SYMPOSIA

S1- TIME-TO-EVENT ENDPOINTS FOR CLINICAL TRIALS IN EARLY ALZHEIMER'S DISEASE.

M. Sano *(New York, USA)*

The goal of this symposium is to evaluate the use of "time-to-event" (TTE) outcomes in clinical trials of cognitive impairment and dementia. There may be particular value of such outcomes in the case of Alzheimer's disease and other neurodegenerative disorders. While the natural history of the deficits may be a progressive worsening, increasing care and supervision is most likely determined by loss that can be marked by specific milestones. Thus the quantification of time to an event such as a stage of AD, or the loss of specific cognitive or functional abilities, can be useful for planning care needs and determining the value of treatments that stave off such events.

Communication 1: *History of Time-to-Event in AD Clinical Trials*
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Dementia is a critical milestone in the progression of AD and originally formed the basis of formal diagnosis. Following the recognition of the Mild Cognitive Impairment (MCI) stage prior to dementia, it was logical that delay or prevention of AD dementia should be a target for treatment. However, progression to dementia as a clinical trial endpoint resulted in a number of challenges, including heterogeneity and issues with statistical utility. Dementia diagnosis is a subjective measure that varies between clinicians,1 has a long time-to-occurrence in the MCI population2-4 and varying sensitivity and utility between populations and trials.1 It is well-established that application of a dementia diagnosis can be biased by the cultural influences inherent in global studies. Attempts to limit this bias led to complex adjudication processes in the execution of TTE studies using dementia diagnosis as an endpoint event. AD is now recognised to be a continuum with preclinical, prodromal and dementia stages (mild, moderate and severe), in which the dementia diagnosis may be viewed as an important milestone, but not one that represents a differentiating boundary in terms of underlying pathophysiology. Thus, for trials spanning the early AD continuum (pAD through mild AD dementia), a further challenge is to define an event that has relevance both pre and post the dementia diagnosis. It is evident that cognitive impairment and functional dependence accumulate both pre- and post- the dementia diagnosis itself. Staging criteria such as the Global Deterioration Scale (GDS), Clinical Dementia Rating – Global Score (CDR-Global) and Dependence Scale have long recognized this progression, but have not typically been employed in TTE analysis approaches. In the context of early AD and the continuum, such staging criteria may lack precision, providing only 5 to 7 stages representing the full continuum of AD, but also be heavily focused on the post dementia stages, with few pre-dementia categories, consistent with their development prior to our current understanding of preclinical AD and MCI due to AD/prodromal AD. Furthermore, current diagnostic criteria now recognize both cognitive and functional impairment pre-dementia and the loss of/dependence in complex functional abilities such as managing personal finances, and loss of ability to engage in work (paid or unpaid). Thus, important changes may occur both pre-dementia, but also between current AD stages. It is not clear whether scale based severity, scale based change, life events, or some composite of these should be employed. However, TTE has potential value in evaluating therapies that may slow disease progression, as a means to better communicate relevance of a treatment effect to key audiences, including clinicians, regulators, caregivers and payors.

Communication 2: *Value of Time-to-Event in the Current Era,*
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A TTE approach to analyses of efficacy and effectiveness for clinical trials in early AD may be critical if we are to robustly demonstrate and effectively communicate, to primary care physicians, the benefits of therapies that may slow progression, rather than improve versus baseline. This approach is acknowledged in regulatory guidance as a potential primary outcome, or as a possible complimentary responder analysis to support relevance.5, 6 A number of clinical trials of potential disease-modifying treatments in Alzheimer's Disease (AD) are now targeted at the early disease stage, where it is thought that there will be the greatest benefit to patients. By targeting the disease at the preclinical, prodromal and/or mild dementia stages, it is hoped to slow progression before extensive, irreversible neurodegeneration occurs. Trials typically employ continuous primary endpoints, rather than categorical, to minimise information loss/maximise power. Furthermore, many current therapies in development will likely result in a slowing of the rate of decline compared to placebo, as opposed to either prevention of further decline, or improvement/recovery of function. The resulting treatment effect, expressed as percent relative reduction, or point estimate versus placebo, may have minimal inherent meaning/face validity. Thus, a time-to-event (TTE) endpoint, defined as delay of 'Clinically Evident Decline', 'Increase in Functional Disability/Dependence', or other related concepts, is attractive as a means to communicate such benefit. In addition, such an analysis may provide useful supportive evidence for evaluating the value of disease-modification at any stage.7 TTE may also be more directly translatable into caregiver and payor relevant concepts, wherein the delay in incurring increased cost, increased need for assistance etc. can be described.

Communication 3: *Establishing Clinical Relevance and Statistical Utility for Time-to-Event Endpoint Definitions,*
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Clinical relevance criteria: In order to explore and define TTE endpoints for early AD an initial foundational understanding of clinical relevance is required in terms of critical measurement concepts and meaningful change/difference. Building on this, the statistical properties of specific operationalized definitions can be explored for their validity, utility and sensitivity as clinical trial endpoints. Finally, consensus amongst the clinical community, supported by patient and caregiver insight where feasible will establish common criteria for meaningful comparative evaluation of different interventions. Clinical relevance may be viewed to constitute two essential properties: the clinical relevance of an event or measure e.g. the content validity/conceptual basis of a scale, which demonstrates that the concepts assessed are relevant to patients and/or clinicians; and the meaningfulness of a particular change or difference (i.e. that magnitude needed to confer a benefit/define a worsening). Content validity/conceptual basis may be apparent (i.e. face validity of outcomes such as mortality and morbidity, or established via initial and iterative development of measures e.g. qualitative research

with patients and caregivers and/or expert clinical insight). For the evaluation of important magnitude of change/difference, this may be approached by establishing clinically important responder (CIR) definitions, which may be done using distribution and anchor-based, or other statistical approaches, and may again make use of insights from patients, caregivers and clinical experts. Statistical evaluation: Given the potential issues regarding information loss/reduced power versus continuous endpoint, TTE endpoints may require even greater statistical scrutiny. Following from an understanding of the magnitude of change/difference need to define progression/benefit, a clear operationalized definition of a TTE endpoint may be created, taking into account issues such as confirmation of the event and handling of missing data/censoring etc. Statistical evaluation of the TTE endpoint definition must also take into account factors including an understanding of the frequency of the event in the target population, the median time to occurrence, and other factors necessary to the design and powering of trials. In all cases defining an event must address the variability with which it occurs, in order to attempt to distinguish true, permanent and real change, from perturbation in performance that will recover over time. Furthermore, an understanding of the wider relevance of the event definition such as association with health economic outcomes, caregiver impact etc. will be needed. Consensus: It may be important to explore multiple event definitions and to seek input regarding their meaningfulness from the perspectives of clinicians, patients, caregivers and payors in an ongoing and iterative fashion throughout such a process. This process of 'triangulation' integrating statistical, clinical and experiential insight may be particularly valuable given the nature of AD and the progressive loss of insight on the part of patients, which can make informant and clinical input more central to our understanding of patient benefit. Conclusion: TTE endpoints may be critical to the communication of benefit in clinical trials of cognitive impairment and dementia. Though there are potential statistical drawbacks in comparison to continuous endpoints and challenges in creating and establishing event definitions, their potential value and inherent meaningfulness should spur on efforts to address and resolve these issues. References: 1. Aisen PS, Andrieu S, Sampaio C, et al. Report of the task force on designing clinical trials in early (predementia) AD. Neurology 2011;76:280-286. 2. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005;352:2379-2388. 3. Feldman HH, Ferris S, Winblad B, et al. Effect of rivastigmine on delay to diagnosis of Alzheimer's disease from mild cognitive impairment: the InDDEx study. The Lancet Neurology 2007;6:501-512. 4. Winblad B, Gauthier S, Scinto L, et al. Safety and efficacy of galantamine in subjects with mild cognitive impairment. Neurology 2008;70:2024-2035. 5. FDA. Guidance for Industry Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease DRAFT GUIDANCE. In: CDER, ed., 2013. 6. EMA. Draft guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease and other dementias. In: CHMP, ed. London, 2015. 7. EMA. Guideline on Medicinal Products for the Treatment of Alzheimer's Disease and Other Dementias. In, 2008. 8. McLeod LD, Coon CD, Martin SA, Fehnel SE, Hays RD. Interpreting patient-reported outcome results: US FDA guidance and emerging methods. Expert Rev Pharmacoecon Outcomes Res 2011;11:163-169. 9. Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR. Methods to explain the clinical significance of health status measures. Mayo Clin Proc 2002;77:371-383.

S2- NON-PHARMACOLOGICAL INTERVENTION IN POPULATIONS AT HIGH RISK OF AD DEMENTIA: RESULTS OF THE MAPT AND LIPIDIDIET STUDIES.

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Introduction: Epidemiological studies indicate that the food pattern of the Mediterranean Diet reduces risk of cognitive decline. The FINGER study was the first large scale multi-modal intervention study reporting that multi-component nutritional intervention, combined with other lifestyle factors, improved cognition in people at risk to developing dementia. More recently the MAPT study (Multi-domain Approach for Preventing Alzheimer's Disease) reported improved cognitive performance after 3 years intervention with multi-domain lifestyle intervention in cognitively frail older subjects, particularly if multi-domain lifestyle intervention was combined with supplementation of omega-3 fatty acids. Recently, early intervention in non-demented biomarker-positive subjects (prodromal Alzheimer's Disease [AD]) has been proposed as another promising strategy to achieve significant clinical benefits in respect to slowing or halting progression of AD. Diet is one of the main AD risk factors, however clinical trials with single nutrient intervention have in general showed no clinical benefit. The long-term LipiDiDiet randomised clinical trial1 (RCT) in prodromal AD investigated a multi-nutrient combination 'Fortasyn Connect' as present in Souvenaid, a Food for Special Medical Purposes for the dietary management of early AD dementia. Extensive preclinical investigation, much of which took place in the LipiDiDiet/LipiDiet programmes, indicated that a nutrient combination has effects on multiple biological pathways that contribute to an overall neuroprotective effect superior to single nutrients. Previous RCTs with this intervention have shown improved memory performance in drug-naïve mild AD dementia patients, and an excellent safety profile. Objectives: The MAPT (NCT00672685) enrolled 1680 subjects (mean age: 75.3 years; female: 64.8%) in 13 memory clinics, which were randomised to one of the following four groups: omega-3 supplementation alone, multi-domain intervention alone, omega-3 plus multi-domain intervention, or placebo. Participants underwent cognitive, functional and biological assessments at month 6, 12, 24 and 36 visits. The primary endpoint was a change of cognitive function at 3 years, as assessed by a composite score. All participants will be followed for 2 additional years after the 3-year intervention (MAPT PLUS extension study). The interventions were 1/ Omega-3 supplementation: two soft capsules daily as a single dose, containing a total of 400 mg docosahexaenoic acid (DHA) each, i.e. 800 mg docosahexaenoic acid per day, for 3 years. 2/ Multi-domain intervention: collective training sessions conducted in small groups (6-8 participants) in twelve 120-minute sessions over the first 2 months (two sessions a week for the first month, and one session a week the second month), followed by one session per month until the end of the 3 years, covering the following three areas: nutrition, physical activity, and cognition. The LipiDiDiet study (NTR1705) is a six year, double-blind, parallel-group, multi-centre, multi-country RCT in 311 subjects with prodromal AD (criteria Dubois 2007), receiving the nutrient combination (DHA, EPA, choline, UMP, vitamins C, E, B12, B6, folic acid, selenium, phospholipids) or an iso-caloric control product once daily. Results of the 2 year intervention phase are reported. Primary outcome was a cognitive function composite z-score based on five items from a modified neuropsychological test battery (mNTB): CERAD 10-word immediate recall, delayed recall and recognition, category fluency and letter digit substitution test. Secondary and exploratory outcomes included the memory domain from the mNTB, MRI brain volumes/atrophy rate, Clinical Dementia Rating - Sum of Boxes (CDR-SB),

other cognitive and laboratory parameters, tolerance and safety. Discussion: For the MAPT study cognitive outcomes, adherences outcomes and safety issues are reported. In terms of efficacy, no significant group differences were observed for the primary outcome but results of subgroup analyses found positive results according to the level of amyloid in a subgroup of 271 individuals who performed PET-AV45. Further analyses and subgroup results will be presented during the conference. For the LipiDiDiet study the latest outcome results, including that annual drop out was approximately 10%, results revealed favourable effects of the nutrient combination on CDR-SB, episodic memory, cerebral atrophy rates and blood-based lipid metabolism-related parameters known to impact cardio- and cerebrovascular health, are reported. No significant group differences were observed on the primary outcome and notably the decline on this outcome parameter in the control group was markedly less than expected. Study product compliance was high and there were no reasons for safety concerns. Further analyses and subgroup results will be presented during the conference. Conclusion: Non-pharmacological lifestyle and nutritional interventions show good safety and efficacy in cognitive and biological outcome parameters in long term early intervention studies. These studies highlight the role of lifestyle and nutritional intervention in reducing risk of AD dementia and provide general support for early intervention approach in AD in biomarker positive at risk populations.1. Funding: EUFP7 project LipiDiDiet, Grant Agreement N°211696.

Communication 1: *The MAPT study: results of multi-domain intervention on cognitive performance in amyloid beta positive subjects,* S. Andrieu (INSERM, University of Toulouse UMR1027, Toulouse, France Department of Epidemiology and Public Health, Toulouse University Hospital, Toulouse, France)

Communication 2: *LipiDiDiet Program on multi-nutrient intervention in prodromal AD: converging mechanism from preclinical and clinical results,* T. Hartmann for the LipiDiDiet study group[a] (Deutsches Institut für Demenz Prävention (DIDP), Medical Faculty, Saarland University, Homburg, Germany; Department of Experimental Neurology, Saarland University, Homburg, Germany)

Communication 3: *New results of the LipiDiDiet study: a 24-month RCT investigating the effects of Fortasyn Connect in prodromal AD,* H. Soininenfor the LipiDiDiet study group (Department of Neurology, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland)

S3- STEM CELLS FOR ALZHEIMER'S DISEASE THERAPEUTICS. L.S. Schneider *(Keck School of Medicine of the University of Southern California, USA)*

Introduction: Although tremendous efforts have been made to delay AD progression, all present-day FDA-approved treatments for AD are symptomatic treatments. These drugs are not designed to halt or reverse the underlying process of AD, but rather to compensate for declining brain function. AD is now recognized as multifactorial and, in addition to being considered an amyloidosis and tauopathy, oxidative stress, mitochondrial dysfunction, hormone dysregulation, inflammation, mitotic dysfunction, calcium imbalance, and genetic risk factors are all involved in Alzheimer pathogenesis. Adult human stem cells and stem cell factors constitute a promising therapeutic approach for the treatment of various neurodegenerative disorders including Alzheimer pathology. Early development phase, FDA-approved trials are currently evaluating the impact of human stem cell technologies on AD. Stem cell-based AD therapies represent untapped potential. *Objectives:* In this symposium Dr. Bolmont we will discuss underlying rationales for stem cells as therapeutics for AD and effects on important components of Alzheimer pathology and the gut microbiome; Dr. Baumel will provide a discussion of the designs and approaches to early phase clinical development and proof of concept. Dr. Doraiswamy will examine the future approaches involving disease-in-a-dish, personalized models of mechanisms, and therapeutic approaches. Discussion Intravenous delivery of hMSC safely reduces cerebral amyloidosis in APPPS1 animals. Both aged and young mice show decreased Abeta pathology. hMSC-treated APPPS1 mice show diminished microglial activation. Intravenously delivered hMSC migrate to the brain, are detected at highest levels in 1 hour, and subsequently drop below detection at 1 week. Proteins secreted by hMSC reduce cerebral Aβ following intranasal applications over three weeks. Furthermore, incubation of cells culture expressing human mutated P301L tau with stem cell factors decreased significantly the extent of hyperphosphorylated tau levels. Although all the details of the action of hMSC on AD are not yet fully understood, solid clinical safety profile and preclinical efficacy of hMSC may open a new area for treatment. Results discussed above supported FDA investigational new drug (IND) applications and subsequent early phase clinical trials. In 2015, the FDA granted IND approval for two clinical trials of mesenchymal stem cells to treat Alzheimer's disease. The first clinical sites are the University of Miami, University of California at Irvine and Emory University. Similar trials are underway or being planned in the USA, Europe, and Asia. Though all details of the mechanism of action of specific stem cells on AD are not yet established, it is important to evaluate the clinical relevance of such treatments. Safety is the initial primary goal. Preclinical studies demonstrated the positive impact of hMSC on Abeta in brain. Therefore, at this stage assessment for ARIA-E and ARIA-H is part of the initial trials. Dr. Baumel reviewed the design and approach of the trials. Currently, only mesenchymal cells of different origin and manufacturing preparation are used. However those products are only small fractions of other types of stem cells which may be used to understand their impact on AD and help to develop better cell-type therapy. For example, the creation of repositories of induced pluripotent stem cell (iPSC) lines from patients with Alzheimer's disease will help with disease modelling and drug screening. Additionally, a three-dimensional human neural cell culture model of stem cells can now recapitulate Abeta and tau pathology. Gene editing techniques can be used to develop iPSC lines from normal cells of patients with familial disease by introducing specific genetic mutations and to create isogenic mutation-free control lines, allowing study of the effects of specific genes and modelling of disease. *Conclusion:* Stem cell based therapies may offer new approaches and opportunities to treat or delay the progression of AD by being able to tackle several factors involved in its pathogenesis at once. Advances in technology allow access to the cells affected by disease in sufficient numbers to address and answer questions about the mechanism of action of candidate therapeutics and their specificity. With iPSCs the ability to use cells from specific individuals and to develop an in vitro sample cohort will enable the development of biomarkers with which to assess and predict treatment response and to improve the effectiveness of current therapies and therapies in development. The advancements of strategies for cell therapy in parallel with neuronal and glial approaches are the next steps for Alzheimer clinical trials

Communication 1: *Stem cells for Alzheimer's disease: Abeta amyloidosis, tau pathology and gut microbiota,* T. Bolmont[1,2], A. Lukashev[2], N. Tankovich[2] ((1) Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland; (2) Stemedica International, Lausanne, Switzerland and San Diego, USA)

Communication 2: *Clinical development for mesenchymal stem cells,* B. Baumel (University of Miami, Miami, USA)

Communication 3: *Phase 2a trial of allogenic human mesenchumal stem cells for Alzheimer's disease,* A. Pierce (UCI Irvine, USA)

S4- THE EUROPEAN PREVENTION OF ALZHEIMER'S DEMENTIA (EPAD) PROGRAMME: FROM READINESS COHORT TO CLINICAL TRIAL AND THE ETHICAL FRAMEWORK FOR RISK DISCLOSURE. J.L. Molinuevo *(Barcelona, Spain)*

Introduction: The European Prevention of Alzheimer's Dementia (EPAD) Programme initiated in January 2015 with the first participant being recruited on schedule into the Longitudinal Cohort Study (LCS) in May 2016. The programme is dedicated to implementing an efficient adaptive standing platform proof-of-concept (PoC) trial for secondary prevention. This raises numerous operational, scientific and ethical challenges as participants are discovered in parent cohorts and then move to EPAD LCS and then onto the PoC trial. Objectives: The objectives are to [1a] describe the complex procedures in EPAD to ensure that the LCS is always optimised in its balance of research participants to achieve its dual aim of being a readiness cohort and resource for disease modelling and [1b] share results on LCS construction and the effectiveness of the activities of the Balancing Committee and Algorithm Running Committee, [2] outline the statistical approach taken to determining proof of concept from an (intermediary) biomarker and cognitive perspective and [3] embed the processes above in an appropriate ethical framework as developed specifically for the innovative EPAD project and its challenges. *Discussion:* A Balancing Committee that ensures that only those participants in parent cohorts, who are likely to be suitable for the clinical trial, are invited to participate in their local Trial Delivery Centre (TDC) for achieving the structure of the EPAD LCS. This is done using a bespoke, state-of-the-art participant discovery software solution (PrePAD). This system is dependent on the creation of time and parent cohort specific risk algorithms applied to data in parent cohorts. The Balancing Committee passes these algorithms to the ARC (Algorithm Running Committee) who communicates directly with parent cohorts who are blind to the algorithm used for selection. Moreover, the inclusion of a random sample and people believed to be at very low risk in EPAD LCS means that Parent Cohorts remain blind to the data and results therein that mediated selection. Algorithms are updated each month on the basis of two factors; [1] structure of the LCS and [2] awareness of the virtual pipeline of candidates which have been selected for the proof of concept (PoC) trial. This PoC trial has two major components namely a master protocol and a series of treatment specific appendices. The single master protocol has been designed to randomize participants from the LCS that are eligible for the proof-of-concept trial. Participants agreeing to participate in the PoC trial are assigned to the different treatment arms (appendices) for which the participant is eligible. In each appendix, the randomization is a 3:1 ratio in favour of active study drug compared to a placebo. The placebo arms across different study drugs are combined together to increase the statistical strength for each individual study arm. This borrowing of arms within the single protocol allows for an increased strength due to the common protocol and shared placebo. A novel disease progression model is utilized to analyse the change in the progression of the disease on the cognitive endpoint. Study drug specific biomarkers can be analysed during the trial for proof of target biomarker modulation in concert with the slowing in the rate of cognitive decline. The concatenation of longitudinal cohort with clinical trial platform within EPAD presents distinct ethical challenges. A unified ethical guidance framework covers the journey of EPAD participants from parent cohorts into the LCS and through to the PoC trial. It involves a staged consent process which provides specific and general information on the whole EPAD process, and covers the transparent recruitment of participants into PoC trials. An education process conducted prior to and during LCS participation precedes the disclosure of biomarker status during PoC recruitment. This is informed by qualitative research with potential EPAD participants which examined the potential implications and perceived value of the disclosure of AD risk status and contributed to the development of recommendations for best practice. Conclusion: In designing the EPAD Platform multiple interacting considerations had to be managed from a scientific, statistical and ethical perspective. Unlike standard research projects, the EPAD research study is constructed in its entirety from four major components (parent cohorts, virtual register, EPAD LCS and the PoC trial) and the three boundaries between each of these components. The effectiveness of the work of the balancing committee in maintaining trial readiness will be presented as will the overarching design of the PoC study with emphasis on the innovative adaptive trial approach. These elements will be framed with reference to the work of the Ethics, Legal and Societal Implications (ELSI) work package including qualitative data on attitudes to risk disclosure which have informed the staged approach to consent and conveyance of information to research participants as they journey through EPAD from parent cohort to PoC trial.

Communication 1: *Ensuring that the EPAD Readiness Cohort remains 'fit for purpose',* C. Ritchie[1], L. Vermunt[2], A. Soloman[3], L. Truyen[4], A. Satlin[5], J.L. Molinuevo[6], G. Muniz Terrera[1], B. Tom[7] ((1) University of Edinburg, Scotland; (2) VUMC, Amsterdam, Netherlands; (3) Karolinska Institute, Stockholm, Sweden; (4) Janssen, Titusville, USA; (5) Eisai Pharmaceuticals, Woodcliff Lake, USA; (6) BBRC, Barcelona, Spain; (7) MRC Biostatistics Unit, University of Cambridge, UK)

Communication 2: *The EPAD Proof of Concept Trial: A Master Protocol for Increasing Efficiency,* S. Berry[1], S. Dhadda[2], V. Dragalin[3], M. Fitzgerald[1], P. Hougaard[4], M. Quintana[1], K. Wathan[3] ((1) Berry Consultants Ltd, Austin, USA; (2) Eisai Pharmaceuticals, Woodcliff Lake, USA; (3) Janssen, Titusville, USA; (4) Lundbeck, Copenhagen, Denmark)

Communication 3: *From parent cohort to clinical trial in EPAD; the ethics of a stepped approach to disclosure and risk communication,* R. Milne[1], A. Diaz[4], S. Bemelmans[2], K. Tromp[3], E. Bunnik[3], D. Gove[4], S. Badger[1], E. Richard[2], M. Maman[5], M. Schermer[3], L. Truyen[6], C. Brayne[1] ((1) Berry Consultants Ltd, Austin, USA; (2) Eisai Pharmaceuticals, Woodcliff Lake, USA; (3) Janssen, Titusville, USA; (4) Lundbeck, Copenhagen, Denmark)

PANEL DISCUSSIONS

PRESENTATION 1: RE-EVALUATION OF THE NIA-AA GUIDELINES FOR ALZHEIMER'S DISEASE. C.R. Jack, Jr[1], D.A. Bennett[2], K. Blennow[3], M.C. Carrillo[4], C. Elliott[5], S.B. Haeberlein[6], D. Holtzman[7], W. Jagust[8], F. Jessen[9], J. Karlawish[10], E. Liu[11], J.L. Molinevo[12], T. Montine[13], C. Phelps[5], K.P. Rankin[14], C.R. Rowe[15], P. Scheltens[16], E. Seimers[17], H.M. Snyder[4], R. Sperling[18] *((1) Radiology Department, Mayo Clinic, Rochester, USA; (2) Neurology Department, Rush University Medical Center, Chicago, USA; (3) Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden; (4) Medical & Scientific Relations, Alzheimer's Association, Chicago, IL, USA; (5) Division of Neuroscience, National Institute on Aging, National Institutes of Health, Bethesda, USA; (6) Biogen idec, Cambridge, USA; (7) Department of Neurology, Washington University, St Louis, St Louis, USA; (8) Department of Neurology, University of California, Berkley, Berkley, USA; (9) Department of Psychiatry, University of Cologne, Cologne, Germany; (10) Departments of Medicine, Medical Ethics and Health Policy, and Neurology, University of Pennsylvania, Philadelphia, USA; (11) Prothena Corporation, San Francisco, USA; (12) Department of Neurology, ICN Hospital Clinic i Universitari and Pasqual Maragall Foundation, Barcelona, Spain; (13) Department of Pathology, Stanford University, Palo Alto, USA; (14) Department of Neurology, University of California San Francisco, San Francisco, USA; (15) Department of Neurology, University of Melbourne, Melbourne, Australia; (16) Alzheimer Center, VU University Medical Center, Amsterdam, Netherlands; (17) Biomedicines Business Unit, Alzheimer's Disease Platform Team, Eli Lilly and Company; (18) Department of Neurology, Harvard Medical School, Brigham and Women's Hospital and Massachusetts General Hospital, Boston, USA*)

Background: In 2011, the National Institute on Aging (NIA) at the National Institutes of Health (NIH) and the Alzheimer's Association published revised guidelines (NIA-AA) for modernization of the diagnosis of Alzheimer's disease. In these guidelines, the workgroups identified Alzheimer's disease as a continuum with three distinct stages: Preclinical due to Alzheimer's, Mild Cognitive Impairment due to Alzheimer's and Dementia due to Alzheimer's. Since the 2011 publication of the NIA-AA guidelines, there have been a number of studies reporting data that support a re-evaluation of the guidelines. Methods: In 2016, the NIA and the Alzheimer's Association convened an international workgroup of scientific experts tasked with the evaluation of the existing guidelines. The workgroup discussions are on-going. *Results:* The NIA-AA workgroup's overall goal is to define Alzheimer's disease and stage it across bo disease should be defined as a pathophysiological construct. Biomarkers alone define the presence of the Alzheimer's disease in a living person, without the requirement of clinical symptoms. The NIA-AA workgroup will share an update on their discussions of this conceptual model and the research needed to validate it. *Conclusion:* The NIA-AA guidelines revision is an on-going process. It is expected that discussions during Clinical Trials in Alzheimer's disease (CTAD) and other forums will involve feedback which will continue to refine the workgroup's thinking and revision process.

PRESENTATION 2: SUBJECT ENROLLMENT' – A MAJOR BARRIER FOR DEVELOPING TREATMENTS FOR DEMENTIA/ALZHEIMER'S. M.W. Weiner[1], M.C. Carrillo[2], L.M. Ryan[3], S.L. Budd-Haeberlein[4], W.Z. Potter[5], Z. Khachaturian[6] *((1) Center for Imaging of Neurodegenerative Diseases, San Francisco VAMedical Center, San Francisco, USA; (2) Alzheimer's Association, Chicago, USA; (3) National Institute on Health / National Institute on Aging (NIH/NIA), Bethesda, USA; (4) Biogen Corporation, Biogen, Cambridge, USA; (5) National Institute of Mental Health (NIMH), Bethesda, USA; (6) Editor in Chief, Alzheimer's & Dementia. Rockville, USA)*

Background: Rapid and efficient enrollment of adequate numbers of subject for clinical trials is crucial for accelerating the development of new treatments for Alzheimer's disease (AD). One of the major rate-limiting factors that slow the development of effective treatments is the speed of subject enrollment into trials, which will become even more limiting as novel agents now in the pipeline become available. The rate of subject enrollment is determined by several factors; the purpose of the Symposia ['Town-Hall'/ meeting] at CTAD is to offer an open forum to discuss this problem and to review various options to address the dilemma. *Methods*: During the past year, a workgroup has been formed to address this issue. The workgroup evolved from a meeting of the Scientific Advisory Board of ADNI, and has been expanded to include industry partners. The workgroup met at AAIC 2016 in Toronto, at a meeting convened by the Alzheimer's Association and the NIA. An 'Editorial' on this topic, in Alzheimer's and Dementia, has delineated the scope of the problem along with a call for commentaries by the scientific community. Additional meetings of a workgroup are being organized by the Alzheimer's Association, the NIA and A&D to discuss options and create an action plan. *Results:* The first major result was a unanimous consensus of workgroup participants that the rate of subject recruitment into AD clinical trials is one of the most serious impediments to finding effective treatments for AD. The second major result was the recommendation that a major public awareness campaign should be initiated as soon as possible. This public awareness campaign will not focus on any specific trial funded by any funding agency or industry. Instead the campaign will concentrate on increasing awareness of the importance of: a) disease understanding as a continuum beginning before symptoms, b) preventions of Alzheimer's disease, and c) the need for many more elders to participate in AD clinical trials. Specifically, the growing number of prevention trials on cognitively normal subjects with preclinical AD has greatly increased the need for recruitment of normal elders. Similarly, the growing number of trials on prodromal subjects has increased the need for recruitment of elders with memory complaints, memory problems, and mild cognitive impairment. The specific nature of the proposed public awareness campaign, and how this will be funded, need to be determined. This Symposium will include brief presentations from the NIA, Alzheimer's Association, the Pharmaceutical industry and ADNI. Sufficient time for public comment will be provided. *Conclusions:* There is general agreement that many more subjects are needed for rapid enrollment of AD clinical trials including preclinical, prodromal, and dementia patients with AD. This Symposium will discuss an emerging plan for a broad based multi-national/multi-cultural/multi-language public awareness campaign aimed at encouraging more elders to participate in AD clinical trials. Audience participation is encouraged.

Workshop: Statistical Short Course:

NEW TRENDS IN CLINICAL TRIAL DESIGNS IN SEARCH OF NEXT GENERATION TREATMENTS

To enhance the theme and focus for the 8th annual meeting of CTAD, this short course will provide some of the latest development and tools in the clinical trial design for AD that will enable the search for the next generation treatments of AD.

Part I: *Assessing a potential disease modifying effect: Delayed Start Design and Analysis*, P. Aisen (Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, USA)

One of the key interests in developing the next generation AD treatments is demonstrating a potential disease modifying effect. Delayed start design has been proposed as a viable clinical trial design to assess whether an observed treatment effect is due to symptomatic effect or disease modifying effect. This approach was endorsed in the FDA draft guidance for clinical development of AD drugs. This short course will introduce the background of the Delayed Start design, provide key considerations of design elements, and describe novel statistical analysis methods and interpretation of results. Examples from actual clinical trials in AD that have implemented the design and analysis will be shared. There will be time for Q&A and interactions with participants.

Part II: *Controlling for false positive findings among primary and key secondary outcomes: Multiple Testing Procedures*, S. Ruberg (Eli Lilly and Company, Indianapolis, USA)

As the AD field is exploring earlier stages of the disease in searching for an effective treatment that alters the underlying disease pathology and slows or prevents the disease progression, special considerations need to be given to the most appropriate primary and secondary endpoints in clinical trials. This in turn presents the needs to control for false positive findings (Type I errors) for label implications and the subsequent technical challenge of how to control for multiple comparisons among primary and key secondary endpoints. Various statistical methods for controlling for multiple comparisons have been established and have been implemented in many other therapeutic areas. In this short course, an overview of the multiple testing strategies will be provided including logical explanations without the math. Various approaches will be described that may be appropriate for future AD trials, such as fixed sequence approach and more flexible and visual approaches. There will be time for Q&A and interactions with participants.

Oral Communications

OC1: PHASE 3 TRIAL OF TAU AGGREGATION INHIBITOR THERAPY WITH LMTM IN MILD ALZHEIMER'S DISEASE. Lon S Schneider[1], Serge Gauthier[2], Howard H Feldman[3], Gordon K Wilcock[4], Giovanni B Frisoni[5], Jiri Hardlund[6], Karin Kook[7], Damon J Wischik[6], Bjoern O Schelter[8], John M D Storey[6,8], Charles R Harrington[6,8], Claude M Wischik[6,8] *((1) Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA; (2) McGill Centre for Studies in Aging, Verdun, Quebec, Canada; (3) University of California San Diego, CA, USA; (4) Oxford University, Oxford, UK; (5) University of Geneva, Geneva, Switzerland; (6) TauRx Therapeutics Ltd., Singapore; (7) Salamandra LLC, Bethesda, Maryland, MD, USA; (8) University of Aberdeen, Aberdeen, UK)*

Background: An exploratory phase 2 trial in mild or moderate Alzheimer's disease (AD) previously identified 138 mg/day as the minimum dose of methylthioninium chloride (MTC) required to reduce rate of disease progression on clinical and imaging endpoints1. A dose of 228 mg/day was found to be ineffective due dose-dependent absorption limitations of MTC. Leuco-methylthioninium bis(hydromethanesulfonate) (LMTM), a novel stabilized reduced form of the methylthioninium (MT) moiety2 which is better absorbed and tolerated3, permits higher doses to be tested. It acts as a selective TAI in vitro2 that reduces brain tau aggregation pathology in transgenic mouse models4. *Methods:* The present 18-month double-blind, placebo-controlled trial (NCT01689233) was performed in subjects with mild dementia and probable AD. It is the second of two phase 3 studies in AD being reported in 2016. Subjects were randomized 1:1 to receive oral LMTM at doses of 200 mg/day or control (containing 8 mg/day, to maintain blinding) respectively. Primary efficacy outcomes were change from baseline scores in cognitive (ADAS-Cog) and functional (ADCS-ADL) scores. Three-monthly assessment included magnetic resonance imaging (MRI) measurement of lateral ventricular, temporo-parietal and hippocampal volume as a key secondary outcomes to determine the effect of treatment on rate of brain atrophy. *Results:* A total of 800 patients were randomized. Approved AD treatments were being taken in 79%. The withdrawal rate from randomized treatment was 32% overall. Dementia was of minimal (CDR 0.5) severity in 62% and mild (CDR 1) severity in 38%. The mean age (standard deviation) was 70.4 (9.0) years and MMSE score at baseline was 23.0 (2.0). The study efficacy and other safety outcomes will be reported. *Conclusion:* The results of this phase 3 trial will highlight the potential therapeutic value of TAI therapy in AD. *References:* 1. Wischik CM, et al. (2015) J. Alzheimer's Dis. 44:705-720; 2. Harrington CR, et al. (2015) J. Biol. Chem. 290:10862-10875; 3. Baddeley T, C., et al. (2015) J. Pharmacol. Exptl. Therapeutics 352:110-118; 4. Melis V, et al. (2015) Behav. Pharmacol. 26:353-368.

OC2: COLLABORATION FOR ALZHEIMER'S PREVENTION: A STRUCTURED APPROACH TO DATA AND SAMPLE SHARING BASED ON CAP PRINCIPLES AND RECOMMENDATIONS. Maria C. Carrillo[1], Stacie Weninger[2], Billy Dunn[3], Paul S. Aisen[4], Randall J. Bateman[5], Joanne D. Kotz[2], Jessica B. Langbaum[6], Eric McDade[5], Susan L. Mills[5], Eric M. Reiman[6], Reisa Sperling[7], Anna M. Santacruz[5], Pierre N. Tariot[6], Kathleen A. Welsh-Bohmer[8] *((1) Medical & Scientific Relations Division, Alzheimer's Association, Chicago, IL, USA; (2) F-Prime Biomedical Research Initiative, Cambridge, MA, USA; (3) Division of Neurology Products, U.S. Food and Drug Administration, Silver*

Spring, MD, USA; (4) University of Southern California Alzheimer's Therapeutic Research Institute, San Diego, CA, USA; (5) Department of Neurology, Washington University, St Louis, MO, USA; (6) Banner Alzheimer's Institute, Phoenix, AZ, USA; (7) Department of Neurology, Brigham and Women's Hospital, Boston, MA, USA; (8) Departments of Neurology & Psychiatry, Duke University, Durham, NC, USA)

Backgound: The Collaboration for Alzheimer's Prevention (CAP) is made up of representatives from the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) Study, Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU), Alzheimer's Prevention Initiative (API), researchers from the TOMMORROW trial, the U.S. Food and Drug Administration (FDA), the National Institute on Aging (NIA), the Alzheimer's Association, and F-Prime Biomedical Research Initiative (FBRI). CAP has proposed principles and recommendations to provide a realistic framework for sharing data and biological samples from preclinical AD trials, published in Alzheimer's & Dementia, 12(2016). This presentation will focus on how CAP proposes to put these principles into practice. *Methods:* CAP recognizes that sharing data and biological samples from preclinical AD trials is critical to ensure that knowledge gained through individual trials will enable progress of the field as a whole. As preclinical trials will be conducted over several years, sharing emerging data and samples with the scientific community as soon as possible is imperative for accelerating progress toward effective treatments. Maintaining the scientific integrity of the trial, including preservation of blinding, is essential. Sharing must not compromise the ability of the study to with- stand independent scientific scrutiny, including regulatory review. Also, maintaining the confidentiality of participants in these trials is of the utmost importance and may pose a particular challenge in certain populations such as those at risk for carrying a dominant mutation causing familial early-onset AD. *Results:* CAP has proposed principles and recommendations to provide a realistic framework for sharing data and biological samples from preclinical AD trials. By establishing principles for data sharing, CAP has outlined a path that we believe will lead to greater insights into AD and, as a result, will catalyze the development of new potential treatments that stand the greatest chance of success.Conclusions: CAP representatives are working together to propose sharing of CAP data, based on CAP agreed upon principles. A discussion on a structured approach to sharing data will be presented.

OC3: EFFECT OF PF-06648671, A NOVEL GAMMA SECRETASE MODULATOR, ON CSF BETA AMYLOID PEPTIDES FOLLOWING ORAL SINGLE AND MULTIPLE-DOSE ADMINISTRATION IN HEALTHY SUBJECTS.

Ruolun Qiu[1], Richann Liu[1], Anne-Marie Wills[1,3], Fernando Dela Cruz[2], Charles Carrieri[2], Ping He[1], Eva Hajos-Korcsok[1], Terrence Fullerton[4], Claire Leurent[1], Robert Alexander[1] *((1) Pfizer Inc, Neuroscience & Pain Research Unit, Cambridge, MA, USA; (2) Pfizer Clinical Research Units, New Haven, CT, USA; (3) Massachusetts General Hospital, Neurology, Boston, MA, USA; (4) Pfizer Inc, Global Innovative Pharma, Clinical Sciences, Groton, CT, USA)*

Background: A considerable body of genetic evidence supports a pivotal role of γ-secretase in Alzheimer's Disease (AD). Through the proteolytic cleavage of the amyloid precursor protein (APP), γ-secretase is responsible for producing amyloid-β (Aβ) peptides containing various carboxy-termini, including the most amyloidogenic peptide, Aβ42. The accumulation and aggregation of Aβ42 peptides in the brain is believed to be one of the underlying causes of AD. PF-06648671 is a potent γ-secretase modulator that inhibits Aβ40 and Aβ42 production by shifting cleavage away from Aβ42 and Aβ40 toward production of truncated and less neurotoxic forms Aβ37 and Aβ38, without blocking APP cleavage and total Aβ production, as demonstrated both in vitro and in preclinical species. Importantly, PF-06648681, as a γ-secretase modulator, did not inhibit the cleavage of Notch or other substrates and therefore has the potential to avoid the mechanism-based toxicity associated with γ-secretase inhibitors (GSIs). Here we report the effect of PF-06648671 on cerebrospinal fluid (CSF) Aβ biomarkers after single and multiple oral dosing in healthy subjects. *Methods:* A single dose CSF biomarker study was conducted in healthy young subjects (18-55 y) to evaluate the effect of PF-06648671 on CSF Aβ following single oral doses. In this study a total of 22 subjects were administered with single doses of PF-06648671 or placebo: 150 mg (N=3), 300 mg (N=11) or placebo (N=8) and CSF was collected serially over 36 hours after dosing via lumbar cannulation. In the Multiple Ascending Dose (MAD) study, six cohorts of healthy young subjects (n=10/cohort, 8 active: 2 placebo) dosed orally at 4 to 200 mg PF-06648671 daily for 14 days have been completed. PF-06648671 200 mg daily dose was also administered to a cohort (8 active: 2 placebo) of healthy elderly subjects (65-85 y) for 14 days. CSF samples were collected on Day 1 prior to 1st dose or Day -3 (a baseline sample) and on Day 14 prior to dose (or Day 15, 24 hours post last dose) in 40, 100 and 200 mg dose groups of healthy young subjects. CSF samples collected in these two studies were analyzed to determine PF-06648671 concentration and Aβ (x-40, x-42, x-38, x-37 and total) levels. *Results:* In both studies reported here, PF-06648671 was safe and well tolerated at the highest doses tested (single dose of 300 mg and multiple doses of 200 mg QD). In the completed single dose CSF study, all reported AEs were attributed to the CSF procedure except one mild dry mouth which was considered drug related. In the ongoing MAD study, the most frequently reported AEs included headache, dizziness, nausea, back pain and vomiting and were considered related to the CSF lumbar puncture procedure. No drug-related clinically significant findings were observed in laboratory tests, ECG and vital signs. Maximum tolerated dose (MTD) was not reached up to 200 mg QD. Following a single dose of PF-06648671, significant CSF Aβx-40 and Aβx-42 reductions were observed with a maximum effect at approximately 16 hours post-dose. The maximum mean reductions in CSF Aβx-40 and Aβx-42 were 22.3% and 38.9% respectively, following a single dose of 300 mg, after correction for a notable placebo response (increase of Aβ over time). Following 14-day multiple doses of PF-06648671, robust and dose-dependent reductions in CSF Aβx-40 and Aβx-42 levels were observed, compared to baseline. Approximately 14%, 43% and 59% reduction (placebo-adjusted) in CSF Aβx-42 were observed at predose on Day 14 (or 15) following repeated doses of 40, 100 and 200 mg, respectively. The CSF Aβx 40 demonstrated a dose dependent reduction to a smaller extent and as a result, CSF Aβ42/Aβ40 ratios decreased with dose. In addition, CSF Aβx-37 and Aβx-38 concentrations were significantly increased in a dose-dependent manner following both single and multiple doses of PF-06648671 while a minimal change in CSF total Aβ was observed across doses. Approximately 335% and 46% increase (placebo-adjusted) in CSF Aβx 37 and Aβx 38 were observed at predose on Day 14 (or 15) following 200 mg repeated daily doses. *Conclusions:* As a γ-secretase modulator, PF-06648671 strongly and dose-dependently reduced Aβx-42 and Aβx-40 and increased the shorter fragments Aβx 37 and Aβx 38 in CSF following single and multiple dose treatment in healthy subjects, while total Aβ production was unchanged. In these studies, PF-06648671 was safe and well tolerated after single dose up to 300 mg and 14-day multiple doses up to 200 mg QD in healthy young and/or healthy elderly subjects. An investigation of a higher dose (360 mg QD) is currently ongoing in a separate cohort of healthy subjects.

OC4: PHASE 3 STUDY DESIGNS TO EVALUATE TREATMENT WITH A BACE INHIBITOR, LY3314814/ AZD3293, IN PATIENTS WITH EARLY ALZHEIMER'S DISEASE. John R. Sims[1], Jamie A. Mullen[2], Jennifer A. Eads[1], AnnCatherine M. Downing[1], Alette M. Wessels[1], Scott W. Andersen[1], Jennifer A. Zimmer[1], Katherine J. Selzler[1], Pierre N. Tariot[3] *((1) Eli Lilly and Company, Indianapolis, IN, USA; (2) AstraZeneca Pharmaceuticals, Cambridge, MA, USA; (3) Banner Alzheimer's Institute, Phoenix, AZ, USA)*

Background: LY3314814/AZD3293 is a potent inhibitor of the β-site amyloid precursor protein-cleaving enzyme 1 (BACE1/β-secretase). It is being developed for the modification of the clinical course of Alzheimer's disease (AD) in patients diagnosed with early AD. Early AD is defined as the continuum of patients with mild cognitive impairment (MCI) due to AD (i.e., prodromal AD) and patients diagnosed with mild dementia of the Alzheimer's type. Two randomized, placebo-controlled Phase 3 trials are currently underway: AMARANTH (NCT02245737) and DAYBREAK-ALZ (NCT02783573). An overview of the primary outcome and designs of both trials will be presented. *Methods:* The initial study, AMARANTH, is a Phase 2/3 design in an early AD population. This design included a safety interim analysis (triggered at 210 patients with 3 months of exposure) prior to initiating the second Phase 3 study, DAYBREAK-ALZ, in a mild AD dementia population. Both trials will test 20 mg and 50-mg doses in a population aged 55-85 years old with cerebrospinal fluid (CSF) or amyloid positron emission tomography (PET) evidence of elevated cerebral amyloid. Both trials use the 13-item Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog13) as the primary outcome and both trials will accommodate delayed-start analyses following the placebo-controlled periods. The primary outcomes for AMARANTH and DAYBREAK-ALZ are assessed at 104 and 78 weeks, respectively. Both trials will also test key secondary functional outcomes, the Alzheimer's Disease Cooperative Study instrumental Activities of Daily Living Inventory (ADCS-iADL) and the Functional Activities Questionnaire (FAQ) with strict Type 1 error control and have extensive disease-progression biomarkers, which will be further discussed. *Results:* The Independent Data Monitoring Committee (IDMC) performed the unblinded safety interim analysis (no efficacy measures were evaluated) in second quarter of 2016. At data lock, at least 415 subjects had received a minimum of one dose and 212 had received 13 weeks of treatment. The IDMC recommended continuing the trial without modification. *Conclusion:* As a result of the safety interim analysis of the AMARANTH data and the recommendation of the IDMC, AMARANTH transitioned to Phase 3 and DAYBREAK-ALZ was initiated in the second quarter of 2016. Both trials are expected to have last patient visit for the primary outcome measures in the second half of 2019. Safety and efficacy results are expected to be disclosed at a forthcoming meeting by 2020.

OC5: A PHASE IB, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTIPLE DOSE STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF ESCALATING DOSES OF CRENEZUMAB IN PATIENTS WITH MILD-TO-MODERATE AD. Geoffrey A. Kerchner[1], Veronica Asnaghi[2], Michael Rabbia[3], Michael Ward[1], Angelica Quartino[1], Lee Honigberg[1], Susanne Ostrowitzki[1], Jillian Smith[2], Robert Paul[1], William Cho[1] *((1) Genentech, Inc., a member of the Roche Group, South San Francisco, CA, USA; (2) F. Hoffman-La Roche AG, Basel, Switzerland 3Roche Innovation Center, New York, NY, USA)*

Background: Crenezumab is a humanized anti-β-amyloid monoclonal antibody in development for the treatment of Alzheimer's disease (AD). Crenezumab binds multiple forms of β-amyloid, with high affinity for oligomers, the form hypothesized to be primarily responsible for neurotoxicity. The molecule was designed as an IgG4 antibody based on the hypothesis that reduced effector function would lower the risk of inducing amyloid-related imaging abnormalities (ARIA). In two Phase II trials, crenezumab was found to be generally safe and well-tolerated at doses of up to 15 mg/kg intravenously (IV) every four weeks in patients with mild-to-moderate AD, with only one case of asymptomatic ARIA-E (sulcal effusion) in both studies combined (out of 347 crenezumab-treated patients, or 0.3%). As the current safety profile allows for the evaluation of higher dose levels, the objective of this study is to evaluate the safety and tolerability of crenezumab up to 120 mg/kg IV every four weeks in patients with mild-to-moderate dementia due to AD. *Methods:* The study is conducted in patients aged 50-90 years old with a diagnosis of probable AD (by NINCDS-ADRDA criteria), a CDR global score of 0.5 or 1, a screening MMSE of 18-28, and a [18F]-florbetapir PET scan positive for cerebral amyloid. There are three cohorts: Cohort 1 randomized patients to crenezumab 30 mg/kg, placebo for 30 mg/kg, crenezumab 45 mg/kg, or placebo for 45 mg/kg in a 5:1:5:1 ratio. Cohort 2 randomized patients to crenezumab 60 mg/kg or placebo in a 5:1 ratio. Cohort 3 randomizes patients to crenezumab 120 mg/kg or placebo in a 5:1 ratio. All patients receive study drug (crenezumab or placebo) IV every 4 weeks for 12 weeks (4 doses). Escalation from Cohort 1 to 2 and from Cohort 2 to 3 occurred after review by an internal, unblinded safety monitoring committee of all available safety and tolerability data up to the date that the last patient in the previous cohort completed the second dose of study drug and subsequent MRI scan. In all cohorts, after completing the 12-week double-blind portion of the study, patients have the option to continue on open-label crenezumab IV every 4 weeks at the dose assigned at randomization, except for Cohort 3, in which the open-label dose will be 60 mg/kg. This open-label study extension is ongoing. All patients undergo regular brain MRI to monitor for ARIA-E and ARIA-H. A secondary objective of this study is to characterize the pharmacokinetics of crenezumab at these doses, and exploratory objectives include assessment of clinical efficacy and effects on imaging and plasma biomarkers. *Results:* Cohort 1 enrolled 26 patients. Cohort 2 enrolled 26 patients. Cohort 3 enrollment is ongoing. Details of the safety and tolerability of crenezumab will be presented. *Conclusion:* The safety and tolerability of crenezumab is being evaluated in patients with mild-to-moderate AD at doses up to 120 mg/kg IV every four weeks. Detailed conclusions will be presented

OC6: RESVERATROL REGULATES NEUROINFLAMMATION AND INDUCES ADAPTIVE IMMUNITY IN ALZHEIMER'S DISEASE. R. S. Turner[1], M. Hebron[1], X. Huang[1], H. Brown, Paul Aisen[2], Robert Rissman[3], Charbel Moussa[1] *((1) Department of Neurology, Georgetown University Medical Center, Washington, D.C., USA; (2) Alzheimer's Therapeutic Research Institute (ATRI), University of Southern California, San Diego, Ca., USA; (3) Alzheimer's Disease Cooperative Study (ADCS), University of California, San Diego, Ca., USA)*

Background: In Alzheimer's disease (AD) brain, elevated CNS sirtuin 1 (SIRT1) decreases matrix metalloproteinase-9 (MMP-9) expression and activity. Treatment of mild-moderate AD subjects (N=119) for 52 weeks with the SIRT1 activator resveratrol (up to 2 g by mouth daily) attenuates progressive declines in CSF Aβ40 levels and activities of daily living (ADCS-ADL) scores. For individuals with CSF Aβ42 < 600 ng/ml at baseline (biomarker-supported AD)

resveratrol treatment also attenuates progressive decline in CSF Aβ42 levels (Turner et al., Neurology 2015;85:1383). *Methods:* For this study, we examined banked CSF and plasma samples from a random subset of AD subjects with CSF Aβ42 < 600 ng/ml at baseline (sample size: N = 19 resveratrol-treated and N = 19 placebo-treated). We utilized multiplex Xmap technology to measure markers of neurodegenerative disease and metalloproteinases in CSF and plasma. *Results:* Compared to the placebo-treated group, at 52 weeks resveratrol markedly reduced CSF MMP9 and increased MDC levels. Compared to baseline, resveratrol treatment decreased CSF MMP9 and increased MDC, IL-4, and FGF2. Compared to placebo, at 52 weeks resveratrol increased plasma MMP10. Compared to baseline, resveratrol increased plasma MMP10 and decreased IL-12P40, IL12P70, and RANTES. In this subset analysis, resveratrol treatment attenuated declines in mini-mental status examination (MMSE) scores, change in activities of daily living (ADCS-ADL) scores, and CSF Aβ42 levels during the 52-week trial. *Conclusions:* Collectively, these data suggest that resveratrol activates the SIRT1 pathway in brain to decrease CSF MMP9, attenuate neuroinflammation, and induce adaptive immunity. SIRT1 activation may be a viable drug target for treatment of neurodegenerative disorders.

OC7: RESULTS OF PHASE I CLINICAL TRIAL OF ABVAC40, AN ACTIVE VACCINE AGAINST AB40. Ana Mª Lacosta[1], Pedro Pesini[1], Virginia Pérez-Grijalba[1], Ivan Marcos[1], Leticia Sarasa[1], Itziar San-José[1], Laura Nuñez[2], Mercé Boada[3], Lluis Tárraga[3], Agustín Ruiz[3], Manuel Sarasa[1] *((1) Araclon Biotech, Zaragoza, Spain; (2) Grifols S.A., Barcelona, Spain; (3) Fundaciò ACE. Barcelona Alzheimer Treatment & Research Center, Barcelona, Spain)*

Background: Aβ40 is the most abundant Aβ species in CSF and plasma and can form diffusible aggregates which are highly toxic to cells. In a study by Näslund et col. (Proc. Natl. Acad. Sci. USA; 1994) it was found that Aβ40 was the predominant variant in sporadic Alzheimer's disease (AD) brains whereas the principal Aβ variant in brains from non-demented elderly controls was Aβ42. Indeed, Aβ40 has been associated with the development of AD, particularly in patients with Down syndrome. Currently, ABvac40 is the only active immunotherapy targeting the C-terminal fragment of Aβ40. *Methods:* A placebo-controlled, parallel groups, phase-I study, was run to assess the safety and tolerability of repeated subcutaneous administration of ABvac40 in patients (16 verum; 8 placebo) with mild to moderate AD. To minimize the risk for the participants, the first four randomized participants received 2 half doses of ABvac40 or placebo as corresponded, the second group of four individuals received 2 entire doses and the remaining 16 individuals received three entire doses at monthly intervals, of verum or placebo as corresponded. The primary endpoint was the occurrence of adverse events (AE) that was compared between the verum and the control group by the chi-square or Fisher exact test. The biological activity of ABvac40 was assessed by titration ELISA of specific anti-Aβ40 antibodies in plasma. The specificity of the antibodies was assessed in plasma sample pre-adsorbed with the same peptide used for immunization. *Results:* The analysis of primary endpoint carried out in the Safety Population (24 patients) showed no statistical significant differences between the verum and control group in the comparisons of the frequency of overall AEs (p=0.6214) and grouped as neurological (p=0.2038), psychiatric (p=1.000) and cardiovascular (p=1.000). The analysis of the immune response induced in participants showed differences between groups of treatment at the end of the study for the mean OD (representing level of anti-Aβ40 antibodies). Eleven individuals (92%) that received three shots of ABvac40 generated antibody titers; five of them (45%) presented titers higher than 1000. *Conclusions:* Given that there was a relevant immune response in all but two of the treated subjects, the clinical trial is considered satisfactory based upon the very low frequency of AEs, which in average was not significantly different between the verum and placebo groups. These results guarantee the progression to a next phase of clinical trial.

OC8: OPTIMIZED MACHINE LEARNING METHOD FOR AUTOMATED PRESCREENING OF PATIENTS FOR CLINICAL TRIALS. Sulantha Mathotaarachch[1], Tharick A. Pascoal, Monica Shin, Andrea L. Benedet, Thomas Beaudry, Min Su Kang, Vladimir Fonov, Serge Gauthier, Pedro Rosa-Neto *(Translational Neuroimaging Laboratory, McGill University Research Centre for Studies in Aging, McGill University, Montreal, Canada)*

Background: Identifying individuals destined to develop Alzheimer's dementia (AD) within time frames acceptable for clinical trials constitutes an important challenge when designing disease-modifying interventions. The enrolment of mild cognitive impairment (MCI) individuals with abnormal amyloid measures or with amnestic symptoms has been postulated as an effective method for population enrichment due to their increased progression rates to dementia. However, studies have repeatedly shown unsatisfactory progression rates in these groups of individuals, leaving researchers perplexed. In fact, recent literature has proposed that the combination of brain amyloidosis and tau biomarkers can better identify MCI individuals on the AD pathway. Using advanced machine learning techniques, we propose an automated prescreening method created to identify the MCI individuals who are more likely to develop AD within 24 months in conjunction with a combination of continuous measurements of cerebrospinal fluid (CSF) amyloid-β and tau. We further created an open access hosted web site to demonstrate its applicability and to make this tool freely available for the use in clinical trials. *Methods:* The features incorporated in our analysis included age, gender, APOE ε4 status, and CSF measurements (amyloid-β1-42, total tau and phosphorylated tau (p-tau) at threonine 181) with their respective ratios from 260 individuals taken from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Out of the 260, we used 182 individuals for training and 78 individuals for the validation of the subsequent prediction. The algorithm trained an ensemble of Random Forest classifiers, each with an under-sampled majority (stable MCI) and the full minority (progressive MCI) class individuals. The final probability of progression was calculated as the average probability of progression across all the Random Forest classifiers. *Results:* The novel classifier obtained an accuracy of 75%, sensitivity of 69%, and specificity of 77% using the combination of the aforementioned features. The prescreening tool is currently available for use at http://predictalz.thebrainconnectome.com/PredictAlz_CSF. This web page also contains other reference algorithms (regularized logistic regression) to compare the final prediction. *Conclusion:* With the comparably high specificity of 77%, this tool has an immediate applicability to reduce the false positive enrolments at the recruitment stage, increasing the rate of progression compared with traditional methods, which in turn, results in an increased statistical power and reduced costs in clinical trials. To the best of our knowledge, this is the first automated prescreening tool incorporating amyloid-β and tau biomarker measurements. It is important to mention that the associated web site provides a user-friendly, interactive interface for a real-time prediction based on the subjects' CSF measurements.

OC9: ADAPTIVE ENRICHMENT TRIAL DESIGN TO LEARN WHICH SUBPOPULATIONS BENEFIT FROM TREATMENTS, BASED ON APOE4 CARRIER STATUS.
Aaron Fisher, Michael Rosenblum *(Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD USA)*

Backgrounds: Prior uncertainty regarding treatment effect heterogeneity can pose a challenge to trial designers. If the treatment only benefits a subset of the population, standard clinical trials enrolling from the entire population may have low power. On the other hand, if the entire population benefits, a standard trial enrolling only one subpopulation will not provide any information about the complementary population. These issues can be mitigated with the use of an adaptive enrichment trial design. Such designs consist of a set of decision rules for early stopping of participant enrollment in different population subsets based on interim analyses of accrued data. For example, early stopping can occur if there is strong evidence early in the trial of the treatment's benefit or harm for a subpopulation. *Methods:* We optimize a hypothetical trial design for a new treatment for progression from mild cognitive impairment to Alzheimer's disease. Simulated scenarios are constructed using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). We focus on subpopulations defined by a participant's apolipoprotein E (ApoE4) allele carrier status, which is associated with increased risk of late onset Alzheimer's disease. The goal is to learn whether the new treatment benefits both subpopulations, just one of them, or neither. We compare designs (both adaptive and standard) that have 80% power to detect treatment effects in each subpopulation and in the overall population. We set the delay time from enrollment to observation of an individual's primary outcome (change in CDR-SB) to be 2 years. Enrollment was assumed to be 500 per year. *Results:* The adaptive enrichment designs we evaluated were able to reduce the expected duration of the trial by 6%, compared to a standard (non-adaptive) design, while achieving the above power goals. The potential benefits of using an adaptive enrichment design are greater when the delay from enrollment to observation of the primary outcome is smaller. *Conclusions:* Adaptive enrichment designs have potential to more efficiently learn which subpopulations benefit from treatments, compared to standard (non-adaptive) designs; however, their utility may be severely limited when the delay time to observe the primary outcome is large relative to the time to enroll the maximum sample size.

OC10: AUTOMATED CLASSIFICATION OF ADVERSE EVENTS IN CLINICAL STUDIES OF ALZHEIMER'S DISEASE.
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Background: USC's Alzheimer's Therapeutic Research Institute (ATRI) was founded in 2015 with the stated mission of accelerating the development of effective therapies to combat Alzheimer's disease. To accomplish this mission, ATRI develops novel methodology and conducts multi-site clinical studies in America and Eurasia in collaboration with scientists, government agencies and industry partners. ATRI has created a Clinical Data Sciences Initiative (CDSI) to identify opportunities for research and innovation in the conduct of clinical studies and promote the formation of multi-disciplinary teams that focus on developing specific projects. With this effort, ATRI has advanced a set of strategies to accelerate the completion of study milestones, improve participant safety, and increase data quality standards. *Methods:* The collection and analysis of adverse event (AE) data during the course of a clinical study plays a critical role in ensuring participant safety. Appropriately, data management and reporting standards for this type of data are strict and typically require ongoing review by safety and pharmacovigilance teams (physicians and biostatisticians), as well as an independent data and safety monitoring board (DSMB). In ATRI studies, adverse event data is managed in accordance with predefined standards. The nature of this data, however, presents unique challenges. In its raw form, the event data collected includes structured data such as the event start date and duration, seriousness, and a determination of relatedness to the study intervention, and unstructured data such as a diagnosis and a narrative of the event. To facilitate downstream analysis and reporting, the unstructured textual data elements must be post-processed. This post-processing involves manual review and classification of each adverse event using a standard medical terminology dictionary, the Medical Dictionary for Regulatory Activities (MedDRA). This process must also account for updates to the MedDRA dictionary which are published on a biannual basis. Due to the amount of effort expended and potential for uncontrolled variation in this process, ATRI performed an analysis of the adverse events review and classification process and issued a set of recommendations that were adopted in the second quarter of 2016. The updated process leverages an algorithmic approach to adverse event classification. To develop this approach, ATRI convened a multi-disciplinary team of physicians, biostatisticians, and informaticians with a focus on data science. The team reviewed existing processes and technology and identified several areas for improvement. Primary among these was the use of text processing algorithms to classify adverse events. After reviewing existing literature on this subject, the team developed an algorithm based on work by Tucker and colleagues (Drug Information Journal, Vol. 36, pp. 927-933, 2002). At a high level, the approach requires the creation and maintenance of a corpus of previously classified adverse events that serves as a benchmark for the classification of new adverse events. Using this benchmark, new data are classified using a series of text transformations and pattern matching operations. New editions of the MedDRA dictionary are incorporated into the corpus and can be used to reclassify existing adverse events. *Results:* In initial testing across multiple clinical study datasets, the ATRI approach auto-classified 85% of adverse events collected per study. Furthermore, a validation study of an auto-classified dataset evaluated with respect to a physician-classified gold standard yielded promising results using standard performance metrics - precision (0.98), recall (0.87) and the weighted harmonic mean of precision and recall, F1 (0.92). *Conclusion:* The ATRI adverse event auto-classification approach has several merits relative to previous processes including performance, consistency, and computational efficiency. Importantly, these efficiencies are achieved without sacrificing physician input and clinical meaningfulness. While initial results have been encouraging, the ATRI approach presents opportunities for further improvement. The addition of statistical model-based approaches, which have gained extensive use in natural language processing applications, may allow further performance improvements and be robust to structural changes in medical dictionaries.

