addition, independently by Abeta status, the two p53-quantotypic peptides had also high performance in identifying asymptomatic and prodromal AD. **Conclusion:** The relevance of 2D3A8 antibody in AD was independent by the technical approach used, thus strengthening its performance in predicting individuals at risk of developing AD. Therefore, we propose 2D3A8 antibody as a high value tool for identifying a conformational Up53 variant, useful in the first phase of the diagnostic workflow to address the subjects at AD risk for further specific examinations. Furthermore, plasma Up532D3A8+ could help in stratifying prodromal as well as asymptomatic AD in clinical trials.

P102- NEURAL INJURY BIOMARKER PROFILES FROM THE EPOCH PHASE 3 TRIAL OF VERUBECESTAT IN PATIENTS WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE. M.E. Kennedy[1], C. Sur[2], J. Kost[3], D. Post[4], C. Furtek[5], J. Stromswold[5], N. Dupre[5], R. Clark[1], M.F. Egan[4] *((1) Department of Neuroscience, Merck & Co., Inc. - Kenilworth, New Jersey (United States), (2) Department of Translational Biomarkers, Merck & Co., Inc. - Kenilworth, New Jersey (United States), (3) Department of Statistics, Merck & Co., Inc. - Kenilworth, New Jersey (United States), (4) Department of Clinical Research, Merck & Co., Inc. - Kenilworth, New Jersey (United States), (5) Department of Clinical Operations, Merck & Co., Inc. - Kenilworth, New Jersey (United States))*

Background: Verubecestat is a β-site APP-cleaving enzyme (BACE) inhibitor developed for disease modification in Alzheimer's disease (AD). In the EPOCH trial (NCT01739348), patients with mild-to-moderate dementia due to AD were treated daily for 78 weeks with 12 mg or 40 mg of verubecestat, which resulted in ~60% and >70% sustained reduction in cerebrospinal fluid (CSF) Aβ, respectively, and dose-related regression of amyloid plaque pathology. These results confirm the intended impact of chronic BACE inhibition. Verubecestat treatment was also associated with a greater reduction in hippocampal and whole brain volume relative to placebo. The mechanism of this volume reduction is uncertain. **Objective:** To determine if patients treated chronically with verubecestat exhibited increased neurodegeneration versus placebo, as measured by CSF levels of neurofilament light chain (NF-L), total tau, glial fibrillary acidic protein (GFAP),

and ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1) as biomarkers of brain injury. NF-L concentration in CSF and plasma is a sensitive measure of acute neuronal damage and chronic neurodegenerative processes such as AD. **Methods:** CSF concentrations of NF-L, total tau, GFAP, and UCH-L1 were determined for patients with matched baseline and end-of-treatment (Week 78) CSF samples. Measurements were made using the Quanterix Neurology 4-Plex A assay (NF-L, total tau, GFAP, and UCH-L1) and read on a SIMOA HD-1 Analyzer (Quanterix Corporation, Lexington, MA). **Results:** Samples from patients receiving placebo (n=37), 12 mg verubecestat (n=31), and 40 mg verubecestat (n=50) were analyzed. Mean (standard deviation [SD]) NF-L concentrations at baseline and Week 78, respectively, were 1509 (744) and 1875 (1416) pg/mL for placebo, 1529 (621) and 1598 (615) pg/mL for 12 mg verubecestat, and 1723 (644) and 1937 (801) pg/mL for 40 mg verubecestat. Mean (SD) UCH-L1 concentrations at baseline and Week 78, respectively, were 2206 (721) and 2556 (975) pg/mL for placebo, 2276 (726) and 2477 (578) pg/mL for 12 mg verubecestat, and 2768 (864) and 2900 (839) pg/mL for 40 mg verubecestat. For total tau, mean (SD) concentrations at baseline and Week 78, respectively, were 265 (351) and 284 (189) pg/mL for placebo, 250 (151) and 246 (123) pg/mL for 12 mg verubecestat, and 319 (229) and 311 (221) pg/mL for 40 mg verubecestat. For GFAP, mean (SD) concentrations at baseline and Week 78, respectively, were 32,071 (12,690) and 33,894 (14,457) pg/mL for placebo, 33,758 (14,454) and 35,760 (16,843) pg/mL for 12 mg verubecestat, and 37,401 (16,439) and 42,850 (16,746) pg/mL for 40 mg verubecestat. There were no significant differences between verubecestat and placebo for changes from baseline for NF-L or other biomarkers of neural injury or gliosis in CSF. **Conclusion:** CSF neural injury biomarker profiles do not support that an increase in neurodegeneration is the cause of increased brain volume loss observed in patients with mild-to-moderate AD chronically treated with verubecestat. **Disclosures:** Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. MEK, CS, JK, DP, CF, JS, ND, RC, and MFE are current or former employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and may own stock and/or stock options in Merck & Co., Inc., Kenilworth, NJ, USA. Medical writing assistance, under the direction of the authors, was provided by Kirsty Muirhead, PhD, of CMC AFFINITY, a division of McCann Health Medical Communications Ltd., Glasgow, UK, in accordance with Good Publication Practice (GPP3) guidelines. This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

P103- A MACHINE LEARNING APPROACH WITH BIOMARKERS FOR CLASSIFICATION OF MIXED DEMENTIA PATIENTS. G. Rosenberg[1], R. Raja[2], J. Prestopnik[1], A. Caprihan[2] *((1) University of New Mexico - Albuquerque (United States), (2) MIND Research Network - Albuquerque (United States))*

Background: Multiple pathological changes are generally found at autopsy in patients with dementia. Alzheimer's disease (AD) and vascular cognitive impairment and dementia (VCID) are commonly found together in the same brains. Mixed dementia (MX) is used to describe brains with dual pathologies. More importantly, there is strong evidence that when both are present, the clinical decline is accelerated due to suspected enhanced neuroinflammation. Multiple pathologies are going to require treatment with several drugs, which may be one of the reasons for the high failure rate of monotherapies. Biomarkers are useful to show the underlying pathological changes, and to follow disease progression and response to therapy. Much has been learned about the appropriate biomarkers for AD, but less is known about biomarkers for vascular disease. We show that multiple biomarkers can be used to identify the patients with MX during life, which could greatly facilitate clinical trials. **Objectives:** Patients with dementia have overlapping clinical symptoms and signs, confounding diagnosis. Biomarkers derived from multiple modalities provide a means for stratification of patients into more homogeneous groups. The major types of biomarkers are clinical and neuropsychological features, MRI, and biochemical analysis of the CSF. It is rare to be able to define a disease by a single biomarker and multiple ones are needed. Patients can be stratified into several major diagnostic categories: 1) Alzheimer's disease (AD); 2) Subcortical ischemic vascular disease (SIVD), which is the small vessel form of VCID; 3) Multiple infarcts (MI); and 4) Leukoaraiosis (LA). AD can be defined by biological biomarkers in CSF and PET for amyloid and tau. SIVD can be shown by injury to the white matter as demonstrated by abnormalities in diffusion tensor imaging (DTI). MI is evident from MRI scans. Importantly for this study, MX has both AD-like proteins in the CSF or PET and white matter injury as shown by DTI. We include LA because the white matter changes seen on FLAIR MRI can be due to aging and these patients need to be excluded from clinical trials. We hypothesized that the use of biological biomarkers could improve accuracy of patient stratification. In an aging population both disease processes can coexist, causing mixed dementia. Identification of the correct dementia subtype is important in order to prescribe the appropriate treatment. We present a machine learning framework based on these dual pathways for identifying mixed dementia subjects. Biomarker-based diagnoses were compared to clinical diagnoses with a goal of determining the number of patients with MX by both approaches. **Methods:** The patientswere recruited into a long-term biomarker study if they had cognitive complaints with or without white matter changes on MRI. They underwent a complete neuropsychological battery of tests, a research MRI with DTI, and lumbar puncture to obtain CSF for measurements of amyloid, tau, and inflammatory biomarkers, including matrix metalloproteinases (MMPs). The data was entered into the NIH REDCap database and analyzed by a machine learning program called Random Forest for statistical analysis. **Results:** We entered 169 patients into the study and 53 healthy controls. Neuropsychological testing showed low scores for memory in the AD (29.6+0.1) and MX (34.2+1.4) groups compared to 53.6+1.2 for controls. The mean diffusivity from DTI was elevated in SIVD and MX and was low in LA. Phosphorylated Tau was high in the MX (118.9+12.3) and AD (87+.8+8.3 with 55.8+2.3 in controls) and were similar to controls in SIVD and LA groups. MMP-10 and MMP-3 were elevated in the MX and AD groups. We used a double dichotomy Random Forest algorithm to separate the results of AD-like proteins and mean diffusivity into the four groups. The overall classification accuracy was 82% with biomarkers from all three modalities, it was 80% from memory and MRI biomarkers, and 73% with only MRI biomarkers. The classification accuracy of the mixed dementia subgroup was 33% with only MRI biomarkers, increasing to 73% with MRI and the memory biomarkers, and to 93% if CSF biomarkers are also included. **Conclusions:** Using

a machine learning framework based on the dual pathways, neurodegeneration and neuroinflammation, to dementia identifies MX patients. Invasive CSF measurements are required for optimal classification. In its absence a combination of MRI and memory biomarkers reduces the overall accuracy by only 2%. Most of the biomarkers were significantly higher in MX compared to controls. Our results show that diagnosis of MX is possible during life with biomarkers and that dual pathology has a detrimental effect on the brain. We propose that this approach could be used to improve outcomes in clinical trials.

P104- BLOOD AMYLOID-B OLIGOMERIZATION ASSOCIATED WITH BRAIN VOLUME REDUCTION IN THE FORM OF ALZHEIMER'S DISEASE. Y.C. Youn[1], S.Y. Kim[2], S. Kang[3], S.S.A. An[4] *((1) Dept. of Neurology, Chung-Ang Univ. Hospital - Seoul (Korea, Republic of), (2) Dept. of Neurology, Seoul National University College of Medicine, Seoul National University Bundang Hospital - Seoul (Korea, Republic of), (3) Research and Development, PeopleBio Inc. - Gyeonggi-Do (Korea, Republic of), (4) Dept. of Bionanotechnology, Gachon University - Gyeonggi-Do (Korea, Republic of))*

Introduction: Oligomeric amyloid-ß is a major toxic species associated with Alzheimer's disease pathogenesis. Methods used to measure oligomeric amyloid-β in the blood have increased in number in recent years. The Multimer Detection System-Oligomeric Amyloid-β (MDS-OAβ) is a specific method to measure oligomerization tendencies in the blood. The objective of this study was to determine the association between amyloid-ß oligomerization in the plasma and structural changes of the brain. **Methods:** We studied 162 subjects composed of 92 community-based normal healthy subjects, 17 with subjective cognitive decline, 14 with mild cognitive impairment and 39 with Alzheimer's disease dementia. All subjects underwent MDS-OAβ and 3 dimensional T1 magnetic resonance imaging. To determine the structural changes of the brain that are statistically correlated with MDS-OAβ level, we used voxel-based morphometry with corrections for age and total intracranial volume covariates. **Results:** We found brain volume reduction in the bilateral temporal, amygdala, parahippocampal and lower parietal lobe, and left cingulate and precuneus regions (family-wise error, $p<0.05$). Reduction was also found in white matter in proximity to the left temporal and bilateral lower parietal lobes and posterior corpus callosum (family-wise error, $p<0.05$). Brain volume increment was not observed in any regions within grey or white matter. **Discussion:** Findings suggest that substantial correlation exists between amyloid ß oligomerization in the blood and brain volume reduction in the form of Alzheimer's disease despite of uncertainty in the casual relationship.

P105- STABILITY OF PLASMA AMYLOID-B 1-40, AMYLOID-B 1-42 AND TOTAL TAU PROTEIN OVER REPEATED FREEZE/THAW CYCLES. H.C. Liu[1], M.J. Chiu[2], C.H. Lin[2], W.P. Chen[3], S.Y. Yang[1] *((1) MagQu Co., Ltd. - New Taipei City (Taiwan, China), (2) National Taiwan University Hospital - Taipei (Taiwan, China), (3) MagQu LLC - City Of Surprise (United States))*

Blood biomarkers of ABlood biomarkers of Alzheimer's disease (AD) attract much attention of researchers recently. In clinical studies, repeated freeze/thaw cycles often occur and may influence the stability of biomarkers. This study is to investigate the stability of amyloid-β 1-40 (Aβ1-40), amyloid-β 1-42 (Aβ1-42) and total Tau protein (T-Tau) in plasma over freeze/thaw cycles. Plasma samples from healthy control (HC, n = 3), AD patients (AD, n = 3) and Parkinson's disease (PD, n = 3) were collected by standardized procedure, immediately frozen at -80 °C. Samples underwent 5 freeze/thaw (-80°C/ room temperature) cycles. The concentrations of Aβ1-40 , Aβ1-42 and T-Tau were monitored during the freeze/thaw tests by using immunomagnetic reduction (IMR) assay. The relative percentage (%) of concentrations after every freeze/thaw cycle was calculated for each biomarker. A tendency of decrease in the averaged relative percentages over samples through the freeze and thaw cycles for Aβ1-40 (100 to 97.37%), Aβ1-42 (100 to 95.56%) and T-Tau (100 to 96.42%) was found. However, the decreases are less than 5%. For all three biomarkers, no statistical significance was found between the levels of fresh plasma and that of the plasma experiencing five freeze/thaw cycles ($p > 0.1$). Plasma Aβ1-40, Aβ1-42 and T-Tau are stable through five freeze/thaw cycles measured with IMR..

P106- CLINICAL CHARACTERISTICS AND AMYLOID ACCUMULATION IN THE BRAIN AND THE BLOOD IN AMNESTIC SUBJECTIVE COGNITIVE DECLINE. Y. Dong Won[1], H. Yun Jung[1], H. Seonghee[1], J. Jee Hyang[2], P. Kee Hyung[3], K. Sangyun[4], W. Min Jeong[4], C. Seong Hye[5], H. Seunghyun[6] *((1) Department of Neurology, Catholic University of Korea - Seoul (Korea, Republic of), (2) Department of Neurology, Ewha Womans University Mokdong Hospital, Ewha Womans University School of Medicine - Seoul (Korea, Republic of), (3) Department of Neurology, Gachon University Gil Hospital, - Inchon (Korea, Republic of), (4) Department of Neurology, Seoul National University College of Medicine, Seoul National University Bundang Hospital - Seongnam (Korea, Republic of), (5) Department of Neurology, Inha University School of Medicine - Incheon (Korea, Republic of), (6) ROWAN Inc. - Seoul (Korea, Republic of))*

Background: Subjective cognitive decline(SCD) has been considered as at risk state to progress to mild cognitive impairment(MCI) or Alzheimer's disease(AD) dementia. SCD showed more positive results in the biomarker tests of Alzheimer's disease. The purpose of this study is to identify cerebral amyloid accumulation status and its relationship with cognitive dysfunction, APOE genotypes, and blood amyloid accumulation in amnestic SCD. **Methods:** We aimed to enroll 120 people who aged 60 years or older presenting with a complaint of persistent cognitive decline with objectively normal cognition. To include higher risk SCD patients who rapidly progress to MCI or AD dementia, SCD subjects needs to have a performance range of 7% to 50% of the verbal memory tests and over 7% of the rest subtests of comprehensive neuropsychological battery. Subjects who have severe uncontrolled depression, schizophrenia, alcoholism, and drug dependence were not included. Brain magnetic resonance imaging (MRI) volumetry, visual and standardized uptake value ratio (SUVR) analysis of 18F-Florbetaben brain amyloid-beta Positron Emission Tomography (PET) and blood-based amyloid quantification were conducted to measure brain atrophy, beta amyloid accumulation in the brain and the blood. Blood amyloid was measured by the Multimer Detection System-Oligomeric Aβ (MDS-OAβ) method. **Results:** We analyzed 33 SCD subjects (male 12, female 21). Mean age of SCD participants was 71.8 and mean education was 11.9 years. From 33 SCD participants, 12 (36%) showed amyloid positive

PET and 22(67%) showed blood amyloid positive findings. Positive amyloid PET SCD had higher frequency of APOE e4 (50%) compared to negative amyloid PET SCD (11%). Positive amyloid PET SCD also had slightly higher blood amyloid positivity (75%) compared to negative amyloid SCD (62%) which was statistically not significant. There was no difference in neuropsychological subtests scores between positive and negative amyloid PET SCD. **Conclusions:** Amnestic SCD subjects in our study showed higher (36%) amyloid pet positivity than the reported PET results in cognitive normal subjects. That verify our recruitment strategy to include higher risk SCD subjects to progress rapidly to MCI or AD dementia. Clinical significance of higher rate of blood amyloid positivity than brain amyloid PET in our study needs follow up PET and neuropsychological evaluation in brain amyloid PET negative and blood amyloid positive SCD.

P107- DEVELOPMENT OF ALZHEIMER'S DISEASE BIOMARKER USING AB*56 SOLUBLE OLIGOMER IN HUMAN NASAL SECRETIONS. I.H. Paik[1], H.K. Lim[2] *((1) Department of Psychiatry, Geyo Hospital - Eui Wang (Korea, Republic of), (2) Department of Psychiatry, Catholic University of Korea - Seoul (Korea, Republic of))*

Although soluble Aβ oligomer (AβO) might play a pivotal role in pathogenesis of Alzheimer's disease (AD), development of biomarker using detection of AβO might be limited due to its structural heterogeneity. Recently, we found the 56kDa soluble Aβ*56(Aβ*56) which is known to be involved in a very early sate of AD, in human nasal secretion. The aim of this study is to explore diagnostic validity of Aβ*56 in nasal secretions in discriminating AD pathology. A total of 60 patients (N=20 for NC, aMCI, and AD) were included in the study. They were dichotomized using 18F-Flutemetamol amyloid positron emission tomography (PET) into with and without detectable amyloid burden. Level of Aβ*56 in nasal secretions were measured using immune blotting. Group differences in nasal Aβ*56 level were analyzed and correlation between nasal Aβ*56 level and mean standardized uptake value ratio were also conducted. In addition, ROC analysis to evaluate the sensitivity and specificity of the nasal Aβ*56 level to discriminate amyloid pathology. There were no group differences in age, gender, and education. The nasal Aβ*56 level were significantly higher in aMCI and dementia than NC group, but no group differences were found between aMCI and dementia. The ROC analysis showed an AUC (area under curve) value of 0.92, sensitivity of 90% and specificity of 86% in discriminating Amyloid positivity. The nasal Aβ*56 level also had a positive correlation with cortical Aβ deposition on 18F-Flutemetamol PET. These results demonstrate that the nasal Aβ*56 level can be easily measured, and it may be utilized as a biomarker for the diagnosis of early AD including aMCI. The study also suggests that nasal Aβ*56 level may predict cortical deposition of Aβ.

P108- QUALIFICATION OF THE FUJIREBIO LUMIPULSE G B -AMYLOID(1-40), B -AMYLOID(1-42), TOTAL TAU, AND PTAU (181) ASSAYS FOR MEASUREMENTS IN CLINICAL STUDY PROTOCOLS. K. Coalier[1], R. Henson[1], N. Le Bastard[2], J. Lawson[3], M. Vandijck[2], A. Fagan[2] *((1) Department of Neurology, Washington University School of Medicine - Saint Louis (United States), (2) Fujirebio Europe - Ghent (Belgium), (3) Fujirebio Diagnostics Inc - Malvern (United States))*

Background: Cerebrospinal fluid (CSF) biomarkers of Alzheimer Disease (AD) are used for enrollment in clinical trials and have the potential for assessing efficacy of clinical study interventions. Despite this potential, current commercially available assays have not proved to be rigorous or robust enough for these uses due to significant variability across parameters required for fit-for-purpose validation. **Objectives:** We sought to qualify the Lumipulse G1200 Fully Automated Chemiluminescent Enzyme Immunoassay (CLEIA) System for use in AD-related clinical study protocols at Washington University School of Medicine. Fit-for-purpose validation was performed by assessing sensitivity, selectivity, linearity, parallelism, and inter-/intra-user and inter-/intra-day variability of the assays for the core CSF biomarkers of AD: Amyloid β(1-40) (Aβ40), Amyloid β(1-42) (Aβ42), total Tau, and pTau(181). **Methods:** Using the Lumipulse G1200 analyzer and analyte-specific immunoreaction cartridges, we established concentrations of control and calibration standards of each analyte. We ran a minimum of nine runs with a comparison performed of experimental sample photon counts and concentrations to the Fujirebio defined concentrations. We assessed specificity of each analyte by running each available control and calibrator on each analyte-specific immunoreaction cartridge to assess immunoreactivity across all four analytes. We developed a validation panel of 6-8 pooled samples across the measurement range of each analyte using anonymized CSF samples in order to test all other parameters. Where available, two clinical sample pools were used to assess the performance of each analyte at the high, mid, and low range of the curve, and single clinical sample pools were used to assess the performance at the respective upper and lower limits of quantitation (ULoQ and LLoQ, respectively). In cases where no clinical sample was appropriate, assay controls (comprised of peptides in buffer) were used. A minimum of six runs/sample/analyte across three users and multiple days were performed to assess accuracy by comparing to the nominal concentration and to assess precision across/within users and days. Bench-top and relative single and double freeze/thaw stability were assessed for each analyte across the panel as compared to the nominal concentration. Proportional and parallel dilutions were prepared from the validation panel samples for each analyte and the values compared with the theoretical concentration. Acceptance criteria for all validation parameters was established prior to validation assays and based on current Food and Drug Administration (FDA) bioanalytical method validation guidance. **Results:** Our analysis showed that the immunoreaction cartridges were specific to each analyte being measured and were not cross-reactive with each other. Accuracy and precision parameters for each analyte across and within testing days and users included coefficients of variation (%CV) <15% and percent errors of <10% from the nominally established concentration at each tested range of the calibration curve. Analyte concentrations across the panel remained constant for up to two additional freeze/thaw cycles, and benchtop stability was valid through four hours.

Linearity and parallelism was also within acceptable CV and percent error across the panel. **Conclusions:** Aβ40, Aβ42, total Tau, and pTau(181) can be measured with high reproducibility across several key validation parameters using the Lumipulse G1200 analyzer and its immunoreaction cartridges. This platform demonstrates the robustness and rigor to qualify as an appropriate bioanalytical method to measure core AD biomarkers in clinical study protocols.

P109- CORRELATION BETWEEN COGNITION AND PLASMA NORADRENALINE LEVEL IN ALZHEIMER'S DISEASE: A POTENTIAL NEW BLOOD MARKER OF DISEASE EVOLUTION. L.E. Pillet[1], C. Taccola[1], J. Cotoni[1], H. Thiriez[2], K. André[3], R. Verpillot[1] *((1) Alzohis - Paris (France), (2) HEC - Jouy-En-Josas (France), (3) Statitec - Vélizy Villacoublay (France))*

Background: Many studies have shown that abnormal structure and function of noradrenergic neurons, originating mostly from the Locus Coeruleus (LC) and projecting to different areas in the brain, were closely related to AD pathophysiology. Neuronal degeneration in the LC appears at an early stage of AD pathogenesis. One of the ideas that emerges today is that the onset of AD is preceded by an abnormal hyperactivation of the LC, resulting in an oversecretion of noradrenaline (NA) in the cortex, leading to a cortical accumulation of Aβ1-42 plaques. The consequence of this accumulation is a coeruleo-cortical network deregulation followed by its disconnection due to dendritic decline of noradrenergic neurons. NA is a catecholamine (with adrenaline and dopamine) that acts as a neuromodulator when synthesized by noradrenergic neurons and as a hormone when synthesized by sympathetic system. Cerebral and cerebro-spinal fluid (CSF) NA deregulation in AD was previously described, and it was shown that cortical NA concentration was correlated with cognition (MMSE or dementia score). At the peripheral level, NA circulates through bloodstream and is known to be involved in the body response to acute stress by modulating, among other physiological parameters, heart rate and blood pressure. Interestingly, LC is known to regulate sympathetic activity that modulates post-sympathetic noradrenergic neurons targeting heart or blood vessels. Different studies showed that plasma NA concentration ([NA]plasma) was altered in AD. Even though these studies show conflicting results, it seems clear that AD pathophysiology is associated with a modulation of [NA]plasma. **Objectives:** Our work combines two independent retrospective studies with patients who consulted for the first time in the cognitive neurology center of Lariboisière (Paris) between 2009 and 2014. Patients involved in our studies were diagnosed for AD, other dementia (frontotemporal dementia, vascular dementia or dementia with Lewy bodies) (OD), or considered as neurological controls (NC). NC patients were defined as patients with memory complains, but for whom no dementia was diagnosed. Diagnoses for AD were performed according to NIA-AA guidelines. The first cohort of 100 patients was analyzed: 1) to explore [NA]plasma in regards to concomitant diagnostic criteria at a cognitive (MMSE score) and a molecular (CSF biomarkers profile (Aβ1-42, Tau and p-Tau)) level, 2) to develop a mathematical model based on catecholamines plasma concentrations, age, MMSE score and hypertension status, in order to aid AD, OD or no dementia diagnosis ; the second cohort of 200 patients was studied: 1) to confirm our results; 2) to validate our mathematical model. **Results:** As previously described in a cortical brain region, we found at the peripheral level a linear correlation between [NA]plasma and MMSE score in AD patients. We could observe that [NA]plasma in AD population seems to follow a binomial distribution. This suggests the existence of subpopulations based on [NA]plasma reflecting the severity of cognitive decline depicted by MMSE score. We observed that high [NA]plasma was associated with an intermediate CSF Aβ1-42 concentration ([Aβ1-42]CSF) and MMSE score between NC patients and other AD patients, suggesting a relative earlier stage of AD. In parallel, we found that low [NA]plasma in AD patients was associated with a lower CSF p-Tau/total-Tau ratio ((p-Tau/Tau)CSF), previously described as a marker of disease evolution, and a lower MMSE score than other AD patients. This implies that low [NA]plasma in AD patients could potentially represent an advanced stage of the disease. Our results suggest that [NA]plasma could possibly illustrate the progression of AD by reflecting the overactivation and regression of the LC during disease evolution. Moreover, we could notice that the percentages of patients with hypertension from AD population with low/normal [NA]plasma, and from AD population with high [NA]plasma were respectively lower and similar than from NC and OD population. Based on these observations, we developed an algorithm based on different parameters: age, MMSE score, hypertension status and plasma concentrations of catecholamines. This mathematical model can discriminate with very good specificity and sensibility AD patients from patients with or without other dementia. **Conclusion:** In this study, we showed for the first time that [NA]plasma was correlated with MMSE score in the context of AD. We were able to observe a binomial distribution of [NA]plasma of AD patients and identify subpopulations based on their [NA] plasma. We described particular profiles of MMSE score and CSF AD biomarkers for AD patients with high and low [NA] plasma. [NA]plasma deregulation could hypothetically reflect overactivation and regression of the LC during AD. These results imply for future research that: 1) [NA]plasma could support early diagnosis of AD, 2) [NA]plasma could help to better characterize AD patients profile during disease evolution, 3) the link between LC degeneration and [NA]plasma in the context of AD needs to be investigated. These observations and perspectives open new possibilities in early diagnosis with our algorithm and digital processing of information obtained with non-invasive practice: MMSE score, hypertension status and plasma catecholamines level.

P110- DIFFERENTIAL EFFECTS OF THE INTERACTION BETWEEN THE EDUCATION AND APOE E4 ALLELE ON AMYLOID-BETA RETENTION AND MEMORY PERFORMANCES IN COGNITIVELY NORMAL OLDER ADULTS AND ALZHEIMER'S DISEASE PATIENTS. D.W. Kang[1], H.K. Lim[2] *((1) Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea - Seoul (Korea, Republic of), (2) Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea - Seoul (Korea, Republic of))*

Background: Despite the effect of education and APOE ε4 allele on amyloid-beta (Aβ) retention and memory, previous studies have not dealt with an interaction between two factors on Aβ deposition and memory function in the course of Alzheimer's disease (AD). **Objective:** To evaluate education by APOE ε4 allele interactions for Aβ retention and neuropsychological test scores in cognitively normal older

adults without Aβ deposition [CN(Aβ-), n=45] and Alzheimer's disease patients with Aβ retention [AD(Aβ+), n=25]. **Methods:** Multiple regression analyses (adjusted for age, gender) were conducted to examine the effects of education, APOE ε4 allele, and the interaction between the two factors on global, regional Aβ load quantified using [18F]flutemetamol standardized uptake value ratio with the pons as reference region and on neuropsychological test scores in each group. **Results:** The interaction between education and APOE ε4 allele had an effect on amyloid load in parietal lobes and striatum in each CN(Aβ-) and AD(Aβ+). There was an interaction effect of education and APOE ε4 allele on delayed recall only in CN(Aβ-). **Conclusions:** The present results highlight the differential effects of education and APOE ε4 allele interactions on AD pathology and memory function, allowing a deeper understanding of the role that protective and risk factors play in the AD pathogenesis.

Theme: CLINICAL TRIALS: COGNITIVE AND FUNCTIONAL ENDPOINTS

P111- DEVELOPMENT OF SOCIAL COGNITION ENHANCEMENT TRAINING PROGRAM FOR AMNESTIC MILD COGNITIVE IMPAIRMENT AND EARLY DEMENTIA OF ALZHEIMER'S TYPE PATIENTS, BASED ON FACIAL EMOTION RECOGNITION PATTERN ANALYSIS. B. Nam[1], T. Kim[1], S.R. Noh[2], W.M. Bahk[3], B.H. Yoon[4], S.Y. Lee[5], K. Lee[6], M.D. Kim[7], S.H. Shim[8], D.B. Lee[9] *((1) Department of Psychiatry, Konkuk University (Korea, Republic of), (2) Department of Psychology, Chungnam National University (Korea, Republic of), (3) Department of Psychiatry, College of Medicine, The Catholic University of Korea (Korea, Republic of), (4) Department of Psychiatry, Naju National Hospital (Korea, Republic of), (5) Department of Psychiatry, College of Medicine, Wonkwang University (Korea, Republic of), (6) Department of Psychiatry, School of Medicine, Dongguk University (Korea, Republic of), (7) Department of Psychiatry, School of Medicine, Jeju National Hospital (Korea, Republic of), (8) Department of Psychiatry, College of Medicine, Soonchunhyang University (Korea, Republic of), (9) Department of psychiatry, Mirae Hospital (Korea, Republic of))*

Backgrounds: Facial expression is an important non-verbal way that plays a crucial role in social communication.. If the process of perceiving facial expression is impaired, the ability to recognize the emotional state of others is degraded, which may make it difficult to maintain smooth interpersonal and social communications. In particular, several studies have reported that impairment of facial emotion recognition (FER) in Dementia of Alzheimer's type(DAT) affects interpersonal behavior. **Objectives:** We assumed that if FER in patients reporting of cognitive impairment [amnestic mild cognitive impairment (aMCI) and DAT] be trained properly , their interpersonal behavior as part of social cognition would be improved accordingly. However, the age-related changes in the facial expression recognition in Asian populations are largely unknown, though ample evidence suggests that facial expression recognition declines with normal aging. Therefore, as a preliminary work to develop the social cognition enhancement training program for aMCI and DAT, the characteristic eye patterns in the normal elderly during FER process were analyzed , which is the first attempt based on Hidden Markov Models(HMMs) as far as we know. **Methods:** The sample included 30 healthy younger (18 females; age range: 18–41 years) and 44 older (16 females; age range 59–84 years) participants. The face stimuli were 48 color photos of six facial expressions of each eight models (4 females, 4 males) selected from the KUFEC. The faces were presented individually for five seconds on a computer screen and participants were asked to choose one of the seven expression labels that was thought to describe the emotional expression. Participants' eye movements were recorded at a rate of 250 Hz with SMI iView RED-m, a remote pupil-tracking system. We made models for eye movement pattern of each individual using an HMM, which can explain the participant's scan paths during facial expression recognition in terms of regions of interest (ROIs) and the transition probabilities between ROIs. Subsequently, using VHEM, the HMMs of the participants were grouped into two clusters according to distinct scanning patterns. Overall, the participants' eye movement patterns could be categorized into analytic or holistic groups, and the probabilities on which of the two groups each individual fell into depended on age groups and types of expressions. **Results:** The recognition of older Koreans was less accurate than that of younger Koreans for expressions of anger (56.8% vs. 56.8%) and disgust (36.1% vs. 59.9%). However, unlike Western elders, older Koreans showed no difficulty in recognizing sadness as compared to younger Koreans. Specifically, about 64% of the younger participants belonged to the analytic pattern, while the older participants were evenly distributed among the analytic and the holistic groups. For anger expressions, while about 75% of the younger participants were categorized into the analytic group, about 78% of the older participants were categorized into the holistic group; for disgust expressions, about 96% of the younger participants were categorized into the analytic pattern, and about 56% of the older participants were categorized into the holistic group. **Conclusions:** This study can be a contribution to meaningful training algorithm to enhance FER ability in cognitively declining patients , which presents a non-invasive, patient-friendly method, easily accessible in both in-hospital and outpatient settings. **Key words:** Mild cognitive impairment; dementia of Alzheimer's type; Facial emotion recognition; Hidden Markov Model; Pattern analysis. **Acknowledgement:** This work was supported by the National Research Foundation of Korea (NRF) (Grant number NRF-2016R1E1A2A01953732 & 2018R1E1A2A02059043).

P112- USING A GLOBAL STATISTICAL TEST AS AN OVERALL MEASURE OF ALZHEIMER'S. N. Ellison, S. Hendrix, N. Knowlton , S. Dickson *(Pentara Corporation, Salt Lake City, Utah (United States))*

Background: Alzheimer's disease (AD) is a multi-factorial disease which has cognitive, behavioral, functional and global symptoms. These symptoms are all important aspects of disease and are driven by the underlying disease process. Outcomes measuring these symptoms provide multiple, potentially conflicting, answers to the question, "Did the treatment work?" **Objectives:** There is a need for one, clear answer to this question. Composite scores have been derived to meet this need, but another attractive alternative is to combine already validated measures of different symptoms of the disease using a Global Statistical Test (GST). A GST can provide a single evaluation of efficacy for a complex disease where treatment is expected to affect the underlying disease and related symptoms. A GST minimizes the impact of ceiling and floor effects by distinguishing patients who are close to the extreme scores on

each scale by ordered ranking thereby increasing the power of the outcome to detect treatment differences. The GST has been used for neurological applications in clinical trials, including a National Institute of Neurological Disorders and Strong stroke trial (Kwiatkowski et al. 1999) and a creatine study in Parkinson's Disease (Huang et al. 2009). While GSTs have not been used in AD, this approach provides a broad assessment of symptoms associated with disease progression across the disease severity continuum (Huang et al. 2009; Ramchandani et al. 2016). **Methods:** We illustrate the value of GSTs in AD by combining the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) 13, Clinical Dementia Rating Scale Sum of Boxes (CDR-sb) and Functional Activities Questionnaire (FAQ) scores in a GST at baseline, 6- and 12- months in the Alzheimer's Disease Neuroimaging Initiative (ADNI) data. The ADNI data used for this analysis included all subjects who had a baseline diagnosis of late mild cognitive impairment (MCI) or AD. We implemented the GST approach with an averaged percentile rank across the three selected totals at each visit. Each total score was ranked across all visits within each baseline diagnosis subgroup using a percentile (i.e. percentile rank). The percentile ranks from each of the three total scores were averaged for each subject to obtain an averaged percentile rank at each visit – the GST score. Change from baseline in the GST score was calculated by subtracting the baseline GST score for each subject from each post-baseline GST score. Percentile ranks allow the scores to have added meaning and interpretability over standard count ranks since the maximum possible rank is 100 for any study. Previous GST calculations have used a summed rank across items resulting in a maximum score of n times the number of items in the GST which varies by study. The performance of the GST and standard total scores was evaluated by the mean-to-standard-deviation ratio (MSDR) of the change from baseline. The MSDR represents the signal relative to the noise in the outcome measure, with higher MSDRs indicating an outcome that is closer to the actual disease. An additional analysis was performed using 10,000 simulations to estimate the statistical power with a GST. An identical treatment effect was simulated for the ADAS-cog and the CDR-sb and the GST was the averaged percentile rank of the two change from baseline scores. The power to detect a treatment effect was compared between the ADAS-cog, CDR-sb and the GST. **Results:** In the ADNI data, the GST showed similar or improved sensitivity compared to standard efficacy measurements of ADAS-Cog, CDR-sb and FAQ in all explored scenarios. The MSDR for the GST at 12 months in the late MCI population was 0.5160, which was higher than all other outcome measures, the CDR-sb being the closest with an MSDR of 0.4945. The GST showed significant improvements in sensitivity at months 6 and 12 in the AD subgroup with MSDRs of 0.7785 and 1.0784, respectively, with the closest MSDRs being 0.4980 (CDR-sb) and 0.8410 (FAQ), respectively. The CDR-sb (MSDR=0.33) showed equal sensitivity to the GST (MSDR=0.33) in late MCI subjects at 6 months. In the simulation analysis, the power of the GST was 83.2% and was more than 13% higher than the power for the two individual tests (69.6% and 69.7%). **Conclusion:** Based on these results, the GST performed better than the standard outcomes for the AD population and performed similarly for those late MCI. A composite score such as ADCOMS may be a more appropriate measure of disease in the MCI stage than a GST. Simulations showed that the GST had added power when compared to two individual scores with identical effect sizes. GSTs have been used to assess treatment effect for other degenerative diseases and may add power to detect treatment effects in AD as well. Combining multiple clinically meaningful outcomes in one overall disease measure results in a relevant, disease related disease progression marker.

P113- LEVERAGING SEX DIFFERENCES IN COGNITION AND ALZHEIMER'S TO OPTIMIZE CLINICAL TRIAL DESIGN. S. Banks, B. Shifflett, E. Sundermann, S. Edland *(University of California, San Diego - La Jolla (United States))*

Background: There are known sex differences in Alzheimer's disease. Women have a verbal memory reserve which, once depleted, results in an accelerated decline in cognition. Despite these well known patterns, and a tendency for cognitive outcomes to rely on verbal memory measures, sex is rarely given consideration beyond its use as a covariate. This strategy is unlikely to grasp the complexity of the known sex differences, which impact trajectories of decline as well as lifelong differences. Building on our earlier work showing that men and women have distinct optimized cognitive composites to accurately capture change over time in Alzheimer's disease, we applied similar methods to data from a recent clinical trial in participants with mild cognitive impairment (MCI). **Objectives:** To compare patterns of decline in cognitive measures in men versus women in the non-medication arms of an MCI clinical trial. **Methods:** Using a preexisting longitudinal dataset, we applied Mixed Models Repeated Measures (MMRM) techniques controlling for age and baseline score to compare rate of decline on components of the neuropsychometric battery in men (N=276) versus women (N=240) with MCI in the non-medication arms of the trial. We then completed power analyses to see how many participants in each of the sex-specific groups would be needed to detect treatment effect in a hypothetical 24-month trial. **Results:** In this population, women declined more quickly than men on all components of the neuropsychometric battery, and, moreover, variability in cognitive change over 24 months was consistently lower in women than men. Differences in rate of decline reached statistical significance for memory components. The faster rate of decline with reduced variability in rate of decline make the women more sensitive to potential drug effects in a clinical trial in this population over a standard trial period. A composite outcome measure constructed from the cognitive battery would require substantially less subjects to detect treatment effects in women than men. **Conclusion:** When selecting outcome measures, and in all aspects of trial design, the impact of sex differences should be considered. The heavy reliance on verbal memory measures, which women are better at throughout life, but decline more quickly on during MCI and dementia phases of the disease, are problematic if sex is not examined separately. When designing new trials, using cognitive tests with less bias toward one particular sex, and performing sex stratified analyses should be considered. Reanalyzing datasets from earlier trials using this strategy may hint at different results in men and women.