OC11: QUANTITATIVE PET STUDY OF THE EFFECTS OF THE P38A KINASE INHIBITOR VX-745 ON BRAIN AMYLOID PLAQUE LOAD IN PATIENTS WITH EARLY ALZHEIMER'S DISEASE (AD). Philip Scheltens[1], Niels Prins[1], Adriaan A Lammertsma[2], Maqsood Yaqub[2], Hui-May Chu[3], John Alam[4], Bart NM Van Berkel[2] *((1) Department of Neurology and Alzheimers Center, VU University Medical Center; and the Alzheimers Research Center (ARC), Amsterdam, NL; (2) Department of Radiology & Nuclear Medicine, VU University Medical Center, Amsterdam, NL; (3) Anoixis Corporation, Natick, MA, USA; (4) EIP Pharma LLC, Cambridge, MA, USA)*

Background: In the healthy brain, p38α regulates inflammation through effects within microglia and astrocytes. Under stress and in disease, p38α is also expressed in neurons, where it plays a critical role in inflammation-driven synaptic toxicity (Watterson 2013; Pietro, 2015). Treatment for 2-3 weeks with selective p38α chemical inhibitors reversed spatial learning deficits in APP/PS1 transgenic mice (Roy, 2015) and aged rats (Alam, 2015). Furthermore, p38α modulates microglial phenotype (Adolfsson, 2012) and therefore has potential to increase microglial-mediated plaque clearance. In aged TG2576 mice, two weeks treatment with the highly selective p38α inhibitor VX-745 reduced amyloid plaque levels (Alam, 2015). Independent of this, it was shown that selective genetic knock-out of p38α in neurons of APP/PS1 mice significantly reduced amyloid pathology (Schnöder, 2016); providing further support that p38α inhibition could reduce brain amyloid plaque burden. Following phase 1 and phase 2a non-CNS clinical studies in which VX-745 was given to approximately 150 subjects, the purpose of the present phase 2a study was to assess its effects in patients with very mild or prodromal AD. Specific objectives were: (1) safety (2) pharmacokinetics (3) effect on amyloid plaque load (4) effects on brain connectivity and cognition. *Methods:* Sixteen patients (aged 60 to 85 years) with MCI due to AD or mild AD were included. Patients had MMSE scores of 20-28 inclusive and elevated brain amyloid plaque load by [11C]PiB PET scan. Patients were randomized on a blinded basis to 40mg or 125mg VX-745 twice daily with food for 12 weeks. Based on preclinical data, 40mg was the expected therapeutically active dose; while higher doses were not expected to increase, and perhaps decrease efficacy (Alam, 2015). Nevertheless, as these dose levels had not been studied previously, the higher dose level was included to ensure adequate plasma drug exposure. The primary endpoint was change in amyloid load as measured quantitatively using dynamic [11C]PiB PET scans (Yaqub, 2008), performed at baseline and at end of treatment, and analyzed by reference parametric mapping (RPM2) using cerebellum as reference tissue. As this approach reduces test-retest variability to 2-3%, the pre-specified responder definition was a >7% reduction in [11C]PiB BPND, allowing for both group level and responder analyses. Secondary outcome measures included a change in MMSE score, WMS, and in brain functional connectivity as derived from rsFMRI and MEG. Results: Enrollment has been completed. Of 16 randomized patients, twelve have completed treatment and four are still on treatment. VX-745 was well tolerated. No SAEs or liver enzyme elevations were reported. One subject interrupted treatment due to diarrhea after 4 weeks treatment. This resolved and the subject restarted treatment after 4 days and successfully completed treatment without recurrence. Pharmacokinetic analyses revealed 40mg achieved peak plasma drug concentrations that were two to three-fold higher than the IC50 for p38α enzyme inhibition. Drug concentrations were approximately another factor of two higher in the 125mg dose group when compared with the 40 mg dose group. The study statistician performed a pre-planned interim analysis after both baseline and end-of-treatment PET data were available on for the first 8 evaluable subjects (n=4 per dose group). Individual subject treatment assignment was not un-blinded to the study team. [11C] PiB BPND showed a median 4.6% reduction in the 40mg group and a median 2.8% increase in the 125 mg group. One of the four subjects in the 40mg group met the protocol specified response criteria by achieving an 11.6% reduction in BPND. Although MMSE assessments were included primarily to monitor for any potentially deleterious effects, a trend towards an improvement in MMSE in the 40mg group was evident. The median increase in MMSE from screening to day 84 (end-of-treatment) was +2.5 (baseline MMSE ranged from 22 to 26). No such trend was observed in the 125mg group, with median change of 0 from screening to day 84. Analysis of all evaluable subjects and functional connectivity results will be available for the meeting. *Conclusions:* The present (interim) results suggest that p38α inhibition with 40mg VX-745 significantly reduces brain amyloid plaque load, while no effect was seen with 125mg VX-745; both results consistent with preclinical findings. These results further support the use of quantitative amyloid PET scanning to detect pharmacological activity as proof-of-principle in early clinical studies of novel treatment modalities for AD.

OC12: OUTCOMES FROM THE PREVENTION OF ALZHEIMER'S DISEASE WITH VITAMIN E AND SELENIUM TRIAL. Erin L. Abner[1,2], Frederick A. Schmitt[1,3], Richard J. Kryscio[1] *((1) Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, USA; (2) Department of Epidemiology, University of Kentucky, Lexington, KY, USA; (3) Department of Neurology, University of Kentucky, Lexington, KY, USA; (4) Department of Biostatistics, University of Kentucky, Lexington, KY, USA)*

Background: Oxidative stress is an established pathway for dementing brain disorders, but it is unknown if the use of anti-oxidant supplements can prevent dementia. The Prevention of Alzheimer's Disease with Vitamin E and Selenium (PREADVISE) trial was designed to determine if low dose anti-oxidant supplements (vitamin E or selenium) used alone or in combination could prevent dementia in asymptomatic older men. *Methods:* PREADVISE was ancillary to the Selenium and Vitamin E Cancer Prevention Trial (SELECT), a randomized controlled trial of the same anti-oxidant supplements for preventing prostate cancer, and began as a double-blind, randomized controlled trial in 2002. PREADVISE planned to recruit 10,000 of the 35,553 SELECT participants. However, SELECT closed in 2009 due to a futility analysis, and both were transformed into exposure cohort studies from 2009-2015. Participants were at least 60 years old at study entry and were enrolled at one of 130 SELECT sites in the U.S., Canada, and Puerto Rico. SELECT randomized participants to vitamin E (400 IU/day) and/or selenium (200 mg/day) using a 2x2 factorial design. While taking supplements, PREADVISE men visited their SELECT site and were evaluated for dementia using a two-stage screen. During the exposure study, men were screened by telephone using similar methodology. In both phases, men were encouraged to visit their doctor if screening indicated possible cognitive impairment. Case ascertainment relied on a consensus review of the cognitive screens and medical records for those men who visited their doctor for an evaluation. For men who did not visit their doctor ascertainment relied on all available supplemental medical information, including self-reported diagnoses of dementia, memory enhancing prescription medication use, and functional assessment (AD8). *Results:* PREADVISE recruited 7,540 men over the age of 60, of whom 3,786 continued into the cohort study. Under an intent-to-treat analysis, dementia incidence (4.43%) was not different among the four study arms. A Cox model, which adjusted incidence for participant demographics and baseline self-reported co-morbidities,

yielded hazard ratios of 0.88 (95% CI: 0.64-1.20) for vitamin E, 1.00 (95% CI: 0.75-1.35) for the combination, and 0.83 (95% CI: 0.60-1.13) for selenium compared to placebo. When weighted by compliance and time on supplements, the hazard ratio for selenium was 0.80 (95% CI: 0.59-1.09). *Conclusions:* The basic sciences have established oxidation as a critical pathway in neurodegeneration, which has spawned several therapeutic and prevention studies for AD. Neither vitamin E or selenium supplementation have proven to be therapeutic. Although PREADVISE was underpowered to detect the observed effect sizes, this study showed that selenium may have a therapeutic effect and for the first time fills a void in the literature, which calls for long-term duration studies on the efficacy of selenium as preventative supplement. Further studies into selenium are warranted.

OC13: A STATISTICAL APPROACH TO CENTRALIZED RISK-BASED MONITORING OF AD CLINICAL TRIALS USING AN INTERACTIVE OPEN-SOURCE PLATFORM. Rema Raman[1], Gustavo Jimenez-Maggiora[1], Yanxin Jiang[1], Michael Donohue[1], Chung-Kai Sun[1], Karin Ernstrom[1], Michael Rafii[1,2], Paul Aisen[1] *((1) Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, CA, USA; (2) Department of Neurosciences, University of California, San Diego, CA USA)*

Background: Comprehensive study monitoring is critical to assure the safety of study participants as well as the validity and integrity of analyses in any clinical investigation. In Alzheimer's disease (AD) therapeutic trials, cognitive and functional measures, used as primary and secondary endpoints, may be prone to variability and scoring errors. Rapid identification of these errors is essential to allow remedial plans to be implemented to minimize extraneous variability. *Methods:* The Alzheimer's Therapeutic Research Institute (ATRI) of USC was established in 2015 with the objective of developing effective treatments for Alzheimer's disease through innovative, collaborative, multicenter clinical trials. Taking a multi-disciplinary approach and utilizing an open-source, interactive, real-time platform, the ATRI team has implemented a centralized, risk-based monitoring methodology for use in AD clinical trials. Using a general strategy of evaluating data centrally across and within study sites, the emphasis is on assessing and improving data quality in real time using objective risk indicators as well as statistical and clinical review. These monitoring reports use real-time data and visual analytics with the functionality built using the platform independent Clinical Data Acquisition Standards Harmonization (CDASH) Analysis Data Model (ADaM) structure and the open-source R Shiny web application framework. *Results:* Risk indicators are assessed in four distinct categories: efficacy, safety, study conduct and data completeness/quality. Indicators of efficacy are focused on key highly subjective aggregate efficacy outcome measures used in AD trials with the aim of allowing early identification of scoring and procedural errors to minimize measurement error and variance. This approach is implemented utilizing univariate and multivariate statistical modeling and graphical techniques, including distributions of means and variances, correlations, event rates, and detection of outliers/inliers, across study sites and participants within study sites. The approach is designed to monitor data in an aggregate manner with the blind maintained for a clinical study at all times. A multi-disciplinary central pharmacovigilance team reviews these reports weekly to identify study data of concern and generate corrective action. *Conclusions:* ATRI's continuous and adaptive data monitoring and evaluation paradigm establishes effective monitoring processes and procedures to improve data quality and minimize measurement data variance in AD clinical trials. The use of statistical techniques with objective criteria to quantify risk permits study monitoring to be adaptive, reliable and cost-effective. Data integration across multiple databases, and model implementation using the ADaM standard, R packages and the R Shiny dashboard provides a framework that allows for greater collaboration and facilitates reproducible research.

OC14: ALLOPREGNANOLONE AS A REGENERATIVE THERAPEUTIC FOR ALZHEIMER'S DISEASE: PHASE 1B/2A UPDATE. Roberta Diaz Brinton[1], Ronald Irwin[2], Kathy Rodgers[3], Gerson Hernandez[4], Meng Law[5], Yonggang Shi[6], Dogu Aydogan[7], Wendy Mack[8], Lon S. Schneider[9] *((1) Department of Pharmacology and Neurology, College of Medicine, University of Arizona, Tucson, AZ USA; (2) Department of Pharmacology, School of Pharmacy, University of Southern California; (3) Department of Pharmacology, School of Pharmacy, University of Southern California; (4) Department of Pharmacology, School of Pharmacy, University of Southern California; (5) Department of Neuroradiology, University of Southern California; (6) USC Stevens Neuroimaging and Informatics Institute, Laboratory of Neuro Imaging (LONI), Keck School of Medicine, University of Southern California; (7) USC Stevens Neuroimaging and Informatics Institute, Laboratory of Neuro Imaging (LONI); (8) Keck School of Medicine, University of Southern California; Department of Preventive Medicine, Keck School of Medicine, University of Southern California; (9) Department of Psychiatry, Keck School of Medicine, University of Southern California)*

Background: Regenerative therapeutics hold the promise of self-renewal and repair. Alzheimer's and the aging brain are marked by a decline in self-renewal and repair, but a capacity for regeneration is retained. Allopregnanolone (Allo) is a pleiotropic regenerative therapeutic that promotes neurogenesis and restores cognitive function in a preclinical AD model and wild type aged mice while also reducing AD pathology in AD mouse brain. Further, Allo promoted regeneration of human neural stem cells. Allo is a neurosteroid endogenous to the brain of low molecular weight and blood brain barrier penetrant with abundant existing safety data in animals and humans. Its mechanisms of neural stem cell proliferation, restoration of cognitive function and AD pathology reduction are well characterized and unlikely to induce amyloid related imaging abnormalities (ARIA). Collectively, the regenerative processes of neurogenesis, oligogenesis and synaptogenesis (as evidenced by restoration of learning and long-term memory), coupled with reduction in pathological burden, provide multiple lines of preclinical evidence of efficacy that support the potential for Allo as a safe and efficacious therapeutic agent for regeneration and repair. Based on a foundation of preclinical discovery, translational research, clinical development with NIA USC ADRC and FDA assessment and IND approval, a Phase 1b/2a multiple ascending dose clinical trial of Allo doses administered in a regenerative regimen of once-per-week for twelve weeks to establish a safe and tolerated dose of Allo necessary to advance to a Phase 2 efficacy trial. *Methods:* Phase 1b/ 2a clinical trial to establish safety and maximally tolerated. Dose: Allopregnanolone for Mild Cognitive Impairment Due to Alzheimer's Disease or Mild AD. ClinicalTrials.gov Identifier: NCT02221622; https://clinicaltrials.gov/ct2/show/NCT02221622?term=brinton+allopregnanolone&rank=1. Primary safety objectives are to determine: maximally tolerated dose; incidence and severity of treatment emergent adverse events; designated medical events; clinically important changes in safety assessments including ARIA. Secondary objectives are to: assess potential short-term effects of Allo dosing on cognition and MRI indicators of AD; inform subsequent phase 2 proof of concept trial

with MRI-based biomarkers of regenerative efficacy. Statistical Parametric Mapping (SPM8) an automated region-of-interest, Axial Dual Echo T2 FSE or Axial FLAIR , Axial Gradient Echo/SWI , Multi Shell, Multi Band DTI (B 1000, 2000), Resting state functional connectivity (rs-fMRI, EPI BOLD) (7.5") were used to compare baseline and end of study MRIs. Biomarker development using lymphocyte derived iPSCs to identify potential responders. *Results:* Successful completion of Allopregnanolone 2mg was intravenously infused once per week for 12 weeks to the first dosing cohort of 8 participants (6 allopregnanolone + 2 placebo). Within 15 minutes of start of infusion, the peak plasma level was reached Cma = 46.34 +/- 23 nanomolar. Total infusion time of 30 minutes ensured the peak concentration remained for 15 minutes. No sedation was observed for any subject during or after infusion indicating a tolerable dose. The Cmax closely correlated (R=0.77) with Allo delivered in mg/kg dose . Mean AUC was 9.33 +/- 3.99 hr*ng/ml. Based on the measured blood level ~50 nanomolar at 2mg dose, we predict that a 6mg dose will yield ~150 nanomolar; a 12mg dose ~300 nanomolar, and a 20mg dose will result in ~500 nanomolar plasma (i.e., increasing by ~50 nanomolar for each additional 2mg.. Based on animal dosing studies, 500 nanomolar (160ng/ml) is well below tolerability limits of ~3,000 nanomolar (955 ng/ml). Twelve-week exposure to 2mg Allopregnanolone once per week had no detectable adverse effects. Dose cohort 2 is underway, with completion of final dose cohort projected for late fall. Primary safety outcomes coupled with secondary exploratory outcomes of MRI based biomarkers, cognition and iPSC derived neural stem cell response to Allo will be presented. *Conclusion:* Allopregnanolone is a first in class regenerative therapeutic for MCI and AD that targets endogenous neural stem cells and disease modifying mechanisms. Trial outcomes will provide: 1) an estimated safe and well-tolerated dose of Allo; 2) parameter estimates for MRI based markers of regeneration, cognitive efficacy and iPSC / neural stem cell based indicator of responders will provide foundation on which to advance to a Phase 2 proof of concept trial of Allo in persons diagnosed with early AD. Research supported by grants from the National Institute on Aging U01AG031115 to RDB; U01AG047222 to RDB; UF1AG046148 to RDB & LS; Alzheimer Drug Discovery Foundation to RDB

OC15: EFFECT OF S 47445 ON FUNCTIONAL CONNECTIVITY AT REST AND DURING A TASK, AND ON GLUTAMATE CONCENTRATIONS IN ELDERLY SUBJECTS. Philippe Ciuciu[1], Salma Bougacha[1], Fawzi Boumezbeur[1], Severine Desmidt[1], Chantal Ginisty[1], Laurence Laurier[1], Jean-Robert Deverre[1], Lucie Hertz-Pannier[1], Nadège Tardy[2], Maria Pueyo[2], Katy Bernard[2] *((1) CEA/DRF/I2BM/NeuroSpin, Gif-sur-Yvette, France; (2) Pôle Innovation Thérapeutique Neuropsychiatrie, Institut de Recherches Internationales Servier, Suresnes, France)*

Background: S 47445 is a potentiator of AMPA receptors that possesses both procognitive and antidepressant-like properties. Further, S 47445 modulates markers of synaptic plasticity such as Long Term Potentiation, neurotrophic factors expression…. Based on these observations, S 47445 has emerged as a favourable candidate for the treatment of memory deficits, depressive symptoms and synaptic dysfunction associated with Alzheimer's disease. fMRI provides a unique approach to understand drug mechanism of action and potential impact on brain networks. In the last decade, exploration of the resting-state connectivity has received great attention. One brain network particularly well studied is the default mode network (DMN). The more demanding a task is in terms of cognitive load, the stronger the "deactivation" of the DMN, suggesting that the balance between task-positive networks and the DMN is critical for effective cognitive processing. The objective of this study was to examine the effects of 2 doses of S 47445 versus placebo on: 1) the functional connectivity pattern of DMN measured by functional Magnetic Resonance Imaging (fMRI) in resting-state and during a working memory task (N-back) and 2) Absolute concentrations of major brain metabolites (Ins, Glu, Gln, GABA, Asp, NAA+NAAG GPC+PCh, GSH+ASC, PE+EA) assessed using Nuclear Magnetic Resonance Spectroscopy (NMRS) in a key component of the DMN: the posterior cingulate cortex (PCC). *Methods*: The clinical study was a double-blind, placebo-controlled cross-over randomized phase I study performed in healthy elderly female volunteers aged between 65 and 75 years. Subjects received oral administration of S 47445 at 5 (n=21) or 20 (n=19) mg/day for 16 consecutive days or placebo in a randomized order. During each assessment period, fMRI data were recorded first at rest and then during the task. The participants were engaged in N-back tasks (1, 2 and 3-back) controlled with a 0-back condition, in separate runs lasting about 8 minutes each. Data were collected between Days 12 and 16 of placebo or drug administration. During this evaluation, NMRS data were acquired for each subject in the PCC and studied as relative metabolite concentration normalized by the total Creatine concentration. Seed-based functional connectivity (FC) analysis was performed on both the resting-state and task-related fMRI datasets. Pairwise Pearson's correlation was computed between brain regions located in the Attention (AN), working-memory (WMN) and Default Mode (DMN) networks and statistical analysis was performed using pairwise t-tests (within-group comparisons) or two-sample t-tests (between group comparisons) on the Fisher's transformed correlations, corrected for multiple comparisons using False Discovery at p=0.05Rate. *Results*: Population: All participants were female. Mean age [± standard deviation (SD)] was 69.2 ± 3.1 years, ranging from 65 to 75 years; mean weight ± SD was 65.41 ± 8.46 kg; and mean BMI ± SD was 25.9 ± 2.3 kg/m2. Overall, the median duration of education was 9.0 years, and the median score for the Mini Mental Status Exam (MMSE) was 29.0. *Results:* Following placebo, FC analysis demonstrated that some regions within the task-positive networks (AN, WMN) were more strongly coupled during task than at rest. Also, a significant anti-correlation was found between task-positive (AN, WMN) and task-negative (DMN) networks during task (2 and 3-back) whereas these networks were segregated (did not significantly interact) at rest. These results are in line with the available literature in healthy subjects. Two major positive effects of S 47445 at dose 5 mg were seen during the 2-back task as compared to Placebo: 1) significant stronger correlations between task-positive networks (WMN* and AN*) and 2) a significant anti-correlation of the DMN* with AN. These results suggest that S 47445 at a dose of 5 mg facilitates interactions between brain regions during task performance as compared to Placebo. Weaker effects for the drug dose of 20 mg were observed. The results did not demonstrate correlations with behavioral performance on a per individual basis. For absolute concentrations of major brain metabolites, a significant difference of relative concentration of Glutamate was found between Placebo and S 47445 at 5 mg (p = 0.043) and 20 mg (p=0.006) in the PCC. The increase of glutamate concentrations under S 47445 is around 2.4% for both doses. *Conclusion:* The main finding is that S 47445 5 mg showed a significant positive effect on functional connectivity during the 2-back task as compared to placebo with a stronger correlation between task-positive networks (attention, working memory) and a negative correlation of the DMN with the attention network. A slight yet significant increase of glutamate concentration (2.4%) was observed with S 47445 at both 5 mg and 20 mg versus placebo assessed by MRS. Collectively, these results suggest that S 47445 enhances functional connectivity between brain networks and induces

an increase of excitatory neurotransmission in PCC. *WMN: (L) middle Frontal Gyrus (LMFG), Right cerebellum posterior lobule (RCPL). *AN: ventral intraparietal sulci (vIPS), middle temporal lobes (MT). *DMN: bilateral angular gyri (AG), posterior cingulate cortex (PCC).

OC16: FLORBETAPIR F 18 PET: FROM DUAL-PHASE TO DUAL-BIOMARKER IMAGING. Sergey Shcherbinin[1], Jennifer A. Eads[1], Adam J. Schwarz[1], John R. Sims[1], For the Alzheimer's Disease Neuroimaging Initiative[2] *((1) Eli Lilly & Co, Indianapolis, IN, USA; (2) Data used in preparation of this abstract were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database)*

Background: Dual-phase florbetapir positron emission tomography (PET) imaging constitutes a combination of two image acquisitions performed (a) at the time of the tracer administration (wash-in phase to measure regional cerebral perfusion) and (b) 50 minutes after tracer administration (equilibrium phase to measure plaque binding). This dual-phase scanning session holds promise as a dual-biomarker imaging approach delivering two independent pieces of diagnostic information, that is, presence of amyloid pathology and downstream neuronal injury (hypoperfusion) while reducing radiation exposure and time commitment of subjects. While delayed 50 minute florbetapir imaging is widely used to provide evidence of the presence of amyloid plaques, the ability of the perfusion measurement to reliably reflect neuronal dysfunction and track severity of Alzheimer's Disease (AD) needs to be further verified. The goal of this study was to optimize the hypoperfusion quantification methodology and thereby improve performance of perfusion florbetapir imaging as a neurodegeneration biomarker. *Methods:* We analyzed dual-phase florbetapir scans from 58 healthy controls (HC, age 75.1±6.7 mean±standard deviation, Clinical Dementia Rating – Sum of Boxes [CDR-SB] 0.1±0.3) as well as for 28 mild cognitive impairment (MCI, age 74.8±8.8, CDR-SB 1.4±1.1) and 17 AD (age 74.7±7.7, CDR-SB 5.0±2.5) participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, all of whom also had fludeoxyglucose (FDG) PET scans. First, the presence of amyloid plaques was quantitatively assessed using delayed 50-70 minute images and a sub-group of amyloid-positive participants was identified. Specifically, average 50-70 minute images were spatially normalized to the atlas space using florbetapir PET template and standardized uptake value ratio (SUVR) values reflecting amyloid status (aSUVR50-70) were then calculated using six target cortical regions and whole cerebellum as a reference region. The amyloid abnormality was established based on aSUVR50-70>1.10. Second, several hypoperfusion indices derived from early 0-5 minute images were compared in terms of their relationship to disease stage and clinical scales, especially for amyloid-positive participants. Specifically, 0-5 minute dynamic frames were averaged and spatially normalized to an FDG PET template in the atlas space. The same normalization was applied to the average 30-60 min FDG acquisitions. For perfusion florbetapir images, we explored three reference regions: whole brain, cerebellar grey matter, and pons. Hypoperfusion was measured in a target region of interest (ROI) defined from a voxel-wise T-test between FDG maps from amyloid-negative HC (HC-) and amyloid-positive AD (AD+) groups (uncorrected $p<0.01$, cluster size >1mL, temporal and parietal lobes only). The resulting three regional perfusion indices (pSUVR0-5) were compared with cognitive (mini–mental status examination [MMSE] and 13-item Alzheimer's Disease Assessment Scale – Cognitive subscale [ADAS-Cog13)]) and functional activities questionnaire (FAQ) assessments across amyloid-positive subjects. In addition, perfusion-based differentiation between diagnostic groups was examined using Areas under Receiver Operating Characteristic curves (AUROC). The perfusion pSUVR0-5 results were compared to the same analysis results based on the corresponding three indices from the FDG PET scans. *Results:* Quantitative amyloidosis measurements using delayed florbetapir scans enabled participants to be split into amyloid-positive (17 HC+, 9 MCI+ and 13 AD+) and amyloid-negative (41 HC-, 19 MCI- and 4 AD-) subgroups. Perfusion pSUVR0-5 values confirmed ability of the early florbetapir scan to differentiate diagnostic groups. In particular, pSUVR0-5 values using whole brain as a reference region enabled good group separation between AD+ and MCI+ (AUROC= 0.93) and between MCI+ and HC+ (AUROC=0.76), in addition to the AD+/HC- segmentation (AUROC=1.00). Moreover, these perfusion indices showed significant ($p<0.0001$) linear association with ADAS-Cog13 ($R2=0.72$), MMSE ($R2=0.58$) and FAQ ($R2=0.54$) across amyloid-positive subjects. Similar, but nominally better linear association with ADAS-Cog13 ($R2=0.77$), MMSE ($R2=0.68$) and FAQ ($R2=0.61$) was observed for corresponding FDG images. However, using population-independent target ROIs (either atlas-based or the FDG meta-ROI from ADNI) resulted in less favorable biomarker properties of pSUVR0-5. Normalization to either cerebellar grey matter or pons, rather than whole brain, led to worse group separation and linear association in our group-level cross-sectional analyses. Although whole brain normalization resulted in smaller mean pSUVR0-5 difference between AD+ and HC- groups, the lower intra-group variability yielded an increased effect size overall. *Conclusions:* These exploratory analyses based on cross-sectional data with a small sample size encourage the further examination of regional perfusion estimates derived from early-phase florbetapir scans as a candidate biomarker of neurodegeneration in AD. In particular, optimization of target and reference regions improved the accuracy of tracking AD severity as well as both cognitive and functional decline. Additional evaluation of perfusion indices in independent samples and longitudinal (test-retest and follow-up) data for individual participants with different diagnoses will be important to further establish florbetapir PET as a dual-biomarker imaging approach.

OC17: A NOVEL DISEASE PROGRESSION MODEL FOR CLINICAL TRIALS IN DOMINANTLY INHERITED ALZHEIMER'S DISEASE. Guoqiao Wang[1], Scott Berry[2], Eric M. McDade[1], Chengjie Xiong[1], Jason Hassenstab[1], Melanie Quintana[2], Randall J. Bateman[1] *((1) The Dominantly Inherited Alzheimer Network Trials Unit, Department of Neurology, Washington University School of Medicine, St. Louis, MO; (2) Berry Consultants, Austin, TX, USA)*

Background: Conventional trial designs in Alzheimer's disease (AD) have focused on comparing the absolute change from baseline in cognition to measure that change. However, subjects typically enter trials at different stages of disease, thus statistical models that ignore disease stage may introduce spurious variability in measurement of cognitive change as subjects that enroll with early-stage disease have different trajectories than those who enroll with more advanced disease. This can result in trial designs that require extremely large sample sizes in order to achieve acceptable statistical power. Within the Dominantly Inherited Alzheimer Network (DIAN) observational study, we have shown that a parental or mutation-specific estimate of years to symptom onset (EYO) is an extraordinarily reliable predictor of disease severity.1,2 EYO can be used as an indicator of each subject's appropriate stage of disease at enrollment and provides a highly accurate prediction of disease progression, which reduces a large portion of subject-to-subject variability and enhances statistical power. As such, we have developed a disease progression model (DPM) with a DIAN trials unit (DIAN-TU) cognitive composite

endpoint that estimates the expected rate of cognitive decline from untreated mutation carriers. Based on the DIAN observational study and assuming a proportional treatment effect, we applied the DPM across mutation carriers and compare these results to the more conventional mixed model with repeated measures (MMRM). *Methods:* The DIAN-TU Cognitive Composite combines measures of episodic memory, complex attention and processing speed, and a general screen of mental status. Episodic memory measures include delayed recall from a verbal list learning test (DIAN Word List Test) and story recall (Wechsler Memory Scale-Revised Logical Memory). Complex attention and processing speed are assessed with the total correct score from the Wechsler Adult Intelligence Scale Digit Symbol Substitution Test. Mental status is provided by the total score on the Mini Mental State Examination (MMSE). Each component was normalized using the mean and standard deviation of mutation carriers well before symptom onset (EYO <-15). The four z-scores are averaged using equal weighting to construct a z-score composite. The natural disease progression model incorporates: 1) a subject-level random effect to explicitly measure subject-to-subject variability in cognitive scores, 2) a subject-level random effect to adjust a subject's predicted EYO based on the cognitive endpoint, and 3) fixed effects to estimate the rate of decline as a function of EYO. To reflect the treatment effect, the fixed effects for the treatment group was assumed to be a proportion of that of the placebo group. The MMRM included fixed effects such as baseline EYO, baseline score on the DIAN-TU composite, gender, group, time since baseline, interaction between group and time, and random effects such as intercept and slope for each individual and intercept for each cluster family. *Results:* We simulated 5000 trials using the DIAN observational population with variations in a number of trial scenarios (distribution of baseline EYOs, enrollment rate, drop-out rate, standard deviation of the composite, decline rate of the placebos). For each scenario we investigated the applicability and validity of the DPM in the DIAN-TU clinical trial. Our simulation results showed that the DPM was robust to the various scenarios. We also demonstrated that the DMM generated much larger power than the traditional MMRM (Table 1) while also including a robust Type I error procedure. *Conclusion:* The DPM provides substantially better fit for cognitive decline observed in ADAD mutation carriers by incorporating EYO, a reliable marker of disease stage for each subject. The DPM provides a powerful method for simulating future clinical trials in ADAD populations. In comparison to traditional models, such as MMRM that have less robust estimates of treatment effects over time and are unable to effectively utilize EYO as a covariate, the DPM exhibits dramatically increased power. Generalization of the DPM from ADAD to sporadic AD may help increase statistical power in sporadic AD trials, thereby increasing the likelihood of detecting futility or effective treatments for AD. Founding: The DIAN observational study is supported by grant U19 AG032438. Reference: 1. Bateman, R. J. et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. New England Journal of Medicine 367, 795-804 (2012). 2. Ryman, D. C. et al. Symptom onset in autosomal dominant Alzheimer disease A systematic review and meta-analysis. Neurology 83, 253-260 (2014).

Table 1

The power at the 4-year analysis for disease progression rate (DPR) reduction from 30% to 60% under the MMRM primary analysis compared to the DPM analysis with the total sample size 80

DPR Reduction	3: 1 treatment to placebo ratio	
	Success MMRM	Success DPM
30%	0.162	0.634
40%	0.267	0.911
50%	0.407	0.989
60%	0.562	1.000

OC18: OPTIMAL REFERENCE REGION TO MEASURE LONGITUDINAL AMYLOID-BETA CHANGE WITH F-18 FLORBETABEN PET. Santiago Bullich[1], Victor L Villemagne[2], Christopher C Rowe[2], Susan De Santi[3] *((1) Piramal Imaging GmbH, Berlin, Germany; (2) Department of Nuclear Medicine and Centre for PET, Austin Hospital, Melbourne, VIC, Australia; (3) Piramal Pharma Inc, Boston, MA, USA)*

Backgrounds: Accurate measurement of changes in amyloid-beta (Aβ) deposition over time is important in anti-Aβ therapeutic trials. Selecting the optimal reference region (RR) is essential to reduce the variance of the Aβ burden PET measurements, allowing early detection of treatment efficacy. This study investigated the influence on RR selection on earlier detection of subtle Aβ changes over time using F-18 florbetaben (FBB) PET. *Methods:* FBB PET scans from 45 mild cognitively impaired (MCI) patients (72.69 ± 6.54 yrs., 29 male/16 female) who underwent three FBB scans were included (baseline (n=45), one-year (n=41) and two-years (n=36)) (Ong et al. Alzheimer's Research & Therapy 2013, 5:4; Ong et al. J Neurol Neurosurg Psychiatry. 2015 Apr;86(4):431-6). Baseline FBB scans were visually classified as high (Aβ+) and low (Aβ-). Cortical regions (frontal, lateral temporal, occipital, parietal, anterior cingulate and posterior cingulate) were quantified using the standardized AAL region-of-interest (ROI) atlas applied to the spatially normalized gray matter PET image obtained from the segmentation of the participant's baseline T1-weighted volumetric MRI. Four reference regions (gray matter cerebellum (CGM), whole cerebellum (WCER), pons and subcortical white matter) were studied. Cortical standardized uptake value ratio (SUVR) for each RR was calculated dividing cortex activity by the RR activity. SUVs across RRs were compared using one-way ANOVA. A composite SUVR averaged all cortical regions investigated. Independent samples t-test compared SUVR increase from baseline to one- and two-years follow-up scans across visually classified groups (Aβ+ and Aβ-). A linear regression was fitted to the SUVR versus scan time (t) (SUVR = a + b . t). The percent of Aβ accumulation (Aβ-Acc) over time was calculated as Aβ-Acc = 100 . b / SUVRb (SUVRb= Baseline SUVR). Independent samples t-test was used to compare percent of Aβ accumulation (Aβ-Acc) over time across visually classified groups. *Results:* SUVs for any RR were not significantly different over time. Both CGM and WCER RRs enabled early detection of cortical SUVR changes in MCI patients. Average percent of Aβ accumulation per year (mean±SD) derived from composite SUVR was 0.13±1.68(Aβ-)/1.39±2.02(Aβ+) (p=0.02) for CGM, 0.16 ± 1.43(Aβ-)/1.36±1.79(Aβ+) (p=0.01) for the WCER. Composite SUVR increase in Aβ+ scans was significantly larger than those in Aβ- scans between baseline and 1-year follow-up (p(CGM)=0.04, p(WCER)=0.02) and between baseline and 2-year follow-up scans (p(CGM)=0.04, p(WCER)=0.02). PONS detected significant changes only at 2-year follow-up (p(1-yr)=0.71, p(2-

yrs)=0.001) while SWM did not show significant difference in either follow-up (p(1-yr)=0.50, p(2-yrs)=0.14). *Conclusion:* Reference region selection influences the reliable and early measurement of Aβ changes over time. Compared with WM or PONS, cerebellar reference regions (CGM and WCER) are recommended as RR for F-18 florbetaben PET since they allow earlier detection of Aβ accumulation.

OC19: THE ACTIVE VACCINE AGAINST ALZHEIMER TAU PROTEIN "AADVAC1" CONFIRMED THE FAVOURABLE SAFETY PROFILE AND SHOWED PERSISTENT ANTIBODY RESPONSE IN THE LONG-TERM FOLLOW-UP STUDY "AC-AD-002". Petr Novak[1], Matej Ondrus[1], Reinhold Schmidt[2], Stanislav Katina[1], Eva Kontsekova[1], Michal Novak[1] *((1) AXON Neuroscience, Bratislava, Slovakia; (2) Department of Neurology, Medical University of Graz, Austria)*

Background: We have developed an active vaccine against neurofibrillary tau pathology, AADvac1. The vaccine induces antibodies against a pathological conformational epitope found in the microtubule binding domain of diseased tau protein. This epitope is functionally important for tau aggregation, and found both in early and in mature pathological tau species. In transgenic models, AADvac1 reduced both neurofibrillary pathology and insoluble hyperphosphorylated tau in a titre-dependent manner, and improved the neurobehavioral status and survival of the animals. AADvac1 has been assessed for safety and tolerability in the 6-month first-in-man study Axon CO18700, which was completed in March 2015. The study did not reveal any safety or tolerability concerns, proved high immunogenicity of AADvac1 and so clearly supported initiation of the phase II study, currently ongoing in 8 European countries. All patients, who completed the first-in-man study Axon CO18700 had the opportunity to continue in the follow-up study AC-AD-002. *Methods:* This was an 18-month, open-label, follow-up study, assessing safety and immunogenicity in patients originally diagnosed with mild-to-moderate Alzheimer's disease (MMSE 15-26) who completed the phase 1 Axon CO18700 study. All patients received 2 boosters of AADvac1 in 6-month intervals. In addition, patients originally allocated to placebo in the Axon CO18700 study received additional 3 doses of AADvac1 in monthly intervals to bring their vaccination regimen in line with patients treated with AADvac1 from the beginning of the Axon CO18700 study. In total, the 20 patients who completed this follow-up study received 8 doses of AADvac1. The safety and tolerability outcomes were assessed based on the reported AEs, blood and urine laboratory tests, MRI and ECG, and clinical and neurological examinations. ADAS-Cog, COWAT and CFT were also employed as supportive safety and exploratory measures. *Results:* 26 subjects signed informed consent and were included into the study, 20 of them completed the planned 18-month investigational period. Within this long-term follow-up period, the study confirmed the favourable safety profile of AADvac1 based on assessments of adverse events, laboratory tests, ECG and MRI results. After the booster vaccinations, the patients developed an immune response to AADvac1 equal or better than the immune response achieved after the initial 6-dose vaccination regimen of AADvac1. Additional analysis including also data from the Axon CO18700 study revealed, that the observed IgG titres of antibodies against Axon peptide 108 (the tau antigenic determinant of AADvac1) correlated with immune competence of patients assessed as baseline levels of CD3+/CD4+ lymphocytes. A vast majority of patients developed antibodies against truncated AD tau. Immunoblotting also confirmed the ability of the raised antibodies to target the pathological forms of tau proteins isolated from the brains of AD patients. The large variance and the limited size of the study sample preclude the assessment of efficacy based on cognition. *Conclusion:* This long-term follow-up clinical study assessing safety, tolerability and immunogenicity of AADvac1 confirmed the favourable safety results of the preceding phase 1 Axon CO18700 study. The study showed also an excellent long-term immunogenicity of the booster vaccination regimen and additional analyses confirmed important predictive factors of the immune response. The current and planned phase II studies are designed aiming to address safety and tolerability objectives, as well as clinical efficacy, target engagement and immunogenicity objectives.

OC20: CLINICAL PHARMACOLOGY STUDY OF P38 ALPHA MAP KINASE INHIBITOR, NEFLAMAPOMID (VX-745), IN MILD COGNITIVE IMPAIRMENT (MCI) DUE TO ALZHEIMER'S DISEASE (AD) OR MILD AD. John Alam[1], Hakop Gevorkyan[2,3], Stanford Jhee[2], Lovingly Park[2,3], Jee-Hyun Kim[2], Noel Alaka[2], Larry Ereshefsky[2,4] *((1) EIP Pharma LLC, Cambridge, MA, USA; (2) Los Angeles EPCU, PAREXEL International, Glendale, CA, USA; (3) California Clinical Trials Medical Group, Glendale, CA, USA; (4) Currently retired Regents Professor The University of Texas at Austin and Follow the Molecule: CNS Consulting)*

Background: In the healthy brain, the alpha isoform of p38 mitogen activated protein kinase (p38α) regulates inflammation through effects within microglia and astrocytes. Under stress or in disease, p38α is also expressed in neurons; where it plays a critical role in inflammation-driven synaptic toxicity (Watterson 2013; Pietro, 2015; Sandersen, 2016). Further, selective p38α chemical inhibitors reverse spatial learning deficits in APP/PS1 transgenic mice (Roy, 2015) and in aged rats (Alam, 2015); and neuronal knockout of p38α in APP/PS1 mice significantly reduces amyloid pathology (Schnöder, 2016). Neflamapomid (previously named VX-745) is a highly selective oral small molecule p38α antagonist that achieves brain concentrations pre-clinically approximately two-fold higher than in blood. Neflamapomid was previously in the clinic for non-CNS indications but was not pursued beyond phase 2a. More recently, pre-clinical studies (presented at CTAD 2014; Alam, 2015) indicated that doses required for CNS activity are 5-fold lower than that required for non-CNS activity; with pro-cognitive effects in the aged rat apparent at one-third lower dose than that required to reduce cytokine production. The presumed mechanism of pro-cognitive effect is the reversing of effects of cytokines on synaptic function (Alam, 2015). The primary objective of the current study was to evaluate pharmacokinetic/pharmacodynamics (PK/PD) in patients with early AD and correlate them to PK/PD outcomes in preclinical studies, thereby identifying optimal dose(s) for a subsequent proof-of-concept (POC) clinical study. *Methods*: Inclusion criteria: MCI due to AD or mild AD; age 60 to 85; CDR > 0.5; MMSE 18-30; MRI consistent with AD. Originally, patients randomized to either 40 mg or 125 mg neflamapomig twice daily with food for 42 days. However, after 3 subjects were enrolled, the higher dose group was discontinued due to US-specific regulatory authority requirement to limit dosing to expected plasma drug exposure levels providing ten-fold safety margin relative to long-term animal toxicology findings. CSF TH1/TH2 cytokines and Aβ 38/40/42 collected 6 times over 24 hours at Baseline and end-of-treatment (EOT). Plasma and CSF PK profiles obtained on day 1 and at EOT. Verbal learning/episodic memory was assessed with the Hopkins Verbal Learning Test – Revised (HVLT-R) at screening, and HVLT-R alternate forms at Days -2, 14 and 40; HVLT-R is known to have minimal learning (practice) effects with repeated assessment (Schretlen, 1998). MMSE evaluated at screening and Day 40. *Results:* 9 subjects enrolled (8 at 40 mg; 1 at 125 mg); 5 were female. Baseline MMSE ranged from 23 to 28. One subject discontinued within the first week because of headache and vomiting,

attributed to persistent CSF leak after baseline CSF collection; all other subjects completed treatment, with no safety signal identified. PK: Median CAVG (average plasma drug concentration over dosing period) was ~8ng/mL. There was a weight dependency of plasma drug levels, with weight <60 Kg being associated with higher plasma drug exposure. CSF drug concentrations on Day 41 were 6% of plasma drug concentrations at matched time points; this CSF:plasma percentage was associated in pre-clinical studies to brain concentrations ~2-fold higher than in plasma. The combined results indicate that brain concentrations are similar to neflamapomid's IC50 of 10-15 ng/mL for inhibition of IL-1β signaling. Cytokines: CSF IL-8 was the only cytokine quantifiable at all time points. TNFα was also detectable, and often quantifiable, in all subjects at baseline. CSF IL-8 at EOT was significantly reduced compared to Baseline ($p<0.001$) in the three subjects who had the highest plasma drug levels; a similar trend was seen for TNFα. IL-8 and TNFα levels did not appear to be impacted in the remaining subjects. CSF amyloid beta: Median Baseline CSF Aβ42 concentration was 407 pg/mL (range: 199-683). A concentration dependent trend was seen: the three subjects with the highest plasma drug exposure had higher levels of Aβ peptides at EOT compared to Baseline; while the remaining subjects had similar or lower levels of Aβ peptides at EOT compared to Baseline. Cognition: Mean HLVT-R Total Recall improved from 19.1 (+/-1.5) at Baseline to 22.6 (+/-2.1) at EOT ($p=0.029$ EOT vs. Baseline); Delayed Recall increased from 5.4 (+/-0.6) to 7.5 (+/-1.1) ($p=0.055$). Median increase in Total Recall score was 4.5 (range: -2.5 to +9.5), with only one subject with a decrease during treatment. MMSE scores improved by mean of 0.5 (+/-0.7) and median of 1.0 point. *Conclusions:* Neflamapomid is well tolerated in an early AD patient population, is brain penetrant, and demonstrates pharmacological activity in the brain. These results, along with the positive trends on cognitive function, support evaluation of neflamapomid in a placebo-controlled POC study with cognitive endpoints. An ongoing comprehensive PK/PD analysis of this and a companion phase 2a study will provide the dose(s) for this next study that would optimize for cognitive effects and amyloid beta dynamics. The current results also provide insight on the relationship between inflammation and amyloid beta dynamics in human AD.

OC21: ADUCANUMAB TITRATION DOSING REGIMEN: 12-MONTH INTERIM ANALYSIS FROM PRIME, A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 1B STUDY IN PATIENTS WITH PRODROMAL OR MILD ALZHEIMER'S DISEASE. Vissia Viglietta[1], John O'Gorman[1], Leslie Williams[1], Tianle Chen[1], Ahmed Enayetallah[1], Ping Chiao[1], Christoph Hock[2], Roger M Nitsch[2], Samantha Budd Haeberlein[1], Alfred Sandrock[1] *((1) Biogen, Cambridge, MA, USA; (2) Neurimmune, Schlieren-Zurich, and University of Zurich, Switzerland)*

Background: Aducanumab (BIIB037), a human anti-amyloid beta (Aβ) monoclonal antibody, is being investigated as a disease-modifying treatment for early Alzheimer's Disease (AD). PRIME is an ongoing Phase 1b study evaluating the safety, tolerability, pharmacokinetics, and pharmacodynamics of aducanumab in patients with prodromal or mild AD. An interim analysis found that amyloid related imaging abnormalities-vasogenic edema (ARIA-E) were the main safety and tolerability findings; these were dose and apolipoprotein E4 (ApoE ε4) dependent.1 It is hypothesized that higher doses of aducanumab can be administered in a titration regimen in ApoE ε4 carriers without incurring the same extent of ARIA observed with a fixed-dose regimen. PRIME, therefore, included an aducanumab titration regimen in addition to fixed dosing regimens. *Methods:* Patients included in this multicenter, randomized, double-blind, placebo-controlled, multiple-dose study (PRIME; NCT01677572) were aged 50-90 years, had a positive florbetapir (18F-AV-45) positron emission tomography (PET) scan, and met clinical criteria for prodromal or mild AD. During the double-blind, placebo-controlled phase, patients received aducanumab or placebo once every 4 weeks for 52 weeks. In a staggered, parallel-group design, patients were randomized to fixed doses of aducanumab or placebo (ratio of 3:1 active vs placebo) stratified by ApoE ε4 status (carrier/non-carrier). After patient enrollment into the fixed-dose cohorts was complete, the protocol was amended to include a cohort of ApoE ε4 carriers who received either titrated doses of aducanumab (up to 10 mg/kg) or placebo. For those receiving titrated doses, the dosing regimen was 1 mg/kg for the first 2 doses, 3 mg/kg for the next 4 doses, 6 mg/kg for the next 5 doses, and 10 mg/kg thereafter. By Week 52, the average expected dose in the titration arm was 5.3 mg/kg. While 12-month interim data from the fixed-dose cohorts have been reported previously,1 we report here the interim data for the fixed as well as titration dose regimens regarding Aβ reduction using amyloid PET, exploratory clinical endpoints (Clinical Dementia Rating-Sum of Boxes [CDR-SB] and Mini-Mental State Examination [MMSE]), and safety. A long-term extension of PRIME is ongoing. *Results:* A total of 196 patients were randomized and dosed in PRIME, including 31 patients in the titration cohort. After 12 months, significant decreases in brain amyloid plaque burden (as assessed by standard uptake value ratio [SUVR]) were observed with titrated aducanumab compared with placebo (adjusted mean [standard error] change from baseline in PET SUVR: -0.171 [0.029] vs 0.014 [0.018], respectively; $P<0.001$). Slowing of clinical decline as measured by the CDR-SB and MMSE was also observed with titrated aducanumab as compared with placebo at 12 months. Results for titrated aducanumab were generally consistent with those observed with fixed doses of aducanumab. The incidence of the most common adverse event (ARIA) appeared to be lower with titrated dosing compared with higher fixed dosing of aducanumab in ApoE ε4 carriers. *Conclusions:* Titration dosing of aducanumab up to 10 mg/kg resulted in significant reductions in amyloid plaque burden during 12 months of treatment in ApoE ε4-positive patients with prodromal or mild AD compared with placebo. The clinical effects in the titration cohort were generally consistent with those observed in the fixed dosing cohorts1 and the slowing of decline on the CDR-SB was statistically significant with titrated aducanumab versus placebo. Titration of aducanumab appears to reduce the incidence of ARIA-E compared with fixed dosing in this patient cohort. These results support the study design of the ENGAGE and EMERGE Phase 3 clinical trials,2 which are investigating the clinical efficacy and safety of aducanumab in patients with early AD. References: 1. Sevigny J et al. Nature 2016;537:50-56; 2. Viglietta V et al.

OC22: PRE-CLINICAL DEVELOPMENT OF GMP-1, A COMPOUND THAT PROTECTS MITOCHONDRIAL FUNCTION OF NEURONS BY COMBATING PROTEIN MIS-TARGETING. Bengt Winblad[1,4], Alexandra Bernadotte[2,4], Gunilla Johansson[1,4], Gustavo Montero[4], Manfred Windisch[3], Pavel Pavlov[1,4] *((1) Dept NVS, Center for Alzheimer Research, Div of Neurogeriatrics, Huddinge, Sweden; (2) Dept of Medicinal Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden; (3) NeuroScios GmbH, Graz, Austria; (4) Great Matter Pharma AB, Sundbyberg, Sweden)*

Backgrounds: Mitochondrial dysfunction is a prominent pathological hallmark of AD. At least partially it has been attributed to accumulation of amyloid precursor protein (APP) and amyloid beta (Aβ) peptide in mitochondria isolated from AD patients. APP

has been shown to associate with mitochondrial protein translocation machinery blocking protein import, whereas Aβ was associates with several complexes in mitochondria including cytochrome c oxidase and mitochondrial permeability transition pore contributing to mitochondrial dysfunction. Therefore strategies aiming to counteract accumulation of APP and Aβ inside mitochondria hold a potential to combat mitochondrial dysfunction associated with AD. We have developed GMP-1, a molecule that decreased mitochondrial uptake of APP and improved overall mitochondrial function in cell and animal models of AD. *Methods:* GMP-1 has been identified via in silico docking of ZINC compound database using mitochondrial protein import receptor Tom70 as a target. Binding of GMP-1 to Tom70 has been confirmed in vitro using AlphaScreen and dot blot techniques. SH-SY5Y neuroblastoma cells were used to confirm GMP-1 effect on association of APP with mitochondria. Drosophila AD models expressing various Aβ constructs in the neurons were used to evaluate efficacy and toxicity of GMP-1. We used 5xFAD mice to evaluate acute and chronic effects of GMP-1 on memory, behavior, brain Aβ load, inflammation and mitochondrial function. *Results:* SH-SY5Y cells treatment with GMP-1resulted in decreased amount of APP associated with mitochondria. GMP-1was also protected SH-SY5Y cells from toxicity of externally added Aβ42. In fly AD models GMP-1 added to the food improved survival, expanded drosophila lifetime, improved locomotion and alleviated defects in the structure of the compound eye. We have treated 5xFAD mice with GMP-1 via oral administration in drinking water ad libitum. Both acute (2 weeks) and chronic (5.5 month) treatment with GMP-1 was well tolerated and without sighs of toxicity in the Irwin test. We have found statistically significant improvement in the overall behavior (open field test) of GMP-1 treated mice over placebo treatment. GMP-1 treatment also improved memory measured with contextual fear conditioning test. We have also found significant decrease in total Aβ and Aβ plaque load, decreased astrocytosis and microglia activation. We have also found GMP-1 protecting mitochondrial function using activity measurement of mitochondrial respiratory complexes. Using isolated brain mitochondria isolated from placebo or GMP-1 treated mice we found a trend towards decrease of APP amounts associated with mitochondria in the GMP-1 treated mice. *Conclusions:* GMP-1 represents a class of molecules with novel mechanism of function. GMP-1 protects neurons via decrease of protein mis-targeting to mitochondria. Pre-clinical data indicate that GMP-1 is well tolerated and is a good candidate to enter human clinical trials.

OC23: DRUG INTERACTION BETWEEN INTEPIRDINE (RVT-101), A 5-HT6 RECEPTOR ANTAGONIST, AND MEMANTINE IN HEALTHY SUBJECTS. Ilise Lombardo[1], Lori Jones[2], Stephen C. Piscitelli[2], Jason T. Olin[1], Lawrence Friedhoff[1] *((1) Axovant Sciences, Inc., New York, NY, USA; (2) Roivant Sciences, Inc., Durham, NC, USA)*

Background: Intepirdine (RVT-101) is an orally administered, 5-hydroxytryptamine 6 (5-HT6) receptor antagonist currently in Phase 3 for the treatment of mild-to-moderate Alzheimer's disease (AD). It includes a number of favorable properties including once daily dosing, lack of a food effect, and the low potential for drug interactions. Although intepirdine and memantine do not share common pathways for metabolism and elimination, we evaluated the potential for a pharmacokinetic interaction since they may be used concomitantly in patients with moderate disease. *Methods:* This was an open-label, single dose, single sequence, three-period, crossover study to assess the effect of a PK drug interaction between intepirdine and memantine in healthy subjects. A single dose study design was employed given the long half-life of memantine (60 to 80 hours) and intepirdine (30 hours) and the challenge of retaining healthy subjects over a lengthy study duration. On Day 1 of Period 1, subjects received a single 10 mg dose of memantine followed by a washout period of at least 17 days. Period 2 began on Day 18 and subjects received a single 35 mg dose of intepirdine on Day 1 of Period 2, followed by a washout period of at least 10 days. Period 3 began on Day 28 and subjects received a combination of memantine 10 mg and intepirdine 35 mg. Subjects had PK samples collected for 168 hours following the dose of study drug during each dosing period. Safety assessments including AE assessments, physical examinations, ECGs, vital signs, and clinical laboratory evaluations were collected throughout the treatment period. PK parameters of intepirdine and memantine were determined using standard noncompartmental methods. The effect of intepirdine on plasma PK of memantine were analyzed using a mixed effect model with treatment as a fixed effect and subject as a random effect. PK parameters were log transformed prior to analysis. The geometric least squares mean ratios and 90% CIs were estimated between test (memantine + intepirdine) and reference (memantine alone) treatments for memantine AUC(0-∞), AUC(0-t), and Cmax. The effect of memantine on plasma PK of intepirdine was analyzed in the same manner. *Results:* Sixteen subjects were enrolled and 15 subjects completed the study. One subject withdrew consent and did not complete all study periods. The median age of subjects in this study was 40.5 years (range 34 to 48 years). The majority of subjects were male (14 of 16 subjects [87.5%]) and subjects were mostly White (13 of 16 subjects [81.3%]. Safety: Safety assessments including AEs, vital signs, ECGs, and clinical laboratory evaluations were overall unremarkable. Memantine and intepirdine were generally well tolerated by subjects and there were no severe AEs, no SAEs, and no withdrawals due to AEs. There was a low incidence of AEs in the study (3 Treatment Emergent Adverse Events (TEAE) reported) with 2 mild and 1 moderate in severity. In addition, no laboratory abnormalities were reported as AEs and none were considered clinically relevant. All TEAEs were considered by the Investigator to be unrelated to intepirdine and all TEAEs were resolved by the end of the study. Pharmacokinetics: Pharmacokinetic parameters of memantine and intepirdine were similar following administration individually or in combination in healthy male and female subjects. Mean concentration-time plots were similar and there were no statistically significant differences in any of the measured parameters. For intepirdine, geometric least square means for Cmax and AUC ranged from 1.11 to 1.13 with 90% confidence intervals of 0.95 to 1.13. For memantine, geometric least square means for Cmax and AUC ranged from 0.98 to 1.01 with 90% confidence intervals of 0.82 to 1.18. Based on these data, there was no PK drug-drug interaction between memantine and intepirdine when coadministered based on single dose data. *Conclusion:* Single dose administration of memantine 10 mg, intepirdine 35 mg, and the combination of memantine and intepirdine was well tolerated in healthy male and female subjects. The PK of both drugs were similar when administered alone or in combination. No pharmacokinetic drug interaction was observed between intepirdine and memantine.

OC24: EARLY PREVENTION APPROACHES TARGETING Aβ-LOWERING KINASE INHIBITION. Claire Paquet, Julien Dumurgier, François Mouton Liger, Marion Tible, Sarah Gourmaud, Jacques Hugon *(Memory Center, Lariboisiere Hospital Paris France; Inserm U942 Paris France Lariboisiere Hospital Paris France)*

Background: Alzheimer's disease (AD) is characterized by an early brain accumulation of Aβ peptides which could occur one or two decades before the first clinical signs. The cause of this accumulation

is unknown but it could result from increased production through secretase activation and to a decreased degradation in neurons. Among putative contributing brain factors, oxidative stress, calcium signaling, neuroinflammation, arteriosclerosis, lipid stress and insulin resistance could play a role in triggering some signals exacerbating abnormal Aβ metabolism. In addition they are also clinical risk factors for the occurrence of AD. The approach targeting early modifications of brain Aβ levels faces several difficulties including 1- the definition of a good pathway, 2- the way to assess these pathways in humans 3- the method to determine persons at risk who could benefit from this therapeutic approach 4- the knowledge of specific molecules able to modulate these abnormal signalings. The assessment of brain Aβ accumulation is now possible in humans using cerebrospinal evaluation (CSF) of Aβ 1-42, tau and phosphorylated tau or amyloid and tau PET imaging. Individuals with Aβ positive biomarkers or bearing ApoE4 genotypes are at risk for AD and obesity, type 2 diabetes and neuroinflammation are contributing risk factors. Stress kinases are specific enzymes that are activated in case of various cellular stresses including oxidative, calcium, inflammatory, glucose and lipid stresses. They are activated in AD brains, are triggered also by Aβ and can lead to neuronal apoptosis. Among these kinases, C-Jun kinase (JNK) and PKR have been extensively studied in patients with AD and in experimental models. *Methods:* Cognitive tests, western blots, immunohistochemistry, ELISA and Luminex methods have been used to assess stress kinase activities, Aβ levels and neuroprotection in AD patients, AD brains and AD CSF as well as in transgenic 5XFAD models exposed or not to JNK of PKR inhibitors. *Results:* Activated JNK3 is increased in AD brains and in AD CSFs and the levels in the CSF correlate with cognitive decline. JNK can control the production of Aβ and can phosphorylate tau protein. The JNK inhibitor XG 102 reduces Aβ accumulations, apoptosis and improves cognition in 5XFAD transgenic mice. Activated PKR is also augmented in AD brains and CSF as well as in the CSF of MCI patients and CSF PKR concentrations are a good predictor of further cognitive decline in patients. PKR inhibitors reduce brain Aβ accumulations and afford neuroprotection in experimental models. They also enhance memory in experimental animals. In neuronal cultures, the dual inhibition of JNK and PKR completely blocks Aβ neurotoxicity. Altogether these kinases, which are activated by early stress metabolisms in neurons such as oxidative stress and neuroinflammation could contribute to early Aβ accumulations then could be secondarily activated by Aβ, induce tau phosphorylation and create a vicious circle exacerbating brain lesions and neuronal demise. The levels of JNK and PKR have been already assessed in the CSF of patients in addition to the regular markers Aβ, tau and ptau and correlates with phosphorylated tau. They could constitute possible surrogate markers if a new therapeutic approach using JNK and PKR inhibitors are put in place in the future in early MCI or in patients at risk for AD. *Conclusion:* In conclusion, targeting early and abnormal neuronal signaling pathways by kinase inhibition as an approach for prevention trials could reduce the metabolic vicious circle partly at the origin of Aβ accumulation while also affording neuroprotection and might contribute, in association with Aβ immunotherapy or BACE 1 inhibition, to delay the cognitive decline in persons at risk for AD.

OC25: A RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL TO STUDY DIFFERENCE IN COGNITIVE LEARNING ASSOCIATED WITH REPEATED SELF-ADMINISTRATION OF REMOTE COMPUTER TABLET-BASED APPLICATION ASSESSING DUAL-TASK PERFORMANCE BASED ON AMYLOID STATUS IN HEALTHY ELDERLY VOLUNTEERS

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Background: Many cognitive assessments exist to characterize the earlier stage of memory deficits associated with AD pathology, however it is now accepted that the disease spectrum develops over 20 years before the clinical symptoms appear. Academic and industrial researchers lack reliable endpoints to assess cognitive domains which may be affected earlier than memory, this impedes earlier diagnosis and potential therapeutics. Subtle cognitive changes in attention, more specifically impairment in divided attention, the ability to cope with dual-tasking/distractions, have been reported in subjects at the early stage of AD. As accumulation of amyloid in the brain is both a biomarker and a risk factor for progression toward the development of cognitive symptoms associated with AD, it is hypothesized that subjects with brain amyloidosis may have higher cognitive vulnerability and reduced learning associated with cognitive intervention. This hypothesis is being examined in this study A9001489 using Akili's Project EVO assessment in a healthy aging, cognitively normal population of subjects with and without cerebral amyloidosis. EVO is a computer tablet-based cognitive tool deployed to the user as an engaging videogame, the construction of which is based on a novel dual-task paradigm. The prototype of EVO, Neuroracer, was shown to enhance the ability of healthy adults (N=203) to resolve cognitive interference in a controlled study. The dual-task conditions displayed on the Neuroracer prototype are a Go/No-Go perceptual task (targeting) combined with a visuomotor function task (navigating). These tasks can be performed in isolation or combined (interference). The loss of performance detected in interference condition when compared to isolation, is called "interference cost". EVO is available on mobile platforms such as iPad, which enables remote, self-administration and training. The game employs adaptive algorithms, which allows the program to automatically tune the difficulty (Threshold) relative to the study participant. *Methods:* Cognitively normal, healthy elderly subjects (N=97) were randomized in the study, at a ratio of no greater than 3:2 in each of the two amyloid groups (amyloid (-) /amyloid (+)). The cognitive assessments were conducted on site at Day -28 (Screening), Day 0 and Day 28. Following read-out of the screening amyloid PET scan, eligible subjects were randomized on a 1:1 basis to blinded drug (20 mg MPH or placebo). Subjects self-trained remotely on EVO during the training period of Day 1 through Day 27. Subjects were assessed at the study centers on Day 0 (pre-EVO training) and Day 28 (post-EVO training) both pre and post single administration of the assigned study drug. In this study the primary objective was to compare the effect of cognitive training on divided attention performance between brain amyloid (+) and amyloid (-) populations as measured by reaction time on hits using EVO. Specifically, the primary endpoint was the difference in effect of cognitive training on divided attention performance as measured by the pre/post training change in interference cost on EVO dual-task assessment between Day 0 and Day 28. The impact of amyloid status and EVO-based training on traditional cognitive measures such as TOVA and RAVLT were also evaluated as secondary endpoints. An exploratory objective of the study was to evaluate the effect of the CNS stimulant, methylphenidate (MPH), on study endpoints. The dose of methylphenidate used in

this study, 20mg, was previously reported to improve performance in an attentional task in elderly volunteers with subjective memory complaints. The amyloid status was determined by the use of a hybrid visual/quantitative reading method designed to increase concordance of visual and quantitative methods, thus minimizing the impact of non-specific binding, image noise, and cortical thinning which could result in readings inconsistency with quantitative results. *Results:* A total of 199 subjects were screened, 97 were randomized at 4 sites in the USA, 54 were 70 years- old or above. The age inclusion criteria from 60-80 was adjusted to 70-80 for the remainder of recruitment to adjust for the observed low rate of amyloid prevalence. The primary analysis was based on the subset of subjects who were 70 years old or older in the Per Protocol Analysis Set (N=54). *Conclusions:* The primary endpoint, the effect of cognitive training on divided attention performance between amyloid (+) and amyloid (-) as measured by reaction time on hits using EVO are presented, along with the secondary endpoints including the effect of EVO cognitive training on sustained attention and episodic memory as measured by the Test of Variables of Attention (TOVA) and Rey Auditory Verbal Learning Test (RAVLT).

OC26: TIO2-NANOWIRED CEREBROLYSIN POTENTIATES NEUROPROTECTIVE EFFECTS OF ANTI-TAU (PHOSPHO S422) ANTIBODY IN ALZHEIMER'S DISEASE.

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Background: Brain pathology in Alzheimer's Disease (AD) is quite complicated. In spite of our knowledge and research in the field of AD induced brain pathology our understanding regarding critical players in AD pathology e.g., amyloid beta protein (AβP), tau, ubiquitin and/or alpha synuclein (α-synuclein) are still unclear. Increased levels of these proetins or enzymes could either be interpreted as harmful agents as this could occur in association with AD brain pathology. On the other hand, alternative theory could also indicate that an upregulation of these proetins and enzymes in AD could results in some kind of endogenous neuroprotective approach against toxic events. Interestingly inhibitors of these proteins and enzymes sometimes produce conflicting results. Thus, AD-induced brain pathology is still not very well know and require additional investigation using novel approach for the treatment strategies. Our laboratory is engaged in exploring possible mechanisms of AD-induced brain pathology so that novel therapeutic strategies may be worked out that could be relevant in clinical trials of AD in future. In this investigation, we examined the role of tau in the brain pathology of AβP infusion induced AD in our rat model using antibodies of phosphorylated tau. In addition, we also used co-administration of TiO2-nanowired cerebrolysin (NWCBL) that is known to reduce brain levels of tau in our model of AD. Thus, it would be interesting to see whether a combination of tau antibodies and nanodelivery of cerebrolysin could potentiate neuroptective effects of each other in our AD model. *Methods:* Experiments were carried out on Male Sprague Dawley rats (250-300 g, Age 30 to 35 weeks). AD like symptoms was produced by intraventricularly (i.c.v.) administration of AβP (1-40) in the left lateral ventricle in a dose of 250 ng/10 μl once daily for 4 weeks. Control group received physiological saline (0.9% NaCl) instead of AβP infusion. After 30 days of the 1st AβP or saline infusion, the rats were examined for blood-brain barrier (BBB) disturbances to endogenous/exogenous protein tracers, brain edema formation, AβP deposits and brain pathology comprising, neuronal, glial and axonal changes using standard procedures. In addition these animals were also tested for behavioral disturbances using Rota Rod treadmill, inclined plane angle test and water maze performances. Separate group of rats received Anti-Tau (phospho S422) antibody [EPR2866] (ab79415) 10 μl (1:20 dilution in phosphate buffer pH 7.0) i.c.v. into the left lateral ventricle after 1 week of the start of A-P infusion that was repeated 3 more times (10 μl each) at the interval of 5 days. Another group of rats received co-administration of nanowired cerebrolysin (NWCBL 25μl, i.c.v.) after 1 week of AβP infusion in tau antibodies treated group daily for 2 weeks. In all these antibodies treated animals with or without NWCBL co-administration, brain pathology and behavioral functions were analyzed using standard protocol. *Results:* Our observations showed marked AD like symptoms in untreated AβP infusion group as described earlier. Thus, AβP deposits in the cortex and in hippocampus, neuronal damage and cell death, activation of astrocytes as seen using glial fibrillary acidic protein (GFAP) immunoreactivity, loss of myelin basic protein (MBP) and increase in albumin immunoreaction were prominent in AβP administered group as compared to saline treated rats. Breakdown of the BBB to Evans blue albumin or radioiodine ([131]-I) and edema formation was much more pronounced in several brain areas following AβP infusion. The behavioral disturbances on Rota Rod performances and inclined plane angle tests were significantly deteriorated along with the ability to retrieve platform in water maze tests in AβP infused rats as compared to saline treated control group. When tau antibodies were administered (4 times) alone in AβP infused group, the AD-like brain pathology e.g., neuronal glial and axonal damages, AβP deposits, BBB breakdown and behavioral functions were slightly but significantly reduced. Likewise, when the NWCBL (25 μl) alone was administered in AβP group, the reduction in pathological changes and improvement in behavioral parameters were moderately enhanced. On the other hand, when tau antibodies were co-administered with NWCBL infusion in AβP group the reduction in brain pathology and improvement in behavioral functions were significantly potentiated. *Conclusions:* These observations are the first to suggest that phosphorylated tau participates in AD-induced brain pathology and neutralization of tau-antigen with monoclonal tau-specific antibody in vivo is capable to markedly reduce AD-induced brain pathology. Furthermore, a combination of tau antibodies together with nanodelivery of cerebrolysin- a multimodal drug with balanced composition of several neurotrophic factors and active peptide fragments significantly potentiated tau-antibodies induced neuroprotection in AD, not reported earlier. *Supported by Air Force Material Command, USAF, under grant number FA8655-05-1-3065; Alzheimer's Association (IIRG-09- 132087), the National Institutes of Health (R01 AG028679) Swedish Medical Research Council (Nr 2710-HSS), India-EU Co-operation Program (RP/AS/HSS) IT 794/13 (JVL), and UFI 11/32 (JVL) Basque Science Foundation, Spain, & SSNN, Romania.