P114- THE OLFACT TEST BATTERY (OTB) PREDICTS ALZHEIMER'S DISEASE. L. Hastings[1], M.E. Lafaille-Magnan[2], S. Howe[3], R. Wilson[4] *((1) Osmic Entreprises - Cincinnati (United States), (2) McGill University - Montreal (Canada), (3) SRH Associates LLC - Cincinnati (United States), (4) RUSH - Chicago (United States))*

Background: 5.8 million Americans are living with Alzheimer's disease (AD). AD prevention is an urgent priority. Tests that identify individuals at risk for AD are necessary for such strategies. We need non-invasive, inexpensive, and scalable biomarkers to measure pathophysiological changes in preclinical AD. An olfactory function task appears well suited to evaluate the conservation, recovery, and deterioration of the olfactory network in clinical trials. **Objective:** To study the utility of the OLFACT Test Battery to predict AD dementia. **Method:** 588 individuals were administered the OLTACT Test Battery (OTB; odor identification, threshold, and memory) on one or more occasions from the 1674 participants in the Rush Memory and Aging Project (MAP). Two rules of inclusion were applied: (a) patients with at least one OTB administration with a CN status or an MCI status which reverted back to CN, and (b) patients with at least two neuropsych assessments, one at the time of OTB testing and a second to provide a basis for a diagnosis of dementia. As of 7/30/2019, N = 544 patients met these criteria. The approach to predict dementia uses of proportional hazards survival models with competing outcomes. The two competing outcomes were (a) that patients died prior to dementia diagnosis and (b) that patients received a dementia diagnosis based on cognitive evaluations and history. If patients had not yet died and developed dementia, their observation was censored (i.e., they could be diagnosed eventually). Time to event was defined as the elapsed time from initial OTB test to a diagnosis of dementia for the first group and as the elapsed time from initial OTB test to death for the second group. For censored patients, the time to event was the elapsed time from initial OTB test to the last cognitive evaluation. **Results:** N = 110 patients (22%) developed dementia. Of these, 43 (39%) died and autopsy results (available for N = 40) showed that 45% were possible AD and 33% were likely AD. These 110 patients had a mean age of 85.7 years at the time of OTB testing and mean time to dementia of 4.1 years. Their average neuropsych standardized score was -0.17 at the time of OTB testing. The OTB performance measure reported here is d', which represents familiarity and measures discriminability or the standardized difference between the old and new odors (signal detection variables from the episodic memory test). While values of d' less than 0 can occur because of guessing, it is useful to think of d' = 0 indicates the patient has no discriminability. The mean d' was 0.42. For the N=333 patients still alive and undemented at the last neuropsych evaluation (61%), the mean age was 78.9 years, the mean censored time elapsed from OTB testing to last assessment was 6.6 years, the mean cognitive score at OTB testing was 0.42 and the mean d' was 1.38. Four survival models were examined for each of the two outcomes (death without dementia, and dementia regardless of death). The first model examined time-to-event as a function of age only. The second used age and as predictors, the third used age and cognitive test performance as predictors, and the fourth used age and both d' and cognitive performance. Age predicts death without dementia in all four models. We reproduce several findings that impaired olfactory functions are associated with increased mortality. The important survival models relevant to olfaction test examined elapsed time from the OTB test and cognitive evaluation to a diagnosis of dementia. In these results, age is not as important a predictor of time to dementia as it was for predicting time to death without dementia. And, the effect of d and cognitive testing are stronger for predicting time to dementia than for predicting time to death without dementia. In conjunction with only age, a one-point (i.e., 1 SD) increase in d' is associated with a 44% (1 - 0.56) reduction in the risk of dementia. It is noteworthy that d' significantly contributes to the prediction of time to dementia even controlling for age and cognitive test results. An 80-year-old with poor OTB performance has a ~35% chance of developing dementia within 8 years whereas a 80-year-old with good performance has around a ~12% chance i.e., only 1/3 the chance. The same relationship holds for the 70-year-old groups. **Conclusion:** A brief procedure that involve the OTB test can be used to make predictions that a person of a given age will develop dementia in a certain number of years. The prediction of the probability of a subject developing dementia within a specific time span would be important information to have when selecting subjects into a clinical trial. Testing olfactory function with the OLFACT TB battery in ongoing studies represents a unique opportunity to mitigate recruitment costs and reduce time.

P115- IDENTIFYING WHAT MATTERS TO PEOPLE WITH AND AT RISK FOR ALZHEIMER'S DISEASE AND THEIR CARE PARTNERS: CONCEPT ELICITATION AND ITEM DEVELOPMENT. B. Hauber[1], D. Dibenedetti[1], G. Vradenburg[2], L. Callahan[3], M. Potashman[4], H. Krasa[5], A. Hartry[6], G. Wunderlich[7], D. Hoffman[8], D. Wieberg[9], I. Kremer[10] *((1) RTI Health Solutions - Research Triangle Park, NC (United States), (2) UsAgainstAlzheimer's - Washington, DC (United States), (3) University of North Carolina - Chapel Hill, NC (United States), (4) Biogen, Inc. - Cambridge, MA (United States), (5) OTSUKA Pharmaceutical Development & Commercialization - Rockville, MD (United States), (6) Lundbeck LLC - Deerfield, IL (United States), (7) Boehringer Ingelheim (Canada) Ltd. - Burlington, ON (Canada), (8) Takeda Pharmaceuticals - Cambridge, MA (United States), (9) Home Instead, Inc. - Omaha, NE (United States), (10) LEAD Coalition (Leaders Engaged on Alzheimer's Disease) - Washington, DC (United States))*

Background: Recent guidance from the US Food and Drug Administration (FDA) indicates that measures of treatment effect in early Alzheimer's disease (AD) must be clinically meaningful (FDA, 2018; Edgar et al., 2019). Researchers have taken different approaches to eliciting what matters to individuals with or at risk for AD and their caregivers. Such approaches include reviewing existing instruments to develop conceptual models of patient-relevant concepts (e.g., Hartry et al., 2018); conducting qualitative interviews and instrument reviews to develop composite measures of patient-relevant changes in early AD (e.g., Ropacki et al., 2017; Gordon et al., 2016); and developing instruments to measure progression from normal aging to dementia (Jutten et al., 2017). The Alzheimer's Disease Patient and Caregiver Engagement (AD PACE) What Matters Most (WMM) study is a two-part study designed to better understand and assess treatment-related needs, preferences, and priorities among individuals with or at risk for AD and their care partners. Phase 1 involved in-depth interviews with 60 individuals and care partners (12 individuals with unimpaired cognition but evidence of AD pathology, 12

with mild cognitive impairment and evidence of AD pathology, 12 with mild AD, 12 dyads of individuals with moderate AD and their care partners, and 12 care partners of individuals with severe AD) to elicit symptoms and behaviors that matter most to patients and care partners across the continuum of AD (Vradenberg et al., 2019). Phase 2 will quantitatively estimate how much each potential treatment related outcome matters and which potential outcomes matter most to these populations. **Objectives:** Compare WMM qualitative results and existing literature to develop a list of symptoms and behaviors important to people with and at risk for AD and care partners to inform the WMM quantitative study. **Methods:** Concepts from the WMM interviews and relevant literature were compiled. Redundancies were removed, resulting in a list of 83 potential concepts of interest (COI). Reduction of this list involved deleting redundancies, dividing "double-barreled" concepts into simpler concepts and streamlining remaining concepts. Further reduction and revisions were based on consensus of two researchers who conducted the WMM interviews and reviewed by a third researcher not involved in the WMM interviews, resulting in a total of 57 concepts. Through further iterative rounds of review and streamlining, 45 concepts were identified as sufficiently distinct and items were developed for each. Items were pretested in in-person interviews with 8 patients and 7 care partners prior to WMM Phase 2. **Results:** During pretesting, 4 items were removed, 2 items were combined, and 2 new items were developed. The final set comprised 42 items. **Conclusion:** Recent work in this area has primarily focused on identifying concepts that are relevant to people with early signs of cognitive impairment or mild AD. The concepts identified in the WMM study can be used to measure what matters most to patients and care partners across the entire continuum of AD and eventually inform the development of an AD-specific instrument. Having a standard set of AD COIs will provide a potentially important tool to assure that current and future clinical outcome assessments measure changes that matter most to patients and care partners across the lived experience with AD. **References:** Edgar CJ, Vradenburg G, Hassenstab J. The 2018 Revised FDA Guidance for Early Alzheimer's Disease: Establishing the Meaningfulness of Treatment Effects. J Prev Alzheimers Dis. 2019. https://doi.org/10.14283/jpad.2019.30; Food and Drug Administration (FDA). Early Alzheimer's disease: developing drugs for treatment guidance for industry. Draft guidance. 2018. Available at: https://www.fda.gov/media/110903/download. Accessed August 17, 2019; Gordon MF, Lenderking WR, Duhig A, Chandler J, Lundy JJ, Miller DS, et al. Patient-Reported Outcome Consortium's Cognition Working Group. Development of a patient-reported outcome instrument to assess complex activities of daily living and interpersonal functioning in persons with mild cognitive impairment: The qualitative research phase. Alzheimers Dement. 2016 Jan;12(1):75-84; Hartry A, Aldhouse NVJ, Al-Zubeidi T, Sanon M, Stefanacci RG, Knight SL. The conceptual relevance of assessment measures in patients with mild/mild-moderate Alzheimer's disease. Alzheimers Dement. 2018;10:498-508; Jutten RJ, Peeters CFW, Leijdesdorff SMJ, Visser PJ, Maier AB, Terwee CB, et al. Detecting functional decline from normal aging to dementia: Development and validation of a short version of the Amsterdam IADL Questionnaire. Alzheimers Dement. 2017;8:26-35; Ropacki MT, Hannesdottir K, Hendrix S, Gordon MF, Stephenson D, Coons SJ, et al. Clinically Meaningful Outcomes in Early Alzheimer Disease: A Consortia-Driven Approach to Identifying What Matters to Patients. Therapeutic Innovation & Regulatory Science 2017; 51(3):380-390; Vradenburg G, DiBenedetti DB, Hauber B, Slota C, Wronski SL, Comer M, et al. Findings from the Alzheimer's Disease Patient and Caregiver Engagement (AD PACE) Initiative's What Matters Most Qualitative Study. Poster presented at the 2019 Alzheimer's Association international Conference, Los Angeles, CA. July 17, 2019.

P116- ANALYSIS OF THE RATES AND TYPES OF ERRORS ON PAPER ADMINISTRATION OF THE NEUROPSYCHIATRIC INVENTORY. S. Karas, T. Feaster, B. Hong *(Signant Health - Wayne (United States))*

Background: Data quality programs that reduce rater error are beneficial to clinical trials, especially those in Alzheimer's disease (AD). Given the high failure rate in AD drug development over the past 20+ years, ensuring optimal data quality is paramount. One potential means of addressing data quality in global AD trials is the implementation of data quality surveillance programs that utilize audio review. Further, the use of audio recording scale administration, as part of a surveillance program, allows for additional review of both standardization and quality of collected data. However, the use of audio recording, particularly when assessing caregiver interview scales such as the Neuropsychiatric Inventory (NPI) in Alzheimer's disease clinical trials does not appear to be widespread. The NPI was developed to obtain information on the presence of psychopathology in subjects with Alzheimer's disease and other dementias. The assessment is a structured, clinician-guided interview of a well-informed caregiver about the subject's behavior in 12 different domains. For a domain, if an initial screening question is answered yes, sub-questions are administered, followed by an assessment of the frequency and severity of a subject's specific behaviors, and the extent of caregiver distress. Given the limited data in the field related to scoring and administrative errors on the NPI, in this analysis, we evaluated the rates and types of errors on the paper and pencil version of the NPI. **Objective:** Identify common administration and scoring errors on paper administration of the NPI in AD clinical trials. **Methods:** Data from the NPI, at pre-determined study visits, were evaluated in two multi-national clinical trials of subjects with agitation in AD. In each of the trials, raters were trained and certified on the administration and scoring of the NPI. Further, each of the trials had a comprehensive in-study data quality surveillance program where data was reviewed for administration and scoring errors by a calibrated, local language speaking clinician. Each of the data quality programs also included audio recordings of the assessments that were reviewed in conjunction with the paper source document. Raters who were identified as having administration and/or scoring errors were remediated and re-educated to the standard scoring and administrative conventions of the NPI. **Results:** A total of 2,582 NPIs were reviewed by calibrated clinicians including paper source along with audio recordings of administrations. Any scoring or administrative issues were identified though pre-determined flags. Of these reviews, 25.8% (666) contained at least one administrative or scoring error flag. Given that a review may contain more than one flag, a total of 1,735 scoring and administrative flags were identified. Of the the flags that were triggered, 27.9% (484) were identified due to raters either referencing the incorrect time frame for the assessment or not referencing the time frame at all. Overall,

the majority of errors identified were administrative nature. **Conclusions:** Given the low success rate in AD clinical trials, it is essential that any and all methodologies that could maximize data quality be considered. The implementation of an in-study data quality program has been shown to reduce rater error. The addition of audio review for the NPI is likely more beneficial than worksheet review alone due to the high number of administrative errors detected. Additionally, rater training programs for the NPI may want to emphasize correct time frame references, and proper administration of the frequency, severity, and distress items. As the NPI is often a key efficacy measure, even a modest reduction in error rate and improvement in standardization could prove beneficial to outcome data. Additionally, previous research has demonstrated that identifying scoring and administrative errors early on in a trial, for example at the Screening Visit, will lead to longitudinal improvement in rater performance and data quality during the course of the trial.

P117- ANALYSIS OF THE RATES AND TYPES OF ERRORS ON THE COHEN-MANSFIELD AGITATION INVENTORY IN AGITATION IN DEMENTIA CLINICAL TRIALS.

H.T. Feaster, B. Hong, S. Karas *(Signant Health - Wayne (United States))*

Background: The Cohen-Mansfield Agitation Inventory (CMAI) is a commonly used efficacy measure in Alzheimer's disease (AD) clinical trials to assess agitation. The CMAI is a structured interview with a subject's study partner and is used to assess the frequency of agitated behaviors in elderly persons over the preceding pre-defined time frame. Data quality is crucial to clinical trials and making sure all raters follow the standardized administration and scoring of assessments like the CMAI is essential. However, the use of audio recording, particularly when assessing caregiver interview scales such as the CMAI in AD clinical trials does not appear to be wide spread. In this analysis, we evaluated the type of errors on the paper-pencil version of the CMAI. **Objectives:** Identify common administration and scoring errors on the CMAI in multi-national agitation in AD clinical trials. **Methods:** Data from the CMAI (long-form version), at various study visits, were evaluated in two multi-national clinical trials of subjects with agitation in AD. Each of the trials had an in-study data quality program where the data were reviewed for administration and scoring errors. CMAI reviews were completed by calibrated clinicians in local language. Each of the data quality programs also included audio recordings of the assessments that were reviewed in conjunction with the paper assessment source document. Raters who were identified as having administration and/or scoring errors were remediated and re-educated to the standard scoring and administrative conventions of the CMAI. **Results:** A total of 2,611 CMAI administrations were reviewed in this analysis. Roughly, one-sixth (16%) (N = 410) of the scales reviewed were flagged for an administration or scoring error. When evaluating the administration versus scoring error flags, administration errors accounted for 69% (N=283) while scoring errors accounted for the remaining 31% (N=127). The most common error noted, at almost 50%, was an administration error where the correct time frame was not referenced as part of the standard instructions given to study-partners for the reporting of subject symptoms. **Conclusions:** Maintaining the integrity of data quality is essential for clinical trials, and continued development of comprehensive data quality programs targeting efficacy measures that have not been previously evaluated for rater performance, such as such as the CMAI, are vital. This analysis provides further support to using an in-study ratings surveillance program, even for scales that may seem straightforward in scoring and administration. Understanding these common performance errors raters have on key outcome measures, such as the CMAI, will help to promote more nuanced rater training, and improve data quality.

P118- FUNCTIONAL ACTIVITY OF THE MUSCARINIC POSITIVE ALLOSTERIC MODULATOR VU319 DURING A PHASE 1 SINGLE ASCENDING DOSE STUDY.

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Background: The development of neurotransmitter based cognitive enhancers for Alzheimer's disease have focused recently on allosteric modulation, as a way of reducing potential drug-limiting toxicities that have been the hallmark of earlier orthosteric compounds. VU319 is an investigational positive allosteric modulator of the M1 muscarinic acetylcholine receptor that has recently finished initial testing in healthy volunteers. Cognitive tasks and event-related potentials (ERPs) have been used during the randomized, double-blind, placebo-controlled Single Ascending Dose (SAD) study of VU319. This presentation includes both data from the initial SAD study, and the Food Effect substudy. **Objectives:** The main pharmacodynamic objectives of the SAD were to identify early markers of functional engagement. Following the ascending dose cohorts, a Food Effect substudy was conducted to assess whether there was any change in the cognitive performance if VU319 was dosed with food compared to in a fasted state. **Methods:** VU319 was given orally to 52 healthy volunteers aged 18-55 years. The SAD study tested 40 participants in five dose escalating cohorts of eight participants, in which six received VU319 and two received placebo. The Food Effect substudy consisted of 12 participants, in which ten received oral VU319 and two received placebo. The five doses for the SAD study were 60, 120, 240, 400 and 600mg. Participants in the Food Effect substudy received VU319 at a single dose of 120mg. For the 5 cohorts of the SAD study, all participants were dosed in a fasted stated. In contrast, all 12 participants in the Food Effect substudy completed were dosed twice; once fasted, and once following breakfast. Cognitive and electrophysiological tasks were examined pre-dosing and at 5 hours post-dose. The tasks were selected for their sensitivity to cholinergic tone. Cognitive tasks tested spatial and sustained attention, episodic and working memory, perceptual vigilance and psychomotor speed. Recorded ERP examined auditory and visual discrimination using oddball tasks, and an incidental memory task in which participants passively observed novel and repeated complex images. **Results:** The analysis showed a trend for improvements in cognitive and ERP performance on the higher doses of VU319 compared to placebo. Participants on the highest dose of VU319 responded significantly faster to targets on the continuous performance test compared to participants

on placebo ($p = 0.03$, effect size $d = 1.2$). Additionally, on the incidental memory task, participants who received the higher two doses of VU319 exhibited larger P300 amplitudes compared to placebo, when present with repeated compared to novel images ($d > 0.8$). Examination of the relationship between plasma levels of VU319 and cognitive performance showed that the response time on the continuous performance task decreased in relation to increasing concentration of VU319 in the bloodstream. **Conclusion:** We conclude that these results demonstrate potential enhancement of the cholinergic system functioning in healthy adults following a single dose of VU319. These results provide an indication of the potential measures that are sensitive to cognitive activity by VU319 and therefore provide a potential framework to examine the cognitive impact of multiple doses of VU319 in AD patients.

P119- LIFE-DSR STUDY: A 3-YEAR LONGITUDINAL OBSERVATIONAL COHORT STUDY. W. Mobley[1], J. Hendrix[2], A. Burke[3], G. Capone[4], B. Chicoine[5], A. Costa[6], A. Esbensen[7], S. Hart[8], E. Head[9], P. Kishnani[8], F. Lai[10], I. Lott[9], C. Ochoa-Lubinoff[11], H.D. Rosas[10], T. Rosser[12], S. Santoro[10], F. Schmitt[13], S. Sherman[12], B. Skotko[10], A. Talboy[12] *((1) UCSD - La Jolla (United States), (2) LumindIDSC - Burlington (United States), (3) Barrow Neurological Institute - Phoenix (United States), (4) Kennedy Krieger Institute - Baltimore (United States), (5) Advocate Health - Park Ridge (United States), (6) Case Western Reserve University - Cleveland (United States), (7) Cincinnati Children's Hospital - Cincinnati (United States), (8) Duke University - Durham (United States), (9) UCI - Irvine (United States), (10) Massachusetts General Hospital - Boston (United States), (11) Rush University Medical Center - Chicago (United States), (12) Emory University - Atlanta (United States), (13) University of Kentucky - Lexington (United States))*

Background and Objectives: In recent decades, significant improvements in early medical care and enhanced delivery of services have led to increased vitality, wellbeing and life expectancy for people with Down syndrome (DS). However, older adults with DS face a markedly increased risk of Alzheimer disease (AD) due, in part, to an extra copy of the Amyloid Precursor Protein gene present on chromosome 21. It is estimated that by age 55–60 years at least 70% will develop Alzheimer's dementia. Identifying interventions to prevent or mitigate cognitive deficits associated with AD has the potential to improve health outcomes and quality of life for adults with and without DS. To better understand the progression of AD in the population with DS, the Longitudinal Investigation For Enhancing Down Syndrome Research (LIFE-DSR) study has been launched. The primary objective is to characterize trajectories of change in the adult DS population through longitudinal collection of measures of cognition, function, behavior, and health status. **Method:** The LIFE-DSR study is a 3-year longitudinal observational cohort with a goal to enroll 270 adults with DS over the age of 25. LIFE-DSR is being supported by the Down Syndrome Clinical Trials Network (DS-CTN), a consortium of 11 leading DS research centers in the United States. **Result:** LIFE-DSR will employ cognitive, functional, behavioral and health measures and will bank plasma samples from each participant at baseline and follow-up visits at 1 and 2 years. Primary outcome measures will be evaluated across the sample and by age strata. **Conclusion:** The study is currently recruiting subjects and plans to provide de-identified, open access data as early as 2020 for the broad research community. **Key Words:** Alzheimer disease, Down syndrome, cognition, function, behavior

P120- AN OBSERVATIONAL STUDY IN REAL WORLD DAILY CLINICAL PRACTICE TO EVALUATE THE EFFECT OF THE MEDICAL FOOD SOUVENAID ON INSTRUMENTAL ACTIVITIES OF DAILY LIVING IN PEOPLE WITH MILD ALZHEIMER'S DISEASE. G. Ziere[1,2], V. Vanneste[3], K. Kalisvaart[4], J. De Wilde[5], M. Herbert[5], L. Boelaarts[6], S. Sikkes[7] *((1) Department of Geriatrics, Havenpolikliniek, Maasstad Ziekenhuis - Rotterdam (Netherlands), (2) Alzheimer Center Zuidwest Nederland, Erasmus Medisch Centrum - Rotterdam (Netherlands), (3) Franciscus Ziekenhuis - Roosendaal (Netherlands), (4) Department of Geriatrics, Spaarne Gasthuis - Haarlem (Netherlands), (5) Danone Nutricia Research - Utrecht (Netherlands), (6) Department of Geriatric Medicine, Noordwest Hospital Group - Alkmaar (Netherlands), (7) Alzheimer Center)*

Background: Alzheimer's disease (AD) leads to a progressive decline in both cognitive performance and instrumental activities of daily living (iADL). The decline in iADL, such as cooking, handling finances and everyday technology, is especially relevant for the quality of life of AD patients and their caregivers. Nutrition is an important modifiable risk factor in AD and has been gaining interest in the management of the early disease stages. Souvenaid is a medical food for early AD containing the specific nutrient combination Fortasyn Connect designed to enhance synapse formation and function. Randomized controlled trials showed beneficial effects of this medical food on memory in drug-naïve mild AD patients1,2 and on the cognitive-functional outcome Clinical Dementia Rating - Sum of Boxes (CDR-SB) and hippocampal atrophy in prodromal AD3. In this observational study we evaluated whether Souvenaid has a benefit on iADL. **Objective:** The objective of this observational study was to evaluate the effects of nutritional support with Souvenaid on iADL of people with mild AD in real-world daily clinical practice. **Methods:** Participants were recruited from specialized memory clinics in the Netherlands and received the medical food as a 125-mL once-a-day drink. The decision to start with nutritional support was made by the health care professional prior to enrollment. iADL were assessed at baseline, 6 months follow-up, and optionally at 12 months follow-up, using the Amsterdam Instrumental Activities of Daily Living questionnaire (A-IADL). Changes in A-IADL scores were compared with a reference population consisting of memory clinic patients with dementia (n=57)4, using a one-sample t-test. Results will be presented for people with valid A-IADL scores at both baseline and 6 months (modified intention-to-treat population). The exploratory 12-month results will also be presented. **Results:** Between March 2013 and March 2016, 116 participants were enrolled in the study. Valid A-IADL scores at both baseline and 6 months were available for 73 (63%) participants. The mean age was 75.7 (SD 7.1) years, 56.2% were male, and the mean mini-mental state examination score was 23.7 (SD 2.9). Of those enrolled, 27 (23%) participants also had valid A-IADL scores at 12 months. Self-reported adherence to the medical food was high, both when calculated over the 6-month intervention period (88.0%, [SD 24.3], n=44) and over the 12-month intervention period (82.2% [SD 24.7], n=15). The baseline A-IADL score was 46.61 (SD 7.91) in this mild AD population. The 6-month change from baseline in A-IADL was significantly less than the dementia reference

population (-1.56 [SD 6.71] vs. -3.68 respectively, p=0.009). The effect was maintained in participants who completed the 12-month period with a mean change from baseline of -3.12 (SD 8.04) compared with the 12-month reference value of -7.35 (p=0.011). **Conclusion:** People with mild AD receiving the medical food showed less decline in iADL over 6 and 12 months compared with a reference population. In addition to the previously demonstrated benefits of Souvenaid on memory, cognition and hippocampal volume, this observational study suggests that this specific medical food has beneficial effects on instrumental activities of daily living in mild AD in a real-world clinical setting. **References:** 1. Scheltens, P., et al., Efficacy of a medical food in mild Alzheimer's disease: A randomized, controlled trial. Alzheimers Dement, 2010. 6(1): p. 1-10.e1. 2. Scheltens, P., et al., Efficacy of Souvenaid in mild Alzheimer's disease: results from a randomized, controlled trial. J Alzheimers Dis, 2012. 31(1): p. 225-36. 3. Soininen, H., et al., 24-month intervention with a specific multinutrient in people with prodromal Alzheimer's disease (LipiDiDiet): a randomised, double-blind, controlled trial. The Lancet Neurology, 2017. 16(12): p. 965-975. 4. Koster, N., et al., The sensitivity to change over time of the Amsterdam IADL Questionnaire ©. Alzheimers Dement, 2015. 11(10): p. 1231-40.

P121- COMPARING THE RESULTS OF A CONSENSUS EXPERT DIAGNOSIS WITH OUTCOMES BASED ON THE SYNDROM-KURZTEST (SKT), A SHORT COGNITIVE PERFORMANCE TEST: INDICATIONS FOR CONVERGENT VALIDITY. M. Stemmler[1], H. Lehfeld[2], K. Numbers[3], P. Sachdev[3], H. Brodaty[3] *((1) University of Erlangen-Nuremberg - Erlangen (Germany), (2) University of Erlangen-Nuremberg, Department of Psychiatry and Psychotherapy, Paracelsus Medical University - Nuremberg (Germany), (3) Centre for Healthy Brain Ageing (CHeBA), University of New South Wales, School of Psychiatry - Sydney (Australia))*

Background: The Syndrom-Kurztest (SKT; Erzigkeit, 2001) is a short cognitive performance test for the assessment of cognitive decline, which has recently been normed for English speaking countries. The SKT consists of nine subtests, three of which assess memory and six of which assess attention/speed of information processing. Currently, the SKT is being administered as part of the ongoing Sydney Memory and Aging Study (MAS; Sachdev et al., 2010). MAS began in 2005 to study the clinical characteristics and prevalence of mild neurocognitive syndromes to determine the rate of change in cognitive functioning over time. MAS is currently in its 7th wave of testing with the addition of the SKT to the neuropsychological test battery occurring midway through wave 6. At baseline, and each wave thereafter (every 2 years), MAS participants who meet criteria are brought to a review meeting where a panel of experts discuss all available clinical, neuropsychological, laboratory and imaging data to make a consensus diagnosis. The present study compares consensus diagnoses from the 6th and 7th waves of MAS to the results from the SKT. A traffic light system was developed based on optimal cutoffs for the discrimination between three diagnostic groups (cognitively healthy, mild cognitive impairment (MCI) or dementia). Summary scores between 0 and 4 suggest normal cognitive aging or cognitive health (green), scores between 5 and 10 suggest MCI (yellow), and scores above 11 are likely to represent pathological cognitive decline due to dementia (red). **Objectives:** To find evidence for convergent validity of the regression-based norming (Crawford & Garthwaite, 2006; Stemmler, Lehfeld & Horn, 2015) of the SKT for English speaking countries in a well-characterized longitudinal cohort of older adult native-English speakers. **Methods:** Participants were 75 older adults aged 83 – 96-years old (29 men and 46 women) with complete data and available expert consensus diagnoses. Sixty-one of the participants were diagnosed as cognitively normal (healthy), 6 as MCI, and 8 as cognitive impairment due to beginning dementia. Participants' average age was 87.31-years old (SD = 3.40) with an average education of 13.24-years (SD = 3.58). **Results:** Using the traffic light coding system from the SKT, of the 61 cognitively normal participants, 52 (85.3%) were coded as green, 9 (14.8%) were coded as yellow, and none were coded as red. Of the 6 MCI participants, 2 (33.3%) were coded as green, 4 (66.7) were coded as yellow, and none were coded as red. Of the 8 demented participants, 2 (25%) were coded as green, 4 (50%) were coded as yellow, and 2 (25%) were coded as red. Having a previous dementia diagnoses was an exclusion criteria for administration of the SKT. So far, the results indicate satisfactorily specificity of the SKT for MCI and/or dementia (.85 for MCI and close to 1.00 for dementia). The correlations of the SKT summary score together with the subscales memory and attention with the MMSE (adjusted for age and education; measure at wave 7) were r = -0.50 for summary, r = -.43 for memory, and r = -0.32 for attention. **Conclusion:** This was the first empirical study on the convergent validity of the newly-normed SKT for English speaking countries. The data analyses are preliminary while more and complete data will be presented at the conference. The first results show evidence for convergent validity in detecting normal cognitive development as well as MCI in aging adults. The SKT was somewhat less sensitive for detecting beginning dementia, considering half of the subjects still as MCI. As the number of participants transitioning from normal cognition to MCI or dementia that have been administered the SKT increases, these relationships are expected to get stronger. **References:** Erzigkeit H. A short cognitive performance test for assessing deficits of memory and attention – User's manual. Geromed; 2001. Crawford, J. R. & Garthwaite, P. H. Comparing patients' predicted test scores from a regression equation with their obtained scores: A significance test and point estimate of abnormality with accompanying confidence limits. Neuropsychology 2006, 20, 259–271. Sachdev, P. S., Brodaty, H., Repprermund, S., Kochan, N. A., Trolloer, J. N., Draper, B., (…) the Memory and Ageing Study Team (2010). International Psychogeriatrics, 22 (8), 1248-1264. Stemmler M, Lehfeld H, & Horn R. SKT Manual. 4th extended and revised edition. Spardorf: Geromed; 2015.

P122- COMPARISONS BETWEEN ADAS-COG 11 AND CDR SYSTEM MEASURES IN THE ASSESSMENT OF COGNITIVE DYSFUNCTION IN MILD TO MODERATE ALZHEIMER'S DISEASE. P. Goetghebeur[1], D. Digregorio[2], M. Micaletto[1], M. Roy[3], J. Rouru[4], K. Wesnes[5] *((1) Signant Health - Reading (United Kingdom), (2) Signant Health - Wayne (United States), (3) Signant Health - Prague (Czech Republic), (4) Signant Health - Turku (Finland), (5) Signant Health - Streatley On Thames (United Kingdom))*

Background: The CDR System, a computerised cognition assessment battery designed for use in all phases of drug development, measures core cognitive domains. The System has been used widely in the assessment of cognitive function in

Alzheimer's disease. In a recent Phase II study, the battery was used in conjunction with the Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-cog), to assess the effect of ORM-12741 on cognition in patients with mild to moderate Alzheimer's disease. **Objectives:** The aim of this analysis was to evaluate the correlations between various CDR System measures and the ADAS-Cog. **Methods:** Data from 299 subjects with diagnosis of probable AD according to the National Institute on Aging - Alzheimer's Association diagnostic criteria were available. The CDR System assesses both the accuracy and speed of each response, except in word recall where the patients are given 1 minute to recall as many words as possible. In this analysis, in addition to the word recall measures and the established core domain scores, overall accuracy and speed scores were derived. These were used to create ratio scores which integrated accuracy and speed measures for attention and memory, as well as an overall score. Spearman's correlations between the various CDR System measures and ADAS-Cog total score and the sub score for memory at baseline were performed. Additionally, we compared the Immediate Word Recall score (IWR) from the CDR System with ADAS-Cog overall Word Recall and Word Recall first attempt. **Results:** The CDR system IWR score when compared both to overall Word Recall from the ADAS-Cog and the first recall from this scale, showed moderate to strong correlations (R = -0.67). The CDR System overall accuracy and ratio of accuracy to speed measures correlated strongly with ADAS-cog total score (R = -0.74 ; R = -0.78 respectively), whilst for overall speed it moderately correlated (R = 0.57). A similar pattern was observed for overall CDR System measures correlation with the ADAS-Cog memory sub-score, with strong correlations for accuracy and ratio accuracy to speed (R = -0.72 and R = -0.73 respectively) and moderate correlation for overall speed (R =0.56). Finally, moderate correlation between ADAS-Cog total or memory sub-score and CDR System individual cognitive domain accuracies (R ranging from -0.42 to -0.62), speeds (R ranging from 0.34 to 0.56) and ratios accuracy to speed (R ranging from -0.66 to -0.52) were seen. **Conclusions:** Statistically significant moderate and strong correlations were found between ADAS-Cog11 and the various CDR System measures including Word Recall, confirming the system's validity in assessing cognition in Alzheimer's disease patients. Additionally, the strongest correlations were observed for the accuracy to speed ratios, which is a novel finding. Such ratios capture two important aspects of cognition in patients with Alzheimer's disease, decreased accuracy performance together with slowed response times. Overall, the advantage of computerised testing is that it can discriminate between these two important facets of performance, and identify speed-accuracy trade-offs; whereas instances of patients sacrificing speed to maintain accuracy cannot be captured if only accuracy is assessed.

P123- PRECISION FUNCTIONAL ASSESSMENT FOR ALZHEIMER'S DISEASE (PFA-AD): A PILOT STUDY FRAMEWORK. G. Hernandez[1], C. Lopez[1], T. Gisler[2], D. Wershiner[2], V. Seyfert-Margolis[2], R. Brinton[1] *((1) CIBS, University of Arizona - Tucson (United States), (2) Myownmed - Bethesda (United States))*

Background: Current clinical trial assessment of cognitive function and activities of daily living are based on periodic assessments conducted under controlled clinical conditions using standardized clinical measures. This approach is highly correlated with diagnosis of Alzheimer's but has varied relevance to the personal real-life daily challenges to those living with the disease and to those caring for the patient. A recent noted Alzheimer's Association roundtable discussion on digital technologies, noted that the use of digital technologies in clinical trials is actively encouraged. While the field is still new and not completely validated, the opportunity to embed these tools in clinical trials in parallel with other more traditional measures is needed to move the field forward. This study provides a plan to pilot this approach as a means for building on it for expanded use in clinical trials and potentially as part of patient care management in the future. Alzheimer's disease is personal. Assessment of functional capacity should be too. Our goal is to develop a technology-based tool that will enable real-time assessment of real-life function that really matters for persons with Alzheimer's disease and their caregivers. **Objectives:** Precision Functional Assessment for Alzheimer's Disease (PFA-AD) in real-time under real-life conditions will enable: 1) identification of key behavioral challenges that are relevant to the person with AD and their caregivers; 2) assessment of therapeutic effect in real time across multiple domains of behavioral function; and 3) innovate clinical trial measures of daily activities by conducting functional assessments that are personalized and relevant to the patient and caregiver. **Methods:** PFA-AD proof of concept development will be embedded as part of a clinical trial to further develop Allopregnanolone, a first in class regenerative therapeutic for AD with the potential to promote self-renewal and repair. This clinical trial is an intravenous (IV) to intramuscular (IM) formulation bridging study to identifying the IM dose equivalent to a pre-established IV dose (4mg) and assess its safety and tolerability as a weekly injection in 12 persons (6 women and 6 men) diagnosed with AD (https://clinicaltrials.gov/ct2/show/ NCT03748303). MyOwnMed (MOM), Inc has created a 360° digital platform that captures first person patient experience and facilitates better patient engagement, measures clinical treatment efficacy and outcomes from real world patient experiences. The PFA-AD digitally-powered platform will enable AD researchers to: 1) connect and analyze data from the Alzheimer's patients and their caregivers; 2) Create digitally-powered real-world studies to gather real-time, real world data; 3) Integrate data across clinical trial measures to generate predictive indicators of therapeutic impact. Initially, the platform will support simple measures of lifestyle and daily function as defined by the team working with patients and will include surveys to be delivered digitally to both the patient and caregiver using the MOM portal and mobile software. This will allow content to be personalized for each patient/caregiver, while at the same time providing for consistent data capture. Control for survey presentation timing, and determination of lifestyle indicators will be via the study coordinator using the MOM software platform. This will allow for the study team to define key time periods for survey administration, while at the same time capturing daily life data more continuously. Wearable technologies will be integrated to capture physical activity and sleep, using available application interfaces (API's) that will be seamlessly integrated into the MOM mobile application for patients/caregivers. **Results:** Analysis of PFA-AD data will include: 1) Ease of use; 2) Fidelity of personalized functional profile (did the survey questions measure the function); 3) Correlation of personalized real-life functions with clinical trial standardized cognitive assessments; 4) Correlation of personalized real-life functions with clinical trial MRI-based

brain analytics (gray and white matter structure, diffusion tensor imaging for white matter tracks and resting state default mode network as an indicator of synaptic connectivity); 5) Feasibility of scale up for inclusion in Allo Phase 2 clinical trial. **Conclusions:** Alzheimer's disease is personal, and assessment of function can be too. The PFA-AD application innovates precision analytics to measure cognition and behavior that really matters, in real time, that is personalized to both the person living with Alzheimer's disease and their caregiver. Outcomes of this research will advance precise and personalized analysis of real-life function to assess therapeutic response.

P124- EFFECTS OF DIETARY FLAXSEED ON MEMORY AND COGNITION. B. Albensi, C. Cortes-Perez, A. Adlimoghaddam *(St Boniface Hospital Research - Winnipeg (Canada))*

Background: Currently there is no cure for Alzheimer's disease (AD), which is associated with memory loss, cholinergic changes, amyloid plaques, tangles, inflammation, and brain metabolic changes. Furthermore, all drug treatments to date targeting plaques and cholinergic neurotransmission have shown only mild benefit, if any benefit at all. Mild cognitive impairment (MCI) is a transitional stage between normality and progression to AD. These patients report memory and cognitive problems that are not yet severe and so they are able to still function independently. Preventing AD in these patients may be within reach, if appropriate measures are taken. In this study, we are testing the effect of flaxseed containing milk on memory and cognition in MCI (due to AD) participants. **Objectives:** 1) To investigate the effect of flax milk on memory and cognition (primary outcome). We will also measure blood pressure, lipid biomarkers (omega-3 and 6 fatty acids) as well as AD biomarkers (inflammation, NF-kB, and glucose uptake). 2) To estimate the economic impact of flaxseed's beneficial effects on the demand for flaxseed milk and flaxseed. **Methods:** Thirty individuals will be given flax milk (30 g/day) and thirty participants will be given a control milk once daily for 180 days. Upon confirmation of eligibility and signing an informed consent form, participants will complete a general health assessment and Clinical Dementia Rating (CDR) at baseline. Participants will also take the Montreal Cognitive Assessment (MoCA), a short screening test sensitive to MCI at baseline and during the final follow up. Along with blood pressure measurements, blood samples will be collected to detect AD and lipid biomarkers at baseline and at the final follow up. Also, a subset of participants will be asked to have a FDG-PET scan at the start of the study and at the final follow up. **Results:** We expect flax milk to improve memory and cognition in MCI subjects. Additionally, we expect omega-3 and 6 fatty acids (ALA, EPA, DHA, END, ENL, AA, and GLA) blood levels to increase in two weeks after the start of flaxseed milk diet. We also expect flax milk to reduce blood pressure, reverse hypometabolism (glucose uptake measured by FDG-PET) as well as lower AD biomarkers (for inflammation and NF-kB). **Conclusions:** Anticipated results from this study will show flax milk as an effective and preventative AD treatment achieved by a dietary intervention. Additionally, an increased demand for flaxseed will increase flax prices and cause an increase in flaxseed acreage for production. Furthermore, it will encourage research on flax varieties to improve the quality of flaxseed and to increase the yield of flax.

P125- NEUROPSYCHOLOGICAL CORRELATES OF ALZHEIMER DISEASE BIOMARKERS. M. Riepe, C. Lanza, K. Sejunaite *(Ulm University - Ulm (Germany))*

Many clinical trials fail to demonstrate a correlation between biomarkers of Alzheimer's disease (AD) and cognitive function. Lack of correlation between cognitive function and biomarkers may result from neglecting gender specificities of cognitive function, stage dependency of cognitive functions in AD, and task difficulty. We will present data on gender-dependency of veridical memories in a verbal and visual episodic memory task associated with phospho-tau and correlation of false memories with amyloid-beta-protein 1,42. Veridical memories were assessed with the California Verbal Memory test. False memories were assessed in healthy elderly controls and patients with AD using real-life tasks of watching news and commercials. Both, performance for veridical memories and false memories in both the news and the commercials task were significantly worse in patients with AD compared to controls. In patients with AD, were correlated with false memories in both tasks. Everyday memory deficits in patients with AD may be impaired more due to the increase of false memories rather than the decrease of veridical memories. Considering that false memories correlate with amyloid burden as assessed with analysis of cerebrospinal fluid levels of amyloid-beta-protein 1,42 future studies will need to investigate whether amyloid burden as assessed with amyloid PET correlates with false memories.

P126- EFFECTS OF SUPPLEMENT CONTAINING ANSERINE ON COGNITIVE FUNCTIONS IN PEOPLE WITH MILD COGNITIVE IMPAIRMENT: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL. N. Masuoka[1], S. Shiotani[2], N. Yanai[2], K. Sato[2], T. Hisatsune[1] *((1) The University of Tokyo - Tokyo (Japan), (2) Tokai Bussan Co., Ltd - Tokyo (Japan))*

Background: Although mild cognitive impairment (MCI) is sometimes a transition between aging and dementia, current pharmacologic treatments are not proven to be effective for cognitive protection in persons with mild cognitive impairment. Dietary supplements made from chicken extract containing anserine and carnosine (3:1) were shown to benefit cognitive functions in healthy older adults and in persons with mild cognitive impairment [1-4]. In Alzheimer's Disease model mice, anserine as well as carnosine has an effect to protect cognitive declines of these mice [5, 6]. **Objective:** In this study, we evaluated the effects of anserine supplement, which is made from salmon meat and free of carnosine, on cognitive functions in people with MCI. **Method:** Thirty-five MCI subjects who scored 25 points or less in the Montreal cognitive assessment scale were assigned to either the active group, who received 500 mg anserine /day in ingestible powder, or a placebo group, who received identical placebo. To assess cognitive functions, we performed psychometric battery including the Mini-Mental State Examination and others at baseline and after 12 weeks. **Results:** The data of cognitive tests from the subjects who completed the follow-up tests, 15 in the active group and 17 subjects in the placebo group, were analyzed. The score change of MMSE was 1.9 ± 2.0 in the active group ($n = 15$) and 0.29 ± 2.5 in the placebo group ($n = 17$) ($p = 0.07$). A post-hoc analysis of Japanese pre-older and older subjects, who aged 65 or above, revealed the greater improvement 1.9

± 2.0 in the active (n = 14) and 0.10 ± 2.5 in the placebo (n = 15) (p = 0.04). No adverse event caused by the supplement was observed. **Conclusion:** Our results provide support for the use of anserine supplementation for improving cognitive function in persons with MCI. **References:** [1] Rokicki, J., Li, L., Imabayashi, E., Kaneko, J., Hisatsune, T. and Matsuda, H. (2015) Daily carnosine and anserine supplementation alters verbal episodic memory and resting state network connectivity in healthy elderly adults. Frontiers in Aging Neuroscience, 7, 219. [2] Hisatsune, T., Kaneko, J., Kurashige, H., Cao, Y., Satsu, H., Totsuka, M., Katakura, Y., Imabayashi, E. and Matsuda, H. (2016) Effect of Anserine/Carnosine Supplementation on Verbal Episodic Memory in Elderly People. Journal of Alzheimer's Disease, 50, 149-159. [3] Katakura, Y., Totsuka, M., Imabayashi, E., Matsuda, H. and Hisatsune, T. (2017) Anserine/Carnosine Supplementation Suppresses the Expression of the Inflammatory Chemokine CCL24 in Peripheral Blood Mononuclear Cells from Elderly People. Nutrients, 9, 1199. [4] Ding, Q., Tanigawa, K., Kaneko, J., Totsuka, M., Katakura Y., Imabayashi, E., Matsuda, H. and Hisatsune, T. (2018) Anserine/carnosine supplementation preserves blood flow in the prefrontal brain of elderly people carrying APOE e4. Aging and Disease, 9, 334-345. [5] Herculano, B., Tamura, M., Ohba, A., Shimatani, M., Kutsuna, N. and Hisatsune, T. (2013) β-Alanyl-L-histidine rescues cognitive deficits caused by feeding a high fat diet in a transgenic mouse model of Alzheimer's Disease. Journal of Alzheimer's Disease, 33, 983–997. [6] Kaneko, J., Enya, A., Enomoto, K., Ding, Q. and Hisatsune, T. (2017) Anserine (beta-alanyl-3-methyl-L-histidine) improves neurovascular-unit dysfunction and spatial memory in aged AβPPswe/PSEN1dE9 Alzheimer's-model mice. Scientific Reports, 7, 12571.

P127- AN OBSERVATIONAL STUDY IN REAL WORLD DAILY CLINICAL PRACTICE TO EVALUATE THE EFFECT OF A MEDICAL FOOD ON ACTIVITIES OF DAILY LIVING IN PEOPLE WITH EARLY ALZHEIMER'S DISEASE. G. Ziere[1], V. Vanneste[2], K. Kalisvaart[3], J. De Wilde[4], M. Herbert[4], L. Boelaarts[5], S. Sikkens[6] *((1) Department of Geriatrics, Havenpolikliniek, Maasstad Ziekenhuis - Rotterdam (Netherlands), (2) Franciscus Ziekenhuis - Roosendaal (Netherlands), (3) Department of Geriatrics, Spaarne Gasthuis - Haarlem (Netherlands), (4) Danone Nutricia Research, Nutricia Advanced Medical Nutrition - Utrecht (Netherlands), (5) Department of Geriatric Medicine, Noordwest Hospital Group - Alkmaar (Netherlands), (6) Alzheimer Center Amsterdam, Amsterdam University Medical Centers (Location VUmc) - Amsterdam (Netherlands))*

Background: Background: Alzheimer's disease (AD) leads to a progressive decline in cognitive performance and activities of daily living. However, AD medications are limited in number and effectiveness. The role of nutrition in AD management is gaining interest. A medical nutritional intervention for early AD comprising a specific nutrient combination designed to enhance synapse formation and function has been tested in several trials. Benefits were observed in memory, cognition and function, and in markers of disease progression in early AD (Soininen et al., 2017; Scheltens et al., 2010 & 2012). **Objective:** The objective of this observational study was to evaluate the benefits of this specific nutritional intervention on daily functioning of people with early AD in a real-world setting. **Methods:** In this observational study, the decision to include medical nutrition as part of post-diagnostic support was made prior to enrolment. The medical nutritional product was to be consumed according to the instruction given by the health care practitioner. Daily functioning was assessed prior to starting medical nutrition (baseline), at 6-month follow-up, and optionally at 12-months using the Amsterdam Instrumental Activities of Daily Living questionnaire (A-IADL). Changes in A-IADL scores will be compared with a reference population consisting of memory clinic patients with dementia (Koster et al. 2014) using a one-sample t-test. **Results:** Between March 2013 and March 2016, 116 participants were enrolled in the study. Valid A-IADL scores at both baseline and 6-months were available for 73 participants (63%; 41 men and 32 women). Of these, 27 (23%) participants also had valid A-IADL scores at 12 months. A full overview of the results including participant characteristics, intervention compliance, and reference group comparison will be presented. **Conclusion:** Results of this observational real-world study will provide insights into the effect of medical nutrition on the activities of daily living of people with early AD.

P128- SEX DIFFERENCES IN PREDICTORS OF COGNITIVE AND FUNCTIONAL OUTCOMES IN PATIENTS WITH ALZHEIMER'S DISEASE. C. Wattmo, Å.K. Wallin, E. Londos *(Clinical Memory Research Unit, Department of Clinical Sciences, Malmö, Lund University - Malmö (Sweden))*

Background: Background: About two-thirds of patients with Alzheimer's disease (AD) are women, mostly because of their longer life-span and the higher prevalence of AD among older persons. A more-pronounced association between AD pathology and dementia (faster brain atrophy) and more-rapid cognitive decline have been reported in women. The AD prognosis might be affected by, e.g., size of cerebral hemispheres, role of sex hormones, cerebro- and cardiovascular comorbidities, psychiatric symptoms, and concomitant medications, which are all influenced by sex differences. A better cognitive response to cholinesterase inhibitors (ChEI) was observed in men compared with women. Thus, the predictors (genetic, sociodemographic, and clinical factors) of longitudinal cognitive and functional outcomes including aspects of ChEI treatment (e.g., drug agent, dose) may differ between sexes. In a study that included both sexes, our group previously found that male sex, older age, absence of the apolipoprotein E (APOE) ε4 allele, use of nonsteroidal anti-inflammatory drugs (NSAIDs)/acetylsalicylic acids, and receiving a higher ChEI dose (regardless of type of drug), were independent predictors for a slower cognitive deterioration. Reports of sex-specific characteristics and effects of ChEIs that might affect the long-term course of AD are scarce. **Objectives:** This study aimed to identify sex-specific factors, including aspects of ChEI therapy, that may predict cognitive and functional progression rates in AD. **Methods:** The Swedish Alzheimer Treatment Study (SATS) is a prospective, open, nonrandomized multicenter study for the assessment of longitudinal effectiveness of ChEI therapy in a routine clinical setting. Among the 1,258 outpatients clinically diagnosed with probable or possible AD, 1,021 (367 men and 654 women) had mild-to-moderate AD (Mini-Mental State Examination [MMSE] score, 10–26) at the start of ChEI treatment (baseline) and were included in the current study. The participants were evaluated using cognitive tests (MMSE and Alzheimer's Disease Assessment Scale–cognitive subscale [ADAS-cog]) and functional capacity scales (Instrumental Activities of Daily Living scale [IADL] and Physical Self-Maintenance Scale [PSMS]) at baseline and every 6 months for 3

years. Mixed, linear, and nonlinear fixed and random coefficient regression models were performed. The dependent variables were the scores (ADAS-cog, IADL, or PSMS) assigned at the second and subsequent visits for each individual. The following potential predictors were investigated: APOE genotype, solitary living, duration of AD, age at baseline, years of education, type of ChEI, dose of ChEI, specific concomitant medications (antihypertensive/cardiac therapy, antidiabetic drugs, asthma medication, thyroid therapy, lipid-lowering agents, estrogens, NSAIDs/acetylsalicylic acid, antidepressants, antipsychotics, and anxiolytics/sedatives/hypnotics), cognition, IADL, and basic ADL at baseline. **Results:** Better cognitive or IADL abilities at the initiation of ChEI treatment implied a slower cognitive decline over time in both sexes. An interaction effect showed that the difference in cognitive status at baseline between ages was more pronounced among older men (but not women) who were more cognitively impaired. In women, the absence of the APOE ε4 allele or receiving NSAIDs/acetylsalicylic acid therapy were protective factors for a lower rate of cognitive progression. Regarding IADL, patients of both sexes with better cognitive performance at baseline exhibited a more favorable long-term outcome in IADL capacity. The use of antidepressants in men and solitary living in women predicted worsening IADL. In basic ADL, lower cognitive ability at baseline predicted a faster deterioration among both sexes. Women living alone demonstrated poorer prognosis in basic ADL. For women, there was a significant interaction effect in all three scales between time in months and years of education, i.e., a higher level of education implied increased cognitive or functional impairment over time. Men and women who received a higher mean dose of ChEI during the study showed a slower decline in cognitive ability, while men who received higher ChEI doses also exhibited lower progression rates in both IADL and basic ADL. **Conclusion:** The predictors of cognitive and functional deterioration differed between the sexes. Use of NSAIDs/acetylsalicylic acid was a protective factor for better cognitive outcome in women, which suggested that women might have greater cerebral inflammation and additional advantages of treatment with these drugs. Antidepressants in men and solitary living among women were risk factors for more-rapid worsening in IADL and basic ADL (only women living alone), which underlined the risk of apathy and social isolation among those individuals. Cognitive reserve capacity could have a larger impact on AD prognosis in women because a higher level of education implied increased cognitive or functional impairment over time. In women, the presence of the APOE ε4 allele led to lower cognitive performance. These risk factors indicate more hereditary and advanced forms of AD in women. A higher mean dose of ChEI (irrespective of drug agent) was associated with slower cognitive decline in both sexes and lower functional progression rate among men, which might support the better ChEI response among men described previously. The findings stress the importance for clinicians to optimize the ChEI dose in AD regardless of sex to improve therapeutic effectiveness.

P129- THE ADAS-COG-EXEC: A NOVEL COGNITIVE COMPOSITE OUTCOME TO ASSESS THERAPEUTIC EFFECTS OF EXERCISE IN THE EXERT TRIAL FOR ADULTS WITH MCI. D. Jacobs[1], R. Thomas[1], D. Salmon[1], S. Jin[1], H. Feldman[1], C. Cotman[2], L. Baker[3] *((1) Alzheimer's Disease Cooperative Study, UC San Diego - La Jolla (United States), (2) Institute for Memory Impairments and Neurological Disorders, UC Irvine - Irvine (United States), (3) Wake Forest School of Medicine - Winston-Salem (United States))*

Background: Background: The EXERT trial (NCT02814526) is a Phase 3, multicenter, randomized single-blind study to examine the effects of a 12-month structured aerobic exercise intervention on cognition and other measures of brain function in 300 adults with amnestic mild cognitive impairment (MCI). The primary outcome was prespecified as an optimized cognitive composite that is maximally sensitive to both change over time in MCI and to beneficial effects of aerobic exercise on cognition. This composite, referred to as the ADAS-Cog-Exec, was to include subtests of the ADAS-Cog, version 13 (with Delayed Word Recall & Number Cancellation) and additional tests of executive function (EF): Trail-Making Test, Digit Symbol Substitution Test, and Category and Letter Word Fluency.1,2 It was hypothesized that adding EF measures to the ADAS-Cog13 would increase sensitivity given prior evidence of beneficial exercise effects on executive functioning.3,4 Here we describe the development and validation of the ADAS-Cog-Exec. **Objective:** To develop a cognitive composite outcome that is sensitive to both longitudinal change in MCI and the beneficial effects of exercise on cognition in MCI. **Methods:** First we identified ADNI-1 as the longitudinal cohort best suited for modeling the ADAS-Cog-Exec composite given its large MCI cohort and the availability of nearly all EXERT test scores (except Letter Fluency). The ADNI-1 MCI cohort was randomly split into "training" and "validation" cohorts. Data from the baseline and 12-month follow-up visits were used to model longitudinal change. Next, combinations of cognitive measures were selected for inclusion in the composite based on a priori knowledge and hypotheses about sensitivity to longitudinal change in MCI and documented sensitivity to the effects of exercise1-4. Three combinations were selected: Composite 1 = ADAS-Cog13 Total Score + EF measures (Trails A & B, Digit Symbol, Category Fluency); Composite 2 = ADAS-Cog13 subtests with demonstrated high sensitivity to change in MCI (Word Recall, Delayed Word Recall, Orientation, Cancellation)2 + EF measures; Composite 3 = Composite 2 + CDR Sum of Boxes for the cognitive component scores (Memory, Orientation, Judgement & Problem Solving), which has demonstrated utility in improving sensitivity of a cognitive composite outcome in MCI.2 Finally, optimal weights for each of the three combinations were calculated using the method described by Xiong5 wherein weights are derived for each variable minimizing the standard deviation (SD) of composite change over time. The mean to SD ratios (MSDR) of the three ADAS-Cog-Exec composites were compared to one another and to the ADAS-Cog13 Total Score. **Results:** The ADNI training and validation cohorts did not differ significantly from one another nor from the EXERT cohort recruited to date in terms of age (overall mean[SD]=74.9[6.9]; p=0.75), education (overall mean[SD]=15.9[2.8]; p=0.78), or baseline scores on the MMSE (overall mean[SD]=27.3[1.9]; p=0.85) or ADAS-Cog13 (overall mean[SD]=17.4[6.4]; p=0.35). There were significantly more men in the ADNI cohorts (64% training cohort, 65%

validation cohort) than in the current EXERT cohort (46%). The MSDR for each of the constructed ADAS-Cog-Exec composites (validation cohort MSDR=0.27, 0.34, 0.48 for Composite 1, 2, & 3, respectively) exceeded the MSDR of the ADAS-Cog13 Total Score (validation cohort MSDR=0.26). Of note, using targeted subtests of the ADAS-Cog13 (Composite 2) rather than the ADAS-Cog13 Total Score improved the MSDR from 0.27 to 0.34. Incorporating scores from the CDR Sum of Boxes for cognitive components with the ADAS-Cog13 subtests and EF tests resulted in the highest MSDR (0.48). **Conclusion:** We developed and validated by split sample a novel cognitive composite outcome measure, the ADAS-Cog-Exec, for use in EXERT, a rigorous 12-month RCT designed to assess the therapeutic and potential disease-modifying effects of aerobic exercise in participants with MCI. Modeling of potential composites, which were constructed using optimal weighting of three different combinations of cognitive measures, revealed that sensitivity to detect 12-month change was highest when the composite included subtests of the ADAS-Cog13 most sensitive to early changes in cognitive function (Word Recall, Delayed Word Recall, Orientation, Number Cancellation), EF tests (Trails A & B, Digit Symbol, Category Fluency), and CDR Sum of Boxes for cognitive components (Memory, Orientation, Judgement & Problem Solving). Based on these results, this composite is selected to serve as the primary outcome measure for the ongoing EXERT trial. **Funding:** NIH/NIA U19AG010483 (ADCS); NIH/NIA U19AG024904 (ADNI). **References:**
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P130- A MULTICENTER, OPEN-LABEL, 24-WEEK FOLLOW-UP STUDY FOR EFFICACY ON COGNITIVE FUNCTION OF DONEPEZIL IN BINSWANGER-TYPE SUBCORTICAL VASCULAR DEMENTIA. J. Kwon[1], K. Lee[2], N.C. Choi[2] *((1) Changwon Fatima Hospital - Changwon (Korea, Republic of), (2) Samsung Medical Center - Changwon (Korea, Republic of))*

Background: Objectives: To evaluate the efficacy and tolerability of donepezil in patients with Binswanger type subcortical vascular dementia. **Methods:** Patients(n=34, mean age=71.8 ± 7.12) with Binswanger type subcortical vascular dementia from 8 multicenter, according to clinical and neuroradiological working criteria, were selected to receive donepezil 5mg/day(n=2) or donepezil 10mg/day(n=32, after 5mg/day) for 24 weeks. Our primary endpoints were change from baseline to weeks 12 and 24 in the Dementia version of Seoul Neuropsychological Screening Battery(SNSB-D) and Korean version neuropsychiatric inventory(K-NPI). **Results:** 24 patients received donepezil completed the study(mean age= 72.0 ± 7.5 K-MMSE= 21.0 ± 5.1). After 12 weeks and 24 weeks, patients showed improvements in cognitive function on the SNSB-D compared baseline of 16.29 points at 12 weeks($p<0.05$) and 12.44 points at 24 weeks($p<0.05$). Significant improvements were shown in only memory domain, immediate verbal recall and delayed recall tests. Subgroup with better cognitive function(SNSB-D>100) were more effective in frontal and memory domains than the other subgroup(SNSB-D<100). Withdrawal rates due to adverse events were very low(4.16%). **Conclusions:** Donepezil-treated patients with Binswanger type subcortical vascular dementia demonstrated significant improvement in cognition compared with baseline, and donepezil was well tolerated.

P131- HAPPCAP-AD (HUMAN-APPLICATION COMBINED APPROACH FOR PREVENTION OF ALZHEIMER'S DISEASE). I. Ganmore[1], R. Ravona-Springer[1], A. Matatov[1], A. Ben-Moshe[1], M. Beeri Schnaider[1,2] *((1) Joseph Sagol Neuroscience Center at Sheba Meidcal center - Tel-Hashomer (Israel), (2) The Icahn School of Medicine at Mount Sinai - New-York (United States))*

Background: Alzheimer's disease (AD) has no cure so developing efficient AD prevention strategies is imperative. Seven major potentially modifiable risk factors show consistent association with AD (type 2 diabetes [T2D], hypertension, obesity, physical inactivity, depression, smoking, and low educational attainment), with combined population-attributable risk of 30%. A recent extensive literature review of randomized control trials on single lifestyle interventions for AD yielded negative results. The multidomain studies raised concerns regarding the multidomain approach, although the FINGER study brought some optimism after it presented positive results; several replication trials around the world have been launched. However, 1) all trials focus on the elderly, 2) the impact of midlife risk factors on dementia risk is stronger than late life, and 3) the neurodegenerative changes in AD begin decades before its clinical manifestations. **Objectives:** We propose a feasibility study of a novel «real-life» personalized 18-months intervention for prevention of cognitive decline in middle-aged individuals at high AD risk due to AD parental family history. We will implement an innovative approach combining a smartphone application (app) with study team guidance. Our aims are: 1) To investigate the feasibility of our novel intervention and the factors associated with adherence to it; 2) To examine whether our intervention improves AD risk factors and whether greater adherence to it is associated with larger improvement; 3) To explore whether our intervention improves cognition and cerebral blood flow (CBF). We hypothesize that our approach is feasible, and that better adherence to our intervention will result in better balanced risk factors as well as better cognitive function and CBF compared to control group. **Methods:** We will recruit 40-65 years old offspring of AD patients, to two groups (intervention and passive control), with 100 participants in each. All participants will have at least two risk factors of the seven major modifiable AD risk actors. The 18-months intervention will include detailed advice for risk factors improvement, interactive follow-up using the smartphone app and dynamic feedback on risk factors management for its modification, through both the app and the study team. **Results:** The recruitment for study had recently begun, through publishing an online eligibility questionnaire. Thus far, 175 individuals has completed the questionnaire, with 106 fulfilling eligibility criteria- among them 50% with T2D, 27% with hypertension, 86% with obesity, 87%

with physical inactivity, 28% depression, and 20% smoking. Among these individuals- 28% have 2 risk factors, 52% 3 risk factors, 14% 4 risk factors, 5% 5 risk facros, 1% 6 risk factors. **Conclusions:** Results of this feasibility study will provide data on the adherence of participants to the human-app approach, on characteristics of those who adhere, will indicate whether the approach improves the risk factors, will provide initial data on whether the intervention improves or maintains cognition.

Theme: COGNITIVE ASSESSMENT AND CLINICAL TRIALS

P132- ESTIMATING SUBJECT-SPECIFIC VARIANCE IN UNSUPERVISED, HIGH-FREQUENCY, MOBILE APP BASED COGNITIVE TESTING: FEASIBILITY OF USING MOBILE APPS FOR MONITORING COGNITIVE SAFETY.

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Mobile app based unsupervised, high-frequency monitoring of cognition holds the promise to facilitate the individual detection of cognitive change. This can for instance enable cognitive safety monitoring in clinical trials. A viable safety signal would be a drop in performance in a cognitive measure relative to previous performance levels in the same test. The ability to detect such a safety signal depends on the knowledge of how many measurement points are necessary to reliably establish a robust variance estimate of a participant's test performance using an unsupervised mobile app. We conducted a Germany wide Citizen Science Project (after accreditation with the Citizen Science Portal BürgerSchaffenWissen) with the goal to detect the impact of sleep and common cold on individual cognitive trajectories acquired via smartphone-based assessments. To that end, every participant was pseudo-randomly assigned to one of three memory tests: 1) mnemonic discrimination of objects and scenes; 2) complex (photographic) scene recognition memory; 3) pattern completion of object-in-scene associations. 1814 participants (72% female) completed 7900 test sessions over 15 weeks. The age-range of participants was between 16 and 85 years of age. Mean age was 61. Mean test scores showed a decline with age for each of the three tests. Study participants completed up to 15 sessions of a test allowing a robust estimation of individual variance measures and to estimate how many test sessions were needed for each of the three tests to reliably determine subject specific variance. In addition, we assessed psychometric properties in order to ensure a significant drop in performance can be detected (absence of floor effects). Our results indicate that for each of the memory tests a minimum number of individual measures can be defined to reliably estimate subject-specific variance which is critical for the detection of safety signals defined as a drop in performance that exceeds the individually defined variance estimate.

P133- INTER-SITE VARIABILITY AND STANDARDIZATION OF AD AND MCI DIAGNOSES.

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Background: Grading the stages of Alzheimer's Disease (AD) from Mild Cognitive Impairment (MCI) to dementia is of critical importance for understanding and modeling the disease course, providing accurate clinical diagnosis, and enabling therapeutic effect monitoring. Coming to a reliable and accurate diagnosis is challenging, especially in multicentric studies and in cases where there is clinical uncertainty about the presence of dementia. Guidelines have been put in place (e.g. ADNI) to help standardize assessments based on cognitive tests, but the final diagnosis is still subject to a clinician's interpretation and subjectivity. In a multicentric context, this variability introduces site-specific dependency that reduces the statistical reliability of subsequent analyses. In addition, when combining clinical trials, the inconsistency in diagnostic labels leads to uncertainty in the quantification of disease progression. **Objectives:** 1) To characterize the inter-site variability in diagnosing MCI and AD. 2) To propose a data-driven approach to data standardization. **Methods:** Cognitive scores from ADNI1/GO/2/3 databases were first aggregated and a multi-step analysis was performed: 1) To quantify the clinician assessment variability, z-scores for MCI and AD cases were computed for each cognitive summary score at subject baseline, then averaged to obtain a mean z-score for each subject. The cognitive tests included summary scores from CDR, MMSE, ADAS, MOCA, FAQ, CCI and sub-categories of the Neuropsychological Battery. The mean z-score serves as a summary measure of all cognitive testing scores available to the clinician. Comparison was made across 69 different sites and was adjusted for age, gender, education and APOE using analysis of covariance (ANCOVA). The optimal mean z-score cutoff between MCI and AD classes was also computed. 2) A novel classifier (dx-labeler) was built on ⅔ of the data (2242 CN, 2925 MCI and 1521 AD) using Darmiyan's proprietary algorithm to determine CN, MCI and AD class probabilities. The other ⅔ of the data was reserved for blind testing (1059 CN, 1476 MCI and 704 AD). The algorithm inputs were all available cognitive scores, as well as age, gender and years of education, equivalent to what the clinician's judgement is mostly based on. Performance of the classifier was evaluated through both nested cross-validation and blind testing. Inter-site variability was re-calculated using dx-labeler's decision and compared with the variability based on clinician's decision. **Results:** Highly significant difference was found for MCI between sites on mean z-score ($p<1e-10$) but was not significant for AD. Darmiyan dx-labeler's balanced-accuracy (BA) on cross-validation was 89.8±1.2% with the following recall/precision per class: AD=89.7±2.8/85.1±2.6%, CN=95.2±1.2/94.2±1.3% and MCI=84.4±2.0%/88.3±2.2% (precision not corrected for prevalence). Performance on the blind test set agreed with the cross-validation: BA=90.8%, AD=90/88%, CN=96/94%, MCI=87/90%. The standard-deviation on the BA per site was 9.2%, demonstrating variability in the agreement between Darmiyan's dx-labeler and clinician assessment per site. Most of the mismatch cases were found in the MCI class (63%) with 57% predicted as AD and 43% predicted as CN. When using the ADNI diagnostic label, the distribution of the optimal mean z-score cutoffs between MCI and AD spanned over max-min=0.96 and did not follow a normal distribution (Shapiro-

Wilk, p<0.02), demonstrating high variability in the clinician assessment of uncertain cases. When using the class predicted by Darmiyan's dx-labeler instead, the min/max span in the cutoff distribution was reduced by 30% and the test for normality was not rejected. **Conclusion:** We demonstrated that, even under a well controlled protocol, diagnosis of MCI and AD can vary depending on clinician subjectivity. Darmiyan's proprietary classifier algorithm (dx-labeler) shows high accuracy (90-91% BA) in the diagnostic task compared to the clinician. Interestingly, the 9-10% drop compared to ground truth (defined collectively by each clinician) was in the same range as the inter-site standard-deviation of BA, suggesting that the inter-clinician agreement and the agreement between the dx-labeler and the ground truth are alike. In addition, we showed that using the dx-labeler algorithm reduces the variability in defining MCI and AD for borderline cases, helping with standardization and consistency, and is a solution to help clinicians with diagnosing uncertain cases. Finally, Darmiyan's dx-labeler can also be used to classify subjects from various cohorts and/or clinical trials, so that data from multiple data sources can be merged and mined in a consistent way and proper statistical conclusions can be drawn accordingly.

P134- FREQUENCY OF AND FACTORS ASSOCIATED WITH ENVIRONMENTAL DISTRACTION DURING UNSUPERVISED DIGITAL COGNITIVE ASSESSMENT.

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Background: While the availability of computerized cognitive assessments has increased rapidly over the past decade, the clinical validity of computerized assessments remains a significant issue for researchers and clinicians. Moreover, the use of computerized cognitive assessments in unsupervised settings raises a separate but equally important issue, that of environmental validity. The modality of data collection with computerized cognitive assessments precludes the ability to assess aspects of the physical environment during assessment administration, and as a result, analysis of environmental validity in unsupervised cognitive assessment has gone virtually unexamined. The recording of eye movements to assess cognition is a burgeoning area of research. Now that web cameras are increasingly part of the standard hardware of smart phones, tablets and laptop computers, we have the opportunity to develop eye movement tasks to efficiently and quickly assess cognitive function using these devices. Visual paired comparison (VPC) task paradigms assess recognition memory and have been shown to reliably detect memory dysfunction in both primates and humans, representing a paradigm deployable via devices with web cameras for the rapid assessment of declarative memory dysfunction. **Objectives:** This study aimed to investigate the frequency of, and factors associated with environmental distractions during a brief, unsupervised digital cognitive assessment in a real-world setting. **Methods:** This was a retrospective study of 1442 adults (aged 23 to 84) who completed a brief 5-min VPC decision task in an unsupervised, remote setting. Subjects completed the task utilizing a device-embedded camera. Automated scoring algorithms flagged low data capture across the 20 test trials of the task and frequency of environmental distractions resulting in subjects looking away from the camera were manually counted on a per-frame and per-trial basis. A Fisher's exact test was used to compare the frequency of distractions during the assessment by sex. A Welch's t-test was used to compare the age of subjects across assessment administrations with and without environmental distractions. **Results:** Of the 1442 assessment administrations, 106 (7.4%) included environmental distraction resulting in subjects looking away from the screen. Assessment administrations including environmental distraction were more frequently completed by men (39:311) than women (54:1038) with an odds ratio of 2.41 (p<.001). Age of assessment administrations including environmental distractions (mean=52.6) was lower than the age (mean=58.0) of assessment administrations without the presence of environmental distractions (p<.001). **Conclusion:** The frequency of environmental distractions present during a brief unsupervised, asynchronous cognitive assessment (7.4%) are comparable to those reported during cognitive testing batteries in group administration environments (9.7%). Both age and gender are associated with more frequent presence of environmental distractions during task administration. Unsupervised, asynchronous neuropsychological assessment is a novel method for efficient remote measurement of cognition. These results underscore the challenges of high quality data collection associated with unsupervised assessment of cognition, even over brief periods of time. Methods of data collection that provide for rigorous qualification of data are needed to confirm data quality, usability and actionability when screening and recruiting for clinical trials.

P135- EVALUATING A METHOD FOR AUTOMATIC AND OBJECTIVE SCORING OF VERBAL RESPONSES FOR THE MONTREAL COGNITIVE ASSESSMENT (MOCA).

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Background: The current cost estimate for bringing an Alzheimer's Disease (AD) therapeutic to market is $5.6 billion, nearly 3 times higher than the cost of other therapies. Phase I to III clinical trial expenses are responsible for more than 65% of this cost 1. The tools used in these trials to measure cognitive performance are partially responsible for this expense. Existing measures such as the ADAS-Cog and MMSE have well established psychometric limitations 2,3, and require a significant amount of time, expertise and rater training to administer correctly. Deviations in administration and errors in scoring are common 4 and their inclusion as outcomes in AD trials necessitate lengthy assessment periods (>3 hours) 5 at a high cost to the sponsor. Using computerized batteries does reduce administration error, though evaluation against traditional cognitive batteries has shown that they do not align with the gold standard measures of core cognitive domains in some populations 6. Together, these multiple sources of error reduce the overall precision of measurement, putting upward pressure on the AD trial sample sizes. To improve precision, many trials rely on recording the administration of all primary cognitive outcomes so that they can be reviewed for errors by independent, often PhD level raters. This process is both time consuming and costly. Recent advances in speech recognition and Natural Language Processing (NLP) could make identifying errors and scoring individual tasks significantly more efficient. Automatic scoring and error identification could open the door to streamlined quality assurance evaluation and

dramatically reduce the cost of deploying these measures in a clinical trial. **Objectives:** In this proof of concept study, we explored the feasibility of automatically scoring the delayed recall task from audio recordings of the Montreal Cognitive Assessment (MoCA). **Method:** Fully automatic scoring of the MoCA from a single recording requires four components: automatic diarization (speaker differentiation), automatic speech recognition (ASR), automatic task segmentation and automatic task scoring. For this study, we chose to focus on evaluating task segmentation and scoring. MoCA recordings from 50 individuals were taken from a longitudinal natural history study of older adults (aged 55-90), recruited from the community and independent living facilities in Canada and the US. Recordings were manually diarized, transcribed, segmented and scored to produce a gold standard dataset. We then tested two conditions, automated scoring alone and automated scoring with automatic task segmentation. Delayed recall scores were calculated by comparing the words spoken by the participant to the MoCA word list. Automatic segmentation was done by matching each rater's ASR-transcribed utterances to the standard MoCA administration script and labelling that utterance with the best matching MoCA subtask. **Results:** Using automatic scoring alone (i.e. with manual diarization, transcripts and task segmentation), the Delayed Recall score was 100% accurate. Using automatic segmentation, 84.5% of task boundaries were identified correctly. The algorithm matched the exact start of the task 85.1% of the time and the exact end of the task 79.3% of the time. Exact matching of both start and end of task was achieved 78.0% for the time. Using automatic score with automatic task segmentation Delayed Recall scores were 85% accurate (Mean Absolute Error of 15.2%, 0.76 / 5 points) compared automatic scoring alone. ASR errors resulting in mislabeled task boundaries accounted for the majority of the observed scoring errors. **Conclusions:** The results of this proof of concept study show that transcribed audio recordings can be used to automatically calculate Delayed Recall scores on the MoCA. Using an ASR-based algorithm to automatically segment MoCA tasks resulted in a mean error of 15.2% in Delayed Recall scores. Together these results suggest that automatic segmentation and scoring of audio recordings of cognitive assessments is feasible and further work is needed to fine tune the algorithms and improve scoring accuracy. **References:**
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P136- STAGING EARLY ALZHEIMER'S DISEASE USING THE ALZHEIMER'S DISEASE COMPOSITE SCORE (ADCOMS).
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Background: The Alzheimer's disease (AD) composite score (ADCOMS) was developed to measure outcomes among patients with mild cognitive impairment (MCI) due to AD and mild AD dementia, and was shown to be more sensitive to cognitive changes than the component measures from which it was derived. The component measures include the mini mental state examination (MMSE), clinical dementia rating scale—sum of boxes (CDR-SB), and the AD cognitive subscale (ADAS-Cog). However, the validity of using ADCOMS to stage AD severity has yet to be established in patients with earlier disease. **Objective:** This study was to derive ADCOMS scores to stage severity of dementia and to evaluate the utility of the derived scores in distinguishing patients across AD stages, especially patients with MCI due to AD from the mild AD dementia stage. **Methods:** Patients enrolled (N = 2,073) in the Alzheimer's Disease Neuroimaging Initiative (ADNI) (data downloaded on December 13, 2018) were assessed at baseline and split into a derivation sample (n = 1,034; cognitively normal [CN] = 393, MCI = 464, and AD = 177) and a validation sample (n = 1,035; CN = 384, MCI = 474, AD = 177). Data from assessments at visit 24 (N=1,262) were used to determine ADCOMS cutoff scores to stage moderate and severe AD (derivation sample: CN=231, MCI=246, and AD= 54; validation sample: CN=209, MCI=237, AD=185). Stage classification based on the existing criterion measures of CDR global, CDR-SB, ADAS-Cog, and MMSE were used to generate receiver operating characteristic (ROC) curves to indicate the optimal ADCOMS cutoff scores for each disease stage. This analysis was conducted in the derivation sample at baseline and visit 24 for every two adjacent scores on the criterion measures that are indicative of each AD stage (e.g., CDR global scores of 0 and 0.5). The optimal ADCOMS cutoff was established using an empirical estimation method based on maximizing the product of sensitivity and specificity. Equality of the ROC curves between the derivation and validation samples was tested using a $\chi 2$ test. The diagnostic accuracy in distinguishing between patients with MCI due to AD and mild AD dementia was assessed within the validation sample. This was achieved by restricting the analysis of baseline data to patients within the validation sample whose global CDR score was 0.5 (MCI=471 and AD=84) and calculating an ROC curve using the ADCOMS scores. To evaluate the diagnostic accuracy of the ADCOMS scores in distinguishing between patients with mild AD and moderate/severe AD, this process was repeated using data from visit 24 within the validation sample among patients with a global CDR score of 1 (n = 70 mild AD and n = 24 moderate or severe AD). **Results:** The following cutoff ADCOMS scores were identified to stage AD severity: < 0.29 is indicative of normal cognition, 0.29 to < 0.50 is indicative of MCI, 0.50 to 0.80 is indicative of mild AD, and > 0.80 is indicative of at least moderate AD. The reliability of these cutoff ADCOMS scores was supported by the tests of equality between the derivation and validation samples: all $\chi 2$ test results indicated no significant difference between the samples. When applied to the validation sample, the diagnostic accuracy test showed that 82% of patients with MCI and mild AD, and 73% of patients with mild and moderate/severe AD were correctly classified against the classification based on CDR-global score.

When applied to the data at visit 24, the proportion of correctly classified patients ranged from 72% to 92%. The study is limited by the small sample size at the moderate (n=94) and severe AD stages (n=8). **Conclusions:** The ADCOMS scores can be consistently mapped to the existing criterion measures including CDR-SB and other instruments in AD severity classification. Further validation efforts may help establish ADCOMS as a new diagnostic tool and criterion measure to quantify AD progression and staging.