OC27: THE A4 STUDY: UPDATE ON ENROLLMENT AND PRELIMINARY TAU PET ANALYSES. Reisa Sperling[1, 2], Keith Johnson[2], Dorene Rentz[1], Aaron Schultz[2], Jason Karlawish[3], Eric Siemers[4], Roy Yaari[4], Michael Rafii[5], Tiffany Chow[5], Cecily Jenkins[5], Michael Donohue[5], Paul Aisen[5] *((1) Brigham and Women's Hospital; (2) Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; (3) University of Pennsylvania, Philadelphia, PA, USA; (4) Eli Lilly & Co.; (5) Alzheimer Therapeutic Research Institute, Keck School of Medicine, University of Southern California, San Diego, CA, USA)*

Background: One of the pressing dilemmas in the Alzheimer's disease field remains how best to identify individuals who are clearly on the AD trajectory but at an early enough stage of the pathophysiological process to be maximally responsive to therapeutic intervention. The Anti-Amyloid Treatment in Asymptomatic AD (A4) Study will enroll approximately 1150 clinically normal older individuals with evidence of elevated amyloid accumulation on screening PET scans to determine if treatment with solanezumab, an anti-amyloid-beta monoclonal antibody, when initiated prior to clinical impairment, can slow the neurodegeneration and cognitive decline associated with early AD. *Methods:* The A4 Study is a placebo controlled, double blind Phase 3 trial lasting 168 weeks. Eligible participants are 65-85 years old, clinically normal (CDR=0; MMSE >25. Logical Memory IIa 18-6), are in general good health, and show elevated amyloid levels on screening Amyloid PET imaging with 18-F-Florbetapir. Participants who "screen-fail" on the basis of below threshold amyloid levels on screening PET imaging are eligible for the Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN) companion observational study. The primary endpoint is the Preclinical Alzheimer Cognitive Composite, which includes the Free and Cued Selective Reminding Test, Logical Memory Delayed Recall, Digit Symbol, and Mini-Mental Status Examination scores. Secondary clinical endpoints include computerized testing on an iPAD, Participant Reported Outcomes, and self and study partner reports on Activities of Daily Living. The A4 Study also imbeds a number of biomarker outcomes, including PET amyloid imaging, structural and resting state functional MRI, with cerebrospinal fluid markers and Tau PET imaging with 18-F-AV1451 in a subset of participants. Preliminary Tau PET substudy analyses utilized cerebellar grey reference region with partial volume correction, with age included as a covariate in the models. *Results:* As of early September 2016, we have screened over 4500 older individuals, with 400 currently in screening, and randomized over 710 participants across 66 sites in the US, Canada, Australia and Japan. We have acquired over 2700 Amyloid PET scans, 210 CSF samples, and 200 Tau PET images. The process of consenting, screening, and disclosing amyloid status is working well. As expected, 30% of clinically normal older individuals (mean age at screening = 71.8 +/- 4.9 years; 57% female) show elevated amyloid levels on screening PET scans. Preliminary analyses of eligible participants with elevated amyloid on screening PET scans revealed that 58% are APOE e4 carriers compared to only 24% APOE e4 carriers in the non-elevated amyloid group who screen-failed for the A4 Study ($p<0.001$). Elevated amyloid eligible clinically normal participants, compared to screen-fails with non-elevated amyloid levels, are slightly older (72.0 vs. 71.0; $p<0.001$) and show a trend towards lower performance on screening Logical memory scores (11.5 vs. 11.8; $p=0.063$). Preliminary analyses of baseline Amyloid and Tau PET measures in the elevated amyloid eligible population demonstrate significant relationships between these estimates of neuropathology, such that higher amyloid in an aggregate cortical region is correlated with higher Tau in the entorhinal (partial $r=.36$; $p<0.0001$), inferior temporal (partial $r=.38$; $p<0.0001$), inferior parietal cortices (partial $r=.33$; $p<0.005$) and the precuneus (partial $r=.34$; $p<0.001$). *Conclusion:* Ongoing analyses of the screening data suggest that the A4 Study is recruiting a cohort with similar demographic characteristics to populations in trials at later stages of AD, with the elevated amyloid A4 eligible cohort including approximately 60% APOE e4 carriers. Preliminary analyses of the Tau PET data suggest that neocortical amyloid and regional tau levels are significantly associated prior to clinically evident symptoms, even within the restricted ranges of amyloid and tau seen in the clinically normal, elevated amyloid population eligible for the A4 Study. These preliminary Tau sub-study findings suggest that we will be able to test the hypothesis whether decreasing amyloid accumulation during the preclinical stage of AD can slow the spread of tau pathology. Although efficiently screening the large number of clinically older individuals required to identify those with elevated amyloid remains challenging, the A4 Study has surpassed its halfway mark for enrollment and will complete enrollment in 2017.

OC28: EXOGENOUS INFUSION OF NEPRILYSIN INDUCES NEUROPROTECTION IN ALZHEIMER'S DISEASE PATHOLOGY. POTENTIATION WITH CO-ADMINISTRATION OF NANOWIRED CEREBROLSYIN. Aruna Sharma[1], José V Lafuente[2], Dafin F Muresanu[3], Rudy J Castellani[4], Mark A Smith[5], Ranjana Patnaik[6], Z Ryan Tian[7], Asya Ozkizilcik[7], Herbert Mössler[8], Hari S Sharma[1] *((1) Uppsala University, Uppsala, Sweden; (2) Dept of Neurosciences, University of Basque Country, Bilbao, Spain; (3) Dept. Clinical Neurosciences, University of Medicine & Pharmacy, Cluj-Napoca, Romania; (4) University of Maryland, Dept. of Pathology, Baltimore, MD, USA; (5) Case Western Reserve Medical University, Dept. of Pathology, Cleveland, OH, USA; (6) School of Biomedical Engineering, Dept. of Biomaterials, Indian Institute of technology, Banaras Hindu University, Varanasi, India; (7) Dept. Chemistry & Biochemistry & bBiomedical Engineering, University of Arkansas, Fayetteville, AR, USA; (8) Ever NeuroPharma, Oberburgau, Austria)*

Background: The pathophysiology of Alzheimer's Disease (AD) and its regulating mechanisms are still not well known. Neprilysin (NPL) also known as membrane metallo-endopeptidase (MME) is an endogenous enzyme that is responsible in degradation or clearance of the amyloid-beta peptide (AβP) responsible for the pathogenesis of Alzheimer's disease (AD). It appears that an imbalance between production and clearance of AβP results in its accumulation leading to development of AD. Several evidences show that the NPL levels are decreased in AD cases that are accompanied with increased levels of AbP in the brain. A clear role of NPL is AS also supported further in NPL knocked out mice that exhibit AD like brain pathology and behavioural dysfunctions. Thus, several lines of evidences suggest a decreased level of NPL is associated with AD. Accordingly, exogenous administration of NPL could be a good therapeutic tool to reduce brain pathology in AD. Previous reports from our laboratory suggests that continuous infusion of Cerebrolysin-a multimodal drug with a balanced composition of several neurotrophic factor and active peptide fragments if delivered through TiO2 nanowired technology is able to reduce AbP deposits in the brain and attenuate brain pathology in AD. Recently an interaction between NPL and neurotrophic factors is suggested to be important factors in regulating AbP levels in health and disease. Thus, a possibility exists that co-administration of neprilysin and nanowired delivered cerebrolysin (NWCBL) may have an additive neuroprotective effects in AD. This hypothesis was examined in this investigation in AβP infusion induced AD like brain pathology. *Methods:* AD like brain pathology was induced by AβP (1-40) administration intraventricularly (i.c.v.) in the left lateral

ventricle 250 ng/10 μl once daily for 4 weeks. Control rats received physiological saline (0.9 % NaCl) instead of AbP in identical manner. After 30 days of the 1st AβP infusion breakdown of the blood-brain barrier (BBB) extravasation of endogenous/exogenous protein tracers, brain edema formation, and AβP deposits in several parts of the brain were examined using standard protocol. Histopathological and immunohistochemical analysis on paraffin sections from various brain areas were evaluated for neuronal, glial and axonal changes in control and AD brains. In separate group of rats, TiO2 nanowired Cerebrolysin (25 μl, NWCBL) either alone or together with NPL (2.5 μg in 10 μl) was infused into the left cerebral ventricles daily starting from 1 week after the onset of AβP infusion and terminated 1 week before the last infusion. After 30 days, brain pathology was evaluated in these drug treated AD group and compared with untreated rats in a blinded fashion by two independent investigators. *Results:* Our results show that AβP infusion resulted in profound brain pathology as compared to saline treated group in various regions e.g., cerebral cortex, hippocampus, thalamus, hypothalamus and cerebellum. TiO2 NWCBL was able to thwarts brain pathology, BBB breakdown and AβP deposits in AD cases. However, NPL alone was able to reduce some of the brain pathology, AβP deposits and BBB breakdown after AβP infusion. On the other hand a combination of NWCBL and NPL resulted in profound neuroprotection, AβP deposits and BBB breakdown following AβP infusion. *Conclusions:* Our results are the first to show that a combination of NPL and NWCBL reduced AβP deposits inn the brain and thus potentiated neuroprotective effects in AβP infusion induced brain pathology in AD, not reported earlier. *Supported by grants from the Air Force Office of Scientific Research (EOARD, London, UK), and Air Force Material Command, USAF, under grant number FA8655-05-1-3065; supported by Grants from the Alzheimer's Association (IIRG-09- 132087), the National Institutes of Health (R01 AG028679) and the Dr. Robert M. Kohrman Memorial Fund (MAS, RJC); Swedish Medical Research Council (Nr 2710-HSS), Göran Gustafsson Foundation, Stockholm, Sweden (HSS), Astra Zeneca, Mölndal, Sweden (HSS/AS), The University Grants Commission, New Delhi, India (HSS/AS), Ministry of Science & Technology, Govt. of India (HSS/AS), Indian Medical Research Council, New Delhi, India (HSS/AS) and India-EU Co-operation Program (RP/AS/HSS) and IT 794/13 (JVL), Government of Basque Country and UFI 11/32 (JVL) University of Basque Country, Spain and Society for Study on Neuroprotection and Neuroplasticity (SSNN), Romania.

OC29: SERUM PROTEIN BIOMARKERS OF Δ FULLY MEDIATE MULTIPLE AD CONVERSION RISKS AND OFFER TARGETS FOR INTERVENTION. Donald R. Royall[1-4], Safa Al-Rubaye[1], Ram Bishnoi[1], Raymond F. Palmer[3] *((1) Department of Psychiatry, The University of Texas Health Science Center at San Antonio (UTHSCSA), San Antonio, Texas, USA; (2) Department of Medicine, UTHSCSA, San Antonio, Texas, USA; (3) Department of Family & Community Medicine. UTHSCSA, San Antonio, Texas, USA; (4) South Texas Veterans Health Administration Geriatric Research Education and Clinical Center (GRECC) , San Antonio, Texas, USA)*

Background: The latent variable "δ" (for "dementia") appears to be uniquely responsible for the dementing aspects of cognitive impairment. Age, depressive symptoms, gender and the apolipoprotein E (APOE) ε4 allele are independently associated with δ. We have identified the serum protein mediators of their individual associations with an ethnicity equivalent δ homolog ("dEQ"). Here we test selected proteins' ability to also mediate those variables' associations with prospective conversion to clinical "Alzheimer's Disease" (AD) from non-demented states [i.e., Normal Control (NC) and Mild Cognitive Impairment (MCI)]. *Methods:* We previously identified serum protein mediators of each risk factor's unique association with dEQ among n = 1191 Mexican-American and n = 2124 non-Hispanic White participants in the Texas Alzheimer`s Research and Care Consortium (TARCC). N = 712 participants had biomarker data and were adjudicated as NC or MCI at visit 1. They were followed annually for up to 6 years [ṁ = 4.7(0.6)]. Each risk factor's independent association with conversion was confirmed by logistic regression. Each risk factor's strongest mediators were sequentially entered to test their ability to attenuate that risk factor's specific independent effect on conversion risk. All models were additionally adjusted for education, ethnicity, self-reported diabetes mellitus and hypertension. *Results:* n = 70 non-demented participants at baseline converted to "AD" (9.8%). Age >80yrs (OR = 3.1), GDS30 > 10/30 (OR = 2.3), female gender (OR = 2.2) and the presence of an apolipoprotein E (APOE) ε4 allele (OR = 2.4) were independently associated with prospective conversion. These effects were fully mediated by five serum proteins. AGE: Insulin-like Growth Factor-Binding Protein 2 (IGF-BP2), Epidermal Growth Factor Receptor 1 (EGFR); Depression: Resistin; Gender: Thrombopoeitin (THPO); APOE: C-Reactive Protein (CRP). *Conclusions:* Clinical dementia arises from the sum of independent δ-related processes. We have used that insight to rationally select five serum proteins which independently contribute to a nine-fold risk of AD conversion over five years. Modulating any of them might lower dementia conversion risk in specific demographics. This analysis provides proof of concept for the rational selection of anti-dementia targets, and offers a foundation for precision anti-dementia therapy.

OC30: INCREASED HIPPOCAMPAL VULNERABILITY IN TRANSGENIC MICE OVEREXPRESSING APP AND TRIPLE REPEAT TAU. Andrew Arner Edward Rockenstein, Michael Mante, Jazmin Florio, Deborah Masliah, Anthony Adame, Eliezer Masliah, Robert A. Rissman *(University of California, San Diego, La Jolla, CA, USA)*

Background: Tauopathies encompass several of the most prevalent neurodegenerative diseases that consistently progress to severe dementia and motor impairments. They involve tau hyperphosphorylation, which is hypothesized to lead to detachment from associated microtubules, and a decline in the structural integrity of the cytoskeleton. Alzheimer disease (AD) is the most common tauopathy that it is uniquely associated with extracellular accumulation of amyloid beta plaques. *Methods:* We generated a novel transgenic mouse line carrying the human amyloid precursor protein gene (hAPP) and crossed it to our recently generated line of mice that overexpress a variant of the human triple repeat tau gene (3R Tau), to create a novel bigenic mouse AD model. *Results:* We characterized the pathological and cognitive changes associated with this model, both in young and aged mice. Our results demonstrate higher levels of phosphorylated tau in the mice carrying the 3R Tau gene. Interestingly, bigenic mice had higher levels of phosphorylated tau than all other groups. Increased levels of tau kinases were observed in the 3R Tau mice, with levels in bigenic mice exceeding these levels. Our immunohistochemical data suggest increased levels of glial scarring and neuronal loss in 3R Tau mice, and this finding was exacerbated in bigenic mice. Beta-amyloid was only detected in the detergent soluble fraction of the hAPP mice. *Conclusions:* Our results suggests that in addition to 4RTau, APP/Aβ might also enhance accumulation of 3RTau which might be relavant to understand pathogenic pathways relevant to AD.

OC31: ADUCANUMAB 24-MONTH DATA FROM PRIME: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 1B STUDY IN PATIENTS WITH PRODROMAL OR MILD ALZHEIMER'S DISEASE. Vissia Viglietta[1], John O'Gorman[1], Leslie Williams[1], Tianle Chen[1], Ahmed Enayetallah[1], Ping Chiao[1], Christoph Hock[2], Roger M Nitsch[2], Samantha Budd Haeberlein[1], Alfred Sandrock[1] *((1) Biogen, Cambridge, MA, USA; (2) Neurimmune, Schlieren-Zurich, and University of Zurich, Switzerland)*

Background: Aducanumab (BIIB037), a human anti-amyloid beta (Aβ) monoclonal antibody, is being investigated as a disease-modifying treatment for early Alzheimer's Disease (AD). PRIME is an ongoing Phase 1b study evaluating the safety, tolerability, pharmacokinetics, and pharmacodynamics of aducanumab in patients with prodromal or mild AD at 54 weeks. Here, we report 24-month data from the 12-month placebo controlled period and first 12 months of the long term extension (LTE) period. *Methods:* Patients included in this multicenter, randomized, double-blind, placebo-controlled, multiple dose study (PRIME; NCT01677572) were aged 50-90 years, had a positive florbetapir (18F AV 45) positron emission tomography (PET) scan, and met clinical criteria for prodromal or mild AD. During the double-blind, placebo controlled phase, patients received aducanumab or placebo once every 4 weeks for 52 weeks. In a staggered, parallel-group design, patients were randomized to fixed doses of aducanumab (1-10 mg/kg) stratified by apolipoprotein E4 (ApoE ε4) status (carrier/non-carrier). The study also included a dose titration cohort (not reported here; 24-month data for the titration cohort are not yet available). To be eligible for inclusion in the LTE period (a period of up to 3 years), patients at Week 56 must have completed the placebo-controlled portion of the study, received 11 or more doses, not missed more than 2 consecutive doses, and had an Mini-Mental State Examination (MMSE) score >10 at Week 52. For the LTE, all patients were assigned to receive aducanumab 3, 6, or 10 mg/kg. Their dose assignments in the LTE were as follows: patients who had received placebo during the double-blind phase received either aducanumab 3 mg/kg or a titration regimen of aducanumab 3 to 6 mg/kg (2 doses of 3 mg/kg followed by subsequent doses of 6 mg/kg) in the LTE. Patients who were randomized to receive aducanumab 1 mg/kg during the double-blind phase subsequently were assigned to receive aducanumab 3 mg/kg in the LTE. All other patients receiving aducanumab 3, 6, or 10 mg/kg during the double-blind phase continued at their original dose assignment or reduced dose (aducanumab continuers). The primary endpoint for the LTE was safety and tolerability as measured by incidence of adverse events (AEs)/serious AEs (SAEs). Exploratory endpoints for the LTE included a measurement of Aβ reduction using amyloid PET (as assessed by standard uptake value ratio [SUVR]) and change from baseline in clinical endpoints, including the Clinical Dementia Rating-Sum of Boxes (CDR-SB) scale and the MMSE. A mixed model for repeated measures (MMRM) was used for the analysis of change from baseline in amyloid PET, CDR-SB, and MMSE. *Results:* Of 165 patients randomized and dosed in PRIME within the fixed-dose cohorts, 117 were dosed in the LTE and 91 completed treatment at Month 24. After 24 months, a significant decrease in brain amyloid plaque burden was observed in those patients from the 10 mg/kg and 6 mg/kg groups continuing treatment in the LTE compared with those patients who had switched from placebo (adjusted mean [standard error] change from baseline in PET SUVR: -0.329 [0.031] and -0.284 [0.028] with aducanumab 10 mg/kg and 6 mg/kg, respectively vs -0.162 [0.027] for placebo switchers; P<0.001 and P<0.01, respectively; Figure). Decreases in brain amyloid plaque burden were also observed among patients switched to aducanumab in the LTE. After 24 months, patients in the aducanumab continuer groups also demonstrated consistent slowing of clinical decline in the LTE. For amyloid-related imaging abnormalities (ARIA), the incidence of ARIA cases in patients who switched from placebo or aducanumab 1 mg/kg to aducanumab 3 mg/kg or the titration regimen was generally consistent with that observed during the double-blind phase of the study. No new ARIA-E cases were observed in the LTE in those patients in the aducanumab continuer groups. *Conclusions:* At 24 months, patients who were treated with aducanumab from the beginning of the double-blind phase through the LTE period continued to show a decrease in brain amyloid plaque burden in a dose- and time dependent manner as measured by amyloid PET. CDR-SB and MMSE data over 24 months also suggest a sustained benefit from aducanumab for those patients who continued treatment. The incidence of ARIA in patients switching to aducanumab treatment was consistent with that observed during the double-blind phase of the study, and no new cases of ARIA-E were observed in patients in the aducanumab continuer groups. Reference: 1. Sevigny J et al. Nature 2016;537:50-56.

OC32: AMYVID IMAGING IN A MURINE MODEL OF ALZHEIMER'S DISEASE (AD) AS A NON-INVASIVE METHODOLOGY TO EVALUATE THE REDUCTION IN BETA AMYLOID PLAQUES AFTER CRANIAL IRRADIATION. Brian Marples[1], Sarah A. Krueger[1], Daniel B. Michael[2], George D. Wilson[1], Alvaro A. Martinez[3], James Fontanesi[4] *((1) Department of Radiation Oncology, Beaumont Health Systems, Royal Oak, MI; (2) Beaumont Neurosurgery, Beaumont Health Systems, Royal Oak, MI; Michigan Head and Spine Institute; (3) 21st Century Oncology of Michigan, Farmington Hills, MI; (4) Department of Radiation Oncology, Beaumont Health Systems, Farmington Hills, MI)*

Background: The cognitive deficit associated with Alzheimer's disease (AD) has been causatively linked with the progressive accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles of Tau protein. Our prior studies have demonstrated external beam X-irradiation significantly reduced insoluble amyloid-β plaques in the cortex and hippocampus regions of the brain of a transgenic mice strain (B6.Cg-Tg (APPswePSEN1dE9)85Dbo/J) [Radiother Oncol. 2016 118(1):43-51]. The radiation-mediated reduction in plaque burden was associated with improved cognition as assessed using a Morris Water Maze. Although the mechanism was not fully elucidated, alterations in inflammatory biomarkers were detected using immunohistochemistry as well as changes in the expression of AD specific genes (84 genes: Mouse Alzheimer's Disease RT^2 Profiler™) in the irradiated brain. The aim of the current study was to investigate if the radiation-mediated reduction or clearance of Aβ could be detected using non-invasive positron emission tomography (PET) imaging using 18F-Florbetapir (Amyvid); with the longer-term goal of non-invasively defining the longevity of this radiation-mediated response. *Methods:* 5-6 month old male and female B6.Cg-Tg (APPswePSEN1dE9)85Dbo/J mice were treated with hemi-brain irradiation (5 doses of 2 Gy in 5 days). Radiation was delivered only to the right (R) side of the brain in test mice using a cabinet X-ray irradiation system (160 kVp, 40 mA, HVL: 0.77mm Cu, cabinet temperature 30-32°C) (Faxitron Bioptics, Tucson, AZ) at a dose rate of 0.69 Gy/min, the left (L) side of the brain was not irradiated. Another cohort of control mice was never irradiated. 8 weeks post-irradiation the animals were injected with Amyvid (PETNET Solutions, Detroit, MI). PET/CT images were acquired using a FLEX TriumphTM tri-modality MicroPET/SPECT/CT system (TriFoil Imaging, Northridge, CA). Briefly, 0.5 mCi of Amyvid was injected (0.2 mL) via tail vein, followed by a 30 min uptake period,

after which animals were anesthetized with 1-3% isoflurane and PET/CT imaging performed (30 min acquisition time). *Results:* PET images were reconstructed using a 3D-OSEM reconstruction algorithm and fused with murine brain MRI atlas. Amyvid uptake (SUVmean VOI) was significantly different between R and L hemispheres in irradiated animals, p=0.02 (n=11). Also, uptake was significantly different between right hemispheres in irradiated mice and never-irradiated control mice, p=0.01. Uptake was not significantly different between R and L hemispheres in never irradiated animals, or left hemispheres in irradiated mice and never-irradiated control mice, p=0.76, p=0.27 respectively. The histological assessment of the Aβ plaque burden in the harvested brains of irradiated and PET-imaged animals is on-going. *Conclusion:* In summary, we have demonstrated that Amyvid can be used to non-invasively monitor radiation-mediated changes in Aβ plaques in AD transgenic animals. This work was supported by Department of Radiation Oncology, Royal Oak, Beaumont Health System, MI, Botsford Hospital Foundation, Farmington Hills, MI and Michigan Head and Spine Institute, Southfield, MI.

OC33: SAFETY, TOLERABILITY AND PHARMACOKINETICS OF ABBV-8E12, A HUMANIZED ANTI-TAU MONOCLONAL ANTIBODY, IN A PHASE 1, SINGLE ASCENDING DOSE, PLACEBO-CONTROLLED STUDY IN SUBJECTS WITH PROGRESSIVE SUPRANUCLEAR PALSY. Tim West[1], Joel B. Braunstein[1], Ilana Fogelman[1], Adam L. Boxer[2], Helen Hu[1], Philip B. Verghese[1], Elizabeth John[1], David M. Holtzman[3], Randall J. Bateman[3], Bradley Boeve[4], Yvette M. Bordelon[5], Jared Brosch[6], Daniel Claassen[7], Jason Connor[8], Erica Driver-Dunckley[9], Lawrence S. Honig[10], Irene Litvan[11], Nick McFarland[12], Erik D. Roberson[13], Zbigniew K. Wszolek[14], Davis Ryman[15], Hana Florian[15], Sandra Goss[15], Diana Kerwin[16] *((1) C2N Diagnostics LLC, Saint Louis, MO, USA; (2) University of California San Francisco, San Francisco, CA, USA; (3) Washington University, St. Louis, MO, USA; (4) Mayo Clinic Rochester, Rochester, MN, USA; (5) University of California Los Angeles, Los Angeles, CA, USA; (6) Indiana University, Indianapolis, IN, USA; (7) Vanderbilt University, Nashville, TN, USA; (8) Berry Consultants, LLC, Austin, TX, USA; (9) Mayo Clinic Arizona, Scottsdale, AZ, USA; (10) Columbia University, New York, NY, USA; (11) University of California San Diego, San Diego, CA, USA; (12) University of Florida, Gainesville, FL, USA; (13) University of Alabama at Birmingham, Birmingham, AL, USA; (14) Mayo Clinic Florida, Jacksonville, FL, USA; (15) AbbVie Inc, North Chicago, IL, USA; (16) Texas Health Presbyterian Hospital, Dallas, TX, USA)*

Background: ABBV-8E12 (formerly known as C2N-8E12) is a humanized anti-tau monoclonal antibody currently being developed for the treatment of Alzheimer's disease and progressive supranuclear palsy (PSP). Administration of anti-tau antibodies to transgenic mice that develop tau pathology showed (i) reduction in the progression of tau pathology, (ii) reduction in brain volume loss, and (iii) improvements in various cognitive and behavioral tests when compared to placebo-treated mice. This evidence supported further development and testing of ABBV-8E12 in human tauopathies. Here we present the results of a placebo-controlled phase 1 trial of ABBV-8E12 in subjects with Progressive Supranuclear Palsy (PSP), a disease marked by intraneuronal tau aggregates. *Methods:* This was a phase 1, double-blind, placebo-controlled, continual reassessment method single dosing study to assess the safety, tolerability, and pharmacokinetics of ABBV-8E12 in subjects with PSP (NCT02494024), conducted at 12 clinical study sites. A total of 30 patients were randomized 3:1 to either drug or placebo in blocks of four subjects. Dose escalation followed a continual reassessment method (CRM) based on a Bayesian logistic model for identifying the probability of dose-limiting toxicities by dose level. The CRM allows for rapid dose escalation in a controlled manner through the lower dose levels where the likelihood of adverse events is lower (on a relative basis to higher doses), and increases subject exposure at the highest dose level where the likelihood of drug related adverse events is higher. In total, five dose levels (2.5, 7.5, 15, 25, and 50 mg/kg) were administered by intravenous infusion, with 13 participants enrolled in the highest dose level cohort, and four to five participants in each of the lower dose level cohorts. Blood samples were collected at multiple time points after drug administration for pharmacokinetic and immunogenicity assessments. Cerebrospinal fluid was collected at baseline and on Day 14. Safety assessments included periodic clinical monitoring out to 84 days post-dosing, physical examinations, centrally assessed electrocardiography, and centrally assessed brain magnetic resonance imaging. *Results:* At the time of submission of this abstract the study is still blinded according to the block randomization design. Of 38 subjects screened, 30 were enrolled and randomized. The mean age of the enrolled patients at screening was 69.4 years (SD 7.4, range 54.1 to 86.0); 16 (53%) were male, and the average PSP Rating Scale score at screening was 35.6 (SD 7.6, range 20 to 50). Twenty-nine subjects completed the primary safety assessment period of 14 days post-dosing, and 25 patients completed the entire 84-day study follow-up period, as of this data tally on August 19th, 2016. Three patients withdrew from study prior to the final follow-up visit: one each due to withdrawal of consent, investigator-recommended withdrawal (due to surgical procedure and logistics of travel to the study site), and an adverse event (AE). A total of 58 AEs occurred in 20 of the 30 participants (66.7% incidence); 52 of these AEs occurred post dosing. Adverse events experienced by more than one patient included AEs often seen in this patient population (15 falls, experienced by 9 patients and 6 urinary tract infections, experienced by 5 patients) as well as headache (6 headaches, experienced by 5 patients), redness and blistering at site of ECG sticker (6 reports, experienced by 5 patients), increased fatigue (2 reports, experienced by 2 patients), and sore throat (2 reports, experienced by 2 patients). Three serious adverse events were reported (10% incidence), one in each of the 15, 25, and 50 mg/kg cohorts. These blinded events included two deemed "possibly related to study participation" (subdural hematoma following fall, and, increased agitation) and one determined "unrelated to study participation" (a case of hypertension in the 50 mg/kg cohort). Noncompartmental analysis of interim data measuring the concentration of drug in plasma samples taken at various time points after dosing indicates dose-proportional increases in AUC and less than dose-proportional increases in Cmax from 2.5 to 50 mg/kg. The estimated half-life of ABBV-8E12 is approximately 1 month. CSF concentrations measured 14 days after ABBV-8E12 administration from the 2.5 mg/kg and 7.5 mg/kg dose groups had an observed CSF:plasma concentration ratio of approximately 0.4%. The CSF:plasma ratio in the higher dose groups (15 to 50 mg/kg) ranged from 0.16% to 0.27%. *Conclusion:* ABBV-8E12 exhibited an acceptable safety and tolerability profile and predictable pharmacokinetic behavior in PSP patients when administered as a single dose of up to 50 mg/kg. The CNS penetration of ABBV-8E12 is consistent with what has been observed for other immunoglobulins. These data support repeat-dose testing of ABBV-8E12 in larger cohorts of subjects with tauopathy.

OC34: BACE INHIBITOR CNP520 PROPOSED FOR THE ALZHEIMER'S PREVENTION INITIATIVE GENERATION STUDY. Ulf Neumann[1], Fonda Liu[2], Marie-Laure Rouzade-Dominguez[1], Marie-Emmanuelle Riviere[3], Mike Ufer[1], Gunilla Huledal[1], Nicole Pezous[1], Derya Shimshek[1], Carine Kolly[1], Ronald G. Thomas[4], Angelika Caputo[3], Jessica B. Langbaum[5], Pierre N. Tariot[5], Eric M. Reiman[5], Ana Graf[3], Cristina Lopez Lopez[3] *((1) Novartis Institutes for Biomedical Research, Basel, Switzerland; (2) Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; (3) Novartis Pharma AG, Basel, Switzerland; (4) University of California San Diego, San Diego, USA; (5) Banner Alzheimer's Institute, Phoenix, AZ, USA)*

Background: The development of drugs for the treatment of Alzheimer's Disease has increasingly focused on mild cognitive impairment (MCI) due to AD and on preclinical AD. It is hypothesized that Aβ-lowering therapies might be most effective in preventing or slowing the progression of the disease during these early stages. If one or more forms of Aβ play an early role in the development and if an appropriately specific treatment is safe, tolerated and started early enough in the disease course, this treatment could have a profound clinical and public health impact. The Alzheimer's Prevention Initiative (API) APOE4 Trial, also known as the Generation Study, is evaluating the effects of two β-amyloid targeted therapies (CAD106 and CNP520) in cognitively normal people who, on the basis of age and apolipoprotein E4 (APOE4) homozygote genotype, are at particularly elevated risk of developing symptoms of AD. CAD106 is an active immunotherapy against Aβ; CNP520 is a Beta-site-APP cleaving enzyme-1 (BACE-1) inhibitor. BACE-1 inhibition is considered a promising approach for AD. However, limited selectivity and other findings have led to termination of clinical trials in some cases, indicating a need for more selective and safer compounds. With these goals in mind Novartis developed the BACE inhibitor CNP520. Human data on CNP520 have become recently available. *Methods:* CNP520 was profiled pre-clinically, and in a randomized, double-blind, placebo-controlled, single and multiple ascending dose first-in-human study to assess the safety, tolerability, PK and PD of CNP520 in healthy adult and elderly subjects. *Results:* CNP520 is selective for BACE-1 over BACE-2 and highly selective over pepsin, cathepsin D & E, and renin. CNP520 reduced levels of soluble Aβ in the brains of rats, mice, dogs and humans in a dose and time-dependent manner. The free concentration of CNP520 in the animal brain, and the concentration of CNP520 in the CSF in human, was comparable to free plasma concentrations, indicating good brain penetration. No hypopigmentation or retina changes were observed in chronic studies in normal or transgenic mice, and during long-term toxicology studies. CNP520 appeared generally safe and well-tolerated in humans. Single doses up to 1125 mg were tested in healthy adults. The single maximum tolerated oral dose (MTD) of 750 mg identified in healthy adults also appeared to be safe and well-tolerated in healthy subjects≥60 years of age. Multiple oral doses up to 300 mg daily (maximum dose tested) over 2 weeks appear to be safe and well-tolerated in subjects ≥60 years of age. There was no indication of any major imbalance of AEs between CNP520 and placebo. In healthy subjects ≥ 60 years of age, CNP520 reduced CSF Aβ concentrations in a dose-dependent manner by up to 95% after multiple dosing at the highest dose tested (300 mg q.d.). Pharmacokinetic properties included lack of relevant food effect and a terminal elimination half-life that allows once-daily dosing. *Conclusion:* The current pre-clinical and clinical profile of CNP520 supports long-term clinical studies in people at risk for the onset of clinical symptoms of Alzheimer's disease, such as the API Generation Study (pending regulatory approval).

OC35: EFFECTS OF A COMBINED TRANSCRANIAL MAGNETIC STIMULATION (TMS) AND COGNITIVE TRAINING IN ALZHEIMER PATIENTS: RESULTS OF MEDICAL DEVICE PIVOTAL MULTI-CENTER STUDY. Marwan N. Sabbagh[1], Alvaro Pascual-Leone[2], Carl H. Sadowsky[3], Babak Tousi[4], Marc E. Agronin[5], Gustavo Alva[6], Carmel Armon[7], Charles Bernick[8], Andrew P. Keegan[9], Stella Karantzoulis[10] *((1) Barrow Neurological Institute, Phoenix AZ USA; (2) Berenson-Allen Center for Noninvasive Brain Stimulation and Division of Cognitive Neurology, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, MA; (3) Department of Neurology, Nova SE University, Ft Lauderdale, FL; (4) Lou Ruvo Center for Brain Health Cleveland Clinic, Neurological Institute, Cleveland, OH; (5) Mental Health and Clinical Research, Miami Jewish Health Systems, Miami, FL; (6) ATP Clinical Research, Costa Mesa, CA; (7) Department of Neurology, Assaf Harofeh Medical Center, Zerifin, Israel; (8) Lou Ruvo Center for Brain Health, Cleveland Clinic, Las Vegas, NV; (9) Roskamp Institute Clinic, Sarasota, FL; (10) Alzheimer's Disease Center, Center for Cognitive Neurology, New York University Langone Medical Center, New York, NY)*

Background: Noninvasive brain stimulation with trains of repetitive Transcranial Magnetic Stimulation (TMS) can modulate activity in specific cortical brain regions and networks, and thus affect cognitive function. The neuroAD™ Therapy System delivers brain MRI neuro-navigated, focal TMS concurrently with Cognitive Training exercises. The Cognitive Training tasks are designed to engage the cognitive functions of the brain networks targeted by a preceding train of TMS. *Methods:* This pivotal, aimed to gain regulatory clearance, randomized, double-blind, sham-controlled clinical trial was designed to evaluate the efficacy and safety of a 6 week course of daily neuroAD™ Therapy in the treatment of cognitive impairment in subjects with mild to moderate Alzheimer's disease (NIA-AA criteria). In a multi-center study at 10 sites, 131 subjects were enrolled and randomized to neuroAD™ Therapy versus Sham treatments (placebo). Participants were 60-90 years old, with MMSE scores between 18-26, CDR scores of 1 or 2, and either unmedicated for AD or on stable doses of an acetylcholinesterase inhibitor and / or memantine. Informed consent was obtained from all subjects. A brain MRI was obtained and they were administered the ADAS-Cog and CGI-C at baseline. Enrolled subjects were randomized to either Active or Sham treatments involving hour long sessions five days / week over six weeks, for a total of 30 sessions. The ADAS-Cog and CGI-C were repeated at the end of treatment (week 7) and at week 12. *Results:* The pivotal, regulatory-targeted study is complete. The results will be presented at the meeting. *Conclusions:* Study outcomes support an on-going FDA application for clearance of the neuroAD™ Therapy System. ClinicalTrials.gov Identifier: NCT01825330

OC36: PREDICTING ONSET AND SPATIOTEMPORAL SPREAD OF AD TAU PATHOLOGY USING GRAPH DIFFUSION MODELING ON INTRINSIC STRUCTURAL BRAIN NETWORKS. Duygu Tosun[1,2], Roksana Sadeghi[2], Ashish Raj, Michael Weiner[1,2], for the Alzheimer's Disease Neuroimaging Initiative *((1) Department of Radiology, University of California – San Francisco, CA, USA; (2) Center for Imaging of Neurodegenerative Diseases, San Francisco, CA, USA; (3) Computer Science in Radiology, Weill Cornell Medical College, New York City, NY, USA)*

Backgrounds: Alzheimer's disease (AD) is a progressive neurodegenerative disease preceded by a long prodromal phase. Biomarkers not only play an important role in identifying the

pathophysiological processes underlying clinical symptoms but also help to predict time to onset of the neurodegenerative process and onset of disease. Identifying people who are in the very early stages with respect to the targeted molecular pathway is crucial for therapeutic treatments to have a beneficial effect at individual patient level. Furthermore, modeling the progression of individuals with respect to the targeted molecular pathway will potentially facilitate greater power in clinical trial efficacy. Tau pathology is known to undergo inter-neuronal transmission, and animal models suggest the transmission occurs along anatomic connections. Here we aimed to mathematically characterize the onset and spread of the AD tau pathology by analyzing AV-1451 positron emission tomography (PET) imaging data from Alzheimer's Disease Neuroimaging Initiative (ADNI-2) study. The mathematical characterization was based on a network diffusion model parameterized on structural connectomes from diffusion-weighted magnetic resonance image (DW-MRI). *Methods:* Subjects of this study were ADNI-2 participants who recently underwent AV-1451 PET imaging for in vivo detection of regional tau pathology and DW-MRI. The study cohort was composed of fifty-seven adults (mean age = 76.1+7.0) with normal cognition (n=28 with Clinical Dementia Rating (CDR) of 0), early AD symptomology (n=25 with CDR=0.5), or AD (n=4 with CDR=1). PET imaging were performed at each ADNI site according to standardized protocols. AV-1451 data were realigned, and the mean of all frames was used to coregister AV-1451 data to each participant's MRI acquired closest to the time of the AV-1451 PET scans. In each participant's MRI native space, AV-1451 SUVR images were created based on mean AV-1451 uptake normalized to uptake in a gray matter masked cerebellum reference region. Structural MRIs were processed using the FreeSurfer v5.3, automatically labeling 86 brain regions, including gyri and subcortical structures. Average AV-1451 SUVR values were estimated for each FreeSurfer regions-of-interest (ROIs). Raw DW-MRIs were corrected for Eddy current, motion, and echo-planer-imaging artifacts using FSL. A single diffusion tensor was modeled at each voxel in the brain from the corrected DW-MRI scans using FSL. Basic streamline tractography was performed using Camino toolkit (http://camino.cs.ucl.ac.uk/) using directional information derived from the diffusion tensors. Structural connectivity matrices (connectomes) were constructed with the 86 ROIs as the network nodes and the number of streamlines connecting each pair of ROIs as the undirected edges. The central role of brain connectivity in trans-neuronal proteopathic transmission has been exploited in a recent work on a graph-theoretic network diffusion model[1], suggesting that the process of spread should be deterministically quantifiable and predictable once the state of the brain's intrinsic connectivity network is known. Furthermore, the spread could be captured by a network heat equation[2], , where is the regional concentrations of pathology over time and H is the normalized graph Laplacian matrix of the connectome matrix C of the subject. Here, was the regional AV-1451 binding at 86 ROIs. The backward solution of the proposed model with partial least squares optimization on 86 modes of the connectome matrix was performed to estimate (1) as an estimate of tau pathology onset pattern and (2) dominant intrinsic brain networks facilitating the spread of tau pathology from predicted pattern to final pattern detected in in vivo AV-1451 PET scans. *Results:* In this sample we found that the onset site of the tau pathology spread included entrohinal, hippocampal, parahippocampal, amygdala, and orbital frontal cortices, with a left hemisphere dominance. Spread from these onset sites was facilitated primarily by three intrinsic brain network modes: 1) connections between left frontal and right temporoparietal regions; 2) connections between left parietal and right frontal regions; and 3) frontoparietal and temporal connections in the left hemisphere. The network spread dynamics predicted by the model highly correlated with the in vivo AV-1451 regional estimates (R=0.82; p=0.013). *Conclusion:* Our data-driven approach recapitulates the ubiquitous result from autopsy studies that AD tau pathology progresses in a stereotypical manner with the first lesions appearing in the medial temporal lobe structures. Furthermore, our results suggest that the dynamic inter-neuronal transmission of tau pathology could be mathematically modeled, potentially providing a computational biomarker of AD progression. Such dynamic biomarker models could convert descriptive understanding of degenerative pathophysiology into a fully predictive model of disease trajectory. References: 1. Raj, A., A. Kuceyeski, and M. Weiner, A network diffusion model of disease progression in dementia. Neuron, 2012. 73(6): p. 1204-15. 2. Kondor, R.I. and J. 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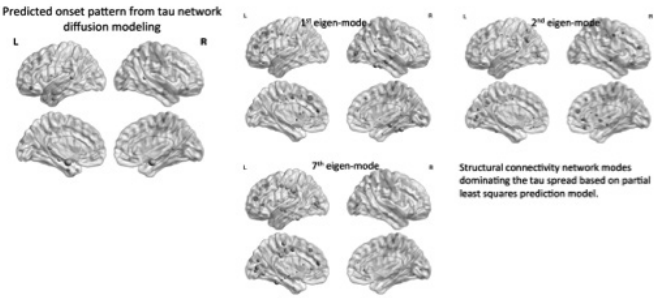

OC37: EARLY- AND LATE-ONSET ALZHEIMER'S DISEASE SHOW DISTINCT TAU PATHOLOGY AS EXAMINED WITH 18F-AV-1451 TAU POSITRON EMISSION TOMOGRAPHY.

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Background: Alzheimer's disease (AD) has been associated with clinical and pathological variability. For instance, patients with late-onset Alzheimer's disease (loAD) typically present with medial temporal lobe neurodegeneration and predominantly amnestic symptomatology, while patients with early-onset (eoAD) tend to exhibit greater neocortical involvement causing a more non-amnestic clinical presentation. Positron emission tomography (PET) employing ligands for hyperphosphorylated tau protein have enabled the study of regional tau accumulation in vivo. We explored whether eoAD and loAD exhibit differential regional tau pathology using tau PET. *Methods:* Nineteen patients with eoAD (mean age 62.5 ± 6.7 y, MMSE 21.4 ± 5.0), 16 patients with loAD (mean age 75.5 ± 4.5 y, MMSE 20.6 ± 5.2), and 12 cognitively healthy elderly controls (HC, mean age 73.1 ± 6.1 y, MMSE 29.4 ± 0.9) underwent PET scanning with the tau ligand 18F-AV-1451. First, we performed voxelwise multiple regressions (SPM12) to examine the effect of age on AV-1451 uptake in the in eoAD and loAD patient groups, respectively. We then performed voxelwise t-tests (SPM12) comparing AV-1451 uptake patterns in the group of HC with the respective AD

groups. Cerebrospinal fluid (CSF) measures for β –amyloid (Aβ)1-42 were available for all loAD and 13 of the eoAD patients, a voxelwise regression model exploring the interaction effect of age and CSF levels of Aβ1-42 on AV-1451 retention was also examined. *Results:* Higher age did not reveal any positive effect on tau ligand uptake in neither AD group. Comparing eoAD with HC showed significantly posterior-predominant isocortical AV-1451 uptake (Figure 1A), comparing HC with loAD resulted in a distinct pattern of higher AV-1451 retention in medial temporal lobe regions (all results at $p < 0.05$ corrected for family-wise error). *Conclusion:* Preliminary analyses provided evidence for clearly distinct regional tau pathology in eoAD and loAD confirming earlier findings of atrophy and glucose hypometabolism in corresponding brain regions.

OC38: NILVAD: A EUROPEAN MULTICENTRE DOUBLE-BLIND CONTROLLED PHASE III TRIAL OF NILVADIPINE IN MILD TO MODERATE ALZHEIMER'S DISEASE. Brian Lawlor[1], Sean Kennelly[1], Sarah ODwyer[1], Fiona Cregg[2], Cathal Walsh[2], Robert Coen[1], Rose Anne Kenny[1], Robert Howard[3], Caroline Murphy[3], Jessica Adams[3], Leslie Daly[4], Ricardo Segurado[4], Siobhan Gaynor[5], Fiona Crawford[6], Michael Mullan[6], Ugo Lucca[7], Florence Pasquier[8], Laetitia Breuilh[8], Matthias Riepe[9], Janos Kalman[10], Anders Wallin[11], Anne Borjesson[11], William Molloy[12], Magda Tsolaki[13], Marcel Olde Rikkert[14] *((1) Mercer's Institute for Research on Ageing, St. James's Hospital, Dublin, Ireland; (2) Trinity College Dublin (TCD), Dublin, Ireland; (3) King's College London (KCL), London, UK; (4) University College Dublin (UCD), Dublin, Ireland; (5) Molecular Medicine Ireland (MMI), Dublin, Ireland; (6) Archer Pharmaceuticals Inc, 2040 Whitefield Avenue, Sarasota, Florida, USA; (7) IRCCS—Istituto di Ricerche Farmacologiche "Mario Negri" (IRFMN), Milan, Italy; (8) Centre Hospitalier Regional et Universitaire de Lille (CHRU- LILLE), Lille, France; (9) Universitaet Ulm, (UULM), Ulm, Germany; (10) Szegedi Tudomanyegyetem (SZEGED), Szeged, Hungary; (11) Göteborgs Universitet (UGOT), Gothenburg, Sweden; (12) University College Cork (UCC), Cork, Ireland; (13) Aristotle University of Thessaloniki (AUTH), Greece; (14) Radboud Alzheimer Centre; Radboud University Medical Centre, Nijmegen, The Netherlands)*

Background: NILVAD is an investigator led phase III study evaluating the safety and efficacy of Nilvadipine and is funded by the European Commission's Framework 7 programme. Nilvadipine is a dihydropyridine calcium channel blocker which is licensed for the treatment of hypertension. Nilvadipine enhances the clearance of amyloid in transgenic mouse models, increases cerebral blood flow and has anti-inflammatory effects. *Methods:* NILVAD is a randomised, double blind, placebo controlled trial. The study duration is 18 months and Investigative medicinal product is 8mg of Nilvadipine or placebo. A number of substudies have been included to determine whether blood and cerebrospinal fluid biomarkers, APOE genotype, and frailty markers predict the response to Nilvadipine and also to investigate the effects of Nilvadipine on Cerebral Blood Flow. The primary outcome measure is the Alzheimer's Disease Assessment Scale-Cognition (ADAS-12), the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) is co-primary and the secondary outcome measure is the Disability Assessment for Dementia (DAD). A gatekeeper approach will be used to promote CDR-sb from a key secondary outcome to a co-primary outcome, if statistical significance is achieved for ADAS Cog. These tests will compare group differences in the change in the outcome from baseline, at trial end – 78 weeks. A further gated step will contrast the groups' change over time. Secondary analyses will include examination of all other outcomes. For all analyses significance is based on a two-sided p-value of less than 0.05. *Results:* Recruitment finished in April 2015 and 511 patients were recruited across the 23 study sites in 9 EU countries. The mean age of the patients is 70.5(SD+/- 7.5), 38% are male, 62% female and the mean MMSE (Mini Mental State Examination) score is 20.53(SD+/- 5.3). The trial is currently in the follow up phase and follow up will finish in November 2016. Overall, the study medication has been well tolerated with 22% of the patients off study medication. This is comprised of 12% who are lost to follow up and 10% who are off IMP but ongoing with assessments. To date there have been 111 Serious Adverse Events (SAEs), 5 SUSARs and 7 deaths (none of which were related to the IMP). One SUSAR was due to cognitive deterioration and agitation, a second was due to an overdose of Nilvadipine and an associated circulatory collapse and three SUSARs were associated with syncope. Syncope has now been added to the Investigators Brochure as an expected side effect of Nilvadipine. The data will be analysed from December 2016 to February 2017 and the results of the study should be published in early 2017. *Conclusion:* NILVAD has been a successful investigator led clinical trial, recruitment targets have been met, the medication has been well tolerated and the attrition rate is expected to be in the region of 15% by the end of the study. We expect that the analysis will provide us with a definitive answer as to whether Nilvadipine is an effective disease modifying treatment for mild to moderate Alzheimer's Disease. This project has received funding from the European Union's Seventh Framework Programme for research; technological development and demonstration under grant agreement no 279093.

OC39: COGNITIVE IMPROVEMENT IN MILD TO MODERATE ALZHEIMER'S PATIENTS: PRELIMINARY RESULTS OF AN OPEN LABEL, PHASE 2A STUDY OF T3D-959. John Didsbury[1], Suzanne de la Monte[2] *((1) T3D Therapeutics, Inc., Research Triangle Park, NC, USA; (2) Neurology Department, Rhode Island Hospital and the Warren Alpert Medical School of Brown University, Providence, RI, USA)*

Background: T3D-959 is a small molecule, orally-delivered, brain-penetrating PPAR delta/gamma dual nuclear receptor agonist designed to improve neuro-metabolic dysfunction in Alzheimer's disease (AD), an aspect of AD that is now recognized as a potential upstream driver of AD pathologies. *Methods:* Thirty six subjects with mild-to-moderate AD (MMSE= 14-26, average age = 73.6y, MMSE average = 19.9), were randomized to receive 1 of 4 doses of T3D-959 q.d. for 14-days (3mg, 10mg, 30mg, 90mg, N=9 per dosing cohort). Primary objectives were to evaluate; (1) changes in cerebral metabolic rate of glucose (CMRgl) measured by FDG-PET imaging; (2) changes in hippocampal functional connectivity (resting state default mode network activity) measured by BOLD fMRI; (3) changes in cognitive function measured by the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog11) and the Digit Symbol Substitution Test (DSST) and (4) safety and tolerability. Cognitive testing was administered at baseline, pre-dosing day 1 of treatment, day-14 end of treatment, and at 7-days post-dosing followup. FDG-PET and BOLD fMRI scans were administered at baseline and end of treatment (day-14). This trial is registered at ClinicalTrials.gov (NCT02560753). *Results:* Thirty four subjects completed the study. Results demonstrated that T3D-959 was well tolerated with no significant safety findings and lack of negative effects on cognition. All thirty four subjects were evaluable for cognitive testing at followup, thirty two subjects were evaluable at end of treatment. The cognitive effects of T3D-959, as measured by change in ADAS-cog11 score from baseline, demonstrated an average improvement across all dose groups at end of treatment (day-14) of -1.11 points and -1.26 points at followup (day-21). The cognitive

effects of T3D-959, as measured by change in DSST score from baseline, demonstrated an average improvement across all dose groups at end of treatment 1.72 points and 4.71 points at followup. Applying a definition of 'responder' as a 3-point or greater improvement in ADAS-cog11 score at end of treatment (day-14), 10 of 32 subjects were responders with an average -5.74 point improvement in ADAS-cog11 score from baseline at end of treatment [change in ADAS-cog11 score range = -3.34 to -10.0] DSST scores of these 10 responders improved by an average of 3.00 points at end of treatment. Five responders were moderate AD patients (MMSE = 14-19) [change in ADAS-cog11 score range = -3.34 to -10.0] and five responders were mild AD patients (MMSE = 20-25) [change in ADAS-cog11 score range = -4.00 to -6.68]. Improvement was sustained at followup in 9 of these 10 responders with an average -6.74 point improvement [range = -3.34 to -10.67]. DSST scores of the 10 responders improved by an average of 9.27 points at followup. Applying a definition of 'responder' as a 4-point or greater improvement in DSST score at end of treatment (day-14), 9 of 32 subjects were responders with an average 6.33 point improvement from baseline at end of treatment [range = 4 to 23]. Three responders were moderate AD patients and six responders were mild AD patients. Improvement was sustained at followup in 8 of these 9 responders with an average 14.0 point improvement from baseline [range = 6 to 29]. Neuroimaging analyses are in progress and results will be presented. Preliminary results of cognitive tests (ADAS-cog11, DSST and CIBIC+) from a six-month open label extension study in 5 subjects who completed the main study will also be presented. *Conclusion:* Together with pre-clinical evidence of disease reversal, these results provide evidence for targeting neuro-metabolic dysfunction in AD, and the further clinical development of T3D-959 to evaluate its efficacy, safety and support potential for disease modification. Sustained improvement in cognitive tests in responders, 7-days after dosing cessation, indicate potential long-acting pharmacodynamics. An FDA-approved 6-month extension study in a subset of study subject completers has been initiated. The results herein support the clinical testing of T3D-959 in a larger randomized controlled trial and guide dose selection. This study was supported in part by grant AG-049510 from the National Institutes of Health and the North Carolina Biotechnology Center.

OC40: TAU PET IMAGING IN ALZHEIMER'S DISEASE AND OTHER TAUOPATHIES. Ruben Smith[1], Tomas Ohlsson[2], Michael Schöll[3], Martin Schain[3], Andreas Hahn[4], Olof Strandberg[3], Jonas Jögi[5], Oskar Hansson[1,6] *((1) Department of Neurology, Skåne University Hospital, Lund, Sweden; (2) Department of Radiation Physics, Skåne University Hospital, Lund, Sweden; (3) Clinical Memory Research Unit, Department of Clinical Sciences, Malmö, Lund University, Sweden; (4) Department of Psychiatry and Psychotherapy, Medical University of Vienna, Austria; (5) Department of Clinical Physiology and Nuclear Medicine, Skåne University Hospital, Lund, Sweden; (6) Memory Clinic, Skåne University Hospital, Malmö, Sweden)*

Background: Several Tau PET ligands, including 18F-AV1451, are available that can detect tau aggregates in vivo. Visualization of regional deposition of tau aggregates might improve the diagnostic work-up of Alzheimer's disease (AD) and other tauopathies, including progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and patients with MAPT mutations. Tau PET imaging might also be used to study the regional spread of tau pathology in both observational cohort studies as well as when evaluating the effects of disease-modifying therapies. *Methods:* In the Swedish BioFINDER study we have used 18F-AV1451 PET to examine ca 110 cases, including heathy controls, patients with AD, PSP, CBD and MAPT R406W mutation carriers. Scans have been performed 80-120 min post injection of 18F-AV1451, except in a subcohort of cases (n=15) where we have performed dynamic scans 0-180 min together with arterial blood sampling. *Results:* Using arterial input functions, the Logan plot provide the best estimate of tau binding. Assuming that cerebellum is a valid reference region, simplified methods seem to provide robust alternatives for quantification, such as the Logan reference plot with 100 min scan time. Furthermore, SUVR ratios between target and cerebellar activities obtained from a 80-100 min static scan offer promising potential for clinical routine application. In patients with AD we observed a robust retention of 18F-AV1451 in the temporoparietal cortex, with a relatively higher uptake in posterior cingulate, precuneus, parietal and occipital cortices in early-onset AD cases with PSEN1 mutations compared to late-onset sporadic AD. Further, the tau pathology, but not amyloid pathology, exhibited a very clear inverse relationship with 18F-fluorodeoxyglucose-metabolism, indicating neuronal hypometabolism in regions affected by tau aggregates. In patients with MAPT R406W mutations we found that the tau pathology starts in the hippocampus and adjacent temporal lobe regions, correlating with glucose hypometabolism in corresponding regions. Later in the disease the basal ganglia and frontal lobe are affected. Post mortem examination of one case that 2 weeks before death had been examined with PET provided strong evidence that 18F-AV-1451 PET can be used to accurately quantify in vivo the regional distribution of hyperphosphorylated tau protein. In patients with PSP we did not find any significant uptake in cortical regions, but increased uptake in the basal ganglia, which correlated with disease severity. However, age-dependent off-target binding of 18F-AV-1451 in the basal ganglia of many cases, including healthy controls, makes the clinical relevance of this finding less obvious. In cases with CBD we observed an asymmetry in the uptake of 18F-AV-1451 in the basal ganglia and the cortex on the affected side, which is clearly different from the patterns observed in AD or other tauopathies. *Conclusions:* 18F-AV1451 PET can accurately determine the amount of tau aggregates found in AD as well as in MAPT R406W mutations carriers, which was confirmed using neuropathology. The pattern of tau pathology differs between early-onset AD with PSEN1 mutations compared to late-onset AD. Patients with CBD exhibit a specific pattern of 18F-AV1451 uptake. The regional uptake of 18F-AV1451 correlated well with hypometabolism in patients with AD, MAPT R406W mutation and CBD.

OC41: REGIONS OF INITIAL AMYLOID-B ACCUMULATION IN ALZHEIMER'S DISEASE. Sebastian Palmqvist[1], Michael Schöll[1,2,3], Olof Strandberg[1], Niklas Mattsson[1], Erik Stomrud[1], the Alzheimer's Disease Neuroimaging Initiative, the Swedish BioFINDER study, William Jagust[3], Susan Landau[3], Oskar Hansson[1] *((1) Lund University, Faculty of Medicine, Department of Clinical Sciences in Malmö, Clinical Memory Research Unit, Lund, Sweden; (2) Gothenburg University, MedTech West and the Department of Clinical Neuroscience, Gothenburg, Sweden; (3) University of California, Berkeley, Helen Wills Neuroscience Institute, Berkeley, California, USA)*

Background: Accumulation of beta-amyloid (Aβ) aggregates in the brain is believed to be the initial mechanism of Alzheimer's disease (AD). Using longitudinal data combining cerebrospinal fluid (CSF) and positron emission tomography (PET) measures of Aβ pathology, we examined where in the brain the accumulation of Aβ fibrils starts, and if brain atrophy and decreased regional glucose metabolism were evident already at this stage. *Methods:* Baseline and two-year follow-up data from 473 non-demented individuals from the

ADNI study were examined. Initial alteration of Aβ was estimated using levels of CSF Aβ42, and accumulation of brain Aβ fibrils was measured with 18F-florbetapir PET. Based on previous findings, we defined early Aβ accumulator as those with abnormal CSF Aβ42 and normal Aβ PET (CSF+/PET-) and compared change over two years in florbetapir uptake in these subjects to non-accumulators (CSF-/PET-) and late accumulators (CSF+/PET+) to identify regions where Aβ fibrils start to accumulate. Yearly Aβ accumulation was measured in anatomical and functional network ROIs as well as with voxel-wise analyses. Longitudinal changes in metabolism and neurodegeneration were examined with FDG PET and volumetric MRI measures. The main results were replicated in an independent cohort of 406 non-demented subjects (the Swedish BioFINDER study). *Results:* Early accumulators (CSF+/PET-) had 4-6 times higher mean Aβ accumulation rates compared to non-accumulators in mainly in the posterior cingulate, precuneus and orbitofrontal cortex ($p<0.001$). Similar results were seen in BioFINDER. Late accumulators (CSF+/PET+) had significantly higher rates compared to early accumulators mostly around the sensorimotor cortex and occipital lobe. Among the functional network ROIs, the greatest significant difference between early and non-accumulators were seen in the default mode network. Significant FDG-PET and volumetric MRI changes we only seen in late accumulators when compared to early accumulators. *Conclusion:* Across cohorts and statistical methods, we consistently found that Aβ accumulation mainly starts in the posterior cingulate, precuneus and orbitofrontal regions. We could also identify previously known regions in late Aβ accumulation stages such as the sensorimotor cortex. Changes in metabolism or atrophy were not observed in early accumulators, supporting the hypothesis that amyloid accumulation is an upstream mechanism and not triggered by overtly decreased energy metabolism or cell death. The early Aβ regions were mostly seen within regions involved in the default mode network, which could indicate that Aβ aggregation occurs primarily in this network during the earliest stages of the disease.

OC42: PET IMAGING OF TAU DEPOSITION IN DOWN SYNDROME: RESULTS FROM THE DOWN SYNDROME BIOMARKER INITIATIVE (DSBI). Michael S. Rafii[1,2], Ana S. Lukic[3], Randolph D. Andrews[3], Robert A. Rissman[2], James B. Brewer[2], William C. Mobley[2], Seth Ness[4], Dawn C. Matthews[3] *((1) Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego CA; (2) Department of Neurosciences, University of California, San Diego, La Jolla CA; (3) ADM Diagnostics, LLC, Chicago, IL; (4) Janssen Research and Development, LLC, Titusville, NJ)*

Background: Individuals with Down syndrome (DS) represent a population at high risk for Alzheimer's disease (AD). Tau pathology, in addition to amyloid plaque deposition is a hallmark of AD. Using the tau PET agent 18F-AV-1451, we examined retention patterns in adults with DS as part of the 3-year longitudinal Down Syndrome Biomarker Initiative (DSBI) in order to better understand the relationship between tau pathology and age, amyloid deposition, neurodegeneration (as assessed by structural MRI and FDG PET) and cognitive performance in adults with DS. We also sought to differentiate, using image analysis, AD-specific changes from DS-specific brain changes. *Methods:* Tau PET (AV1451) scans were acquired for 9 of the DSBI participants (ages 30-60) at year 2, and T1 MRI scans were acquired at year 1 and year 2 for 11 of the participants, adding to FDG PET, T1 MRI, and amyloid PET (AV45) scans previously acquired at baseline. All scans were spatially transformed to a common template, which also produced modulated gray MRI segments for analysis. Tau scans were intensity normalized to gray cerebellum, and regions of interest (ROIs) corresponding to Braak staging (Scholl et al, 2016) were measured. Tau scans were also evaluated using a multivariate tau classifier that determines a single numeric score corresponding to a subject's expression of an overall tau deposition pattern typical of AD. A 5-class multivariate voxel-based analysis of the MRI segments was performed using machine learning software, NPAIRS (Strother et al, 2010) to compare scans from Normal amyloid negative (NL Am-), AD Am+, and DS subjects at baseline, Y1 and Y2. A 3-class analysis (NL Am-, AD Am+, DS baseline) had previously been performed on the baseline DSBI FDG PET and MRI scans. ROI values and numeric scores corresponding to each subject's expression of patterns differentiating groups, were examined in relationship to one another and to age, amyloid status, and cognitive and functional scores. *Results:* Of three Am- or threshold subjects who had tau scans, all were negative for tau. Of the six Am+ subjects who had tau scans available, three had tau deposition in regions associated with Braak stages I-VI, two with stages I-V (one hippocampal sparing), and one with stages I-II. Amyloid and tau both correlated with age. The MRI analysis produced two distinct patterns. The first (NPAIRS CV1) pattern differentiated DS from both NL and AD, did not correlate with age or amyloid status, and was longitudinally stable, while the second (NPAIRS CV2) pattern differentiated NL- from AD+. The NPAIRS CV2 scores of Am- DS subjects and the Am+ tau stage I-II DS subject were aligned with NL- values and generally longitudinally stable, whereas the Am+ DS subjects showed varying degrees of longitudinal increase in NPAIRS CV2 expression. The baseline FDG NPAIRS scores similarly produced two such patterns. Tau PET scores correlated with the CV2 (AD-associated) pattern for both MRI ($R=0.89$) and FDG (trend), but not with the CV1 (DS-associated) patterns, and also correlated with several cognitive and functional measures including Observer Memory Questionnaire – Parent Form (OMQ-PF), Total Memory, and Daily Living ($R = -0.72, -0.64, -0.47$, respectively), as did the CV2 MRI and FDG scores. *Conclusions:* Despite a limited sample size, results suggest that in DS adults, tau accumulation is associated with amyloid positivity and age, and with progressive neurodegeneration as measured using FDG and MRI. Tau accumulation correlates with clinical decline in these subjects, as do AD-specific aspects of hypometabolism and atrophy that can be dissociated from DS effects using optimized multivariate image classifiers.