P137- ALTOIDA NEURO MOTOR INDEX (NMI): DIGITAL BIOMARKERS FOR RAPID AND RELIABLE COGNITIVE AND FUNCTIONAL ASSESSMENT IN ALZHEIMER'S DISEASE CLINICAL TRIALS. I. Tarnanas[1], I. Meier[1], M. Bügler[1], R. Harms[1], C. Babiloni[2], M. Balasa[3], G. Frisoni[4], M. Rampini[4], R. Whelan[5], V. Panayiotis[6] *((1) Altoida - Houston (United States), (2) Sapienza University of Rome - Rome (Italy), (3) Hospital Clinic de Barcelona - Barcelona (Spain), (4) IRCCS S Giovanni di Dio-Fatebenefratelli - Brescia (Italy), (5) Trinity Inst. of Neurosciences - Dublin (Ireland), (6) Ionian University - Corfu (Greece))*

Background: Research investigating treatments and interventions for cognitive decline and Alzheimer's disease (AD) fail due to difficulties in accurately identifying individuals at risk of AD or recognizing a signature in the pre¬symptomatic stages of the disease. There is an urgent need for better identification of such individuals in order to enable earlier treatment and to properly stage and stratify participants for clinical trials and intervention studies. Biomarkers enable the identification of AD-related changes before significant cognitive or functional changes occur, but the false positive ratio is high and some of these individuals may never actually develop symptomatic disease. Two tests have been used for screening of presymptomatic AD based on real world functional abilities, namely a dual task walking test and a day-out task. A multisite clinical trial, financed by the European Institute for Innovation & Technology (EIT), the Global Brain Health Institute and Alzheimer's Association USA, aimed at validating a novel digital biomarker of cognitive decline, the Altoida Medical Device (AMD). **Method:** A group of pre-¬identified healthy older adults with a genotype that puts them at increased risk for AD and individuals in prodromal stages of AD (n=410) were studied for a 24-months period. Demographics, CSF markers of Aβ and tau, MRI, EEG, and APOE status were collected and subjects underwent a comprehensive cognitive assessment. The Neuro Motor Index (NMI) was included as a secondary outcome measure of cognitive ability and real world function. AMD is administered by means of a tablet in less than 10 minutes and tracks 320 real world metrics. The individual places three virtual objects in a real environment with their subsequent recovery after a distraction task, aside from motor and reaction time assessments. **Result:** Altoida NMI demonstrated high test-retest reliability and was able to accurately discriminate between healthy controls, high risk individuals and prodromal stages of AD with high sensitivity (Mean ROC (AUC=0.94 + 0.02)). NMI was also able to differentiate between people with mild cognitive impairment that converted to AD from those who did not progressively decline, and correlated with existing measures of cognitive function and biological biomarkers. **Conclusion:** Altoida NMI is rapid, ecological and cheaper than current neuropsychological tests that decreases patient burden. It is a useful tool to assist physicians in real world clinical settings, opens the doors to large scale population screening for the early detection of cognitive impairment, and allows for monitoring of patients over time by clinicians or in clinical trials.

P138- EARLY DEVELOPMENT OF A UNIFIED, SPEECH AND LANGUAGE COMPOSITE TO ASSESS CLINICAL SEVERITY OF FRONTOTEMPORAL LOBAR DEGENERATION (FLTD). A. Balagopalan[1], L. Kaufman[1], J. Novikova[1], O. Siddiqui[2], R. Paul[2], M. Ward[2], W. Simpson[3] *((1) Winterlight Labs - Toronto (Canada), (2) Alector - South San Francisco (United States), (3) McMaster University - Hamilton (Canada))*

Background: Frontotemporal Lobar Degeneration (FTLD) is a progressive neurodegenerative disorder that presents in a heterogeneous manner depending on the localization and molecular basis of the underlying neuropathology. Clinical syndromes include behavioural variant Frontotemporal Dementia (bvFTD), and the primary progressive aphasias; semantic (svPPA), non-fluent (nfvPPA) and logopenic (lpPPA), supranuclear palsy and corticobasal syndrome. The heterogeneous presentation of the disease can make diagnosis, clinical staging and longitudinal tracking of decline challenging. Some specialized scales have been developed and are useful in research settings (e.g. CDR® plus NACC FTLD 1,2), though in routine clinical practice, many use a patchwork of assessments examining cognition, activities of daily living, and neuroanatomical data to stage and subtype FTLD 3. A valid measure of severity must have good construct validity, test-retest reliability and be highly sensitive to change over time. In FTLD, this measure has the added requirement of being sensitive across distinct clinical presentations (such as bvFTD and PPA) while still maintaining reasonable specificity. The pronounced language deficits observed in PPA suggest that a detailed, computational analysis of speech may be a suitable approach for developing such a metric. Previously, our group used natural language processing (NLP) and machine learning (ML) algorithms to evaluate whether extracted speech and language variables could be used to distinguish between PPA subtypes. We found that these variables could reliably distinguish svPPA and nfvPPA from controls with >95% accuracy and svPPA from nfvPPA with 80% accuracy 4. Speech and language variables identified using similar approaches could be used to derive a 'speech assay' of FTLD which may serve as an accurate marker of clinical severity. **Objectives:** Our primary objective was to examine which computationally derived characteristics of speech were correlated with aphasia severity, using a large academic database. Our secondary objective was to assess the test-retest reliability of these variables alone and when combined into a composite score in healthy individuals and those with FTLD (bvFTD and PPA). **Methods:** More than 500 acoustic and linguistic variables were extracted using Winterlight's linguistic analytic software from samples of spontaneous speech. To determine which variables were most relevant to aphasia, we analyzed picture descriptions from the AphasiaBank (https://aphasia.talkbank.org/) corpus. AphasiaBank is a large academic database of multimedia files from patients with Transmotor, Broca's, Wernicke's, Anomic, and Conduction aphasias and is therefore a good test dataset to examine which speech and language variables may be most relevant. We selected Winterlight-extracted variables which exceeded a Spearman (rho) correlation of 0.5 with the Spontaneous Speech Score, Object Naming Score or Fluency

Score from the Western Aphasia Battery (WAB). Using picture descriptions from two prospective cohort studies (Healthy older adults (n=111) and FTLD (n=19)), we then examined: the sensitivity of the selected variables for detection of? FTLD and test-retest reliability. **Results:** Of the ~500 variables produced by the Winterlight software, 42 exceeded rho=0.5. These variables related to syntactic complexity, discourse mapping, coherence, lexical complexity, pauses and fundamental frequency of speech. In comparing the healthy and FTLD cohorts, 31 variables (73.8%) (20 (47.6%) after Bonferroni correction) were significantly different between the two groups. Test-retest reliability for individual variables in the FTLD cohort was modest, with 17 variables (40.5%) exceeding a rho value of 0.7. To examine test-retest reliability of a composite of these 42 variables, we used them as inputs for a ridge regression model to estimate the WAB score. The computed WAB model had a Mean Absolute Error (MAE) of 17.9% and demonstrated excellent test-retest reliability (rho=0.87, p<0.00001). **Conclusions:** Preliminary results indicate that computationally derived speech and language variables extracted from spontaneous speech correlate with overall aphasia severity and can separate healthy from FTLD individuals. Test-retest of individual variables was variable, but a simple composite measure showed excellent test-retest reliability. This suggests that these variables could be useful for building a unified language composite score for FTLD which would be easier to measure and more objective than existing clinical instruments. Future work should focus on further verifying the selected variables in larger FTLD samples with longer observation windows. **References:** 1. Miyagawa, T. et al. Use of the CDR® plus NACC FTLD in mild FTLD: Data from the ARTFL/LEFFTDS consortium. Alzheimers. Dement. (2019). doi:10.1016/j.jalz.2019.05.013; 2. Knopman, D. S. et al. Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. Brain 131, 2957–2968 (2008); 3. Mioshi, E., Hsieh, S., Savage, S., Hornberger, M. & Hodges, J. R. Clinical staging and disease progression in frontotemporal dementia. Neurology 74, 1591–1597 (2010); 4. Fraser, K. C. et al. Automated classification of primary progressive aphasia subtypes from narrative speech transcripts. Cortex 55, 43–60 (2014).

P139- THE COMPARISON OF COGNITIVE INCLUSION SCORES BETWEEN SUBJECTS SCREENED IN THE MORNING VERSUS SCREENED IN THE AFTERNOON. K. Kruczek, P. Voccia *(Bioclinica Research - The Villages (United States))*

Objective: Scheduling a subject to screen for an Alzheimer's Dementia trial takes the coordination of several employees' schedules as well as the subject's and caregiver's schedule. Time of administration was analyzed to see if scheduling a subject during the morning versus the afternoon had any impact on the cognitive scores used for inclusion and exclusion. Since the MMSE is used as inclusion criteria for a vast number of AD trials, analysis was also done to see if administering the MMSE prior to other cognitive tests, rather than post, had an impact on the MMSE scores. **Method:** All subjects were screened for Mild Cognitive Impaired studies. Administration times were split into two groups, morning (07:00-12:30) and afternoon (12:31-17:00). The screening scores of three often used cognitive inclusions, RBANS Delayed Memory Index (DMI), the International Shopping List Test (ISLT) Total and Delayed scores, and the MMSE scores were examined. Comparison was also made between the scores of the MMSE tests which were administered prior to any other cognitive testing versus those which were administered after another cognitive test. **Result:** 35 subjects were administered the ISLT in the morning and 47 in the afternoon. There was no significant difference between the means of the morning and the afternoon group for either the total recall score or the delayed recall score (TR p=0.4864; DR p=0.1761). For subjects screening into a study using the RBANS DMI, there was not a significant difference between the means of the groups who were tested in the morning compared to those tested in the afternoon (n=168, p=0.7600). The total scores for the MMSE were compared between the morning and afternoon administrations, resulting in no significant difference as well (n=351 p=0.4525). Each scale was also analyzed by age for the morning and afternoon administrations. The only group which resulted in a significant difference was the 75 to 79 year old subjects and only for the MMSE (p=0.0051), showing a higher average score in the afternoon. Since the MMSE is used so often as a screening test, total scores of the MMSEs administered as the first scale were compared to the scores of the MMSEs which were administered after another cognitive test. Results showed that there was no significant difference between the scores of the MMSEs which were administered before or after another cognitive scale (p=0.7032). **Conclusion:** Based on these screening scores, results suggest that time of day for test administration does not affect the final score. When analyzed by age, the only group which showed some impact of time administered were subjects ages between 75 and 79 and only for the MMSE. Order of administration did not impact the scores on the MMSE.

P140- UNDERLYING POTENTIAL MECHANISM OF ANTI-ALZHEIMER'S DISEASE USING MAYSIN DERIVATIVE ISOORIENTIN 2-O-A-L-RHAMNOSIDE USING IN VITRO ASSAY SYSTEM. G. Lena, H.D. Kim *(New York Medical College - Valhalla (United States))*

Alzheimer's disease (AD) is the progressive mental deterioration of the brain overtime (1). Past studies have found that factors that increase amyloid beta production in the brain or make it difficult to remove amyloid beta plaques are risk factors or possible causes of AD (4). Maysin is a flavone C-glycoside from corn silks and maize (1,3). Past studies have shown Maysin from Centipedegrass (CG) to be protective against the formation of amyloid beta plaque build-up and tangles as well as helping to counteract oxidative stress. Isoorientin 2-O-rhamnoside (IT) is a flavonoid compound similar to maysin also found in CG. Little work in the past has been done with IR compounds and discovering its use as an anti-AD measure. β-secretase (BACE) is an amyloid precursor protein cleaving enzyme that is believed to be responsible for initiating the amyloid beta protein formations. We hypothesis that IR flavonoid compounds can exert anti-AD properties such as an inhibitory of amyloid beta oligomerization process and the ability to counteract BACE activation. In neuronal PC12 cellular model, potentiality anti-AD appeared that inhibitory activity of BACE increased in the IR dose-dependent manner, for example 35%, 55%, and 78% equivalent to dosage of 10, 25, and 50 IR (μg/ml), providing evidence in support of the hypothesis. In the future, we hope to continue this research in hopes of finding a pharmecutical treatment for problems relating to Alzheimer's disease.

P141- EVALUATION OF PROPER NAMES IN SEMANTIC MEMORY TASKS WITH SUBJECTS PRESENTING FOR ALZHEIMER'S DEMENTIA RESEARCH TRIALS. P. Voccia, K. Kruczek, M. Cohen *(Bioclinica Research - The Villages (United States))*

Background: Clinical trials in dementia research tend to incorporate a variety of memory tasks in the rating scales, including semantic memory measures. Many semantic memory tasks utilized in AD research require the subject to identify as many words as they can think of within a specified category but restrict the inclusion of proper names. **Objectives:** The purpose of this study was to evaluate the validity of a semantic memory task targeting only proper names, to determine if the exclusion of proper names is necessary for identifying semantic memory impairments in this research population. **Methods:** A semantic memory task involving proper geographical location names (cities) was administered to 2,474 subjects who presented for Alzheimer's Dementia trials. The mean number of proper nouns identified across trials was evaluated for subjects who were identified during screening as falling into one of three categories: Healthy/Normal (n=1680), Mildly Cognitive Impaired/MCI (n=686) and Impaired (n=108). A t-test was used to compare means of Normal vs MCI groups, and MCI vs Impaired groups. In addition, subjects were asked how they came up with the location names, to determine if the names were recalled using episodic strategies (i.e. route of travel, places where one lived). **Results:** The average number of location names for Normal subjects was 11.6. The average number of location names identified for MCI subjects was 7.8. The average number of location names identified for Impaired subjects was 3.9. There were statistically significant discrepancies between the means of the Normal vs MCI groups, and between the means of MCI vs Impaired groups, respectively. Normal/Healthy subjects were able to identify significantly more location names, on average, than subjects meeting criteria for MCI (t Stat = 29.28, t Critical = 1.65). Similarly, subjects meeting criteria for MCI were able to identify significantly more location names, on average, than subjects meeting criteria for the Impaired group (t Stat = 13.35, t Critical = 1.65). In comparing means between groups using episodic and semantic strategies, subjects in the MCI group who reported employing episodic strategies identified significantly more locations than subjects who reported not using an episodic strategy. No statistical significance was noted between episodic and non-episodic strategies for subjects in the Normal or Impaired groups. **Conclusions:** A semantic memory task which requires free recall of proper names, exclusively, appears to be a valid measure of cognitive decline related to dementia. Based on this data, semantic memory tasks would not have to restrict responses to common nouns or generic terms. Further, it appears that the use of episodic strategies did not have a statistically significant impact on the average number of locations recalled for Normal or Impaired subjects, but my have had an impact on the average number of locations recalled by the MCI group. Further investigation into the impact of the use of mnemonic strategies for this population may be warranted.

P142- GENDER BIAS IN CLINICAL TRIAL RECRUITMENT IN AD: AN ANALYSIS BY FUNDACIO ACE. M. Boada[1,2], C. Abdelnour[1,2], A. Santuccione[3,4], M.T. Ferretti[3,5], P. Maguire[6], I. Hernández[1,2], A. Lafuente[1], J.P. Tartari[1], M. Buendia[1], A. Pancho[1], L. Tárraga[1,2], A. Benaque[1], M.J. Gurrutxaga[1], A. Ruiz[1,2], S. Valero[1,2] *((1) Research Center and Memory Clinic. Fundació ACE. Institut Català de Neurociències Aplicades. Universitat Internacional de Catalunya, Barcelona (Spain), (2) Networking Research Center on Neurodegenerative Disease (CIBERNED), Instituto de Salud Carlos III, Spain - Madrid (Spain), (3) Women's Brain Project, Gunterhausen (Switzerland), (4) Global Medical and Scientific Affairs, Roche Diagnostics International Ltd., Rotkreuz (Switzerland), (5) Institute for Regenerative Medicine-IREM, University of Zurich, Schlieren, Zurich (Switzerland), (6) European Institute of Womens Health, Dublin (Ireland))*

Background: The U.S. Food and Drug Administration (FDA)has made great efforts to promote the representation of women in clinical trials including guidance, regulation and recommendations. The aim is to protect specific biological sex and gender conditions and to encourage drug developers to consider the part played by sex and gender in clinical outcomes and drug-safety profiles by ensuring women are included in clinical trials. (1,2,3,4). Alzheimer's Diseases (AD) is a common neurodegenerative disorder, that starts with cognitive impairment and results in dementia. It affects predominantly women; according to a European policy report, the number of women living with dementia accounts for almost double that of men and they deserve to be more visual and accurately represented in health systems. (5). AD is a highly complex multifactorial biological disease representing a major health challenge. It is now an enormous societal problem, a model for biomedical, ethical, legal, and public/private health research. As a chronic disease, it requires a holistic person-centred approach, in which sex and gender play a relevant role, as recently highlighted by the scientific community (6). Fundació ACE. Institut Català de Neurociències Aplicades (FACE) is a private non-profit foundation providing health services to Catalan Public Health System. Its activity is focused on diagnosis, treatment, day-care, clinical, basic and social research, education and awareness in the dementia continuum (5). Aware of the relevance of sex and gender differences in AD clinical trials design and the lack of specific analysis of the results from this perspective, FACE has built a successful model approach to patient engagement in order to improve AD clinical trial management. With expertise gained from over 20 years' experience, FACE together with the Women's Brain Project, a non-profit organization acting for considering diversity in the design or solutions for brain and mental diseases, aim to explore sex and gender differences as a priority in the patient selection process for clinical trials in the AD continuum. **Objectives:** To detect a differential distribution of sex and gender at different stages of the clinical trials recruitment process and to identify the factors associated with this difference in the AD continuum, from 2017 to 2018. **Methods:** Patient distribution at pre-Screening in the Memory Unit (MU), and screening in the Clinical Trials Unit (CTU) and at post-inclusion in CTU were analysed. Two pre-screening scenarios are possible at MU: selection at daily clinical session by phenotype (2,874 subjects) and from FACE database and followed up in-house (4,710) according to study-specific criteria algorithm. For screening and selection at CTU, current clinical status was checked (268 subjects) and screening failures were detected at that time.

During the study process, after subject randomization, dropout numbers, adverse events and early terminations were analysed. Potential causes of sex and gender distribution were statistically analysed throughout. **Results:** In the MU daily clinical session scenario, women and men were equally selected (17% of 2,874 subjects). Of the not-selected patients, women were the most represented due to being older, to having lower MMSE and lower scholastic level (all p>.05) despite having fewer medical comorbidities than men(p<.05). In the second scenario, based on MU database, women are statistically less often selected at pre-screening (32.3% of 4,710 subjects) than men. Being older, with lower MMSE and lower school level appeared as discriminant factors against women (p<.05) even though in this scenario they also presented with lower comorbidity status (p<.05). However, when subjects reached screening at CTU (268 subjects), both women and men were equally likely to be screened or to refuse to participate (48%). Throughout the clinical trial process, women and men showed the same completion ratio. This is, nevertheless, far from the prevalence of the disease in the general population. Regarding dropouts, women and men abandoned for the same reasons and in similar proportions. **Conclusion:** according to the present study findings, biased selection criteria occur resulting in the exclusion of women at pre-screening. At screening stages and follow-up, a process of democratization in gender is evident in regard to participation and completion. Participation of women in clinical trials does not reflect the prevalence of AD among women and is, therefore, not representative of reality. In order to ensure that no selection bias occurs at the recruitment phase of AD clinical trials leading to a negative impact on clinical outcomes, efforts should be made to provide equal opportunities regardless of gender. To achieve this goal, clinical trials should reflect the "real world" and patient engagement actions should consider the challenges of gender (6). The authors are conscious that this study provides merely a single-site experience with a small sample. The authors consider that the more agents involved in addressing gender and clinical trials the better. 1. 1U.S. Department of Health and Human Services, FDA, General Considerations for the Clinical Evaluation of Drugs, (1977); 2. N. Eshera, et al, D. Am. J. Ther. 22 (6) (2015) 435–455; 3. R. Poon, S. Umarjee, J. Women's Health 22 (7) (2013) 604–616; 4. U.S.G.A. Office, Women Sufficiently Represented in New Drug Testing, but FDA (2001); 5. MANIFESTO Women and Dementia in Europe Position Paper. European Insitute of Women's Health 2018; 6. Ferretti MT et al..Nat Rev Neurol. 2018 Aug;14(8):457-469; 7. Boada M et al. Alzheimers Dement. 2014 May;10(3):409-15; 8. Rodríguez -Gómez et a; Alzheimer and Dement. ..2019.

P143- A LOOK AT PRACTICE EFFECT FOR WORD LIST RECALL IN SUBJECTS PRESENTING FOR CLINICAL TRIALS IN ALZHEIMER'S DISEASE. P. Voccia, K. Kruczek, M. Cohen *(Bioclinica Research - The Villages (United States))*

Background: A word list recall test was administered to subjects ages 55-85 for the purposes of prescreening for Clinical trials in Alzheimer's Dementia research. The task included an initial (immediate) administration, a second (review) administration, and a delayed recall task. **Method:** Word recall results were collected and analyzed for 401 subjects. Mean number of words recalled for immediate, review and delayed trials was evaluated for subjects meeting criteria for one of three categories: Normal (n=194), Mildly Cognitive Impaired/MCI (n=146) and Impaired (n=61). **Results:** Healthy subjects recalled an average of 5 words after the immediate presentation, 7 words after the review, and 6 words after a delay. MCI subjects recalled an average of 3 words after the immediate presentation, 5 words after the review, and 3 words after a delay. Impaired subjects recalled an average of 1.5 words after the immediate presentation, 2.5 words after the review words after the review, and 0 words after a delay (x=0.34). **Conclusion:** After two administrations of a word list: Healthy subjects recalled an average of one more word on the delayed task than they did on the initial task; MCI subjects recalled, on average, the same number of words on the delayed task as they did on the initial task; Impaired subjects recalled fewer words on the delayed task than on the initial task. These findings may indicate that practice (review) may be beneficial to healthy subjects but may not impact delayed recall for subjects in initial or mid stages of cognitive impairment.

P144- USING HIERARCHICAL BAYESIAN COGNITIVE PROCESSING AND LATENT-MIXTURE MODELS TO PREDICT IMPENDING COGNITIVE DECLINE WITH COMMON MEMORY TESTS. J. Bock[1], M. Lee[2], W. Shankle[1,2], J. Hara[1,3], D. Fortier[1], T. Mangrola[1], R. Petersen[4] *((1) Medical Care Corporation - Newport Beach (United States), (2) Dept. of Cognitive Sciences, University of California at Irvine - Irvine (United States), (3) Pickup Family Neurosciences Institute, Hoag Memorial Hospital - Newport Beach (United States), (4) Mayo Clinic - Rochester (United States))*

Background: Hierarchical Bayesian Cognitive Processing (HBCP) models measure unobservable (latent) cognitive processes that underlie learning and recall of information, such as measured by cognitive tests. These processes, representing encoding, storage, or retrieval of the list items in wordlist memory tasks, after accounting for individual differences, are able to characterize individuals and the groups that they comprise. In subjects with high risk for Alzheimer's disease (AD) dementia but with normal cognitive function, fMRI and FDG PET studies have shown increased medial temporal lobe activity, which may represent increased encoding and/or storage to compensate for decreased retrieval capacity. This suggests that individuals who are cognitively normal but who will cognitively decline in the future have patterns of cognitive processing distinguishable from those who are cognitively normal and will remain so. We have previously demonstrated this with group-level aggregate data. These distinguishable patterns, when modeled at the individual level, are able to be predicted with partially-observed latent-mixture models. Such models are defined in terms of a number of subjects who are known to belong to each subgroup. Based on this initial information, latent-mixture models are able to infer the different memory processes associated with each subgroup, as well as measure the probability with which each remaining subject belongs to each subgroup. **Objective:** To test the hypothesis that HBCP models applied to wordlist memory task data can predict the latent class of an individual, between cognitively normal subjects who would progress to amnestic MCI (aMCI) or AD dementia stages (Progressor) vs. those who would remain normal (Non-Progressor), through estimation of underlying cognitive processes. **Methods:** Subjects were classified at baseline and at each subsequent assessment as having no cognitively degenerative disease (normal; NL), presenting aMCI, or AD dementia. Subjects were annually assessed for up to 10 years. Subjects who were NL at baseline were divided into

2 groups based on whether the diagnosis progressed to greater severity at any point during the study (progressor) or remained unchanged over the study (non-progressor). The AVLT 15-word memory task item responses from the baseline assessments of each diagnostic group were used as input data to the model. The AVLT includes five immediate free recall tasks and two delayed free recall tasks. However, a sufficiently informative pattern of recall was able to be generated using item responses from only four of the seven tasks: three immediate free recall tasks and one delayed free recall task. Using an HBCP partially-observed latent-mixture model, cognitive processing parameters and the latent class parameter were estimated for each subject and group, with 50% of individual subjects' progressor or non-progressor group observed in the model and 50% withheld from the model to be predicted. Posterior predictive distributions were estimated and examined to determine model fit. Samples from the posterior distribution of predicted subjects' latent class parameter were used in generation of receiver operating characteristic (ROC) curves for demonstration of accuracy in prediction of individuals' observed groups withheld from the model. We computed Savage-Dickey density ratios on the changes between groups for key cognitive processing parameters to determine the significance of differences generating distinct group patterns. **Results:** Our findings on modeling cognitive processes at the individual level corroborate our previous findings at the group level. Notably, progressors are characterized with lower probability for retrieval on the delayed free recall task as compared to non-progressors. Such group differences allow for relatively accurate prediction of individuals with respect to progressor and non-progressor groups. **Discussion:** HBCP models have shown clear differences between progressor vs. non-progressor groups, and these differences extend to the individual level. Such differences could be explained by cortical functional changes due to accumulating AD pathology or may be observable through the increased granularity of measurement that cognitive processing parameters provide as compared to summary score measurement traditionally used for wordlist memory tests. The results suggest the ability to diagnose preclinical AD in a patient without the use of, or as a supplement to, biomarker imaging. This requires further validation with imaging studies and may be supported by demonstrating that those subjects predicted to progress with the HBCP latent mixture model are in fact positive for accumulating beta amyloid or pathologic tau. Furthermore, the results identify specific cognitive processes that are impaired in the course of progressive decline, which may be a benefit to emerging targeted treatments.

P145- CHANGES IN SEMANTIC MEMORY DUE TO COGNITIVE IMPAIRMENT IN ALZHEIMER'S PATIENTS.

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Background: In free recall tasks, participants often group their responses by semantic similarity. This response strategy presupposes the existence of an intact similarity-based semantic representation. However, various forms of cognitive impairment could disrupt access to semantic representations. In a previous study, we analyzed observations from 3,635 clinical patients between 16 and 104 years of age, diagnosed with functional assessment staging test (FAST) scores ranging from 1 to 6, where higher FAST scores represent greater impairment. Participants completed triadic comparisons of animal names and an unexpected delayed free recall task of those animal names. Analyses included a multi-dimensional scaling analysis of semantic representation based on similarity judgments inferred from the triadic comparison data. We calculated a spatial statistic dependent on nearest-neighbor distances to quantify the degree of clustering in each semantic representation [Lee, Abramyan, & Shankle (2016). Behavior Research Methods, 48, 1492-1507]. We also calculated conditional response probabilities (CRP) from the free recall data. We visualized changes in nearest-neighbor distances, CRP, and the relationship between semantic similarity judgments and CRP as a function of FAST stage. **Objective:** While it is clear that memory performance changes as cognitive impairment increases, it is not clear whether this change is the result of noisy access to an intact semantic representation or a restructuring of the representation itself. The goal of the current analysis is to understand the relative importance of changes in access to a stable representation versus changes in the semantic representation itself, as patients' semantic memory becomes progressively more impaired. **Methods:** We developed and applied a model of triadic comparison performance across FAST stage in the clinical data set. With the Leuven Concept Database as a source of potential features that participants use to judge the similarity of animals, the model uses latent-mixture methods to infer which features explain participants' triadic comparison choices, and how consistently they make these choices. The importance of a feature in describing animal similarities is represented by a binary inclusion parameter [Zeigenfuse & Lee (2010). Acta Psychologica, 133, 283-295]. Additionally, the model uses a Luce-choice rule approach with a response determinism parameter that controls the extent to which participants make triadic comparison choices consistent with the semantic proximity of the words [Lee, Abramyan, & Shankle (2016). Behavior Research Methods, 48, 1492-1507]. **Results:** For clinical patients, as FAST stage increased, semantic representations became less clustered and CRPs were less related to semantic structure. We also found a curvilinear relationship between semantic similarity and CRP in early FAST stages, but this relationship became less evident as FAST stage increased. We applied the cognitive model to the data set, resulting in a qualitative representation of access to the semantic network. The response determinism parameter decreased with increasing FAST stage. This pattern indicates a greater tendency towards variable responding in the triadic comparison choices for patients with greater cognitive impairment relative to those with little to no impairment. We also measured the change in relative importance of the semantic features in judging the similarities between animals across FAST stages. **Conclusion:** In a clinical population, semantic structure appears to break down as FAST stage increases. Through the use of cognitive models, we are able to measure the relative importance of changes in the ability to access a stable representation versus changes in the semantic representation itself, as participants' semantic memory becomes progressively more impaired.

P146- PROGRESS & CHALLENGES IN THE DEVELOPMENT OF ELECTRONIC INSTRUMENTS TO PREDICT AND MONITOR COGNITIVE DECLINE.
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Background: A critical need for clinical researchers are psychometrically validated resources to identify older adults at risk for cognitive decline and dementia due to Alzheimer's disease (AD). The Clinical Dementia Rating scale (CDR®) and the Financial Capacity Instrument-Short Form (FCI-SF) are two instruments that are currently well validated in-clinic. However, limitations that hinder their accessibility include the need and substantial time commitment of a trained assessor to administer the instruments. Electronic versions of the CDR® and FCI-SF that can be administered remotely have the potential to greatly impact their scalable use. The CDR®, developed at the Washington University in St. Louis (WU), is used to determine the presence and severity of dementia due to Alzheimer's disease (AD). Semi-structured interviews with a participant and collateral source are used to calculate cognitive and functional status across six domains, as well as a composite or global CDR® score. The FCI-SF, developed at the University of Alabama at Birmingham (UAB), is used to detect decline in everyday financial capacity in older adults, which has been associated with dementia progression. The FCI-SF assesses and scores four financial activity domains, as well as processing speed. **Objectives:** The goal of the Electronic Validation (e-VAL) project is to develop, implement, and validate electronic versions of the CDR® and FCI-SF (eCDR and eFCI) to remotely predict and monitor cognitive and functional decline. The progress and challenges in adapting these instruments for online use are summarized below. **Methods:** To adapt the CDR® and the FCI-SF for online administration: Each item was reviewed to determine if it can be reasonably translated into an online format. Items with discrete responses (ex. yes/no) were adapted verbatim in survey format. Items with open-ended responses were altered to have multiple-choice options. For some items that may show practice effects, alternate versions of items were developed. Item Response Theory (IRT) analysis of existing data from WU (n>3300), UAB (n>3000), and Mayo Clinic (n=3000) was used to evaluate item-level characteristics of the CDR® and FCI-SF. Regression analysis was used to measure associations between individual items and overall instrument score and financial ability. The items that were identified to be the most important and predictive were kept in the electronic instrument. Conversely, the items that were identified to be least predictive were eliminated. Input from clinicians familiar with the in-clinic administration of the instruments was also used to further inform item selection for the eCDR® and eFCI. All potential items were evaluated by experts to determine item content and wording, as well as the importance of clinical judgement. The instruments were adapted for online use via Qualtrics, a survey software tool. **Results:** A number of challenges were encountered during electronic instrument development. Some items in the CDR® were eliminated because they could not reasonably be translated into an online format due to their open-ended nature, even though they were identified as predictive by IRT analysis. In clinic, administrators are physically present and can provide the participant with more details or ask follow up questions or instructions to probe for a satisfactory response in both instruments. To adapt this for online administration, the extra details that administrators most frequently provided in-clinic were included as supplemental text of the electronic instrument. When the CDR® is administered in clinic, an overall clinical judgement may be made based on particular responses to assign a score. This clinical judgement is removed when the instrument is administered online, so all scoring must rely solely on the electronic response. To address this, items identified as those that significantly influence clinician judgement, and ultimately attribute to score assignment, were incorporated in the electronic instrument. To preserve the integrity of online data collection for these instruments, some questions with open-ended responses were altered to have multiple-choice answer responses in the electronic instrument. However, presenting a list of multiple-choice answers may prompt participants, eliminate use of abstract thinking to craft a response, and change the construct of the question. To compensate for this, a wide range of answer options, including the most frequent responses from prior instrument datasets, were incorporated. For numerical questions, the "slider" Qualtrics question type was utilized, in which a wide range of numerical responses can be captured. Presenting a list of multiple-choice answers may also change how the instrument is scored and adaptations to any existing scoring algorithms may be necessary. **Conclusion:** These results demonstrate the progress and challenges of developing electronic versions of the CDR® and FCI-SF. The development and validation of electronic instruments is likely to facilitate scalable remote screening and longitudinal monitoring of older adults at risk for cognitive decline, preclinical and prodromal AD, and dementia. This digital approach can impact clinical research, clinical treatment trials, and can ultimately have practical clinical applications to diagnosis and identify individuals for treatment in the future.

P147- ELUCIDATING THE RISK FACTORS FOR DISEASE PROGRESSION TO DEMENTIA IN PATIENTS WITH AMYLOID NEGATIVE AMNESTIC MILD COGNITIVE IMPAIRMENT.
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Background: Amyloid PET scan allows for the assessment of beta amyloid status in the brain, distinguishing true Alzheimer's disease from Alzheimer's mimicking conditions. 15 to 20% of patients with clinically probable Alzheimer's disease (AD) have been shown to have no significant Alzheimer's pathology on amyloid PET. Fewer studies, however, have been done about this subpopulation in terms of clinical progression. **Objective:** We investigated the risk factors that influence progression to dementia in patients with amyloid negative amnestic mild cognitive impairment (aMCI). **Methods:** This study was a single-institutional, retrospective cohort study of patients with amyloid-negative aMCI who visited the memory clinic of Asan Medical Center aged over 50, from March 2013 to February 2019 with more than 36 months of follow-up period. All participants underwent 3 Tesla brain MRI, detailed neuropsychological testing, and fluorin-18[F18]-florbetaben amyloid PET. [F18]-florbetaben scans were assessed according to the predefined

the brain amyloid plaque load (BAPL) scoring system. The diagnosis of MCI was defined according to the criteria proposed by Petersen et al. The aMCI subtype was determined when the score was below the 16th percentile (-1SD) for demographically matched norms in verbal and visual memory tasks. Both single- and multiple-domain aMCI were included. The cognitive status change in each subject was judged by a physician based on history-taking and neuropsychological test result including clinical dementia rating (CDR) score, stratifying into progressed to dementia vs. stationary MCI. **Results:** Of 120 amyloid-negative aMCI subjects, 52 progressed to dementia and 68 remained aMCI. In progression group (n=52), AD-like dementia was found in 39 patients, behavioral variant frontotemporal dementia 3, primary progressive aphasia 3, corticobasal degeneration 3, idiopathic Parkinson's disease 2 and diffuse Lewy body dementia 2. There was no statistically significant difference in demographic characteristics including age, sex, education years, geriatric depression scale, hypertension, diabetes, levels of LDL, and HDL between the two groups. In addition, the proportion of APOE4 carrier status was not statistically different between the two groups. The more severe the hippocampal atrophy on MRI imaging, the more likely to progression to dementia. In terms of neuropsychological data, we found that patients with progression to dementia had lower initial Korean version Mini-Mental Status Examination (K-MMSE) score, Global Deterioration Scale (GDS), Clinical Dementia Rating (CDR) scores as compared with stationary group. In addition, episodic memory (delayed recall on verbal learning test and Rey Complex Figure test), visuospatial memory (RCFT immediate recall), word fluency task (COWAT animal and supermarket) and confrontation naming (Boston Naming test) were significantly impaired in progression group relative to stationary group. **Conclusion:** The progression group had more impairment in verbal, visual episodic memory function and hippocampal atrophy than the stationary group, which is a AD-like signature, despite the lack of evidence for Alzheimer's pathology. Although, additional neuroimaging analysis is needed to corroborate our findings. AD-mimicking clinical progression may be caused by other pathologies, such as TDP-43 or tau protein. Further research of biomarkers for non-AD dementia is warranted for these specific population.

P148- COMPARING THE STANDARD AND ELECTRONIC VERSIONS OF THE ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITIVE SUBSCALE: A VALIDATION STUDY. T.M. Solomon[1,2], J.M. Barbone[1], H.T. Feaster[1], D.S. Miller[1], G.B. Debros[3], C.A. Murphy[3], D. Michalczuk[3] *((1) Signant Health - Wayne, Pennsylvania (United States), (2) Boston University School of Medicine - Boston, Massachusetts (United States), (3) The Memory Clinic - Bennington, Vermont (United States))*

The Alzheimer's Disease Assessment Scale (ADAS-Cog) has become the de facto gold-standard for assessing the efficacy of putative anti-dementia treatments. There has been an increasing interest in providing greater standardization, automation, and administration consistency to the scale. Recently, electronic versions of the ADAS-Cog (eADAS-Cog) have been utilized in clinical trials and demonstrated significant reductions in frequency of rater error as compared to paper. In order to establish validity of the electronic version (eADAS-Cog), 20 subjects who had received a diagnosis of probable Alzheimer's disease (AD) at a private US Memory Clinic completed a single-center, randomized, counterbalanced, prospective trial comparing a version of the eADAS-Cog to the standard paper scale. Interclass Correlation Coefficient on total scores and Kappa analysis on domain scores yielded high agreement (0.88 - 0.99). Effects of order and mode of administration on ADAS-Cog total scores did not demonstrate a significant main effect. Overall, this study establishes adequate concurrent validity between the ADAS-Cog and eADAS-Cog among an adult population with diagnosed AD.

P149- ASIAN AND NON-ASIAN COUNTRIES SCREEN SUBJECTS WITH SIMILAR MMSE SCORES TO THE ELENBECESTAT MISSIONAD GLOBAL PHASE 3 STUDIES IN EARLY ALZHEIMER'S DISEASE. J. Murphy[1], T. Doherty[2], M. Gee[3], S. Ito[4], K. Michio[4], B. Albala[5] *((1) Syneos Health - San Francisco (United States), (2) Syneos Health - London (United Kingdom), (3) Eisai - London (United Kingdom), (4) Eisai - Tokyo (Japan), (5) Eisai - New York (United States))*

Background: AD patients living in Asian countries have been shown to present to clinics with a more advanced stage of disease as compared to their counterparts living in Western countries, hypothesized as resulting from cultural differences in expectations of aging and reluctance for treatment-seeking (Chow, et.al. 2002). The MMSE is considered a global standardized assessment, yet there is evidence that Attention, Calculation, and Repetition subtests have unique variation in some Asian countries (Shim, 2017) with MMSE scores being adjusted for country-specific nomenclature for orientation to place items and education-adjustments to accommodate patients with little formal education, such as in Korea (Shim, 2017; Ng, 2007). The Japanese Alzheimer's Disease Neuroimaging Initiative (ADNI) data provide broad reassurance that Japan cognitive measures are equivalent to North American ones (Iwatsubo, 2018), yet the equivalence of Chinese MMSE scores is relatively unknown because few data exist for this region. **Objectives:** To analyze screening MMSE data from the large global MissionAD program, specifically comparing the data from Asian and non-Asian subjects. **Method:** MMSE screening data were pooled from Eisai's MissionAD1 & MissionAD2 global phase III trials (N=10,848) and divided into Asia (N = 1,774) and Non Asia regions (N=9,074). Asia was defined as China, Japan, South Korea, Taiwan, and Singapore. Using SPSS v25, ANOVAs were performed to compare total score and sub-score regional differences. Secondary analyses compared sub-score mean differences between the highest screening individual countries from the Asia region (Japan N=1,218, South Korea N=269 and China N=174) versus the non-Asia region. Further analyses of within-Asia differences were conducted as needed. Korea, Japan and China-specific ANOVAs were based on pre-identified hypotheses. **Results:** No regional differences were found for Total MMSE score when comparing Asia (mean =25.87 (SD=2.8)) with non-Asia (mean=25.94 (SD=2.9)). The three individual countries of interest from the Asia region (China, Japan and Korea) all had total MMSE scores equivalent to the non-Asian mean. ANOVAs comparing Asia vs non-Asia sub-scores were significant for Attention/Calculation ($p<0.0001$), Repetition ($p<0.0001$) and Orientation to Place ($p<0.0001$), with Asian subjects scoring higher on all sub-scores. Post-hoc tests revealed that China and Japan had slightly higher Calculation and Orientation to Place scores than non-Asian countries and other Asian countries. Chinese performance was significantly lower than all other countries on Repetition

(China mean=0.21; (SD=.40) vs non-Asia mean=.76 (SD=.43); p<0.0001). Further analysis of within-Asia differences revealed that Korea had lower but clinically insignificant total MMSE scores (Mean=25.23; SD=2.8) than the other 4 Asian countries (Mean=25.87; SD=2.8). Repetition scores had the most variability across countries, with China and Taiwan having the lowest Repetition scores (China mean=0.21; (SD=.41) and Taiwan mean=0.37; (SD=.49)), Japan and Korea having higher scores (Japan mean=0.98; (SD=.13), Korea mean=0.95; (SD=.22)). **Conclusion:** Sites in Asia refer patients at the same disease stage as compared to non-Asia regions, based on MMSE screening scores in these early-AD trials. Sites in the three Asian countries that screened the largest number of subjects (Japan, South Korea and China) screened subjects with the same mean MMSE scores as non-Asian sites. Minor Asia-specific differences did exist among 3 sub-tests, yet the magnitude of the Asian countries' slightly higher scores was not clinically meaningful (less than one tenth of a point). Although South Korean scores on Orientation to Place and Calculation were equivalent to non-Asian sites, they did perform lower than other Asian countries on both subtests. While test developers may consider reducing the difficulty of the Repetition phrases on the China and Taiwan scales, its significance is mitigated by the fact that it is a single point of a 30-point exam, and this language and culture-specific item will remain uniquely difficult to calibrate due to regional specificity. Follow-up ANCOVAs are required to control for education, age and sex variables. This large global sample provides reassurance that these differences are not clinically significant and no meaningful heterogeneity was observed in the screening data from this large Phase 3 program. **References:** Chow, T.W. et al. (2002) Neuropsychiatric symptoms of Alzheimer's disease differ in Chinese and American patients. International Journal of Geriatric Psychiatry, 17: 22-28. Shim, Y.S. et al. (2017) Characteristic differences in the mini mental state examination used in Asian Countries. BMC Neurology 17:141; Ng TP, et al. (2007) Ethnic and educational differences in cognitive test performance on mini-mental state examination in Asians. Am J Geriatr Psychiatry. 2007 Feb;15(2):130-9; Iwatsubo T1, et al. (2018) Japanese and North American Alzheimer's Disease Neuroimaging Initiative studies: Harmonization for international trials. Alzheimers Dement. Aug;14(8):1077-1087.

P150- COMPARING A SPEECH-BASED DIGITAL BIOMARKER TO THE MONTREAL COGNITIVE ASSESSMENT (MOCA) FOR TRACKING COGNITION OVER A 6 MONTH PERIOD IN A NATURALISTIC COHORT OF OLDER ADULTS.

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Background: A lack of precision in quantifying cognitive performance is a key pillar in the overwhelmingly negative results obtained from clinical trials in Alzheimer's Disease (AD). For example, both the ADAS-Cog (1) and MMSE (2) have well established limitations, including floor/ceiling effects, practice effects and poorer psychometric properties for milder forms of impairment. This can lead to masking or false amplification of clinically relevant treatment effects particularly within the short time frame of a clinical trial. Computerized cognitive assessment batteries have ameliorated some issues but are also far from perfect (3). Effective use of language reflects intact cognitive processing through the coordinated use of working memory, semantic memory and attention. Language performance can therefore be a proxy for the strength of these underlying cognitive capabilities (4). In AD, changes in speech rate, utterance length, word-frequency, pronoun usage, repetitions, word finding difficulties, content units and efficiency are notable language specific disease characteristics 5. These changes are progressive and detectable years before a clinical diagnosis is made (6). Speech, therefore, represents an excellent, novel input for a digital biomarker. It has a stable, linear association with AD severity (7) and is simple to collect, requiring minimal equipment and rater training. Speech-based digital biomarkers developed using natural language processing and machine learning could significantly reduce measurement variance by producing objective, consistent estimates, thereby yielding greater precision and greater sensitivity to change compared to existing gold standards. **Objectives:** The objective of this study was to compare how cognition changed over a 6 month period in a naturalistic cohort of older adults when measured via a gold standard brief cognitive assessment and speech-based digital biomarker. **Methods:** Participants were 111 older adults (aged 55-90), recruited from the community and independent living facilities in Canada and the US. Participants completed a tablet-based speech assessment which included two picture description tasks at Baseline, 1 month and 6 month timepoints. At baseline and 6 months, a MoCA was administered by a trained psychometrist. The MoCA was chosen for its superior detection of milder forms of cognitive impairment relative to the MMSE. Verbal responses were recorded, transcribed and analyzed to produce more than 500 individual speech and language markers. From these markers, 7 aggregate scores, chosen for their previous association to AD (5), were produced describing: discourse, information units, word finding difficulty, syntax, coherence (global and local), and sentiment. Baseline to endpoint changes were evaluated using a non-parametric, within-subjects T-test. Threshold p-values were set using a Bonferroni correction. **Results:** A total of 59 individuals completed baseline and 6-month assessments. Spearman correlations between total MoCA scores and individual aggregate measures ranged from none (discourse mapping, rho=-0.02) to moderate (word finding difficulty, rho=-0.4). Syntactic complexity (0.34), local coherence (0.36) and word finding difficulty (-0.40) showed the highest absolute degree of correlation. Using a Bonferroni adjusted threshold p = 0.0025, within-subjects analysis showed a small non-significant increase in MoCA total score (mean change = + 0.79, p=0.003). Significant baseline to endpoint reductions were seen in global coherence and information units (both p<0.000001) while a significant increase was seen in syntactic complexity (p=0.0017). **Conclusions:** This preliminary study highlights statistically significant reductions in two components of language previously associated with AD severity (coherence and information units) over a 6 month period, with no accompanying reductions in cognitive status as measured by the MoCA. These data provide preliminary support for the use of speech-based digital biomarkers as sensitive tools for detecting subtle changes in cognition within clinical trials. Replication with larger cohorts, followed for >6 months is required. **References:** 1. Cano, S. J. et al. The ADAS-cog in Alzheimer's disease clinical trials: psychometric evaluation of the sum and its parts. J. Neurol. Neurosurg. Psychiatry 81, 1363–1368 (2010). 2. Nieuwenhuis-Mark, R. E. The death knoll for the MMSE: has it outlived its purpose? J. Geriatr. Psychiatry Neurol. 23, 151–157 (2010). 3. Lenehan, M. E., Summers, M. J., Saunders,

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P151- DISCRIMINATION OF ALZHEIMER'S DEMENTIA FROM OTHER DEMENTIA WITH THREE DIFFERENT DEMENTIA SCREENING QUESTIONNAIRES. S. Ho[1], D.W. Yang[1], A. Kim[1], D.W. Lee[2], H.J. Han[3], J.H. Jeong[4], J.H. Lee[5], J.Y. Lee[6], K.H. Park[7], K.W. Park[8], S. Kim[9], S.H. Choi[10], Y.C. Youn[11] *((1) The Catholic University of Korea, Seoul St. Mary's Hospital - Seoul (Korea, Republic of), (2) Inje University Sanggye Paik Hospital - Seoul (Korea, Republic of), (3) Myongji Hospital - Goyang (Korea, Republic of), (4) Ewha Womans University Mokdong Hospital, Ewha Womans University School of Medicine - Seoul (Korea, Republic of), (5) National Health Insurance Corporation Ilsan Hospital - Goyang (Korea, Republic of), (6) Seoul National University College of Medicine & SMG-SNU Boramae Medical Center - Seoul (Korea, Republic of), (7) Gachon University Gil Hospital - Incheon (Korea, Republic of), (8) Cognitive Disorders and Dementia Center, Dong-A University College of Medicine - Busan (Korea, Republic of), (9) Seoul National University College of Medicine, Seoul National University Bundang Hospital - Seongnam (Korea, Republic of), (10) Inha University School of Medicine - Incheon (Korea, Republic of), (11) Chung-Ang University Hospital - Seoul (Korea, Republic of))*

Objectives: Alzheimer's dementia (AD) is the most frequent cause of dementia accounting for 50%–70% of dementia cases. Other common causes of dementia include vascular dementia (VD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD). The earliest and most common clinical manifestation of AD is an impairment in episodic memory. In contrast, VD, DLB, and FTD often begin with symptoms other than memory. In this study, we investigated whether AD and other dementia have the similar dementia detection rate using three different screening questionnaires. **Methods:** 120 people with Alzheimer's disease and 50 people with vascular dementia, dementia with Lewy bodies, and frontotemporal dementia were recruited for this study. Korean Dementia Screening Questionnaire-cognition (KDSQ-C), Alzheimer's disease 8 (AD8), and Subjective Memory Complaints Questionnaire (SMCQ) were rated separately by patients and their caregivers to evaluate their functions of cognition and the capability in activity of daily living. Statistically, we used ROC curve to derive the sensitivities and specificities of each test. **Results:** Alzheimer's dementia group included more females (65.8% vs. 42.0%, $p = 0.006$), slightly older (78.2±6.0 vs. 75.6±6.2, $p = 0.013$) and lesser family history (15.8% vs. 30.0%, $p = 0.036$) than the other dementia group. The area under curve (AUC) of the three screening questionnaires (KDSQ-C, AD8, SMCQ) rated by patients were 0.74, 0.81, 0.73 in AD and 0.76, 0.79, 0.72 in other dementia, respectively. The AUC of the three tests (KDSQ-C, AD8, SMCQ) rated by their caregiver were 0.93, 0.93, 0.93 in AD and 0.90, 0.93, 0.90 in other dementia, respectively. This result showed that all of three dementia screening questionnaires had a high dementia detection rate in both AD and other dementia. In addition, most of neuropsychological tests for screening dementia in Korea showed no statistically significant difference in scores between Alzheimer's dementia and other dementia. Only memory scores in KDSQ-C questionnaire were rated higher by caregiver in Alzheimer's dementia (6.7±3.1 vs. 5.5±3.2, $p = 0.03$). **Conclusions:** Dementia screening tests currently conducted in Korea (KDSQ-C, AD8, SMCQ) had no difference in distinguish Alzheimer's dementia from other dementia. There was no significant difference between the two groups even in SMCQ that assessed mainly on memory function. Diagnosis of dementia may be affected by Alzheimer's diagnosis which is most common cause of dementia. This might be the reason why there was no difference in detection rate between AD and other dementia groups using the three different screening tests.

P152- NOVEL DIGITALIZED MARKERS FOR SCREENING, COGNITIVE ASSESSMENTS AND DISEASE TRAJECTORY TRACKING IN CLINICAL TRIALS. A. König[1], N. Linz[2], J. Tröger[2], R. Guerchouche[3], Z. Radia[4], R. Inez[5], A. Pauline[5], P. Philipp[5] *((1) INRIA, Cobtek (Cognition, Behaviour, Technology) Lab, University Côte d'azur - Nice (France), (2) German Research Center for Artificial Intelligence (DFKI) - Saarbrücken (Germany), (3) INRIA - Sophia Antipolis (France), (4) Cobtek (Cognition, Behaviour, Technology) Lab, University Côte d'azur - Nice (France), (5) Alzheimer Limburg Center, Maastricht University - Maastricht (Netherlands))*

The current procedures for selecting participants for (pharmaceutical) trials developing drugs for Alzheimer's (AD) are lengthy, costly, invasive and characterized by a very high exclusion rate - only one of ten initial candidates is selected. Moreover, patients living in rural areas rarely onboard into trials due to limited access to assessments and long travel times to clinical sites. Today, there is an increasing need for harmonization and innovation of outcome measures in AD trials; ecologically valid and sensitive methods are required to improve accessibility as frontline screening in the general population for clinical trials as well as remote disease tracking. Smart digital technologies may serve as additional noninvasive and/or cost-effective tools, allowing identification of subjects in the early clinical stages who could be suitable as well as more continuous monitoring of the disease trajectory. Additionally, more standardized measures could lead to a reduction in errors due to human annotations facilitating better data comparisons across clinical sites. Implementation of such new measurement methods may facilitate early diagnostics and potentially more effective preventative strategies and treatment of dementia. However, before applying them in clinical practice and trials, these tools should be examined in ongoing large cohorts. Hinging on existing speech-based neurocognitive tests (today done in expert-participant f2f setting with manual test score evaluation), the DeepSpa project will render this procedure in a telecommunication-based service (video-call or telephone) using artificial intelligence (AI) and automatic speech, language and image analysis. This will allow to cut down costs: previous research shows that a telephone-based AI empowered system is able to discriminate with up to 90% accuracy between AD vs. healthy controls and mild-cognitive impairment. The resulting

remote service can be either operated entirely autonomous (dialogue system operating on phone) or semi-automatic with trained personnel. The project explores two use cases with a clinical study for each in a different setting; the first one assesses the feasibility, usability and further refinement of a phone-based neurocognitive assessment tool for patient pre-screening at the Alzheimer Center in Maastricht University, Netherlands. Furthermore, the predictive potential (sensitivity/specificity) for differential/prognostic diagnosis is examined 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. Longitudinal data is collected and results extracted remotely validated against face-to-face results. We will prospectively include 120 new pre-clinical patients from an ongoing cohort with a minimal dataset consisting of clinical data and a cognitive assessment. In addition, a MRI of the brain, and blood samples and CSF samples (optional) are collected for biobanking purpose. Additionally, to these procedures, after 6 and 15 months patients will be called for a brief (30 min) remote follow up evaluation on the phone. A research nurse or researcher will introduce and guide the assessment session in which speech parameters will be collected through a semi-automatic phone-based interface. The assessment consists of a short interview on how the patients perceive their memory and overall mental state, a verbal memory task, digit span and fluency tasks, being comparable to the baseline assessment, e.g. care as usual. In addition, the regular cognitive assessments at baseline and 12 month will be audio-recorded. The second use case will test the use of a tele-conference system (including video) for remote cognitive testing and monitoring of isolated elderly in rural areas in South of France (Digne-les-bains). The system uses automatic speech and image analysis for a precise and potentially more timely detection of cognitive decline. In order to assess how the systems performs in such a context, a beta version will be evaluated for its feasibility and usability. A hundred of volunteers with memory complaints will be included from the Dignes-les-bains region in the protocol. The aim for this first full-scale study is to carry out a battery of clinical interview and tests (visual memory, attention, language, and mood – 80 min) through the system and compare to face to face results in order to assess its reliability for potential remote diagnosis, with support from Nice University Hopsital and Memory Clinics specialists. Speech features as well as information on facial expressions and posture are extracted automatically and compared to classical assessment scales. Moreover, these variables might help indicating levels of engagement, stress, fatigue or mood. User experience on the participant as well as on the clinician side will be assessed with the help of extensive qualitative interviews and satisfaction questionnaires. The protocols are submitted to the ethical comittees and first results can be expected after the summer. A demo of the system for both use cases will be presented at the conference.

P153- TRACKING FUNCTIONAL DECLINE IN MILD COGNITIVE IMPAIRMENT. K. Duff, S. Porter, K. Suhrie, A. Dixon, D. Hammers *(University of Utah - Salt Lake City (United States))*

Backgrounds: Diagnostically, significant functional decline is needed to indicate that a patient has progressed from Mild Cognitive Impairment (MCI) to dementia. Typically, the report of functional changes is a subjective report of the patient or a family member, which may be difficult to track over time. **Objectives:** The current study sought to objectively evaluate functional abilities in individuals with MCI and track them over approximately one and a half years. **Methods:** Eighty-one older adults (age M=75.5 years, education M=16.5 years, 56% male) with amnestic MCI (single- or multi-domain) were assessed at baseline and one and a half years follow-up visits with three subscales of an objective measure of daily functioning, the Independent Living Scales (ILS: Managing Money, Managing Home and Transportation, and Health and Safety), and an objective measure of cognition, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Dependent t-tests compared the baseline and follow-up scores on the ILS and RBANS. **Results:** Despite no change on the RBANS across one and a half years (e.g., Total Scale score: t[80]=-0.69, p=0.50), 2 of the 3 ILS subscales showed a statistically significant decline across this same period: Managing Home and Transportation, t[80]=2.75, p=0.007, and Health and Safety, t[79]=2.10, p=0.04, with the third scale showing a trend towards decline (Managing Money, t[80]=1.68, p=0.09). **Conclusion:** Although the declines on the ILS tended to be relatively small (e.g., approximately 2 T-score points), this objective measure of daily functioning does appear sensitive enough to track these changes in this mildly impaired cohort that is at risk for progressing to dementia. Such results have implications for future clinical trials in MCI and Alzheimer's disease. For example, the sensitivity of objective, performance-based measures, like the ILS, may be superior to patient- and collateral-subjective rating scales that are currently used, which would allow for another important outcome measure in these trials.

P154- COGNITIVE FUNCTIONING ON THE RBANS AND APOE STATUS. K. Duff, K. Suhrie, S. Porter, A. Dixon, D. Hammers, J. Hoffman *(University of Utah - Salt Lake City (United States))*

Backgrounds: Although the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a widely-used brief battery for the evaluation of cognitive changes in later life, no studies have examined performance on the RBANS in older adults based on APOE genotype status, for which the e4 allele is a risk factor for Alzheimer's disease. **Objectives:** The primary objective of this study was to examine performance on the RBANS in older adults based on APOE genotype status. **Methods:** Thirty-nine older adults (M age = 75.6 years (6.8); 14 males and 25 females) were classified using ADNI diagnostic classification criteria: 8 as cognitively intact, 18 as amnestic MCI, and 13 as Alzheimer's disease. They were all administered the RBANS as part of a baseline assessment for a study of biomarkers of Alzheimer's disease. A blood sample was obtained from each participant and APOE genotype was determined by conducting Polymerase Chain Reaction and Fluorescence Monitoring using hybridization probes. The participants were divided into two groups based on their APOE genotype status: no copies of the e4 allele (n=14) or one or more copies of the e4 allele (n=25). Groups were comparable in terms of age, education, sex, estimate of premorbid IQ, and current depressive symptoms. Independent t-tests examined the differences in RBANS index scores (M = 100, SD = 15) between the two e4 alleles groups. **Results:** indicated that although the two groups were comparable in terms of age, education, sex, an estimate of premorbid intellect,

and current depressive symptoms, they showed statistically significant differences on three RBANS Indexes: Immediate Memory Index (t[37]=2.8,p=0.008, d=0.09), Delayed Memory Index (t[37]=4.5,p<0.001, d=1.5), and Total Scale score (t[37]=3.2,p=0.003, d=1.0). For each of these Indexes, those with no copies of the e4 allele had better cognitive scores than those with one or more copies of the e4 allele: Immediate Memory Index (1.15 SD difference, 91.2 vs. 73.9), Delayed Memory Index (2.15 SD difference, 91.9 vs. 59.7), and Total Scale score (1.27 SD difference, 96.1 vs. 77). No differences were observed on the Visuospatial Constructional, Language, or Attention Indexes. **Conclusion:** Although the RBANS is widely used in clinical and research settings, including in individuals with suspected Alzheimer's disease, this is the first study to show how genetic factors, such as APOE, negatively affect performance on this brief battery. Such results have implications for future clinical trials in Alzheimer's disease. For example, low RBANS scores on certain Indexes may indicate increased risk for Alzheimer's disease, which could be used to enrich samples during recruitment. Additionally, if the RBANS is used as a cognitive outcome measure, then it may be important to conduct analyses that consider APOE genotype as a moderator.

P155- THE PREDICTIVE VALIDITY OF THE SKT SHORT COGNITIVE PERFORMANCE TEST FOR THE DETECTION OF EARLY COGNITIVE DECLINE. K. Stemmler[1], B. Hessler[2], H. Bickel[3], H. Lehfeld[4] *((1) University of Erlangen-Nuremberg - Erlangen (Germany), (2) Technical University of Munich (TUM) - Munich (Germany), (3) Technical University of Munich (TUM) - München (Germany), (4) Paracelsus Medical University - Nuremberg (Germany))*

Backgrounds: The assessment of cognitive decline is an important and necessary first step of the diagnostic procedure for the assessment of dementia due to Alzheimer's disease or any other dementia type (McKhann et al., 2011). Next to assessing the degree of cognitive impairment, it is desirable to have measurement tools that are able to predict the cognitive deterioration of an older adult in the future. **Objectives:** A cognitive test with high predictive or criterion-related validity may help to predict the onset of clinical dementia during preclinical and mild cognitive impairment (MCI) stages, which often last several years (Anastasi, 1986). The present study investigated the predictive validity of the SKT short Cognitive Performance Test (SKT = Syndrom-Kurztest), a short test for the detection of early cognitive decline in older persons. The SKT was newly normed in 2015 based on continuous regressions; the testing material was not changed. **Methods:** The cognitive ability was tested with the SKT in a sample of 546 cognitively healthy adults aged 65 to 85 years (Bickel et al, 2006). New cases of MCI or dementia were determined in three follow-up investigations at one-year intervals. In addition, each participant's cognitive status was rated on the Clinical Dementia Rating Scale (CDR). The cognitive status according to the SKT is presented in terms of a traffic light system (green = healthy, yellow = MCI, red = probable dementia). **Results:** Based on Kaplan-Meier estimators, the trajectories of the different SKT traffic light labels were investigated over three years. The trajectories were significantly different, representing differential risks for dementia onset. In comparison to the green group, the hazard ratio (HR) for the development of dementia and MCI amounted to HR 6.63 (95% CI 2.75–15.96) and HR 2.34 (95% CI 1.37–3.99), respectively, in the yellow group, and to HR 25.40 (95% CI 10.73–60.14) and HR 3.83 (95% CI 1.86–7.86), respectively, in the red group. With a green SKT label at baseline, the risk of developing a severe dementia was very low in the first two years of the study and about 5 % at the end of the total study period (3.5 years). The relationship between the SKT traffic light labels at baseline and the cognitive status at follow-up (one year, two years and three years later) was evaluated. For 'cognitive deterioration', the sensitivity for the SKT label yellow or red was 0.93. The sensitivity declined to 0.82 after two years and to 0.80 after three years. The specificity was much lower with 0.48; the PPV was also low. For the endpoint MCI, the sensitivity was 0.92; the specificity for predicting MCI after one year was 0.54. **Conclusions:** The high predictive validity of the SKT (Stemmler, Hessler & Bickel, 2019) may be useful in prospective clinical studies, which are attempting to enroll a sample of older adults at preclinical or MCI stages who are at high risk of developing dementia within the near future. **References:** Anastasi A. Evolving concepts of test validation. Annu Rev Psychol 1986;37(1): 1–16. Bickel H, Mösch E, Seigerschmidt E, Siemen M, Förstl H. Prevalence and persistence of mild cognitive impairment among elderly patients in general hospitals. Dement Geriatr Cogn Disord 2006;21(4): 242–250. Erzigkeit, H. (2001). SKT: Kurztest zur Erfassung von Gedächtnis- und Aufmerksamkeitsstörungen. Manual [SKT: A short cognitive performance test for the assessment of memory and attention deficits]. Erlangen: Geromed. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7(3):263–269. Stemmler, M., Lehfeld, H., & Horn, R. (2015). SKT Manual, 4. erweiterte und überarbeitete Auflage [SKT manual, 4th revised and extended revision]. Erlangen: Geromed. Stemmler, M., Hessler, J. B. & Bickel, H. (2019). Predicting cognitive decline and dementia with the newly-normed SKT Short Cognitive Performance Test. Dement Geriatr Cogn Disord Extra, 9, 184 -193. https://doi.org/10.1159/000497308

P156- THE FREQUENCY OF ORTHOSTATIC HYPOTENSION IN OLDER PATIENTS WITH ALZHEIMER DISEASE IS SIMILAR IN THOSE WITH LEWY BODY DEMENTIA. A.T.I. Isik[1], S.E.K. Kocyigit[1], L.S. Smith[2], A.E.A. Aydin[1], P.S. Soysal[3] *((1) Unit for Aging Brain and Dementia, Department of Geriatric Medicine, Faculty of Medicine, Dokuz Eylul University, Izmir, Turkey - Izmir (Turkey), (2) The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge. - Cambridge (United Kingdom), (3) Unit for Aging Brain and Dementia, Department of Geriatric Medicine, Faculty of Medicine, Dokuz Eylul University, Izmir, Turkey - Istanbul (Turkey))*

Background: Orthostatic hypotension (OH) is reported to be more prevalent particularly in patients with Dementia with Lewy bodies (DLB) because of the autonomic dysfunction, but prevalence of OH is not known in patients with Alzheimer Disease (AD). **Objectives:** The aim of the present study was to determine whether OH can be used to distinguish DLB from AD. Methods: 38 patients with DLB, 88 patients with AD and 521 patients without dementia, underwent Comprehensive Geriatric Assessment. OH were evaluated for the 1st (OH1) and 3rd (OH3) minutes, taking the data in supine position as the

basis, by Head-Up-Tilt Test. **Results:** Prevalence of OH1 was 33%, 43.2% and 18.6% and OH3 was 33%, 44.4% and 18.6% in AD, DLB and no dementia group, respectively. The frequency of OH1 and OH3 was higher in the AD and DLB groups than in the non-demented group ($p<0.001$), but there was no significant difference between DLB and AD in terms of OH ($p>0.05$). The percentage of asymptomatic patients with OH was 87.2% and 89.6% during 1st and 3rd minutes, respectively, and this percentage was similar in three groups ($p>0.05$, for each). There was no significant difference between the two dementia groups in terms of comorbidities, drugs and laboratory values($p>0.05$). **Conclusion:** OH is more prevalent in patients with AD than controls and similar levels are observed in those with DLB. The prevalence of OH equally is greater with DLB or AD disease progression. Clinicians should be aware of OH and its related consequences in the management of the AD in older adults.

P157- NEUROPSYCHOLOGICAL, PSYCHIATRIC, AND FUNCTIONAL CORRELATES OF CLINICAL TRIAL ENROLLMENT. D. Hammers, N. Foster, J. Hoffman, T. Greene, K. Duff *(University of Utah - Salt Lake City (United States))*

Objective: Screen failure rates in Alzheimer's disease (AD) clinical trial research are unsustainable, with participant recruitment being a top barrier to AD research progress. To begin to address potential solutions to the ever-present recruitment shortage, AD-related programs and task forces have focused on patient registries, raising participant awareness, site performance and funding, and reducing barriers to participation. Unfortunately, there is little to no emphasis on reducing screen failure rates based on study inclusion criteria. The purpose of this project was to understand the neuropsychological, psychiatric, and functional features of individuals who failed screening measures for AD trials. **Method:** The current study is a retrospective, cross-sectional analysis of the neuropsychological, psychiatric, and functional predictors of AD clinical trial enrollment. A database in the Division of Cognitive Neurology at a university in the western United States was searched for participants having (1) previously received a clinical diagnostic workup (including dementia-expert cognitive evaluation and diagnostic neuropsychological assessment) at the university's transdisciplinary cognitive specialty clinic and (2) previously screened for a specific industry-sponsored clinical trial of MCI/early AD (Biogen 221AD302, Phase 3 Study of Aducanumab in Early Alzheimer's Disease [EMERGE). Twenty-nine participants (aged 50-85) met the inclusion criteria for this retrospective study, and their previously collected clinical data were analyzed to identify predictors of AD trial screen pass/fail status. **Results:** Of the 29 participants in the current study, 14 participants screen passed this AD clinical trial, and 15 screen failed. Higher screen failure rates were significantly related to female gender, with 77% of female participants screen failing this AD trial versus 31% of male participants. There was no difference in performance on visual memory, or verbal memory tasks between screen pass/fail groups. In contrast, performance differences were observed between screen pass/fail groups on non-memory cognitive domains. Specifically, the screen fail group for this AD clinical trial tended to perform worse on tasks of general fund of knowledge, working memory, executive functioning, phonemic verbal fluency, and the MOCA. Additionally, the screen fail group reported greater levels of anxiety, but not depression. Endorsements on the FAQ were not significantly different between the screen pass/fail groups. **Conclusions:** Our results revealed that worse performance on non-memory neuropsychological domains was related to screen failure status for the EMERGE AD clinical trial. This finding may be explained by the typical recruitment pathway from clinic to trials, which typically involves physicians erroneously viewing more globally-impaired patients with AD as being better fits into clinical trials, resulting in greater recruitment of those patients and subsequently higher screen failure rates for those patients whose disease severity is too advanced for a particular trial. These results consequently suggest that recruiting patients into clinical trials earlier in their disease course, when their disease severity is less, may result in reduced screen failure rates in AD trials. Conversely, we were not able to detect a relationship between memory-related tasks and screen fail/pass status. One explanation may be that the measures used in the EMERGE trial to gauge memory severity are not as sensitive to subtle changes in memory as aged-normed neuropsychological memory measures that approximate a normal distribution of test performances. An alternative explanation may be that memory dysfunction is so common in AD and for patients considered for an AD trial that it is not necessarily surprising that memory performance does not distinguish who will be successfully screened into an AD clinical trial. As such, these results suggest that such memory dysfunction may be necessary but not sufficient to screen pass into an AD clinical trial, and that performances on other non-memory cognitive domains possess higher discriminative value. Our finding related to higher rates of screen failure among female participants seems counter to research suggesting that women tend to worry more about health-related factors and men tend to minimize health-related risks, though this result potentially sheds light on the importance of spousal and care partner involvement in patients with MCI or AD. By identifying predictors of AD trial screen failure that are already available to AD clinical trial teams, we hope to influence decision-making about which participants are most likely to be successfully enrolled in a trial with minimal additional effort required by the AD trial team. Consequently, by building upon these initial findings, this research has potential to reduce screen fail rates in AD clinical trials, which will lower participant burden, maximize study resources, and cut costs. Overall, these findings have the potential to advance the field by helping to enhance trial-recruitment infrastructure and to encourage greater engagement of older adults in AD research.

Theme: BEHAVIORAL DISORDERS AND CLINICAL TRIALS

P158- RELATIONSHIP BETWEEN AWARENESS DISTURBANCE AND BEHAVIOURAL DISORDERS IN ALZHEIMER DISEASE. S. Rossi[1], G.C. Riccitelli[1], N. Parietti[1], P. Tiraboschi[2], C. Defanti[3], L. Sacco[1] *((1) Neurocenter of Southern Switzerland, Neuropsychological Service, Ospedale Regionale di Lugano - Lugano (Switzerland), (2) Fondazione IRCCS Istituto Neurologico Carlo Besta, Unit of Neurology 5 and Neuropathology - Milan (Italy), (3) Centro Alzheimer, Fondazione Europea di Ricerca Biomedica - Bergamo (Italy))*

Background: The inability to perceive impairments and limitations occurring throughout the disease course is one of the core features of Alzheimer's disease (AD). Findings about awareness disorders in dementia are controversial.

Objectives: In this study, we investigated the effect of the awareness domains (global, cognitive, emotional, and functional) on behavioural disturbances in AD patients. **Methods:** The awareness profile was investigated in 60 mild/moderate AD patients using an appropriate interview and questionnaire. Cognitive functioning was assessed using a composite index score. Neuropsychiatric Inventory (NPI), and Geriatric Depression Scale (GDS) were administered to assess psychiatric symptoms, while caregiver stress was investigated using the Caregiver Burden Inventory. Linear models were performed to explore the effects of the awareness domains on behavioural measures. **Results:** From the comparison between AD patients with and without awareness impairment, AD patients with intact awareness had higher depression ($p=0.001$), and anxiety ($p=0.028$), while those with impaired awareness had higher apathy NPI scores ($p=0.001$). Apart from emotional awareness domain, strong correlations between caregiver stress and the other awareness domains were found (p value from <0.001 to 0.018; r-value from=0.313 to 0.809). In AD patients with intact awareness, higher levels of global and emotional domains of awareness were predictive of depression (GDS: $\beta=-0.559$; $R2=0.326$; NPI: $\beta=-0.485$; $R2=0.221$, for both $p<0.001$) and anxiety ($\beta=-0.372$; $R2=0.227$, $p=0.003$) symptoms; whereas for impaired awareness AD patients, lower level of global awareness was predictive of apathy symptom ($\beta=0.511$; $R2=0.328$, $p<0.001$). No association between awareness domains and cognitive impairment was found. **Conclusion:** In AD patients awareness may be differentially related to psycho-affective and behavioural symptoms: such that the intact awareness contributes to explain emotional disturbances; while impaired awareness is associated with behavioural symptoms of apathy. Moreover, the lack of awareness may contribute to the decrease of the quality of relationship between AD patients and caregivers. The assessment of awareness could help in providing the most appropriate intervention in subject with dementia.

P159- SEARCHING FOR THE BEST OUTCOME FOR CLINICAL TRIALS FOR AGITATION SYMPTOMS IN AD: CMAI VS NPI-C. RESULTS FROM THE A3C STUDY.

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Background: There is a lack of available longitudinal data on agitation from observational studies in Alzheimer's Disease (AD) populations to guide treatment development. Although drug development for agitation in AD has seen great advances in recent years, there remain methodological controversies such as the choice of outcome. The 2017 EU-US-CTAD Task Force (TF) on Agitation/Aggression (A+A) highlighted the importance of targeting moderate or larger improvements in clinical trials as key to treatment development for agitation. The TF proposed a clinician rated global measure combining patient- and caregiver-derived information as the primary efficacy outcome. In addition, the TF encouraged the evidence-based development of a single rating scale tailored to the International Psychogeriatric Association (IPA) "Provisional Diagnostic Criteria for Agitation in Cognitive Disorders" using existing datasets, pulling from items of existing scales such as NPI-C and CMAI. This presentation follows up the 2017 TF work by reporting on initial findings of the A3C study, an excellent setting to study the longitudinal course of A/A and to assess the utility of existing scales. A partner presentation will showcase the Delphi process used for the creation of the scale tailored to the IPA criteria including item selection and validation in A3C. **Objectives:** The primary aim of the A3C study was to assess the relationship between severity of agitation rated on validated scales (NPI (Neuropsychiatric Inventory), NPI-clinician rating (NPI-C) agitation/aggression (A+A) and Cohen Mansfield Agitation Inventory (CMAI)) and clinical ratings of agitation over time on the modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC). A secondary aim was to estimate minimal clinically important differences (MCID) over time on the scales by comparing them to big improvements on the global rating. **Methods:** A3C is a prospective, longitudinal, multicenter, cohort study implemented at 8 memory clinics and associated nursing homes (NH) in France. Participants lived at home or in a NH. We included AD patients at all stages of disease severity with clinically significant agitation defined by the presence of an NPI domain score ≥ 4 and frequency score ≥ 2 on at least one of the following: A+A, disinhibition, aberrant motor behavior and/or irritability. The agitation syndrome also met IPA «Provisional Diagnostic Criteria for Agitation." Clinical visits occurred at baseline, monthly during the first 3 months of follow-up, and at 6, 9 and 12 months after entry. Socio-demographics, psychotropic medication use, non-pharmacological approaches, adverse outcomes, resource utilization, quality of life, cognitive status and disability were assessed over the course of the study. **Results:** A3C included 262 AD patients; 86 (33%) dropped out over follow-up. At baseline, mean age was 82 years (range 25-75% = 75.2-89.6 years), and 61% were women (n=159). 70% lived at home. The mean entry MMSE was 10.8 (range 25-75% = 3.1-18.6). Mean entry CMAI score was 62 (range 25-75% = 46-78) and NPI-C A+A severity score was 16 (range 25-75% = 5-18). Moderate to marked severity agitation was evident in 181 (69%) at baseline. According to the IPA agitation definition, more than 70% showed an excessive motor activity (n = 197, 76%) and/or a verbal aggression (n = 197, 76%) while 115 patients (44%) displayed physical aggression. In the current analyses, mADCS-CGIC was the gold standard with moderate or greater improvement as the target. Results of the following analysis will be presented: (1) estimates of concurrent validity by assessing variation over time in NPIC-A+A or CMAI versus mADCS-CGIC, including calculating the MCID for NPIC-A+A and CMAI vs. the mADCS-CGIC; (2) comparisons of predictive validity for NPIC-A+A or CMAI versus measures of cognitive decline (MMSE) and physical disability (Katz ADL scale). The results of these analyses will answer if the two most used validated outcome measures in trials for treating agitation in AD today are "good" outcomes or if otherwise the field needs to move into developing another measure. **Conclusion:** Little is known about the natural course of clinically significant agitation symptoms in AD nor the variability of different outcome measures over time, such as the NPI or CMAI, or the definition of a clinically meaningful improvement in these scales. This is even more evident for new scales such as the NPI-C rating. The A3C study may provide useful data in order to optimize future clinical trials of treatments for agitation symptoms in AD.

P160- MEASURING APATHY IN ALZHEIMER'S DISEASE IN THE APATHY IN DEMENTIA METHYLPHENIDATE TRIAL 2 (ADMET 2): A COMPARISON OF INSTRUMENTS. K. Lanctot[1], R. Scherer[2], A. Li[3], M. Saleem[3], D. Vieira[3], P. Rosenberg[2], N. Herrmann[4], A. Lerner[5], P. Padala[6], O. Brawman-Mintzer[7], C. Van Dyck[8], A. Porsteinsson[9], S. Craft[10], A. Levey[11], W. Burke[12], J. Mintzer1[3] *((1) Sunnybrook Research Institute - Toronto (Canada), (2) Johns Hopkins University - Baltimore (United States), (3) Sunnybrook Resesarch Institute - Toronto (Canada), (4) Sunnybrook Health Sciences Centre - Toronto (Canada), (5) Case Western Reserve University - Beachwood (United States), (6) University of Arkanas for Medical Sciences - Little Rock (United States), (7) Medical University of South Carolina - Charleston (United States), (8) Yale University - New Haven (United States), (9) University of Rochester - Rochester (United States), (10) Wake Forest School of Medicine - Winston-Salem (United States), (11) Emory University - Atlanta (United States), (12) Banner Alzheimer's Institute - Phoenix (United States), (13) Roper St. Francis Healthcare - Charleston (United States))*

Background: Apathy is the most common neuropsychiatric symptom in Alzheimer's disease (AD), affecting 70% of patients, and yet it is often under-recognized and underdiagnosed. A wide variety of assessment scales have been developed to assess apathy; however, none have been determined as a "gold standard". While diagnostic criteria for apathy (DCA) in AD have been published, these have yet to be taken up by clinical trials. The Apathy in Dementia Methylphenidate Trial 2 (ADMET 2) has operationalized the criteria into a clinician-rated questionnaire informed by interviews with the patient and caregiver. **Objective:** The present study aims to determine the agreement between the DCA and other measures of apathy used in ADMET 2 – the Neuropsychiatric Inventory, apathy subscale (NPI-apathy) and the Dementia Apathy Interview and Rating (DAIR). **Methods:** ADMET 2 is a randomized, double-blind, placebo-controlled phase III trial examining the effects of 20mg/day methylphenidate treatment on symptoms of apathy in patients with mild to moderate AD over 6 months. Participants scoring at least 4 on the NPI-Apathy subscale were recruited. This interim analysis focuses on cross-sectional data obtained from participants at baseline. Comparisons between the DCA, NPI-Apathy and DAIR were done using t-tests or Fisher's exact tests. **Results:** Of 128 participants in this analysis, the median age was 78 years (25th percentile = 70.5 years, 75th percentile = 80.2 years) and they were predominantly white (93.8%), non-Hispanic, and male (67.2%). All participants had at least high school level of education, and most (82.8%) were married. The mean score on the NPI-apathy subscale was 7.5±2.4, and the mean score on the DAIR was 1.9±0.5. Of the 128 participants with clinically significant apathy on the NPI (apathy score >3), 118 (92.9%) met DCA diagnostic criteria. The DAIR identified 121 (94.5%) participants with clinically significant apathy, of whom 112 (88.2%) met DCA diagnostic criteria. There were no differences between those who were apathetic and non-apathetic by the DCA in terms of demographics. The mean NPI score in those who were apathetic on the DCA was 7.5±2.4, and mean NPI score in those that were non-apathetic on the DCA was 6.0±2.8 (t=-1.9, p = 0.060). There were no significant differences in DAIR scores between the two groups (1.9±0.5 vs. 1.7±0.5, t=-0.94, p=0.347). **Conclusion:** The DCA was highly concordant with other apathy measurements in the detection of apathy in patients with AD. The NPI-apathy subscale cut-off used to determine apathy in ADMET 2 selects those likely to meet DCA criteria.