OC43: XANAMEMTM: AN 11B-HSD1 INHIBITOR IN CURRENT DEVELOPMENT FOR THE MANAGEMENT OF ALZHEIMER'S DISEASE (AD). Craig Ritchie *(Centre for Dementia Prevention, University of Edinburgh. UK)*

Introduction: The epidemiological association between conditions affecting the Hypothalamic Pituitary Adrenal (HPA) Axis and neurodegenerative disease has been recognised for many years. Flattening of the diurnal variation of cortisol levels has been observed in depression and may underpin the association between mood disorders over the life course and dementia in later life. The hippocampus is exquisitely sensitive to the deleterious effects of chronic exposure to abnormally elevated levels cortisol as seen in mood disorders and chronic stress. In addition to cortisol derived directly from the circulation, a proportion of intracellular cortisol is generated locally from (inactive) cortisone metabolism by the enzyme 11β-HSD1. Inhibition of this enzyme has been achieved pharmacologically with benefits shown in cognition with carbenoxolone in human studies as well as in numerous animal models. Xanamem™, a potent 11β-HSD1 inhibitor is now in Phase 2 testing as part of a development pathway for both symptomatic and disease modifying treatment of Alzheimer's disease. The underpinning

science, epidemiological evidence from observational studies and key design considerations and progress to date in the Phase 2 trial will be discussed. *Objectives:* The objectives are to [1] describe the basic science from both laboratory and animal models which underpins the development of Xanamem™ for the management of AD. This The symposium will include results of the Phase 1 studies and conclusions regarding the distinctive profile of Xanamem compared to previously studied 11β-HSD1 inhibitors, [2] outline the evidence from the Australian Imaging, Biomarker and Lifestyle (AIBL) study that have supported a critical role for HPA function in the genesis of AD pathology and clinical symptoms and [3] present the Phase 2 trial program to date for Xanamem™ including focussing on key design issues in the on-going XanADu trial and progress therein. *Discussion:* Xanamem™ (UE2343) is a potent and selective 11β-HSD1 inhibitor. 11β-HSD1 amplifies the active glucocorticoid hormone cortisol in brain regions, including hippocampus, and in peripheral tissues, such as liver and adipose tissue. There is abundant evidence from animal and clinical studies linking chronic cortisol excess with hippocampal dysfunction, leading to poor learning, recall and objective memory impairment. Abnormalities in the hypothalamic-pituitary-adrenal (HPA) 'stress' Axis throughout life relate to depression and stress and its cortisol effector hormone may explain the link between these psychiatric conditions and an increased risk of dementia. Thus, interventions that reduce intracellular cortisol levels may induce short-term improvements in cognition and have long-term benefits in reducing the risk of glucocorticoid toxicity to the hippocampus and in reducing the risk of dementia. 11β-HSD1 catalyses the intracellular regeneration of active cortisol from its inert metabolite cortisone. Inhibitors of 11β-HSD1 lower cortisol selectively within the tissues without preventing the normal elevation of plasma cortisol during stress. These agents have been shown repeatedly to have beneficial effects on metabolic control in patients with Type 2 diabetes. In addition, beneficial effects of 11β-HSD1 inhibitors on cognition and amyloid deposition have been described in preclinical animal models of ageing and dementia. Xanamem™ has been extensively profiled in preclinical and clinical studies. The drug has successfully completed Phase 1 clinical trials in the UK and Australia with twice daily doses of 10-35mg achieving adequate plasma levels to achieve full pharmacodynamic inhibition of 11β-HSD1 in peripheral tissues as evidenced by urinary steroid measurements. Xanamem™ was also present in the CSF of individuals given 35mg bd for 4 days at levels expected to deliver relevant inhibition of 11β-HSD1 enzyme in brain. As epidemiological evidence is also supportive of the link between cortisol and neurodegenerative disease, the mechanistic basis of this is being defined from large-scale cohort studies. In the Australian Imaging, Biomarker and Lifestyle (AIBL) Study we sought to evaluate the independent and interactive effect of plasma cortisol levels and Aβ status in predicting changes in cognition through the preclinical phase of Alzheimer's Dementia. Four hundred one cognitively normal older adults from the AIBL study had plasma cortisol levels, 11C-Pittsburgh Compound B (PiB), 18F-florbetapir or 18F-flutemetamol-derived measures of Aβ and a comprehensive neuropsychological evaluation undertaken. It was demonstrated that high plasma cortisol levels at baseline were associated with 2.2 times the risk of Aβ+. High levels of cortisol were also associated with greater global cognitive decline generally with a modifying effect of Aβ+ on decline in global cognition, episodic memory, and attention after adjusting for genetic and other confounders. This work demonstrates that in cognitively healthy older adults, higher plasma cortisol levels are associated with greater decline in global cognition and accelerate the effect of Aβ+ on decline in global cognition, episodic memory and attention over a 54-month period. These results suggest that therapies targeted toward lowering peripheral and central cortisol and Aβ levels may help mitigate cognitive decline in the preclinical phase of AD. Since cortisol excess is implicated both in the early development and on-going progression of dementia, it is unclear at what stage in the progression of cognitive dysfunction 11β-HSD1 inhibitors will be most effective. Preclinical data show that 11β-HSD1 inhibition results in early improvement in cognition, within days or hours, as well as longer term protection from cognitive decline. In humans, early proof of concept was obtained with the non-specific prototype 11β-HSD inhibitor carbenoxolone, which showed cognitive improvement in otherwise healthy unimpaired elderly men and in patients with Type 2 diabetes without symptomatic cognitive dysfunction. The XanADu study is targeting a sample size of 200 people diagnosed with Mild Alzheimer's Dementia. It is a Phase II, Double-Blind, 12-Week, Randomised, Placebo-Controlled Study to Assess the Safety, Tolerability and Efficacy of Twice Daily Xanamem™. The study is being conducted in the USA, UK and Australia. The co-primary outcomes will be ADASCog14 and ADCOMs chosen for its documented psychometric utility in this population. Secondary cognitive measures include the RAVLT to benchmark results from this trial with the previous carbenoxolone study. *Conclusion:* The inhibition of central cortisone production remains an elegant and scientifically robust target for both symptomatic treatment and disease course modification in Alzheimer's disease. Xanamem is a potent, bioavailable, and centrally penetrant 11β-HSD1 inhibitor in Phase 2 testing in a global, multicentre, double-blind Randomised Controlled Trial. This trial is the first clinical trial with this intervention and will act as a catalyst for further development for the symptomatic treatment of Alzheimer's disease. Additionally this will generate potential development in pre-clinical and prodromal neurodegenerative and other mental health conditions where central cortisol levels impact deleteriously on neuronal and synaptic function.

OC44: THE NEUROBIOLOGICAL SUBSTRATES OF DYNAMIC COGNITIVE RESERVE. Laura Serra[1], Michela Bruschini[1], Camillo Marra[2], Carlo Caltagirone[3,4], Mara Cercignani[5], Marco Bozzali[1] *((1) Neuroimaging Laboratory, Santa Lucia Foundation, IRCCS, Rome, Italy; (2) Institute of Neurology, Catholic University, Rome, Italy; (3) Department of Clinical and Behavioural Neurology, Santa Lucia Foundation, IRCCS, Rome, Italy; (4) Department of Neuroscience, University of Rome 'Tor Vergata', Rome, Italy; (5) Brighton & Sussex Medical School, CISC, University of Sussex, Brighton, Falmer, UK)*

Background: Cognitive reserve (CR) explains the individual resilience to neurodegeneration (1). It is possible quantify CR as an effect of changes in memory. Indeed, modifications in the residual memory variance (accounted for demographical and brain damage variables) have been considered as a dynamic measure of CR (d-CR) (2,3). Aim of the present study was to investigate for the first time the neural substrate associated with the changes in the residual memory variance overtime in patients with a-MCI. Methods: 34 a-MCI patients followed-up for 36 months and 48 healthy elderly individuals (HE) were recruited. All participants underwent a 3T MRI acquisition protocol including T1-weighted images for voxel-based morphometry (VBM). They underwent an extensive neuropsychological battery (patients both at baseline and follow-up, HE at baseline only), including six episodic memory tests. In patients and controls separately, factor analyses were used on the episodic memory scores to obtain a composite memory score (C-MS); the Partial Least Square analyses were used to decompose the variance of C-MS in latent variables (LT scores), accounting for demographic variables and for the general cognitive efficiency level; linear regressions were

applied on LT scores to obtain the residual value of memory variance considered as an index of dynamic CR (d-CR). Finally, LT scores and d-CR were used as variable of interest in the VBM correlations' analyses. Results: we found significant direct correlations between LT and GM volumes both in a-MCI and HE groups. In particular association with parahippocampal cortices were found only in the a-MCI patients. Conversely, correlations with orbito-frontal cortex and thalami were found only in the HE group. When considering the d-CR index significant correlations with GM volumes in the middle part of the anterior cingulate cortex (ACC), in the superior frontal gyrus in the orbito-frontal and temporal gyrus were found in the a-MCI patients. On the contrary, in the HE group we found specific association in the left dorsolateral pre-frontal cortex and in the most medial part of the pre-motor cortex. In addition both patients and controls showed correlations between LT scores and gray matter volumes in the anterior part of ACC and the posterior cingulate. Finally, both groups showed correlations between d-CR and the anterior ACC bilaterally and left amygdala. Conclusions: CR measured as decomposition of memory variance associated differently with brain volumes in a-MCI patients and controls expressing differently the ability to withstand to neurodegeneration. References: 1) Barulli, D., Stern, Y. 2013. Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. Trends Cogn Sci 17, 502-509. 2) Reed BR, Mungas D, Farias ST, Harvey D, Beckett L, Widaman K, Hinton L, DeCarli C. Measuring cognitive reserve based on the decomposition of episodic memory variance. Brain. 2010 Aug;133(Pt 8):2196-209. 3) 3)Zahodne LB, Manly JJ, Brickman AM, Narkhede A, Griffith EY, Guzman VA, Schupf N, Stern Y. Is residual memory variance a valid method for quantifying cognitive reserve? A longitudinal application. Neuropsychologia. 2015 Oct;77:260-6.

OC45: EFFECTIVENESS OF ALZU.ORG ON ALZHEIMER'S DISEASE PREVENTION CLINICAL TRIAL RECRUITMENT, REGISTRY ENROLLMENT AND ADVOCACY.

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Background: There is a critical need for rapid and cost-effective recruitment for clinical trials in Alzheimer's disease (AD) prevention. Strategies that reduce enrollment barriers and increase participation would help to accelerate research advances and allow for more rapid regulatory approval of therapeutics. Alzheimer's Universe (www.AlzU.org) is an online tool created to raise awareness about AD among patients, family members at risk, caregivers, and healthcare providers. AlzU.org provides an evidence-based course, including interactive lessons and activities, that has previously been shown to improve AD learning and subjective willingness to participate in AD clinical trials. Our conceptual framework aims to impart knowledge in order to influence beliefs, willingness and intentions, with the ultimate goal of driving behavioral change. *Methods:* Men and women age 25 and over were recruited via Facebook (www.facebook.com), and referred from a variety of internet sites. After informed consent was obtained, the AlzU.org course was provided free of charge and consisted of 5 interactive lessons available via web or mobile device. Each lesson was evidence-based, ranged from 6-16 minutes (64 minutes, total), was created by a multi-disciplinary team of AD healthcare providers, and was independently peer-reviewed. Topics included: AD Statistics & Public Policy, Stages of AD, AD Risk Factors, AD Diagnosis, and AD Management. A 3-question multiple choice quiz was administered before and after each lesson. Optional activities included links to clinical trial screeners, patient registries, advocacy initiatives, validated cognitive assessments, a diet and lifestyle tracker, and other resources. Google Analytics was used to corroborate referral link tracking between AlzU.org and external sites. Questionnaires were collected at baseline, within 14 days post-course completion, and again between 90-105 days post-course completion. Our primary outcome measures included the rate, number and characteristics of AlzU.org course completers who later screened for, and/or enrolled in, the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study. Secondary outcomes: Rate of joining Alzheimer's clinical trial registries (endalznow.org, brainhealthregistry.org) and/or an Alzheimer's advocacy initiative (Us Against Alzheimer's). *Results:* From June-December 2015, 3810 participants were recruited. Users were primarily women (85.7%) who most commonly self-identified as a child of a person with AD. 729 met entrance criteria for the A4 study. Of these, 191 (26.2%) visited the online A4 screener (www.a4study.org/screener/) directly from AlzU.org, and 149 (20.4%) completed the three-month post-course follow-up survey. Among this group, 31 self-reported screening for the A4 study, and 10 who qualified reported that they were later enrolled. Of A4-eligible participants, 4.3% were screened, and 1.4% were enrolled. Evaluating the characteristics of the 31 users who screened for A4, 31% self-declared as a person with memory loss, but not AD; 12.5% self-declared as having a spouse or partner with AD; 31% self-declared as the child of a person with AD; 6.3% reported their relative has memory loss or dementia, but not AD; and 6.3% have no personal connection to AD, but want to learn more. Comparing the results of the 3-month post-course survey from members who were screened for A4 (N=31) to those we were not (N=118), an independent samples t-test showed differences on willingness to participate in: cognitive testing $t(238)=4.320$, $p<.001$, two-tailed; blood testing $t(239)=5.604$, $p<.001$, two-tailed; brain scan $t(238)=4.968$, $p<.001$, two-tailed; genetic testing $t(239)=3.946$, $p<.001$, two-tailed; AD prevention research $t(237)=5.601$, $p<.001$, two-tailed; seeing a doctor to be evaluated for memory loss $t(235)=2.850$, $p=.005$, two-tailed; and seeing a doctor to discuss ways to lower AD risk $t(238)=2.906$, $p=.004$, two-tailed. Secondary outcomes: Of the 729 A4-eligible participants, 50.0% joined endalznow.org; 36.6% joined brainhealthregistry.org; 47.2% joined Us Against Alzheimer's email list. *Conclusion:* AlzU.org introductory course completion resulted in screening and enrollment rates from pre- to post-course of 4.3% and 1.4%, respectively. With the goal of the A4 study to enroll 1000 subjects, AlzU.org has helped to contribute a small yet impactful number of subjects through its ability to effectively educate, and encourage users at risk for AD to take further action, including joining clinical trials. The use of social media, collaborative internet marketing with peer sites, and online news media outreach led to rapid and cost-effective recruitment. While our prior randomized study demonstrated the effectiveness of the AlzU.org course on knowledge changes and subjective willingness to participate in a clinical trial, our new data suggests behavioral changes are also possible via online education. Limitations of our current study include the observational nature and lack of a control group, as well as the use of self-reported questionnaires. To address this, we used Google Analytics tracking for our primary and two of the three secondary outcomes, and found high correlation with reciprocal data. Further enhancements are ongoing of the AlzU.org tool (in both English and Spanish via web and mobile-app), with launch in mid-2016. Key words: Alzheimer's prevention

education, Alzheimer's education, neurology education research, Alzheimer's patient education

OC46: AN ASSESSMENT OF DEPENDENCE LEVEL PROGRESSION USING A CONVERSION ALGORITHM OF ACDS-ADL TO DEPENDENCE SCALE AND DATA FROM A DOUBLE BLIND PLACEBO CONTROLLED TRIAL OF INTEPIRDINE (RVT-101). Ebenezer Asare[1], Carolyn Zhu[2], Yaakov Stern[3], Lawrence Friedhoff[1] *((1) Axovant Sciences NY, NY; (2) Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai, NY, NY; (3) Cognitive Neuroscience Division, Department of Neurology and Taub Institute, Columbia University College of physicians and Surgeons NY, NY)*

Backgrounds: Although Alzheimer's disease (AD) clinical trials typically focus on cognitive and functional outcomes, there has recently been increased interest in using the Dependence Scale to capture and better characterize drug effects. As compared to the typical functional scale, the Dependence Scale assesses the degree to which things must be done for the patient. Several studies have suggested that this dependence captures or is influenced by a combination of the cognitive, functional, and psychiatric changes that occur in AD. Rated dependence as measured by the Dependence Scale closely correlates with cost of care, and is predictive of subsequent rate of decline. In addition, dependence is a concept readily understood by clinicians and caregivers. We therefore examined dependence as a potential outcome in a study of intepirdine (RVT-101) an orally administered, 5-hydroxytryptamine 6 (5-HT6) receptor antagonist being investigated for the treatment of mild-to-moderate Alzheimer's disease (AD). *Methods:* Data are from a randomized double blind placebo controlled trial. In this study, 684 subjects with mild to moderate AD (MMSE score 10-26 points), and receiving stable donepezil treatment, were randomized to receive 35 mg intepirdine, 15 mg intepirdine, or placebo. Only the placebo and 35mg data are included in this report. Data from baseline, and weeks 12, 24, 36 and 48 were examined. ADCS-ADL was converted to Dependence level (DL) using a published algorithm which assigns DL based on patterns of IADL/BADL impairment. Estimated DL ranges from level 0, equivalent to no IADL/BADL impairment and no care needs, to level 5: impaired transfer/complete incontinence in ADCL-ADL, representing needing nursing home care. Estimated DL at baseline were first compared between treatment (n=230) and placebo groups (n=218). To assess relationship between treatment and DL, we then compared proportion of subjects whose DL changed from baseline at each follow up period. We further defined progression in DL from baseline as one or more level increase in DL, and compared rate of DL progression between treatment and placebo groups. Parallel analyses were performed by dementia severity, defined by baseline MMSE. *Results:* At baseline, 0.7%, 0.9%, 31.5%, 31.0%, 33.0%, and 2.9% were DL groups 0 to 5 respectively. Distribution of DL was similar between treatment and placebo groups (p=0.354). It was also comparable to the distribution seen in the published conversion algorithm. Correlation between DL and ADCS-ADL was 0.448 at baseline (0.360 for all visits, both p<.0001). At each assessment period, the percentage of subjects whose DL was either unchanged or improved was higher in the treatment group than in the placebo group, although differences were statistically insignificant at 24 weeks (p=.229) and marginally significant at 36 and 48 weeks (p=.093 and .108). We then examined the percentage of subjects defined as progressors, based as an increase in one or more levels of DL from baseline. At 24 weeks, 23.8% of subjects in the placebo group progressed 1 or more levels in DL, compared to 16.8% in the treatment group (p=.08). At 36 weeks, 28.2% of subjects in the placebo group progressed 1 or more DL, compared to 17.7% in treatment group (p=.02). At 48 weeks, 30.5% of subjects in the placebo group progressed 1 or more DL, compared to 19.4% in treatment group (p=.02). Similar results were found by baseline MMSE groups. Within each MMSE group, proportion of subjects who progressed 1 or more levels in DL was higher in the placebo group than in the treatment group;the rate of progression was highest in the most severe group. *Conclusion:* Here we demonstrate that an add-on therapy of intepirdine was associated with reduced progression in DL over 48 weeks, thus indicating that patients are spending more time in the earlier stages of the disease. It must be recognized that DL was not measured directly here, but estimated from ADCS ADL using a published paradigm. Still, this study helps establish the Dependence Scale as a meaningful and potentially sensitive outcome measure for describing the real-world impact of a therapeutic agent. An ongoing study of intepirdine in a similar population utilizes the Dependence Scale. Because the scale is readily translated into cost, as well as into meaningful outcomes such as need for full-time care, it is a potentially powerful approach for quantifying the value of a therapeutic effect.

OC47: VALIDATION OF ADFLAG®, A DIAGNOSTIC BLOOD-TEST FOR PRE-DEMENTIA STAGES OF ALZHEIMER'S DISEASE. Beatrice Blanc[2,3], Nicolas Pelletier[1,2], Clotilde Biscarrat[1], Pauline Martinasso[1], Samantha Galluzzi[4], Moira Marizzoni[4], Jorge Jovicich[4,6], Giovanni B. Frisoni[4,5], Gianluidgi Forloni[7], Diego Albani[7], Jill Richardson[8], Lucilla Parnetti[9], Magda Tsolaki[10], Flavio Nobili[11], David Bartrez-Faz[12], Mira Didic[13], Peter Schoenknecht[14], Pierre Payoux[14], Andrea Soricelli[16], Paolo M Rossini[17], Pieter Jelle Visser[18], Regis Bordet[19], Ute Fiedler[20], Olivier Blin[21], Julien Dupouey[2,21], Joëlle Micallef[22], Laura Lanteaume[22], Nathalie Sambuchi[23], Isabelle Muraccioli[23], Bernard Michel[23], Nathalie Compagnone[1,2,3] *((1) ICDD, Translational Med. Dept; (2) ICDD, Pharmacog Project Mgmt.; (3) ICDD, Diagnostic Dept Gemenos, France; (4) Lab Alzheimer's Neuroimaging & Epidemiology, IRCCS Fatebenefratelli, Brescia, Italy; (5) University Hospitals and University of Geneva, Geneva, Switzerland; (6) Center for Mind/Brain Sciences, University of Trento, Trento, Italy; (7) Department of Neuroscience, Mario Negri Institute for Pharmacological Research, Milan, Italy; (8) Neurosciences Therapeutic Area, GlaxoSmithKline R&D, Stevenage, UK; (9) Clinica Neurologica, Università di Perugia, Ospedale Santa Maria della Misericordia, Perugia, Italy; (10) Third Neurologic Clinic, Medical School, G. Papanikolaou Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece; (11) Clinical Neurology, Department of Neurosciences, Rehabilitation, Ophthalmology and Maternal-Fetal Medicine, University of Genoa, Genoa, Italy; (12) Department of Psychiatry and Clinical Psychobiology, Faculty of Medicine, University of Barcelona and Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Catalunya, Spain; (13) Service de Neurologie et Neuropsychologie, APHM Hôpital Timone Adultes, Marseille, France; (14) Department of Psychiatry and Psychotherapy, University of Leipzig, Leipzig, Germany; (15) Dept. Medecine Nucléaire, CHU de Toulouse, Toulouse, France; (16) SDN Istituto di Ricerca Diagnostica e Nucleare, Naples, Italy; (17) Department of Gerontology, Neurosciences & Orthopedics, Catholic University, Rome, Italy; (18) Department of Neurology, Alzheimer Centre, VU Medical Centre, Amsterdam, the Netherlands; (19) University of Lille, Inserm, CHU Lille, U1171 - Degenerative and Vascular Cognitive Disorders, Lille, France; (20) Department of Psychiatry and Psychotherapy, Faculty of Medicine, LVR-Hospital Essen, University of Duisburg-Essen, Essen, Germany; (21) Pharmacol. and Pharmacovigilance, Aix-Marseille Univ., Marseille, France; (22) Service de neurologie et*

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Background: Alzheimer's disease (AD) affects 47 million people worldwide, however, there are currently no disease-modifying drug (DMD) approved to delay disease progression. Moreover, AD drug development is currently on hold due to decades of failure to demonstrate efficacy in clinical trials. One of the reasons for these failures lies in the lack of efficient patient stratification tools to support demonstration of DMD efficacy. Hence, AD progression represents a significant societal and healthcare burden. Despite significant progresses in medical imaging and availability of cerebrospinal fluid (CSF) markers AD diagnosis remains challenging. AD patients are currently diagnosed over the course of 2 years, during which disease progression impedes their chance for treatment. To address this medical need, we attempted to validate the ADFlag® blood panel of circulating markers previously identified to be associated with pre-dementia AD. ADFlag® markers are peripheral inflammatory signals relating to neuroinflammatory response to early amyloid fibrillation in AD brain. The role of chronic inflammation in AD is well established, but the factors responsible for amyloid deposition and persisting inflammation are only beginning to be understood. *Methods:* ADFlag® test was used as a stratification tool in the Pharmacog multicentric cohort. Along with the ADFlag® test, amyloid CSF markers (amyloid-beta 1-42, Tau, pTau) and clinical progression (cognitive decline) were investigated in 147 aMCI patients who underwent clinical, neuropsychological, and blood data collection over a 2 year period. Baseline results are presented. ADFlag® classification on a scale of 1 to 5 was analyzed within the different subpopulations based on amyloid beta stratification in aMCI patient and disease progression measured on memory, attention/executive function and language neuropsychological scales. *Results:* The results demonstrated that, compared with the negative aMCI groups, the positive aMCI groups were globally characterized by a higher ADFlag® score. ADFlag® subgroups represented distinct patient populations based on the evaluation of executive and language functions assessed by the MMSE, ADAS-Cog and BNT. A progression of the decline in executive, cognitive and language function decline was apparent with increase in the ADFlag® scale. Rey auditory verbal learning scales, Cantab paired associated learning and ADAS-Cog word recall subscore showed significant association with the ADFlag® scores. Contingency analysis demonstrated that good digit span forward scores were only seen in the patients who scored below or at 2 in the ADFlag® score (person p=0.0486). Orientation subscales in the ADAS-Cog score were also associated with the ADFlag scores. Low scores in the ADAS-Cog orientation subscales were associated with higher probability that patients be scored below or at 2 in the ADFlag® score (OR = 0.59, p=0.0112). The 5 ADFlag® subgroups also significantly differed when measuring either the letter or the category fluency scores. Testing the hypothesis that ADFlag® score above 2 was indicative of latent AD, we performed logistic regression analyses. They demonstrated that patients above 65 years old, being a female or expressing at least one ApoE4 allele had an increased likelyhood ratio to score above 2 in the ADFlag® scale (OR=1.44; OR=1.33; OR=1.54 respectively). However, having an ADFlag® score above 2 at baseline significantly increased the likelihood that conversion to dementia occurred within the 24 months of follow up in the Pharmacog study (OR=4.11, chi sq=0.0030).

OC48: TRAMIPROSATE EFFICACY IN APOE4 CARRIERS WITH MILD TO MODERATE AD: SENSITIVITY ANALYSES BY BASELINE SEVERITY SUGGEST LARGE EFFECTS IN HOMOZYGOUS SUBJECTS WITH MILD AD. S. Abushakra[1], J.A. Hey[1], A. Power[1], P. Wang[2], L. Shen[2], S. Hendrix[3], S. Gauthier[4], B. Vellas[5], A. Porsteinsson[6], M. Kivipelto[7], M. Tolar[1] *((1) Alzheon Inc., Boston, MA, USA; (2) Pharmapace Inc., San Diego, CA; (3) Pentara Corporation, Salt Lake City, Utah; (4) McGill University and Montreal Neurological Institute, Montreal, Canada; (5) University of Toulouse, Toulouse, France; (6) University of Rochester, Rochester, NY; (7) Karolinska University Hospital, Stockholm, Sweden)*

Background: ALZ-801 is a novel oral pro-drug of tramiprosate in development as a potential disease-modifying treatment for Alzheimer's Disease (AD). In Phase 1 studies, the pro-drug (tramiprosate conjugated to valine) has demonstrated improved gastrointestinal tolerability and sustained exposures to the active agent tramiprosate (J. Hey et al. CTAD 2016). Tramiprosate is an amyloid anti-aggregation agent that inhibits the formation of Aβ oligomers and neurotoxicity. In a Phase 3 study, tramiprosate did not demonstrate efficacy in overall population (Aisen et al. 2011) but showed a compelling efficacy signal in apolipoprotein E4 (APOE4) carrier subgroup. In a protocol-specified analysis based on APOE4 genotype, tramiprosate showed meaningful effects that were related to dose of APOE4 allele: highest in APOE4 homozygotes, intermediate in heterozygotes, and no benefit in non-carriers (Porsteinsson et al. CTAD 2015). This "APOE4 gene-dose" effect may be explained by high rates of amyloid positivity (Jansen et al. 2015) and enhanced diagnostic accuracy in homozygotes and heterozygotes (respectively 90% and 70-80%) versus non-carriers (~60%). Most amyloid-targeted agents have shown preferential efficacy in Mild AD, we therefore analyzed tramiprosate efficacy in carrier subgroups based on baseline MMSE. *Methods:* Tramiprosate was evaluated in two 78-week Phase 3 studies in North America (NA) and EU in approximately 2,000 Mild to Moderate AD patients. The NA study had 3 parallel arms (placebo, low dose 100mg BID, high dose 150mg BID) and enrolled patients with baseline MMSE 16-26 on stable symptomatic AD drugs. Efficacy and safety results were published (Aisen et al. 2011). The EU study was of similar design but was prematurely discontinued after the NA study topline results, when ~2/3 of the patients had completed week 52, and a small number had reached 65 and 78 weeks. Co-primary outcome measures in both studies were ADAS-cog and CDR-SB. Efficacy outcomes (LS means of drug-placebo difference in changes from baseline) were analyzed by MMRM. ITT analyses included subjects of all ages, and up to 85 years (upper limit in planned Phase 3 study). For each APOE4 subgroup, efficacy at the last 3 visits (weeks 52, 65 and 78) was determined by baseline MMSE category. LS means and corresponding nominal p-values were plotted for the following MMSE categories: 16-19; 16-21; 16-22; 16-23; and up to 16-26. *Results:* In both studies, baseline demographics of APOE4 subgroups were similar, except for lower median age in APOE4/4 subgroups.. The NA study included 141 APOE4/4 homozygous patients up to age 85 years (placebo 54, low dose 47, high dose 40); and 432 heterozygotes (placebo 143, low dose 141, high dose 148). Corresponding numbers in EU study were: a total of 108 APOE4/4 homozygotes (placebo 37, low dose 37, high dose 34); and 422 heterozygotes (placebo 150, low dose 136, high dose 136). Approximately 60-65 % had baseline MMSE ≥ 20. At 150 mg BID, heterozygous subgroup showed no ADAS-cog benefit at 78 weeks and positive trends at 52 weeks (delta 1.6, p< 0.05). On CDR-SB, same dose showed significant effect at all 3 visits (delta 0.6-0.7, p< 0.05). For both outcomes, drug effects were greater in lower MMSE

category (MMSE < 21-22). At same dose, APOE4/4 homozygous group showed significant cognitive benefit at last 3 visits (delta 3.0-3.9, p< 0.02); and CDR-SB showed positive trends at last visit (delta 0.9, p= 0.07; at 65 weeks delta 1.1, p= 0.01). For both outcomes, drug effects were greater in higher MMSE category that included subjects with MMSE > 22-23. *Conclusions:* APOE4/4 homozygous AD patients have the highest rates of amyloid positivity by imaging studies even at MCI stage, thus providing a naturally amyloid-enriched AD population (Jansen et al, 2015); while heterozygotes have lower rates of amyloid positivity, especially at Early/Mild stage. Consistent with this hypothesis, tramiprosate efficacy in heterozygotes appears highest in patients at Moderate AD stage who likely have higher prevalence of amyloid positivity and diagnostic accuracy. In homozygotes, efficacy is seen across the Mild-Moderate range but highest efficacy was observed in Mild AD patients, consistent with findings with other amyloid-targeting therapies. Inclusion of high proportion of Mild AD patients and stratification for stage of disease is therefore important in future trials in Mild to Moderate disease. These findings also suggest a potential application for ALZ-801 in treatment of earlier stages of AD.

OC49: THE EFFECT OF APOE GENOTYPE AND LOW CSF ABETA 42 ON DHA BRAIN BIOAVAILABILITY IN ALZHEIMER'S DISEASE. Hussein N. Yassine[1], Wendy J. Mack[2], Joseph F. Quinn[3], Karin Yurko-Mauro[4], Eileen Bailey-Hall[4], Paul S. Aisen[5], Helena C. Chui[6], Lon S. Schneider[6,7] *((1) Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, USA; (2) Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, USA; (3) Department of Neurology, Oregon Health and Science University; (4) Clinical Research Department, DSM Nutritional products, Columbia, MD, USA; (5) Alzheimer's Therapeutic Research Institute, University of Southern California, Los Angeles, USA; (6) Department of Neurology, Keck School of Medicine, University of Southern California, Los Angeles, USA; (7) Department of psychiatry and the behavioral sciences, Keck School of Medicine of the University of Southern California, Los Angeles, USA)*

Background: Apolipoprotein (APOE) e4 and low CSF Abeta 42 levels are predictors for developing Alzheimer's disease (AD). Several studies indicate an interaction between docosahexaenoic acid (DHA) consumption and cognitive outcomes by APOE genotype. The main finding of the Alzheimer's Disease Cooperative Study (ADCS)-sponsored DHA trial was that the allocation to DHA treatment did not influence the rate of cognitive decline in patients with dementia. A secondary analysis suggested benefit in ADAS cog scores in non-carriers of e4 genotype. We hypothesized that the DHA-associated cognitive improvement in non-e4 carriers could be related to greater CSF DHA delivery. Our objective was to examine whether APOE e4 genotype and low CSF Abeta 42 levels were associated with reduced delivery of DHA to cerebrospinal fluid (CSF) in the ADCS sponsored DHA clinical trial. *Methods:* Phospholipid DHA was assayed in the plasma of 384 participants and CSF of 70 participants at baseline. Forty four of the 70 participants completed the 18 month visit after allocation to placebo (n=15) or DHA (n=29). Plasma and CSF DHA levels, CSF Abeta 42, Tau and pTau were measured at baseline and after the 18 month intervention. Participants were divided into tertiles based on baseline Abeta 42 CSF levels. To assess DHA delivery across the blood-brain barrier, the ratio of CSF to plasma DHA levels was calculated. *Results:* At baseline, there were no significant differences between CSF or plasma phospholipid DHA level by CSF Abeta 42 tertiles or e4 status. After 18 months of DHA treatment, participants at the lowest baseline Abeta 42 tertile had significantly less CSF DHA levels (p=0.01) and lower CSF to plasma DHA ratio (p=0.05) compared to the other tertiles. Baseline CSF Abeta 42 levels were significantly lower in e4 carriers compared to non-e4 carriers (p=0.01). Participants carrying an e4 allele (n=25) demonstrated a less pronounced increase in the CSF DHA level compared to non-carriers (n=4), with a possible interaction effect between treatment and APOE genotype (p=0.07). *Conclusions:* APOE e4 allele and lower CSF Abeta 42 levels were associated with less transport of DHA to CSF. AD amyloid pathology may limit DHA bioavailability in the brain. These findings can help inform future DHA trials aimed at preventing cognitive decline in persons at risk of AD.

OC50: HIGHLY SPECIFIC MODIFICATION OF TAU PHOSPHORYLATION STOICHIOMETRY IN AD CSF IMPACTS T217, S199, S202 AND T205 SITES BUT NOT T181. Nicolas R. Barthélemy[1,2], Audrey Gabelle[2], Chihiro Sato[1], Randall J. Bateman[1], Sylvain Lehmann[2] *((1) Neurology Department, Washington University School of Medicine, St. Louis MO, USA; (2) CHU Montpellier, Montpellier, France)*

Backgrounds: Microtubule-associated protein tau and tau phosphorylation levels in cerebrospinal fluid (CSF) are currently used as biomarkers for the diagnostic of Alzheimer Disease (AD) by ELISA. The increasing of p-tau is interpreted as consequence of hyperphosphorylation due to tangles formation. This assumption is challenged, as no evidence demonstrated that the increasing of CSF p-tau results from a change in tau phosphorylation stoichiometry. Mass spectrometry (MS) appears as a promising technique to simultaneously monitor phosphorylated sites and corresponding unmodified sites to evidence change in tau phosphorylation state in CSF. Nevertheless, CSF tau concentrations are particularly low and to date, no detection of CSF tau phosphopeptides was reported in vivo by MS. *Methods:* We developed a MS-based strategy to monitor for the first time the extend of phosphorylation of 5 sites in CSF tau (T181, S199, S202, T205 and T217). Corresponding tau phosphopeptides and their unmodified counterparts were simultaneously quantified using labeled standards. To determine the diagnostic relevance of these new p-tau biomarkers, we analyzed of a cohort of CSF from 50 participants affected by various neurological disorders including AD, Lewy Body Dementia and Frontotemporal Dementia. In addition, we are analyzing a second cohort of CSF from 100 participants characterized according to amyloid status and CSF amyloid-beta kinetic. This second study will assess putative link between amyloidosis and changes in CSF tau phosphorylation. *Results:* We demonstrate that abnormal tau metabolism reported in AD brain leads to a specific phosphorylation status of AD CSF tau, distinct from concomitant tau level increasing. These phosphorylation changes were not observed in other tauopathies nor controls. We evidenced that pT217 hyperphosphorylation is highly specific to AD. Conversely no significant hyperphosphorylation was found on pT181, commonly used to monitor p-tau in practice. Interestingly, we found in AD group a significant impoverishment of the phosphorylation state on S199 and S202 comparing to non-AD. This relative hypophosphorylation was concomitant to the appearance and increasing of T205 phosphorylation in AD CSF tau. S202 and T205 are involved in brain in the formation of a phospho epitope found specifically in AD tau aggregates and recognized by the AT8 antibody. The decreasing of S199 and S202 phosphorylation in AD CSF could support a mechanism of tau aggregation consequently to the formation of AT8-immunoreactive tau isoforms in neurons. Furthermore, the detection of T205 hyperphosphorylation mainly in AD CSF argues in favor of an important role of this site in AD tauopathy mechanism. The second clinical cohort analyzed in this study will refine the diagnosis power of these new tau

biomarkers. *Conclusion:* In vivo monitoring of site-specific extent of phosphorylation on pT217, pS199, pS202 and pT205 in CSF tau may provide new clinical avenue in refining novel AD-specific phenotypes. These phenotypes are likely related to sequential events of tau hyperphosphorylation and aggregation currently observable only in AD brain autopsies. Importantly, caution needs to be paid when linking pT181 level to neurofibrillary tangles pathology based on the difficulty to discern a clear modification of the phosphorylation stoichiometry on this site. Our MS method opens a new field of investigation in studying in vivo this AD-tau specific process and underlying abnormal metabolism. The outperforming of pT217 in comparison to current tau and p-tau biomarkers already recognized as ones the most sensitive and selective molecular targets for AD diagnosis, raises henceforth question on its performance to identify prodromal and even pre-symptomatic AD.

OC51: INDIVIDUALIZED TRAJECTORIES IN PRE-SYMPTOMATIC AND PRODROMAL AD: SUBJECT-SPECIFIC JACK CURVES ESTIMATED USING STATISTICAL MODELS. Robin Wolz[1,2], Adam J. Schwarz[3], Ricardo Guerrero[1,2], Derek Hill[1] *((1) IXICO Plc, London, UK; (2) Imperial College London, London, UK; (3) Eli Lilly and Company, Indianapolis, USA)*

Background: Prodromal and pre-symptomatic populations within the AD spectrum are characterized by substantial inter-subject variability in their biomarker signatures and rates of progression. Stratification schemes play an increasingly important role in clinical trial design, and (when disease modifying treatments are available) an improved ability to project the likely disease course for individual patients will be a crucial enabler for personalized medicine. In clinical trials, patient demographics, clinical scores and different biomarkers have been used for defining trial inclusion criteria. A hypothetical model of biomarker development during the evolution of AD has been proposed [1] and the temporal ordering of biomarker changes confirmed experimentally at the population-average level by different statistical modeling approaches [2-4]. Model [2] has been successfully applied in a post-hoc analysis of the SCarlet RoAD study to identify a treatment effect in a sub-population [5]. Regulatory agencies are increasingly supportive of disease progression models for patient selection in trials. *Methods:* Disease progression models are typically estimated to describe population averages but heterogeneity between individuals remains a key challenge. We developed two approaches to individualize progression models: a) Using a multivariate baseline signature to identify where a subject lies on the modeled trajectory (as opposed to a naive single variable like age/time); b) Inferring model parameters only from training subjects that are similar to a given test subject based on the multivariate baseline signature. We compared models that apply concept (a) only («Global Models») to models that apply (a) and (b) («Subject-specific Models») [6, 7]. In summary, a Global Model uses multivariate longitudinal measurements of clinical scales and biomarkers from all training cases to define parametric progression models, while a Subject-specific Model only uses the most relevant training cases to build an individualized model. Either model can then be applied to predict change of all measurements for a test subject based on its respective baseline assessments. We previously presented the superiority of a Subject-specific Model for an application in trial enrichment in MCI subjects [7]. Here, the model was extended into the presymptomatic population and applied to predict an approximation of the ADCS Preclinical Alzheimer's Cognitive Composite (PACC) scale in healthy elderly control subjects from the ADNI I /II cohorts. Based on the availability of scores in ADNI, the PACC was approximated from total MMSE and the delayed recall measurements from the Wechsler Memory Scale and ADAS-Cog. Each sub-score was modeled independently using a training database of healthy, MCI and AD subjects. The «biomarker signature» was defined by the three clinical scores at baseline together with subject age, baseline FAQ and baseline hippocampal volume. Individualized models were then applied to predict 3-year progression on PACC in the 215 healthy subjects from both ADNI cohorts for which the three sub-scales were available at baseline and month 36. Subjects were then stratified based on the predicted rate of decline and a signal to noise ratio (SNR) was defined as the mean change in the simulated PACC score divided by the standard deviation in the included patient population. *Results:* Figure 1(a) illustrates the concept of an individualized progression model. For the approximated PACC and the Wechsler Memory Scale subscore, the Global Model (black curve, concept (a)) and the Subject-Specific Model (dotted magenta curve, concept (b)) are presented together with a model fitted to the real longitudinal data of the test subject (red curve). The green horizontal line shows the true measurement of the respective clinical scales at baseline. Both models provide an individualized fit of Jack's hypothetical model by providing an estimate on where the subject lies along the disease trajectory. Furthermore, the presented example illustrates how the Subject-Specific Model provides both an improved fit to the baseline measurement as well as a tightened confidence interval around the predicted disease course. Figure 1(b) illustrates individualized trajectories for two exemplar subjects. Figure 1(c) shows SNR values on 3-year PACC when screening out 25%, 50% or 75% of subjects based on the predicted rate of decline from the Subject-specific Model (green bars) compared with screening based on baseline PACC alone (red bars) or baseline hippocampal volume alone (HCV, blue bars). *Conclusions:* The presented results show that using a multivariate disease progression model that combines clinical and biomarker variables outperforms individual measures in predicting 3-year progression at the same screen failure rate. The model can also estimate trajectories for other outcome variables (e.g., biomarkers). This approach is also applicable to estimating individualized patient trajectories on a subject-wise basis, which could be useful for patient management in clinical practice. References: [1] Jack, Lancet Neurology, 27:685-691, 2010. [2] Delor, CPT: Pharmacometrics & Systems Pharmacology, 2:e78, 2013. [3] Ito. Alzheimers Dement. 7(2):151-60, 2011. [4] Donohue. Alzheimers Dement., 10(5):400-410, 2014. [5] Lasser. CTAD, Barcelona, 2015. [6] Guerrero. AAIC, Washington, 2015. [7] Wolz. ATT, Athens, 2016

OC52: CLINICAL TRIALS IN CTE – MOVING AHEAD. Charles Bernick *(Cleveland Clinic, USA)*

Introduction: It has long been recognized that repetitive head trauma can lead to permanent neurological injury, either static or progressive in nature. Though there is yet no consensus on terminology used to describe the neurological consequences of cumulative head trauma, the term Chronic Traumatic Encephalopathy (CTE) has been generally associated with a characteristic pathology featuring tau deposits favoring a perivascular and depth of sulci distribution. CTE has been primarily reported in individuals participating in contact sports and military veterans. There is no reason to suspect that these activities are going to cease in the near future. Yet, to our knowledge, there has not been any attempts to conduct organized clinical trials in this condition. There are certainly reasons why some may believe we are not ready for clinical trials in CTE. The incidence, prevalence, and natural history of CTE is not well known. We don't have consensus diagnostic criteria or established biomarkers. Yet, in truth, much information already exists: growing amounts of work have been published (and is ongoing) on

the pathophysiology of traumatic brain injury, including expanding knowledge of the effects of axonal injury, chronic inflammation, and biochemical changes that occur from injury. Clinicopathological work has provided information on clinical features of CTE and several clinical diagnostic criteria have been proposed. Experience with neuroimaging in cumulative head trauma continues to expand and PET tau imaging studies have started. Finally, there are agents available that target several of the proposed mechanisms of repetitive head injury. Because CTE is commonly thought to be a neurodegenerative disease, and many individuals in the Alzheimer's disease space have become interested in this condition, we believe CTAD is the best forum to initiate a discussion regarding designing clinical trials in CTE: what is possible now and what do we need to learn to optimize trials in the future. *Objectives:* 1. Review the major issues involved in clinical trial design in CTE; 2 Present current update on outcome measures related to CTE; 3 Discuss potential therapeutic strategies for CTE; 4 Bring together those interested in, and identify a roadmap for, conduct of clinical trials in CTE

OC53: COMPUTERIZED IPAD COGNITIVE TESTING USING NIH TOOLBOX AND COGSTATE C3 FOR USE IN CLINICAL TRIALS. Dorene M. Rentz[1,2,3], Rachel F. Buckley[1,2,4,5], Kathryn P. Sparks[1,2], Maria Dekhtyar[1,2], Courtney Martin[6], Julia Sherman[1], Sarah Aghjayan[1,2], Samantha Burnham[7], Reisa A. Sperling[1,2,3] *((1) Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts, USA; (2) Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts, USA; (3) Harvard Medical School, Boston, Massachusetts, USA; (4) Florey Institutes of Neuroscience and Mental Health, Melbourne, Australia; (5) Melbourne School of Psychological Sciences, University of Melbourne, Australia; (6) Northeastern University, Boston, Massachusetts, USA; (7) Commonwealth Scientific and Industrial Research Organization, Perth, Australia)*

Background: As prevention trials for Alzheimer's disease (AD) move into asymptomatic populations, identifying older individuals who manifest the earliest cognitive signs of AD is critical. This requires large-scale population screening to recruit for these trials, and computerized testing, if validated, provides a clear pathway for identifying those individuals with subtle cognitive impairment. However, it is unclear whether computerized tasks can completely substitute for the diagnostic sensitivity of conventional paper-and-pencil tests or whether computerized tests can provide complementary or unique information. Validating these measures against conventional tests is critical in order to determine whether they can be used effectively in a large-scale, population-based cognitive screening role. Our objective was to investigate the performance of Cogstate (C3) and NIH Toolbox Cognition Battery (NIHTB-CB) against conventional paper and pencil neuropsychological tests. *Methods:* Fifty clinically normal older subjects (CDR=0, age = 68.5±7.6, education = 15.6±3.1) were recruited from research centers at the Massachusetts General Hospital and Brigham and Women's Hospital. The sample was 54.7% White and 45.3% Black. Of these subjects, 2 were of Hispanic origin. Participants completed three in-clinic visits over the course of six weeks. At Visit 1 they took conventional paper-and-pencil tests of memory, executive function and processing speed. At Visit 2 they completed the iPad version of NIHTB-CB and at Visit 3, the iPad version of the Cogstate C3 battery. Convergent validity was assessed between the computerized tasks and conventional paper-and-pencil tests. Principal component analyses were used to create global composite measures for the NIHTB-CB, Cogstate C3 and paper-and-pencil batteries. Exploratory cluster analyses were conducted to determine the similarity of computerized and paper-and-pencil tests to each other. Finally, a series of t-tests were conducted to determine which computerized tests best discriminated between high and low performance on the Preclinical Alzheimer's Cognitive Composite (PACC), a validated composite of cognitive change that is currently being used in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) prevention trial. *Results:* NIHTB-CB demonstrated medium to strong relationships with all conventional paper-and-pencil measures (r= 0.33 to 0.59). The C3 battery also exhibited medium to strong relationships with conventional memory, attention and processing speed tests (r= 0.32 to 0.47). When clustering the tasks, the NIHTB-CB grouped closely with most paper-and-pencil tests, while the C3 tended to cluster into two distinct groups (i.e., learning and memory vs. processing speed and attention). When assessing which computerized tests best distinguished between high and low performers on the PACC composite, the NIHTB-CB showed a numerically greater magnitude of effect in comparison with C3 (Cohen's d > 1.0). Both computerized batteries displayed alignment with conventional paper-and-pencil tests, however, the two batteries displayed different testing profiles. The NIHTB-CB exhibited the strongest alignment with conventional tests and could substitute for a conventional battery. Cogstate C3, on the other hand, demonstrated better assessments of processing speed and attention. *Conclusions:* The findings of this pilot study suggest that both computerized batteries could substitute for conventional paper-and-pencil tests; however, each battery provides unique information about different aspects of cognition. The NIHTB-CB has the advantage of showing the strongest overall clustering and alignment with conventional paper-and-pencil tasks. By contrast, the Cogstate C3 displayed clearer domain-specific measurement, with the ability to clearly distinguish processing speed, cognitive flexibility and attention from other cognitive domains. The Cogstate brief battery has been validated specifically in dementia cohorts, and has shown sensitivity to early emergent AD biomarkers. However, the NIHTB-CB covers a wide age range across the developmental trajectory, which is a particular strength, as AD prevention trials are focusing on younger cohorts. As such, both computerized batteries have the potential to be used in a cognitive screening role. It remains to be seen how either the NIHTB-CB or Cogstate C3 identifies the presence of AD biomarkers for recruitment purposes or to track cognitive decline over time.

OC54: WHAT IS THE BEST QUESTION? THE FUNCTIONAL ACTIVITY QUESTIONNAIRE IN THE SYSTOLIC PRESSURE REDUCTION INTERVENTION TRIAL (SPRINT) AND SPRINT-MIND. Alan J. Lerner[1], Gordon Chelune[2], Carolyn Harmon-Still[1], Steve Rapp[3], Kaycee Sink[4], Virginia Wadley[5], Jeff Williamson[4], Nicholas Pajewski[6] *((1) Departments of Neurology and Medicine, Case Western Reserve University, Cleveland, OH; (2) Center for Alzheimer's Care, Imaging and Research, University of Utah Salt Lake City, UT; (3) Department of Psychiatry, Wake Forest School of Medicine, Winston-Salem, NC; (4) Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC; (5) Department of Medicine, UAB School of Medicine, Birmingham, AL; (6) Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC)*

Background: the Functional Activity Questionnaire (FAQ) is a 10 question survey of Activities of daily living (ADLs) which has been used in numerous dementia studies. Its utility in predicting cognitive deficits in clinical trials of non-demented subjects is unclear. The Systolic Pressure Reduction Intervention Trial (SPRINT) is a multi-NIH institute study assessing the comparative effectiveness of two blood pressure goals (140/90 vs. 120/80) in adult non-diabetics with or without Chronic Kidney Disease stage 3-4 (eGFR 25-59 ml/

min/1.72m2) with high degree of cardiovascular risk factors. Pre-existing dementia or stroke were exclusion criteria. The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes. The trial recruited 9361 subjects with a large senior cohort of age>75 years (N=2636). SPRINT-MIND is a SPRINT sub-study involving three components: all subjects received a screening battery (Montreal Cognitive Assessment (MOCA), Logical memory and Digit symbol substitution); 2800 subjects received an extended battery (Rey Complex figure test, Hopkins verbal learning test, animal naming task, Trails A/B, Digit span). The main study was stopped early after a median follow-up of 3.26 years in August 2015 owing to a significantly lower rate of the primary composite outcome in the intensive-treatment group than in the standard-treatment group (1.65% per year vs. 2.19% per year; hazard ratio with intensive treatment, 0.75; 95% confidence interval [CI], 0.64 to 0.89; P=0.003). The main study results have been published: A Randomized Trial of Intensive versus Standard Blood-Pressure Control N Engl J Med 2015; 373:2103-16. DOI: 10.1056/NEJMoa1511939). The Cardiovascular outcomes of the Senior cohort have been published as well (Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥75 Years: A Randomized Clinical Trial. JAMA. 2016 May 19. doi: 10.1001/jama.2016.7050.) We report the relationship of demographic and life style variables and cognitive testing to the FAQ results at baseline in SPRINT-MIND. *Methods:* The FAQ was given to subjects who score below the established cut-point (22/30 on MOCA) on the Screening Battery at baseline. The test was administered to an identified proxy informant, either at the SPRINT clinical sites or via telephone from the coordinating center at Wake Forest University within 30 days of cognitive testing. We modeled the relationship between dysfunction specific FAQ items (normal versus any difficulty) and Neuropsychological test scores in the SPRINT cognitive battery using quantile regression. Quantile regression models were fit using the quantreg package and included adjustments for age, sex, race/ethnicity and education. FAQ scores were divided into no dysfunction, mild dysfunction (1-4 items endorsed) or severe dysfunction(>5 items endorse). *Results:* FAQ was obtained in 2710 SPRINT subjects and compared to 6710 without an FAQ. There were significant differences in age, gender (Female>male), Race/Ethnicity, Education, smoking status, daily vigorous activities, alcohol consumption, eGFR, Gait speed between those who triggered the FAQ and those who did not. and Body mass index. Mean total severity was 1.6(SD 3.3) and Total deficits (answers>0) were 1.0(SD 1.9). The mean severity of deficit was 1.4(0.5). Adjusted odds ratios (95% CI; p-value) for MOCA percentiles (based on scores relative to normative data from Kenny et al (2013) were 1.7 (1.26-2.3; 5x10-4), 2.4(1.69-3.32;5.1x10-7), 3.20(2.29-4.48;1.31x10-11) for 10-25th, 5-10,<5 percentiles respectively. Subjects with gait speed <0.8m/sec had adjusted OR 2.5591.75-3.71; 1.06x10-6). Individual items correlated with median change on Neuropsychological tests comparing with those with any difficulty on the FAQ(adjusted for age, sex, race/ethnicity, and education): Trails A with "Assembling tax/business affairs" (10.33(5.56-15.1;2.4510-5); Trails B with Shopping alone (68.2 (42.3-94.1;3.16x10-7); MOCA scores were significantly associated with all FAQ items, with most significant changes in "keeping track of current events" (-1.32(-1.75—0.88; 3.2x10-9)," Remembering appointments and Events" (-0.81(-1.12—0.5);4.26x10-7). Logical memory test scores were significantly associated with all items, with most significant items "writing checks"(-1.18(-1.63—0.72);5.46x10-7) and keeping track of current events (-0.96(-1.44,-0.48;9.34x10-5). All items were significantly associated with Digit symbol substitution test(DSST) scores, with the greatest associations with writing checks (2.27x10-12) and assembling tax/business records (1.1x10-8). *Conclusions:* All of the FAQ items were significantly associated with NP test score change, but different NP tests were highly associated with specific items. These findings can help with designing sensitive tests and specific item dysfunction helps predict NP deficits. These changes may help with enriching cohorts with patients with prodromal and subclinical AD with the easily administered and scored FAQ. (Funded by the National Institutes of Health; ClinicalTrials.gov number, NCT01206062.)

OC55: 36 WEEKS OF TREATMENT WITH PXT-864 IN MILD ALZHEIMER'S DISEASE: RESULTS FROM THE PLEODIAL EXTENSION STUDY. Jacques Touchon[1], Pierre-Jean Ousset[2], Florence Pasquier[3], Claude Guériot[4], Philippe Robert[5], Sophie Auriacombe[6], Jean-Marc Orgogozo[6], Jacques Hugon[7], Anne-Claire Coyne[8], Viviane Bertrand[8], Rodolphe Hajj[8], Peter Schmitt[8], Mickaël Guedj[8], Daniel Cohen[8], René Goedkoop[8] *((1) University of Montpellier, France; (2) Alzheimer's Disease Clinical Research Centre, Gérontopôle, Toulouse University Hospital, France; (3) Memory Clinic, University Hospital Lille, France; (4) Univ Lille, U1171, Distalz, Memory Resources and Research Centre, F-59000, Lille, France; (5) Memory Centre CHU -EA CobTeK, University of Nice Sophia Antipolis, Nice, France; (6) Memory Research Resource Centre for Alzheimer's disease, University Hospital Pellegrin, Bordeaux, France; (7) Memory Clinical Centre CMRR Paris Nord Ile-de-France, Saint Louis-Lariboisiere, Fernand Widal Hospital, AP-HP, Paris, France; (8) Pharnext SAS, Issy les Moulineaux, France)*

Background: Combination therapy is an attractive option for the treatment of Alzheimer's disease (AD) as several pathophysiological mechanisms leading to neurodegeneration may need to be addressed to achieve improved efficacy in terms of cognition and function. PXT-864 combines very low doses of two drugs currently approved for other indications: baclofen, a GABAB receptor agonist approved for spasticity, and acamprosate, an anti-craving agent that is thought to influence glutamatergic transmission. PXT-864 is thought to block the toxic effect of Aß protein in neuronal and endothelial cells by decreasing activity of excitatory glutamate NMDA receptors and by activating inhibitory GABAB receptors, restoring balance between inhibitory and excitatory influences in the brain. PXT-864 was shown to protect neuronal and endothelial cells from amyloid toxicity in vitro in cell cultures and in vivo in animal models, and to prevent the development of the symptoms of AD in rodent models. It was also able to reverse age-related deficits and to prevent induced amnesia in two other animal models for memory loss (aged mice and scopolamine-induced cognitive deficit in a mouse model; Chumakov et al., 2015). Consequently, clinical efficacy of PXT864 was assessed in 45 treatment-naïve patients with mild AD in a pilot study (PLEODIAL I). Three doses of PXT864 were administered for 4 weeks followed by 4 weeks of placebo and then a 4-week re-challenge with PXT864 (Scart-Gres et al., CTAD 2014). This showed excellent short term safety and tolerability, as well as a positive effect of PXT-864 on the primary efficacy endpoint (ADAS-Cog-11) during the challenge periods and a worsening effect during placebo treatment. *Methods*: Patients who completed PLEODIAL-I and who were considered to have benefited were invited to continue treatment for a further 24 weeks in the PLEODIAL-II extension study, so long as they met inclusion criteria, which included: a Mini Mental State Examination (MMSE) score ≥ 20 at the beginning of PLEODIAL-II (visit V5), absence of major or severe depressive disease or other psychiatric disease, and compliance of at least 80% in PLEODIAL-I. Patients were continued on one of 3 doses of PXT-864 (the same

received in the preceding study). The patients remained blinded to the treatment dose as did the independent neuropsychologist raters who conducted the efficacy assessments at each site. Patients were allowed to introduce donepezil 5 mg from 12 weeks (V6) onwards in this extension study if their condition warranted treatment with a symptomatic agent, per the investigator. The efficacy of PXT-864 was assessed through cognitive and behavioural tests performed at entry into the extension study (V5), 12 weeks (V6) and 24 weeks later (V7). These were compared to the baseline values from the PLEODIAL-I study (V1): ADAS-Cog 11, Isaacs Set Test (IST), Wechsler Digit Symbol Substitution test (DSST) , Zazzo Cancellation test (ZCT), free and cued recall test (FCSRT), assessment of instrumental daily activities (IADL) and the clinical Dementia Rating-Sum of Boxes (CDR-SB) assessment. Scores were assessed via summary statistics at each visit. Further, changes in ADAS-Cog score with PXT-864 were compared to historical published placebos and donepezil treatments in AD. *Results*: Of the 45 patients who completed PLEODIAL-I, 37 (mean age 73.9±6.1 years (range 60-88 years), 56.8% female) enrolled in this extension study: 11 patients in the Dose 1 group, 11 in the Dose 2 group and 15 in the Dose 3 group; 36/37 patients completed the 36 weeks treatment period (PLEODIAL-I plus PLEODIAL-II). Seven patients experienced mild to moderate treatment emergent adverse events (TEAEs) considered related to treatment: 2 patients in the Dose 1 group, 3 in the Dose 2 group and 2 in the Dose 3 group. No treatment related serious AEs were reported. On the primary endpoint of ADAS-Cog, mild increases were seen in all dose groups between V1 and V7 (32 weeks of treatment over 36 period), increasing from a mean of 14.1 to 14.9, 11.1 to 12.7, and 10.8 to 12.8, in dose groups 1, 2 and 3 respectively (ITT population analysis). However, donepezil use was greater in the Dose 1 group (n=7) vs Dose 2 group (n=2) vs Dose 3group (n=1). For the DSST, there was a slight improvement between V1 and V7 in the Dose 2 and 3 groups. Similar findings were seen with the TMT assessments. *Conclusion:* These additional findings to those obtained from the positive PLEODIAL-I trial suggest a promising efficacy of PXT-864, which will be explored dose dependently in future studies. The excellent safety and tolerability of PXT-864 was also confirmed in patients with mild AD after 36 weeks of treatment. Further analyses and comparisons to historical control data will be presented.

OC56: UNIQUE METHODOLOGY FOR A PHASE 2 CLINICAL TRIAL EVALUATING OMEGA-3 FATTY ACIDS FOR THE PREVENTION OF VASCULAR COGNITIVE IMPAIRMENT. Lynne Shinto[1], Lisa Silbert[1], Hiroko Dodge[1,2], Joseph Quinn[1], Ashely Bailey[1], Chad Murchison[1], Diane Howieson[1], Jeffrey Kaye[1], Gene Bowman[3] *((1) Neurology Department, Oregon Health & Science University, Portland, OR, USA; (2) Neurology Department, University of Michigan, Ann Arbor, MI, USA; (3) Nutrition and Brain Health, Nestle Institute of Health Sciences, EPFL campus, Lausanne, Switzerland)*

Background: Here we present key methodologic features and baseline data from a National Institutes of Health funded study that is evaluating omega-3 fatty acids, in the form of fish oil, for older adults at risk for cognitive decline. This study is based upon a variety of clinical and pre-clinical evidence suggesting omega 3 fatty acids operate upon "vascular" mechanisms that have emerged as risk factors for Alzheimer's disease. A unique feature of the study is inclusion criteria that required participants to have low plasma levels of combined eicosapenataenoic acid (EPA) and docosahexaenoic acid (DHA) and a threshold level of white matter hyperintensity burden (WMH) on brain MRI, thus enriching the study cohort for omega-3 related vascular risk factors. To achieve these inclusion criteria relatively rapid methods for screening blood fatty acid levels and WMH were used that contributed to the success of enrollment. *Methods:* The study is designed as a double-blind, placebo-controlled phase 2 clinical trial with a 3-year intervention period. Participants were randomized to receive fish oil concentrate (daily dose 975 mg EPA and 675 mg DHA) or placebo oil (soybean). Key inclusion criteria include age 75 years and older, 5.5 weight percent or less of EPA plus DHA or equal to or less than absolute plasma EPA plus DHA levels at 110 mcg/ml, WMH volume equal or greater than 5 cc, not demented (Clinical Dementia Rating (CDR) at 0 or 0.50), Mini Mental State Examination score (MMSE) equal or greater than 24, absence of significant depression (Geriatric Depression Scale less than 6), ability to undergo brain MRI. The primary endpoint is WMH change over 3 years using an automated segmentation algorithm developed at Oregon Health and Science University. Blood fatty acid levels were screened by using a blood spot test that allowed for individual results within 2 weeks of screening. Secondary endpoints capture blood-based biomarkers related to endothelial and adjacent cell function, amyloid and lipid metabolism, and cognitive parameters that emphasize prefrontal cortical activity. Participants are enriched for vascular risk factors associated with Alzheimer's disease that include, older age, low plasma EPA and DHA levels, and MRI evidence of WMH burden. *Results*: The study screened 1,100 participants by phone and 300 in-clinic for inclusion criteria, 102 participants met inclusion and were randomized to treatment. Baseline characteristics (n=102) include: mean age 80.8 years (SD 4.5), 62/102 (60.8 percent) female, mean education level 16.1 years (SD 3.4), mean WMH 15.7 cc (SD 15.3), mean plasma EPA plus DHA 3.30 (SD 0.80) percent of total fatty acids, mean plasma EPA plus DHA absolute value 84.5 mcg/ml (SD 28.4), Mean MME Score 28 (SD 1.8). The correlation between absolute plasma EPA plus DHA and EPA plus DHA as percent of total fatty acids was 0.68, $p<0.001$. *Conclusion:* This trial will test the effects of raising plasma omega 3 fatty acids on WMH progression over 3 years in older adults at high risk for dementia. Careful population enrichment including non-demented mental state, "suboptimum" plasma omega 3, and presence of WMH at baseline are unique and important features of this nutritional intervention. The study design streamlines sample size and treatment duration, as most primary prevention trials for Alzheimer's disease require a larger number of participants followed for 5 years or longer. We hypothesize that down regulation of inflammatory processes via enriching cell membranes with long chain omega 3 polyunsaturated fatty acids will slow WMH progression; an early and significant risk factor for age-related cognitive decline.

OC57: PREDICTION OF CONVERSION FROM MILD COGNITIVE IMPAIRMENT TO DEMENTIA WITH NEURONALLY-DERIVED BLOOD EXOSOME PROTEIN PROFILE. Charisse N. Winston[1], Edward J. Goetzl[2], Jonny Akers[1], Bob S. Carter[1], Edward Rockenstien[1], Douglas R. Galasko[1], Eliezer Masliah[1], Robert A Rissman[1] *((1) University of California, San Diego, La Jolla, CA, USA; (2) ewish Home of San Francisco, San Francisco (UCSF), San Francisco, CA, USA)*

Background: Levels of AD-related proteins in plasma neuronal-derived exosomes (NDEs) were quantified to identify biomarkers for staging in AD. Additionally, plasma NDEs were injected in naive mice to determine the pathogenic potential of NDE cargo. *Methods:* Plasma exosomes were extracted, precipitated and enriched for neuronal source by anti-L1CAM antibody absorption. NDEs were characterized by size (Nanosight) and shape (TEM), and extracted NDE protein biomarkers were quantified by ELISAs. One month post

injection, characterization of NDE cargo was conducted using IHC. *Results:* Plasma NDE levels of P-T181-tau, P-S396-tau, and Aβ1-42 were significantly higher, whereas those of neurogranin (NRGN) and the repressor element 1-silencing transcription factor (REST) were significantly lower in AD and MCI converting to AD (ADC) patients compared to cognitively-normal controls (CNC) and stable MCI (MCI) patients. Mice injected with NDEs from AD plasma displayed p-tau (PHF-1 antibody)-positive cells in the CA1 region of the hippocampus. *Conclusions:* Abnormal NDE levels of P-tau, Aβ1-42, NRGN, and REST demonstrated high predictive accuracy for the conversion of MCI to AD dementia. NDE from demented patients seeded tau aggregation and induced neuropathology in normal mouse CNS.