P161- BEHAVIORAL SYMPTOMS IN ALZHEIMER'S DISEASE: RESULTS OF CHOLINERGIC LOADING THERAPIES WITH A CHOLINESTERASE INHIBITOR AND THE CHOLINERGIC PRECURSOR CHOLINE ALPHOSCERATE. A. Carotenuto[1,2], A. Fasanaro[2], V. Manzo[2], E. Traini[3], F. Amenta[3] *((1) Clinical Research, Telemedicine and Telepharmacy Centre, University of Camerino, - Camerino (Italy), (2) Neurology Unit, National Hospital, "A. Cardarelli" - Naples (Italy), (3) Clinical Research, Telemedicine and Telepharmacy Centre, University of Camerino - Camerino (Italy))*

Background: Behavioral and psychological symptoms of dementia (BPSD) are a group of psychological reactions, psychiatric symptoms, and behaviors commonly found in Alzheimer's disease (AD). BPSD are gathered into four groups: mood disorders (depression, anxiety, and apathy), psychotic symptoms (delusions and hallucinations), aberrant motor behaviors (pacing, wandering, and other purposeless behaviors), and inappropriate behaviors (agitation, disinhibition, and euphoria). Most of them can be related to brain acetylcholine deficiency. **Objectives:** This study has evaluated if a higher cholinergic challenge obtained by associating the cholinesterase inhibitor donepezil and the cholinergic precursor choline alphoscerate has a favorable effect on BPSD. **Methods:** Analysis was made on 113 mild/moderate AD patients included in the double-blind randomized trial ASCOMALVA. The Neuropsychiatric Inventory (NPI) was used for assessing incidence and severity of BPSD and patients were observed for 36 months. Two matched groups of patients were compared: group A treated with donepezil (10mg/day) plus choline alphoscerate (1,200mg/day), and group B treated with donepezil (10mg/day) plus placebo. **Results:** Data of NPI revealed a significant decrease of BPSD severity and distress of the caregiver in patients of the group A compared with those of the group B. Analysis of the functions explored revealed a different response to the NPI. Mood disorders (depression, anxiety and apathy), which represent approximately the half of the NPI scores were the area most beneficially influenced in patients of the group A. The response to pharmacological treatment was different depending on the parameters considered, although the association donepezil plus choline alphoscerate resulted in a significant decrease in the severity and frequency of several BPSD compared with treatment with donepezil alone. **Conclusions:** The above results collectively suggest that treatment with donepezil plus choline alphoscerate induces a decrease of behavioral disturbances more pronounced than in subjects treated with donepezil monotherapy. This suggests that the cholinergic association tested may have a positive influence on BPSD in AD.

P162- EMPIRICALLY-DEFINED NEUROPSYCHIATRIC SYNDROMES OF DEMENTIA. L.S. Schneider[1], A.Y. Bespalov[2,3], H.J. Moebius[3], T.L. Galankin[2] *((1) Keck School of Medicine of USC - Los Angeles, California (United States), (2) Valdman Institute of Pharmacology, Pavlov First Saint Petersburg State Medical University - St. Petersburg (Russian Federation), (3) Exciva UG - Heidelberg (Germany))*

Background: Behavioral and psychological symptoms of dementia (BPSD) are poorly characterized and clinically diverse. Syndromes or groupings of symptoms are sometimes used to characterize BPSD; but these groupings are often done ad hoc, defined by consensus committees, and without validation. They may be modelled on psychiatric syndromes observed in non-cognitively impaired adults. Most commonly, the frequency and severity of one prominent symptom, typically agitation, delusions, or depression, is used to characterize and define patients with BPSD and to determine their eligibility for clinical trials. Counterintuitively, this may result in substantial and broadly heterogeneous groups, e.g., a patients identified with agitation, may or may not have delusions, depression, or anxiety, or other combinations. Under these circumstances it is challenging to select patients for clinical studies without creating participant samples with heterogeneous and uncertain behavior characteristics and course. There is a need to better describe and validate BPSD than by ad hoc or consensus-based selecting. **Objectives:** The primary aim of this study is to characterize dimensions of disruptive symptoms or neuropsychiatric symptoms in older people with cognitive impairment in order to identify clinically valid and relevant syndromes or groupings. **Methods:** Using the population-based Aging, Demographics, and Memory Study (ADAMS) Wave A that consists of 856 subjects aged 71 and older, we focused on associations between the 10 behavior/symptom domains of the Neuropsychiatric Inventory (NPI): delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, and aberrant motor behaviors. A total of 823 (96.1%) of 856 subjects had NPI data and were included. Prior to analyses we conducted a series of simulation experiments with different degrees of complexity. K-means cluster analysis outperformed principal component and factor analyses in the ability to correctly detect the simulated associations of symptoms. Cluster analysis is a straightforward method to detect and describe associations of symptoms that are clinically meaningful, and allows easily interpretable graphical presentations of the results. The optimal number of clusters for the ADAMS NPI data was determined manually using visualizations of 2 - 20 clustering solutions. The number of clusters was chosen that provided distinct patterns before increasing the clusters in the analysis resulted in some being "torn apart" into several clusters that contained identical or nearly identical patterns. Since K-means clustering is an iterative algorithm, the optimal number of clusters had to provide a stable and reproducible result. The resulting clusters were further analyzed to extract the most prevalent symptom associations that they contained. We used graphs to visualize the outcomes in the form of combinations of clinically significant NPI symptoms within each cluster, simplifying the output, and preserving the most important information. **Results:** A total of 507 (61.6%) of 823 subjects with NPI data did not have an NPI score > 0 on any domain; 316 (38.4%) subjects had at least 1 NPI domain score > 0 and were included in the analyses. The largest cluster of those that had a domain score > 0 (165 of 823, 20.0%) identified subjects with no clinically significant elevation, i.e., ≥ 4, on any NPI domain score, leaving 18.4% who had at least one clinically elevated domain score. Six clusters were characterized by greater than 80% of subjects showing clinical significance in only one domain: apathy was the largest with 3.8% of the 823 subjects, aberrant motor behavior, agitation, depression, anxiety and delusions ranged from 1.6% to 2.2%. Three smaller clusters contained subjects with 2 clinically elevated domains in over 80% of the subjects: irritability and agitation, anxiety and apathy (half with agitation, irritability, and/or aberrant motor behavior), and apathy and depression (half with anxiety). There was one small cluster of predominant hallucinations, about half with accompanying delusions, agitation, and/or irritability. Two yet smaller poly-symptomatic clusters contained 3 elevated domains: agitation, disinhibition and aberrant motor behavior; and depression, apathy, and irritability (both clusters were associated with delusions in about half). The most common clinically elevated symptoms/domains occurring at > 80% in any cluster included apathy (4) depression (3), irritability (2), and agitation (2). **Conclusions:** We identified several key clinical clusters of neuropsychiatric symptoms, the largest of which consisted of no symptoms or symptoms below clinical threshold. The majority of the clusters are mood-related, including most clusters in which agitation is prevalent. Delusions tend to distinguish between some mood-related clusters. Defining BPSD on the basis of only clinically significant agitation would create a heterogeneous group associated with disparate symptoms, and also strongly associated with depression, irritability, and anxiety. Similarly, using clinically significant agitation as the main eligibility criterion for a BPSD clinical trial may make it challenging to see a therapeutic effect because of the resulting marked clinical heterogeneity of the study population. Selecting or stratifying study participants with BPSD based on clinically-relevant clusters may allow for clearer determinations of effectiveness in clinical trials.

P163- REIMAGINE-AD: SAFETY AND EFFICACY OF VAFIDEMSTAT FOR THE TREATMENT OF ALZHEIMER'S DISEASE RELATED AGGRESSION. M. Ropacki[1], M. Boada[2], S. Gutierrez[1], R. Bullock[1], C. Buesa[1] *((1) Oryzon Genomics SA - Cornella De Llobregat (Spain), (2) Fundació ACE. Barcelona Alzheimer Treatment and Research Center, UIC-Barcelona - Barcelona (Spain))*

Introduction: Agitation and aggression affect approximately 50% of Alzheimer's disease (AD) patients and are the reason number one to institutionalize these patients. To date, the treatments used for agitation and aggression have generally had small effect sizes and undesirable side effects, including sedation and increased death rates. Therefore this remains an important area of unmet need that requires both a better understanding of the causes and therapeutic interventions to match. Vafidemstat is a small molecule, highly brain penetrant dual LSD1/MAO-B inhibitor that modifies transcription in the brain and has a host of epigenetic effects, including increasing neuroplasticity and decreasing neuroinflammation. Preclinical work has shown that vafidemstat restores memory, decreases neuroinflammation, eliminates aggressiveness and restores sociability in rodent models. In the Alzheimer's SAMP8 mice, vafidemstat reverses strong aggressive behavior and corrects the abnormal response to stress of immediate early genes (IEGs) like c-Fos in the prefrontal cortex of these animals. On the basis of the epigenetic findings, vafidemstat has been successfully

studied in a basket trial, REIMAGINE (EudraCT No. 2018-002140-88), across a number of neurologic and psychiatric conditions including borderline personality disorder, autistic spectrum disorder and adult attention deficit hyperactivity disorder. REIMAGINE is an open-label, Phase IIa trial exploring the safety and efficacy of vafidemstat as a treatment for aggression across these conditions and is now moving in to neurodegenerative disorders. Data to date support the finding that vafidemstat is a novel, non-sedating potential treatment option for aggression and is ideally suited for conditions including AD-related aggression. **Objectives:** The primary objective of REIMAGINE-AD (EudraCT No. 2019-001436-54) is to explore the efficacy of vafidemstat in the treatment of AD-related aggression. The secondary objectives of this study are to investigate other changes in behaviour, cognition and caregiver burden, along with the further evaluation of the safety and tolerability of vafidemstat in more advanced AD patients. **Methods:** REIMAGINE-AD is an open-label, single-centre Phase IIa study (Fundació ACE, Barcelona). It is 13-weeks duration (1-week screening period, 8-week treatment period and 4-week follow-up period). It is planned to include 12 AD patients with significant or persistent agitation or aggression. Vafidemstat treatment will be administered in addition to standard of care (acetylcholinesterase inhibitors or memantine). Participants should be on stable AD treatment for at least two months prior to screening and remain so throughout the study. Patient inclusion criteria includes diagnosis of probable AD, with a MMSE score at screening ≤20 and a significant or persistent agitation or aggression that was disruptive to patient's daily living or put the patient in harm´s way for at least 3 days in the last 7 days prior to screening visit and that represents a change from the patient's usual behaviour. Primary endpoints include change from baseline to week 8 and over time in the Neuropsychiatric Inventory (NPI) 4-item Agitation/Aggression subscale (NPI-4 A/A); in the Cohen-Mansfield Agitation inventory (CMAI) and in the Clinical Global Impression (CGI) scale focused on aggression. Secondary endpoints include change from baseline to week 8 in the NPI, Zarit Burden Interview (ZBI) and MMSE, and several safety parameters such as adverse drug reactions (ADRs), physical examination, vital signs, ECG and clinical laboratory parameters. **Results:** The study is recruiting and will be completed in time to present full data on the REIMAGINE-AD cohort at CTAD. **Conclusions:** The REIMAGINE concept of using a basket study to investigate aggression across diverse conditions is new to CNS and has already produced successful and interesting data, both in terms of efficacy and safety. We have reported previously that vafidemstat reduces aggression in patients with borderline personality disorder and ADHD, and we expect to present data in patients with autistic spectrum disorder soon. In terms of tolerability and participant acceptance the drug has also shown a remarkable profile. Focussing now on aggression in AD, vafidemstat offers a unique therapy option, which is not sedating and in over 200 participants who have been treated with vafidemstat in Phase I and II trials so far has proved both safe and very well-tolerated. This profile suggests vafidemstat is particularly suited to further exploration in this vulnerable group of AD patients, who remain currently underserved with good treatment options.

P164- SEX DIFFERENCES IN SUBJECTIVE AGE-ASSOCIATED CHANGES IN SLEEP: A PROSPECTIVE ELDERLY COHORT STUDY. S.W. Suh *(Kangdong Sacred Heart Hospital, Hallym University College of Medicine - Seoul (Korea, Republic of))*

Backgrounds: Subjective age-associated changes in sleep (AACS) and its difference between sexes have never been prospectively investigated within elderly populations. **Objectives:** To investigate the difference of the AACS over 6 years between men and women aged 60 years or older. **Methods:** We followed 1,412 community-dwelling individuals aged 60 years or older who participated in the Korean Longitudinal Study on Cognitive Aging and Dementia every 2 years during 6 years of follow-up. Sleep parameters including sleep duration, midsleep time, latency, efficiency, daytime dysfunction, and overall quality were measured using the Pittsburgh Sleep Quality Index at baseline and at each follow-up waves. The effect of time and sex on subjective sleep parameters was analyzed by the repeated-measures linear mixed model. **Results:** During the 6 years of follow-up, we observed that, for every 2 years, sleep duration shortened (estimate [SE]; -7.82 [1.32], $p < .001$), midsleep time advanced (-11.06 [2.52], $p < .001$), daytime dysfunction worsened (.01 [.01], $p = .003$), and sleep quality worsened (.04 [.01], $p < .001$). Only sleep latency showed the sex difference in AACS with increasing latency found for women (1.07 [1.02], $p < .001$) but not for men (1.01 [1.02], $p = .622$). **Conclusion:** For elderly, age-associated changes in subjectively reported sleep parameters do occur in sleep duration, midsleep time, daytime dysfunction, and sleep quality, while increase in sleep latency can only be found in women. Researchers should be cautious in determining whether sleep disturbances are present or not when designing clinical trials of this population.

Theme: HEALTH ECONOMICS AND CLINICAL TRIALS

P165- THE EFFECTS OF PHYSICAL, INTELLECTUAL, SOCIAL AND HEALTHY DIET ACTIVITIES TO THE INSTRUMENTAL ACTIVITIES OF DAILY LIVING AND CAREGIVER BURDEN OF THE PATIENTS WITH MINOR OR MAJOR NEUROCOGNITIVE DISORDERS. B.D. Ku[1,2], Y.S. Park[1], J.Y. Kim[1], H.G. Park[3], Y.J. Kim[3], J.H. Seo[3] *((1) Department of Neurology, International St. Mary's Hospital, - Incheon (Korea, Republic of), (2) (Catholic Kwandong University College of Medicine - Incjeon (Korea, Republic of), (3) Catholic Kwandong University College of Medicine - Incheon (Korea, Republic of))*

Background: The life style activities such as exercise, intellectual challenge, social engagement and healthy diet can affect the instrumental activities of daily living (IADL) and caregiver burden in the patients with dementia. We evaluate the effects of physical, intellectual, social and healthy diet to the IADL and caregiver burden of the patients with minor and major neurocognitive disorder. **Methods:** We performed diagnostic evaluation to the referred patients who are suspecting mild cognitive impairment (MCI) or dementia by the initial screening tests in the regional public health care center in Incheon, South Korea from March 2016 to April 2019. All patients completed a structured medical and neurological

evaluation, neuropsychological tests, computed tomography and laboratory evaluations including Seoul IADL and caregiver administrative neuropsychiatric inventory (CGA-NPI). The physical exercise, intellectual challenge, social engagement and diet profiles of the patients were calculated by the weighted aggravated formula methods. The low or high weighted numbers (from one to three) were given according to the level of difficulties in each activity. The total caregiver burden score are calculated by the sum of the caregiver burden score in twelve neuropsychiatric inventory items. **Results:** One hundred and twenty six patients with minor or major neurocognitive disorder were recruited: MCI (n=48, 38.1%), vascular cognitive impairment (n=5, 4.0%), Alzheimer's disease (n=53, 42.1%) and vascular dementia (n=20, 15.9%). The mean duration of disease, Korean version of the mini-mental status examination, clinical dementia rating (CDR) are 4.6±4.2 years, 16±7.7 and 1.2±1.0 respectively. The physical exercise activities were associated with Seoul IADL (r=-0.49, p=0.40), CDR (r=-0.47, p=0.048). The intellectual challenge activities were associated with body weight (r=0.55 p=0.017) and folate level (r=0.840, p<0.001). The social engagement activities were associated with focal neurological sign (r=0.52, p=0.028). The healthy diet activities were associated with euphoria or happiness item of neuropsychiatry inventory. The caregiver burden scores were associated with physical exercise (r=-0.31, p=0.03), age (r=0.274, p=0.002), Seoul IADL (r=0.501, p<0.01), the total score of CGA-NPI (r=0.932, p<0.001), K-MMSE score (r=-0.49, p=0.038), CDR (r=0.57, p=0.014), depressive symptoms (r=0.53, p=0.022) and decreased body weight (r=-0.67, p=0.002) of the patients. The estimated caregiver burden score model is -1.35+0.53K-MMSE+0.81Seoul IADL+0.507total score of CGA-NPI. The estimated IADL score is 22.4-0.71exercise activities score (r2=0.422, p<0.001). **Conclusion:** In our study the caregiver burden was associated with decreased cognition, physical activities IADL and increased behavioral and psychological symptoms of dementia. The depressive symptoms and decreased body weight of the patients were also the cause of the caregiver burden. The healthy life styles are associated various cognitive and neurological profiles. Among the healthy life styles the most important factor to affect the IADL was exercises activities. The estimated caregiver burden score model may be useful to interfere of the caregiver burden of individual patient with minor or major neurocognitive disorder.

Theme: EPIDEMIOLOGY AND CLINICAL TRIALS

P166- TUMOR NECROSIS FACTOR BLOCKING AGENTS REDUCE RISK FOR ALZHEIMER'S DISEASE IN PATIENTS WITH CO-MORBID RHEUMATOID ARTHRITIS AND PSORIASIS.

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Background: A case-control analysis of insured adults in the USA reported increased risk for Alzheimer's disease (AD) in patients with rheumatoid arthritis (RA) consistent with the hypothesis that systemic inflammation may influence chronic inflammation in the brain and thereby contribute to risk for AD (Chou et al. 2016 CNS Drugs 30:1111). Etanercept, a TNF blocking agent prescribed for the treatment of RA, was reported to reduce the risk for AD (Adjusted Odds Ratio (AOR) 0.30; 95% Confidence Interval (CI) 0.08-0.89. P-value = 0.02). AD is underrepresented in US private insurance databases as most patients with AD are older than 65, an age in the US when patients transition from employer-provided, private insurance to Medicare, a national health insurance program. We, therefore, undertook a retrospective study of the de-identified, electronic health records (EHRs) of nearly 56 million unique patients with age 18 years and older from 26 healthcare systems across all 50 states in the US. **Objectives:** To assess if treatment with a TNF blocking agent (etanercept, adalimumab, and infliximab) or methotrexate reduces the risk for AD in patients with RA or other inflammatory diseases. **Design:** We performed a large-scale, retrospective, case-control study of de-identified, population-level EHRs using the IBM Watson Health Explorys database. Data are de-identified in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and normalized using the clinical ontologies from United Medical Language System. Disease diagnoses, clinical findings, and procedures are normalized based on the systematized nomenclature of medicine – clinical terms (SNOMED-CT); pharmacological drug classes and individual drug names are normalized based on RxNorm. For HIPAA-compliance, Explorys reports cohort counts over 10 to the nearest 10 and does not report cohort counts less than 10. **Main Outcomes and Measures:** The analysis selected for patients with a diagnosis of RA, psoriasis, or other inflammatory diseases involving TNF. The analysis compared the diagnosis of AD as an outcome measure in patients receiving at least one prescription for one of the three TNF blocking agents or for methotrexate. Results are presented as the AOR and 95% CI for co-morbid AD in patients with inflammatory disease and older than 65 years. The Cochran-Mantel-Haenszel method was used to adjust the Odds Ratio using two gender subgroups (female and male), and two race subgroups (Caucasian and non-Caucasian). **Results:** RA increased the risk for AD (AOR = 2.06, 95% CI: (2.02-2.10), P-value <0.0001) in patients ≥ 18 years. Increased risk for AD also was found in patients ≥ 18 years with psoriasis (AOR = 1.37, 95% CI: (1.31-1.42), P-value <0.0001), ankylosing spondylitis (AOR = 1.57, 95% CI: (1.39-1.77), P-value <0.0001), inflammatory bowel disease (AOR = 2.46, 95% CI: (2.33-2.59)), P-value <0.0001), ulcerative colitis (AOR = 1.82, 95% CI: (1.74-1.91), P-value <0.0001), and Crohn's disease (AOR = 2.33 95% CI: (2.22-2.43), P-value <0.0001). The risk for AD in patients over 65 years with RA was reduced by treatment with etanercept (AOR = 0.34, 95% CI: (0.25-0.47), P-value <0.0001), adalimumab (AOR = 0.28, 95% CI: (0.19-0.39), P-value <0.0001), infliximab (AOR = 0.52, 95% CI: (0.39-0.69), P-value <0.0001) or methotrexate (AOR = 0.64, 95% CI: (0.61-0.68), P-value <0.0001). Etanercept and adalimumab also reduced risk for AD in patients over 65 years with psoriasis. There was limited effect of gender or race. Comparing the reduction in risk to the population risk for AD, and also adjusting for the potential confounds of gender and race, treatment with adalimumab reduced the risk for AD in patients with psoriasis older than 65 years below the population risk (AOR = 0.47, 95% CI: (0.23,0.82), P-value = 0.014) as did etanercept (AOR = 0.58, 95% CI: (0.37,0.90), P-value = 0.019). **Strengths and Limitations:** The strength of the current study is that large-scale EHRs allow us to perform hypothesis-driven studies using the full spectrum of disease diagnoses and drug prescription history across the massive volume of a real-world patient population including patients with private insurance or Medicare. A limitation of the study is that de-identification of patient-level data does not allow an analysis of the exposure-

response relationship for the reduction in risk due to use of a TNF blocking agent as patients receiving a single prescription for a TNF blocking agent are grouped with patients who may have been treated for many years. Since Explorys aggregates EHRs from nearly 56 million patients 18 years and older, this source of bias may underestimate the true treatment effect of a TNF blocking agent. **Conclusions and Relevance:** This new study indicates that TNF blocking agents reduce the risk for AD in patients with RA and other inflammatory diseases with etanercept and adalimumab having the greatest benefit. Our analysis indicates that risk for AD due to systemic inflammation is reduced by treatment with a TNF blocking drug.

P167- ANTIVIRAL THERAPY REDUCES THE RISK OF DEMENTIA IN PATIENTS WITH HERPES ZOSTER: A PROPENSITY SCORE-MATCHED ANALYSIS. W. Yoon[1], S. Bae[1], S.C. Yun[2], M.C. Kim[3], S.O. Lee[1], S.H. Choi[1], Y.S. Kim[1], J.H. Woo[1], S.Y. Kim[1], S.H. Kim[1] *((1) Asan Medical Center - Seoul (Korea, Republic of), (2) Asan Medical Center - Seoul (Korea, Republic of) - Seoul (Korea, Republic of), (3) Chung-Ang University Hospital - Seoul (Korea, Republic of))*

Background: Antiviral treatment for herpes zoster (HZ) is recommended to reduce the duration and severity of symptom and prevent complications including postherpetic neuralgia. Recently, there have been growing epidemiologic data that HZ infections may be associated with dementia. **Objectives:** We investigated whether HZ was associated with the subsequent dementia in a nationwide population-based (dynamic) cohort, and further evaluated whether antiviral therapy in patients with HZ might reduce the risk of dementia. **Methods:** The South Korea has a universal, single government-payer health coverage system in which the National Health Insurance (NHI) covers approximately 98% of the national population. We analyzed the National Health Insurance Service-National Sample Cohort (NHIS-NSC) database established by the National Health Insurance Service (NHIS) in the South Korea, which is a representative, population-based cohort proportionally stratified by age, sex, and income levels. It comprises 2.2% (n=1,025,340) of the total eligible Korean population in 2002 (n=47,851,928). New events of HZ and dementia were identified using the International classification of Diseases, 10th edition (ICD-10) based codes from the reimbursement claim data. Dementia subjects were further limited to only those who were prescribed with anti-dementia drugs for more than 90 days, as well as the diagnostic codes for dementias. We excluded patients with past histories of herpes zoster and dementia from January 1 to December 31 in 2002. For the propensity score-matched analysis, each HZ patient receiving antiviral therapy was 1:1 matched with an untreated HZ patient having the same propensity score in the relevant year. **Results:** A total of 229,594 individuals of ≥ 50 years were identified and followed up for 11 years until 2013. The incidence of the first-diagnosed HZ cases was 16.69 per 1000 person-years (n=34,505), and that of the first-diagnosed dementia was 4.67 per 1000 person-years(n=10,482). The risk for dementia was higher in patients who had previous HZ episodes than in those who had never experienced HZ (incidence rate ratio 1.74; 95% CI 1.64-1.84 and adjusted hazard ratio [HR] 1.12; 95% CI 1.05-1.19). Of the 34,505 patients who were diagnosed as the first-ever HZ, 84% (n=28,873) received antiviral treatment and 16% (n=5,632) did not. The crude incidence rates of the subsequent dementia were 7.79 per 100 person-years for treated groups and 12.27 per 1000 person-years for untreated groups, giving incidence rate ratio of 0.63 (95% CI, 0.56-0.72) and the covariate-adjusted HR of 0.79 (95% CI, 0.69-0.90). The HZ patients who received antiviral therapy had a significantly lower risk of dementia than those who did not; HR after propensity score-matching were 0.77 (95% CI, 0.64-0.91). The effect of antiviral therapy on reduction of the subsequent dementia decreased according to age (HR 0.46 in 50- to 60-year-olds, 0.58 in 60- to 70-year-olds, and 0.81 in those > 70 years old). **Conclusion:** HZ infection is associated with the following first-diagnosed dementia event. The use of antiviral agents in patients with HZ reduces the incidence of the subsequent dementia by a third. Impact of antiviral treatment on reduction of the risk of dementia appears to be higher in relatively younger patients.

P168- EFFECTIVENESS OF THE OPEN SCREENING PROGRAMS IN RECRUITING SUBJECTS TO PRODROMAL AND MILD ALZHEIMER'S DISEASE CLINICAL TRIALS. D. Wójcik[1,2], K. Szczechowiak[1], M. Zboch[1] *((1) Wroclaw Alzheimer's Center - Wroclaw (Poland), (2) Division of Quality Services, Procedures and Medical Standards, Medical University in Lodz, Lodz, Poland - Lodz (Poland))*

Backgrounds: Due to worldwide elderly population growth and lifespan extension, the number of patients with dementia, most often caused by Alzheimer disease (AD), will probably increase exponentially. The 2015 World Alzheimer Report estimates that the number of people with dementia worldwide (46.8 million) will almost double every 20 years. Moreover, persons with mild cognitive impairment (MCI) belong to the group of the high risk of developing dementia or AD when compared with similarly aged individuals in the general population. Therefore, creating screening programs for the elderly including early diagnosis of MCI and dementia, are highly recommended. There is a pressing demand for testing new treatments and interventions which can slow or halt the progression of AD, and increase the pool of potential participants. The National Institute of Aging (NIA) counted more than 150 open studies calling for more than 70,000 patients which could require screening of more than 700,000 potential participants. Moreover, following the data, a combination of restrictive inclusion and exclusion criteria determine a small proportion of AD patients who are eligible for trials, 27% of patients from the research and 10-13% from the clinical settings. Due to the challenges faced by Alzheimer's disease research to enroll the specified number of participants and the problems with slow recruitment to AD clinical trials, it is noteworthy that open-access screening programs could be an effective method to improve AD trial recruitment. It is especially valuable in recruiting prodromal AD patients who would probably not have come to the doctor or to the memory clinic otherwise. **Objectives:** There is a lack of scientific data comparing the success and cost-effectiveness of trial recruiting strategies. Therefore, the main goal of this paper is to present our results and experiences in recruiting participants to prodromal and mild AD clinical trials from an open-access screening program conducted in 2018 and 2019 for 18 months in Wroclaw Alzheimer's Center. **Methods:** In this report, we will focus on the open-access screening program conducted in Wroclaw Alzheimer's Center for 18 months (2018-2019) as a valuable trial recruitment strategy. The program was implemented to increase awareness in the local society of early diagnosis of cognitive disorders and memory problems, and to improve

the prevention of cognitive decline and dementia. The interest in screening tests of individuals with memory problems was gained due to the advertising campaign and appearance in the local media (newspapers, television, and radio), as well as on the internet. We invited individuals age 50 or older who have memory complaints to cognitive screening tests which were free for participants. The screening procedure includes combined tests administration by experienced neuropsychologist: Mini-Mental State Examination (MMSE) and Auditory-Verbal Learning Test (AVLT). The clinical evaluation was based on test scores, patient interview, and the health questionnaire - self-reported health information such as age, family history, medical history, and medication information. It is noteworthy that the applied screening procedure as a part of the evaluation for dementia and cognitive impairment was quickly administered and relatively cheap – approximately 30 USD per individual. **Results:** The total number of subjects examined in the open screening program (2018-2019) in Wroclaw Alzheimer's Center was 730 (N=730). Due to our research, the detection rate in the screened population was 0,7% for severe dementia, 4,1% for moderate dementia, 18,6% for mild dementia, and 28,9% for MCI. We investigated the proportion of people with MCI and dementia who were eligible for clinical trials. The number of individuals with mild dementia and MCI screened in prodromal and mild AD clinical trials was 248 (34% of all individuals). Furthermore, 63 from 730 (8,6%) patients were randomized in clinical trials, which includes 4,9% MCI and 3,7% mild dementia cases screened in our program, with 74,6% screen failure rate. Moreover, 19,9% of patients with mild dementia, and 17,1 % of individuals with MCI diagnosed in our program were randomized in prodromal and mild AD clinical trials. **Conclusion:** Summarizing, open-access screening programs can improve detection of MCI and dementia in society, help to distinguish demented from non-demented elderly, and improve recruitment of prodromal AD patients who would probably not have come to the memory clinic otherwise. Our findings may help elucidate the role and importance of the screening process in detecting cognitive impairment in the elderly as an effective and relatively cheap recruitment method in AD clinical trials. There is an urgent need for research focusing on the cost-effectiveness, applicability, and barriers of different recruitment strategies. It is noteworthy that the improvement of clinical trial recruitment strategies, including open screening programs can result in more rapid drug development.

P169- TRANSITION OF PRESCRIPTION PATTERN OF ANTIDEPRESSANTS IN PARKINSON'S DISEASE AND DEMENTIA PATIENTS; 2012-2015, SOUTH KOREA. Y. Park *(Koshin university Gospel hospital - Busan (Korea, Republic of))*

Background: It is well known that patients with neurologic disorders are vulnerable to depression and it affects not only quality of lives of patients, but also suicidality risk and medical costs. Therefore, appropriate management of depression should be emphasized. The paradigm of pharmacotherapy in depression had transited from the monoamine oxidase inhibitors(MAOIs) and the tricyclic acids(TCAs) to the selective serotonin receptor inhibitors(SSRIs) in 1990s, due to efficacy and side effects. However, south Korea government policy prohibited neurologist to prescribe SSRIs more than 2 months until January 2017. As a result, TCAs and MAOIs had been more commonly used than SSRIs in clinical practice. Fortunately, the prohibition was withdrawn in January 2017. We performed this study to analyze the pattern of prescribing pattern of Antidepressants in dementia and parkinson's disease and contribute the establishment of future government policy. **Objectives:** The aim of this study is to contribute to future health policy formulation and education by analyzing and predicting prescription patterns of antidepressants in neurological patients. **Method:** Using National Health Insurance service database, patients diagnosed with dementia and parkinson's disease from 2012 to 2015 were selected. Among those patients, the annual number of patients with antidepressant prescription for more than 2 weeks during 2 months was obtained. The data was temporally analyzed for the class of medication, department which prescribed antidepressants and anti-anxiolytics. **Result:** During 2012-2015, the number of patients with dementia and parkinson's disease was 1,714,776 and 363,347 each. Amongst dementia patients, 10.0% (171,925) were prescribed antidepressants. Amongst parkinson's disease patient, 11.4%(41,504) were prescribed antidepressants. In dementia patients, most frequently used antidepressant was SSRIs. However TCAs still occupied large proportion. In parkinson's disease patients, the most frequently used antidepressants class in 2012 was TCAs. SSRIs became the most frequently used antidepressants in 2013, and the proportion of TCAs had been decreased continuously. **Conclusion:** In this study, we found the transition in pharmacotherapy of depression in clinical practice. TCAs still occupied a large proportion. However, the proportion of TCA use is steadily decreasing, replaced by new antidepressants. As the prohibition relieved, this change will become more notable. This change will improve treatment of patients with epilepsy and ultimately the quality of their lives. Therefore, we insist the education and support is needed to encourage this change for providing ideal medical services to patients with neurologic diseases.

P170- RISK OF STROKE IN PATIENTS WITH ALZHEIMER'S DISEASE. J.H. Lee *(National Health Insurance Service Ilsan Hospital - Goyang-Si (Korea, Republic of))*

Background and objective: The relationship between dementia and stroke has been significant attention because planning future needs for health services and improved primary and secondary prevention of stroke are important. We evaluated the relationship between AD and the subsequent development of stroke within 11 year follow-up. **Methods:** This retrospective, nationwide, longitudinal study used National Health Insurance Service –Senior cohort (NHIS-Senior) 2002-2013, which was released by the KNHIS in 2016, comprising 550,000 random subjects who were selected from over than 60 years old. The study included a cohort of 3,524 patients who were first diagnoses as AD between 2003 and 2005. To match each dementia patient, 19,013 control subjects were selected from the data-base. **Results:** We enrolled 4,790 patients for analysis in this cohort and the prevalence of AD was higher in female(19.29%) than in male(17.71%). A higher prevalence of AD was observed in the 70-84 year age group and in the higher income status group. A total of 6,102 strokes occurred within the observation interval. AD was associated with risk of all strokes and Cox regression analysis showed that the HR of all stroke was 2.87 times greater for patients with AD (95% CI 2.707-3.042) than for control group after adjusting for other risk factors. **Conclusion:** Our findings suggest that Alzheimer's disease may be independent risk factor for all strokes, hemorrhagic stroke

and ischemic stroke. So we need to control and pay attention to cerebrovascular events also in patients with AD.

P171- POTENTIALLY INAPPROPRIATE MEDICATION OF PSYCHOTROPIC DRUGS AMONG ELDERLY PEOPLE WITH DEMENTIA. R. Morales-Delgado, R. Salinas-Martinez, D. Gamez-Treviño, E. Jimenez-Alarcon, A. De La Garza-Villarreal, D. Aguilar-Macias *(Geriatrics Unit Hospital Universitario «Dr Jose Eleuterio González» UANL - Monterrey N.l. (Mexico))*

Background: People with dementia have a higher frecuency of psychotropic drug prescriptions compared with people without dementia. Those with dementia have a higher risk of adverse effects of any kind of medication especially psychotropic drugs. Antipsychotics and other types of psychotropic drugs are used to treat related symptoms of dementia and are associated to serious adverse effects like stroke. **Objective:** Assessment of potentially inappropriate medication (PIM) using STOPP criteria for psychotropic drugs among people with dementia in the outpatient clinic, to optimize the PIM of these drugs in our clinic. **Methods:** Retrospective and cross-sectional study based on a longitudinal data base from june 2018 to april 2019. Dementia was defined using DSM V criteria for any kind of dementia, were included 60 years old and older, whose prescription drugs included at least one psychotropic drug with an adequate attachment and no dose modification for the last three months. Exclusion criteria included: hospitals admissions, institutionalized patients and those in palliative care. For the statistical analysis: quantitative descriptive statistics with measures of central tendency and measures of dispersion were used. Mann Student's T and Whitney's U were used for the continuous variables. The prevalence of PIM was determined according to each STOPP criterion by presenting absolute and relative frequencies (percentages). **Results:** 162 patients were included with a PIM prevalence of 43.2% (n=70, IC 95% 35.5-50.9) based on STOPP criteria. It was found an inadequate prescription (n=21, 13%) for the subsection B "central nervous system and psychotropic drugs", of wich 1.9% were for the long-term use of neuroleptics in parkinsonism and the prescription of Selective serotonin reuptake inhibitors (SSRIs) for patients with history of significant hyponatremia (5.6% IC 95% 2.0 – 9.1). The most prevalent (n=37 22.8%) STOPP criterion was for the prescription of drugs on negative impact for those patients at higher risk of falling: neuroleptics were the most frecuent drug (n=21, 13% IC 95% 7.7-18.2), followed by benzodiazepines drugs (N=10, 6.2% IC 95% 2.4 – 9.9). **Conclusion:** Based on this study performed in people with Dementia, it was observed that PIM of psychotropic drugs in these patients are prevalent in our population of the outpatient clinic. We found no association between risk factors and PIM. Observing this high prevalence in our population makes us raise the need to be more cautious and aware of the prescription of these drugs and to take measures to improve it.

Theme: ANIMAL MODEL AND CLINICAL TRIAL

P172- NEURONAL PENTRAXIN 2: BIOMARKER AND MECHANISM ACROSS THE AGING/ALZHEIMER'S SPECTRUM. M. Gallagher, A. Branch, R.P. Haberman *(Johns Hopkins University - Baltimore (United States))*

Background: Neuronal Pentraxin 2 (NPTX2) has emerged as a biomarker in Alzheimer's disease (AD) with lower NPTX2 prognostic for greater medial temporal lobe (MTL) atrophy and memory decline in the dementia phase of illness (Swanson et al. 2016). A significant role for NPTX2 is further supported by a strong correlation between NPTX2 and cognitive status across the spectrum of aging and AD (Xiao et al. 2017). Notably Xiao et al. (2017) included evidence for a preservation of NPTX2 in well-characterized autopsy samples of asymptomatic AD, in which AD pathology exists with relative clinical/cognitive preservation. Thus, reduced NPTX2 may represent an additional hit alongside the amyloid and tau pathology of AD to drive disease progression. As a signaling molecule, NPTX2 is critical for circuit and network function by connecting principle neurons in the hippocampus and cortex with fast spiking (PV) interneurons to regulate excitability. Loss of homeostatic control with reduced NPTX2 contributes to neural overactivity in affected circuits. A condition of neural hyperactivity exists in the MTL/hippocampus in aging and most prominently in early phases of AD. Here we examined the status of NPTX2 in relation to age-related cognitive decline but in the absence of AD pathology to assess the possibility that lowered NPTX2 might contribute to risk of aging itself for late onset AD. **Objective:** We assessed the relationship of NPTX2 in the MTL with individual differences in neurocognitive aging in a well-characterized study population of biologically diverse outbred Long-Evans rats. **Methods:** Aged Long Evans rats are characterized for impaired or intact (unimpaired) spatial memory performance on a standardized behavioral protocol that depends upon the function of the medial temporal lobe memory system. This model first revealed the existence of localized hyperactive circuits within the hippocampal formation in memory-impaired aged rats that was not observed in aged cohorts with preserved memory. Both the localization of overactivity and therapeutic efficacy of targeting it in this preclinical model has translated in clinical studies of humans with age-related memory impairment and patients with amnestic MCI, in the latter case serving as a background to the ongoing clinical development of AGB101 (NCT03486938). Here NPTX2 mRNA is assessed in the hippocampus and entorhinal cortex using in situ hybridization, a technique that enables sensitive, quantitative measurements with high anatomic specificity. Since NPTX2 gene expression is responsive to neural activity, NPTX2 levels were evaluated both at baseline (homecage) and after induction of neural activity using a method validated to robustly increase gene markers of neural activity. **Results:** In the CA3 and dentate gyrus subfields of the hippocampus, regions that exhibit localized hyperactivation by fMRI in clinical studies of aging and aMCI, NPTX2 levels are reduced in memory impaired aged rats relative to their unimpaired aged counterparts. Furthermore, NPTX2 levels significantly correlate with memory performance such that lower levels of NPTX2 are associated with poorer memory performance. In groups of aged rats in the neural activation

protocol a remarkable subregional pattern was observed in the entorhinal cortex. Notably, the lateral division of the entorhinal cortex (LEC) showed a several fold-greater NPTX2 increase than the medial entorhinal cortex (MEC), a pattern we previously observed under this activation protocol in young adult rats (unpublished data). An additional notable finding was observed in a comparison of memory-impaired aged rats treated with AGB101 (low dose levetiracetam minipumps) alongside behaviorally-matched aged controls (vehicle alone minipumps) in that drug treatment significantly augmented expression of NPTX2 under homecage and activated protocols, including a significant increase in the LEC. **Conclusions:** The current findings confirm that NPTX2 in aging is associated with cognitive status in the absence of AD pathology. Notably, an increase in NPTX2 produced by low dose levetiracetam administration may contribute to the reduction of neural overactivity and cognitive improvement previously reported with this aged rat model of memory impairment (Koh et al. 2010; Haberman et al. 2017). While demonstrating an association between NPTX2 and cognition, independent of AD pathology, it should also be noted that experimentally reducing NPTX2 greatly augments pathological and deleterious effects in AD mouse models (Xiao et al. 2017). Thus, augmenting NPTX2 could have beneficial effects in the context of emerging AD pathology in early disease. Several additional findings here are noteworthy in the context of human neurocognitive aging and AD. Human clinical studies have pointed to a relative vulnerability of LEC in neurocognitive aging and recent research has indicated that neural activity drives the spread of tau/tangle pathology. The localization of tau/tangle pathology in aging (Braak Stage 1) is relatively confined to LEC (transentorhinal region). The pronounced activation of NPTX2 in the LEC points to a robust recruitment of homeostatic control of excitability that may play a role in limiting the neural activity causing a spread of pathology in the anatomical progression of Braak staging.

P173- ISOGENIC IPSC MODEL OF CHRFAM7A EFFECT ON A7 NICOTINIC ACETYLCHOLINE RECEPTOR FOR PRECLINICAL HIGH THROUGHPUT SCREEN. I. Ihnatovych[1], B. Birkaya[1], D. Indurthi[1], R. Gnanasambandam[1], A. Ouf[1], N. Sule[2], L. Chaves[1], A. Auerbach[1], K. Szigeti[1] *((1) SUNY at Buffalo - Buffalo (United States), (2) Roswell Park Comprehensive Cancer Center - Buffalo (United States))*

Backgrounds: The $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChR) has been a promising target for diseases affecting cognition and higher cortical functions, however the effect observed in animal models failed to translate into human clinical trials identifying a translational gap. CHRFAM7A is a human specific fusion gene between CHRNA7 and FAM7A/ULK1, and as it is not present in any other species the CHRFAM7A effect was not accounted for in preclinical studies. We hypothesized that CHRFAM7A may account for this translational gap and understanding its function may offer novel approaches to explore $\alpha 7$ nAChR as a drug target in a genotype specific manner. Human relevant models are needed and iPSC is a novel strategy. **Objectives:** To establish and validate a human relevant model using iPSC and genome editing strategy. **Methods:** We previously described the generation of the null iPSC line harboring two ancestral alleles and no CHRFAM7A. We genome edited the null background to insert the direct (UB068i_KI) and inverted (UB068i_KIΔ2bp) CHRFAM7A into the AAVS1 safe harbor site of the constitutively expressed gene PPP1R12C on chr19 (position 19q13.42) using TALEN mediated gene editing. We utilized the vector system from GeneCopoeia (Cat. No.: DC-DON-SH01 - AAVS1 donor vector). The expression vector harbors puromycin resistance gene for selection and fluorescent signal (GFP) for visualization in downstream experiments. CHRFAM7A cDNA was amplified from pcDNA3.1-CHRFAM7A (Addgene 62284) and CHRFAM7ADelta2bp (Addgene 62515), respectively and inserted into the AAVS1 donor vector. In the presence of a homologous knock-in donor, homologous recombination (HR) occurs, leading to integration of the DNA fragments in the donor into the safe harbor AAVS1 site. Insertion at this site has been shown to be safe with no phenotypic effect, and the remaining open conformation of DNA facilitates expression of the transgene (GeneCopoeia (Cat. No.: DC-DON-SH01 - AAVS1 donor vector). **Results:** Individual colonies are picked under visual inspection guided by GFP expression. Breakpoint PCR is performed to screen for the insertion. Three independent positive single colonies are propagated. Breakpoint specific TaqMan assay and RT-qPCR confirmed copy number and expression of the inserted gene. iPSCs characterization according the industry standards included morphological assessment and live staining with the TRA-1–60 Alexa Fluor 488 Conjugate Kit (Life Technologies). Gene and protein expression for pluripotency/self-renewal and the three germ layer markers at gene and protein levels was assessed by reverse transcription–quantitative polymerase chain reaction (RT–qPCR) and immunocytochemistry (ICC). Whole genome sequencing of the parent and isogenic lines is performed to screen for aneuploidy, de novo copy number variation, missense and nonsense mutations. No aneuploidy was detected. Limited number of de novo mutations between parent and isogenic lines are reviewed for potential interference. Lineage preference of each clone is assessed by the TaqMan hPSC Scorecard Assay (Thermo Fisher Scientific). Disease relevant phenotyping includes amyloid beta uptake (neurodegeneration in AD) and single channel patch clamp (cognition and schizophrenia) of the $\alpha 7$ nAChR is performed. Direct CHRFAM7A carrier isogenic line showed mitigated Abeta uptake compared to parent line. CHRFAM7A decreases channel open probability. Inverted CHRFAM7A carrier isogenic line behaved as a null allele. **Conclusions:** CHRFAM7A modulates $\alpha 7$ nAChR phenotype in disease relevant readouts. High throughput screening of small molecules in this model of CHRFAM7A in the human context could lead to novel treatment strategies.

P174- PHARMACOLOGICAL PROFILES OF ANTI-AMYLOID B AGGREGATE-SPECIFIC ANTIBODY KHK6640 BOTH IN VITRO AND IN VIVO INCLUDING A NOVEL CLINICALLY RELEVANT RODENT MODEL OF ALZHEIMER'S DISEASE. S. Uchida , K. Yamada, T. Horita, N. Suzuki, Y. Suzuki, K. Sugiyama *(Kyowa Kirin Co., Ltd. - Shizuoka (Japan))*

Background: KHK6640 is a novel humanized anti-amyloid β (Aβ) aggregate-specific IgG4-based monoclonal antibody. Three phase 1 studies (SAD/MAD using iv infusions up to 20 mg/kg KHK6640) have been conducted in Caucasian and Japanese patients with prodromal and mild to moderate Alzheimer's disease (AD). KHK6640 exhibited good safety/tolerability and linear PK profiles. In addition, dose-related increases in Aβ aggregates bound to KHK6640 in the cerebrospinal fluid

(CSF) provided evidence of target engagement. **Objectives**: Pharmacological profiles of KHK6640 were investigated using in vitro and in vivo studies including a novel clinically relevant rodent model of AD. **Methods:** Two in vitro studies were conducted. A Dot blot analysis to evaluate the binding specificity of KHK6640 to human Aβ aggregates (i.e., oligomers and fibrils) and Aβ monomers, and a neutralization study to evaluate KHK6640 neutralization of Aβ1-42 oligomers in primary cultures of neuronal cells obtained from the cortex of fetal Wistar rats. The viability of the cells were measured using alamarBlue. To assess in vivo effects of KHK6640 on cognitive impairment induced by Aβ, synthetic Aβ1-42 oligomers were administered into both sides of cerebral ventricles in mice on Day 0. KHK6640 was administered intravenously (iv) on Day 1. The spontaneous alternation test and object recognition test (ORT) were performed on Days 4-7. We also evaluated the chronic effects of KHK6640 in two transgenic (Tg) mouse models of AD (APP and APP/PS2 mouse), where the murine parent antibody of KHK6640 (6E4) was used to avoid immunogenicity. 6E4 was repeatedly administered once a week to each Tg mouse for about 3 months. The spontaneous alternation test and the ORT was performed at 3-5 days after the last 6E4 treatment. To further investigate therapeutic benefit of KHK6640 against naturally occurring pathogenic Aβ oligomers in AD patients, the cerebrospinal fluid (CSF) from an AD patient (AD CSF) or CSF from cognitively normal subject (normal CSF) was injected intracerebroventricularly (icv) in normal mice or rats (WO2015159963A1). KHK6640 was administered iv one day before each CSF injection. The spontaneous alternation test was performed after the CSF injection. To evaluate the effect of KHK6640 on impairment of synaptic plasticity induced by AD CSF, the long term potentiation (LTP) in the field excitatory postsynaptic potential (fEPSP) was induced in the hippocampal CA1 region of anesthetized rats by high frequency stimulation (HFS) in Schaffer collateral. AD CSF or normal CSF was injected icv at 30 min before the HFS. KHK6640 was administered iv one day before CSF injection. **Results:** In the dot blot assay, KHK6640 was shown to selectively bind to human Aβ aggregates (i.e., oligomers and fibrils), but not to Aβ monomers. In addition, KHK6640 could bind broad range of Aβ aggregates. Results from the cell-based in vitro study demonstrated the neutralizing effects of KHK6640 against neurotoxicity induced by human Aβ1-42 oligomers. In vivo study of Aβ injected mouse model, KHK6640 (0.5 and 1 mg/kg) significantly ameliorated Aβ1-42 oligomers-induced cognitive impairment in the spontaneous alternation test and the ORT in mice. In another in vivo study in Tg mouse model, 6E4 (the mouse parent antibody of KHK6640, 1-10 mg/kg) significantly reversed the cognitive impairment in the spontaneous alternation test and the ORT in both APP and APP×PS2 mice. Microhemorrhage was not observed after chronic administration of 6E4 in both Tg mouse models. To evaluate the effect of KHK6640 using a more clinically relevant model, a novel rodent models using AD CSF was developed. Centrally administered AD CSFs, but not normal CSFs, induced cognitive impairment in mice and rats. KHK6640 (3 mg/kg) significantly improved AD CSF-induced cognitive impairment in mice. In rats, KHK6640 (10 mg/kg) significantly improved AD CSF-induced cognitive impairment, and significantly prevented AD CSF-induced LTP impairment. In normal CSF treated group, HFS produced sustained potentiation of fEPSP slope. **Conclusions:** There is controversy about which form of Aβ is responsible for AD pathogenesis; many of the synthetic, cell culture, and Tg animal-derived AD forms seem quite different from what has been observed in humans. Recently, however, research progress in the AD field support that AD pathogenesis is associated with soluble toxic Aβ oligomers and not with insoluble Aβ species. KHK6640 exhibited a binding profile selectively for Aβ aggregates (i.e. oligomers and fibrils). Accordingly, KHK6640 neutralized in vitro neurotoxicity induced by human Aβ1-42 oligomers. In vivo studies demonstrated that KHK6640 (or 6E4) ameliorated cognitive impairment in both synthetic Aβ-injected and Tg mouse models of AD. Importantly, chronic administration of the antibody did not reveal histological microhemorrhage. Moreover, KHK6640 significantly improved the cognitive impairment and hippocampal LTP impairment induced by AD CSF, which presumably does not contain insoluble Aβ. Taken together, KHK6640, with its unique and tolerable pharmacologic profile selectively targets pathogenic Aβ oligomers and may provide a novel treatment option for AD, with minimized risk of Aβ-related imaging abnormalities (ARIA).

P175- THE BUENA STUDY: A PHASE 2A CLINICAL TRIAL TO TEST SAFETY AND EFFICACY OF MONTELUKAST VERSAFILM™ IN ALZHEIMER'S PATIENTS. L. Aigner[1], J. Michael[1], J. Conway[2], F. Pietrantonio[2], H. Zerbe[2], N. Paiement[2]
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Leukotrienes are mediating a number of pathological hallmarks of Alzheimer's Disease (AD) such as neuroinflammation, blood-brain-barrier disruption, and reduced neurogenesis. Leukotriene receptors are therefore recognized as potential drug targets in AD. In animal models of AD, we demonstrate that inhibition of leukotriene signaling using the approved anti-asthmatic drug montelukast is reducing AD pathology and improving cognitive functions. We have developed a novel formulation of montelukast, i.e. a buccal mucoadhesive film of montelukast, that has improved bioavailability compared to the standard montelukast tablet and has demonstrated a CNS pharmakokinetic profile suggesting a pharmacological active concentration. Here, we present i) our results from the preclinical experiments, and ii) the design of a phase 2A clinical trial testing safety and efficacy of this novel montelukast formulation, i.e. Montelukast-VersafilmTM(IntelGenx), in patients with mild to moderate AD (NCT03402503). The primary study objective isto evaluate whether 26 weeks of treatment with 10 mg montelukast administered once a day is safe as well as superior to placebo, assessed at week 26 using the global Neuropsychological Test Battery (NTB) composite score. This composite score is based on an equally weighted average of standardized change from baseline scores on the ISLT, ISLT-Delay, One Back Test, One Card Learning Test, Verbal Fluency Test, Category Fluency Test, Identification Test and Detection Test. Given the inherent attributes of Montelukast VersaFilmTM, this might be a novel effective therapeutic and treatment modality as part of the armamentarium against AD.

P176- MECHANISMS OF INTERFERENCE BY ALZHEIMER'S DISEASE SYMPTOMATIC TREATMENTS WITH TAU AGGREGATION INHIBITOR ACTIVITY IN A TAU-TRANSGENIC MOUSE MODEL. G. Riedel[1], J. Klein[2], G. Niewiadomska[3], C.R. Harrington[1,4], C.M. Wischik[1,4] *((1) University of Aberdeen - Aberdeen (United Kingdom), (2) Goethe University Frankfurt - Frankfurt Am Main (Germany), (3) Nencki Institute - Warsaw (Poland), (4) TauRx Therapeutics Ltd - Aberdeen (United Kingdom))*

Background: Given the widespread use of currently available symptomatic treatments for Alzeimer's disease (AD) (acetylcholinesterase inhibitors (AChEIs) and/or memantine), it is commonly assumed new AD treatments need to work as add-on therapy in order to be viable clinically. In recently completed Phase 3 trials testing the tau aggregation inhibitor leuco-methylthioninium bis(hydromethanesulfonate (hydromethylthionine, LMTM), we found that significant treatment effects on clinical decline and brain atrophy were dependent on plasma concentration of the drug, and that these were seen whether LMTM was given alone or as add-on to symptomatic treatments. However, compared to patients receiving LMTM as monothertherapy, the treatment effects were reduced by about half in patients receiving LMTM as add-on to symptomatic treatments. This suggests that symptomatic treatments attenuate, but do not eliminate entirely, responses to LMTM. **Objectives:** We used a well characterised tau transgenic mouse model (Line 1, L1) expressing the aggregating core tau domain of the AD PHF (residues 296-390) to determine whether the treatment effects of LMTM are attenuated by concomitant symptomatic treatments. **Methods:** L1 and wild-type NMRI mice (n = 7-16 for each group) were pre-treated with rivastigmine (0.1 or 0.5 mg/kg/day) or memantine (2 or 20 mg/kg/day) or vehicle for 5 weeks by gavage. For the following 6 weeks, LMTM (5 and 15 mg/kg) or vehicle were added to this daily treatment regime, also by gavage. Animals were tested behaviourly during weeks 10 and 11 using a problem solving task in the open field water maze and then sacrificed for immunohistochemical and other tissue analyses. For measurement of acetylcholine (ACh) levels in hippocampus, animals (wild-type or L1) were treated with LMTM (5 mg/kg/day for 2 weeks) by oral gavage after prior treatment for 2 weeks with or without rivastigmine (0.5 mg/kg/day) administered subcutaneously using an Alzet minipump. Levels of ACh were measured in hippocampus using an implanted microdialysis probe and HPLC analysis of the extracellular fluid. For measurement of glutamate release from whole brain synaptosomal preparations, animals were treated for 4 weeks by oral gavage with either vehicle or LMTM (15 mg/kg/day). Glutamate release from potassium-spiked synaptosomal preparations was measured using an enzyme-linked spectrofluorimetric assay. **Results:** In the tau transgenic mice, LMTM given alone significantly increased hippocampal acetylcholine (ACh) levels, increased glutamate release from brain synaptosomal preparations, increased synaptophysin levels in multiple brain regions, increased brain mitochondrial complex IV activity, reduced tau pathology, restored choline acetyltransferase (ChAT) immunoreactivity in basal forebrain and reversed deficits in spatial learning. Chronic pretreatment with rivastigmine was found to reduce or eliminate almost all these effects, apart from reduction in tau aggregation pathology and restoration of ChAT immunoreactivity in basal forebrain. LMTM effects on hippocampal ACh and synaptophysin levels were also reduced in wild-type mice by pretreatment with rivastigmine. Likewise, preliminary data available for memantine pretreatment shows similar elimination of effects of LMTM on spatial learning deficits (neurobiological studies are still ongoing). **Conclusion:** The interference with LMTM treatment effects by symptomatic drugs can be reproduced in a tau transgenic mouse model. Pretreatment with an AChEI alters a broad range of brain responses to LMTM across different transmitter systems and cellular compartments at multiple levels of brain function. There is therefore no single locus for the negative interaction. Rather, the chronic neuronal activation induced by symptomatic treatments produces compensatory homeostatic downregulation in multiple neuronal systems. This has the effect of reducing a broad range of treatment responses to LMTM that result from reduction in tau aggregation pathology when LMTM is given as an add-on. Since the interference is dictated by homeostatic responses to prior symptomatic treatment, it is likely that there would be similar interference with other drugs tested as add-on to ongoing symptomatic treatment, regardless of the intended therapeutic target or mode of action. These results imply that only very large treatment effects are likely to be detected in clinical trials in which new drugs are tested as add-on to existing symptomatic drugs and that this may help explain the failure seen in many trials to date.

P177- LOW DOSE BRAIN IRRADIATION REDUCES AMYLOID B AND TAU IN 3X-TG MICE. J. Fontanesi[1], T.G. Wilson[1], A. Hanna[1], D.B. Michael[1], P. Chinnaiyan[1], M.M. Madden[1], A.A. Martinez[2], G.D. Wilson[3] *((1) Beaumont Health Systems - Royal Oak (United States), (2) Michigan Healthcare partners - Madison Heights (United States), (3) Beaumont Heal Sysytems - Royal Oak (United States)*

Background: We have previously reported that low doses of external beam ionizing irradiation reduced the number and size of amyloid beta (Aβ) plaques and improved cognition in a standard double transgenic AD mouse model expressing a chimeric mouse/human amyloid precursor protein and a mutant human presenilin 1. **Objective:** To determine if low dose hemi brain radiation would impact amyloid plaque number/volume and Tau in a triple transgenic model. **Methods:** We investigated an age-matched series (16 months old) of B6;129-Tg(APPSwe,tauP301L)1Lfa Psen1tm1Mpm/Mmjax (3xTg-AD) mice which were hemi-brain irradiated with 5 fractions of 2 Gy using an image-guided small animal radiation research platform. Mice were sacrificed 8 weeks after the end of treatment and Aβ and tau were assessed using immunohistochemistry and quantified using image analysis. **Results:** Hemi-brain irradiation significantly ($p=0.028$) reduced Aβ plaques in the 3xTg-AD mice regardless of location (cortex or hippocampus) the reduction in plaque number and burden on the irradiated side of the brain is clearly visible. The number of plaques in the irradiated side of the brain averaged 23.6±5.2 whilst it was 40.2±8.9 on the unirradiated side. Hemi-brain irradiation also reduced neurofibrillary tangles by an average of 20% on the irradiated side of the brain ($p=0.0024$). When the data for each individual animal was pooled and compared for the irradiated and non-irradiated side of the brain, there was a significant correlation between tau and Aβ plaques. This suggests a consistent effect of irradiation irrespective of the tau and plaque burden. **Conclusions:** We have previously shown that low total doses of radiation reduce Aβ plaques and improve

cognition in B6.Cg-Tg (APPswePSEN1dE9)85Dbo/J (005864) mice . This preliminary study provides evidence that similar low total doses of radiation can not only reduce Aβ plaques but also reduce tau-associated NFTs in the triple transgenic 3xTg-AD mouse model. In the time-scale of the experiment, the effect on Aβ plaques was more dramatic than the effect on tau but the reduction in both was highly correlated. We plan to conduct further studies to confirm these exciting results and also to evaluate other unique radiation targeted delivery systems.

Theme: NEW THERAPIES AND CLINICAL TRIALS

P178- A 12-WEEK PHYSICAL EXERCISE INTERVENTION TO PREVENT COGNITIVE DECLINE AND DISABILITY IN KOREAN AT-RISK ELDERLY PEOPLE: A PILOT STUDY. S.M. Lee[1], H.S. Song[2], M. Cho[3], H.M. Kwon[1], H. Jeon[4], D.E. Seo[4], S. Choi[5], S.Y. Moon[1] *((1) Department of Neurology, Ajou University School of Medicine - Suwon (Korea, Republic of), (2) Department of Sports Sciences, Korea Institute of Sports Science - Seoul (Korea, Republic of), (3) College of Physical Education and Sports Science, Kookmin University - Seoul (Korea, Republic of), (4) Department of Psychology, Ajou University - Suwon (Korea, Republic of), (5) Department of Neurology, Inha University College of Medicine - Incheon (Korea, Republic of))*

Objectives: This is a pilot study to investigate feasibility of a 12-week physical exercise intervention (12WPEI) to prevent cognitive decline and disability in Korean at-risk elderly people. **Methods:** 26 participants (68.2 ± 3.9 years, 84.6% female), at-risk of dementia and disability, were enrolled from a community health center:. institutional 12WPEI (15 participants, 3 visits/week, 50-mintute/visit) and home-based 12WPEI (11 participants, 1 visit and 2 self-exercise at home/week, 50-minute/session) as preference. The visit session was performed as a group with 4-13 individuals and consisted of muscle strength training, aerobic exercise, postural balance and stretching using elastic bands and floor plate. The primary outcome was retention and adherence rates. Retention rate was represented by proportion of participants who completed final session among enrolled participants. Adherence rate was determined by participants' mean ratio of participated sessions to total sessions. Secondary outcomes were safety and changes of physical fitness and cognitive function after 12WPEI, which were analyzed by paired t-tests. **Results:** Total retention and adherence rates were 84.6% and 77.7%, respectively. For the institutional 12WPEI group, retention and adherence rates were 86.7% and 88.3%. Those for home-based 12WPEI group were 81.8% and 62.3%. No significant adverse effects were reported. Both physical fitness and cognitive function were significantly improved: 30-seconds sit-stand test (19.9±3.6 vs 23.5±3.7, $p<0.001$), 2-minutes stationary march (107.4±13.9 vs 120.7±16.7, $p<0.001$) and ADAS-cog (10.7±4.2 vs 8.8±4.1, $p=0.007$). **Conclusions:** This study suggests that our 12WPEI program could be feasible, safe and helpful for the at-risk elderly with lower extremity muscular and cardiopulmonary endurance as well as cognition. **Disclosure:** This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI18C0479)

P179- BAN2401 IN EARLY ALZHEIMER'S DISEASE: A PLACEBO-CONTROLLED, DOUBLE-BLIND, PARALLEL-GROUP, 18-MONTH STUDY WITH AN OPEN-LABEL EXTENSION PHASE TO CONFIRM SAFETY AND EFFICACY (CLARITY AD). S.Y. Lynch[1], M. Irizarry[1], S. Dhadda[1], Y. Zhang[1], J. Wang[1], T. Bogoslovsky[1], L. Reyderman[1], J. Kaplow[1], H. Bradley[1], M. Rabe[1], K. Totsuka[2], L.D. Kramer[1], H. Hampel[1], C.J. Swanson[1] *((1) Eisai Inc - Woodcliff Lake (United States), (2) Eisai Co., Ltd - Tokyo (Japan))*

Background: BAN2401 is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds to large soluble Aβ aggregate species, while demonstrating low affinity for Aβ monomer. Although BAN2401 does interact with Aβ monomers and Aβ fibrils, it demonstrates at least 1000-fold selectivity for protofibrils over Aβ monomers and approximately 10- to 15-fold higher selectivity for protofibrils over fibrils. A large, 18-month phase 2 proof of concept study (BAN2401-G000-201; NCT01767311) using Bayesian adaptive design was recently conducted in 856 patients with early Alzheimer's disease (AD); mild cognitive impairment (MCI) due to AD or mild AD dementia. Although the threshold for the primary Bayesian analysis at 12 months was not met, results from pre-specified 18-month frequentist analyses indicated that BAN2401 treatment produced consistent and clinically meaningful reduction in clinical decline and brain amyloid burden in patients with early AD at the highest dose (10 mg/kg biweekly). These reductions were accompanied by effects on CSF biomarkers of neurodegeneration. Based on the encouraging results from the phase 2 study, a phase 3 study (BAN2401-G000-301 [CLARITY AD], NCT03887455) was designed to confirm the efficacy and safety of BAN2401 in patients with early AD. **Objective:** To describe the study design for the ongoing CLARITY AD study. **Methods:** CLARITY AD is an 18-month treatment (core study), multicenter, double-blind, placebo-controlled, parallel-group study with open-label extension in patients with early AD. Eligibility criteria include age 50 to 90 years old, MCI due to AD with intermediate likelihood or mild AD dementia with amyloid pathology confirmed by amyloid positron emission tomography (PET) or CSF assessment of t-tau/Aβ(1-42) ratio. Patients are required to 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 (subscale) II (WMS-IV LMII). A total of 1566 patients will be randomized in the core study across 2 treatment groups (placebo and BAN2401 10 mg/kg, biweekly) according to a fixed 1:1 (placebo: BAN2401) schedule. Randomization will be stratified according to clinical subgroup (MCI due to AD or mild AD dementia); presence or absence of ongoing approved AD treatment (eg, acetylcholinesterase inhibitors, memantine, or both); ApoE4 status (ie, carriers or non-carriers); and geographical region. Treatment in the core study will be for 18 months. During the core study, patients will have the option to participate in one or more of the three optional sub-studies that evaluate longitudinal changes in brain amyloid burden, brain tau pathology, and CSF biomarkers of neurodegeneration. At the end of the core study, patients who qualify may participate in the open-label extension phase for up to 2 years. The primary efficacy endpoint in the core study is change in CDR-SB from baseline at 18 months. Key secondary endpoints include change from baseline at 18 months in amyloid PET standardized uptake value ratio (in patients participating in the sub-study), ADCOMS, and ADAS-Cog14.

Safety will be monitored throughout the study by the sponsor and by an independent data safety monitoring committee. The open-label extension phase will evaluate the long-term safety and tolerability of BAN2401 10 mg/kg biweekly in patients with early AD and whether the long-term effects of BAN2401 (as measured on clinical outcome measures and biomarkers) at the end of the core study is maintained over time in the extension phase. **Conclusion:** Building on the positive findings from the BAN2401 phase 2 study, the phase 3 CLARITY AD study is designed to confirm clinical efficacy and safety of BAN2401 versus placebo in patients with early AD. Enrollment is ongoing.

P180- MASUPIRDINE (SUVN-502), IN COMBINATION WITH DONEPEZIL AND MEMANTINE IN MODERATE ALZHEIMER'S DISEASE - EFFECT OF AD DURATION SINCE DIAGNOSIS ON EFFICACY ENDPOINTS. R. Nirogi[1], J. Ieni[1], V. Goyal[1], P. Jayarajan[1], V. Jasti[1], J. Cummings[2] *((1) Suven Life Sciences, Serene Chambers, Banjara Hills, Hyderabad - Hyderabad (India), (2) Department of Brain Health, School of Integrated Health Sciences, University of Nevada, Las Vegas; Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas - Las Vegas (United States))*

Background: Masupirdine (SUVN-502) is a selective 5-hydroxytryptamine-6 (5-HT6) receptor antagonist currently under investigation for the treatment of moderate Alzheimer's disease (AD). Animal data show that masupirdine has potential to improve cognitive performance. Phase-1 studies of masupirdine in healthy volunteers suggest favorable properties including once daily oral treatment andlack of food, gender and age effects. Masupirdine added to background treatment with donepezil and memantine was evaluated in moderate AD subjects in a double-blind placebo controlled, randomized 26-week treatment Phase-2 study. **Objectives:** To assess the impact of AD duration since diagnosis on the effects of Masupirdine on clinical function in moderate AD patients who are on stable treatment with donepezil and memantine. **Methods:** Masupirdine was studied in a phase 2, multicenter, randomized, double-blind, parallel group, 26-week, placebo-controlled proof-of-concept study in subjects with moderate AD receiving stable doses of donepezil and memantine. A total of 564 moderate AD patients with MMSE scores between 12–20 were randomized (1:1:1) to receive either 50 mg or 100 mg of masupirdine or placebo once daily for 26 weeks. All subjects were treated with donepezil 10 mg + memantine 10 mg BID or Namenda XR 28 mg QD; or Namzaric (donepezil 10 mg + 28 mg Namenda XR). The primary efficacy endpoint was change from baseline in the Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog11). In subgroup analyses of the mITT and EP populations, impact of AD duration on the effects of Masupirdine on clinical function were analysed using MMRM. **Results:** The randomized subjects had a diagnosis of AD at least 1 year prior to screening and imaging MRI or CT scan consistent with an AD diagnosis. The mean duration of AD diagnosis was approximately 3 years and 9 months. At the CTAD-2019 meeting, we will be presenting the results of the exploratory subgroup analyses of the impact of AD duration on the effect of masupirdine on clinical function. **Conclusions:** The study has been completed. The impact of the AD duration on clinical function will be presented at CTAD-2019.

P181- AD DIAGNOSIS DURATION IN COMBINATION WITH MEMANTINE EXPOSURES ON MASUPIRDINE (SUVN-502) EFFICACY - MASUPIRDINE IN COMBINATION WITH DONEPEZIL AND MEMANTINE IN MODERATE ALZHEIMER'S DISEASE PATIENTS. R. Nirogi, P. Jayarajan, J. Ravula, V. Goyal, A. Shinde, S. Jetta, A. Renny, G. Bhyrapuneni, V. Jasti *(Suven Life Sciences, Serene Chambers, Banjara Hills, Hyderabad - Hyderabad (India))*

Background: Masupirdine (SUVN-502) is a pure 5-hydroxytryptamine-6 (5-HT6) receptor antagonist evaluated for the symptomatic treatment of moderate Alzheimer's disease (AD) dementia. In phase-1study, masupirdine is well tolerated in healthy humans and has no effect of food, gender and age on the pharmacokinetics. Masupirdine in combination with donepezil and memantine as a background therapy was evaluated in moderate AD subjects in a multicenter, randomized, double-blind, placebo controlled, 26-week treatment in a phase 2 study. **Objectives:** To evaluate the effect of AD diagnosis duration in combination with memantine exposures on masupirdine efficacy in patients with moderate AD. **Methods:** A total of 564 moderate AD patients with MMSE scores ranging between 12–20 were randomized (1:1:1) to receive either 50 mg or 100 mg of masupirdine, or placebo once daily for 26 weeks. The primary efficacy endpoint was change from baseline in the Alzheimer's Disease Assessment Scale -Cognitive Subscale (ADAS-Cog 11). In this subgroup analyses subjects with lower memantine concentrations were stratified based on the AD diagnosis duration (> 2 years) were analyzed. Change from baseline in the ADAS-Cog 11 scores at week-26 was evaluated. **Results:** Out of 564 randomized patients, 183 patients in the placebo group, 184 in 50 mg masupirdine and 176 in 100 mg masupirdine groups were included in the final analysis. Patient baseline characteristics are consistent with moderate AD with MMSE scores ranging from 12 -20. The mean (SD) duration of AD diagnosis was 3.73 (2.7) years. The results from the subgroup analyses evaluating the effect of AD diagnosis duration (> 2 years) on masupirdine efficacy in combination with exposures of memantine will be presented at CTAD-2019. **Conclusions:** The results from the subgroup analyses evaluating the effect of AD diagnosis duration (> 2 years) in combination with exposures of memantine on masupirdine efficacy will be presented at CTAD-2019.

P182- EXPLORATORY SUBGROUP ANALYSES BASED ON PATIENT'S AGE AND ITS EFFECT ON COGNITIVE ENDPOINTS - MASUPIRDINE (SUVN-502), TRIPLE THERAPY WITH DONEPEZIL AND MEMANTINE IN MODERATE ALZHEIMER'S DISEASE PATIENTS. PR. Nirogi, A. Shinde, V. Benade, G. Bhyrapuneni, S. Jetta, P. Jayarajan, V. Goyal, S. Pandey, V. Jasti *(Suven Life Sciences, Serene Chambers, Banjara Hills, Hyderabad - Hyderabad (India))*

Background: Alzheimer's disease (AD) is a heterogeneous disorder and age is one major factor that influences the heterogeneity of this neurodegenerative disease. Clinical trialsfor AD do not account for age as a factor in trial design, that hinders the development of prospective treatment for the disease. Masupirdine (SUVN-502) is a selective 5-hydroxytryptamine 6 (5-HT6) receptor antagonist being investigated for the treatment of moderate Alzheimer's disease (AD). Masupirdine added to background treatment with donepezil and memantine was evaluated in moderate AD

subjects in a double-blind placebo controlled, randomized 26-week treatment Phase 2 study. **Objectives:** To assess the effects of masupirdine on cognitive functions stratified by patient's age at screening. **Methods:** The effect of masupirdine was studied in a total of 564 moderateAD patients with Mini Mental State Examination (MMSE) s cores between 12–20 receiving stable doses of donepezil and memantine. The study recruited patients in the age range of 55-85 years, both inclusive. Treatment duration of the trial was 26 weeks. The primary efficacy endpoint was change from baseline in the Alzheimer's Disease Assessment Scale -Cognitive Subscale (ADAS-Cog 11). In this exploratory subgroup analysis of 55-70 years and 71-85 years of age at screening visit, both inclusive were performed. Further stratification was carried out based on memantine concentrations at week 26. Change from baseline in ADAS-Cog 11 score at week 26 was evaluated for these subgroups. **Results:** Out of 564 randomized patients, 183 patients in the placebo group, 184 in 50 mg masupirdine and 176 in 100 mg masupirdine group were included in the final analysis. Baseline patient characteristics are consistent with moderate AD with MMSE scores ranging from 12 -20. The mean (SD) age of patients was 73.6 (7.46) year and the mean (SD) duration of AD diagnosis was 3.73 (2.7) years. Results from this exploratory subgroup analysis will be discussed. **Conclusions:** Together with the safety profile of masupirdine, the outcome from this exploratory subgroup analysis supports the clinical utility of masupirdine in patients with AD.

P183- BASELINE ADAS-COG 11 SCORES AND ITS EFFECT ON COGNITIVE ENDPOINTS - MASUPIRDINE (SUVN-502), TRIPLE THERAPY WITH DONEPEZIL AND MEMANTINE IN PATIENTS WITH MODERATE ALZHEIMER'S DISEASE. R. Nirogi, S. Jetta, G. Bhyrapuneni, R. Palacharla, A. Shinde, P. Jayarajan, V. Goyal, S. Ramkumar, V. Jasti *(Suven Life Sciences, Serene Chambers, Banjara Hills, Hyderabad - Hyderabad (India))*

Background: There exists a scope and need for improved treatment options for patients with Alzheimer's disease (AD) dementia. The current approved SOC (cholinesterase inhibitors and NMDA receptor antagonist) though provide modest efficacy but show dose limiting side effects. Masupirdine (SUVN-502), a selective 5-HT6 receptor antagonist demonstrated efficacy in animal models of cognition and neurochemistry. Phase-1 studies of masupirdine in healthy humans suggested favorable properties like once daily oral treatment, no effect of food, gender and age. Masupirdine in combination with donepezil and memantine is in development as a novel approach in the symptomatic treatment of AD. **Objectives:** To assess the effect of masupirdine on cognitive improvement in AD patients stratified based on baseline ADAS-Cog 11 scores. **Methods:** In this phase 2 study, a total of 564 moderate AD patients with mini-mental state examination (MMSE) scores between 12–20 receiving stable doses of donepezil and memantine were randomized (1:1:1) to receive either 50 mg or 100 mg of masupirdine, or placebo once daily for 26 weeks. The primary efficacy endpoint was change from baseline in the Alzheimer's Disease Assessment Scale -Cognitive Subscale (ADAS-Cog11). The efficacy endpoint wasanalyzed using mixed model repeated measures (MMRM) of the modified intent to treat (mITT) and the evaluable population (EP). Safety was assessed by recording adverse events andlaboratory measurements, vital signs, electrocardiograms, physical examination,neurological examinations and C-SSRS. A pre-specified subgroup analysis based on median baseline ADAS-Cog score of ≤ 27 and > 27 (Median) was performed. Further exploratory subgroup analysis was also carried out based on mean baseline ADAS-Cog scores i.e.≤ 28 and >28 (Mean). **Results:** Out of 564 randomized patients, 183 patients in the placebo group, 184 in 50 mg masupirdine group and 176 in 100 mg masupirdine group were included in the final analysis. Patient baseline characteristics were consistent with moderate AD with MMSE scores ranging from 12 -20. The mean, standard deviation (SD) age of patients was 73.6 (7.46) years. About two-thirds of the patients were APO-E4 carriers and the mean (SD) duration of AD diagnosis was 3.73 (2.7) years. At baseline the median ADAS-Cog11 is 27 and the mean (SD) is 28 (7.92). The population distribution in these subgroups was similar. The incidences of adverse events were balanced between groups. **Conclusions:** Together with the safety profile of masupirdine, the pre-specified analysis based on median ADAS-Cog11 baseline score of ≤ 27 and > 27 (Median) and other exploratory analysis data, masupridine demonstrates clinical utility in AD patients. Results of these exploratory subgroup analyses will be presented at CTAD-2019.

P184- REPURPOSING IGMESINE FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES. V. Villard[1,2], J. Meunier[1], A. Pregizer[2], D. Buttigieg[3], F. Roman[1,2] *((1) Amylgen SAS - Montpellier (France), (2) SigmaThera SAS - Montpellier (France), (3) NeuronExperts SAS - Marseille (France))*

Background: Igmesine, a selective and potent sigma-1 receptor agonist, has been developed in the past by Parke-Davis for the treatment of Major Depression and development was stopped for strategic reasons. The compound is being repurposed by SigmaThera for the treatment of neurodegenerative diseases. The compound has been tested by Amylgen in a mouse model of Alzheimer's disease (AD) and in vitroby Neuron Experts on several models of Parkinson's disease (PD), Huntington disease (HD) and Amyotrophic Lateral Sclerosis (ALS) using appropriate primary neuronal preparations in culture. **Methods:** In vivo studies: Male Swiss mice 5-6 weeks old were anesthetized with isoflurane 2.5% and injected i.c.v. with Aβ25-35 peptide (9 nmol/mouse) or Scramble Aβ(Sc. Aβ) peptide (9 nmol/mouse), in a final volume of 3 μl/mouse, according to the previously described method [2]. Mice were treated by intra-peritoneal (IP) injection according to a preventive or curative protocol until the end of the behavioral experiments, that was also the day of their sacrifice. The daily doses of igmesine were 0.1, 0.3, 1 mg/kg.Mice were tested for assessing short and long-term memory abilities. For short memory, mice performed spontaneous alternation in the Y-maze, a three arms apparatus that gives an index of spatial working memory according to the procedure already described [3, 4]. Step through passive avoidance (STPA), an index of contextual long-term memory, was tested using the apparatus described previously [3, 4] and consisting of two compartments, one white and one black separated by a guillotine door. Step-through latency, i.e., the latency spent to enter the dark compartment, and escape latency, which is the time to get out from the dark compartment, were recorded. After the last behavioral test animals were euthanized, their brain was removed, and hippocampus and cortex were dissected out. The hippocampus was used to determine lipid peroxidation (LPO), a marker of oxidative

stress, using a colorimetric method [5]whereas cortex was used for the determination of Aβ1-42,phosphorylated tau protein, cytokines and caspases. In vitro studies: Igmesine has been tested on neurons prepared from rat embryonic midbrains for studying 6-0HDA injury, on medium spiny GABAergic neurons after glutamate injury or on motor neurons isolated from spinal cord and intoxicated by glutamate. **Results:** In vivo, igmesine dose-dependently prevented memory deficits characteristic of the Aβ25-35model. in the Y-maze and in the passive avoidance tests measured 10 days after i.c.v injection. The effect of igmesine was observed at doses as low as 0.3 mg/kg, when given as a preventive treatment, or 1 mg/kg as a curative treatment (starting 1 day after induction of the toxicity). These are up to 100-fold lower than those originally reported for pre-clinical efficacy in models of depression that occur at doses higher than 30 mg/kg. In the same animals, this protective effects were correlated to an effect on two parameters related to oxidative stress we could measure in the hippocampus: lipid peroxidation (LPO) and ER stress (caspase 12). Further analysis of cortical tissue showed that igmesine treatment was able to regulate neuroinflammation activation as demonstrated by the decrease of GFAP, a marker of astrocyte activation, as well as apoptosis activation by using the elevation of the ratio Bax/Bcl2 as a marker. Two surrogate markers of the pathology were also normalized in our model: Aβ1-42(and not Aβ1-42) elevation and pTauS199. In the same animal model, subclinical (non-effective) 0.1 mg/kg dose of igmesine resulted in a full reversal of memory deficits, when combined with non-effective doses of other anti-AD medications like donepezil. Very interesting synergistic effects were also found with ibuprofen, atorvastatine and selegiline, but not memantine. These results position igmesine as a strong candidate for a combination therapy of AD. In vitro studies have demonstrated total neuroprotection in models of PD, HD and ALS. **Conclusion:** These encouraging preclinical results prompt us to evaluate the efficacy of igmesine in Phase 2A trials in human. **References:** [1] Maurice T, Lockhart BP, Privat A., Brain research. 1996; 706:181-93. [2] Haley TJ, McCormick WG, British journal of pharmacology and chemotherapy. 1957; 12:12-5. [3] Meunier J, Villard V, Givalois L, Maurice T, European journal of pharmacology. 2013; 698:193-9. [4] Villard V, Espallergues J, Keller E, Vamvakides A, Maurice T, Journal of psychopharmacology (Oxford, England). 2011; 25:1101-17. [5]Hermes-Lima, M., Willmore, WG, Storey, KB, Free Radic Biol Med. 1995; 19: 271-280.