OC58: OUTCOMES OF A 3-YEAR, MULTICENTER, RANDOMIZED DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2 TRIAL TO ASSESS SAFETY AND EFFICACY OF LOW-DOSE LADOSTIGIL IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT. Lon S. Schneider[1], Yona Geffen,[2], Reinhold Schmidt[3], Stefan Ropele[3], Ronald G. Thomas[4], Jonathan Rabinowitz[5], Martha Weinstock-Rosin[6] *((1) Keck School of Medicine of USC, Los Angeles, CA, USA; (2) Avraham Pharmaceuticals, Ltd, Yavne, Israel; (3) Medical University, Graz, Austria; (4) University of California, San Diego, CA, USA; (5) Bar Ilan University, Ramat Gan, Israel; (6) Hebrew University, Jerusalem, Israel)*

Background: Ladostigil is a small molecule composed of a carbamate moiety fused to a propargyline moiety. It was initially designed for Alzheimer's disease as in high doses it is both a cholinesterase inhibitor and brain-selective monoamine oxidase inhibitor. In low doses, however, ladostigil has neuroprotective activity, reducing oxidative stress and microglial activation, inhibiting pro-inflammatory cytokines, and does not inhibit cholinesterases or monoamine oxidase. We assessed safety and potential efficacy of low-dose, ladostigil over the long-term in patients with MCI. *Methods:* This Phase 2, 3-year, multicenter, randomized, double-blind, placebo-controlled trial included 210 MCI patients (allocated 1:1, ladostigil, 10 mg per day vs. placebo in identically appearing capsules) in 16 centers in Austria, Germany, and Israel. Main inclusion criteria were: men and women age 55-85 years, fulfilling MCI criteria (Albert et al 2011), and with WMS-revised Verbal Paired Associates score < 19, Clinical Dementia Rating (CDR) = 0.5, MMSE 25 to 30, medial temporal lobe Scheltens scale > 1, Modified Hachinski Scale < 5, Geriatric Depression Scale (GDS) < 6, general cognition and functional performance sufficiently preserved such that a diagnosis of AD can be excluded, and provision of written informed consent. Primary objectives were to assess safety, tolerability, and the potential for ladostigil to delay the progression to Alzheimer's disease dementia. Secondary objectives were to assess MRI biomarkers and clinical ratings. The primary outcome was Alzheimer's disease dementia assessed by the site investigator. Secondary clinical outcomes were safety and tolerability, MRI whole brain and hippocampus volumes, a Neurocognitive Test Battery (NTB) z-score, and RAVLT delayed memory. The sample size estimate of 200 assumed a 30% rate of progression to Alzheimer's disease in the placebo group and 12% in the ladostigil group over 3 years, a 20% dropout rate, and an alpha error P<0.05, two-sided, to have 86% power of finding a statistically significant difference. (ClinicalTrials.gov Identifier: NCT01429623). *Results:* Outcomes reflect data from the modified ITT patient population who were randomized and had at least one follow-up evaluation. Treatment discontinuation, adverse events, and SAEs will be reported. The primary outcome, Alzheimer's disease dementia, clinical efficacy outcomes, and MRI whole brain and hippocampal volumes will be reported at the meeting. *Conclusions:* Ladostigil was safe and well-tolerated and appeared to have the potential for improving memory, and delaying progression to dementia. These findings were supported by relative preservation of brain and hippocampus volumes. Next steps include the advancement to pivotal trials in order to assess the magnitude and the extent of clinical efficacy of ladostigil for MCI or prodromal Alzheimer's disease.

OC59: IDENTIFICATION OF ASYMPTOMATIC INDIVIDUALS AT RISK OF ALZHEIMER'S DISEASE USING CHARIOT-PRO OBSERVATIONAL SUBSTUDY AS A TRUE HISTORICAL CONTROL TO IDENTIFY RISK FACTORS FOR AMYLOID PATHOLOGY. Nzeera Ketter[1], Nandini Raghavan[1], Ziad Saad[1], Chi Udeh-Momoh[2,3], Martin Cohn[2], Nina Mansoor[2], Michael Arrighi[1], Sherry Meeh[1], Dolores Szemborski[1], Robert Perneczky[2], Steve Einstein[1], Gary Romano[1], Lefkos Middleton[2] *((1) Janssen Neuroscience LLC, New Jersey, USA; (2) Neuroepidemiology and Ageing research unit, Imperial College London, UK; (3) MRC Centre for Synaptic Plasticity, Bristol University, Bristol, UK)*

Background & Methods: The Chariot Pro Sub-study is enrolling 500 cognitively normal 65-85 year olds, 50% with above threshold amyloid load based on PET/CSF studies. Comprehensive cognitive assessments e.g. ADCS-PACC and RBANS are conducted for up to 4 years to provide external concurrent historical control data used to select the most relevant combination of endpoints for clinical trials in pr-symptomatic at- risk individuals and/or prodromal AD, provide assumptions about disease progression and inform recruitment strategies. Imperial College London recruits cognitively normal volunteers either directly from a Register (N=28,000) cognitively normal volunteers or from the Chariot Pro Observational Main Study (N=720). Clinical, clinical laboratory and MRI assessments are performed prior to amyloid PET using any one of 3 tracers (florbetapir, florbetaben, flutemetamol). Cortical tracer uptake relative to the cerebellar grey is determined visually and by SUVR. All subjects and staff are blinded to APOE and amyloid status except selected personnel at Janssen and relevant contract laboratories. Interim results on the rate of detectable PET amyloid are presented. *Results:* During the first 37 weeks of the study 13/133 subjects (9.8%) were above the defined amyloid threshold. A re-analysis of PET images using independent assessment by internal J&J staff and an external group confirmed the validity of the SUVR estimates. Further analysis risk factors showed that few subjects were over age 74 and few had a family history of dementia. We subsequently introduced screening priority criteria to include over 74 year olds or who subjects aged 60-74 with first or second degree family history of dementia. During the next 10 weeks, we have obtained a 30% rate of subjects who met the detectable amyloid threshold. *Discussion:* Recruitment for interventional treatment studies in AD relies heavily on informational advertising about the study and may result in self-selection of participants who have a perceived risk such as advancing age, family history of dementia or subjective cognitive concerns. Registers of healthy volunteers may represent a pool that more closely reflects the general population and may require low cost pre-screening methodologies to select candidates for PET imaging and other expensive and/or invasive investigations to screen and identify a suitable population for study and for treatment in the future. *Conclusions:* Among healthy volunteers aged 65-85 from a general population sample, the presence of family history and age >74 increased the above threshold amyloid positivity rate threefold to 30%.

OC60: 9-MONTHS AND 12-MONTHS SAFETY AND EXPLORATORY EFFICACY DATA OF ANAVEX 2-73 IN A PHASE 2A STUDY IN MILD-TO-MODERATE ALZHEIMER'S DISEASE PATIENTS. Stephen Macfarlane[1], Marco Cecchi[2], Paul Maruff[3], Kristina M Kapiak[4], Christopher U Missling[4] *((1) Caulfield Hospital, Melbourne, Australia; (2) Neuronetrix, Louisville, KY, USA; (3) Cogstate Ltd., Melbourne, Australia; (4) Anavex Life Sciences Corp., New York, NY, USA)*

Background: ANAVEX 2-73, a selective sigma-1 and muscarinic receptor agonist was tested in a Phase 2a study in patients with mild-to-moderate AD. Adverse Events (AEs) were recorded for assessment of safety and maximum tolerated dose (MTD), the Primary Endpoint of the study. Cognitive (MMSE, Cogstate, QEEG/ERP) and the functional (ADCS-ADL) marker were measured so as to establish a functional relationship between dosing regimen and exploratory efficacy outcomes, the Secondary Endpoint. *Methods:* Thirty-two AD patients 55-85 years old with MMSE between 16 and 28 were recruited. After establishing the MTD and dose response in PART A of the trial, in PART B, all patients received ANAVEX 2-73 between 10mg and 50mg daily orally and re-assessed at 12, 26, 36, 48 weeks. For safety and MTD determination, mathematical modeling was fitted to the recorded AEs to establish the dose-risk relationship. For efficacy, statistical hypothesis tests were performed on cognitive and functional markers. These functional markers were compared to the corresponding baselines. *Results:* Safety: ANAVEX 2-73 demonstrated a favorable safety profile when administered to a clinical population of elderly AD patients with varying degrees of physical fragility. The most common side effects across all AE categories tended to be of mild severity grade 1, and were resolved with dose reductions that were anticipated within the adaptive design of the study protocol. Positive unexpected therapeutic response events, such as improved mood, improved social engagement and increased independent activities were recorded. Exploratory Efficacy: 9-months and 12-months data of all available patients demonstrate that ANAVEX 2-73 preserves average MMSE and ADCS-ADL (PART B) scores across the entire patient group. ANAVEX 2-73 continues to show benefits over baseline for both Cogstate and QEEG/ERP. *Conclusions:* The safety of ANAVEX 2-73 was assessed and MTD was determined. Despite not optimal dosing in the longitudinal PART B of the study, both cognitive and functional performance is sustained over at least 9 months, suggesting that the effect of the compound does not seem to worsen AD symptoms with repeated dosing. In a disease state where progression is invariable over time, a stable MMSE and ADCS-ADL score is considered a positive outcome. Population pharmacokinetic analysis is currently ongoing. The data collected so far support further clinical development of ANAVEX 2-73 and preparation for a larger confirmatory study is underway.

OC61: REMOVAL OF SUBJECTS WITH A "FALSE POSITIVE" DIAGNOSIS OF MILD COGNITIVE IMPAIRMENT FROM THE ALZHEIMER'S DISEASE COOPERATIVE STUDY (ADCS) DONEPEZIL TRIAL STRENGTHENS POSITIVE EFFECTS. Emily C. Edmonds[1,2], M. Colin Ard[3], Steven D. Edland[3,4], David P. Salmon[3], Douglas R. Galasko[1,2,3], Mark W. Bondi[1,2] *((1) Department of Psychiatry, University of California, San Diego, CA, USA; (2) Veterans Affairs San Diego Healthcare System, San Diego, CA, USA; (3) Shiley-Marcos Alzheimer's Disease Research Center, Department of Neurosciences, University of California, San Diego, CA, USA; (4) Division of Biostatistics, Department of Family and Preventative Medicine, University of California, San Diego, CA, USA)*

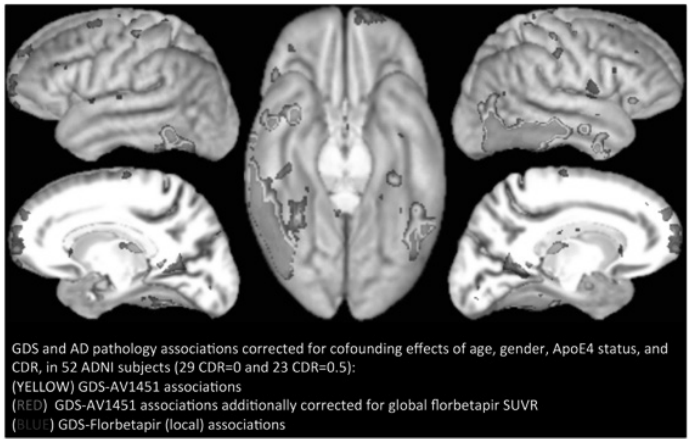
Background: The diagnostic criteria for mild cognitive impairment (MCI) employed by many large-scale studies rely on a single impaired memory score, subjective cognitive complaints, normal performance on a screening test, and clinical judgment of mild impairment. Using cluster-analytic statistical techniques, we have shown in multiple independent datasets that more than one-third of individuals diagnosed in this conventional manner actually perform normally on more extensive cognitive testing. Individuals in this purported "False Positive MCI" group also have normal CSF and imaging biomarker profiles, have low rates of progression to AD, and over-report subjective complaints, further supporting the conclusion of a false positive diagnosis of MCI. Inclusion of such individuals in MCI cohorts involved in clinical trials has the potential to weaken or obscure meaningful findings. We aimed to identify and remove subjects with potential "false positive" diagnosis of MCI from the Alzheimer's Disease Cooperative Studies (ADCS) donepezil trial to determine whether this would strengthen the effects observed in the trial. *Methods:* The study included 756 participants who were originally classified as MCI at screening by conventional diagnostic criteria. Diagnostic criteria included a memory complaint, abnormal memory function (based on education-adjusted cutoffs on one paragraph from the Wechsler Memory Scale-Revised Logical Memory II), a Mini-Mental State Exam score of 24-30, and a Clinical Dementia Rating global score of 0.5. In addition to the measures that were used to establish an MCI diagnosis, all participants also underwent more extensive neuropsychological testing at baseline. This testing was completed after randomization but before drug/placebo administration. We selected six of these neuropsychological measures (two attention/executive function, two language, and two memory measures) and converted them into z-scores using normative data. The z-scores were then subjected to cluster analysis in order to identify potential "false positive" MCI subjects. There were no significant differences between the placebo and vitamin E groups on any measure examined; therefore, they were collapsed to form one comparison group. Independent samples t-test were used to compare the donepezil group to the placebo/vitamin E group. These analyses were performed separately for (1) the entire MCI sample and (2) the MCI sample that remained once the "false positive" participants were removed. *Results:* Three cluster-derived groups were identified: "Amnestic MCI" (n=235; 31%), "Mixed MCI" (n=295; 39%), and "False Positive (FP) MCI" (n=226; 30%). The FP MCI group scored within normal limits on neuropsychological tests not used in making the original MCI diagnosis, and they had a lower rate of progression to dementia (6%) relative to the other two MCI subgroups (35%-38%), both supportive of their "false positive" diagnostic label. FP MCI participants were evenly distributed across the donepezil and placebo/vitamin E groups. When FP MCI participants were excluded from analyses of donepezil versus placebo/vitamin E, significant differences were found on measures of immediate memory which were not

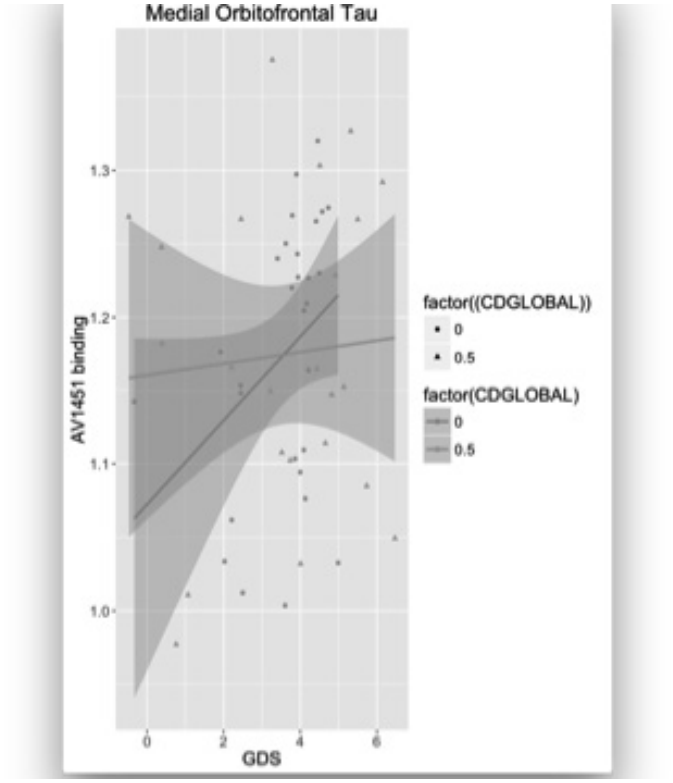
observed in the analyses with the full MCI sample. On a measure of word-list learning (ADAS-Cog Immediate Word Recall), the donepezil group recalled more words relative to the comparison group at their 6 month (p<.001, d=.37), 12 month (p<.001, d=.42), 24 month (p=.02, d=.26), and 36 month (p=.02, d=.28) follow-up visits, although the groups had equivalent baseline performance (p>.05, d=.02). In the original full sample, this difference was only seen at the 6 month (p<.01, d=.25) and 12 month (p<.01, d=.26) follow-ups, but not at 24- or 36-months (p's>.05, d's=.17). On a test of paragraph learning (New York University-Immediate Paragraph Recall), the donepezil group had better immediate recall than the comparison group at their 6 month (p=.03, d=.22), 12 month (p=.02, d=.25), 18 month (p=.02, d=.25), 24 month (p=.04, d=.24), and 30 month (p=.02, d=.29) follow-up visits, despite equivalent baseline performance (p>.05, d=.03). In the full MCI sample, there were no differences in paragraph learning between the donepezil and comparisons groups (p's>.10, d's=.01 to .14.). *Conclusion:* Removing subjects with a false positive diagnosis of MCI from the ADCS donepezil trial significantly strengthened the apparent beneficial effects of donepezil on immediate memory performance, and revealed more beneficial effects of donepezil at later time points than observed in the original analyses. The observed improvements in sensitivity occurred despite considerably fewer participants in each group since one-third of the original sample was removed. Results support the use of more comprehensive neuropsychological test data and the application of actuarial methods to select subjects and improve statistical power for clinical trials of MCI. The application of such methods, and less reliance on the use of cognitive screens, staging-based rating scales, and limited neuropsychological testing in diagnosing MCI, will enhance the ability to discover significant drug effects and lead to more efficient trials. Funding: Original data collection was funded by the Alzheimer's Disease Cooperative Study (NIA U01 AG10483), Pfizer, and Eisai. New data analysis was funded by NIA P50 AG05131, R01 AG049810, and K24 AG026431. None of the authors have relationships with Pfizer or Eisai.

OC62: THE MONTREAL COGNITIVE ASSESSMENT (MOCA) IN 8,724 SPRINT PARTICIPANTS: IMPLICATIONS FOR USE AS A SCREENING TOOL IN CLINICAL TRIALS.

Kaycee M Sink[1], Gordon Chelune[2], Laura Coker[1], Sarah Gaussoin[1], Alan Lerner[3], Linda Nichols[4], Nick M Pajewski[1], Steve Rapp[1], Virginia Wadley[5], Jeff Williamson[1] *((1) Wake Forest School of Medicine, Winston-Salem, NC, USA 27157; (2) University of Utah; (3) Case Western Reserve; (4) VA Medical Center, Memphis, TN; (5) University of Alabama)*

Background: The MoCA is increasingly used in practice and research studies. However, normative data are currently lacking for minority populations and the older old (≥80 yrs), limiting its usefulness as a screening tool for cognitive impairment, We present normative data and cut-points for identifying impaired individuals in a large, diverse sample of older adults enrolled in a clinical trial. *Methods:* The Systolic Blood Pressure Intervention trial (SPRINT) randomized 9,361 adults aged 50 and older with hypertension to intensive (SBP <120) or standard (SBP <140) goals. Participants with dementia were excluded. All participants were administered the MoCA and the WAIS-IV Logical Memory (LM), and Digit Symbol Coding (DSC) tests. In this analysis we excluded participants with missing data, significant depressive symptoms (PHQ-9 >=15), or a history of stroke (final N=8,724). We defined cognitive impairment as a score >1.5 SD below published age and education adjusted means on LM delayed recall or DSC. In participants without impairment, we derived regression-based norms for the MoCA by age, education, and race using Beta-Binomial models. We generated Receiver Operating Curves to evaluate the MoCA's ability to classify participants with suspected cognitive impairment. *Results:* Participants had a mean age of 68±9.4 yrs, 13% were ≥80 yrs; 36% were female; 59% White, 30% Black, and 11% Hispanic. 74.8% had >12 yrs of education. The mean MoCA score was 23±4.1. 15% were considered possibly impaired by LM or DSC. MoCA scores decline with increasing age and with lower education for all race/ethnicity groups. However, scores for black and Spanish speaking participants were consistently lower than those of whites, independent of age and education. For example, the 50th percentile MoCA score for a 75 year old white participant with 12 years of education is 23, compared to 20 for black and Hispanic (Spanish and English speaking) participants of the same age and education. The AUC for detecting possible cognitive impairment was 0.77. Using the recommended cut-off of 26, the sensitivity=91.6% and specificity=36.9%. A cut-off of 23 yielded sensitivity=71.4% and specificity=68.4% in the SPRINT population. The best race specific cut-offs were 23 for whites, 21 for blacks, and 20 for Spanish speakers, after education corrections (+2 points for education <9 years and +1 point for 9-12 years). *Conclusion:* We provide normative data for the MoCA on the largest, most diverse sample of older


GDS and AD pathology associations corrected for cofounding effects of age, gender, ApoE4 status, and CDR, in 52 ADNI subjects (29 CDR=0 and 23 CDR=0.5):
(YELLOW) GDS-AV1451 associations
(RED) GDS-AV1451 associations additionally corrected for global florbetapir SUVR
(BLUE) GDS-Florbetapir (local) associations



adults to date, allowing for more meaningful interpretation of MoCA scores. As with other studies, we found the recommended cut-off of 26 to have poor specificity. In addition, MoCA scores are notably influenced by education and race and thus if MoCA is used as a screening tool for clinical trial entry criteria, cutoffs may need to be different based on age, education, and race.

OC63: EFFECT OF SYMPTOMS OF DEPRESSION ON TAU PATHOLOGY IN ASYMPTOMATIC ELDERLY INDIVIDUALS AND INDIVIDUALS WITH EARLY AD SYMPTOMOLOGY. Duygu Tosun[1,2], Scott Mackin[2,3], Mitzi M. Gonzales[4], David Bickford[3], Craig Nelson[3], Michael Weiner[1,2] for the Alzheimer's Disease Neuroimaging Initiative *((1) Department of Radiology, University of California – San Francisco, CA, USA; (2) Center for Imaging of Neurodegenerative Diseases, San Francisco, CA, USA; (3) Department of Psychiatry, University of California – San Francisco, CA, USA; (4) VA Northern California Health Care System, San Francisco, CA, USA)*

Backgrounds: Depressive symptoms is a commonly co-occurring feature of several neurodegenerative diseases, including Alzheimer's disease (AD), in older adults, and depressive symptoms are associated with accelerated cognitive decline in older adults. The identification of neurobiological substrates of cognitive impairment represents a significant opportunity to improve health and disability outcomes for older adults with depressive symptoms as well as to decouple sources of cognitive impairment/decline in clinical trials. Tau accumulation in the brain has recently emerged as a significant factor influencing cognition in normal cognitive aging and for individuals with Alzheimer's disease, however the association of tau with cognitive impairment in the presence of depressive symptoms has not yet been evaluated. The role of tau accumulation contributing to cognitive impairment in the presence of depressive symptoms is particularly salient if depressive symptoms give rise to increased brain accumulation of tau due to depressive symptoms associated changes in the brain structure and/or function. Here we report effect of symptoms of depression on tau pathology in asymptomatic elderly individuals and individuals with early AD symptoms. *Methods:* Subjects of this study were Alzheimer's Disease Neuroimaging Initiative (ADNI-2) participants who recently underwent AV-1451 positron emission tomography (PET) imaging for in vivo detection of regional tau pathology and structural magnetic resonance imaging (MRI). The study cohort was composed of fifty-two adults (mean age = 76.1+7.0) with normal cognition (n=29 with Clinical Dementia Rating (CDR) of 0) or early AD symptomology (n=23 with CDR=0.5). In this study we evaluated the association of elevated depressive symptoms, based on Geriatric Depression Scale (GDS), and AV-1451 binding. PET imaging were performed at each ADNI site according to standardized protocols. AV-1451 data were realigned, and the mean of all frames was used to coregister AV-1451 data to each participant's MRI acquired closest to the time of the AV-1451 PET scans. In each participant's MRI native space, AV-1451 SUVR images were created based on mean AV-1451 uptake normalized to uptake in a gray matter masked cerebellum reference region. Structural MRI processing was performed to established anatomical correspondences across subjects in order to perform voxel-wise PET data analysis. The structural MRI processing was based on the publicly available and open-source Advanced Normalization Tools (ANTs, http://stnava.github.io/ANTs/) and the associated pipelining framework PipeDream (http://neuropipedream.sourceforge.net). AV-1451 SUVR images were mapped onto the common image space via the spatial normalization parameters estimated for the anatomical correspondences. We employed a generalized linear model (GLM) for voxel-wise analysis of the AV-1451 SUVR data as the independent variable regressed against GDS as the dependent variable with additional explanatory variables age, gender, APOE ε4 allele status, and CDR. To assess the independent association of GDS with AV-1451 SUVR at voxel level, we compared pair-wise full GLM models with and without the AV-1451 SUVR term, fitted by maximum likelihood (ML) via F-tests. Clusters of voxels exceeding a predetermined threshold ($p < 0.05$) were identified, and cluster-wise statistical significances were calculated via 1000 instances of a Monte Carlo simulation. The GLM was repeated with the addition of global cortical florbetapir SUVR as an additional explanatory variable, to assess the GDS versus AV-1451 associations independent of global brain amyloidosis. *Results:* In this sample we found that severity of depressive symptoms was associated with greater AV-1451 binding primarily in the left medial and lateral orbitofrontal, caudal middle frontal, isthmus cingulate, and right inferior temporal, and these GDS versus AV-1451 SUVR associations were independent of the global cortical florbetapir SUVR. The positive association between the severity of depressive symptoms and AV-1451 binding was more pronounced in CDR=0 cases, without any significant difference than the associations observed in CDR=0.5 cases. *Conclusion:* These results suggest that depressive symptoms independent of amyloid pathology may be associated with tau pathology in frontal brain regions, a pattern that is distinct from binding patterns typically seen in the progression of AD. The presence of individuals with depressive symptoms in a clinical trial cohort may represent a potential confound.

OC64: BASELINE CHARACTERISTICS FOR PARTICIPANTS ENROLLED IN THE PHASE II/III EPOCH ALZHEIMER'S DISEASE TRIAL OF THE BACE INHIBITOR VERUBECESTAT (MK-8931). Michael Egan[1], Tiffini Voss[1], Yi Mo[1], Yuki Mukai[1], Christine Furtek[1], James Kost[1], Paul S Aisen[2], Jeffrey L. Cummings[3], Pierre N. Tariot[4], Bruno Vellas[5], David Michelson[1] *((1) Merck & Co., Inc., Kenilworth, NJ, USA; (2) University of Southern California, San Diego, CA, USA; (3) Cleveland Clinic, Las Vegas, NV, USA; (4) Banner Alzheimer's Institute, Phoenix, AZ, USA; (5) Gerontopole, INSERM U 1027, Alzheimers' Disease Research and Clinical Center, Toulouse University Hospital, Toulouse, France)*

Background: Verubecestat (MK-8931) is a potent, oral beta-secretase 1 inhibitor currently in development for treatment of Alzheimer's disease (AD). Verubecestat reduces Aβ levels by over 80% in cerebrospinal fluid (CSF) and brain of rodents and primates, and as well as CSF in subjects with AD. Verubecestat is therefore being evaluated for its ability to slow AD progression. A Phase II/III trial (EPOCH) is testing verubecestat in mild-to-moderate AD and has completed enrollment. Baseline clinical characteristics are presented below. *Methods:* EPOCH (clinicaltrials.gov NCT01739348) is an ongoing randomized, double-blind, placebo-controlled trial in mild-to-moderate AD. Key entry criteria included: diagnosis of probable AD (based on NINCDS ADRDA and DSM IV TR criteria); MMSE of 15-26; MRI/CT findings consistent with AD; a trial partner with frequent contact with participant; and no uncontrolled medical conditions. Use of a stable dose of acetylcholinesterase inhibitors (AChEI) and memantine is permitted. Exclusion criteria included modified Hachinski>4, severe white matter disease, and other active neurological/psychiatric disorders. Co-primary outcome measures are change from baseline in ADAS-Cog and ADCS-ADL scores at Week 78. *Results:* 2,211 participants were randomized between 2012 and 2015 from 239 sites in 21 countries worldwide, with 44% recruited from US/Canada, 31% from Europe/Australia/New Zealand, 13% from Japan, and 12% from other countries. Screening failure was

34%. Preliminary baseline demographic data include the following: 55% female, mean (SD) age of 71.8 (7.5) years, 80% white race (17% Asian, 3% other) and 10% Hispanic or Latino. Most participants (89%) had been diagnosed with AD for at least six months before study entry. Most (88%) were on AChEI and/or memantine therapy. Regarding education level, 40% had 16 or more years. Enrollment was balanced regarding baseline disease severity: 48% mild (MMSE ≥21) and 52% moderate (MMSE ≤ 20). Approximately 62% were APOE4 positive. Mean (SD) baseline scores for the key efficacy measures were ADAS-Cog: 21.4 (7.5), ADCS-ADL: 62.6 (10.0), CDR-SB: 5.4 (2.2) and MMSE: 20.3 (3.3). *Conclusions:* Baseline characteristics of the population included in the EPOCH trial are similar to those from prior published trials in participants with mild-to-moderate AD. Trial results will be available in 2017.

POSTER

Thursday, December 8

Theme : Clinical Trials Methodology

P1-1 INNOVATIVE PHASE II STUDY DESIGN FOR STUDYING THE GLUTAMINYLCYCLASE INHIBITOR PQ912 IN EARLY ALZHEIMER'S DISEASE. Niels D. Prins[1], Frank Weber[2], Suzanne Bruins[3], Inge Lues[2], Philip Scheltens[1] *((1) Alzheimer Centre and Department of Neurology, VU University Medical Centre, Amsterdam, The Netherlands; (2) Probiodrug AG, Halle, Germany; (3). Julius Clinical, Zeist, The Netherlands)*

Backgrounds: The enormous medical need for disease modifying drugs in AD resulted in a significant increase of clinical trial programs. Many of the product candidates showed interesting but not clearly positive early study results, and subsequently failed in later stages after consuming significant resources. We present a new 3 months study design and development concept for early development in early AD for a disease modifying small molecule product candidate PQ912. PQ912 targets the inhibition of Glutaminyl cyclase resulting in a reduction of the formation of neurotoxic pyro-Glu-Abeta and related oligomers. It has been extensively investigated in Phase I MAD showing good tolerability and a dose dependent QC-inhibition in the spinal fluid. *Methods:* In this proof of concept study 'SAPHIR' the safety, tolerance and effects on memory function, RSfMRI, EEG and CSF based biomarkers of PQ912 are currently investigated. The two arm double blind placebo controlled 3 months trial is recruiting 110 treatment naïve patients in seven European countries with patients having either MCI due to AD or mild AD (MMSE 21-30). The study applies a series of methodological innovations which in this combination have never been executed: All patients need to undergo a lumbar puncture prior to randomization and meet thresholds for both Abeta (<638ng/ml) and total tau (>375 ng/ml, or p-tau > 52ng/ml) to ensure proper diagnoses. During the study an independent unblinded safety expert assesses each SAE and SUSAR immediately in order to enable protocol recommendation within minimal delay in a study with an unprecedented target. MMSE and Cogstate test battery assessments at baseline are monitored blindly every 25 recruited patients to ensure consistency and reliability of ratings. A number of exploratory endpoints like EEG, RSfMRI and a series of CSF based biomarkers including QC-activity pyro-Glu-Abeta, Abeta oligomers, neurogranin as well as inflammation markers are centrally analyzed for understanding the profile of PQ912 and validation for use in future studies. *Results:* EEG and fMRI central reading requires dummy runs for each site before inclusion of the patient resulting in a 20% repetition rate in order to ensure full eligibility. The screen failure to randomization rate based on 110 screened patients is 1:1 (50% screen failed patients). Half of the screen failures are due to CSF results with even distribution of not meeting the Abeta or tau thresholds. The unblinded independent safety expert has issued 6 safety recommendations based on 45 randomized and 30 completed patients (all for continuation of study without modification). The first monitoring of MMSE and Cogstate test battery based on 25 patients showed a high correlation between four Cogstate tasks and the MMSE (p= 0.05 to 0.01). *Conclusion:* Short term placebo controlled studies in treatment naïve patients are feasible to characterize the safety and pharmacodynamic profile of an innovative new product candidate with an unprecedented mechanism of action. The advantage of a short term study is that it can be done without delaying the start of standard treatment unduly. Safety monitoring and biomarker validation are feasible in this setting and can be applied to design a more robust phase IIbproof of concept study as a next step. While this two stage phase 2 procedure will probably consume more time than a single longer Phase II proof of concept study, it has the advantage that each of the 2 studies can be designed to answer specific questions allowing for a solid phase III design. Go no-go criteria have been pre-set leading to either a stop, a disease modification phase IIb disease modification study or a combined Phase IIb / III program.

P1-2 ALZHEIMER'S PREVENTION REGISTRY: LESSONS LEARNED IN DEVELOPING A SHARED RESOURCE TO THE SCIENTIFIC COMMUNITY. Nellie High[1], Jodie Nichols[1], David Gordon[1], Trisha Walsh[1], Raj Aggarwal[2], Paul S. Aisen[3], Marilyn S. Albert[4], Meryl Comer[5], Jeffrey L. Cummings[6], Jennifer J. Manly[7], Ronald C. Petersen[8], Reisa A. Sperling[9], Gabrielle Strobel[10], Michael W. Weiner[11], Eric M. Reiman[1], Pierre N. Tariot[1], Jessica B. Langbaum[1] *((1) Banner Alzheimer's Institute, Phoenix, AZ, USA; (2) Provoc, Washington, DC, USA; (3) Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, CA, USA; (4) Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA; (5) Geoffrey Beene Foundation Alzheimer's Initiative, Washington, DC, USA; (6) Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA; (7) Department of Neurology, Columbia University College of Physicians and Surgeons, New York, NY, USA; (8) Department of Neurology, Mayo Clinic, Rochester, MN, USA; (9) Department of Neurology, Harvard Medical School, Boston, MA, USA; (10) Alzforum, Cambridge, MA, USA; (11) Department of Radiology and Biomedical Engineering, University of California San Francisco, San Francisco, CA, USA)*

Background: Recruitment and enrollment into clinical trials is a major obstacle faced by researchers and study sponsors. It has been estimated that fewer than 10% of Americans participate in clinical trials, mostly due to lack of awareness about study opportunities, resulting in approximately 80% of research studies failing to meet their enrollment goals in the stated timeframes. Given the growing number of preclinical and symptomatic treatment trials being conducted or in the planning stages, in 2012 we developed a web-based Alzheimer's Prevention Registry (APR) to help studies make enrollment more efficient and timely. Serving as a shared resource to the Alzheimer's scientific community, the APR has been designed to complement and enhance local recruitment efforts. Recent efforts have focused on enhancing APR member experience and engagement, while developing methods to measure the success of the APR at facilitating enrollment into studies. *Methods:* Prior to creating the

APR, a national survey of 1,024 adults age 18-75 was conducted for planning purposes to help guide Registry development and outreach strategy. In addition, A/B testing and usability research is consistently conducted to enhance user experience and registration conversion rates. Interested adults age 18+, with and without memory and thinking problems, are eligible to join at www.endALZnow.org. Based on lessons learned from the Arizona Alzheimer's Research Registry and modeled after other web-based research registries, this Registry was purposely designed to have a low threshold of commitment at entry. At enrollment, individuals are asked to provide their name, email address, zip/postal code and year of birth; after enrollment they can complete additional contact and demographic information at their discretion. APR members receive regular email communication to keep them apprised of the latest news in Alzheimer's prevention research. In addition, enrollees receive email notifications when study opportunities become available in their communities, with information on next steps to explore the possibility of their participation. *Results:* As of June 2016, over 216,000 individuals have joined the APR. APR members are predominantly women (78%), report a family history of dementia (70%) and have no diagnosis of cognitive impairment (95%). 36% of members are between the ages of 46-60; 41% are between the ages of 61-75. An option to create an APR user account will be implemented in Q3 2016 to enable members to update account information, view matched studies based on provided criteria, and the option to opt in to share contact information with sites to begin the enrollment process. Concurrently, a Researcher Portal will be available in Q3 2016 which will allow investigators and sponsors to receive and track referrals for their respective studies. This will allow APR to monitor study enrollment metrics to help demonstrate the utility and impact of the APR. *Conclusion:* The APR is an engaged community of individuals who want to stay abreast of the latest in Alzheimer's news and scientific advances, and to be connected to research studies taking place in their communities. The APR has been well-received and enrollment continues to increase; results from A/B testing and the impact that website modifications had on enrollment will be discussed. Efforts are underway to significantly increase the APR study listing portfolio to allow more opportunities for participation. The planned Researcher Portal will enable us to report the success of APR in facilitating enrollment into studies. We continue to explore novel approaches for increasing enrollment and engagement of enrollees, as well as collaborating with researchers to help promote relevant studies taking place in their catchment areas.

P1-3 AGE INCREASES RATE OF AB AND E4 RELATED MEMORY DECLINE IN PRECLINICAL ALZHEIMER'S DISEASE. Paul Maruff[1,2], Yen Ying Lim[2], Peter Snyder[3], Victor Villemagne[2,4], Chris Rowe[2,4], Colin Masters[2] *((1) Cogstate Ltd New Haven, CT, USA; (2) Florey Institute for Neuroscience, Melbourne, Australia; (3) Lifespan Hospital, RI, USA; (4) Austin Health. Heidelberg, Australia)*

Background: In non-demented adults, both high amyloid (Aβ+) and carriage of the apolipoprotein E (APOE) ε4 allele increase risk for cognitive decline and dementia. Further, Aβ+ related cognitive decline is increased substantially by the presence of at least one copy of the APOE ε4 allele. Despite advances in Aβ biomarkers, age remains the greatest risk factor for dementia, particularly Alzheimer's disease (AD). As APOE ε4 increases risk for Aβ+ and older adults are also more likely to be Aβ+, it is important to understand the extent to which age influences the effects of ε4 on Aβ+ related memory decline. This study aimed to determine the extent to which the APOE ε4 allele influenced Aβ related cognitive change in adults aged between 60-74 and 75-90 years old. *Methods:* Non-demented adults (n=485) enrolled in the AIBL study underwent Aβ neuroimaging and ε4 genotyping. Episodic Memory was assessed at baseline, 18-, 36-, 54- and 72-month follow-ups. Participants were classified as Aβ- or Aβ+ using PET neuroimaging and into two age groups (<75 and ≥75) according to their age at baseline. Data were analysed using linear mixed model analyses. *Results:* In adults aged <75, when compared to the Aβ- group, there was a significant rate of memory decline only in Aβ+ ε4 carriers (d=1.25). In adults aged ≥75, when compared to the Aβ- group, both Aβ+ ε4 carriers (d=1.23) and non-carriers (d=0.35) showed significant rates of memory; however, the memory decline in Aβ+ ε4 carriers was substantially greater when compared to non-carriers (d=0.82). This faster rate of memory decline in adults aged ≥75 was reflected in a 43% of Aβ+ ε4 carriers meeting clinical criteria for dementia at the 72-month assessment, in contrast to just 24% of Aβ+ ε4 non-carriers and 10% of Aβ- participants. *Conclusions:* Previous studies investigating the relationship between ε4 and Aβ+ have not accounted for potential non-linear effects of age on memory decline. The rate of Aβ+ related memory decline was greatest in adults aged ≥75, particularly in those who were also APOE ε4 carriers. This suggests that the combined effects of Aβ+ and ε4 on risk for dementia increases substantially in older adults. It also demonstrates that age and ε4 carriage should be taken into account in clinical trials of preclinical AD.

P1-4 PHASE 3 CLINICAL TRIAL IN MCI DUE TO AD TARGETING HIPPOCAMPAL HYPERACTIVITY. Richard Mohs[1], Sharon Rosenzweig-Lipson[1], Marilyn Albert[2], Michela Gallagher[1,3] *((1) AgeneBio, Inc. Baltimore, MD, USA; (2) Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD, USA; (3) Department of Psychological and Brain Sciences, Johns Hopkins University, Baltimore, MD, USA)*

Background: There is now strong evidence from preclinical models and human patients, particularly in early stages of AD, that neuronal circuits become hyperactive contributing to neuronal pathology and brain dysfunction (recent review Busche et al. 2015; also Busche et al. 2012; Ewers et al. 2011). Many studies using functional magnetic resonance imaging (fMRI) have demonstrated that hippocampal hyperactivity is a highly consistent and characteristic signature in amnestic mild cognitive impairment (aMCI) (Bakker et al., 2012, 2015; Celone et al., 2006; Dickerson et al., 2004; 2005; Hamalainen et al., 2007; Yassa et al 2010; Ewers et al 2011 for review) and its magnitude is both significantly correlated with the extent of neuronal injury affecting AD-specific regions of the brain (Putcha 2011) and predicts subsequent cognitive decline/conversion to a dementia diagnosis (Sperling, 2007; Dickerson et al., 2008; Miller et al., 2008). Moreover, greater hippocampal hyperactivity occurs in MCI due to AD determined by PET amyloid imaging and persists in the MCI phase of the disease over a three year follow up during which time greater worsening on the Clinical Dementia Rating Scale-sum of boxes (CDRsb) is evident in MCI due to AD relative to patients with amyloid negative PET scans (Huijbers et al., 2015). These data support a novel therapeutic approach to target hyperactivity, especially in the aMCI phase of AD when hippocampal hyperactivity is most pronounced. A Phase 2 study of the atypical antiepileptic levetiracetam in patients with aMCI used hippocampal hyperactivity for target engagement and to assess the functional significance of reducing hyperactivity. Levetiracetam demonstrated therapeutic efficacy for reduction of hyperactivity in a low dose range that concurrently improved memory task performance in aMCI patients (Bakker et al. 2012; 2015). Based on a close parallel in the amount of drug exposure required for efficacy in both preclinical studies and MCI patients (plasma level μg/mL), AGB101 was formulated as an extended release once-a-day

medication and is now supported by the FDA for use in the Phase 3 trial to test its efficacy on slowing progression in patients with MCI due to AD. *Study Design Methods:* A multicenter, randomized, double-blind, placebo-controlled study will evaluate the efficacy and safety of AGB101 (low-dose levetiracetam, 220 mg, extended release tablet) on slowing progression of amnestic mild cognitive impairment due to Alzheimer's disease. A total of 830 subjects will be randomized (415/treatment group). Participants who meet criteria for enrollment with MCI due to AD will be treated with AGB101 or placebo in a 78-week protocol. The primary efficacy evaluation will be the change in CDR-SB from baseline to 78 weeks. Secondary cognitive and functional efficacy assessments will include both MMSE and FAQ. Biomarkers for neuronal injury including entorhinal cortex thinning and volume and hippocampal volume will be evaluated in structural MRI assessments. Subjects enrolled with MCI due to AD will have amnestic mild cognitive impairment as defined by: (1) MMSE scores between 24 and 30, inclusive; (2) A memory complaint reported by the subject or their study partner that is verified by the study partner; (3) Abnormal memory function documented by an education adjusted score on the Logical Memory II subscale (delayed paragraph recall) from the Wechsler Memory Scale-Revised; (4) A Clinical Dementia Rating Scale (CDR) score of 0.5; Memory Box score of ≥ 0.5; (5) General cognitive and functional performance sufficiently preserved that a diagnosis of Alzheimer's dementia cannot be made at the time of the screening visit and essentially preserved activities of daily living; and (6) Florbetapir PET brain scan positive for amyloid. In addition to the screening and the baseline visit, the protocol will consist of 3 major visits and 3 minor visits during the 78-week study. This study will be conducted at approximately 116 study sites in the Americas, Europe, Asia, and Australia. Worldwide Clinical Trials, a contract research organization, will oversee operational aspects of this study on behalf of AgeneBio, Inc., the sponsor of the study. *Conclusion:* The Phase 3 trial of AGB101 represents a novel treatment approach to address the hippocampal overactivity in the earliest symptomatic phase of Alzheimer's disease, with potential to slow progressive decline in this population at high risk for AD dementia.

P1-5 PRIMARY PREVENTION TRIALS IN DOMINANTLY INHERITED ALZHEIMER'S DISEASE: CONSIDERATIONS IN THE DOMINANTLY INHERITED ALZHEIMER NETWORK TRIALS UNIT. Eric McDade[1], Guoqiao Wang[2], Tammie Benzinger[3], Anne Fagan[1], Jason Hassenstab[1], Chengjie Xiong[2], Randall J. Bateman[1] *((Washington University School of Medicine at St. Louis: (1) Department of Neurology; (2) Department of Medicine, Division of Biostatistics; (3)Department of Radiology)*

Background: The development and implementation of secondary prevention trials for Alzheimer's disease has provided hope of significant delay of cognitive and functional decline associated with abnormal Alzheimer's disease biomarkers. These secondary prevention AD trials have been facilitated by the development of increasingly predictive diagnostic biomarkers that can more accurately predict disease risk and progression, and by the development of more pathology specific therapies. Symptom onset in dominantly inherited Alzheimer's disease (DIAD) populations is highly predictable, and using a parental or mutation-specific estimate of years to symptom onset (EYO), the emergence of biomarker abnormalities can be tracked prior to onset of overtly symptomatic disease. The combination of certainty of future disease, precise biomarkers and predictable disease staging, enables the development of primary prevention trials in the DIAD population that could prevent the development of the pathology of AD (as evidenced by AD biomarkers) and subsequently prevent cognitive decline and dementia. Leveraging the serially collected cerebrospinal fluid (CSF) and amyloid positron emission tomography (PET) data available in the Dominantly Inherited Alzheimer Network (DIAN) observational cohort, we simulated treatment effects for a trial consisting of individuals with preclinical AD. The goal of the study was to provide estimates of trial enrollment that would result in a trial with optimal power to detect target engagement in preclinical AD. *Methods:* Using Data Freeze 10 from the Dominantly Inherited Alzheimer Network (DIAN) longitudinal, observational study, we estimated the difference in annual rate of change of amyloid PET and CSF Aβ-42 between mutation carriers and non-carriers who were more than 15 years before their estimated years of symptom onset (EYO <=-15). To estimate the annual rate of change of these biomarkers we used a mixed effects model for repeated measures (MMRM). The fixed effects in MMRM included: mutation status, time since baseline, and interaction between these two; and the random effects included: random intercept and slope for each individual. We also estimated the variances of the intercept, the slope, and the residuals. From the results of the MMRM we estimated the sample size for a primary prevention trial considering a 50% effect size on slowing of biomarker progression with a type I error of 0.05, a power of 80% with a 3:1 (active:placebo) randomization ratio over a 5 year trial with annual assessment and a 5% annual drop-out rate. *Results:* Of 431 participants, 49 (53% mutation carriers) with a baseline EYO<=-15 had 2 or more biomarker assessments. Mutation carriers declined an average of 38 pg/ml faster per year than non-carriers in CSF Aβ-42 and increased an average of 0.06 SUVR more per year in amyloid PET. Assuming a treatment effect of 50% reduction in the rate of change, a well-powerful trial could enroll as few as 84 subjects if CSF Aβ-42 were the primary outcome, and 168subjects if the primary outcome was amyloid PET. *Conclusions:* Utilizing data from the DIAN observational study, we show that longitudinal changes in the progression of key biomarker targets for primary prevention can been detected prior to significant biomarker abnormalities crossing a threshold of normality and well before the emergence of symptomatic disease. Further, we found that relatively small samples would be needed to show a 50% slowing of biomarker changes over 5 years in asymptomatic DIAD mutation carriers. A future direction will be to explore the numbers needed to consider a longer trial, i.e. 10 years, which would measure cognitive outcomes. The ability to enroll, maintain and engage DIAD populations in secondary prevention has been demonstrated in the DIAN-TU trial and the Alzheimer's Prevention Initiative. Given the achievement of these critical milestones in the DIAD population and the ultimate goal of preventing Alzheimer's disease the next logical step are primary prevention trials. Should primary prevention prove feasible and successful in the DIAN population these efforts will undoubtedly inform the development of primary prevention trials in sporadic AD.

P1-6 IMPROVING PRECISION AND POWER BY ADJUSTING FOR PROGNOSTIC BASELINE VARIABLES IN ALZHEIMER'S DISEASE CLINICAL TRIALS. Michael Rosenblum[1], Elizabeth Colantuoni[1], Jon Steingrimsson[1], Arnold Bakker[2], Michela Gallagher[3,4] *((1) Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD USA; (2) Department of Psychiatry and Behavioral Sciences, Johns Hopkins Medical School, Baltimore, MD USA; (3) AgeneBio, Inc. Baltimore, MD USA; (4) Department of Psychological and Brain Sciences, Johns Hopkins University, Baltimore, MD USA)*

Backgrounds: There is potential to improve precision in randomized trials by appropriately adjusting for baseline variables that are prognostic for the primary outcome. Improved precision leads to greater power. A key challenge to achieving substantial precision

gains from adjusting for baseline variables is to identify, before the trial starts, variables that are likely to be strongly correlated with the primary outcome. A second challenge is to choose a statistical analysis method that (i) fully leverages the prognostic information in the identified baseline variables, and (ii) has the key statistical properties required by regulators such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). There is little available guidance on how to best choose the set of variables and statistical analysis method to maximize precision gains from covariate adjustment. *Methods:* We consider hypothetical trials for preventing progression from mild cognitive impairment to Alzheimer's disease (AD). Simulation studies are conducted based on resampling from an Alzheimer's Disease Neuroimaging Initiative (ADNI) data set, to identify prognostic baseline variables. We consider multiple types of primary outcomes, and baseline variables that include both clinical and neuroimaging measurements. We compare statistical methods for covariate adjustment that leverage these baseline variables and that possess the key statistical properties (such as Type I error control and being robust to model assumptions) required by regulators. We demonstrate the potential added value of these methods for future trials. *Results:* We demonstrate that in AD trials, there are multiple baseline variables that are moderately to strongly prognostic for the primary outcome of CDR-SB. This means there is potential to improve trial precision and power by appropriately adjusting for these variables in the primary analysis (which must be specified in the statistical analysis plan of the trial before the trial starts). *Conclusion:* If study populations in future randomized trials are similar to those in the ADNI data set we simulated from, then there is potential to improve precision and power by appropriately adjusting for prognostic baseline variables.

P1-7 SENSITIVITY OF TRIAL PERFORMANCE TO DELAYED OUTCOMES, ACCRUAL RATES, AND PROGNOSTIC VARIABLES BASED ON A SIMULATED RANDOMIZED TRIAL WITH ADAPTIVE ENRICHMENT. Michael Rosenblum[1], Tianchen Qian[1], Elizabeth Colantuoni[1], Aaron Fisher[1] *((1) Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA)*

Backgrounds: Adaptive enrichment designs involve rules for restricting enrollment to a subset of the population during the course of an ongoing trial. This can be used to target those who benefit from the experimental treatment. It is an open question how sensitive the trial performance (in terms of Type I error, power, expected sample size, trial duration) is to different design characteristics. *Methods:* Our simulation distributions mimic features of data from the Alzheimer's Disease Neuroimaging Initiative, where there are two subpopulations of interest. Specifically, the data consist of 286 patients who entered the ADNI study with mild cognitive impairment (CDR 0.5 with a SOB score 2.5 or less) and who remained in the study for 12 months of follow-up. We investigate the impact of the following design characteristics: the accrual rate, the delay time between enrollment and observation of the primary outcome, and the prognostic value of baseline variables and short-term outcomes. We apply information-based monitoring, and evaluate how accurately information can be estimated in an ongoing trial. We consider trials where the primary outcome is observed a fixed amount of time from enrollment (called the delay). We set the primary outcome to be the change in CDR-SB from baseline to 1 year of follow-up. Also recorded are baseline variables and the short-term outcome of change in severity of dementia symptoms measured at 6 months of follow-up. *Results:* We found that delay, accrual rate, and prognostic value of baseline variables can have substantial impact on the adaptive design performance. The added value of prognostic short-term outcomes was very small. *Conclusions:* Adaptive enrichment designs have potential to be useful in AD trials, but care should be taken to conduct simulation studies to assess their robustness to deviations from the projected delay time, accrual rate, and prognostic value of baseline variables.

P1-8 EFFECTS OF POTENTIALLY SELECTIVE END OF FOLLOW-UP IN A POPULATION WITH LATE MILD COGNITIVE IMPAIRMENT USING A DISEASE SIMULATION. Anuraag Kansal[1], Ali Tafazzoli[1], Stanimira Krotneva[2], Rodrigo DosSantos[1], Jack Ishak[2] *((1) Evidera, Bethesda, MD, USA; (2) Evidera, Montreal, QC Canada)*

Background: Longitudinal studies are susceptible to selective loss-to-follow-up, whereby patients with longer or complete follow-up are likely healthier or less severe subset of the starting population. The problem may be particularly more pronounced in older populations or in patients with debilitating disease like Alzheimer's disease (AD). Therefore, results from the study may have limited generalizability since they reflect the specific pattern of loss to follow-up of that study. We evaluated the potential magnitude of such a bias in the Alzheimer's Disease Neuroimaging (ADNI) study by comparing predicted disease progression with and without the observed loss to follow-up in ADNI in a simulation of a cohort of patients with LMCI. *Methods:* This study relied on the Alzheimer's Disease Archimedes Condition-Event (AD ACE) simulator, which is a disease simulator that predicts the progression of AD in terms of multiple interacting trajectories for key biomarkers and cognition, behavior, function, and dependence markers. In particular, it is constructed using predictive equations for rate of change in cerebrospinal fluid (CSF) amyloid-beta, CSF t-tau, FDG-PET, hippocampal volume, MMSE, CDR-SB, ADAS-Cog, and NPI derived from statistical analyses of the Alzheimer's Disease Neuroimaging Initiative (ADNI). To assess the impact of potentially selective loss to follow-up, we replicate the follow-up observed in ADNI in the simulator by truncating the follow-up of patients as in ADNI by applying appropriate probabilities of end-of-follow up at each simulated visit. These were obtained from analyses of the longitudinal data from the ADNI1 study to develop an equation predicting the probability that a patient's follow-up would end after that visit. Patients' last visit in the dataset was flagged as the visit preceding loss of follow-up. The last visit could have been determined by death, withdrawn consent, pre-scheduled end of observational follow up (e.g. an AD patient ending follow-up at 24 months), or other loss to follow-up. A logistic regression was fitted on all visits, testing demographics (age and years of education), time since enrollment, and baseline and current cognition scores for MMSE, CDR-SB and ADAS-cog as predictors. We then simulated the progression of disease in a cohort of all patients with LMCI in the ADNI1 and ADNI2 studies with and without predicted loss to follow-up using the AD ACE. *Results:* The resulting logistic regression equation for end of follow-up had a c-statistic of 0.740, suggesting reasonable discrimination ability between patients who dropped out and those who did not. The strongest predictors in the equation were time since enrollment (odds ratio [OR] = 1.029; $p < 0.0001$), CDR-SB score at baseline (OR = 1.266; $p < 0.0001$), MMSE score at baseline (OR = 0.902; $p = 0.001$), and most recent ADAS-Cog score (OR = 1.032; $p < 0.001$). The latter implies loss to follow-up may be selective, as probabilities are affected by recent cognitive ability. When all patients with LMCI were simulated without any loss to follow-up mean MMSE of the cohort was predicted to decline rapidly, with mean change from baseline reaching 3.9 and 6.0 points at 48 and 84 months, respectively. These declines were nearly twice the observed declines of 2.2 and 3.2 points at the same times. When

simulating the same population, but permitting patients to be lost to follow-up selectively based on their characteristics, the mean MMSE of the cohort at 48 and 84 months were 3.3 and 4.4 points, respectively, which is in agreement with the observed data. Similar differences between the simulated outcomes with and without selective loss to follow-up were observed for CDR-SB, ADAS-Cog and NPI. Despite the potentially selective drop out in ADNI, the equations and simulator have shown strong external validity in tests against published data for times to development of AD, institutional care, and mortality. *Conclusion:* The potentially selective loss of follow-up of patients in ADNI can significantly impact the predicted trajectory of LMCI patients over 48 to 84 months. Predictions of the natural history of AD made based on ADNI data must account for this effect. Simulation tools like the AD ACE can help by allowing simulation of results with or without loss to follow-up, or with a different pattern of attrition that is closer to the setting of interest.

P1-9 SAMPLE SIZE CONSIDERATIONS FOR ASSESSING AGREEMENT AMONG MULTIPLE RATERS IN A STUDY WITH AMNESTIC MILD COGNITIVE IMPAIRMENT. Ying Zhang[1], James Kost[1], Michael Egan[1] *((1) Merck Sharp and Dohme, Upper Gwynedd, PA, USA)*

Background: Progression to probable Alzheimer's Disease (AD) dementia has historically been used as the efficacy measure in amnestic mild cognitive impairment (aMCI) trials. A significant challenge with using this measure is that defining precisely when subjects are sufficiently impaired to meet diagnostic criteria involves relatively subjective judgments. A Phase III trial in aMCI subjects is being conducted with MK8931, a potent inhibitor of beta secretase (BACE), in which progression to AD was included as a secondary endpoint. A central adjudication committee (CAC), consisting of five independent raters, was established to judge whether subjects meet criteria for AD dementia. This decision is to be based on a narrative summary from the sites in addition to trial outcome measures (Clinical Dementia Rating Sum of Boxes (CDR-SB) and ratings of cognition and function). Throughout the trial, only two of the five raters will adjudicate a given case (with a third used to tie-break if needed). However for the first N cases, all five raters were to examine the cases to generate data on agreement. It was of interest to determine how many cases should be initially adjudicated by all five raters in order to provide some confidence that the whole of the CAC is adjudicating consistently. *Methods:* The Kappa statistic1, due to Cohen, is often used to measure the degree of agreement between two raters. Fleiss2 extended Cohen's Kappa for the case with multiple raters. We conducted simulations to generate the expected value of Fleiss' Kappa, along with the associated expected confidence intervals (CIs), in order to inform the choice of N. Multiple simulation scenarios were examined, varying in the selection of N, the correlation between the raters, and the underlying probability of each rater adjudicating positively. *Results:* Simulations indicated that N=50 cases would be sufficient to lower the expected half-width of the CI to an acceptable level (between 0.1 and 0.2). From trial data based on the first 50 cases, Fleiss' Kappa and the associated 95% CI were calculated as 0.54 (0.32, 0.76), respectively, which correspond very closely with the simulated results. *Conclusions:* Fleiss' Kappa should not be evaluated in a vacuum or in an absolute sense. Knowledge of what to expect, given the likely expected correlations and underlying probabilities of a positive response across raters should be factored into the final interpretation. 1. Cohen, Jacob A. A coefficient of agreement for nominal scales. Educational and Psychological Measurement, 1960, 20, 37-46. 2. Fleiss, Joseph L. Measuring nominal scale agreement among many raters. Psychological Bulletin, Vol 76(5), Nov 1971, 378-382.

P1-10 THE INCREMENTAL VALIDITY OF SHORT-TERM PRACTICE EFFECTS IN DETERMINING AMYLOID POSITIVITY. Bonnie C.A. Dalley[1], Kayla R. Suhrie[1], Taylor J. Atkinson[1], Britney Beardmore[3], Kevin Horn[3], Kelli Rasmussen[3], Lance Burrell[3], Dustin B. Hammers[1,2], Norman L. Foster[1,2], Kevin Duff[1,2], John M. Hoffman[3] *((1) Center for Alzheimer's Care, Imaging and Research, Department of Neurology, University of Utah; (2) Center on Aging, University of Utah; (3) Center for Quantitative Cancer Imaging, Huntsman Cancer Institute)*

Backgrounds: As clinical trials in Alzheimer's disease shift towards prevention, simpler and more economical methods are needed to identify those who are amyloid positive. *Methods:* The current study compared baseline cognitive performances and short-term practice effects across one week in determining amyloid burden in 27 non-demented, community-dwelling older adults. *Results:* Amyloid deposition (via 18F-flutemetamol) was significantly correlated with all seven baseline cognitive scores (p's < .05) with greater amyloid deposition being associated with poorer cognitive scores. After controlling for baseline cognition, amyloid deposition was significantly correlated with practice effects on 4 of the 7 cognitive tests (p's < .05), accounting for an additional 5-20% of the variance, with greater amyloid deposition being associated with lower practice effects. *Conclusion:* Although baseline cognition provides valuable information about amyloid burden, short-term practice effects incrementally adds to this association. Both baseline cognition and practice effects should be used to enrich samples in preventative clinical trials where amyloid burden is an inclusion criterion, potentially identifying those who would be most appropriate for amyloid imaging.

P1-11 THE ALZHEIMER'S PREVENTION REGISTRY GENEMATCH PROGRAM. Trisha Walsh[1], David Gordon[1], Jason Karlawish[2], Angela Bradbury[2], Beth McCarty Wood[2], J. Scott Roberts[3], Scott Kim[4], Linda Patrick-Miller[5], Richard J. Caselli[6], Gary E. Marchant[7], Doris Zallen[8], Carolyn Langlois[1], Eric M. Reiman[1], Pierre N. Tariot[1], Jessica B. Langbaum[1] *((1) Banner Alzheimer's Institute, Phoenix, AZ; (2) University of Pennsylvania, Philadelphia, PA; (3) University of Michigan, School of Public Health, Ann Arbor, MI; (4) National Institutes of Health, Bethesda, MD; (5) University of Chicago, Chicago, IL; (6) Mayo Clinic Arizona, Scottsdale, AZ; (7) Arizona State University, Tempe, AZ; (8) Virginia Tech University, Blacksburg, VA)*

Background: The Alzheimer's Prevention Initiative (API) is a collaborative funded by the NIH, philanthropy, and industry to conduct preclinical Alzheimer's disease (AD) trials in people who, based on age and genetics, are at elevated risk of developing AD symptoms. Given that enrollment is one of the biggest obstacles faced by research studies, there is a need to establish a registry database that includes genetic information in order to more efficiently match interested individuals to studies. The API's Generation Study is currently enrolling apolipoprotein E (APOE) ε4 homozygotes age 60-75. API established a trial-independent, internet-based APOE genetic testing program, known as GeneMatch, to enrich referrals to the API Generation Study while also serving as the basis for an enduring recruitment infrastructure for the API program. GeneMatch aims to enroll tens of thousands of participants. *Methods:* GeneMatch is a trial-independent program performing APOE genotyping in individuals age 55-75 to enrich referrals to prevention studies. Participants review a brief, online education video providing an

overview of Alzheimer's disease and the APOE gene prior to electronically signing an informed consent. Participants use a buccal swab kit for collection of DNA; APOE genotyping is done by a CLIA-certified lab. Based in part on APOE genotype, participants may be contacted to complete additional online questionnaires, learning modules, surveys, or to notify them about new research studies. GeneMatch does not disclose APOE results to participants, either directly or inadvertently through referral to studies. Recruiting studies, however, may ask or invite individuals to learn their APOE results. *Results:* GeneMatch launched in November 2015; as of June 9th, 2016, 2,870 people have enrolled. 4.5% of participants are APOE ε4/ε4, 29.9% APOE ε3/ε4, 52.8% APOE ε3/ε3, 9.5% APOE ε2/ε3, and 0.4% APOE ε2/ε2. Participants have a mean age of 64 years old, 70% are female, and 68% report having a family history of Alzheimer's or other dementia. To help facilitate enrollment into GeneMatch, the protocol was modified in Q2 2016 to become a multi-site program to allow partner sites to enroll individuals into GeneMatch onsite, rather than waiting to receive the buccal swab kit in the mail. The API Generation Study is the first trial to recruit from GeneMatch; discussions are underway with other studies to use GeneMatch as a recruitment tool. *Conclusion:* GeneMatch is a key element of the API, facilitating enrollment into a range of research studies, including the Generation Study, and serving as a resource to the Alzheimer's scientific community. During the initial pilot phase, several barriers to enrollment were observed and modifications to the enrollment process are being made on a rolling basis. Preliminary results and lessons learned to date from GeneMatch will be presented.

P1-12 RISK-BENEFIT PREFERENCES FOR DELAYING THE ONSET OF ALZHEIMER'S DISEASE IN HEALTHY, ASYMPTOMATIC OLDER ADULTS. Rachael L. DiSantostefano[1], Shelby D. Reed[2], Jui-Chen Yang[2], Bennett Levitan[1], Johannes Streffer[3], F. Reed Johnson[2] *((1) Janssen R&D, Titusville, NJ, USA; (2) Duke Clinical Research Institute, Duke University, Durham, NC, USA; (3) Janssen R&D, Beerse, Belgium)*

Background: Currently there are no treatments to modify the progressive cognitive impairment, memory loss, and behavioral changes associated with Alzheimer's disease (AD). However, disease-interception treatments given to asymptomatic individuals who test positive for amyloid beta deposits may delay the onset of symptoms. The early treatment initiation will result in potentially long treatment durations, and may lead to side effects years before onset of AD symptoms. *Methods:* We conducted a best-practice stated-preference study in a web-based research panel of U.S. adults aged 60-85 years to quantify their willingness to accept treatment-related risks in return for benefits of AD interception therapy that could extend periods of normal memory over their remaining life expectancy (12 years for 75-84 year olds; 12 years or 16 years for 60-74 year olds). Respondents were presented with 10 choice questions consisting of pairs of alternatives: a constant, no-treatment condition and an interception treatment. No treatment was characterized as 4 years (12-year version) or 8 years (16-year version) with normal memory, 3 years with mild cognitive impairment, and 5 years with AD. Treatment entailed varying reductions of time with mild cognitive impairment and of time with AD, with corresponding increases in time with normal memory. Description of the interception treatment also included treatment-related nausea of varying severity and varying risks of disabling stroke or of sudden death in the first year of treatment. Two analytical approaches were used to model choices as a function of preference weights for benefits and risks: random-parameters logit (RPL) and scale-adjusted latent-class analysis (LCA). *Results:* Respondents (n=1004, mean age=70) were evenly divided by gender, mostly Caucasian (92%), and well-educated (42% with ≥four-year college degree). Nearly two-thirds (64%) had a friend or family member with AD. The RPL model indicated that among the respondents presented with choice questions representing 12 years of remaining life expectancy, respondents aged 60-74 were willing to accept higher risks of disabling stroke and sudden death for more years of normal memory than respondents aged 75-85. Respondents aged 60-74 who evaluated choice questions based on 12-year life expectancy were willing to accept higher risks of disabling stroke and sudden death for a given treatment efficacy relative to respondents who evaluated choice questions based on 16-year life expectancy. For 2 more years of normal memory, the maximum acceptable risks ranged from 8% to 16% increased chance of disabling stroke or of sudden death. The LCA model identified three latent classes with distinctively different preferences for benefit-risk tradeoffs. Group 1 (42% of study sample) included respondents who generally preferred treatment to no treatment when benefits were perceived to offset the associated risks. These respondents tended to be relatively younger and were less likely to have AD caregiving experience than other groups. Group 2 (30%) included respondents who were risk-averse to the constructed treatment option and indicated strong preferences for the no-treatment option. These respondents more frequently reported no health problems and were less likely to have AD caregiving experience than other groups. Group 3 (28%) included respondents who more frequently selected treatment options with better efficacy, even if accompanied by higher risks. These respondents tended to be older and were most likely to have AD caregiving experience. *Conclusions:* Screening and initiating disease-modifying therapies for AD years prior to symptoms and diagnosis requires careful consideration of the patient's perspective on the benefits and risks. While AD presents a serious burden to patients and caregivers, nearly one-third (30%) of respondents had a strong preference for no AD interception treatment when presented with a constructed AD disease interception treatment with attendant risks. However, most respondents (70%) were willing to accept risks of serious adverse events in the first year of treatment 5-9 years before onset of AD-related cognitive symptoms in exchange for 1 – 2 years additional normal memory.

P1-13 ALZHEIMER'S DISEASE CLINICAL TRIALS: THE IMPACT OF DIGITAL TECHNOLOGIES. Amir Kalali[1], Arshya Vahabzadeh[2] *((1) Neuroscience Center of Excellence, Quintiles Inc, San Diego, CA, USA; (2) Harvard Medical School, Boston, MA, USA)*

Background: Digital technologies are beginning to impact the design and conduct of clinical trials. These include the use of real world data to design trials, digital recruitment, virtual trials, remote symptom monitoring, and new ways of administering outcome measures. *Methods:* A landscape survey was taken to establish the current use of digital technologies in Alzheimer's trials and the plans to employ them in the future. *Results:* Currently some digital technologies are already being utilized in the design and conduct of clinical trials in Alzheimer's disease. Initial data collected from clinical researchers indicate a dramatic rise in the utilization of these technologies in future trials. *Conclusion*: The use of digital technologies may improve many aspects of clinical trial methodology. The uptake of digital technologies in Alzheimer's clinical trials is only likely to increase in the future.

P1-14 UTILIZING MOBILE CLINICAL TRIAL UNIT TO ENHANCE RECRUITMENT AND RETENTION IN CLINICAL TRIALS FOR ALZHEIMER'S DISEASE. Jill Smith, Amanda Smith, Dave Morgan *(Byrd Alzheimer's Institute, University of South Florida, Tampa FL, USA)*

Background: Clinical trials for Alzheimer's disease presently involve long enrolment periods (up to two years from enrolling first patient to enrolling last patient), and long treatment durations to see effects (1.5-2 years in people with mild dementia; up to 5 years in prevention trials). These long durations delay the availability of treatments for the general patient population and reduce the available period of sales exclusivity for therapeutics. Moreover, during these long trials, participant retention can be impacted by problems in transportation to the clinical trial sites. Patients may travel an hour or more to access the nearest clinical trial locations in Florida. Florida has a large number of senior residential communities. While some of these communities are conveniently located near clinical trial sites, others are not. Florida also has an excellent series of state-supported Memory Disorders Clinics (MDCs) through the Alzheimer's Disease Initiative. Although these clinics care for 10,000 memory-impaired cases annually, many do not have the resources or expertise to offer their patients the opportunity to participate in clinical research. *Methods:* We conducted a workshop December 2014 near Orlando FL, USA. The workshop included experts on the conduct of Alzheimer's disease clinical trials, representatives of the MDCs, representatives of the agencies supervising the clinical trials (CRO's, ADCS), the Alzheimer's Association and individuals with experience operating mobile clinical research units. During the workshop, we identified possible concerns and barriers to successfully implementing this mobile unit idea in regards to space, noise, privacy, and security. The current design addresses all issues identified and modifications to the unit have been made to ensure optimal operational capability. *Results:* Our facility has acquired funding from the State of Florida in July 2015. Design plans began in September 2015 with initiation of manufacturing the unit in January 2016. The final "Memory Research Suite" unit was delivered in May 2016. The current unit has the complete capacity to conduct clinical trial visits. We estimate ability to conduct 5-8 study visits daily with a team of study physician, study nurse, and two clinical raters. The unit will visit approximately 2 sites per week on a rotating schedule. This mobile clinical trial unit offers potential benefits to both pharmaceutical sponsors and community dwelling Alzheimer's patients including: A) increasing the availability of Alzheimer's clinical research, B) taking advantage of the clinical diagnosis provided by MDCs for recruitment, and C) increasing the number of clinical trial participants evaluated by the same individuals. The current FACT mobile unit model includes: reception, exam room, two consultation/testing rooms, and a phlebotomy suite. It is approximately 50 feet x 8 feet. We estimate the capacity to conduct 5-8 study visits a day with a team of a study physician, study coordinator/research nurse, and two clinical raters for cognitive and global assessments. The unit will be scheduled at approximately 2 sites per week on a rotating schedule to return for study visits per the protocol schedule. This mobile unit will include a number of features to ensure quality and security of clinical research supplies and data including secure storage for study medication, study supplies, and source documents. It will also be equipped with phone/fax/internet for study communications. *Conclusion:* The proposed mobile unit can provide multi-center recruitment and enrollment which would be the equivalent of the produced activity in a minimum of 5 clinical research centers. It also offers pharmaceutical sponsors the benefit of having single research site for monitoring, contracts/budget/ payments, and single group of qualified raters and research staff to reduce variability of research data and outcome measures collected. The mobile unit offers the benefit of reduced travel to potential participants and clinical research opportunities that otherwise may not be available to them. We project the enrollment capacity on this mobile unit for a clinical trial to be 60-80 participants per trial. We expect that sites will be located within 90 minutes of the Institute. This includes Sarasota and Orlando areas (two sites with MDCs lacking research activity). St. Petersburg is also within range of the Institute and has a high population of older adults with a concentration of African Americans in South St Pete as well as Orlando, FL which offers a high concentration of Hispanic Americans. Outreach efforts have already begun to communities in the Villages and Sun City Center. Clinical trial activity aboard the mobile unit is schedule to begin August 2016.

P1-15 THE CHALLENGE OF EFFECTIVE MANAGEMENT FOR AN ACADEMIC INVESTIGATOR-INITIATED INTERNATIONAL MULTI-SITE CLINICAL RESEARCH IN JAPAN. Hisako Fujii[1], Hiroyuki Shimada[1], Mikio Shoji[2], Takeshi Ikeuchi[3], Kazushi Suzuki[4], Michio Senda[5], Kenji Ishii[6], Hiroshi Matsuda[7], Atsushi Iwata[4], Ryoko Ihara[4,8], John Morris[8], Randall Bateman[8], Yuichi Kato[1], Hiroshi Mori[1] and The DIAN Study Group *((1) Osaka City University Graduate School of Medicine, Osaka, Japan; (2) Hirosaki University Graduate School of Medicine, Aomori, Japan; (3) Brain Research Institute, Niigata University, Niigata, Japan; (4) Graduate School of Medicine, University of Tokyo, Tokyo, Japan; (5) Institute of Biomedical Research and Innovation, Hyogo, Japan; (6) Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan; (7) National Center of Neurology and Psychiatry, Tokyo, Japan; (8) Knight Alzheimer Disease Research Center, Washington University School of Medicine, MO, USA)*

Background: Alzheimer's disease (AD) is the most common cause of dementia. Several clinical studies of AD patients have been conducted globally in multiple countries. The DIAN (Dominantly Inherited Alzheimer Network) Observational Study is coordinated by Washington University (WashU) in St. Louis, Missouri as the coordinating center and also is one of the performing sites. The purpose of the DIAN study is to maintain the established international ADAD registry, to determine the order and rate of longitudinal changes in dominantly inherited AD and to utilize the DIAN data and biospecimen to support new clinical studies, including future drug trials. Researchers in the dementia field in Japan volunteered to join the DIAN study under the cooperative collaboration with WashU, and subsequently the researchers initiated trial implementation in an academic environment. The requirements for implementing interventional clinical trials and observational clinical research is different in Japan. There are two different regulations for clinical studies, Good Clinical Practice "GCP" for clinical trials for NDA, and the other is "Ethical Guidelines for Medical and Health Research Involving Human Subjects" for other clinical research. The DIAN observational study is classified into latter case, which has fewer regulatory requirements. In Japan, it is much more difficult to obtain the corporation of coordinators or any supporting personnel for clinical research for non-NDA research. The DIAN-Japan researchers originally started only with themselves for central organization. The DIAN-Japan study is the first investigator-initiated international clinical research in dementia field in Japan. Because of fewer regulatory requirements, operational implementation of a uniform and consistent protocol is provided by the global DIAN observational study in collaboration with the DIAN-Japan. *Methods:* At the beginning of participation of DIAN-Japan team, researchers including the DIAN-Japan project director visited WashU to learn DIAN observational study in detail. Those researchers established

several central cores for organization development as same as with the US organization, and started documentation work. After about one year, a supporting personnel participated to DIAN-Japan team in order to contact and work directly with WashU as driving force. The DIAN-Japan team better understood the global DIAN protocol from WashU, and was able to closely work with the DIAN coordinating center at WashU. The supporting personnel, including project managers, study coordinators and others have a key role of project management. The DIAN-Japan academic group approached the incorporation of the study by determining which task and documents are required from the DIAN Coordinating Center at WashU by communicating mostly by email, to share all information with DIAN-Japan team, and to update the Coordinating Center at WashU regarding the status of DIAN-Japan and to clarify all questions that DIAN-Japan have. *Results:* The outcomes are (1) generated the protocol appendix for DIAN-Japan (2) translated Informed consent, visit packet and any other DIAN documents into Japanese, then back-translated into English for WashU review and approval, (3) discussed and developed a monitoring plan, (4) confirmed custom procedures for import study supplies and provided importation documentation, and (5) supported sites initiation by providing documentation required and scheduling teleconferences. All tasks have been done in corporation with each core leader of DIAN-Japan. One conclusion is that a project management person is essential for academic investigator-initiated international clinical research. In the case of DIAN observational research, the management has worked well for all of the performing sites to move forward smoothly. It is suggested that requirements of the project management for DIAN is (1) to be specialized project managers, (2) to be fluent in English and local languages communication skills, (3) to have knowledge and/or experience in clinical research, and (4) to have schedule and milestones management skills. Supporting the framework of investigator-initiated international clinical research in Japan should be developed similar to clinical NDA regulated trials in Japan. This framework may be generalized for other countries, regions, and researchers to be involved in global clinical research, including DIAN, and would have the added benefit of improving clinical research in Japan. *Conclusion:* Implementation of a project management team will facilitate and accelerate clinical studies. The DIAN observational study is a good case that this project management worked effectively.

P1-16 SIMAMCI: A RANDOMIZED CONTROLLED TRIAL OF SIMVASTATIN IN AMNESTIC MCI PATIENTS FOR THE PREVENTION OF CONVERSION TO ALZHEIMER´S DEMENTIA. Brigitte Haas, Arne Klostermann, Oliver Peters, Isabella Heuser *(Department of Psychiatry, Charité University Medicine Berlin, Berlin, Germany)*

Background: Epidemiological studies point to a link between the effects of statins on inflammatory processes in the brain, amyloid processing and the prevalence of dementia. Exploratory clinical trials demonstrated that treatment with statins reduces the production of different ß-amyloid species and /or act as an anti-inflammatory agent and thus may modify the course of neurodegeneration in patients, especially in the very early stages of Alzheimer's disease (AD). The SIMaMCI dementia prevention trial started in 2009 as a multicenter randomized controlled trial to test the hypothesis if daily administration of 60 mg/d simvastatin compared to placebo for at least 2 years in "statin-naïve" patients significantly reduces the progression rate to AD in patients with amnestic mild cognitive impairment (aMCI). Here we describe baseline characteristics and progression over time in patients receiving either 60 mg simvastatin or placebo daily for up to five years. *Methods:* Patients with a diagnosis of aMCI were recruited in 13 memory clinics in Germany based on CERAD (Consortium to Establish a Registry for Alzheimer`s Disease) neuropsychological test battery and CDR (Clinical dementia rating) scores. Patients had to perform 1 SD below age-, gender- and education-corrected norms in the ten-item word list learning task of the CERAD or below 1.5 SD in Wechsler Memory Scale – Logical Memory (WMS-LM). Patients who attained pathological test scores (z-score minus 2) at neuropsychological CERAD tests, which would indicate cognitive impairment beyond memory, were excluded. CDR global score had to be 0.5, reflecting normal basic activities of daily living (ADL). Other conditions that may possibly result in cognitive impairment were excluded. CSF-concentrations of Abeta1-42, Abeta1-40, h-tau and P181-tau and MRI (hippocampal atrophy) were not used as inclusion criteria, but were assessed. Diagnosis of aMCI was based solely on neuropsychological and clinical criteria. As primary efficacy endpoint the change in CDR-sum of boxes (SOB) at 24 months of treatment was chosen. Key secondary endpoints were: 1. Change in ADAS-Cog and FCSRT score; 2. Length of transgression-free interval, starting at the time of randomization, with transgression being defined as an increase of the CDR score beyond 0.5. 3. Change in ADCS-ADL score. *Results:* 220 statin-naïve, amnestic MCI patients fulfilling in- and exclusion criteria have been randomized to the SIMaMCI prevention trial. Mean age was 70.2 years (+/-6.77), gender distribution was equal (51% male), education 13.1 years (+/- 3.56). Mean MMSE at baseline was 27.14 (+/- 1.84), CDR sum-of-boxes (SOB) 1.34 (+/- 0.838), ADAS-cog score 11.44 (+/-5.56), ADL scores 57.37 (+/-9.95). Mean scores in the FCSRT were 21.17 (+/-8.94) for immediate free recall and 7.88 (+/-3.90) for delayed free recall. During the follow-up interval of up to 5 years now, 13.6% of patients transgressed to dementia (CDR score of 1). CDR-SOB changed to 1.56 (+/- 1.25) after two years and 2.30 (+/- 1.85) after 4 years. Although this change in CDR-SOB seems rather small, it is noteworthy that variance (SD) increased considerably; this was also true for all the other cognitive and functional measures. *Conclusion:* Although no un-blinding has been performed at this stage of the trial, preliminary analysis revealed a lower transgression rate than expected. However, the increasing variance of the cognitive and functional measures might indicate a separation of patients into placebo and simvastatin groups and supports our assumption that CDR-SOB might be a sensitive measure for disease progression.

P1-17 DESIGNING A CROSS-OVER RCT INVESTIGATING NABILONE AS A TREATMENT FOR AGITATION IN PATIENTS WITH MODERATE-TO-SEVERE AD. Myuri Ruthirakuhan[1,2], Nathan Herrmann[1,3,4], Celina Liu[1,2], Eleenor H Abraham[1], Paul Verhoeff[4], Alex Kiss[1], Ana C Andreazza[2], Sandra Black[1], Krista Lanctôt[1,2,3,4] *((1) Hurvitz Brain Sciences Program, Sunnybrook Research Institute, Toronto, Canada; (2) Department of Pharmacology and Toxicology, University of Toronto, Canada; (3) Department of Psychiatry, Sunnybrook Health Sciences Centre, Toronto, Canada; (4) Department of Psychiatry, University of Toronto, Canada)*

Background: While current pharmacological recommendations for the management of agitation in Alzheimer's disease (AD) call for the judicious use of antipsychotics, these medications have modest benefits and have been associated with high risk-profiles. Nabilone, a synthetic cannabinoid, has a distinct pharmacological profile which may provide a safer and more effective alternative to treat agitation, while potentially having benefits for weight and pain. Additionally, emerging evidence has shown nabilone to have neuroprotective and anti-inflammatory effects, which can reduce oxidative stress and brain cholesterol metabolism. We describe a clinical trial to investigate the safety and efficacy of nabilone in the treatment of agitation, as well as pain and weight loss, in patients with moderate-to-severe

AD. *Methods:* This will be a double-blind, cross-over randomized placebo controlled trial (RCT) comparing 6 weeks of nabilone to 6 weeks of placebo, with a 1-week washout preceding each treatment phase. Eligible patients with moderate-to-severe AD and clinically significant agitation will be randomized to receive either nabilone (.5 – 2 mg) or placebo (1:1 ratio) for 6 weeks each. The recruitment goal is to randomize 40 patients over 2 years. The primary outcome will be agitation, as measured by the Cohen-Mansfield Agitation Inventory (CMAI). The secondary outcomes will include overall behaviour, cognition and global impression. Exploratory outcomes include pain, nutritional status, safety and biomarkers of oxidative/nitrosative stress, inflammation and cholesterol metabolism. *Results:* To date, 15 participants (age = 86.6±11.3, males = 80%, standardized Mini-Mental State Examination (sMMSE) = 7.2±6.2, CMAI = 71.9±21.8, Neuropsychiatric Inventory (NPI) (total severity) = 11.9 ± 4.9, Pain in Advanced Dementia Scale (PAINAD) = 2.8 ± 1.8, Mini-Nutritional Assessment – Short form (MNA-SF) = 7.9 ± 3.0) have been randomized (18% study completers, 64.2% phase 1 completers, 35.7% phase 2 completers, 35.7% active participants, 28.6% study discontinuations due to adverse drug reactions (ADRs)). Participants were on an average of 13±5.5 concomitant medications, and 2±0.8 psychotropic medications. In total, 80% were on antidepressants, 53.5% on antipsychotics, 6.7% on benzodiazepines and 13.3% on hypnotic agents. Though the average number of ADRs experienced per participant was 0.9 (±0.9), approximately 53.3% experienced sedation during the trial. Of participants who have completed phase 1 of the study, 33.3% were reported to have clinical improvement on the Clinician's Global Impression of Chance (CGI-C) and 66.7% experienced improvement on the CMAI. *Conclusions:* Preliminary data support that we are targeting an appropriate population group given the participants' age, clinical characteristics, medication history and severity of neuropsychiatric symptoms (NPS). If positive, the findings of this study will provide rationale for the feasibility of a larger, multicentre trial. Additionally, a safe and efficacious pharmacological intervention for agitation, pain and weight loss in patients with moderate-to-severe AD could increase quality-of-life, reduce caregiver stress and avoid unnecessary institutionalization and related increases in health care costs.

P1-18 CHARACTERISTICS OF THE ALZHEIMER'S DISEASE (AD) COHORTS IN THE EUROPEAN MEDICAL INFORMATION FRAMEWORK (EMIF). Stephanie Vos[1], Angelika Wientzek[2], Preciosa Coloma[2], Myriam Alexander[2], Nadia Foskett[2], Isabelle Bos[1], Sebastiaan Engelborghs[3], Pieter Jelle Visser[4], H. Michael Arrighi[5], José L Molinuevo[6], Alberto Lleó[7], Andy Simmons[8], Gerald Novak[9], Mark Forrest Gordon[10] *((1) Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University, Alzheimer Center Limburg, Maastricht, the Netherlands; (2) Real World Data Science, F. Hoffmann-La Roche, Basel, Switzerland; (3) Reference Center for Biological Markers of Dementia (BIODEM), University of Antwerp, Antwerp, Belgium; (4) Department of Neurology, Alzheimer Center, Neuroscience Campus, VU University Medical Center, Amsterdam, the Netherlands; (5) Janssen Research & Development, South San Francisco, CA, USA; (6) ICN Hospital Clinic i Universitari, IDIBAPS, Barcelona, Spain; (7) Neurology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; (8) Kings College London, United Kingdom; (9) Janssen Pharmaceutical Research and Development, Titusville, NJ, USA; (10) Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA)*

Background: The European Medical Information Framework in Alzheimer's Disease (EMIF-AD), a project funded by the Innovative Medicine Initiative, aims to improve our understanding of the pathogenesis of Alzheimer's disease (AD) and foster the discovery and development of new biomarkers and research tools for use in clinical trials. We describe baseline demographic characteristics, medical co-morbidities, MMSE scores, and biomarkers of participants in several European cohorts within EMIF-AD. *Methods:* Data from the following multi-country cohorts were included in the analyses: DESCRIPA, AddNeuroMed, IDIBAPS, SantPau, EDAR and UAntwerp. Descriptive statistics for pre-specified relevant variables were generated using TranSMART, a data analytics tool adapted for use in EMIF for DESCRIPA, AddNeuroMed, IDIBAPS and SantPau and using STATA SE 12 for EDAR and Antwerp. *Results:* Per Table 1, the total number of subjects included was 2425 from six cohorts. DESCRIPA only had subjects with subjective cognitive impairment (SCI) or mild cognitive impairment (MCI); AddNeuroMed had cognitively normal controls (C) as well as subjects with MCI or AD; SantPau had controls, SCI or MCI subjects; UAntwerp had subjects with MCI or AD; while IDIBAPS and EDAR included controls, as well as subjects with SCI, MCI, or AD. Baseline MMSE was lowest in UAntwerp at 23 and highest in SantPau at 29. Females comprised the majority of subjects across all cohorts, except in EDAR (45%). The mean age at baseline ranged from 61.3 years old in IDIBAPS and SantPau to 75.6 years in AddNeuroMed. The average number of years of education ranged from 9.3 years in AddNeuroMed to 13.7 years in SantPau. Cardiovascular diseases comprised the majority of comorbidities, with hypertension being the most frequently reported condition (from 37% in UAntwerp to 60% in EDAR), followed by angina pectoris (ranging from 4% in UAntwerp to 13% in AddNeuroMed), myocardial infarction (from 4% in UAntwerp to 12% in EDAR), atrial fibrillation (from 4% in DESCRIPA and UAntwerp to 9% in EDAR), and heart failure (from 1% in UAntwerp and EDAR to 2% in DESCRIPA). Prevalence of type 2 diabetes at baseline ranged from 11% in DESCRIPA to 29% in EDAR while that of cerebral infarction ranged from 2% in DESCRIPA and UAntwerp to 17% in EDAR. Where information is available, use of anti-dementia drugs was reported by more than half of participants overall and as much as 96% in DESCRIPA. More than half of the participants in both DESCRIPA and UAntwerp had abnormal levels of amyloid β1-42, total tau and p-tau. The prevalence of APOE ε4 homozygotes across the cohorts ranged from 3-9%, while that of heterozygotes ranged from 30-40%. Limitations of this analysis include the unavailability of certain variables and the heterogeneity in both the enrollment criteria and the scales used to ascertain clinical parameters, which is primarily due to differences in study protocols. Moreover, the variability of comorbidities across studies is partly related to differences in inclusion criteria. New cohorts are continually being added to EMIF and corresponding information on these shall be presented in the future. *Conclusions:* Our review of summary statistics across several AD observational cohorts enhances our understanding of currently available data regarding demographics, comorbidities, cognitive scores and other clinical outcomes, and biomarker abnormalities at baseline and follow-up and permits a comparison and exploration of these characteristics between cohorts and with the extant knowledge. This work also enables researchers to leverage the EMIF AD collaboration to generate new information and support further research and development of novel therapies for patients with AD. Moreover, the description of emerging clinical outcomes and biomarkers of AD in the context of baseline demographic characteristics and medical history in several cohorts of AD patients is an important step to assess the value of these parameters in real-world situations and their potential clinical applications. *Acknowledgement:* This work has received support from the EU/EFPIA Innovative Medicines Initiative Joint Undertaking (EMIF grant n° 115372).

P1-19 WHAT DOES IT MEAN TO BE TOLD YOU HAVE "ELEVATED AMYLOID"? RESULTS FROM THE SOKRATES STUDY. Jessica Mozersky, Pamela Sankar, Kristin Harkins, Sara Hachey, Jason Karlawish *(University of Pennsylvania, Penn Memory Center / Perelman School of Medicine / Department of Medical Ethics and Health Policy, Philadelphia, PA, USA)*

Background: Recent advances in the diagnosis and treatment of AD have led to clinical trials such as the A4 Study that enroll cognitively normal adults with biomarker evidence of AD pathophysiology described as "elevated" PET amyloid. Little is known about a cognitively normal adults' understanding of this AD biomarker information. *Methods:* The Study Of Knowledge and Reactions to Amyloid TESting (SOKRATES) examines A4 subjects' experience after receiving their PET amyloid result. 80 cognitively normal adults with either "elevated" (n=50) or "not elevated" (n=30) PET amyloid participate in a baseline structured telephone interview 4-6 weeks after receiving their PET result and a follow up interview one year later. Data from the baseline interviews of 50 "elevated" PET amyloid subjects were analyzed using qualitative methods from the following questions asking about the person's PET scan result: "What was the result?", "Can you explain the result in your own words?", "What does it mean to you?", "Did it teach you anything?", and "How would you describe it to a friend?" *Results:* Three themes were identified: I) The risk of developing AD conferred by "elevated" amyloid was understood along a spectrum: definitive and in some cases diagnostic of AD; increased but not definitive; or equivocal and lacking meaning. II) When describing "elevated amyloid" individuals used expressions such as "excessive amounts," "higher levels," having "sufficient," or "just the right amount." III) Individuals wanted more information to make sense of their result, particularly how "elevated" their amyloid was, how close to the threshold for study entry they were, or they desired percentages, numbers, or a scale to help contextualize the meaning of "elevated" and how this compares to an unknown norm. *Conclusions:* Cognitively normal older adults use a variety of meanings and vocabularies to interpret and explain "elevated" amyloid. There is uncertainty about how to interpret the meaning of "elevated" beyond a categorical result that makes them eligible for study entry. These variations and the desire for further information about the meaning of "elevated" amyloid will inform the content and discussion of AD biomarker educational and trial recruitment materials.

P1-20 PHASE 2 TRIAL OF PIROMELATINE FOR MILD ALZHEIMER'S DISEASE (THE RECOGNITION TRIAL). Amnon Katz[1], Anat Frydman[1], Tali Nir[1], Lon S. Schneider[2] *((1) Neurim Pharmaceuticals (1991) Ltd, Tel-Aviv, Israel; (2) University of Southern California Keck School of Medicine, Los Angeles, CA, USA)*

Background: The main experimental approaches for Alzheimer's disease (AD) are prevention of β-amyloid (Aβ) formation (e.g. β-secretase (BACE) inhibitors and newer γ-secretase modulators (GSMs)) and facilitation of Aβ clearance (e.g. anti Aβ antibodies, Aβ vaccines, Aβ aggregation inhibitors). Recent discoveries of the glymphatic system, as a main gateway for brain Aβ clearance during sleep, and the association of poor sleep with Aβ burden and cognitive deterioration open the gate for hitherto unexplored approaches. Sleep disorders are very common among people with AD and in particular, sleep problems among APOE e4 carriers are associated with eventual AD diagnosis. APOE e4 carriers report sleep disturbance almost 7 times more frequently than non-carriers; and as many as 63% of patients with mild cognitive impairment (MCI), and 44% of patients with AD demonstrate sleep disturbance. There are positive correlations between insomnia (as indexed by reduced total sleep time, prolonged sleep onset latency, and poor sleep quality) and increased Aβ burden in hippocampal-neocortical regions within the default mode network (DMN) brain areas that are linked to early AD in demented and non-demented older adults. The presence of sleep disorders is associated with rapid cognitive decline in patients with MCI and AD. Bidirectional relations between Aβ pathology and deep sleep (NREM delta slow wave sleep) are also observed in patients with MCI and AD. In brief, deterioration in cognition from healthy controls through MCI to AD patients may be linked to deterioration in sleep, and increased amyloidosis. This association sets the ground for a new therapeutic approach for patients with AD. Piromelatine is an investigational compound acting at two receptors (melatonin and 5-HT1A receptors) that are linked to sleep regulation and neurogenesis. Piromelatine is orally available, with short half-life (3 hours) and intended to be taken in the evening before bedtime. In preclinical tests in animals piromelatine showed neuroprotective action against Aβ induced neuronal cell death and cognitive decline and promoted sleep and neurogenesis. In previous clinical trials, piromelatine showed beneficial effects on sleep maintenance in patients with insomnia. It also enhanced EEG-recorded NREM delta slow wave sleep that is relevant to glymphatic system activity and brain Aβ clearance and decreased NREM β power, a fast EEG activity that is related to the hyperarousal experienced by patients with insomnia. Both effects are relevant and may be beneficial for AD patients. *Methods:* The ReCOGNITION Trial is a multi-center, double-blinded, randomized, placebo-controlled, dose-ranging trial of piromelatine that will include 500 patients with mild AD (MMSE 21-26) who are maintained on acetylcholinesterase inhibitors. The overall goal is to determine an effective dose to advance to phase 3. Eligible patients start a 2-week, single-blinded, placebo run-in period, are then randomized to one of 3 doses of piromelatine (5, 20, or 50 mg daily) or placebo in a 1.2:1:1:1 allocation ratio, followed by 26 weeks of double blind treatment. The primary objective is to assess outcome on the global composite score of a computerized Neuropsychological Test Battery (consisting of the CogState International Shopping List Test (immediate and delayed recall), One Card Learning, Identification, Detection, and One Back Card) after 26 weeks. Key secondary outcomes include the Alzheimer's Disease Cooperative Study -Global Impression of Change (ADCS-CGIC) and ADCS-Activities of Daily Living scale adapted for MCI patients (ADCS-ADL MCI-version). Other outcomes include the ADAS-cog14, tests of executive function (i.e., Controlled Oral Word Association Test and Categorical Fluency Test), Neuropsychiatric Inventory (NPI), assessment of quality of sleep (Pittsburgh Sleep Quality Index), and of safety and tolerability. Sleep and APOE e4 genotype are not inclusion criteria but will be assessed as covariates. *Results:* Sample size was determined based on the assumption of an effect size between treatment dose and placebo of 0.35 on the primary outcome over 26 weeks, with a significance level (α) of 0.05 and power of 88%. Recruitment is ongoing and planned for 75 sites in the United States. The trial is registered in ClinicalTrials.gov (NCT02615002). *Conclusions:* Approximately half of early-stage AD patients and older APOE e4 carriers have sleep disorders and this is related as well to Aβ pathology and further cognitive impairment. Therefore, treating patients with early-stage AD aiming at improvements in sleep/wake rhythms, cognition and neurogenesis may lead to an improvement in cognitive state. Piromelatine, through its action at melatonin receptors, may improve sleep, circadian rhythms control and subsequently cognition in the patients. Through the 5-HT1A mechanism piromelatine may improve memory and mood, enhance NREM delta slow wave sleep, and reduce wakefulness. Through the combined activation of melatonergic and

5-HT1A receptors, piromelatine may act synergistically to increase neurogenesis and attenuate disease progression.

P1-21 MULTI-MODAL BIOMARKER COMPOSITE FOR DISEASE PROGRESSION IN AD PREVENTION TRIALS. John C.S. Breitner[1], Jeannie M. Leoutsakos[2], Marilyn Albert[3], PREVENT-AD Research Group[4], BIOCARD Research Group[3,5] *((1) Department of Psychiatry, McGill University, Montreal, QC, Canada; (2) Department of Psychiatry, Johns Hopkins School of Medicine, Baltimore, MD, USA; (3) Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD, USA; (4) Douglas Hospital Research Centre, Montreal, QC, Canada; (5) Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA)*

Background: Prevention of AD symptoms requires intervention in the preclinical phase of the disease. Thus, there is growing interest in clinical trials among asymptomatic individuals at risk. Several cognitive composites have been developed for use as endpoints in such studies, e.g., trials now being conducted in autosomal dominant AD or in older individuals who have amyloid positive in PET scans. Beyond cognition, however, there is substantial evidence that pre-symptomatic disease provokes changes in multiple marker systems in CSF (e.g., Aβ or tau levels), amyloid PET, structural or functional MRI modalities, and possibly neuro-sensory functions such as olfactory identification or central auditory processing. We reasoned that a combination of these markers could be a useful outcome measure in trials among persons who are in the preclinical phase of AD. *Methods:* Over five years we have enrolled >400 asymptomatic persons in 'PREVENT-AD', a longitudinal multi-modal cognitive and biomarker study of sporadic AD pathogenesis. Participants have a parental history of AD or multiple affected first-degree relatives, conferring a ~3-fold increased risk of later symptoms. Of these PREVENT-AD subjects, 217 were enrolled in INTREPAD, a nested multi-modal neuro-cognitive and biomarker-endpoint trial of low-dose naproxen sodium. Slightly over half of the latter agreed to serial donation of CSF, and we have now completed >350 LPs. We are presently analyzing longitudinal observations from remaining, non-trial PREVENT-AD participants alongside baseline cross-sectional data from the INTREPAD trial. We are using these data to construct a multi-modal marker composite Alzheimer Progression Score (APS) using Item-Response Theory latent variable modeling. To evaluate the validity of this approach we applied it to longitudinal observational data collected in the BIOCARD study. We propose shortly to use APS trajectory along with cognitive decline as dual primary endpoints for INTREPAD. *Results:* We interrogated attributes of the APS approach in several ways: 1) We examined scores on an APS constructed from the first four years of data (0, 2, and 4 yrs of follow-up) from the BIOCARD study of 349 asymptomatic persons (75% with first-degree family history of AD). We compared scores from 77 persons who "converted" over the following 17 years to MCI or AD vs. others. Although all BIOCARD participants were cognitively "normal" when enrolled, "converters" had substantially higher baseline scores (z-score difference 0.74, SE 0.09; P<0.001). 2) Over the first four years of BIOCARD, the APS slope of "converters" was also significantly steeper (0.06 standardized units / yr; p = 0.006). 3) In survival analyses, the hazard ratio with 1 SD in baseline APS was 5.76 (SE 1.09, p<0.001). ROC analyses showed a corresponding AUC of 0.80 at 10 years and 0.74 at 17 years. 4) The predictive capacity of the APS was markedly lower when CSF markers were excluded. In PREVENT-AD, an APS constructed in the non-trial cohort showed temporal measurement invariance over three years (baseline model parameters being well suited to analysis of follow-up examinations). As well, APS parameters estimated from baseline non-trial PREVENT-AD data applied well to baseline INTREPAD data, yielding correlation in the resulting scores (vs. those derived using parameters estimated from baseline trial data themselves) of r = 0.97. We continue to add new variables to the PREVENT-AD APS to achieve a more powerful endpoint analytic tool for INTREPAD. *Conclusions:* The APS approach appears to provide a valuable composite indicator of progression in preclinical AD for prevention trials. Longitudinal data from BIOCARD suggest its construct validity, and give some indication of the expected slope of scores over time in persons who will subsequently develop dementia symptoms. Further validation of the method will be important to verify its utility. Additional data, possibly using other biomarkers, will provide evidence for which combination of measures is optimal as an outcome measure for future prevention trials.

P1-22 CHARACTERIZATION OF THE SCREENING POPULATION IN THE TOMMORROW STUDY. Ferenc Martenyi[1], Kathleen A. Welsh-Bohmer[2], Carl Chiang[3], Brenda L. Plassman[2], Patrick Harrigan[1], Janet O'Neil[1], Grant Runyan[1], Meredith Culp[1], Ryan Walter[1], Michael W. Lutz[2], Eric Lai[1], Ann M. Saunders[2], Stephen Haneline[3], David Yarnall[3], Deborah Yarbrough[1], Craig Metz[3], Daniel K. Burns[3], Allen D. Roses[3] for the TOMMORROW Study Investigators *((1) Takeda Development Center Americas, Inc., Deerfield, IL, USA; (2) Duke University Bryan ADRC, Durham, NC, USA; (3) Zinfandel Pharmaceuticals, Inc., Durham, NC, USA)*

Background: The TOMMORROW study is a global, Phase 3, multicenter, double-blind, randomized, placebo-controlled clinical trial to simultaneously: (1) qualify a genetic biomarker risk algorithm for assigning 5-year risk for developing Mild Cognitive Impairment due to Alzheimer's disease (MCI-AD), and (2) evaluate the efficacy of low-dose pioglitazone as a treatment to delay onset of MCI-AD in cognitively normal, high-risk individuals, as identified by the genetic risk algorithm. Enrollment began in August 2013 and completed 29 months later in December 2015 utilizing 58 global sites. *Methods:* A biomarker risk assignment algorithm (BRAA) was used to enrich the study population for cognitively normal elderly subjects with an increased risk for onset of MCI-AD during the course of the study period. The risk algorithm included the subject's age at entry along with their APOE and TOMM40'523 genotypes. Subjects determined to be high-risk were randomized equally to pioglitazone or placebo treatment groups, and all low-risk subjects were assigned to placebo treatment. The high-risk arms of the study will be compared to assess pioglitazone efficacy in delaying MCI-AD onset, and the placebo arms of the study will be used to assess the utility of the BRAA for determining near term risk of MCI-AD. To efficiently identify eligible subjects, the TOMMORROW study design included a 3-visit enrollment process with screening, baseline, and randomization visits. The screening visit included the Mini-Mental State Examination (MMSE) to confirm subjects tested as cognitively normal (defined as total score ≥25) after age and education adjustment, and if so, a blood sample was taken for genetic testing. Eligible subjects identified by the BRAA proceeded to the baseline visit to review additional inclusion/exclusion criteria, confirm project partner participation, and assess medical conditions. Subjects who successfully passed baseline testing proceeded to the randomization visit for assignment. Low-risk subjects were assigned to placebo; high-risk subjects were evenly randomized to either pioglitazone 0.8 mg sustained release (SR) or placebo. *Results:* The TOMMORROW study screened a total of 24,235 subjects, of whom 4,851 subjects were assessed at baseline, resulting in the enrollment and randomization of 3,494 subjects. At

screening, 628 subjects tested as cognitively impaired based on their Mini-Mental State Examination (MMSE) scores alone and did not continue to genetic testing. Despite this, as the study design calls for enrollment of an approximately 8:1 ratio of high-risk to low-risk subjects, the primary cause of dropout from screening to baseline was a large number of screened subjects being classified as low-risk by the BRAA. The second most common reason for screen failure was failing the inclusion/exclusion criteria (including MMSE). The most common reason for baseline failure was not satisfying the cognitive normality requirement following more rigorous testing. MMSE data, genetic findings, and demographic characterization of this elderly, self-reported cognitively normal screening cohort will be presented. *Conclusion:* The TOMMORROW study represents the largest ongoing clinical investigation of a treatment to delay the onset of MCI-AD in a cognitively normal elderly population. The experience of screening, enrolling, and characterizing the individuals who volunteer to participate in AD primary prevention-type trials can inform subsequent efforts to build study-ready cohorts, and aid recruitment for future studies in this earliest phase of the AD disease process.

P1-23 DESIGN OF PILOT STUDIES TO INFORM THE CONSTRUCTION OF COMPOSITE OUTCOME MEASURES. Steven D. Edland[1,2], M. Colin Ard[1], Weiwei Li[3], Lingjing Jiang[2] *((1) Department of Neurosciences, University of California San Diego, La Jolla, CA, USA; (2) Division of Biostatistics, Department of Family Medicine and Public Health, University of California San Diego, La Jolla, CA, USA; (3) Department of Mathematics, University of California San Diego, La Jolla, CA, USA)*

Background: Many composite scales have recently been proposed as outcome measures for clinical trials. For example, the Prodromal Alzheimer's Cognitive Composite (PACC) is the sum of z-score normed component measures assessing episodic memory, timed executive function, and global cognition. Alternative methods of calculating composite total scores using the weighted sum of the component measures that maximize signal-to-noise of the total score have been proposed. Optimal weights can be estimated from pilot data, but it is an open question how large a pilot trial is required to calculate reliably optimal weights. *Methods:* We used large-scale computer simulations to investigate the question of how large a pilot study sample is required to inform the calculation of optimal weights. The simulations were informed by the pattern of decline observed in cognitively normal subjects enrolled in the Alzheimer's Disease Cooperative Study (ADCS) Prevention Instrument cohort study, restricting to n=95 subjects age 75 and over with an ApoE E4 risk allele and therefore likely to have an underlying Alzheimer neurodegenerative process. *Results:* In the context of secondary prevention trials in Alzheimer's disease (AD), and using the components of the PACC, we found that pilot studies as small as 100 are sufficient to meaningfully inform weighting parameters. Regardless of the pilot study sample size used to inform weights, the optimally weighted PACC consistently outperformed the standard PACC in terms of statistical power to detect treatment effects in a clinical trial. Pilot studies of size 300 produced weights that achieved near-optimal statistical power, and reduced required sample size relative to the standard PACC by more than half. *Conclusions:* These simulations suggest that modestly sized pilot studies are sufficient to inform the construction of composite outcome measures. Although these findings apply only to the PACC in the context of prodromal AD, the observation that weights only have to approximate the optimal weights to achieve near-optimal performance should generalize. Performing a pilot study to inform the weighting of proposed composite outcome measures is highly cost-effective. The net effect of more efficient outcome measures is that smaller trials will be required to test novel treatments. Pilot registry trials to inform weighting parameters, as described here, are one method of achieving this goal. Alternatively, second generation trials can use prior clinical trial data to inform weighting, so that greater efficiency can be achieved as we move forward.

Theme : Clinical Trials Imaging

P1-24 MICROSTRUCTURAL DAMAGE OF THE WHITE MATTER IN THE FRONTAL ASLANT TRACT ACCOUNTS FOR VISUO-SPATIAL PERFORMANCES IN PATIENTS WITH ALZHEIMER'S DISEASE. Laura Serra[1], Giulia Bechi Gabrielli[1], Elisa Tuzzi[1], Barbara Spanò[1], Camillo Marra[2], Carlo Caltagirone[3,4], Mara Cercignani[5], Marco Bozzali[1] *((1) Neuroimaging Laboratory, IRCCS Santa Lucia Foundation, Rome; (2) Institute of Neurology, Catholic University, Rome; (3) Department of Clinical and Behavioural Neurology, IRCCS Santa Lucia Foundation, Rome; (4) Department of Neuroscience, University of Rome 'Tor Vergata', Rome; (5) Brighton & Sussex Medical School, Clinical Imaging Sciences Centre, University of Sussex, Brighton, United Kingdom)*

Background: Constructional praxis relies on a network consisting of inferior parietal and pre-motor regions, and it is thought to require transformation of spatio-temporal representation (parietal regions) into movement sequences (pre-motor regions) [1]. The Frontal Aslant Tract (FAT) has been recently described as a bundle connecting the Broca's area to the Supplementay Motor Area (SMA) and to the pre-SMA in both hemispheres [2; 3]. The functional properties of this connection are currently unknown especially in dementia, such as Alzheimer's disease (AD). We aimed to explore the microstructural integrity of the FAT in patients with AD and its potential relationship with cognitive functioning. Methods: 23 patients with AD, and 25 healthy subjects (HS) were enrolled All subjects underwent cognitive evaluation and MRI examination at 3T. MRI including diffusion sequences used for probabilistic tractography analysis. We reconstructed individual FAT bilaterally and assessed their microstructural integrity by both mean fractional anisotropy (FA) value and by voxel-by-voxel analysis using SPM-8. Then, we used mean FA values for correlations with cognitive measures. Results: there were no differences in demographic variables between the three groups. Both analysis on mean FA and voxel-wise analyses revealed that patients with AD showed decreased FA in the bilateral FAT respect to HS. In addition, we showed in AD patients positive association between bilateral FAT and tests assessing constructional praxis and visuo-spatial logical reasoning. Discussion: the present results reveled a bilateral damage of FAT in patients with AD. Moreover, we found association between damage to the FAT and constructive abilities, and it fits well with the knowledge of a functional involvement of SMA and pre-SMA in the movement sequences required to successfully execute the constructive praxis task. We speculate that praxis tasks can be mediated by integrity of the FAT in patients with AD. Conclusions: The FAT is an associative bundle critically involved the network sub serving the constructional praxis in patients with AD. References: 1) Serra L, Fadda L, Perri R, Spanò B, Marra C, Castelli D, Torso M, Makovac E, Cercignani M, Caltagirone C, Bozzali M. Constructional apraxia as a distinctive cognitive and structural brain feature of pre-senile Alzheimer's disease. J Alzheimers Dis. 2014;38(2):391-402. 2) Catani M, Mesulam MM, Jakobsen E, Malik F, Martersteck A, Wieneke C, Thompson CK, Thiebaut de Schotten M, Dell'Acqua F, Weintraub S, Rogalski E.A novel frontal pathway underlies verbal fluency in primary progressive aphasia. Brain. 2013 Aug;136(Pt 8):2619-28. 3) Martino J, De Lucas

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P1-25 EFFECTS OF PARTIAL VOLUME DIFFERENCES BETWEEN TIME POINTS ON LONGITUDINAL AMYLOID SUVR MEASUREMENTS. Gregory Klein[1], Joël Schaerer[2], Florent Roche[2], Mehul Sampat[1], Gennan Chen[1], Joyce Suhy[1] *((1) Bioclinica, Newark, CA, USA; (2) Bioclinica, Lyon, France)*

Introduction: Longitudinal analyses of amyloid PET data using a standard uptake value ratio (SUVR) and volume of interest (VOI) approach implicitely assume that the VOIs sample comparable regions at all imaging time points. It is known, however, that considerable volumetric changes can take place during a one-two year interval between PET imaging time points in a clinical trial. Annual cerebral atrophy rates of 2.37% have been reported for the Alzheimer's disease (AD) group, and 0.41% for a control group1. These volumetric changes can not only change the size and shape of each region, but also can change the relative partial volume effects of white matter and CSF areas adjacent to grey matter within a sampling region. A native space approach using VOIs separately defined from time-matched MRI data can help to minimize differences in VOI shape and size, however, a partial volume approach is needed to address differences in relative partial volume contributions. This work investigates the extent of change in partial volume between time points in subjects with AD, Mild Cognitive Impairment (MCI) and Normal Controls (NC). *Methods:* Freesurfer (X-sectional / version 5.3) was used to obtain VOI segmentations on T1 MRI data from 270 Alzheimer's Disease Neuroimaging Initiative (ADNI) subjects (23 with probable AD, 145 with MCI and 102 NC) at two time points approximately 24 months apart. Following the partial volume correction (PVC) approach of Müeller-Gärtner2, Freesurfer segmentations at baseline (TP1) and follow-up (TP2) were used to produce two three-tissue segmentations of grey matter(GM), white matter(WM) and CSF for each subject. Segmentations were smoothed to the same resolution of the PET and the partial volume contributions of each tissue type were computed for each Freesurfer region. Partial volume components of the composite and regional cortical areas were computed, and also for the reference regions to separately analyse longitudinal behaviour of the numerator and denominator components of the SUVR. Florbetapir PET data at matching time points were registered to the MRI data in T1 native space, and composite SUVR's were computed using a grouping of four larger cortical regions, equally weighted as described by Landau3. Twelve potential SUVR reference regions were evaluated including whole cerebellum, cerebellar grey (CG), corpus callosum (CC) and subcortical white matter (SWM). SUVRs were computed with and without PVC. *Results:* Cortical VOIs used in the composite SUVR had 45.1% GM, 25.4% WM, 29.5% CSF components at TP1 and 44.8% GM, 25.1% WM, 30.1% at TP2 for the 270 subject population. The AD group had a slightly smaller grey matter component (higher CSF component) and changed more between time points: 42.4% GM, 25.4% WM, 32.2% CSF at TP1 and 41.7% GM, 25.1 WM, 33.2% at TP2, representing an increase of the CSF component by 3.9%. Regional CSF partial volume increases were 2.4%, 5.2%, 3.1% and 5.0% in the frontal, cingulate, parietal and temporal regions respectively. Generally, these cortical changes would tend to drive the numerator of a SUVR lower, thus under-estimating increase of amyloid burden in an analysis not accounting for partial volume effects. Perhaps more interesting are changes in reference regions, and in particular white matter references. Relative changes between time points to partial volume contributions in the cerebellar and brainstem reference regions were fairly small. However, changes in the corpus collosum and subcortical white matter regions were considerably higher. The CC region CSF contribution increased 7.1% in the AD group between time points, and the WM contribution decreased 3.5%. Both would tend to drive the denominator of the SUVR lower, and therefore the SUVR higher, and thus could potentially overestimate amyloid burden increases. A similar trend, but at a lower level, was seen for the subcortical white matter reference. *Conclusions:* Results indicate that changing partial volume effects in the cortical target regions and reference regions used in a VOI-based SUVR analysis can bias longitudinal results. Care must be taken in interpreting SUVR changes that may be influenced by extent of volumetric changes, particularly in the AD subject group. References: 1. Fox et al. Arch Neurol 2000;57:339-344. 2. Müeller-Gärtner et al. J Cereb Blood Flow 1992, 12:571-583. 3. Landau et al. J Nucl Med 2013; 54:1–8.

P1-26 IMPAIRMENT AND DECLINE ON THE COGSTATE BRIEF BATTERY IS RELATED TO AMYLOID AND HIPPOCAMPAL VOLUME IN VERY MILD DEMENTIA. Paul Maruff[1,2], Yen Ying Lim[2], Peter Snyder[3], Victor Villemagne[2,4], Chris Rowe[2,4], Colin Masters[2] *((1) Cogstate Ltd New Haven, CT, USA; (2) Florey Institute for Neuroscience, Melbourne, Australia; (3) Lifespan Hospital, RI, USA; (4) Austin Health. Heidelberg, Australia)*

Background: In a group of older adults with very mild dementia, we aimed to characterize the nature and magnitude of cognitive decline as measured by the Cogstate Brief Battery (CBB), in relation to Aβ levels and hippocampal volume. *Methods:* Participants were characterized according to their status on the Clinical Dementia Rating (CDR) scale. A total of 308 individuals who were CDR 0 and had low cerebral Aβ levels (Aβ-), 32 individuals who were Aβ- and CDR 0.5, and 43 individuals who were Aβ+ and CDR 0.5 were included in this study. Participants completed the CBB at baseline, 18 months and 36 months. *Results:* Linear mixed model analyses indicated that relative to the Aβ- CDR 0 group, the Aβ+ CDR 0.5 group showed increased rates of memory decline and hippocampal volume loss. However, compared to the Aβ- CDR 0 group, the Aβ- CDR 0.5 group showed no changes in cognitive function or hippocampal volume over 36-months. n*Conclusion:* The results of this study confirm that in individuals with very mild dementia, who also have biomarker confirmation of Aβ+, changes in cognitive function manifest primarily as deterioration in memory processing, and this is associated with hippocampal volume loss. Conversely, the absence of any cognitive decline or loss in hippocampal volume in individuals with very mild dementia but who are Aβ- suggest that some other non-AD disease process may underlie any static impairment in cognitive function.

P1-27 TWO-POINT CORRELATION ANALYSIS OF ABNORMAL WHITE MATTER CHANGES AND THEIR ASSOCIATION TO AMYLOID PET RETENTION. Sepideh Shokouhi[1], Hyeyon Kim[1], Harry E. Gwirtsman[2] *((1) Department of Radiology and Radiological Sciences, Vanderbilt University Medical Center, Nashville, TN; (2) Department of Psychiatry, Vanderbilt University Medical Center, Nashville, TN)*

Background: Previous Aβ-PET imaging studies have detected elevated tracer uptake due to the contribution of cerebral amyloid angiopathy (CAA) in addition to the parenchymal Aβ. While Aβ-PET alone cannot differentiate between these 2 pathologies, several observations implicate CAA as the probable cause of abnormal changes in white matter that can be detected on MRI images. Therefore, there is a need for MRI image analysis methods that can detect subtle changes in T2 intensity structure to potentially correlate the gradual formation of white matter hyperintensity lesions to changes in regional or global amyloid PET uptake. *Method:* In

this study we are evaluating a new method for the quantification of T2-MRI hyperintensity progression. This technique is based on weighted two-point correlation function (wS2), which is a statistical descriptor that performs a texture analysis to detect the increased heterogeneity in T2 images due to the increase in size and number of hyperintensity lesions. We evaluated this method on 31 subjects from Alzheimer's Disease Neuroimaging Initiative (ADNI) database with longitudinal T2-MRI scans who also had longitudinal Aβ-PET scans with both [11C]PiB and [18F]Florbetapir. *Results:* With the wS2 analysis, we were able to quantify gradual changes in white matter structure. In some subjects\regions, these changes also correlated with higher progression in Aβ-PET retention as verified with their [11C]PiB and [18F]Florbetapir images. *Conclusion:* The two-point correlation function is a texture analysis method that evaluates the association between voxel values at different distances. Our preliminary study shows that this method could be used as a quantitative metric to assess subtle changes in white matter structure

P1-28 THE RELATIONSHIP BETWEEN VOLUMETRIC MRI MEASURES, APOE4 AND MMSE STATUS AT BASELINE IN SUBJECTS WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE PARTICIPATING IN THE PHASE 2/3 EPOCH TRIAL OF VERUBECESTAT (MK-8931). Cyrille Sur[1], Yi Mo[1], James Kost[1], Tiffini Voss[1], Joyce Suhy[2], Luc Bracoud[2], Joonmi Oh[2], David Michelson[1], Michael Egan[1] *((1) Merck & Co., Inc., Kenilworth, NJ, USA; (2) Bioclinica, Newark, CA, USA)*

Background: Volumetric MRI is a well suited biomarker to monitor neurodegenerative processes in Alzheimer's Disease (AD) patients. Verubecestat (MK-8931), a potent inhibitor of beta secretase (BACE), is being assessed in a Phase 2/3 trial of mild-to-moderate AD subjects (EPOCH study - NCT01739348). We present analyses of baseline volumetric MR images from an initial partial sample of study participants. The relationship between brain anatomical parameters, cognitive status and APOE4 status of the patients is also examined. *Methods:* Participants between ≥ 55 and ≤ 85 years of age with probable AD and an MMSE score ≥ 15 and ≤ 26 were enrolled. Most subjects received an MRI scan at baseline. Using a standardized imaging protocol 3D T1-weighted MRI sequences were collected on various 1.5T and 3T MRI scanners from more than 200 centers worldwide. Images were centrally collected and quality controlled, and then segmented using Freeesurfer at Bioclinica. *Results:* The mean (S.D.) of the whole brain, hippocampus and ventricles volume were 975.75 (101.78) mL (n=516), 5.86 (1.10) mL (n=518) and 50.56 (22.89) mL (n=517), respectively. The left hippocampus volume (LHV) was 0.117 mL (95% CI: 0.088-0.145) smaller than the right hippocampus volume (RHV) with volumes of 2.87 (0.56) mL (n=518) and 2.99 (0.59) mL (n=518), respectively. Mild AD subjects (MMSE ≥ 21) had a larger brain volume (95% CI:16.392-51.390) and LHV (95% CI:0.012-0.206) than moderate AD patients (MMSE ≤ 20). In contrast significant differences were not observed between mild and moderate AD subjects in the RHV and total hippocampus volume or ventricular volume. Whole brain and ventricles volume were not impacted by APOE4 status of subjects whereas a difference was found for LHV (95% CI:0.074-0.278), RHV (95% CI:0.064-0.283) and total (95% CI:0.148-0.553) hippocampus volume with APOE4-carriers presenting with more atrophied structures. *Conclusions:* These data from a partial sample of EPOCH trial participants showed differences in whole brain atrophy stage between mild and moderate AD patients and a higher hippocampal atrophy in APOE4-carriers They also suggest that the left hippocampus is more vulnerable to atrophy than the right hippocampus. A comparison of our study brain parameters to ADNI data will also be presented

P1-29 INITIAL PH 1 TRIAL THAT WILL EVALUATE THE USE OF WHOLE BRAIN IRRADIATION IN THE TREATMENT OF PATIENTS WITH ALZHEIMER'S DEMENTIA (AD). James Fontanesi[1], Prakash Chinnaiyan[1], Daniel Michael[1,3], Alvaro Martinez[2], Michael Madden[1], George Wilson[1] Brian Marples[1] *((1) William Beaumont Health Systems, Royal Oak, Michigan; (2) 21st Century Oncology, Farmington Hills, Michigan; (3) Michigan Head & Spine Institute, PC, Royal Oak, MI)*

Background: External beam irradiation has a proven to be an effective treatment of non CNS amyloidosis with a published history of long term control with resolution of clinical symptoms. Based on this information and other information that was obtained regarding use of prophylactic cranial irradiation in children with Downs's Syndrome and diagnosed with ALL, our group initiated a series of studies using a genetically altered mouse model. We have reported in the past on our single fraction and fractionated hem CNS data along with our whole brain CNS irradiation and the neurocognitive testing (NCT) results. Based on these results we initiated a process to develop a Ph 1 clinical trial to assess the safety and toxicity associated with whole brain irradiation in patients with AD. We report on the opening of that trial. *Methods:* After written development of the Ph 1 protocol we contacted the FDA to assess the need for an IDE related to use of a linear accelerator in treatment. (IDE # G140132/A0001) In conjunction with the FDA the eligibility criteria was established and included a MMSE score of 10-20 in addition to use of ADAS-Cog evaluation and Rosen Modified Hachinski Ischemic score < 4. QOL instruments be used are the QOL-AD and QUALID test. There are two dose arms (15 patients) both using standard whole brain irradiation techniques: 1) 5 x 200 cGy with patients being followed for 1 year prior to the initiation of arm 2; 2) 10 x 200 cGy. These dose arms were selected based on peer reviewed published clinical non CNS data and our own fractionated whole brain irradiation and the resultant NCT testing. Toxicity will be assessed using CTCAE v 4.0. Stopping rules based on toxicity criteria include any patient death attributed to treatment, any grade IV adverse event, more than 3/15 developing Gr III toxicity. Toxicity will be monitored by an independent safety monitoring board not affiliated with the trial. PET imaging, utilizing Amyvid (FLOEBETA PIR F-18) scans are also included in the evaluation. Primary endpoints are safety / toxicity. *Results*: After completion on the written protocol and with confirmation from the FDA regarding not only the protocol but also issuance of an IDE, the protocol was submitted to the appropriate IRB's for approval. This has been obtained and entry is now open for patient accrual. *Conclusion:* This is the first trial of its kind, using external beam irradiation in the treatment of AD. It is based on previously reported treatment of non CNS amyloidosis and our animal date related to single and fractionated CNS data from our animal studies. We will continue to update the clinical trial information as the data becomes available and welcome patient contact.

P1-30 UNCOVERING THE RELATIONSHIP BETWEEN B-AMYLOID AND GLUCOSE METABOLISM. Felix Carbonell[1], Donald G. McLaren[1], Alex P. Zijdenbos[1], Barry J. Bedell[1,2] *((1) Biospective Inc., Montreal, Quebec, Canada; (2) McGill University, Montreal, Quebec, Canada)*

Background: Recent PET studies have explored the relationship between β-amyloid load, glucose metabolism, and apolipoprotein E ε4 (APOE ε4) genotype. It has previously been reported that APOE ε4, and not aggregated fibrillar β-amyloid, contributes to glucose hypometabolism in Alzheimer's disease (AD) pathology. However, we recently found that aggregated fibrillar β-amyloid, when modeled

as a continuous effect, modulates both glucose metabolism and metabolic connectivity patterns across the AD spectrum, but not within individual AD diagnostic groups (e.g. normal controls, mild cognitive impairment [MCI], AD) (Carbonell, 2016). There are two possible explanations for these findings: (1) no relationship exists between glucose metabolism and aggregated fibrillar β-amyloid; or (2) the utilization of the simple mean SUVR from from a composite region-of-interest (ROI) or dichotomization into low or high β-amyloid burden does not capture the underlying relationship between glucose metabolism and β-amyloid. Given the improvements in modeling β-amyloid as a continuous variable compared to a dichotomized variable, we sought to investigate more complex relationships between β-amyloid and glucose metabolism. *Methods:* In the present study, we have generated a continuous measure of β-amyloid burden based on a joint Singular Value Decomposition (SVD) of cross-correlation structure between glucose metabolism, as measured by [18F]FDG PET, and β-amyloid, as measured by [18F]florbetapir PET, from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study. The joint SVD maximizes the relationship between glucose metabolism and β-amyloid. The SVD yields a set of eigenimages and individual subject loadings (i.e. components) corresponding to both β-amyloid and glucose metabolism. The β-amyloid subject loadings for the first component represent the β-amyloid burden maximally related to metabolism. In order to identify regions where metabolism is statistically related to β-amyloid burden, we regressed β-amyloid subject loadings, a weighted measure of β-amyloid burden, against FDG in a general linear model (GLM) that included age, gender, and APOE ε4 status as covariates. Additionally, we tested the same effect using the mean SUVR from the following composite ROIs: whole cortex, a region-of-interest (ROI) in the right angular gyrus, and an ROI in the left inferior temporal gyrus. *Results:* As an illustrative example, the first SVD component accounted for 90% of the total variability explained by the cross-correlation between β-amyloid and glucose metabolism in MCI subjects. β-amyloid burden in the medial prefrontal cortex, posterior cingulate cortex, lateral inferior temporal gyrus and fusiform gyrus bilaterally were maximally related to glucose metabolism. A GLM using the subject-loadings from first SVD component as the measure of β-amyloid burden revealed a statistically significant negative relationship with glucose metabolism, particularly in the angular gyrus, lateral inferior temporal gyrus, and posterior cingulate cortex after accounting for APOE ε4, age, and gender. For comparison, a more limited set of significant regions were observed when using a whole cortex average of β-amyloid burden. These regions were generally constrained to those found in the initial analysis. Next, we explored the relationship of β-amyloid burden in two additional regions: (1) the right angular gyrus, a region which was significant in our initial GLM of glucose metabolism; and (2) the left inferior temporal gryus, a region where β-amyloid burden is related to glucose metabolism based on the SVD. The β-amyloid burden in the right angular gyrus was significantly negatively related to glucose metabolism in a small cluster within the right angular gyrus, whereas the β-amyloid burden in the left inferior temporal gyrus was significantly negatively related to glucose metabolism in the same areas as the GLM of the subject-loadings and glucose metabolism, although weaker. *Conclusions:* Multivariate, cross-correlation analyses are more powerful in detecting complex brain relationships than univariate analysis approaches. The results of this study support two key notions: (1) glucose hypometabolism is not primarily caused by β-amyloid burden in regions that accumulate amyloid earlier (e.g. posterior cingulate); and (2) spatially distributed, rather than focal, accumulation of β-amyloid leads to metabolic dysfunction in AD. Previous research in MCI subjects has suggested that the there is high covariance in the rates of atrophy in the angular gyrus, lateral inferior temporal gyrus, and posterior cingulate cortex (Carmichael, 2013). Coupling the present findings with the earlier atrophy findings suggests that metabolic impairments may underlie the atrophy seen with AD progression. Future work will expand this analysis to identify the pattern of β-amyloid maximally related to metabolic connectivity and capturing how these relationships evolve within subjects as the disease progresses. References: Carbonell, F., Zijdenbos, A.P., McLaren, D.G., Iturria-Medina, Y., Bedell, B.J. Modulation of glucose metabolism and metabolic connectivity by β-amyloid. J. Cereb. Blood Flow Metab., 2016. Carmichael, O., McLaren, D.G., Tommet, D., Mungas, D., Jones, R.N. Coevolution of brain structures in amnestic mild cognitive impairment. Neuroimage, 66: 449-56, 2013.