P185- EVALUATION OF DIGITAL APPLICATION MUSIC CARE© ASSOCIATED WITH PERSONAL HYGIENE CARE BASED ON THE GOOD PRACTICES OF NURSING AIDES IN LONG-TERM CARE FACILITIES (EHPAD): A CONTROLLED, RANDOMISED STUDY. A. Loko[1], S. Guetin[2], J. Touchon[3,4] *((1) University UPMC Paris - Paris (France), (2) University Paris 5 - Paris (France), (3) University Montpellier 1 - Montpellier (France), (4) INSERM U1061 - Montpellier (France))*

Background: Given its interesting effects observed on pain in other contexts, we hypothesized that the use of the digital application MUSIC CARE© could reduce the aggression associated with hygiene care in Alzheimer patients living in geriatric institutions and could facilitate care. **Objectives:** to compare changes to pain levels experienced during personal hygiene care in an EHPAD associated with: - a validated MUSIC CARE© music intervention using the «U» sequence; - a period of listening to the radio; - "music-free" conditions. The secondary objectives concerned its impact on refusal, aggressiveness, satisfaction and the duration of hygiene care. **Methods:** This was a controlled, "cross-over" randomised study that included institutionalised patients who did not present with any auditory deficiency and agreed to sign a consent form. All patients were coherent and able to communicate verbally. The principal endpoint was a Visual Analogue Scale (VAS) completed by the patient after each session of hygiene care. Secondary endpoints concerned refusal, aggressiveness and the duration of care, which were recorded by the care team. Paired tests on the sessions were used to compare between the use of «MUSIC CARE©» and other interventions: "radio" and "music-free". All the patients included who complied with the eligibility criteria were taken into account in the Intent-to-Treat population (ITT). **Results:** Our sample comprised 21 patients with a mean age of 86.6 years, most of whom were women (66.7%). The diagnosed pathologies included dementia (mild to moderate) in 57% of cases and Parkinson's disease in 19% of patients. Significant differences in the reduction of pain, refusal, aggressiveness and the duration of care were observed between the three interventions, in favour of the MUSIC CARE© intervention ($p<0.01$). A significant difference was also observed with respect to patient satisfaction. **Conclusions:** Within the limitations of this study, MUSIC CARE© mainly enabled a significant reduction in the pain related to hygiene care when compared with "music-free" or "radio" care conditions. It also caused a reduction in refusals of care, violence and aggressiveness. Furthermore, a significant difference was observed concerning the duration of care, reducing the time required by 30% thanks to the use of MUSIC CARE© versus listening to the radio. MUSIC CARE© is perfectly adapted to the principal activities of nursing aides. **References:** Guétin S, Portet F, Picot MC, Pommié C, Messaoudi M, Djabelkir L, Olsen AL, Cano MM, Lecourt E, Touchon J. Effect of music therapy on anxiety and depression in patients with Alzheimer's type dementia: randomised, controlled study. Dement Geriatr Cogn Disord. 2009;28(1):36-46.

P186- IN VIVO EFFICACY OF A SMALL MOLECULE INHIBITOR TARGETING TAU SELF-ASSOCIATION IN BOTH AD AND TAUOPATHY MODELS. J. Moe[1], P. Lopez[1], H. Jimenez[2], L. Adrien[2], P. Davies[2], E. Davidowitz[1] *((1) Oligomerix.com - Bronx (United States), (2) The Feinstein Institutes for Medical Research - Manhasset (United States))*

Background: The premise of this program is that tau oligomers are the acutely toxic species of tau and that their reduction will modify the course of AD. Tau oligomers have a causal role in mediating cytotoxicity, disease propagation, and mitochondrial damage. We have shown that tau oligomers cause disruption of neuronal signaling and inhibit the formation of memory in mice (Fá et al., Sci Rep. 2016 Jan 20;6:19393), and that certain forms of tau oligomers are toxic when applied to cultured neurons (Tian et al., Int J Cell Biol. 2013;2013:260787). Tau aggregates and specifically tau oligomers isolated from AD brain may act as templates for the misfolding and aggregation of native tau, thereby seeding the spread of the toxic forms of the protein. These studies indicate that targeting tau oligomers should improve learning and memory and inhibit disease progression in AD and related tauopathies. This program is highly differentiated in that it targets full-length, non-mutated tau found in AD and targets tau self-association, the initial

step in tau oligomer formation thereby blocking the formation of larger aggregates. Whereas, other tau aggregation inhibitor programs have largely focused on inhibiting formation and or dissociating large and relatively inert fibrils which could generate toxic tau oligomer seeds. Unlike immunotherapeutic approaches, small molecules are agnostic to specific post-translational modifications, conformational changes or strains of tau aggregates, and are a low-cost therapeutic intervention or preventative relative to passive immunotherapy. **Objectives:** The overall goal of this program is to discover and develop small molecule therapeutics targeting tau self-association for the treatment of AD and ADRD. The specific objectives of the work presented here were 1.) to characterize the efficacy of the lead compound in the htau mouse model representing tau aggregation in AD and in the JNPL3 mouse model of inherited tauopathy; and 2.) to characterize the safety of the lead compound in preclinical studies. **Methods:** Preventive studies were performed independently in htau and JNPL3 transgenic mice. Mice were treated with blinded feed vehicle or feed formulated with lead compound from three to seven months of age. The htau mice only express the human CNS tau isoforms, without mutation or truncations, and the JNPL3 mice express the human 4R0N tau isoform with the P301L mutation associated with frontotemporal dementia in addition to the endogenous murine tau. The primary endpoint of the study was reduction of insoluble tau aggregates in the brains of the mice with statistical significance. The secondary endpoints were dose-dependent reduction of insoluble tau aggregates, reduction of phosphorylated tau, and reduction of soluble tau. To quantify levels of Sarkosyl-insoluble tau, self-associated tau, and phosphorylated tau in the treated and control groups of mice ELISAs were performed. Immunohistochemistry was also performed to determine levels of conformationally altered and hyperphosphorylated tau in htau mice and markers of inflammation were also studied in JNPL3 mice. The primary htau study had three treatment groups and a control group (n=25 per group, males and females), a confirmatory study in male htau mice had two treatment groups and a control group (n=15 per group). The JNPL3 study was performed with four groups of mice, a baseline cohort (n=15), and vehicle feed and two treatment groups (n=20 per group). Synthetic and analytical methods were optimized to synthesize the lead compound for the nonclinical safety studies (NCSS). **Results:** During the efficacy studies the compound was well tolerated at all therapeutic doses; there were no adverse events due to the compound and the control and treated mice exhibited similar weight profiles. The male htau mice developed significantly more pathology than the female htau mice. The lead compound reduced self-association of soluble tau and caused a statistically significant, linear, dose-dependent reduction of the levels of insoluble tau aggregates and phosphorylated insoluble tau aggregates in relationship to the levels of compound in the brain in the male htau mice. The study using female homozygous JNPL3 mice showed dose-dependent reduction below baseline and vehicle levels of self-associated tau, insoluble tau aggregates and phosphorylated tau. The NCSS synthesis campaign to prepare 1 kg of lead compound (non-GMP) was completed with a yield of 1.37 kg at >99% AUC HPLC purity and is being used for the ongoing safety studies. **Conclusion:** A lead compound from this program reduced both soluble and insoluble phosphorylated tau aggregates in the htau mouse model best representing tau aggregation in AD and in the JNPL3 mouse model of inherited tauopathy. Therapeutic studies in aged htau and JNPL3 mice are in progress that will also include behavioral analyses. Safety studies are ongoing, and the GMP synthesis of the lead compound for clinical studies is being planned.

P187- THE NEUROPROTECTIVE EFFECT OF A NEW PHOTOBIOMODULATION TECHNIQUE ON AB25-35 PEPTIDE-INDUCED TOXICITY DRAMATICALLY IMPACT GUT MICROBIOTA DYSBIOSIS. G. Blivet[1], L. Auboyer[1], J. Meunier[2], L. Ceolin[2], F.J. Roman[2], R. Burcelin[3], J. Touchon[4,5] *((1) REGENLIFE SAS - Montpellier (France), (2) AMYLGEN SAS - Montferrier-sur-Lez (France), (3) Vaiomer SAS - Labège (France), (4) INSERM U1061 - Montpellier (France), (5) Neurology Department, University of Montpellier - Montpellier (France))*

Background: Backgrounds: Photobiomodulation is a therapeutic strategy based on near-infrared light absorption by the mitochondria, resulting in regulation of mitochondria bioenergetics. We previously showed a neuroprotective effect of RGn530 device in an Alzheimer's disease mouse model, obtained while treating both head and abdomen. **Objectives:** To reconcile the role of gut microbiota dysbiosis in AD with this new biophotonic-based therapeutic strategy, we treated Aβ25-35peptide injected mice with RGn530 device and characterized gut microbiota. **Methods:** Treatment was applied for 6min and 7 days following the injection of Aβ25-35peptide in mice. Microbiota was characterized via 16SrRNA sequencing, and a cognitive and biological evaluation was performed. **Results:** Aβ25-35 injection induced a strong caecal microbiota dysbiosis where the Bacteroidetes to Firmicute ratio was deeply disrupted. Thetreatment reversed this ratio and allowed the emergence of specific microbial communities as biomarkers of the treatment efficacy. In addition, the Actinobacteria and Proteobacteria were two major phyla specifically affected by the treatment. This impact was associated with the total reversal of memory deficits. Oxidative stress elevation and neuroinflammation were fully down-regulated. **Conclusion:** We here show that this model is characterized by a gut microbiota dysbiosis which could be reversed by RGN530 treatment. This treatment appears as an innovative strategy for AD and contributes to the link between mitochondria and microbiota.

P188- A PRECISION MEDICINE MULTIMODAL LIFESTYLE INTERVENTION FOR TREATING COGNITIVE IMPAIRMENT: CONCEPTUAL FRAMEWORK OF THE PREVENTION TRIAL. S. Mcewen[1,2], D. Merrill[1,2], J. Bramen[1,2], V. Porter[1,2], S. Panos[1], S. Kaiser[1], L. Heath[3], C. Funk[3], M. Rapozo[1], N. Price[3], M.K. Ross[3], L. Hood[3], J. Roach[3] *((1) Pacific Neuroscience Institute, - Santa Monica, CA, (United States), (2) John Wayne Cancer Institute, Department of Translational Neurosciences & Neurotherapeutics, - Santa Monica, CA, (United States), (3) Institute for Systems Biology, - Seattle, WA (United States))*

Background: The lack of medical treatments available to stop or slow down the development of Alzheimer's Disease (AD) underscores an urgent need to develop preventative treatments for people at-risk for AD that are sustainable and effective at the individual patient level. Epidemiological studies have linked several key modifiable lifestyle and vascular-related risk with increased risk for late-life cognitive impairment and AD. These population level risk factors can be targeted with multimodal interventions to prevent further cognitive decline. These interventions include increasing physical activity, diet optimization, cognitive stimulation, stress

reduction, and managing physical health conditions. Although there have been promising results from a large lifestyle modification trial of a generalized, multimodal interventions (exercise, diet, cognitive stimulation, vascular risk monitoring) in non-cognitively impaired older adults, there has not been a controlled trial which attempts to apply a precision medicine model of treatment to implement a data-driven, multimodal lifestyle intervention to treat those with cognitive impairment. Further, to enable the successful implementation of such a comprehensive intervention we seek to explore the use of brain health coaching to promote lifestyle behavioral changes by incorporating: health education, collaborative goal- setting, habit building, accountability, and personal support with autonomous choices and positive psychological feedback, which are known to increase compliance with the long-term treatment protocols. **Objective:** The objectives of the PREVENTION (Precision Recommendations for Environmental Variables, Exercise, Nutrition and Training Interventions to Optimize Neurocognition) trial are two-fold: 1) To conduct the first randomized controlled trial of a 12-month precision medicine, multimodal lifestyle intervention in older adults ranging from subjective cognitive impairment to early-stage AD without functional impairments. Our primary outcomes include: memory functioning (RAVLT), global cognitive functioning (NIH Toolbox Cognition Battery) and quantitative structural MRI hippocampal volume. 2) We will also collect exploratory proteomic, metabolomic, neurotrophic and genetic data, which in addition to the clinical work-up data, we will aggregate into personalized, dense dynamic data clouds. With these longitudinal data, we will use statistical and computational methods in an effort to explain the causal underpinning of individual trajectories and to inform the design of future hypotheses and trials. **Methods:** We seek to enroll 60 patients in FAST Stage 2-4 (patients with cognitive but not functional impairments). Participants will be between 50-80 years old and all have a positive amyloid PET scan, indicating AD neuropathology. Participants will be randomized into either a data-driven, multimodal brain health coaching intervention (INT) or routine care with data-driven clinical recommendations (CON). Controls will not receive the brain health coaching or the resources needed to carry out the multimodal intervention. To personalize the clinical recommendations, we will collect a comprehensive clinical work-up on all participants which includes: blood labs (lipids, hormones, metals, metabolic, thyroid, blood count and vitamin levels), structural neuroimaging, neurocognitive testing, physical activity levels, behavioral testing, body composition, genomic (APOE-4), salivary cortisol, and gut microbiome diversity.Both groups will receive 5 study physician clinical visits, in which clinical work-up data will be discussed and a treatment plan implemented. Additionally, the INT group will receive: 13 data-driven brain health coaching calls (and email contact as needed), 7 dietitian visits, 33 exercise and cognitive training classes (2 classes/week for 3 months and then monthly booster classes), and access to an online cognitive training program (BrainHQ from Posit Science). Follow-up testing on most measures will occur every 3 months and we will monitor each participant for 12 months. We will perform a GLMM to explore the changes in trajectories between the two arms. **Results:** The PREVENTION trial recruitment began in June 2019 from our outpatient memory care clinic (Pacific Brain Health Center, Santa Monica, CA) and we are actively enrolling participants in this RCT. We have developed the clinical recommendations engine for implementing the precision medicine, multimodal interventions, which can be used by physicians to determine a personalized treatment plan for treating cognitive impairment and used in collaboration with health coaches, dietitians and personal trainers to assist in a collaborative care model of treatment. Over the next three years we will conduct the multimodal intervention and collect the dense molecular and cognitive assessment data. **Conclusion:** Given the epidemiologically large and increasing economic toll that AD is taking, we must deploy all effective interventions for cognitive decline based on known multimodal therapies for individuals at risk for AD. From this trial we seek to develop an evidence-based framework for a clinical implementation model of reducing cognitive decline at the patient level. We propose that a personalized and biologically data-driven, multimodal brain health coaching intervention will promote adherence and lead to a reduction in cognitive impairment over a 12-month period compared to receiving routine care with data-driven clinical recommendations only. We will seek to conduct a larger, multi-site, confirmatory trial once we have established efficacy from this single site trial.

P189- A NOVEL ORALLY-AVAILABLE DISEASE-MODIFYING SMALL MOLECULE DRUG CANDIDATE FOR THE PREVENTION AND TREATMENT OF ALZHEIMER'S DISEASE: EVALUATION OF PHARMACOKINETIC PROPERTIES IN RAT PLASMA AND CSF FOLLOWING INTRAVENOUS AND ORAL ADMINISTRATION. N. Dewji[1], A. Thurston[2], D. Rideout[3] *((1) Cenna Biosciences Inc. - La Jolla (United States), (2) Admesolutions Inc. - San Diego (United States), (3) DxRx Chemistry - Milford (United States))*

Background: We previously demonstrated that peptides from the Presenilin-1 (PS-1) NH2-terminal domain can substantially and specifically inhibit the production of total Aß as well as Aß40 and 42 in vitro and APP transgenic mice. We also provided evidence that peptides effective in reducing Aß gave a strong, specific and biologically relevant binding with the purified ectodomain of APP 695. Furthermore, since this mechanism does not target the secretases, the reduction of Aß by the peptides did not affect the catalytic activities of ß- or g-secretase, or the level of APP. Our best peptide candidate P8 is in development as a disease-modifying drug candidate for AD. More recently we carried out molecular modeling studies to determine the binding site on APP for P8. We then virtually screened a library of e-compounds to identify those molecules that would be predicted to bind the same sites on APP as P8. Of the ~160,000 structures screened, a total of 249 suggested binding to APP. These compounds were next screened their ability to reduce Aβ production. Several candidates were identified that could reduce both Aß 40 and 42 by 50-80% in AD patient-derived induced pluripotent stem cells. We have three small molecule candidates (ND10, ND20 and ND30) with the ability to reduce Aß 40 and 42 by 50-80% in an AD patient-derived ipsc model of AD by a novel mechanism that does not target, inhibit or modulate the catalytic activities of the ß-or g-secretases. **Objectives:** Evaluation of Pharmacokinetic Properties of ND10, ND20 and ND30 in Rat Plasma and CSF Following Intravenous and Oral Administration: **Methods:** This non-GLP study consisted of dose groups that received the compounds by two modes intravenous (IV) and oral (PO), with three male rats in each group. Rats received an IV dose of ND10, ND20 or ND30 at 1 mg/kg. Rats received a PO dose

of the compounds at 10 mg/kg. Plasma and CSF samples were collected pre-dose and up to 24 hours post-dose. The concentrations of ND10, ND20 and ND30 were determined by LC MS/MS. **Results:** 1) All three compounds reached the brain after oral administration. Of the three compounds, the best oral bioavailability in plasma (%F) was achieved by ND30 at 89%. %F for ND20 was 45% and for ND10 it was ~ 20%. Mean plasma concentration divided by the CSF concentration gave the following ratio for the three compounds following PO administration: ND10: 10 – 150, ND20: 48-186, ND30: 10- 2500. The clearance (CL) values for all three compounds were low, giving measurable values at 24h. The CL values (mL/min/Kg) for the three compounds after IV and PO administration were: ND10: 21.2 (IV) and 72.6 (PO), ND20: 1.17 (IV) and 2.6 (PO). ND30: 21 (IV) and 27 (PO). 2) All three compounds reduced Aß in CSF of rats following PO administration, showing target engagement. Part of the CSF collected from the rat PK study was used for Aß 40 ELISAs to determine target engagement following IV and PO administration of the three compounds. All three compounds showed a reduction in Aß 40 after both IV and PO administration, demonstrating target engagement. ND20 reduced Aß-40 in CSF after IV administration by almost 80% at 12 hours post-dose. After PO administration, ND20 produced a rapid drop in Aß 40 level that increased again after 4 h post administration. ND10 did not produce a very large reduction in Aß 40 after IV administration but produced a large (60%) reduction in Aß 40 by 4h post PO administration. This reduction was sustained beyond 12 hours post-administration. ND30 gave a similar reduction of ~ 50% at 4h post both methods of administration and the levels remained lower than pre- dose levels at 12 hours post-dose. ND10 and ND30 thus appear to be better than ND20 for reducing Aß by oral dosing. **Conclusions:** All three candidates can be delivered to the rat brain by oral administration. All three candidates can reduce Aß 40 and 42 by 50-70% by a novel mechanism that does not target, inhibit or modulate the catalytic actitivites of the ß- or gamma-secretases. Based on %F and Aß reduction in vitro and in CSF of rats, ND30 is selected as the lead candidate, with ND10 and ND20 being very good back-up compounds. Pre-clinical studies to develop this candidate are underway.

P190- SYNAPTIC INTERVENTION IN ALZHEIMER'S DISEASE: SOLUBLE AB OLIGOMER DIRECTED ACU193 MONOCLONAL ANTIBODY THERAPEUTIC FOR TREATMENT OF EARLY ALZHEIMER'S DISEASE.

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The number of patients with Alzheimer's disease (AD) is increasing worldwide as the population ages, and thus far attempts to develop disease modifying treatments for AD have been unsuccessful, despite the realization that the time between the onset of pathological changes and the onset of clinical symptoms may be up to 20 years. The efforts to develop disease modifying therapies have focused mainly on the monomeric Aβ peptide and deposited amyloid plaques, and more recent efforts have begun to target tau and neurofibrillary tangles. Studies of soluble amyloid β oligomers (AβOs) (also known as Aβ-derived diffusible ligands, ADDLs) more than two decades ago showed synaptotoxic properties and functional impairment of neurons, suggesting a role of AβOs as a potential cause for synaptic dysfunction and neurodegeneration in AD. With that understanding, ACU193, a humanized monoclonal antibody, was developed using soluble Aβ oligomers as the antigen. ACU193 binds a broad spectrum of small to large soluble Aβ oligomers. ACU193 showed preferential affinity for AβOs vs monomeric Aβ and Aβ plaque, and no visible binding to vascular amyloid was present. In vitro studies have shown that ACU193 and its murine analogue 3B3 restored long term potentiation (LTP) in rat hippocampal slices incubated with Aβ1-42. sAβO toxicity can be measured in vitro by an increase in intracellular synaptic calcium concentration, and this increase is blocked by ACU193 administration. Further, subchronic administration of 3B3 to transgenic J20 (Swedish and Indiana mutations) and hAPPSL (Swedish and London mutations) mice, which overexpress the mutated human amyloid precursor protein, reduced a variety of memory and behavioral deficits seen in these animals. The differentiation in binding specificity of ACU193 compared to other previously studied monoclonal antibodies may provide enhanced efficacy in the clinic. IND-enabling toxicology studies for ACU193 are planned, and a Phase 1 trial is expected to begin in 2020..

P191- LYSERGIC ACID DIETHYLAMIDE AS A PROSPECTIVE MULTI-TARGET DISEASE MODIFYING THERAPEUTIC IN AD: PHASE 1 SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS.

N. Family, E. Maillet, C. Nichols, S. Raz *(Eleusis - London (United Kingdom))*

Background: The multifactorial nature of early-stage AD suggests multiple potential mechanistic-based therapeutic targets, including neuroinflammation, synaptic plasticity, neuropsychiatric/neuroendocrine dysfunction, and impaired brain bioenergetics. Targeted immunotherapies capable of significantly reducing Aβ and tau burden have failed to modify AD progression in late-stage clinical trials, and the only FDA-approved drug therapies are palliative in nature with marginal clinical efficacy, highlighting the urgent need to evaluate new approaches to disease modification. Multi-targeted drugs (MTDs) with established safety profiles could empirically engage identified therapeutic targets. In this presentation, we propose the hypothesis that microdoses of lysergic acid diethylamide (LSD) represent a promising disease modifying therapeutic for AD and we present findings from a phase 1, double-blind, placebo-controlled, randomized study of repeat dosing of microdoses of LSD. LSD is a classic psychedelic drug, described as "promiscuous" due to its remarkable polypharmacology: it binds with moderate-to-high affinity to several aminergic receptor subtypes. LSD is one of the most well-studied psychoactive drugs in the history of modern pharmacology, and has been evaluated extensively both preclinically and clinically following the serendipitous discovery of its psychoactive properties in 1943. LSD is a mixed agonist or antagonist at a subset of serotonin (5-HT), dopamine and other aminergic receptors, and shares structural similarity to 5-HT. **Objective:** We present findings from a study that evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of orally administered repeat dosing of microdoses of LSD. **Methods:** Healthy male and female volunteers aged 55 to 75 years were screened within 28 days of

randomization. Volunteers were assessed for eligibility based on medical history, physical examination, and inclusion and exclusion criteria. Eligible volunteers were randomised to one of four dose groups (5 μg, 10 μg, or 20 μg LSD or placebo). Volunteers received their assigned study dose in an in-patient setting on 6 separate occasions; each dose was separated by exactly 3 days for 21 days. Safety and tolerability evaluations consisted of adverse event (AE) monitoring, administration of the C-SSRS, blood pressure, and pulse rate at every visit from screening through to follow-up. Clinical laboratory evaluations (i.e. hematology, blood chemistry, urinalysis) at screening, baseline, dose 3, dose 6, and follow-up. Electrocardiogram (ECG) parameters and physical examinations were assessed at screening and follow-up. The raw PK data (i.e. actual drug concentrations over time profiles) were collected following the first and sixth doses. The PK parameters were derived from the individual subject profiles separately using non-compartmental methods. The magnitude of the effect of LSD was explored across specific PD measures, which included the Cambridge Neuropsychological Test Automated Battery (CANTAB), proprioception, and balance. Subjective drug effects were assessed during dose day at multiple time points via visual analogue scale (VAS) and a single administration of the Five Dimensional Altered States of Consciousness (5D-ASC) questionnaire. **Results:** A total of forty-eight older healthy volunteers (mean age = 62.9 yrs) were enrolled in the trial and received placebo (n=12), 5 μg (n=12), 10 μg (n=12), or 20 μg (n=12) LSD on 6 study days. The only minor, though statistically insignificant, difference between placebo and active treatment groups was in the number of headaches reported and these were either mild or moderate in intensity. LSD was well tolerated, and the frequency of adverse events was no higher than for placebo. Other safety assessments performed, including laboratory safety assessments, vital signs, and ECGs support the conclusion that low dose LSD did not present a safety concern. Pharmacokinetic parameters showed that LSD plasma levels were undetectable for the 5 μg group and that peak blood plasma levels for the 10 μg and 20 μg groups occurred at approximately 30 minutes and had a terminal half-life of 8.25 hours (+/-1.6 SE). Assessments balance, and proprioception revealed no impairment, as well as no cognitive impairment or enhancement. While there was no dose-response relationship with cognitive, balance, or proprioceptive tasks, regression analysis on the average maximum rating of the subjective effects questionnaire and the 5D-ASC showed a positive linear relationship between dose and 'vigilance reduction. Three questions from the subjective drug effects VAS including 'feeling bad drug effects,' also exhibited a statistically significant linear relationship with LSD dose. **Conclusion:** In summary, this phase 1 study of intermittent microdoses up to 20μg LSD in a healthy older population yielded reassuring data regarding the safety and tolerability. These findings support the feasibility of this approach for larger studies designed to evaluate possible anxiolytic, anti-depressant, and anti-inflammatory properties of low dose LSD, including specific evaluation as a disease modifying therapy in Alzheimer's Disease.

P192- EPIGENETIC MODULATOR APABETALONE INHIBITS MONOCYTE ADHESION TO BRAIN ENDOTHELIAL CELLS BY DOWNREGULATING KEY NEUROINFLAMMATION MARKERS IN VITRO AND IN VIVO. S. Wasiak[1], E. Daze[1], L.M. Tsujikawa[1], S. Das[1], L. Fu[1], D. Gilham[1], B.D. Rakai[1], S.C. Stotz[1], C.D. Sarsons[1], D. Studer[2], K.D. Rinker[2], R. Jahagirdar[1], N.C.W. Wong[1], M. Sweeney[3], J.O. Johansson[3], E. Kulikowski[1] *((1) Resverlogix Corp - Calgary (Canada), (2) University of Calgary - Calgary (Canada), (3) Resverlogix Corp - San Francisco (United States))*

Background: Circulating cytokines induce inflammatory changes in brain vascular endothelial cells that promote monocyte adhesion and transmigration across the blood brain barrier. This process contributes to the initiation and exacerbation of neuroinflammation, which ultimately leads to neuronal injury and neurodegeneration. Bromodomain and extraterminal domain (BET) proteins are histone acetylation readers that activate cytokine-dependent transcription in monocytes and endothelial cells in chronic vascular inflammation models. Targeting BETs with epigenetic therapies may reduce endothelial activation during neuroinflammation. **Objectives:** To evaluate the anti-inflammatory properties of apabetalone, a clinical stage small molecule that inhibits the transcriptional activity of BET proteins, in cellular models of brain inflammation. **Methods:** THP-1 monocyte gene expression was examined in response to TNFα +/- apabetalone by real time PCR (rtPCR) after 4-24h of exposure. Primary human brain microvascular endothelial cells (HBMVECs) or the brain endothelial hCMEC/D3 cell line were stimulated with IL-1β, TNFα and/or IFNγ +/- apabetalone for 4-24h, and assayed for gene expression (rtPCR), cytokine secretion (ELISA, MILLIPLEX® Multiplex Assays) and/or surface cell adhesion protein abundance (flow cytometry). THP-1 cell adhesion to monolayers of HBMVECs was measured in laminar flow conditions. In vivo neuroinflammation was assessed in C57BL/6 male mice pretreated with apabetalone for 7 days (150 mg/kg b.i.d.), and then injected with 10 mg lipopolysaccharide (LPS) intraperitoneally. mRNA from homogenized brain tissue was analyzed 24h post LPS injection. **Results:** In THP-1 monocytes, apabetalone suppressed the expression of genes induced by TNFα, including IL-1β, the chemokine MCP-1, chemokine receptors CCR1 and CCR2, and the adhesion molecule VLA-4 (40% to 90% reduction, $p<0.05$)). In hCMEC/D3 endothelial cells, cytokine stimulated secretion of key inflammatory chemokines involved in monocyte attraction and vascular inflammation was reduced by apabetalone, including granulocyte-macrophage colony-stimulating factor, fractalkine, MCP-3, IP-10, and IL-6 (40% to 90% reduction, $p<0.05$). In TNFα and IFNγ stimulated HBMVECs, apabetalone inhibited the mRNA levels and the surface abundance of the cell adhesion proteins VCAM-1 (80% reduction) and E-selectin (50% reduction). In agreement with this inflammatory marker downregulation, apabetalone treatment countered THP-1 adhesion to HBMVECs in laminar flow assays. In mice, apabetalone treatment attenuated the LPS-induced mRNA expression of inflammation markers in the brain including E-selectin, ICAM, CCR2, and CD68. **Conclusions:** Apabetalone treatment decreased brain endothelial cell activation and monocyte interactions. By reducing immune cell transmigration in pro-inflammatory conditions, apabetalone may impact brain inflammation and potentially reduce cognitive decline. The effect of apabetalone treatment on the cognition of diabetic

patients ≥70 years old with acute coronary syndrome is being evaluated through repeat MoCA testing in the phase 3 BETonMACE trial (results expected in H2 2019).

P193- ACUPUNCTURE WITH GOLDEN THREAD IN CHRONIC HEADACHE. Y. Park *(Koshin university Gospel hospital - Busan (Korea, Republic of))*

Background: Acupuncture is widespread traditional therapy for chronic headache in east asia. Especially, patients unable to tolerate the medication due to side effects such as gastrointestinal discomfort are used to be dependent with those adjunctive treatments.Acupuncture using golden threads is one of those alternative treatment that is applied to various pain diseases such as arthritis and headache. It is characterized by not removing threads after acupuncture. The application hypothesis is that the golden threads placed on the acupuncture site stimulate the acupuncture site continuously. However, due to these characteristics, it may cause various artifacts in the image. **Case:** 54 year old female have experienced chronic headache for 20 years. She complained of tingling and tightening sensation of the entire head, especially back neck and left side of the head. She was treated at the local hospital, however it didn't help. As a result, she was dependent on various alternative treatment. The headache suddenly deteriorated about a month ago, and symptoms persisted almost daily and continuously. There weren't vomiting, nausea and other neurological symptoms. Neurologic examination revealed no other signs other than tenderness in the neck and shoulder. Though it was thought that the possibility of tension type headache was high, MR imaging was performed because of sudden aggravation from a month ago and invasion of daily life. Brain MR revealed multiple metal-related artifacts around the scalp and back neck. Skull X-ray was taken to clarify this finding, and golden threads inserted about 20 years ago were found at the same site. **Discussion:** Acupuncture is one of popular adjunctive treatments in South Korea and east asia. Especially acupuncture with golden threads is a commonly used treatment for diseases such as osteoarthritis and rheumatoid arthritis. However, as far as the authors are aware, the use of acupuncture in headache has not been reported so far. This insertion of foreign objects can cause artifacts in various imaging tests, and it may cause serious artifacts on MRI images, so caution is needed.

P194- A SINGLE ASCENDING DOSE STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF PU-AD, AN ANTI-ALZHEIMER'S DISEASE EPICHAPEROME INHIBITOR. M.H. Silverman[1], J. Cummings[2], S. Duggan[1], B. Wallner[1] *((1) Samus Therapeutics - Topsfield (United States), (2) Cleveland Clinic Lou Ruvo Center for Brain Health - Las Vegas (United States))*

Background: The breakdown of regulatory pathways designed to prevent aggregation and accumulation of disease-associated proteins contributes to or causes the pathophysiology of many neurodegenerative diseases, including Alzheimer's Disease (AD). Due to age-related protein misfolding or overexpression of mutated dysfunctional proteins, protein degradation systems such as ubiquitin-mediated proteasome or autophagy are overburdened or their activity is decreased, allowing the accumulation of damaged or misfolded proteins potentially leading to neuronal damage. Aggregation of intracellular proteins disrupts important cellular processes resulting in a cellular stress environment and the formation of epichaperomes, which are designed to aid in the folding and stabilization of these aberrant proteins thus contributing to the pathology of the disease. Epichaperomes are complex networks of chaperones, co-chaperones, scaffolding and regulatory proteins nucleated on Heat Shock Protein 90 (Hsp90), facilitating stabilization and aggregation of mutated proteins such as tau, which otherwise would be degraded. We designed a small-molecule, orally bioavailable purine-scaffold inhibitor of epichaperome, PU-AD, that is specific to Hsp90 when incorporated into epichaperome complexes and has little or no effect on Hsp90 in normal cells. Inhibition of the epichaperome network in mouse models of tauopathy (PS301 and PS19) and AD (3xTg-AD) with PU-AD resulted in degradation of soluble and aggregated mutant tau, as well as in decreased levels of hyperphosphorylated-tau, without having an effect on normal tau. A series of memory tests, including Barnes Maze and Radial Arm Water Maze, indicated improved or restored cognitive functions to levels seen in wild type mice after treatment with PU-AD. Thus, inhibition of epichaperomes by PU-AD seems to have multiple effects on the pathology of AD which include increased degradation of soluble and aggregated mutant tau, prevention of tau hyperphosphorylation, and restoration of cognitive functions. **Objectives:** This Phase 1, double-blind, placebo-controlled, single ascending dose study evaluates the safety and pharmacokinetics (PK) of single doses of PU-AD in healthy subjects. **Methods:** Each ascending-dose cohort is comprised of 8 subjects randomly assigned to active treatment or placebo in a 6:2 ratio. The starting dose of PU-AD is 10 mg, with dose escalation in subsequent cohorts contingent upon review of cohort safety and PK data by a clinical oversight committee. Safety is evaluated through observation of adverse event incidence and severity, as well as changes from baseline in clinical laboratory test results, vital signs, physical examinations, or electrocardiogram results. Plasma PK parameters of PU-AD include: maximum observed concentration (Cmax); time to maximum observed concentration (tmax); terminal elimination half-life (t½); area under the concentration-time curve (AUC); and apparent plasma clearance (CL/F). In subsequent patient trials, the effect of treatment on a series of biomarkers known to be associated with AD will be determined, including cerebrospinal fluid levels of total tau (Ttau), phosphorylated tau (ptau), amyloid fragments A-beta 40 and A-beta 42, neurofilament light (NF-L), and chitinase-3-like protein 1 (CHI3L1 or YKL-40). **Results:** To be presented. **Conclusion:** Epichaperomes play a critical role in the pathogenesis and characteristics of neurodegenerative diseases. They function as centers for networks of regulatory pathways controlling neurodegenerative specific processes, thereby representing potent therapeutic targets offering high specificity and potentially greater efficacy than other approaches which target a single specific pathway or protein. PU-AD, a novel and selective epichaperome inhibitor shown to be efficacious in animal AD models warrants further evaluation in an AD population.

P195- CLINICAL PHASE I DATA OF THE FIRST ORALLY AVAILABLE ANTI-AB-PRIONIC PRI-002 THAT REVERSES BEHAVIOR AND COGNITIVE DEFICITS, AND DECELERATES NEURODEGENERATION IN TRANSGENIC AD MOUSE MODELS. D. Willbold[1,2,3], J. Kutzsche[1], A. Willuweit[1,3], D. Jürgens[1,3], M. Windisch[4], M. Wolzt[5] *((1) Forschungszentrum Jülich - Jülich (Germany), (2) Heinrich-Heine-Universität Düsseldorf - Düsseldorf (Germany), (3) Priavoid - Jülich (Germany), (4) Neuroscios - St. Radegund / Graz (Austria), (5) Medical University of Vienna - Vienna (Austria))*

Background: While phase III clinical trials for the treatment of Alzheimer's disease (AD) keep failing regardless of the target, more and more data suggests that the toxic protein assemblies of Aβ and TAU behave prion like. Irrespective of the question, whether AD is theoretically or practically contagious, the presence of a replicating toxic etiologic agent in the brains of AD patients must have decisive consequences for drug development programs and clinical trial designs. The most efficient ways to fight a replicating pathogen is either active immunisation or applying substances that kill or destroy the pathogen directly. The former has already proven non-beneficial for a body's own protein. The latter is e.g. done by antibiotics in the case of bacterial pathogens. **Objectives:** We intend to challenge the hypothesis, that the underlying etiologic agent of AD is behaving prion-like. We want to discuss, whether the outcome of clinical trials could have been predicted, and whether compounds that directly act against the prion, could be beneficial for AD treatment. **Methods:** We collected publically accessible pre-clinical efficacy data of failed compounds and of compounds that are still in phase III targeting Aβ species. We are describing the desired properties of an anti-prionic compound and compare it to the properties of past and current phase III drug candidates. **Results:** We could not find published pre-clinical efficacy of past and current phase III drug candidates on cognition other than obtained in preventive treatment settings. The desired properties of an anti-Aβ-prionic are fulfilled by the drug candidate PRI-002, which has been developed to directly disassemble and destroy toxic Aβ oligomer prions. PRI-002 (alias "RD2") is BBB penetrable [1] and has demonstrated target engagement in vitro and in vivo [2, 3]. Treatments in three different transgenic mouse models in three different laboratories yielded improved cognition and deceleration of neurodegeneration [2-5]. Oral treatment of old-aged transgenic AD mice with full blown pathology reversed cognitive and behavioral deficits to levels indistinguishable from healthy wild-types [3]. The in vivo correlation of Aβ oligomer elimination and reversal of deficits in these old mice supports a promising role of Aβ oligomer prions as the target for causal treatment of AD. Here, we summarize the preclinical in vivo proof-of-concept studies [2-5] and the results of the phase I clinical SAD and MAD trials. **Conclusion:** PRI-002 is the first anti-Aβ-prionic drug candidate. It is able to enhance cognition and to impede neurodegeneration in transgenic AD mouse models under truly non-preventive treatment conditions and even when applied orally. The hereby obtained PRI-002 plasma levels have also been achieved in humans after single oral dosing. In addition, it has proven to be safe in humans in a single ascending dose study and a multiple ascending dose study up to 320 mg/subject/day for 28 days when administered orally to healthy volunteers. PoC studies in humans for anti-prionic compounds may be based on much shorter treatment durations. And anti-prionic treatments of AD patients do not necessarily have to be life-long. [1] Leithold et al., Pharm Res. 33, 328-336 (2016). [2] van Groen et al., Sci. Rep. 7, 16275 (2017). [3] Schemmert et al., Mol. Neurobiol. 56, 2211 (2019). [4] Kutzsche et al., Molecules 22, 1693 (2017). [5] Schemmert et al., Neurobiol. Dis. 124, 36 (2019).