P1-31 ROBUSTNESS OF MRI-BASED VOLUMETRY FOR THE PREDICTION OF SHORT-TERM CONVERSION FROM MILD COGNITIVE IMPAIRMENT TO ALZHEIMER´S DEMENTIA. Oliver Peters[1], Per Suppa[2,3], Brigitte Haas[1], Ralph Buchert[3], Lothar Spies[2], Isabella Heuser[1] *((1) Department of Psychiatry, Charité, Berlin, Germany; (2) jung diagnostics GmbH, Hamburg, Germany; (3) Department of Nuclear Medicine, Charité Berlin, Germany)*

Background: Magnet resonance imaging (MRI)-based hippocampus volumetry (HV) is a clinically relevant measurement for disease staging in Alzheimer's dementia (AD). In addition, MRI-based HV appears to be useful for enriching AD trials that test the efficacy of disease modifying drugs. Problems of HV, especially in clinical routine exams, are slightly differing MRI acquisition protocols. The Alzheimer's Disease Neuroimaging Initiative (ADNI) has therefore suggested harmonization procedures of image acquisition protocols across scanner platforms. The aim of the present study was to investigate the power of MRI-based HV for the prediction of conversion from mild cognitive impairment (MCI) to AD in a large-scale multi-center study. In comparison to the ADNI study, our investigation allowed for considerably more variability of the MRI acquisition protocols between the different sites. *Methods:* MCI subjects from ADNI1 and the German Dementia Competence Network (DCN) study were included. In the ADNI cohort, MR scans were acquired with either a Siemens, Philips or GE 1.5 T MRI system using a sagittal 3-dimensional magnetization prepared rapid gradient echo (3D-MPRAGE) sequence with an approximate TR=2400 ms, minimum full TE, approximate TI=1000 ms and a flip angle of approximately 8°. Scans were collected with a 24 cm field-of-view and an acquisition matrix of 192x192x166 to yield a standard voxel size of 1.25x1.25x1.2 mm3. Images were then reconstructed to give a 256x256x166 matrix and voxel size of approximately 1x1x1.2 mm3. Images were downloaded from the ADNI repository as «unpreprocessed» (no gradwarp, B1 non-uniformity or N3 correction). In total, 134 subjects from the ADNI1 study were included: 32 MCI subjects who had converted to AD within a period of 12 months (MCI-to-AD converters) and 102 MCI subjects who had remained stable over a period of 36 months (MCI-stable subjects). In the DCN study, MR scans were acquired with a Siemens or a Philips 1.5 T MRI system at multiple participating sites with much less stringent harmonization of acquisition protocols. 106 MCI subjects from the DCN study were included: 33 MCI-to-AD converter who had converted to AD within a period of 12 months and 73 MCI-stable subjects who had remained stable over a period of 36 months. All MR scans, both from ADNI and from DCN, were converted into nifti-format using MRIConvert and subsequently were transformed into a common coordinate system. SPM12-rigid body co-registration to a whole brain template in MNI space was used for this preprocessing

step. Hippocampus segmentation was performed using the FIRST module of the FMRIBs software package. The «run_first_all» routine was applied with slight modifications as described elsewhere (Hibar et al., 2011). Total hippocampus volume (FIRST-HV) was obtained by summing the volume in the left and right hemisphere. Total intracranial volume (TIV) was estimated using the method described in (Malone et al., 2015). FIRST-HV values were adjusted for TIV and age using a bilinear regression approach. Regression coefficients were estimated by using a subset of 137 ADNI-Normal subjects who were documented as stable throughout a period of 36 months. ROC analysis was performed for the discrimination of MCI-to-AD converters and MCI-stable subjects by adjusted FIRST-HV in the ADNI sample. The Youden index was used to determine the optimal cutoff value. This cutoff value derived from the ADNI sample was then used to classify DCN MCI patients. *Results:* MR images from the DCN study showed a considerably larger variability of slice thickness: 1.39 ± 0.46 mm (range 1.0 mm to 2.4 mm) and 1.20 ± 0.00 mm for DCN and ADNI, respectively. The difference of the variance was highly significant according to Levene's test for homogeneity of variance ($p < 0.001$). The AUC of adjusted FIRST-HV for the discrimination of MCI-to-ADsubjects from MCI-stable individuals in the ADNI cohort was 0.79. The Youden cut-off (adjusted FIRST-HV = 6.24 ml) provided an accuracy of 76% (sensitivity = 72%, specificity = 77%). Using the same cut-off in the DCN sample resulted in an accuracy of 77% (sensitivity = 75%, specificity = 77%). *Conclusion:* Despite its considerably larger variability in slice thickness, the DCN cohort had similar 12-months prognostic power as the ADNI sample. This suggests that MRI-based hippocampal volumetry with FSL-FIRST is a rather robust protocol with regard to variations as they might occur in routine clinical practice. References: Hibar D, et al. (2011). Enigma Consortium First Protocol. http://enigma.loni.ucla.edu/protocols/imaging-protocols/first-protocol. Malone, I. B., et al. (2015). Accurate automatic estimation of total intracranial volume: a nuisance variable with less nuisance. NeuroImage, 104, 366–72. http://doi.org/10.1016/j.neuroimage.2014.09.034

Theme : Clinical trials: biomarkers including plasma

P1-32 A NOVEL CONFORMATIONAL, PHOSPHO-THREONINE 231 SPECIFIC ASSAY FOR CSF PROTEIN TAU.

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Background: According to the newly established clinical criteria, cerebrospinal fluid (CSF) phospho-tau is considered as one of the three core biomarkers for Alzheimer's disease (AD) diagnosis. In addition, phospho-tau may have value as a tool for target-engagement or for patient stratification in clinical trials. However, most of the clinical evidence on phospho-tau in CSF is based on phospho-threonine (Thr) 181, although many abnormally phosphorylated sites for tau have been identified in brain affected by AD, such as phospho-Thr231. Studies indicate that phosphorylation at this residue occurs even before phospho-Thr181 is present. Findings in CSF indeed suggested that phospho-Thr231 might have an improved diagnostic accuracy compared to phospho-Thr181. Furthermore, the cis-conformational state of phospho-Thr231 has recently been described as pathologically relevant, so-called cistauosis. *Methods:* We generated new tau antibodies directed towards phospho-Thr231 by using a synthetic peptide as immunogen. The novel monoclonal antibodies (mAbs) were characterized and selected based on their affinity and specificity towards phospho Thr231-tau as well as the cis-conformational state of the protein. Phospho-specificity was studied by western blot and ELISA on brain extracts and recombinant tau or synthetic peptides. Cis/trans conformational selectivity was confirmed by using other synthetic, biotinylated peptides, where proline 232 is substituted by homoproline (PiP) or alanine. The former fixes the conformation of the peptide in the cis-state, while in case of the latter, the conformation is the trans-state. To evaluate whether phosphorylation of Thr231 has added value in early clinical diagnosis, different assay set-ups involving the novel mAbs were compared side by side in clinical samples with a phospho-Thr181 ELISA, also based on novel monoclonal Abs. *Results:* Two of the selected phospho-Thr231 mAbs had an affinity comparable to or higher than PHF6 and AT180, the latter being a well-known phospho-tau specific high affinity (nM) mAb. The phospho Thr231-specificity of the two new mAbs was demonstrated by one-site ELISA on synthetic phosphorylated peptides versus the corresponding non-phosphorylated variants. Western blot analysis of extracts from AD and control brains, revealed a strong signal for AD tau compared to the weak signal in control brains. Recombinant tau protein was not detected. Interestingly, cis-selectivity was observed when the antibodies were used to capture the PiP-peptide in ELISA, while no cis-trans selectivity was observed when the peptide was coated on the plate. Finally, two sandwich ELISAs were designed based on each phospho-Thr231 mAb in combination with ADx215, a mAb targeting the N-terminal region of tau. As a proof-of-concept, 90 decoded CSF samples without clinical info were subsequently analyzed and phospho-Thr231 tau could be detected in all but 4 samples. However, total-tau levels could also not be determined in those 4 samples. A clinical study using CSF collected from patients suffering from AD in different clinical stages is ongoing. Results will be reported at CTAD. In this study, total-tau and conformational phospho-Thr231 levels will be analyzed, as well as phospho-Thr181 levels. *Conclusion:* Two novel assays have been designed that can measure cis-conformational CSF tau phosphorylated at Thr231. These assays, in parallel with the novel phospho-Thr181 assay, can now be used as tools to set up clinical studies in CSF. In general, we believe that a combination of molecular characterization of the specificity of (tau) assays and clinical studies comparing assays will further advance the use of CSF biomarkers in clinical trials.

P1-33 CT1812, A DRUG CANDIDATE FOR ALZHEIMER'S DISEASE, ACHIEVES PREDICTED THERAPEUTIC CONCENTRATIONS AFTER MULTIPLE DOSING IN HEALTHY HUMAN VOLUNTEERS.

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Background: Aβ oligomers (Aβos) can cause synaptic dysfunction and synapse loss and may be responsible for cognitive deficits observed in patients with Alzheimer's disease. Preclinical experiments identified brain-penetrant compounds capable of blocking the binding of Aβos to neurons. Using counter screens against a broad panel of

potential CNS targets, these compounds were observed to selectively bind the sigma-2/PGRMC1 receptor with high specificity. The identified compounds restored cognitive function in transgenic Thy1-hAPP Swe/Ldn mice at doses associated with greater than 80% sigma-2/ PGRMC1 receptor occupancy in the brain, but did not affect wild type littermate cognitive function. The CSF concentration of these compounds in mice at pre-clinically efficacious doses was also determined. *Methods:* A Phase 1 multiple ascending dose study in healthy human volunteers was conducted with one of the identified Aβo blocking compounds (CT1812) to determine whether multiple day dosing could achieve CSF concentrations of CT1812 greater than those needed to achieve > 80% sigma-2/ PGRMC1 receptor occupancy in mice. Three cohorts of healthy volunteers (ages 18-64) were dosed orally with CT1812 (n=8) or placebo (n=2) at doses of 280 mg, 560 mg and 840 mg once daily for 14 days. CSF was collected pre-dose between days 7 and 9 in the 560 mg and 840 mg dose cohorts. Safety, tolerability and pharmacokinetics of CT1812 after 14 days of dosing were also assessed. Additionally a healthy elderly cohort (ages 65-75) was similarly dosed with CT1812 (n=8) or placebo (n=2) for 14 days. Cognitive testing (ADAS-COG, COWAT, category fluency, digit span, digit symbol and RAVLT) was performed in the healthy elderly cohort before and after treatment. *Results:* In the 560 mg/day and 840 mg/day dose cohorts, the average CSF concentrations were approximately 7.5 and 15 times higher respectively than the concentrations required to reverse memory loss in Alzheimer's transgenic mice. The CSF concentrations at these doses correspond to 97-98% sigma-2/PGRMC1 receptor occupancy in the brain. Plasma concentrations of CT1812 were linear across doses. Treatment with CT1812 was well tolerated in all cohorts, with no drug-related dropouts. Cognitive scores in the healthy elderly cohort were similar before and after treatment. *Conclusions:* CT1812 is a sigma-2/PGRMC1 receptor allosteric antagonist that blocks Aβo binding to neurons and prevents Aβo-induced synaptic toxicity. Data from this phase 1 study indicate that CT1812 was well tolerated through 14 days of dosing. CSF concentrations were reached that were previously associated with high levels of sigma-2/PGRMC1 receptor occupancy in mouse brain and with cognitive improvement in AD transgenic mice. No safety signals related to cognition were observed in healthy elderly subjects. A clinical trial of CT1812 in AD patients is underway.

P1-34 CIRCULATING BRAIN-ENRICHED MICRORNAS AS BIOMARKERS FOR ALZHEIMER'S DISEASE CLINICAL TRIALS. Kira S. Sheinerman[1], Vladimir G. Tsivinsky[1], Jon B. Toledo[2], Jennifer McBride[2], Elizabeth Grant[3], Anne M. Fagan[3], John Q. Trojanowski[2], Samuil R. Umansky[1] *((1) DiamiR, LLC, Monmouth Junction, NJ, USA; (2) Center for Neurodegenerative Disease and Department of Pathology & Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, USA; (3) Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA)*

Background: Minimally invasive assays capable of detecting Alzheimer's disease (AD) early, preferably at presymptomatic stage, can enable primary screening of larger populations for clinical trials and earlier, more effective therapeutic intervention. Surrogate blood biomarkers reflective of brain processes can also be used for disease progression and treatment monitoring. We have developed a targeted diagnostic platform based on analysis of cell-free brain-enriched microRNAs (miRNAs) in plasma. *Methods:* miRNA biomarker candidates were selected among miRNAs enriched in hippocampus, cortex and midbrain, present in neurites and synapses, and detectable in plasma. Certain inflammation-associated miRNAs were also included in the analysis. The following plasma sample cohorts collected at Washington University and the University of Pennsylvania were analyzed: (i) Clinical Dementia Rating (CDR) >0, Aβ+ vs CDR 0, Aβ- as determined by CSF amyloid status; (ii) CDR 0 at baseline and progressed to CDR>0 ("progressors") vs those who remained CDR 0 during 2-13 years period ("non-progressors"); and (iii) AD vs age-matched controls. Levels of miRNAs were measured by single target qRT-PCR with miRNA-specific stem-loop primers. Statistical analysis of miRNA ratios was performed using customized software, essentially as described in Sheinerman et al. Aging, 5: 925-938, 2013. *Results:* 1. CDR 0.5-1, Aβ+ group (30) was effectively differentiated from CDR 0, Aβ- group (29) by miRNA signatures that include miRNAs enriched in synapses of hippocampus with 78%-86% accuracy. 2. using essentially same miRNA signatures as in 1, "progressors" (42) and "non-progressors" (42) were differentiated with 76% sensitivity and 74% specificity; further, other miRNA signatures distinguished Aβ+ from Aβ- sub-groups in both "progressors" and "non-progressors." 3. 50 AD and 50 controls were divided into training and confirmation sets; same miRNA signatures distinguished AD from control in the two sets, as well as the combined set, with over 85% accuracy. In addition, the analysis of miRNA levels separately in male and female participants further improved the outcome: female and male AD patients were differentiated from respective controls with 92% and 98% accuracy. *Conclusion:* These data further validate and expand our previous results on detection of Mild Cognitive Impairment and presymptomatic AD based on the analysis of brain-enriched miRNAs circulating in plasma. The results demonstrate that: (i) plasma levels of miRNAs enriched in synapses of hippocampus are indicative of early pathology; (ii) analysis of miRNAs present in synapsis and enriched in different brain regions can be used to follow disease progression and, potentially, treatment response; and (iii) use of gender-specific miRNA signatures may improve assay accuracy. Additional studies are in progress towards developing a clinical trial assay.

P1-35 MRI AND EEG BIOMARKERS TO TRACK DISEASE PROGRESSION IN AMCI PATIENTS WITH AD PATHOLOGY. Moira Marizzoni[1], Samantha Galluzzi[1], Clarissa Ferrari[1], Jorge Jovicich[2], Flavio Nobili[3], Jean-Philippe Ranjeva[4], David Bartrés-Faz[5], Ute Fiedler[6], Peter Schönknech[7], Pierre Payoux[8,9], Alberto Beltramello[10], Massimo Caulo[11], Andrea Soricelli[12,13], Lucilla Parnetti[14], Magda Tsolaki[15], Paolo Maria Rossini[16,17], Pieter Jelle Visser[18], Federica Fusco[19], Diego Albani[19], Gianluigi Forloni[19], Regis Bordet[20], Jill Richardson[21,22], Cecilia Estrella[23], Nicola Marzano[24], Claudio del Percio[24], Susanna Cordone[24], Claudio Babiloni[24], Olivier Blin[25], Giovanni Battista Frisoni[1,26] on behalf of the PharmaCog Consortium *((1) Laboratory of Neuroimaging and Alzheimer's Epidemiology, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy; (2) Center for Mind/Brain Sciences, University of Trento, Trento, Italy; (3) Department of Neuroscience, Ophthalmology, Genetics and Mother–Child Health (DINOGMI), University of Genoa, Genoa, Italy; (4) CIC-UPCET, CHU La Timone, AP-HM, UMR CNRS-Universite de la Mediterranee, Marseille, France; (5) Department of Psychiatry and Clinical Psychobiology, Universitat de Barcelona and IDIBAPS, Barcelona, Spain; (6) LVR-Clinic for Psychiatry and Psychotherapy, Institutes and Clinics of the University Duisburg-Essen, Essen, Germany; (7) University Hospital Leipzig, Leipzig, Germany; (8) INSERM, Imagerie cérébrale et handicaps neurologiques, UMR 825, Toulouse, France; (9) Université de Toulouse, UPS, Imagerie cérébrale et handicaps neurologiques, UMR 825, CHU Purpan, Place du Dr Baylac, Toulouse France; (10) Department of Neuroradiology, General Hospital, Verona, Italy; (11) University "G. d'Annunzio" of*

Chieti, Chieti, Italy; (12) IRCCS SDN, Naples, Italy; (13) University of Naples Parthenope, Naples, Italy; (14) Section of Neurology, Centre for Memory Disturbances, University of Perugia, Perugia, Italy; (15) 3rd Department of Neurology, Aristotle University of Thessaloniki, Thessaloniki, Greece; (16) Dept. Geriatrics, Neuroscience & Orthopaedics, Catholic University, Policlinic Gemelli, Rome, Italy; (17) IRCSS S.Raffaele Pisana, Rome, Italy; (18) Alzheimer Center and Department of Neurology, VU University Medical Center, Amsterdam, Netherlands; (19) Neuroscience Department, IRCCS Istituto di Ricerche Farmacologiche «Mario Negri», Milano, Italy; (20) Department of Pharmacology, EA1046, University of Lille Nord de France, Lille, France; (21) Neurosciences Therapeutic Area, U.K., United Kingdom; (22) GSK R&D, China-UK, U.K., United Kingdom; (23) AlzProtect, Loos, France; (24) Sapienza University of Rome, Rome, Italy; (25) Pharmacology, Assistance Publique-Hôpitaux de Marseille, Aix-Marseille University-CNRS UMR 7289, Marseille, France; (26) *Memory Clinic and LANVIE - Laboratory of Neuroimaging of Aging, University Hospitals and University of Geneva, Geneva, Switzerland)*

Backgrounds: Markers of Alzheimer's disease (AD) progression in its pre-dementia stages are important to develop disease modifying drugs. This study is aimed at identifying biomarkers sensitive to change over time in amnestic mild cognitive impairment (aMCI) patients with prodromal AD. *Methods:* 147 aMCI patients were enrolled in WP5 of PharmaCog (E-ADNI) and underwent clinical, neuropsychological, MRI, EEG assessment each 6 months for at least 2 years. Patients converted to AD or other type of dementia were excluded from follow-up visits. Patients were classified into positives or negatives based on their baseline CSF Aβ42/p-tau level. Global cognition: ADAS-cog. AD-related biomarkers analysis: structural MRI (freesurfer)1-2, diffusion MRI (atlas-based approach)3, rs-fMRI (independent component analysis)4-5 and rs-EEG source (eLORETA freeware). Statistical analysis: Linear Mixed Model for repeated measures with repeated ADAS-cog, MRI, EEG measures as dependent variables; time and CSF Aβ42/p-tau status as independent variable (one model for each variable); age and gender (all) and total intracranial volume (volume models only) as covariates. *Results:* The ADAS-cog score showed significant effects for CSF status and for time-CSF status interaction (all $p<0.001$) but not for time. Significant effects for CSF status, time and their interaction was reported for volumes of the hippocampus (all $p<0.001$) and different subfields (all $p<0.019$), lateral ventricles (all $p<0.038$), thalamus (all $p<0.050$), entorhinal thickness (all $p<0.035$), diffusivity in the fornix (all $p<0.024$) and, parietal rs-EEG theta/alpha1 (all $p<0.018$). The explained variability of ADAS-cog, volumes, fornix diffusivity and parietal rs-EEG source was 0.54, higher than 0.82, 0.35 and 0.44, respectively. A clear effect of CSF status or time, but not the interaction, was detected in the other cortical thicknesses considered, in the corpus callosum diffusivity, and in different rs-fMRI measures (e.g. default mode network connectivity). *Conclusion:* Regional atrophy rates (whole hippocampus, hippocampal subfields, and lateral ventricles), entorhinal thinning, fornix diffusivity rates, and parietal theta/alpha1 rs-EEG source rates of change were the biomarkers most sensitive to change in aMCI with AD pathology. Progression of atrophy rates was better than ADAS-cog rate of change in separating CSF positive and negative patients. PharmaCog is funded by the EU-FP7 for the Innovative Medicine Initiative (grant n°115009). References: 1) Marizzoni M et al. 2015. Hum Brain Mapp; 36(9):3516-27. 2) Jovicich J et al. 2013. Neuroimage; 83:472-84. 3) Jovicich J et al, 2014. Neuroimage; 101:390-403. 4) Marchitelli R et al. 2016. Hum Brain Mapp; 37(6):2114-32. 5) Jovicich J et al. 2016. Neuroimage; ;124(Pt A):442-54.

P1-36 STRATIFICATION OF MCI AND COGNITIVELY NORMAL INDIVIDUALS USING POLYGENIC SCORING: EVALUATION OF A NOVEL SNP (SINGLE NUCLEOTIDE POLYMORPHISM) ARRAY IN RISK ASSESSMENT.

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Background: The identification of subjects at high risk of Alzheimer's Disease (AD) will be important for early diagnosis and successful treatment. Strong evidence exists to support a highly significant role for a risk component for the development of Late-Onset Alzheimer's Disease (LOAD). The identification of a panel of genetic risk variants, or SNPs, which could be used in the definition of an algorithm to predict risk of future progression to Alzheimer's Disease in early symptomatic, or pre-symptomatic individuals, would have utility to researchers, drug developers and clinicians alike. It is well documented that early symptomatic (MCI) or elderly pre-symptomatic individuals who are amyloid-positive, as assessed using either PET imaging or CSF testing, are at relatively increased risk of future cognitive decline and AD. *Methods:* We have developed in partnership with Affymetrix (Thermo Fisher Scientific), a novel single nucleotide polymorphism (SNP) genotyping array. The array is a comprehensive panel of AD informative SNPs configured on the Affymetrix Axiom™ plates and processed on an Affymetrix GeneTitan® scanner. Comprising approximately 130,000 novel and known SNP variants in genes pertaining to pathways implicated in AD aetiology, the variaTECTTM SNP Array has been developed from an extensive research effort involving world leading experts. SNPs were selected for the variaTECT panel using a combination of whole exome association analysis, variations identified through Genome Wide Association studies and variants considered to be of importance in AD-associated biological pathways. Disease risk prediction modelling has been further applied to quantify the utility of the associated variants. *Results:* The variaTECT SNP array has been used to genotype ~1,200 well-characterised clinical samples from amyloid biomarker-confirmed AD cases, age-matched, cognitively-normal controls and early symptomatic (MCI) individuals. The genotyping data derived from these samples has been used to derive and test novel polygenic risk score (PS) algorithms. These algorithms have been incorporated into Cytox's SNPfitR™ software and polygenic risk score algorithm. Our results indicate that PS algorithms can be successfully deployed in order to identify and enrich amyloid-positive individuals from early symptomatic and pre-symptomatic (prodromal) cohorts. *Conclusion:* The variaTECT is currently the most wide-ranging research panel available for the detection of AD informative SNPs. variaTECT SNP testing and SNPfitR analysis is easy to administer and provides a high degree of accuracy; in doing so, it has the clear potential to reduce the screening failure rate and current associated costs of testing for amyloid positivity using PET amyloid or CSF examinations, which are not well-suited for high volume screening.

P1-37 LTP-LIKE CORTICAL PLASTICITY IS DISRUPTED IN ALZHEIMER'S DISEASE PATIENTS INDEPENDENTLY FROM AGE OF ONSET. Francesco Di Lorenzo[1,2], Viviana Ponzo[1] Sonia Bonnì[1], Caterina Motta[1,2], Marco Bozzali[1], Carlo Caltagirone[1,2] Alessandro Martorana[2], Giacomo Koch[1,4] *((1) Non Invasive Brain Stimulation Unit/Department of Behavioural and Clinical Neurology, Santa Lucia Foundation IRCCS, Rome, Italy; (2) Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy)*

Objective: Early Onset Alzheimer Disease (EOAD) shares the same pathological features of Late Onset Alzheimer disease (LOAD). However it is unknown if AD pathology induces in EOAD similar modification in synaptic functions as those described in LOAD. We used transcranial magnetic stimulation tools to investigate the mechanisms of cortical plasticity and sensory-motor integration in AD patients with a wide range of disease onset. *Methods:* We evaluated newly diagnosed sporadic AD (n=54) in comparison with healthy age-matched controls (HS n=24). Cortical plasticity mechanisms of long-term potentiation (LTP) or of long-term depression (LTD) were assessed using respectively intermittent (iTBS) or continuous theta burst stimulation (cTBS) protocols. Sensory-motor integration was evaluated by means of short afferent inhibition (SAI) protocol. *Results:* AD showed an impairment of LTP-like cortical plasticity that was reversed to a paradoxical LTD after iTBS in comparison to HS. LTD-like cortical plasticity was similar across groups. LTP-like cortical plasticity did not correlate with age. AD patients presenting with more altered LTP-like cortical plasticity had more severe cognitive decline at 18 months. SAI was impaired in AD and showed a strong correlation with the individual age of subjects rather than with disease age of onset. *Conclusions:* Cortical LTP disruption is a central mechanism of AD that is independent from age of onset. AD can be described primarily as a disorder of LTP-like cortical plasticity not influenced by physiological ageing and associated with a more severe cognitive decline.

P1-38 APOE4 BLOOD MARKER ASSAY. A NEW NON-GENETIC METHOD TO EVALUATE ALZHEIMER´S DISEASE RISK USING CLINICAL CHEMISTRY PLATFORMS. Sergio Veiga[1], Andrés Rodríguez-Martín[1], Olga Calero[2], Luis García-Albert[3], Almudena Pérez [4], Sergi Gassó[4], Miguel Calero[5] *((1) Biocross S.L, Valladolid, Spain; (2) CIBERNED and Chronic Disease Programme, Instituto de Salud Carlos III. Madrid, Spain; (3) Chronic Disease Programme, Instituto de Salud Carlos III. Madrid, Spain; (4) Pragmatic Diagnostics S.L., Bellaterra (Cerdanyola del Vallès), Barcelona, Spain; (5) Chronic Disease Programme, CIBERNED, and CIEN Foundation-Queen Sofia Foundation, Instituto de Salud Carlos III. Madrid, Spain)*

Background: To date only the presence of one or two alleles ε4 of the apolipoprotein E gene (APOE) is accepted as a reliable biomarker and risk factor of developing late onset Alzheimer´s Disease (AD)1, 2. The presence of one allele ε4 of the APOE gene increases the risk of suffering AD by 3-5 fold, while the presence in homozygosis increases the risk by 15-20 fold3. Furthermore, APOE ε4 carriers would progress faster from the preclinical stage of AD (mild cognitive impairment, MCI) to AD than APOE ε4-non carriers4. Therefore, APOE ε4 carriers clearly constitute a target population where research, clinical trials and prevention strategies should be focused. Despite of its clear clinical utility, APOE genotyping is not requested by neurologists because the test is not included within the routine diagnostic workout, in part due to the requirement of informed consent for genetic analysis. *Methods:* Biocross in collaboration with CIBERNED and the Instituto de Salud Carlos III has developed a non-genetic, cost effective and highly reliable method to detect the presence of the apoE4 isoform in human plasma. The method was initially developed as an ELISA and adapted to a turbidimetry-based assay to allow its implementation into the clinical analysis routine. Shortly, the technique uses a highly specific anti-apoE4 antibody, which induces the agglutination of latex (polystyrene) beads in the presence of the apoE4 isoform in plasma. This agglutination is proportional to the concentration of the apoE4 and it can be measured spectrophotometrically. *Results:* The adaptation to immunoturbidimetry was carried out using a semiautomatic biochemistry analyzer (SpinLab 100. Spinreact (Selectra Vital Junior). All the technical verification work included reproducibility, interference, linearity, precision and stability studies and led to the creation of a design-freeze kit, which consist in two ready-to-use reagents. The sensibility and specificity of the design-freeze kit was evaluated in 157 human plasma samples (74 apoe4-non carriers and 83 apoE4 carriers), whose results were compared with APOE genotype determined by Real-Time PCR5. Sensibility and specificity of ApoE4 blood marker assay was found to be 100% and 96% respectively. The assay was adapted for its use in two of the most common high throughput biochemistry analyzers used in hospitals, ARCHITECT and ADVIA 2400. *Conclusion:* Our results show that ApoE4 blood marker assay is a simple, cost effective and highly reliable method that could be easily implemented in the routine setting of hospitals. Identification of APOE ε4 carriers is extremely useful from a clinical point of view, since it allows easy and fast stratification of APOE ε4 carriers in clinical trials. Furthermore, this method would allow regular monitoring of this at-risk population, which would permit the initiation of the treatment at the first symptom, as well as to apply lifestyle preventive interventions that could prevent or delay the development of the disease. References: 1. Corder, E.H. et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261, 921-923 (1993). 2. Michaelson, D.M. APOE epsilon4: the most prevalent yet understudied risk factor for Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association 10, 861-868 (2014). 3. Farrer, L.A. et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. Jama 278, 1349-1356 (1997). 4. Craft, S. et al. Accelerated decline in apolipoprotein E-epsilon4 homozygotes with Alzheimer's disease. Neurology 51, 149-153 (1998). 5. Calero O, et al. Apolipoprotein E genotyping method by real time PCR, a fast and cost-effective alternative to the TaqMan and FRET assays. J Neurosci Methods 183(2):238-40 (2009).

P1-39 [18F]MK-6240 A NOVEL NEUROFIBRILLARY TANGLES PET TRACER: DISCOVERY AND CLINICAL EVALUATION. Cyrille Sur[1], Idriss Bennacef[1], Zhizhen Zeng[1], Talakad Lohith[1], Patricia J Miller[1], Cristian A Salinas[1], Brett M Connolly[1], Liza T Gantert[1], Hyking D Haley[1], Holahan A Marie[1], Stacey S O'Malley[1], Mona L Purcell[1], Kerry Riffel[1], Paul J Coleman[2], Jing Li[2], Jaume Balsells-Padros[2], Aileen Soriano[3], Aimie M Ogawa[3], Serena Xu[3], Zhang Xiaoping[3], Joseph Della Rocca[2], Joel B. Schachter[4], David Hesk[5], Schenk J David[5], Arie Struyk[6], Cyrille Sur[1], Sofie Celen[7], Kim Serdons[7], Guy Bormans[7], Mathieu Vandenbulcke[7], Rik Vandenberghe[7], Jan De Hoon[7], Michel Koole[7], Koen Van Laere[7], Walji Abbas[2], Hostetler Eric[1] Jeffrey Evelhoch[1] *((1) Merck & Co. / Translational Biomarkers,West Point, PA, USA, (2)Merck & Co. / Chemistry, West Point, PA, USA; (3) Merck & Co. / Pharmacology, Kenilworth, NJ, USA; (4) Merck Research Laboratories, West Point, PA, USA; (5) Merck & Co. / Chemistry, Rahway, NJ, USA; (6) Merck & Co. / Translational*

Pharmacology, North Wales, PA, USA; (7) KU Leuven, Leuven, Belgium)

Backgrounds: Historically, robust diagnosis of Alzheimer's disease (AD) has been performed post-mortem by staining of amyloid-beta (Aß) plaque and neurofibrillary tangles (NFTs). Non-invasive clinical imaging Aß can now be performed using Positron Emission Tomography (PET). However, dementia correlates more strongly with the extent of NFT than with Aß. Hence, efforts are currently directed towards the identification of a PET radiotracer suitable for measuring the NFT load clinically, which will be complementary to the Aß probes. Our effort was directed towards identifying a PET radioligand that is specific and sensitive. Here, we present the preclinical characterization of [18F]MK-6240 as well as its clinical evaluation. *Methods:* Immunohistochemistry, autoradiography (ARG) studies and tissue homogenates binding studies were carried out in AD and healthy control (HC) brains. Non-human primate (NHP) brain PET imaging was carried out to determine the pharmacokinetic (PK) profile, brain uptake and non-specific binding as well as lack of off-target binding. A dosimetry study was performed for the first-in-human evaluation of [18F]MK-6240. Study design for the evaluation of [18F]MK-6240 included HC and probable AD patient brain PET scans. *Results:* In vitro experiments using AD tissues showed that MK-6240 is a potent (KD = 0.28 nM) and selective (Ki Aß >10 μM) NFT ligand. Using HC tissues, no saturable MK-6240 binding was observed. [18F]MK-6240 displayed a high initial uptake followed by a fast washout in NHP in vivo. Non-specific and white matter binding were low. Self-block studies showed no off-target binding. Dosimetry evaluation in human resulted in an effective dose of ~29.4 μSv/MBq. A Similar PK profile as in NHP was observed for HCs. *Conclusion:* Extensive in-vitro characterization showed that MK-6240 is a potent and selective tau tracer with great binding potential. In NHP, [18F] MK-6240 displayed a favorable PK profile and no potential liabilities were found. In the clinic, we observed similar results in HC. Further PET evaluation is currently ongoing to evaluate the sensitivity of the radioligand in healthy elderly and AD subjects.

P1-40 TAU PATHOLOGY MEASURED BY 18F-AV1451 POSITRON EMISSION TOMOGRAPHY AND CEREBROSPINAL FLUID BIOMARKERS IN ALZHEIMER'S DISEASE. Niklas Mattsson[1,2,3], Michael Schöll[1], Ruben Smith[3], Olof Strandberg[1], Sebastian Palmqvist[1,2,3], Philip Insel[1,4,5], Henrik Zetterberg[6,7], Kaj Blennow[6], Thomas Olsson[8], Douglas Hägerström[9], Jonas Jögi[10], Lennart Minthon[1,2], Oskar Hansson[1,2] *((1) Clinical Memory Research Unit, Faculty of Medicine, Lund University, Lund, Sweden; (2) Memory Clinic, Skåne University Hospital, Sweden; (3) Department of Neurology, Skåne University Hospital, Sweden; (4) Center for Imaging of Neurodegenerative Diseases, Department of Veterans Affairs Medical Center, San Francisco, CA, USA; (5) Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA, USA; (6) Clinical Neurochemistry Laboratory, Univeristy of Gothenburg, Gothenburg, Sweden; (7) UCL, London, UK; (8) Department of Radiation physics, Skåne University Hospital, Lund, Sweden; (9) Department of Clinical Neurophysiology, Skåne University Hospital, Lund, Sweden; (10) Department of Clinical Physiology and Nuclear Medicine, Skåne University Hospital, Lund, Sweden)*

Backgrounds: Tau pathology is a hallmark of Alzheimer's disease (AD). For several years, cerebrospinal fluid (CSF) measurements of total tau (T-tau) and phosphorylated tau (P-tau) have been used to study tau in AD. More recently, tau positron emission tomography (PET) imaging has become available, but it is unknown if CSF and PET measures of tau provide similar information. *Methods:* We studied 29 AD dementia patients, 8 MCI patients, and 17 healthy controls. CSF T-tau and P-tau were measured using INNOTEST ELISAs. Tau PET imaging was done using 18F-AV1451 with cerebellar cortex as the reference region. We tested associations between CSF and PET measures, using regional data (using FreeSurfer) and voxelwise multiple regression (using SPM12). *Results:* In the whole sample there were strong associations between CSF T-tau and P-tau and retention of 18F-AV1451. The associations were retained in people with low degree of tau pathology, but were weak or non-existant in people with advanced tau pathology or AD dementia. *Conclusion:* Although CSF T-tau and P-tau and 18F-AV1451 correlate well overall, the poor correlations in people with advanced tau pathology or AD dementia indicate that CSF tau biomarkers may be more suitable to measure disease state, i.e. presence or absence of AD, while 18F-AV1451 may also be useful to measure disease stage.

P1-41 LUMIPULSE G B-AMYLOID 1-42: KEY PERFORMANCES OF A FULLY AUTOMATED CHEMILUMINESCENT IMMUNOASSAY. Martine Dauwe[1], Filip Dekeyser[1], Tinne Dumont[1], Roger Moonen[1], Els Huyck[1], Manu Vandijck[1], John Lawson[2], Zivjena Vucetic[2], Johan Gobom[3], Kaj Blennow[3], Vesna Kostanjevecki[1], Geert Jannes[1] *((1) Fujirebio Europe N.V., Ghent, Belgium; (2) Fujirebio Diagnostics Inc., Malvern, PA, USA; (3) Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden)*

Backgrounds: Today β-amyloid(1-42) peptide (Aβ1-42) levels in cerebrospinal fluid (CSF) and amyloid imaging are well-accepted biomarkers representing Alzheimer's disease (AD) progression from the earliest stages on. Widespread use of these biomarkers in AD diagnosis requires reliable, highly precise, and accurate measurements. Analytical requirements and performance on cerebrospinal fluid samples of the novel Lumipulse G β-Amyloid 1-42 assay, a fully automated chemiluminescent enzyme immunoassay were verified and the key features are highlighted in this summary. *Methods:* The LUMIPULSE G instruments use single analyte, ready-to-use immunoreaction cartridges with a throughput of 60 and 120 tests/hour for the G600II and the G1200 instrument, respectively. Sequential immunoreaction steps are carried out at pre-determined intervals while the cartridge is transported through the system. Each cartridge generates quantitative results within approximately 30 minutes and multiple assays can be easily combined in the system enabling full characterization of samples during one run. The Lumipulse G β-Amyloid 1-42 assay has been developed using established monoclonal antibodies. The analytical assay performance was characterized according to CLSI guidelines. Quantitative determination of Aβ1-42 levels on a set of CSF samples from patients visiting a memory clinic was performed at an external lab and used for a measurement comparison versus INNOTEST β-AMYLOID(1-42). *Results:* Using a panel of CSF and control samples, assay variability was determined and the obtained coefficient of variation seen for the different variability components show a high level of precision: a clear result from the use of a standardized and automated assay platform. Analytical sensitivity was investigated on diluted CSF samples and the LoD and LoQ for the Lumipulse G β-Amyloid 1-42 assay were shown to be <10 pg/mL and <40 pg/mL, respectively. Linearity was shown across the clinical application range. The assay was standardized against the recently approved reference measurement procedure for Aβ1-42 (JCTLM ID: C11RMP9). A method comparison study with the routinely used INNOTEST β-AMYLOID(1-42) assay resulted

in a good correlation and confirmed a previously described shift in value assignment. *Conclusion:* Automation, the mono test cartridge principle, short throughput times, and instrument flexibility are key attributes of the LUMIPULSE G instrument series making it the ideal platform to fulfill today's needs for rapid and accurate quantification of CSF biomarkers in both low and high throughput clinical laboratories. The novel Aβ1-42 assay on the LUMIPULSE G instruments shows good sensitivity and precision, is traceable to the standard reference measurement procedure (based on LC-MS/MS) and correlates well with the established INNOTEST assay.

P1-42 CSF MARKERS OF INFLAMMATION RELATE TO AD BIOMARKERS AND COGNITIVE PERFORMANCE IN HEALTHY ELDERLY AT RISK FOR AD.

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Backgrounds: Epidemiological studies have suggested an inverse relationship between use of non-steroidal anti-inflammatory drugs (NSAIDs) and risk of Alzheimer's disease (AD) (Szekely et al., 2008). However, more recent studies suggest that these same drugs may accelerate symptom expression in persons with more advanced disease (Lyketsos et al., 2007, Breitner et al., 2011, Heneka et al., 2015). We are therefore conducting a randomized biomarker-endpoint placebo-controlled trial of the NSAID naproxen as a potential preventive strategy against AD (INTREPAD). Trial participants are 217 cognitively healthy elderly whose parental history of AD dementia implies increased risk of AD symptoms. The effects of naproxen treatment on cerebrospinal fluid (CSF) markers of inflammation are largely unknown, and we are therefore seeking also to observe the drug's effect on inflammatory processes alongside its influence on pre-clinical AD pathogenesis. Here we describe several observed relationships between inflammatory markers and CSF concentrations of total tau (t-tau) and the 42-amino acid amyloid-β (Aβ) peptide – widely used as biomarkers of AD pathogenesis. We further investigated these same markers in relation to cognitive performance, and we observed whether these relationships differed in subjects with and without an ε4 allele at APOE. *Methods:* Among the 217 INTREPAD participants (160 with at least one follow-up observation and therefore to be included in modified-Intent-to-Treat, or m-ITT, analyses), 106 volunteered for a series of four lumbar punctures (LPs) to assess CSF chemistry (94 CSF donors in the m-ITT sample). In pilot experiments among 20 participants, we assayed 45 CSF inflammatory markers using a combination of the Mesoscale V-plex neuroinflammation panel-1 (Mesoscale Discovery, Rockville, MD) and the Milliplex HCYTMAG60PMX29BK xMap kit, or "Milliplex-29" (EMD-Millipore, Billerica, MA). To maintain the "blind" in INTREPAD, data were studied only from the initial (baseline) set of observations. Among the 20 pilot analyses, the two assay systems showed broadly consistent results and suggested relationships between the CSF t-tau/Aβ ratio and seven different inflammatory markers (IL-8, IP-10, MCP-1, IL-1β, TNF-α, MCP-4, and TARC). In the subsequent studies we presently have Milliplex-29 results only. These latter analyses have yielded data on only 14 analytes in 50 or more samples that have rigorous quality control (Figure 1). Notably lacking from the later analyses at present are IL-1β,TNF-α, MCP-4, IFN-γ, IL-4, and TARC. For each participant, there is also a corresponding baseline cognitive score on the Repeatable Battery for Assessment of Neuropsychological Status [RBANS] (Randolph et al., 1998). We used multivariate linear regression models to explore the association of CSF inflammatory and AD biomarkers (CSF t-tau/Aß) as well as total score on the RBANS. At this stage of the work, we have not adjusted P-values for multiple comparisons. *Results:* In the recently enlarged sample (using Milliplex technology only), we found that levels of all 14 inflammatory markers were similar in subjects with and without APOE ε4 (Figure 2). However, the two genetic groups appeared to vary in their correlation of t-tau/Aβ ratio with IL-15 (ε4-carrier vs. non-carrier P=0.004), and with MCP-1 (P =0.004; Figure 3). We also observed genotype-related differences in the correlation of inflammatory markers with cognitive performance. Thus, ε4 carriers showed association of pro-inflammatory signaling (IP-10 and MIP-1ß) with reduced cognitive performance (P for difference by genotype = 0.008 and 0.015, respectively; Figure 4). By contrast, non-carriers showed a relation between increased anti-inflammatory signaling (IL-1RA) or growth-factor expression (VEGF) and improved cognitive scores in non-carriers (P for genotype-related differences = 0.03 and 0.04, respectively; Figure 5). *Conclusion:* These preliminary data suggest possible relationships between several inflammatory markers and AD pathogenesis as well as cognitive scores. For reasons not yet understood, these relationships appear consistently to vary with APOE ε4 status. This study is among the first to investigate a broad range of CSF inflammatory markers in relation to evidence of pre-clinical AD. The work is meant to complement the INTREPAD trial of NSAID treatment for prevention in healthy elderly at risk of AD, to be unmasked in 2017. Additional CSF marker analyses, to be measured using the Mesoscale platform, will be disclosed at the meeting. Along with the forthcoming trial results, these analyses should provide substantial new insights into the role of inflammatory processes in AD pathogenesis as well as the potential of NSAIDs for dementia prevention.

Figure 1

Number of samples within assay range for each inflammatory marker measured using Milliplex technology

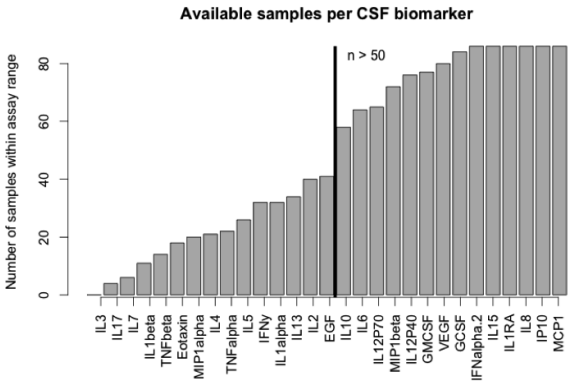


Figure 2

Distribution of values (centered, reduced) for markers with at least 50 samples available. Data is dichotomized in ε4 carriers (red) and non-carriers (blue). No significant differences were observed between the two groups

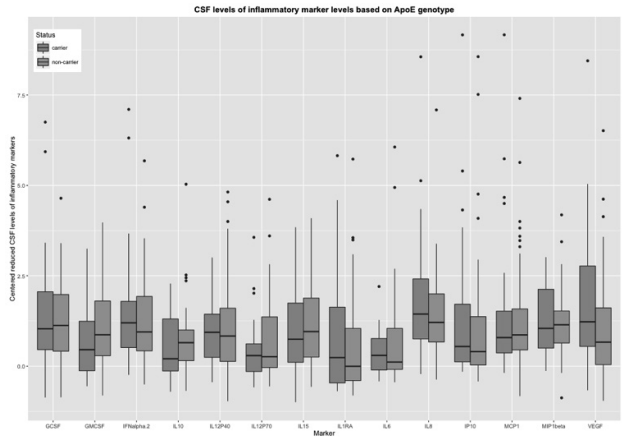


Figure 3

Regression analysis showing interaction of APOE ε4 status with relationship of IL-15 or MCP1 and t-tau/Aß1-42 ratio (for IL-15, P < 0.01 for ε4 carriers and P = 0.052 for non-carriers; for MCP1 P = 0.03 for ε4 carriers and P > 0.4 for non-carriers)

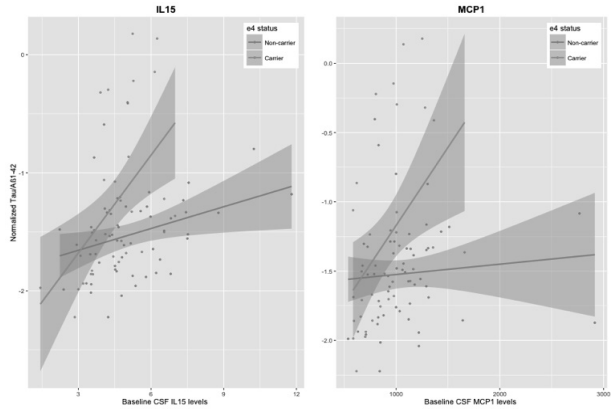


Figure 4

Increased pro-inflammatory signaling is associated with worse scores on the RBANS for ε4-carriers (p-values < 0.05) but not in non-carriers (Not significant)

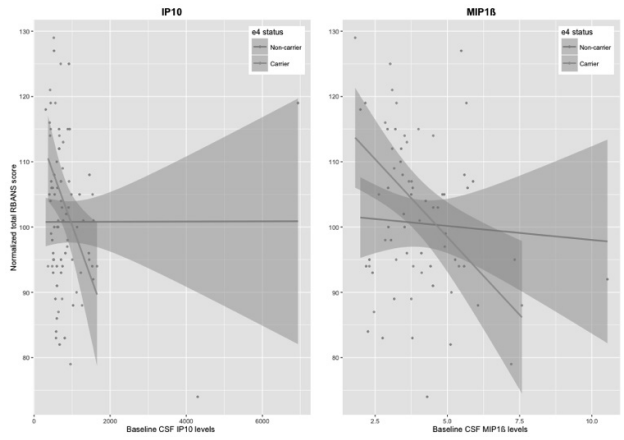
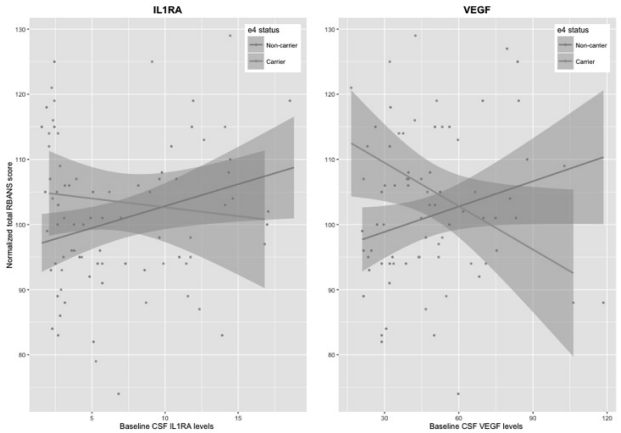


Figure 5

Increased anti-inflammatory signaling (IL1RA, p<0.01) and growth factor expression (VEGF, p<0.02) is associated with better performance on the RBANS in ε4 non-carriers, but not carriers (NS)



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P1-43 AN ELECTROENCEPHALOGRAPHIC MARKER OF CHOLINERGIC ACTIVITY IN THE LIVING HUMAN BRAIN WITH APPLICATION TO ALZHEIMER'S. Magnus Johannsson[1], Jon Snaedal[2], Gisli Holmar Johannesson[1], Thorkell Eli Gudmundsson[2], Ivar Meyvantsson[1], Kristinn Johnsen[1] *((1) Mentis Cura ehf, Reykjavík, Iceland; (2) Memory Clinic, Geriatric Department, National University Hospital, Landakot, Reykjavík, Iceland)*

Backgrounds: Alzheimer's disease (AD) is a chronic neurodegenerative disorder characterized by progressive cognitive decline, starting with impairments in memory and ending in global cognitive deterioration. Converging evidence suggest the role of large-scale neurocognitive networks responsible for memory and other cognitive functions in the brain. Recent studies have shown that in addition to the traditional medial temporal (MTL) systems a set of cortical regions, referred to as the default mode network (DMN) play a role in the brains memory network. The DMN has

been defined as a resting state network that is related to intrinsic brain activities (e.g. retrieval of autobiographical memories and envisioning the future) and is deactivated when engaged in demanding cognitive task. Functional connections have been established between the posteromedial cortices of the DMN network and MTL system, specifically the hippocampal system, where a coordinated deactivation and activation between the two systems is trivial to a successful memory formation. Functional and resting state magnetic resonance imaging (MRI) and electroencephalography (EEG) studies on AD patients, individuals diagnosed with mild cognitive impairment (MCI) and even healthy elderly have shown alterations in these networks related to disease severity. Compared to healthy controls AD patient show decrease activity as a function of disease progression while the MCI patients show increase in activity compared to healthy individuals. Different reasons have been put forward to account for the hyperactive in the MCI group. A common aspect suggests a neuronal compensatory response that is argued by some to be driven by an upregulation of cholinergic or other neurotransmitters. Neuromodulatory systems such as the cholinergic system are known to influence neurocognitive networks to a significant degree. Cholinergic and adrenergic agonists have been found to supress the activity of the DMN shifting brain activity away from default mode to active. The role of acetylcholine (Ach) in learning and memory has been established. Cholinergic blockers such as scopolamine and cholinergic agonist as physostigmine have been found to decrease and enhance memory performance in healthy individuals. Furthermore, studies have shown a positive correlation between cholinergic deficits and disease severity in AD but findings on MCI patients are conflicting where some studies show upregulation of Ach levels while others not. For the treatment of mild-to-moderate AD there are three approved ACHEIs (donepezil, rivastigmine and galantamine) and all have shown to have positive effects on cognition and global functioning in clinical trials. In the clinical settings however some patients have been found to respond to a greater extent to the ACHEIs than others and the differentiation of responders vs. non-responders remains unclear. *Methods:* EEG has proven to be a sensitive measure of functional connectivity and resting state networks in the brain. Furthermore, studies have demonstrated the relevance of EEG as an indirect marker of cholinergic activity. The aims of this study were threefold; to construct a scopolamine based EEG index, aimed to reflect cognitive decline; to investigate the behaviour of the index across progressive stages of dementia; to investigate the applicability of the index to predict response to ACHEIs. The index was developed using Scopolamine challenge data retrived in a trial with 99 elderly subjects. The EEG was recorded during period of resting state with eyes closed for 3 minutes, both before and after the administration of Scopolamine. The index was derived applying multivariate statistical patern recognition methods on the data from 19 of the elderly subjects, and was subsequently validated on the remaining 80 subjects. The derived index was then applied to a database of about 400 subjects at various stages of Alzheimer's disease, from the prodromal stage to the severe stage, as well as healthy controls. *Results:* The analysis of the revealed that the index correlates significantly with cognitive meassures such as the mini mental state examination (MMSE), ($r=0.48, p< 0.001$), in subjects on the Alzheimer's trajectory. We also found significant hyperactivity in terms of the index in the prestages of Alzheimer's disease compared to healthy controls, confirming fMRI findings on DMN hyperactivity in this stage. *Conclusion*: The EEG-based Ach index may provide a physiological means of monitoring aspects of cholinergic activity in the human brain in vivo. This has great potential for aiding diagnosis and patient stratification, for monitoring disease progression and treatment response, and for assisting further research into Alzheimer's dementia.

P1-44 PERFORMANCE CHARACTERISTICS OF CANDIDATE CSF BIOMARKERS OF METABOLIC, INFLAMMATORY, AND VASCULAR CONTRIBUTIONS TO ALZHEIMER'S DISEASE. Aaron M. Koeni[1], Bianca Trombetta[2], Steven E. Arnold[2] *((1) Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA (2); Department of Neurology, Massachusetts General Hospital, Boston, MA, USA)*

Background: Metabolic, inflammatory, and vascular processes likely play important roles in the genesis and progression of Alzheimer's Disease (AD). In the current study, we examined the performance characteristics and potential utility of commercial multiplex panels of key plasma metabolic and inflammatory markers in cerebrospinal fluid (CSF) of human volunteers with mild cognitive impairment and dementia due to AD. We also examined the temporal stability of these markers in a subset of individuals who underwent repeat CSF collection after 8 weeks. *Methods:* CSF samples were collected via lumbar puncture in polypropylene tubes and immediately aliquoted, frozen, and stored at -80°C for subsequent batch-run analyses. MesoScale Discovery (MSD) V-PLEX Human Aβ Peptide Panel 1 and Total Tau kits were used to measure traditional AD disease markers, MSD Human Active GLP-1, Insulin, Glucagon, Leptin, and Adiponectin kit was used to measure metabolic biomarkers, and MSD V-PLEX Human Neuroinflammation Panel 1 kit was used to measure a large set of inflammatory and vascular biomarkers. CSFs were diluted per assay requirements, and run in duplicate. Intra-assay and temporal variability were coded as excellent (<10%), good (10-15%), fair (16-20%), and poor (>20%) using predetermined criteria. *Results:* Twenty-nine CSF samples from 20 subjects with MCI or mild dementia due to AD were examined. Nine subjects underwent repeat CSF collection after 8 weeks. Samples were collected from 9 women and 11 men, all Caucasian, with a mean age of 70.1 years (SD=6.9) and education of 16.7 years (SD=2.8). At baseline, mean MMSE was 25.9 (SD=2.26), median CDR-SOB was 0.5 (range 0.5-3), and mean Hachinski (MHIS) total was 0.32 (SD=0.48). Only 2 of 5 metabolic biomarkers (leptin and adiponectin) were measurable above the assay's lower limit of detection (LLD). Intra-assay stability for leptin was excellent (6.5%), though 8-week temporal stability was poor (22.6%). Seventeen of 39 inflammatory/vascular biomarkers were measurable in CSF above each assay's LLD, including CRP, FABP3, Flt-1, ICAM-1, IP-10, MCP-1, MIP-1β, PIGF, SAA, TARC, VCAM-1, YKL-40, and ILs 6, 7, 8, 12/23p40, and 15. Intra-assay stability was excellent for CRP, Flt1, ICAM-1, ILs 6, 7, 8, 12/23p40 and 15, MCP1, MIP-1β, PIGF, SAA, VCAM-1, and YKL-40. Intra-assay stability was good for FABP3, and poor for IP10 and TARC. Temporal stability was excellent for Flt1, IL-6, IL-8, MCP1, and PIGF, good for FABP3, ICAM-1, IL-7, IL-12, and IL-15, and poor for CRP, IP-10, MIP-1β, SAA, TARC, VCAM-1, and YKL-40. Analytes with excellent intra-assay and temporal stability included tau, Flt1, IL-6, IL-8, MCP-1, and PIGF. Traditional AD CSF biomarkers, including Aβ38, Aβ40, Aβ42, and total tau, showed excellent intra-assay stability (1.2-3.1%). In subjects who underwent repeat CSF after 8 weeks, temporal stability was excellent for tau (7.7%), good for Aβ38 (11.7%) and Aβ40 (12.2%), and fair for Aβ42 (16.6%). Aβ42 and tau concentrations also correlated highly with data from comparable assays on other platforms (Fujirebio Innotest and Luminex Alzbio3). *Conclusion:* Key metabolic and inflammatory biomarkers were present and measurable in the CSF of individuals with neurocognitive impairment due to AD, though these markers demonstrated a range of intra-assay variabilities and temporal stabilities. To be useful for guiding clinical diagnosis or staging, or monitoring treatment effects in AD clinical trials, biomarker assays must demonstrate good technical performance

characteristics (i.e. be within the linear detection range, have low intra- and inter-assay variability) and ideally maintain adequate temporal stability, in order to allow for sensitive recognition of drug effects or longitudinal changes. Temporal stability in dynamic metabolic-inflammatory-vascular biomarkers may be affected by many factors, including diurnal variation, sleep, diet, seasonality, and general health fluctuations. Given their reliability and temporal stability, our preliminary findings suggest that Flt1, IL-6, IL-8, MCP1, and PIGF are excellent candidate biomarkers that should be further evaluated for potential use in clinical trials focused on metabolic, inflammatory, and vascular contributions to the development and progression of AD. Other candidates with high reliability but less temporal stability (e.g. YKL-40) should likewise be explored, especially if normative patterns of variation can be established. Candidates with poor intra-assay and temporal stability are likely of limited utility in longitudinal clinical or research settings.

P1-45 COGNITIVE AND FUNCTIONAL CHANGES ASSOCIATED WITH AB PATHOLOGY AND THE PROGRESSION TO MILD COGNITIVE IMPAIRMENT. Philip S. Insel[1,2,3] Michael C. Donohue[4], R. Scott Mackin[2,5], Paul S. Aisen[4], Oskar Hansson[1,6], Michael W. Weiner[2,3], Niklas Mattsson[1,6,7] and the Alzheimer's Disease Neuroimaging Initiative *((1) Clinical Memory Research Unit, Faculty of Medicine, Lund University, Lund, Sweden; (2) Center for Imaging of Neurodegenerative Diseases, Department of Veterans Affairs Medical Center, San Francisco, CA, USA; (3) Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA, USA; (4) Department of Neurology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; (5) Department of Psychiatry, University of California, San Francisco, CA, USA; (6) Memory Clinic, Skåne University Hospital, Sweden 7Department of Neurology, Skåne University Hospital, Sweden)*

Background: Cognitively-normal people with evidence of β-amyloid (Aβ) pathology and subtle cognitive dysfunction are believed to be at high risk for progression to mild cognitive impairment due to Alzheimer's disease. Clinical trials in later stages of Alzheimer's disease typically include a co-primary endpoint to demonstrate efficacy on both cognitive and functional assessments. Recent trials focus on cognitively-normal people, but functional decline has not been explored for trial designs in this group. The goal of this study was therefore to characterize cognitive and functional decline in (1) cognitively-normal people converting to MCI and (2) cognitively-normal Aβ+ people. Specifically, we sought to identify and compare the cognitive and functional assessments and their weighted combinations that maximize the longitudinal decline specific to these two groups. *Methods:* We studied 68 people who converted from normal cognition to MCI and 70 nonconverters, as well as 137 Aβ+ and 210 Aβ- cognitively-normal people. We used bootstrap aggregation and cross-validated mixed-models to estimate the distribution of weights applied to cognitive and functional outcomes to form composites. We also evaluated best subset optimization. Using optimized composites, we estimated statistical power for a variety of clinical trial scenarios. *Results:* 55.4% of cognitively-normal to MCI converters were Aβ+. Large gains in power estimates were obtained when requiring participants to have both subtle cognitive dysfunction and Aβ pathology compared with requiring Aβ pathology alone. Additional power resulted when including functional as well as cognitive outcomes as part of the composite. Composites formed by applying equal weights to all measures provided the highest estimates of cross-validated power, outperforming both continuous weight optimization and best subset optimization. Using a composite to detect a 30% slowing of decline, 80% power was obtained for predicted Aβ+ converters with 375 completers/arm for a 30-month trial using a combination of cognitive/functional measures. In the Aβ+ group, power to approach levels suitable for a phase III clinical trial would require considerably larger sample sizes. *Conclusion:* Composites incorporating both cognitive and functional measures may substantially increase the power of a trial in a preclinical (Aβ+) Alzheimer's disease population with subtle evidence of cognitive dysfunction.

Theme : Clinical trials cognitive and functional endpoints

P1-46 STRATEGIC MEMORY ALZHEIMERS REHABILITATION TRAINING (SMART): COGNITIVE PROTECTION AND INTERVENTION FOR AMNESTIC-TYPE MILD COGNITIVE IMPAIRMENT (MCI). John W. DenBoer *(SMART Brain Aging, Inc.)*

Background: Dementia is a world-wide phenomenon, impacting more than 6 million people in the United States. Despite its projected prevalence, this is a significantly under-represented phenomena, with underestimate ranges from 15-35%. The combined effects of the aging of the population (caused by the shift of the baby boomer generation into dementia) and significant increase in life expectancy has combined to put dementia into the range of our largest medical, if not societal, problems. *Method:* The SMART Memory Program (DenBoer, 2008) is a cognitive intervention designed to promote the reduction of early-stage dementia. Although it has been found useful in all forms of dementia, it is particularly useful in amnestic-type MCI/VCI. It is a system of nee and novel cognitive exercises (e.g., brain games). *Results:* The current longitudinal study examined 356 non-paid clients (all with amnestic type MCI, mean baseline MoCA = 20) across a two year span of this program, finding an average improvement of 4.25 MoCA points at the conclusion of this 6-week program. Improvements in QOL and mood were also observed as a result of this program. *Conclusion:* The SMART Memory Program has been shown to be significantly helpful in reducing the cognitive and functional deficits associated with amnestic-type MCI/early stage dementia.

P1-47 STRATEGIC MEMORY ALZHEIMERS REHABILITATION TRAINING (SMART) MEMORY PROGRAM: TEMPORARY IMPROVEMENT FOR MCI/ VCI VIA SYSTEMATIC NOVEL COGNITIVE EXERCISE. John W. DenBoer *(Founder and Chief Medical Officer, SMART Brain Aging, Inc.)*

Background: The combined effects of the aging of the population (caused by the shift of the baby boomer generation into dementia) and significant increase in life expectancy has combined to put dementia into the range of our largest medical, if not societal, problems. In the state of Arizona, there is a projected 44-72% increase in dementia! Research has supported the use of cognitive intervention exercises to reduce early-stage dementia. Valenzuela and Sachdev (2009), in a literature review of 22 studies (involving approximately almost 30,000 individuals), found an overall risk reduction of 46% in individuals that were found to engage in a high level of regular cognitive activity. Perhaps more importantly, they found a dose-dependent relationship between cognitive exercise and reduction of dementia, which had not been found previously. *Method:* The SMART Memory Program (DenBoer, 2008) is a cognitive intervention designed to promote

the reduction of early-stage dementia. Results of this program have shown significant promise (e.g., DenBoer, 2013), and the present researchers are currently engaging in multiple research studies. The program is effective via the use of new and novel cognitive exercises. *Results:* The present study focuses on the cognitive and functional trajectory demonstrated by research subjects. Specifically, volunteer participants (all amnestic MCI/VCI individuals, n = 278) demonstrated significant improvement as a result of the program, but only while doing it and immediately after completion. This is line with current research trends. Implications of this "use it or lose it" phenomenon are discussed. *Conclusion:* The SMART Memory Program may be effective in helping mitigate the cognitive/functional decline associated with early-stage dementia/MCI, although these effects were found to be temporary. A randomized clinical trial (RCT) appears needed and will be conducted.

P1-48 NEURAL PREDICTORS OF COGNITIVE IMPROVEMENT BY THE MEMORY TRAINING BASED ON METAMEMORY CONCEPT IN OLDER ADULTS. Jun-Young Lee[1], Soowon Park[2], Seung-Ho Ryu[3], Jung-Hae Youn[4], Jong-Min Lee[5] *((1) Department of Psychiatry, Seoul National University College of Medicine & SMG-SNU Boramae Medical Center, Seoul, Republic of Korea; (2) Department of Education, Sejong University, Seoul, Republic of Korea; (3) Department of Psychiatry, School of Medicine, Konkuk University, Konkuk University Medical Center, Seoul, Republic of Korea; (4) Yongmoon Graduate School of Counseling Psychology, Seoul, Republic of Korea; (5) Department of Biomedical Engineering, Hanyang University, Seoul, South Korea)*

Backgrounds: Many studies have reported that memory-training programs can help older people. However, only some of them benefit from such a program while others do not. Understanding the clinical and neural inter-individual differences for predicting cognitive improvement is important for maximizing the training efficacy of the memory-training programs. The purpose of this study was to find the individual characteristics and brain morphological characteristics that predict the cognitive improvement after the multi-strategic memory training based on metamemory concept. *Methods:* A total of 39 older adults participated in the memory-training program. They underwent magnetic resonance imaging scans at the entry of the training and received the neuropsychological tests twice, before and after the training. *Results:* Stepwise regression analysis showed that lower years of education predicted the cognitive improvement. In MRI, thinner cortices of precuneus, cuneus and posterior cingulate gyrus and higher white matter integrity of the splenium of corpus callosum predicted the cognitive improvement. *Conclusion:* Assessing the initial educational level and brain morphology is important for predicting cognitive enhancement by the memory training. Older adults with poor learning strategies and a higher integrity of hippocampal network may be aided by the multi-strategic training based on metamemory concept.

P1-49 EXPANDING ON THE COGNITIVE FUNCTION INSTRUMENT FOR USE IN SECONDARY PREVENTION TRIALS. Rebecca E. Amariglio[1,2,3], Dylan R. Kirn[2], Rachel F. Buckley[2,3,4,5], Elizabeth C. Mormino[2,3], Dorene M. Rentz[1,2,3], Reisa A. Sperling[1,2,3] *((1) Department of Neurology, Brigham and Women's Hospital, Boston, MA, USA; (2) Department of Neurology, Massachusetts General Hospital, Boston, MA, USA; (3) Harvard Medical School, Boston, MA USA; (4) Florey Institutes of Neuroscience and Mental Health, Melbourne, Australia; (5) Melbourne School of Psychological Science, University of Melbourne, Australia)*

Background: As the field of Alzheimer's disease (AD) moves towards early detection and prevention, new functional endpoints are needed to examine treatment effects in asymptomatic individuals. Patient-reported outcomes are increasingly valued as a way of observing the impact of disease and treatment that may only be perceptible to the individual. Indeed, current FDA guidance states that while sponsors may gain accelerated approval of a preclinical treatment using a primary cognitive outcome, ultimately they will be required to demonstrate clinically meaningful therapeutic effects. Recently, the Cognitive Function Instrument (CFI), a questionnaire designed to detect early changes in cognitive functioning in asymptomatic individuals, was shown to track with longitudinal clinical and cognitive outcomes, particularly when self and study partner report were considered together (Amariglio et al., 2015). Encouraged by these findings, we sought to improve upon the original CFI, by addressing some of its psychometric limitations (e.g., restricted response range, limited time reference) in order to develop and validate a measure that could serve as a gold-standard endpoint for AD secondary prevention trials. Here, we examine a modified self-report CFI. *Methods:* Test Development: The original CFI is comprised of 14 items (herein referred to as CFI-14) that are all in reference to change from 1 year ago and response options are restricted to "yes" "no" and "maybe." Additionally, several items are double-barreled questions making it difficult to know which aspect of the question the participant is responding to. The new version of the CFI is comprised of 20 root items (herein referred to as CFI-20), response options are on a 5-point Likert scale, and questions are asked in reference to Current Functioning ("Never-Always"), Change from 1 year ago ("Much Better-Much Worse"), and Concern about any change in functioning ("Not at all-Extremely"), resulting in three subscales. Participants: Fifty older participants (78.3±5.9 years old, 15.8 ±3.0 years education, 54% female, CDR 0 = 36, CDR 0.5 = 14) from the Harvard Aging Brain Study were administered the CFI-14 and the CFI-20. Average duration between administrations was 95 days (range 9-215 days). Validation procedures: Internal reliability of the CFI-20 items was assessed and compared with that of CFI-14. Exploratory factor analyses were conducted on both the CFI-14 and the CFI-20. To assess external validity, the CFI-20 was correlated with the CFI-14 and the Everyday Cognition Scale (E-Cog). Both versions of the CFI were used to predict concurrent Global CDR in separate logistic regression models. Finally, retrospective change on the Preclinical Alzheimer's Cognitive Composite (PACC) (4-6 years) was used to predict CFI scores using mixed effects models. *Results:* The mean score of the CFI-14 and the mean score for the three subscales of the CFI-20 were explored in the current analyses. When examining the CFI scores, CFI-14 was skewed and had a limited range (average response between "no" and "maybe"). CFI-20 Current functioning and CFI-20 Concerns were normally distributed, but CFI-20 Change from 1 year ago was not normally distributed and had a limited range (average response "same from 1 year ago"). Neither version of the CFI was associated with age, education, or sex. Inter-item consistency on the CFI-20 subscales ranged from Cronbach's α= 0.76-0.94 across the three subscales consistent with CFI-14 (Cronbach's α=0.84). A factor analysis of the CFI-14 revealed two factors (Memory, ADLs). By contrast, a factor analysis of the CFI-20 Current functioning subscale revealed three factors (Memory, ADLs, Normal Aging). Correlations between the CFI-14 and the subscales of the CFI-20 ranged from r =0.44-0.63, p<0.002. Correlations between CFI-20 and the E-Cog ranged from r = 0.41-0.61, p<0.001. In separate logistic regression models, both CFI-14 (B= 7.6, p=0.002) and CFI-20 Current functioning (B= 2.8, p=0.006) significantly predicted concurrent Global CDR. Using linear mixed models, retrospective decline on the PACC predicted

CFI-14 (β= -0.13, p<0.001) and CFI-20 Current functioning (β= -0.04, p=0.03). *Conclusion:* The findings of this pilot study suggest reasonable overlap between the CFI-20 and the CFI-14, but with a few important differences. Correlations between CFI-14 and CFI-20 were significant indicating individuals tended to respond consistently across the two measures. However, CFI-14 showed a non-normally distributed range of responses, compared to the CFI-20 Current functioning. When predicting clinical status and retrospective decline, both versions performed similarly. Interestingly, CFI-20 Change from 1 year ago, was not a normally distributed score. This may be due to the fact that items in this subscale had two response options indicating improvement in functioning, which none of the subjects endorsed in the current study. Nonetheless, if this tool is to be used in clinical trials, being able to demonstrate improvement in functioning is critical. Ultimately, longitudinal studies and biomarker correlations will be most informative in determining whether the CFI-20 will prove to be a sensitive indicator of nuanced functional changes at the preclinical stages of AD.

P1-50 BIAS AND EQUIVALENCE IN CROSS-CULTURAL ITEM EQUIVALENCE OF THE ALZHEIMER'S DISEASE ASSESSMENT SCALE – COGNITION (ADAS-COG). Anzalee Khan[1,2], Ioan Stroescu[1], Alexandra Atkins[1], Rich Keefe[1,3] *((1) NeuroCog Trials; (2) Nathan S. Kline Institute for Psychiatric Research; (3) Duke University)*

Introduction: In cross-cultural studies, the inquiry as to whether test scores obtained in different cultural populations can be interpreted in the same way across these populations has to addressed. Bias and equivalence have develop into the common terms to refer to the issue. Cognitive domains may differ across cultures. Consequently, when assessing cognition using a measure developed elsewhere, it is important to test its cultural equivalence. Clinical studies continue to expand by setting up trials in multiple countries; and although scales may be culturally validated, it does not imply that interpretation and results of scale items are similar across countries, regions and cultures. Examination of the equivalence of rating scales involves several levels, including conceptual equivalence of meaning, in addition to quantitative tests of differential item functioning (DIF). DIF includes the evaluation of conditional relationships between item response and group affiliation. As the ADAS-Cog is translated and utilized across many countries, identifying items that show DIF for various geo-cultural groups, can help guide rater training and data monitoring programs to develop tailored training across cultures. Do test items on the ADAS-Cog function in different ways for different geo-cultural groups? *Methods:* Data from the Critical Path Institute Online Data Repository (CODR) was used. The dataset included 3,939 subjects with AD. For the geo-cultural group: Africa (n = 95), Australia (n = 164), Eastern Asia (n = 46), Northern Europe (n = 503), Southern Europe (n = 162), Russia (n = 23), Southern Europe (n = 334), North America (n = 2,571). Africa, Eastern Asia and Russia were not included in the analysis due to small sample size. A principle components analysis assessed unidimensionality of the subscales. Differential Item Functioning (DIF) analysis examined cross-cultural differences among each item of the ADAS-Cog. *Results:* Across all countries, moderate to severe DIF was observed for the Word Recognition Task, Word Recall Tasks and Comprehension of Spoken Language. The results of the analysis indicate that the content of the item seemed to be related to geo-cultural DIF for Comprehension, Recall Tasks and Comprehension of Spoken Language in Africa; Orientation and Word Recall Task in Australia; and Comprehension of Spoken Language in Southern Europe. *Conclusions:* The strength of item-level analysis as opposed to group mean difference analysis is that geo-cultural differences can be detected at the item level, even when no mean differences can be detected at the group level. The results of the current study further highlight the need for thorough individualized training and data review of scores on the ADAS-Cog across different groups (geo-cultural), to reduce sources of unreliability.

Friday, December 9

Theme : Clinical Trials Results

P2-1 A NOVEL SNP GENOTYPING ARRAY FOR ALZHEIMER'S DISEASE DETECTION AT THE PRECLINICAL STATE. Harald Hampel[1,2], Maryam Shoai[3], Lakshmi Radhakrishnan[7], Richard Pither, Geoff Scopes[7], Marie-Claude Potier[1], Valentina Escott-Price[6], Simon M Laws[5], Simone Lista[2,8], Julie Davis[4], Claire Bloor[7], Bruno Dubois[1], John Hardy[3] *((1) Université Pierre et Marie Curie, Paris, France; (2) AXA Research Fund and UPMC Chair, Paris; (3) UCL Institute of Neurology, London, United Kingdom; (4) Cytox Ltd, UK, Oxford, United Kingdom; (5) Edith Cowan University, and Cooperative Research Centre (CRC) for Mental Health, Perth, Australia; (6) Cardiff University, Cardiff, United Kingdom; (7) Affymetrix UK and USA; (8) IHU-A-ICM – Paris Institute of Translational Neurosciences, Paris, France)*

Background: The INSIGHT study is a mono-centric French cohort at the Pitié-Salpêtrière University Hospital (Paris) including 317 cognitively normal individuals with subjective memory complaints (SMC) and defined brain amyloid status: 88 amyloid positive, showing significantly increased cortical uptake of amyloid tracer 18F-AV-45 (Amyvid) above threshold on positron emission tomography (PET) imaging, and 229 amyloid negative. Demographic, cognitive, functional, nutritional, biological, genetic/genomic, volumetric/functional magnetic resonance imaging (MRI), diffusion tensor imaging (DTI) and arterial spin labelling (ASL) sequences, 18F-fluorodeoxyglucose (FDG)-PET imaging, high-density electroencephalography (EEG) recordings with resting state and event-related potential (ERP) measures, were performed at baseline (actigraphy and cerebrospinal fluid (CSF) investigations are optional). All subjects participate in a 5-year follow-up with comprehensive neuropsychological assessments every 6 months (including new episodic memory tests, functional measures and subjective questionnaires for identifying possible progression), EEG and actigraphy investigations every year, complete MRI, FDG-PET and amyloid-PET scans every 2 years. It is currently considered that the efficacy of disease-modifying treatments should be assessed at earliest stages of the disease, even in the preclinical one. To this aim, we require both sensitive diagnostic and prognostic tools for the asymptomatic at-risk for Alzheimer's disease (AD) (AR-AD) subjects and also to identify variables and biomarkers defining their risk of progression/conversion to full blown disease. In both cases, advanced genetic analysis is a promising route to diagnostic dissection. *Methods:* Whole exome sequencing of well characterised, amyloid-PET stratified, multi-modal biomarker assessed AD cases and healthy controls has been used to define the content of a novel array of single nucleotide polymorphism (SNP) markers. This panel, which performed with high levels of accuracy (AUC) in differentiating AD and healthy controls in an independent test set of samples, is now being used in the SNP genotyping of Paris INSIGHT cohort subjects using Affymetrix Axiom Genotyping technology. *Results:* Genetic risk variants, i.e. SNPs, will be identified. They can be used,

ultimately, to develop an algorithm predicting AD progression. In turn, this is expected to facilitate early AD detection, clinical diagnosis, and therapy trials by reducing both misdiagnosis rates and enabling more accurate prediction of expected disease progression rates to defined milestones. *Conclusions:* The results from initial cross-sectional analysis of the INSIGHT cohort will be presented. The study is supported by the IHU-A-ICM, the Memento cohort, the Fondation Plan-Alzheimer, Pfizer and Amyvid/Lilly.

P2-2 A CLINICAL PRECISION MEDICINE APPROACH REDUCES ALZHEIMER'S, DEMENTIA AND VASCULAR RISK AND IMPROVES COGNITION: RESULTS FROM THE ALZHEIMER'S PREVENTION CLINIC PATIENT REGISTRY AT WEILL CORNELL MEDICINE AND NEWYORK-PRESBYTERIAN. Richard S. Isaacson[1], Robert Krikorian[2], Katherine Hackett[1], Chiashin Shih[1], Mu Ji Hwang[3], Jaclyn L. Chen[1], Josefina Meléndez-Cabrero[4], Randy Cohen[5], Mary Montgomery[6], Jessica Shum[1], Matthew W. Schelke[1], Roberta Marongiu[1], Jeannette Hogg[1], Robert Kachko[7], Cara Berkowitz[1], Emily Caesar[1], Alon Seifan,[8] *((1) Weill Cornell Medicine, New York, NY, USA; (2) University of Cincinnati College of Medicine, Cincinnati, OH, USA; (3) Weill Cornell Medicine – Qatar, Doha, QATAR; (4) Alzheimer's Prevention Clinic and Research Center, San Juan PR, USA; (5) Mount Sinai St. Luke's, New York, NY, USA; (6) NewYork-Presbyterian Hospital, New York, NY, USA; (7) Inner Source Health, New York, NY, USA; (8) Nova Southeastern University, FL, USA)*

Background: The Alzheimer's Prevention Clinic at Weill Cornell Medicine and NewYork-Presbyterian has been providing direct clinical care to patients with a family history of Alzheimer's disease (AD) since 2013. Patients seeking to lower AD risk undergo a comprehensive assessment and receive evidence-based, individualized, early intervention plans applying principles of pharmacogenomics, nutrigenomics and clinical precision medicine. A major focus of the prescribed interventions is to prevent or correct metabolic disturbance and its downstream effects (e.g., cerebral ischemia) on AD risk. *Methods:* In this prospective cohort study, patients with family history of AD and no or minimal cognitive complaints (primary prevention), and those meeting criteria for preclinical AD or mild cognitive impairment were recruited to our clinic registry. Patients with AD dementia were excluded from these analyses. Clinical evaluations were provided by a neurologist at baseline, two-months, and six-months. Clinical measures at baseline and six-months included cognition (e.g., NIH Toolbox Cognition Battery, Verbal Fluency, Trails B, MMSE), anthropometrics, blood biomarkers (lipid, inflammatory, metabolic, and nutritional), and genetic factors. Preliminary evidence-based multi-modal lifestyle recommendations in accordance with clinical history were provided at baseline. Precision medicine recommendations targeting modifiable risk factors were provided at two-month follow-up after clinical measures were obtained and discussed in a multi-disciplinary case conference with a team of neurologists, neuropsychologists, other specialists (e.g., preventative cardiologists, nutritionists, neurogeneticists), and visiting experts. In order to track adherence, attitudes towards AD, cognitive and non-cognitive symptoms, and other lifestyle habits, participants completed ongoing questionnaires. Participants were also educated on concepts of AD prevention via an online course on Alzheimer's Universe (www.AlzU.org) previously shown to enhance AD learning, which also contains validated computer-based cognitive testing, activities, and resources. This study assessed effectiveness of multi-modal interventions from baseline to six-months. Primary outcome measures included change in six AD, dementia, and vascular risk scales. Secondary outcomes included effectiveness of our interventions on blood biomarkers and cognition, stratified by genotype and physician/patient reported adherence, and psychosocial/lifestyle impact. Using SPSS, paired sample t-tests were computed to compare changes in risk scales. Changes in blood biomarkers were compared using ANOVA within and across different genotype and adherence groups. Multiple repeated-measured general linear models were computed to compare changes in cognition per genotype and adherence. NIH Toolbox cognitive scores were corrected for age, gender, ethnicity, and education to account for multiple comparisons across groups. Paired sample t-tests were conducted to analyze changes in the Fear of AD and Rapid Assessment of Physical Activity scales. *Results:* From March 2015-April 2016, 166 participants met inclusion criteria (mean age 56 ±13.6, range 28-92, 60.2% female, 72.9% Caucasian). Across subjects with blood biomarker data at baseline and six-months, improvements were observed in all six validated risk scales (CAIDE Midlife, p=.046, Cohen's d:0.584; MLDRI (Mid-life), p=.006, Cohen's d:0.119; LLDRI (Late-life), p<.001, Cohen's d:0.361; MAYO MCI, p<.001, Cohen's d:2.071; Late-onset AD, p=.001, Cohen's d:1.101; ANU-ADRI, p<.001, Cohen's d:0.902). The primary modifiable scale factor accounting for reduced risk was total cholesterol. Related lipid, metabolic, and nutritional biomarkers (triglycerides, p=.001; sdLDL-C, p<.001; Apo A-I, p<.001; LA-PLA2, p<.001; fasting insulin, p=.028; vitamin D, p<.001; homocysteine, p<.001; Vitamin B12, p<.001; RBC folate, p=.003; adiponectin, p<.001) also improved. Multiple domains including learning/memory (RAVLT 2, p=.02; RAVLT 3, p<.001; RAVLT Delayed, p=.001), executive function (Pattern Comparison, p<.001; Flanker, p<.001; Dimensional Card Sorting, p<.001; Oral Symbol Digit, p<.001) and language (Letter Fluency, p=.036) also improved in participants who completed cognitive assessments at baseline and six-months. Stratification by genotypes resulted in response variations in blood biomarkers and cognition. For example, APOE 3/3 and 3/4 carriers demonstrated a myriad of changes in blood biomarkers, yet only APOE 3/3 carriers showed improvements on learning (RAVLT3, p=.022), executive function (DDCS, p=.012; Flanker, p=.024) and language (Letter Fluency, p=.04). APOE 3/4 carriers outperformed other groups at baseline cognition. For MTHFR (C677T/A1298C mutations), although changes in blood biomarkers occurred across all pairs, participants with greater reduction in enzyme activity showed less robust cognitive improvements. Higher adherence correlated with greater improvements in blood biomarkers and cognition. Significant reduction in fear of AD (p<.001, Cohen's d:0.906) and increased physical activity (p< .001, Cohen's d:0.122) were found. *Conclusion:* These data suggest a clinical precision medicine approach toward AD prevention may reduce AD, dementia and vascular risk and improve cognition across multiple domains. Genotype and adherence appear to influence response. Limitations include the use of a low-compliance intervention group in place of controls, lack of a no- or minimal-intervention control group, the possibility of some degree of practice effects on neuropsychological testing, and lack of AD-specific biomarkers. Further research is ongoing to examine biomarkers and expanded genetics including mitochondrial DNA. We will include a delayed-start minimal-intervention control group, pre vs. post-intervention neuroimaging (FDG-PET, MRI with volumetrics, ASL and DTI) and microbiome assessments. Amyloid PET or CSF amyloid, p-tau, and t-tau will evaluate the effects of a precision medicine approach on AD pathology.

P2-3 PREDICTING RESPONSE TO A SIX MONTH TREATMENT WITH GALANTAMINE IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE BASED ON A SINGLE DOSE PHARMACOLOGICAL CHALLENGE. Anne Catrien Baakman[1], Laura Camps Cardenal[1], Carmen Gavan[2], Ovidiu Bajenaru[2], Marieke de Kam[1], Evelien Lemstra[3], Philip Scheltens[3], Adam Cohen[1], Joop van Gerven[1], Geert Jan Groeneveld[1] *((1) Centre for Human Drug Research, Leiden, The Netherlands; (2) University Emergency Hospital, Department of Neurology, Bucharest, Romania; (3) Alzheimer Centre, VU University Medical Center, Amsterdam, The Netherlands)*

Backgrounds: Cholinesterase inhibitors (CEIs) enhance cognitive functioning in patients with Alzheimer's disease (AD). Only about 35% of patients with AD respond favorably to treatment with a CEI. It is difficult to predict the response of patients. Many patients may therefore be treated in vain and exposed to possible adverse drug effects. Reactivity to an acute cholinergic pharmacological challenge may predict clinical responsiveness to cholinergic treatment in patients with AD. *Methods:* We performed a double-blind, placebo-controlled, randomized crossover study with a single dose of galantamine in 50 patients with mild to moderate AD (MMSE 18-26), followed by a six month open-label treatment with galantamine. In the challenge phase, the first 11 patients received a single dose of galantamine 8 mg and placebo in a cross-over fashion with 1 week washout in between. Based on an interim analysis, the dose was increased to a single dose of 16 mg of galantamine. Pharmacodynamic measurements were performed with the Neurocart, an automated test battery for repetitive cognitive and neurophysiological testing, and included adaptive tracking, facial encoding and recognition task, pharmaco-EEG, pupil size, saccadic and smooth pursuit eye movements, N-back test, visual verbal learning task, simple reaction time task and visual analogue scales. Measurements were done predose and at several timepoints postdose. Data were analysed with a repeated measures mixed effect model with treatment. In the treatment phase, patients received galantamine extended release in an escalating dose, starting with 8 mg per day for one month, and increasing to 16 mg per day if there were no side-effects. Follow-up visits occurred at 2 and 6 months and included the neuropsychological inventory (NPI), disability assessment for dementia (DAD), Alzheimer's disease assessment scale – cognition (ADAS-cog), clinical dementia rating scale (CDR) and mini-mental state examination (MMSE). Response to galantamine in the treatment phase was defined as having no decline on MMSE and NPI and DAD. Based on these scores, the group of patients is devided in responders and non-responders, the challenge effects of the PD variables were re-analysed with a repeated measures mixed effect model with treatment and group (responders and non responders). The contrast of interest is the placebo corrected galantamine response of responders versus non-responders. *Results:* 50 patients were included in the study. 2 patients dropped out during the challenge phase and 5 during the follow-up phase. In the challenge phase, a difference between galantamine and placebo was found on saccadic reaction time (-0.0099, CI -0.0195 - -0.0003, p=0.0430), EEG alpha Fz-Cz (-14.9% change from baseline (CFB), CI -21.0 - -8.3, p=0.0002), EEG beta Fz-Cz (-12.6% CFB, CI -19.4 - -5.3, p=0.0019) and EEG theta Fz-Cz (-17.9% CFB, CI -25.0 - -10.0, p=0.0001). At the end of the treatment phase, 32 patients were defined as non-responder and 11 patients as responder to galantamine treatment. When comparing challenge results between responders and non-responders to the 6 month treatment, the responders had a significantly higher decrease of EEG alpha Fz-Cz (-20.4%, CI -31.6 - -7.5, p=0.0045), EEG beta Fz-Cz (-15.7%, CI -28.3 - -0.9, p=0.0388) and EEG theta Fz-Cz (-25.9%, CI -38.4 - -10.9, p=0.0024) after acute administration of galantamine. *Conclusion:* A pharmacological challenge with galantamine in patients with mild to moderate AD induces acute, measurable effects on saccadic reaction time and frontal EEG parameters. The decrease on frontal alpha, beta and theta EEG activity is significantly more extensive in responders to a six month treatment with galantamine. If a prediction rule is made, based on the effect of a single dose of galantamine on frontal alpha EEG activity, 20 patients are classified as responder, including all patients defined as responder after 6 months of treatment. If this prediction rule could be prospectively validated, this could reduce the number of unnecessarily treated patients with approximately 60%. In this study, a strict definition of response was used. Post-hoc analyses have to reveal whether other definitions of response lead to different outcomes.

P2-4 CLINICAL EXPERIENCE WITH A NOVEL AMYLOID-BETA PEPTIDE VACCINE FOR IMMUNOTHERAPY OF MILD ALZHEIMER'S DISEASE. P. N. Wang[1], M. J. Chiu[2], C. C. Huang[3], C. C. Chang[4], P. A. Frohna[5], Y. T. Tseng[5,6], S. Lynn[6], X. D. Fang[7], C. L. Finstad[7], C. C. Yu[5,6], C. Y. Wang[5,6,7] *((1) Department of Neurology, Taipei Veterans General Hospital, Taipei, Taiwan; (2) Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan; (3) Department of Neurology, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan; (4) Department of Neurology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; (5) United Neuroscience, Inc., Hauppauge, NY, USA; (6) UBI Asia, HsinChu, Taiwan; (7) United Biomedical, Inc., Hauppauge, NY, USA)*

Background: Immunotherapy is a promising strategy for the treatment of Alzheimer's disease (AD) that uses antibodies through active or passive immunization to reduce burden of amyloid beta (Aβ), which is considered a major neuropathological feature of AD. United Neuroscience is developing a novel AD Immunotherapeutic Vaccine (UB-311) comprised of two peptides: synthetic Aβ1-14-targeting peptide immunogens (B-cell epitopes) linked with two proprietary, synthetic helper T-cell peptide epitopes (UBITh®) that maximize immunogenicity, which is formulated in a Th2-biased delivery system designed to minimize T-cell inflammatory reactivity. Preclinical studies in non-human primates with UB-311 have demonstrated safety and an immune response to Aβ that support clinical trials. *Methods:* A Phase 1, first-in-human (FIH), open-label study enrolled 19 patients aged 50 to 80-yrs-old with mild to moderate AD at two sites (Taipei Veterans General Hospital; National Taiwan University Hospital). All patients received intramuscular doses of 300 μg UB-311 at weeks 0, 4, and 12 and among whom, 14 patients of evaluable population were followed until week 48. The primary objective was to characterize the safety and tolerability of UB-311 using adverse events (AEs), blood laboratory tests, MRI and ECG. Immunologic response to UB-311 was assessed using an Aβ enzyme immunoassay (EIA), while the clinical endpoints were changes from baseline in the mini–mental status examination (MMSE), the Alzheimer's Disease Assessment Scale - Cognition (ADAS-Cog) and the Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change (ADCS-CGIC). A second trial, a randomized, double-blind, placebo-controlled, 78-week, multi-center Phase IIa trial was initiated in 2015 at 5 sites in Taiwan to characterize the longer-term safety, tolerability, immunogenicity and efficacy of two different regimens of UB-311 (initial 3 priming doses followed by either 4 booster doses given every 12 wks or 2 booster doses given every 24 wks) in 45 patients with mild AD and a positive Aβ PET scan (read by the central core imaging lab) at baseline. *Results:* In the FIH, an immune response to UB-311 consisting of highly-specific antibodies against the N-terminus of the Aβ peptide represented by Aβ1-10 was found in all patients receiving 3 injections

that persisted at high levels for at least 3 months after the last dose, without signs of meningoencephalitis. No serious drug-related or intolerable AEs were reported. Overall, the ADAS-Cog showed an increase of 4.9 points; the MMSE decreased by 2.2 points; and about 39% of patients showed improvement or no change in the ADCS-CGIC scores during the study. Compared with younger patients (<60 years), older patients (≥60 years) showed a lower rate of increase in ADAS-cog, a lower rate of decline in MMSE, and a higher percentage of patients with improvements or no change in ADCS-CGIC at Week 48 (44 vs. 25%). Patients with mild AD (MMSE ≥20) showed a stable trend of ADAS-Cog over time, a lower rate of decline in MMSE, and a higher percentage of patients with improvement or no change in ADCS-CGIC, compared to those with moderate AD (MMSE <20) (43 vs. 33%). The difference in the rate of ADAS-Cog change was significant between patients with mild and moderate AD (P = 0.0002). A subset of older subjects with mild AD (n = 6; age ≥ 60 years with baseline MMSE ≥ 20) produced high antibody titers to UB-311 and displayed improved neuropsychological outcomes characterized by decreased ADAS-Cog (P = 0.0001), and slower rate of change on the MMSE (P = 0.0071), as compared to the rest of AD cohort. As of June 2016, 20 pts between 60 and 90-yrs-old with mild AD have been enrolled into the Phase IIa trial, which is expected to conclude in 2018. No serious drug-related AEs have been reported to date. Additional design features and blinded safety data will be presented at the CTAD conference. *Conclusion:* UB-311 was considered safe, well-tolerated and produced an immune response in 100% of pts with mild to moderate AD in the FIH study. Exploratory analyses suggested that UB-311 may be more beneficial in subjects >60 yo with mild AD, the patient population for the ongoing Phase IIa trial. The incorporation of amyloid imaging in Phase IIa will serve to further characterize whether production of anti-Aβ1-14 antibodies following UB-311 treatment reduces the amount of brain Aβ and slows disease progression in patients with mild AD.

P2-5 INTEPIRDINE (RVT-101), A 5-HT6 RECEPTOR ANTAGONIST, AS AN ADJUNCT TO DONEPEZIL IN MILD-TO-MODERATE ALZHEIMER'S DISEASE: EFFICACY ON ACTIVITIES OF DAILY LIVING DOMAINS. Jason T. Olin, Ilise Lombardo, Geetha Ramaswamy, Lawrence Friedhoff *(Axovant Sciences, Inc., New York, NY, USA)*

Background: Intepirdine (RVT-101) is an orally administered, 5-hydroxytryptamine 6 (5-HT6) receptor antagonist being investigated for the treatment of mild-to-moderate Alzheimer's disease (AD). It includes a number of favorable properties including oral administration, once daily dosing, lack of a food effect, and the low potential for drug interactions. We present results of a secondary analysis of the 23-item Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL23) from a randomized, double-blind, placebo-controlled Phase 2b study. *Methods:* In this study, 684 subjects with mild to moderate AD (MMSE score 10-26 points), and receiving stable donepezil treatment, were randomized to receive 35 mg intepirdine, 15 mg intepirdine, or placebo. A 48-week study, primary endpoints were assessed at week 24. A pre-specified Mixed-Methods Repeated Measures (MMRM) was used to evaluate the intent-to-treat population at week 24. The ADCS-ADL23 items range from basic to instrumental ADLs. A total score of 0-78 points may be obtained; lower scores indicate greater impairment. For this trial, the following scales were pre-specified: • Basic ADLs. The score was calculated as the sum of questions 1–6b and ranges from 0-22 points (items: eating, walking, using the toilet, bathing, grooming and dressing). • Instrumental ADLs. The score was calculated as the sum of questions 7-23 and ranges from 0-56 points (items: using the telephone, watching television, conversations, clearing dishes, personal belongings, making drinks, making snacks, taking rubbish out, getting out and about, shopping, keeping appointments, being left alone, current events, reading, writing, pastimes/hobbies, household chores). • Total Independence ADLs. This scale was a dichotomous recalculation of the 23 ADCS-ADL items, by scoring an item as 1 point if the highest performance was obtained, and 0 points for any other response. The score ranges from 0-23 points, with a score of 23 suggesting complete independence. *Results:* At Week 24, in subjects receiving stable donepezil treatment, statistically significant treatment differences in favor of intepirdine 35mg over placebo were observed for the Instrumental ADLs scale (Mean treatment difference 1.6 points, p = 0.023) and the Total Independence ADLs scale (Mean treatment difference 1.0 points, p = 0.002). As seen in the primary analysis mean treatment differences for the 15-mg group were generally numerically superior to placebo; however, they were not statistically significant. The mean Basic ADL scale scores remained stable across the 24-week treatment phase for all treatment groups; no clinical or statistically significant treatment differences were observed. *Conclusion:* In this pre-specified secondary analysis of subjects with mild-to-moderate AD completing a Phase 2b study, the 35 mg dose of intepirdine was shown to be effective in improving instrumental ADLs as well as a measure of independence through the total independence scale. These results suggest that intepirdine treatment has the potential to provide benefits on important aspects of function in Alzheimer's disease. The 35 mg dose of intepirdine has advanced into a confirmatory Phase 3 study (Study RVT-101-3001 (NCT02585934)) that is now underway.

P2-6 THE EFFICACY OF INTEPIRDINE (RVT-101), A 5-HT6 RECEPTOR ANTAGONIST, AS AN ADJUNCT TO DONEPEZIL IN ADULTS WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE: COMPLETER ANALYSIS OF A PHASE 2B STUDY. Geetha Ramaswamy[1], Ilise Lombardo[1], Jason T. Olin[1], Stephen C. Piscitelli[2], Lawrence Friedhoff[1] *([1] Axovant Sciences, Inc., New York, NY, USA; [2] Roivant Sciences, Inc., New York, NY, USA)*

Background: Intepirdine (RVT-101) is an orally administered, 5-hydroxytryptamine 6 (5-HT6) receptor antagonist being investigated for the treatment of mild-to-moderate Alzheimer's disease (AD). It includes a number of favorable properties including once daily dosing, lack of a food effect, and the low potential for drug interactions. We present results of a post-hoc analysis of observed data from subjects who completed a randomized, double-blind, placebo-controlled Phase 2b study. *Methods:* In this study, 684 subjects with mild to moderate AD (MMSE score 10-26 points), and receiving stable donepezil treatment, were randomized to receive 35 mg intepirdine, 15 mg intepirdine, or placebo. A 48-week double-blind study, primary outcomes were assessed at week 24. An analysis of covariance (ANCOVA) method was used to evaluate multiple endpoints on cognition and function based on observed data, including the Alzheimer's Disease Assessment Scale- Cognitive Subscale (ADAS-cog), Clinical Dementia Rating- Sum of Boxes (CDR-SB), and the Alzheimer's Disease Cooperative Study: Activities of Daily Living Scale (ADCS-ADL) scales at weeks 12, 24, 36, and 48. *Results:* The proportion of subjects completing the study ranged from 86-89% from week 0 to week 24 and from 87-89% for the proportion of patients from week 24 and continued to week 48. At week 12, subjects on stable donepezil that received 35 mg intepirdine improved by 1.29 (p = 0.008) and 1.72 (p = 0.016) points on the ADAS-cog and the ADCS-ADL respectively compared to those subjects that received placebo. At week 24, subjects receiving 35 mg intepirdine improved

by 1.63 (p = 0.007) and 2.11 (p = 0.016) points on the ADAS-cog and the ADCS-ADL respectively compared to placebo. At week 48, subjects receiving 35 mg intepirdine improved by 1.82 (p = 0.018) and 2.34 (p = 0.048) points on the ADAS-cog and the ADCS-ADL respectively compared to placebo. Subjects who received 35 mg intepirdine achieved a statistically significant benefit on CDR-SB compared to subjects who received placebo solely at week 12. Mean ADAS-cog, ADCS-ADL and CDR-SB scores for the 15 mg group were generally numerically superior to placebo; the differences were not statistically significant. *Conclusion:* In this analysis of subjects completing a Phase 2b study in subjects with mild-to-moderate AD, the 35 mg dose of intepirdine was shown to be effective in improving cognition and function as an adjunct to stable donepezil at all time points measured in this 48-week study. Given the low drop-out rate, this analysis seems to provide an accurate representation of the study. The 35 mg dose of intepirdine has advanced into a confirmatory Phase 3 study that is now underway.

P2-7 COMBINED NEURAL AND MESENCHYMAL STEM CELL THERAPY FOR PATIENTS WITH DEMENTIA: PRELIMINARY RESULTS OF A SAFETY PHASE I STUDY.
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Background: Alzheimer's disease (AD) is a complex pathology of the central nervous system characterized by the degradation of cognitive abilities due to the detrimental effects of Abeta aggregates/oligomers and the formation of neurofibrillary tau tangles. Most of the experimental therapies and clinical efforts currently under development target either Abeta or tau proteins with high specificity. Stem cells may represent a novel multi-target approach to tackle AD. Currently only mesenchymal stem cells are used in few clinical trials for AD. A combination of neural stem cells in addition to mesenchymal stem cells may provide additional benefits for rescuing neurons and possibly restoring their functions. *Methods:* Clinical safety of intravenous (IV) administration of ischemia tolerant mesenchymal stem cells (itMSC) was evaluated in a Phase I/IIa clinical trial in patients with previous stroke. Phase I of this trial was a dose-escalation study evaluating three doses of itMSC, with five subjects per dose receiving 0.5, 1.0 and 1.5 million itMSC per kilogram of body weight. All three doses were found to be safe based on evaluation of vital signs and the occurrence of adverse and severe adverse events (AE, SAE). The safety of a combined administration of neural stem cells (NSC) and itMSC was studied in a Phase I trial in subjects with dementia. Three NSC doses (30, 45 and 60 million cells/4 subjects per dose) was delivered intrathecally followed with intravenous (IV) injection of the maximum safe dose of itMSC (1.5 million cells per kilogram body weight). Brain MRI was performed at the baseline, 3 and 6 months post stem cell administration. During intrathecal injection a sample of CSF was collected for analysis of Abeta/tau. A neurological evaluation including MMSE, ADCS-cog, NPI, etc were performed at the baseline 0.5, 1, 3 months and every 3 months thereafter. The total follow-up period is 12 months. *Results:* Currently 10 patients have enrolled for the study, 8 patients were treated and 6 completed a 3 month follow up evaluation. 3 patients reported transient moderate back pain, which was attributed to the intrathecal intervention. Other 8 AE was considered as unlikely related to the investigational product. There were no serious adverse events or death in the study attributed to the product. The Data Safety Monitoring Board has decided that 30 and 45 million of NSC demonstrated an acute safety and recommended to proceed to the maximum dose of 60 million cells. During the course of the study it was observed that stem cell administration substantially reduced spasticity and patients with MMSE scores 14-19 gained up to 8 points in their scores. *Conclusions:* Safety profile of IV administration of itMSC and two intrathecal doses of NSC allowed to proceeding to the maximum dose of intrathecal NSC injection defined in the trial. The next step is to complete the safety study and continue with evaluating preliminary efficacy in a larger group of patients of combined NSC and itMSC therapy for AD and other dementias.

P2-8 CRENEZUMAB EXPOSURE-RESPONSE ACROSS AD ENDPOINTS SUPPORTS A HIGHER DOSE FOR PHASE 3.
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Background: Crenezumab is a humanized antibody for the treatment of Alzheimer's Disease. It is designed to bind multiple forms of Aβ, with high affinity for oligomers, and may reduce their accumulation and neurotoxicity. Two Phase 2 trials (ABBY and BLAZE) were conducted in the mild-to-moderate AD population, evaluating a high 15 mg/kg IV Q4W dose and a low 300 Q2W SC dose. The Phase 2 studies demonstrated a consistent treatment benefit on cognition in the 15 mg/kg IV dose for the milder population (MMSE ≥ 20), while the low 300 mg q2wk SC dose level lacked a consistent treatment effect across endpoints, suggesting that higher doses are associated with greater efficacy signals. In both Phase 2 studies, crenezumab was well-tolerated with only one case of ARIA-E across both studies indicating that the therapeutic window has not been fully explored. Higher IV doses in mild-to-moderate Alzheimer's disease is currently ongoing (NCT02353598). *Methods:* A disease progression model for mild to moderate AD was established that described the longitudinal changes of the clinical endpoints ADAS-Cog and CDR sum-of-boxes (CDR-SB) simultaneously for patients in the Phase 2 studies. The model was extended to describe the effect of key demographic covariates on disease progression, and the effect of crenezumab on each endpoint as a hyperbolic function. Clinical trial simulations with 1000 replications of Phase 3 study design were conducted across a range of doses, describing the likelihood of achieving a percent relative reduction of disease progression in treated patients compared to placebo for ADAS-Cog and CDR-SB. *Results:* Model validation demonstrated that the model replicated the Phase 2 longitudinal data accurately and is fit for purpose for simulation of the disease progression and crenezumab treatment effect in the population of interest (milder AD population, baseline MMSE 22-26). The analysis showed faster disease progression in patients with moderate AD disease (lower baseline MMSE), ApoE4 positive genotype, female gender, and younger age. A relationship was seen between crenezumab exposure and treatment effect, which appeared to asymptote at the higher end of the range of exposures measured in Phase 2. Crenezumab treatment effect was associated with high baseline MMSE and ApoE4 positive genotype supporting better treatment effect in patients with mild AD. As compared to the 15 mg/kg Q4W dose, a 4-fold increase to 60 mg/kg Q4W dose in Phase 3 is predicted to achieve a 41% greater relative reduction on ADAS-Cog, and 44% on the CDR-SB in the milder AD population (baseline MMSE 22-26). *Conclusion:* A 60 mg/kg Q4W dose was selected for Phase 3, supported by a drug-disease model for mild to moderate AD, that was developed based on crenezumab Phase 2 data. The model adequately summarized longitudinal progression in ADAS-Cog and CDR items, preserving correlation between the endpoints. Clinical trial simulations suggest substantially increased efficacy at higher

exposures in patients with mild AD. As the model was trained on Phase 2 dosing, uncertainty in the predicted efficacy increases with increasing exposure where exposure falls outside that observed in Phase 2.

P2-9 PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY, AND TOLERABILITY OF THE NEW EXPLORATORY ALZHEIMER'S DRUG PIROMELATINE. Moshe Laudon, Amnon Katz, Anat Frydman, Nava Zisapel *(Neurim Pharmaceuticals (1991) Ltd, Tel-Aviv, Israel)*

Background: Piromelatine, (Neu-P11: N-(2-(5-methoxy-1H-indol-3-yl) ethyl)-4-oxo-4H-pyran-2-carboxamide, is a small molecule, developed for sleep disorders and Alzheimer's disease. Piromelatine is a MT1\MT2 melatonin receptor agonist (sleep promoting and neuroprotective effects) and a serotonin 5HT1A\D agonist (antidepressant and anxiolytic effects) with potential neurogenic effects. In mice, piromelatine produced dose-dependent neuroprotection against Aβ induced neurodegeneration, facilitated memory performance and ameliorated cognitive deficits. In other studies in mice and rats, piromelatine attenuated Alzheimer's disease risk factors such as insulin resistance, hypertension and sleep disorders and enhanced neurogenesis. In a Phase-II randomized double blind placebo controlled study in insomnia patients (clinicaltrials.gov identifier NCT01489969), piromelatine demonstrated significant improvements in sleep maintenance based on objective assessments (polysomnography recorded wake after sleep onset (WASO), sleep efficiency and total sleep time) and good safety profile with no detrimental effects on next-day psychomotor performance and memory. a phase II randomized double blind placebo controlled study of piromelatine in mild Alzheimer patients on stable doses of acetylcholinesterase inhibitors (the ReCOGNITION trial) is ongoing (clinicaltrials.gov identifier NCT02615002). The initial human studies (EudraCT No. 2008-002181-59 and clinicaltrials.gov identifier NCT01114126) described herein were a single ascending dose trial in healthy subjects (Study 1) and a multiple ascending dose trial in primary insomnia patients who were otherwise healthy (Study 2). In both studies, safety, tolerability, pharmacokinetics and pharmacodynamics of piromelatine were evaluated. *Methods:* In Study 1 subjects (N=32, males, mean age 29.8, SD 8.5 years) received placebo or piromelatine (5 to 200 mg p.o.) as single doses. Safety, tolerability and pharmacokinetics were assessed for 24 hours. In Study 2, subjects with primary insomnia according to DSM-IV (N=24, 60.7% female, mean age 39.8, SD 11.5 years) received daily doses of placebo or piromelatine (2, 5, 20 and 50mg) nightly for 6 days. Each subject received two ascending doses with 1 month washout between treatments. Safety, tolerability and pharmacokinetics were assessed for 24 hours at run in and at the last end of the study. *Results:* Piromelatine was well tolerated by healthy subjects and insomnia patients at all doses. All adverse events were mild in severity and the incidence was similar between all treatment groups, including placebo. In Study 1, the mean plasma, mean Cmax values, as well as the mean values of AUC[0-24h], AUC[0-t], and AUC[0-inf], respectively, showed a dose proportional linear increase. Maximum plasma concentration of piromelatine were attained (Tmax) at 0.8 to 1.3 hr post dose; thereafter plasma concentration declined with a mean apparent terminal half-life of 2.3 +0.6 hr. Study 2 showed that the pharmacokinetic profile of piromelatine was maintained after multiple dosing (T1/2=1.2-2.9 h). Ratios of (Day 5 – Day 6) over (Day 1 – Day 2) pharmacokinetic parameters were found to be 0.946 (90% CI: [0.799 – 1.119]) for Cmax, 0.930 (90% CI: [0.910 – 1.110]) for AUC0-24 and 1.034 (90% CI: [0.943 – 1.134]) for AUCinf, respectively. These results show that no accumulation of piromelatine has occurred and the pharmacokinetics of piromelatine after a single dose and after multiple daily doses is equivalent. In Study 1, pharmacodynamic effects of piromelatine on sleep were assessed by objective (polysomnography) and subjective (Stanford Sleepiness Scale; SSS) means. Polysomnographic analyses revealed a major effect on sleep induction and maintenance (lower WASO and higher Sleep Stage 2) with maximal response at T+2 (2h after piromelatine administration) of all doses studied concurrently with the changes in plasma piromelatine levels. Analysis of the frequency (%) of subjects reporting an increase in subjectively perceived sleepiness (SSS) indicated a statistically significant effect of piromelatine 5, 20 and 200 mg at T+4h compared to the placebo group (P=0.031). These results demonstrate that piromelatine intake is associated with subjective sleepiness 4 h after administration. In Study 2, polysomnographic recordings indicated that multiple daily doses of piromelatine (20 and 50mg) significantly improved sleep continuity (number of awakenings and sleep fragmentation, P<0.01) in the insomnia patients while sleep latency tended to decrease compared to placebo. Trends towards improvements were also seen in subjective outcomes of sleepiness and sleep quality at the higher doses of piromelatine. The results of the objective memory consolidation test (Word Pair Association Task) indicated that multiple dose treatment had neither detrimental nor beneficial effect on memory consolidation and retrieval the next day as measured by mean response time in the insomnia patients. *Conclusion:* Piromelatine is a well-tolerated investigational drug at all doses tested. It's pharmacokinetic and pharmacodynamics effects support further clinical development of this drug for sleep disorders and Alzheimer's disease.

P2-10 PHASE 1 PROGRAM OF ALZ-801, A NOVEL PRO-DRUG OF TRAMIPROSATE WITH IMPROVED TOLERABILITY: SUPPORTS BRIDGING TO UPCOMING PHASE 3 PROGRAM. J.A. Hey, M. Versavel, S. Abushakra, A. Power, P.L. Kaplan, M. Tolar *(Alzheon, Inc., Framingham, MA, USA)*

Background: ALZ-801 is a novel, orally bioavailable, small-molecule prodrug of tramiprosate with substantially improved pharmaceutical properties. Tramiprosate, the active moiety released after administration of ALZ-801, is a β-amyloid (Aβ) anti-aggregation agent that inhibits the formation of Aβ oligomers and prevents neurotoxicity. A Phase 1 program for ALZ-801 was conducted to bridge to the extensive Phase 3 clinical safety and efficacy database of tramiprosate in Alzheimer's disease (AD), with the objective of assessing the safety and tolerability of ALZ-801 at plasma concentrations that match the 150 mg BID dose of tramiprosate tested previously in Mild and Moderate AD patients. The Phase I program comprising approximately 170 subjects evaluated the single and multiple ascending dose (14-day) safety and tolerability of ALZ-801, when administered with or without food. These bridging studies were conducted using two solid dose formulations: a loose filled capsule and an immediate release tablet. The results demonstrate favorable safety and tolerability of ALZ-801 administered as a loose-filled capsule or tablet with marked improvements in pharmacokinetics (PK) and safety profile over oral tramiprosate. *Methods:* To advance the clinical development of ALZ-801 into Phase 3, we completed single ascending dose (SAD) and 14-day multiple ascending dose (MAD) Phase 1 bridging studies in healthy elderly volunteers to evaluate the safety, tolerability and PK of ALZ-801 administered as a loose filled capsule and an immediate release tablet. In addition, the PK properties of an immediate release tablet administered as sequential single doses (171-342 mg), under both fasted and fed conditions, were evaluated. The studies conducted as part of the bridging Phase

1 program were as follows: *Results:* Phase 1 single dose and multiple dose studies with the ALZ-801 capsule and tablet formulation show that ALZ-801 was well tolerated in healthy elderly subjects. The Phase 1 program comprised of approximately 170 subjects with an average age of the elderly subjects in cohorts A – C (capsule) of 57.1 – 61.6 years, and 65.8 years for cohort D (tablet). All cohorts were balanced for male and female volunteers. There were no severe or serious treatment emergent adverse events (TEAEs) and no adverse events (AEs) leading to discontinuation. All TEAEs except for one moderate event of vomiting were considered mild. The most common AEs were transient mild nausea and some instances of vomiting. There was no evidence of a dose response in the reported AEs. The top ALZ-801 dose of 340 mg (i.e., 200 mg tramiprosate equivalent), administered QD or BID, was well tolerated following initial titration, with a lower dose for one week. The incidence of nausea and vomiting markedly decreased during the second week of treatment, suggesting development of tolerance. The absence of relationship to exposure indicates that nausea and vomiting are likely due to a mild local upper GI irritation. The proposed dose regimen of 265 mg BID (tablet) was very well tolerated at PK exposure equivalent to historic tramiprosate data. The results show that ALZ-801 can be administered with or without food based on the PK profile. Administration with food may reduce the incidence of nausea or vomiting in some subjects. No trends in safety labs, vitals, or ECGs were identified. No dose limiting toxicity or MTD was observed over 2 weeks of dosing at doses up to 340 mg BID. *Conclusions:* In the present ALZ-801 Phase 1 bridging program, we have determined a dose schedule of ALZ-801 that results in equivalent exposure to the active moiety tramiprosate that occurs following administration of tramiprosate 150 mg BID. ALZ-801 was safe and well tolerated with a low incidence of primarily mild AEs in healthy elderly subjects. The safety and tolerability of ALZ-801 administered as a loose filled capsule or an immediate release tablet compares favorably with oral tramiprosate both as a single dose and at multi-dose steady state. These Phase 1 safety bridging data support the upcoming Phase 3 program of ALZ-801 in APOE4 positive AD subjects, with an optimized tablet formulation.

Study	Design	Dose Regimen	Subjects	Objectives
ALZ-801-101 SAD	Double-blind, placebo controlled, single	Single oral administration of ALZ-801, tramiprosate, and an extended release formulation of	Healthy young and elderly male and	Safety, tolerability and PK of single doses
ALZ-801-103 MAD	Double-blind, placebo controlled, multiple ascending dose	Cohorts A – C (capsule without food): Doses: 171 – 340 mg 14 days Cohort D (tablet with food): 265mg- 7 days	Healthy elderly male and female subjects	Safety, tolerability and PK of multiple doses
ALZ-801-104: SD	Open label, four-period, sequential, single dose	ALZ-801 tablet, single dose: 171 – 205 mg, fasted 205 – 340 mg, fed	Healthy young male and female subjects	Safety, tolerability and PK of immediate release tablet formulations; food effect

P2-11 PHASE 2 TRIAL OF PIROMELATINE FOR MILD ALZHEIMER'S DISEASE (THE RECOGNITION TRIAL).

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Background: The main experimental approaches for Alzheimer's disease (AD) are prevention of β-amyloid (Aβ) formation (e.g. β-secretase (BACE) inhibitors and newer γ-secretase modulators (GSMs)) and facilitation of Aβ clearance (e.g. anti Aβ antibodies, Aβ vaccines, Aβ aggregation inhibitors). Recent discoveries of the glymphatic system, as a main gateway for brain Aβ clearance during sleep, and the association of poor sleep with Aβ burden and cognitive deterioration open the gate for hitherto unexplored approaches. Sleep disorders are very common among people with AD and in particular, sleep problems among APOE e4 carriers are associated with eventual AD diagnosis. APOE e4 carriers report sleep disturbance almost 7 times more frequently than non-carriers; and as many as 63% of patients with mild cognitive impairment (MCI), and 44% of patients with AD demonstrate sleep disturbance. There are positive correlations between insomnia (as indexed by reduced total sleep time, prolonged sleep onset latency, and poor sleep quality) and increased Aβ burden in hippocampal-neocortical regions within the default mode network (DMN) brain areas that are linked to early AD in demented and non-demented older adults. The presence of sleep disorders is associated with rapid cognitive decline in patients with MCI and AD. Bidirectional relations between Aβ pathology and deep sleep (NREM delta slow wave sleep) are also observed in patients with MCI and AD. In brief, deterioration in cognition from healthy controls through MCI to AD patients may be linked to deterioration in sleep, and increased amyloidosis. This association sets the ground for a new therapeutic approach for patients with AD. Piromelatine is an investigational compound acting at two receptors (melatonin and 5-HT1A receptors) that are linked to sleep regulation and neurogenesis. Piromelatine is orally available, with short half-life (3 hours) and intended to be taken in the evening before bedtime. In preclinical tests in animals piromelatine showed neuroprotective action against Aβ induced neuronal cell death and cognitive decline and promoted sleep and neurogenesis. In previous clinical trials, piromelatine showed beneficial effects on sleep maintenance in patients with insomnia. It also enhanced EEG-recorded NREM delta slow wave sleep that is relevant to glymphatic system activity and brain Aβ clearance and decreased NREM β power, a fast EEG activity that is related to the hyperarousal experienced by patients with insomnia. Both effects are relevant and may be beneficial for AD patients. *Methods:* The ReCOGNITION Trial is a multi-center, double-blinded, randomized, placebo-controlled, dose-ranging trial of piromelatine that will include 500 patients with mild AD (MMSE 21-26) who are maintained on acetylcholinesterase inhibitors. The overall goal is to determine an effective dose to advance to phase 3. Eligible patients start a 2-week, single-blinded, placebo run-in period, are then randomized to one of 3 doses of piromelatine (5, 20, or 50 mg daily) or placebo in a 1.2:1:1:1 allocation ratio, followed by 26 weeks of double blind treatment. The primary objective is to assess outcome on the global composite score of a computerized Neuropsychological Test Battery (consisting of the CogState International Shopping List Test (immediate and delayed recall), One Card Learning, Identification, Detection, and One Back Card) after 26 weeks. Key secondary outcomes include the Alzheimer's Disease Cooperative Study -Global Impression of Change (ADCS-CGIC) and ADCS-Activities of Daily Living scale adapted for MCI patients (ADCS-ADL MCI-version). Other outcomes include the ADAS-cog14, tests of executive function (i.e., Controlled Oral Word Association Test and Categorical Fluency

Test), Neuropsychiatric Inventory (NPI), assessment of quality of sleep (Pittsburgh Sleep Quality Index), and of safety and tolerability. Sleep and APOE e4 genotype are not inclusion criteria but will be assessed as covariates. *Results:* Sample size was determined based on the assumption of an effect size between treatment dose and placebo of 0.35 on the primary outcome over 26 weeks, with a significance level (α) of 0.05 and power of 88%. Recruitment is ongoing and planned for 75 sites in the United States. The trial is registered in ClinicalTrials.gov (NCT02615002). *Conclusions:* Approximately half of early-stage AD patients and older APOE e4 carriers have sleep disorders and this is related as well to Aβ pathology and further cognitive impairment. Therefore, treating patients with early-stage AD aiming at improvements in sleep/wake rhythms, cognition and neurogenesis may lead to an improvement in cognitive state. Piromelatine, through its action at melatonin receptors, may improve sleep, circadian rhythms control and subsequently cognition in the patients. Through the 5-HT1A mechanism piromelatine may improve memory and mood, enhance NREM delta slow wave sleep, and reduce wakefulness. Through the combined activation of melatonergic and 5-HT1A receptors, piromelatine may act synergistically to increase neurogenesis and attenuate disease progression.

P2-12 RIVASTIGMINE AND CITALOPRAM TREATMENT FOR ALZHEIMER'S DISEASE IN EVERY DAY CLINICAL PRACTICE. Magda Tsolaki[1], Krishna Prasad Pathak[2], Eleni Verikouki [3], Paschalis Devranis[4], Chaido Zachou Messini[5], Konstantinos Lysitsas[6], Tara Gaire[7] *((1) Macedonia of University, Thessaloniki, Greece; (2) Department of Neurology, Aristotle University of Thessaloniki, Greece; (3) Eleni Verikouki, Aristotle University of Thessaloniki, Greece; (4) Paschalis Devranis, Aristotle University of Thessaloniki, Greece; (5) Chaido Zachou Messini, Aristotle University of Thessaloniki, Greece; (6) Konstantinos Lysitsas. Aristotle University of Thessaloniki, Greece; (7) Star Hospital, Lalitpur, Nepal)*

Background: Pharmacological treatment for AD and depression are unfortunately few and of limited efficacy to cure the disease. *Methods:* Longitudinal clinical prospective study with 1278 AD patients on rivastigmine 9,5mg/patch and citalopram 20-40 mg/day over 48 months was assessed on the basis of DSM-IV, NINCDS-ADRDA, MMSE, FRSSD, GDS, HRS-D and follow up of the patients. *Results:* Analysis 1278 patients who were diagnosed with Alzheimer's disease. Overall, there were 470 men and 808 women, with a mean age of 74.63 (SD = 7.72), and a mean education of 6.74 years (SD = 4.15). The proportion of patients diagnosed with depressive symptoms was 41.24 percent. All these subjects were evaluated for four years. At baseline, 751 of these were not diagnosed as depressed and were treated with rivastigmine, 325 were classified as depressed and were treated with rivastigmine only, 89 were not diagnosed as depressed and were treated with rivastigmine and citalopram and 113 were diagnosed with depression and were treated with rivastigmine and citalopram. There were no statistically significant baseline differences between the four groups in terms of soco-demographic characteristics. As expected, there were differences in the GDS and HRS-D scores between patients with depression and patients without depression. After four years of follow up, there were no significant differences in MMSE between the four groups ($p>0.05$). The FRSSD score of patients treated with rivastigmine and diagnosed with depression was significantly higher than patients treated with rivastigmine and no depression (Beta=1.127, 95%CI: (0.128, 2.127), $p=0.027$). The GDS score did not differ between patients with depression who were treated only with rivastigmine and patients with depression who were treated with rivastigmine and citalopram ($p>0.05$). There was also no difference in the GDS score between patients with depression and treated with rivastigmine or rivastigmine and citalopram ($p>0.05$). Similarly, the HRS-D score did not differ between patients with depression who were treated only with rivastigmine and patients with depression who were treated with rivastigmine and citalopram ($p>0.05$). There was also no difference in the HRS-D score between patients with depression treated with rivastigmine or rivastigmine and citalopram ($p>0.05$). The results of the GEE model for each group separately for gender, age groups and years of education for each of the MMSE, FRSSD, GDS and HRS-D scores. Patients without depression, treated with rivastigmine only, who have more than 9 years of education, have significantly better scores for MMSE, FRSSD, GDS and HRS-D measurements. Furthermore, older patients with depression, treated with rivastigmine and citalopram, have significantly higher HRS-D measurements. *Conclusions:* The combination of rivastigmine and citalopram had no better results than rivastigmine alone in patients with AD. Key words: Alzheimer's Disease, Depression, Rivastigmine, Citalopram.

P2-13 MK7622, A POSITIVE ALLOSTERIC MODULATOR OF THE M1 ACETYLCHOLINE RECEPTOR, DOES NOT IMPROVE SYMPTOMS IN ALZHEIMER'S DISEASE: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PROOF OF CONCEPT TRIAL. Tiffini Voss[1], Jerry Li[1], Jeffrey Cummings[2], Rachelle Doody[3], Martin Farlow[4], Christopher Assaid[1], Samar Froman[1], Heather Leibensperger[1], Linda Snow-Adami[1], Kerry Budd McMahon[1], Michael Egan[1], David Michelson[1] *((1) Merck & Co. Inc., Kenilworth, NJ, USA; (2) Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA; (3) Baylor College of Medicine, Houston, TX, USA; (4) Indiana University School of Medicine, Indianapolis, IN, USA)*

Background: Novel symptomatic therapies are needed for the treatment of Alzheimer's disease (AD). Acetylcholinesterase inhibitors and memantine are the current standard of care and widely used, but exhibit modest efficacy and dose-limiting side effects. MK7622 is a selective M1 positive allosteric modulator that amplifies the M1 receptor's response to acetylcholine (ACh) in the nanomolar range while having no effect on M2, M3 or M4 receptors. This mechanism was hypothesized to selectively impact cognitive pathways without the cholinergic side effects associated with stimulation of the other muscarinic receptors. The primary efficacy objective of this trial was to evaluate MK7622 as adjunctive therapy in improving cognition in individuals with mild to moderate AD after 12 weeks of treatment. The primary safety objective was to assess the safety and tolerability of MK7622 for up to 24 weeks of treatment. Prior to this trial, two human pharmacodynamic models (quantitative EEG and scopolamine reversal) predicted target modulation at doses ranging from 1 to 45mg, and a top dose of 45mg was selected for the trial. *Methods:* This was a Phase 2, randomized, placebo-controlled, double-blind trial (NCT01852110). Eligible participants were between 55 and 85 years of age, had been clinically diagnosed with mild to moderate AD according to both the NINCDS-ADRDA and DSM-IV-TR criteria for probable AD, and had a Mini Mental State Examination (MMSE) score of between 12 and 24 at screening. Each participant was also required to be taking a daily stable dose of donepezil, rivastigmine, or galantamine for at least 2 months prior to screening. After a 2-week single-blind placebo run-in period, participants were randomized in a 1:1 ratio to either MK7622 45mg or placebo for 24 weeks. The primary endpoint was the mean change from baseline in ADAS-Cog11 at 12 weeks. Secondary endpoints included the mean change from baseline in ADCS-ADL at 24 weeks and the Composite Cognition Score – 3 Domain at 12 weeks. Analysis was

performed using a constrained longitudinal data analysis model that incorporated the categorical variables of treatment, ApoE4 status, background AD therapy, gender, and the continuous variables of age and baseline MMSE score. The analysis population consisted of all randomized participants who had received at least 1 dose of study medication. The analysis plan included planned interim analyses for safety (after N=60 had reached 8 weeks) and for futility (after N=188 had reached 12 weeks). The futility criteria was set to conclude futility if the conditional power of observing a significant difference on the ADAS-Cog at 12 weeks was less than 20%. *Results:* A total of 240 study participants with mild to moderate AD were randomized at 59 centers in the United States and Canada. The majority of participants (54%) were women, with an average age of 72 years; 58% were ApoE4 positive. The trial was stopped for futility after meeting the prospectively defined stopping criteria outlined above. MK7622 did not improve cognition at 12 weeks as measured by the ADAS-Cog11 (group differences in change from baseline: 0.18 points, 95% CI (-1.0, 1.3), p=0.76). Group differences were also non-significant for ADCS-ADL (0.06 points, 95%CI (-2.4, 2.5), p=0.96) and for the other secondary endpoints. Sensitivity analyses were performed using a full intent-to-treat population; the conclusions did not change. Subgroup analyses examining the impact of disease severity and ApoE genotype did not demonstrate a meaningful difference. A higher proportion of participants taking MK7622 discontinued study medication due to adverse events (AE) (16%) as compared to placebo (6%), and MK7622 participants were more likely to experience a suspected cholinergic-based adverse event (21% vs. 8.3%, p=0.006). The most frequent event was diarrhea, which occurred in 15% of the MK7622 group vs 6% of placebo. Otherwise, there were no meaningful differences in AE profiles, vital signs, ECG parameters or laboratory measurements. *Conclusions:* In participants with mild to moderate AD, MK7622 does not improve cognition or function over a 12 week period when used as adjunctive therapy. MK7622 was generally safe and well-tolerated for up to 24 weeks; however, participants experienced a higher rate of cholinergic-based adverse events, driven primarily by an increase in diarrhea. Support: Merck & Co. Inc., Kenilworth, NJ, USA

P2-14 OPTIMAL ERYTHROCYTE OMEGA-3 FATTY ACID COMPOSITION CUT-OFF FOR PREDICTING COGNITIVE DECLINE AND/OR TREATMENT RESPONSE TO SUPPLEMENTATION: DATA FROM THE MAPT TRIAL.

Nicola Coley, Mike Donohue, Rema Raman, Paul Aisen, Bruno Vellas, Sandrine Andrieu

Background: Docosahexaenoic (DHA) and eicosapentaenoic (EPA) acid are omega-3 polyunsaturated fatty acids (PUFAs) and important phospholipid membrane components in the brain. Several observational studies have observed that higher fish/DHA consumption is associated with a decreased risk of cognitive decline or dementia/Alzheimer's disease (AD) in older adults, and numerous mechanisms of action have been proposed, including the maintenance of membrane integrity and neuronal function, mediation of inflammation, and modification of gene expression. However, results from randomized controlled trials (RCTs) of PUFA supplementation conducted in healthy elderly populations have mostly been negative. One factor which could affect the efficacy of PUFA supplementation is the susceptibility of the study population to benefit from the intervention. Indeed, no previous trial has specifically assessed the effects of omega-3 supplementation on cognitive decline in healthy elderly individuals with low PUFA levels. However, a subgroup analysis from the MAPT trial suggested that PUFA supplementation might be beneficial in subjects with low DHA and EPA (defined by being in the lowest quartile) at baseline. This finding was in line with the results of a 6 month trial in young adults, with low dietary intake of DHA. Furthermore, subjects with low baseline DHA and EPA underwent more cognitive decline in the MAPT trial than those with higher baseline levels. It would seem logical, therefore, to test the efficacy of PUFA supplementation in individuals with low DHA and EPA levels in a trial specifically designed for this purpose. However, it is not clear what criteria should be used to identify "low" DHA and EPA. The aim of this analysis was to identify the optimal erythrocyte DHA+EPA cut-off for predicting cognitive decline and/or treatment response to PUFA supplementation using data from the MAPT trial. *Methods:* MAPT was a 3-year RCT involving 1680 community-dwelling individuals aged 70 and older with memory complaints, a limitation in one instrumental activity of daily living (IADL) and/or slow walking speed (≤ 0.8 m/s). Participants also had to be free of dementia at baseline, with a Mini Mental State Examination (MMSE) score ≥24, and have no difficulties in basic ADL. Participants were randomized into 4 groups, receiving a multidomain lifestyle intervention and/or PUFA supplementation or placebo. For the present analysis, we only included participants from the intention to treat (ITT) population who were randomized, in a double-blind fashion, to receive either PUFA supplementation (2 capsules/day, containing a daily dose of 800mg DHA and a maximum of 225mg EPA) alone or placebo alone. Erythrocyte membrane DHA+EPA content was measured at baseline and 1 year, and results are expressed as % of total fatty acids. Cognitive status was evaluated at baseline, 6 months, and 1, 2 and 3 years, and the primary outcome measure was a composite score calculated as the average of the following z-scores: MMSE orientation items, Free and Cued Selective Reminding Test (sum of free and total recall scores), category fluency and Digit Symbol Substitution Test. *Results:* Placebo group participants in the lowest quartile of baseline erythrocyte DHA+EPA content (N=85) were older (76.0 versus 74.8 years, p=0.025) and had poorer cognitive function (composite score -0.12 versus 0.07, p=0.022) than participants in the other three quartiles (N=277), and mean DHA+EPA was 3.97 versus 6.59% (p<0.001). After adjustment for age, sex, and education, cognitive function was not significantly different between the lowest quartile and the three higher quartiles (difference: 0.09, p=0.269), and a 1% increase in baseline DHA+EPA was associated with a 0.04 point increase on the composite score (p=0.074). Spline regression plots did not reveal a clear optimal DHA+EPA cut-off for predicting cognitive decline. In a ROC curve analysis, the optimal DHA+EPA cut-off for predicting "substantial" cognitive decline (i.e. being in the lowest quartile of 3-year change from baseline, with a change in composite score ≤-0.23 points) was 5.3. However, the area under the ROC curve was only 0.60. In longitudinal mixed effects models, a lower cut-off was associated with larger treatment effects and greater cognitive decline. When "low" DHA+EPA was defined by the 15th (i.e. ≤4.35%), 25th (≤4.83%), 35th (≤5.27%) and 45th (≤5.62%) percentiles of the baseline distribution, the adjusted between-group difference (PUFA versus placebo) in 3-year change from baseline on the composite score in subjects with low baseline DHA+EPA was 0.24 (95%CI -0.01, 0.48; p=0.056), 0.19 (0.00, 0.38; p=0.049), 0.15 (-0.01, 0.30; p=0.060) and 0.04 (-0.09, 0.18; p=0.540), respectively. *Conclusion:* Lower levels of DHA+EPA at baseline were associated with greater cognitive decline and larger treatment effects in a "dose-dependent" fashion. However, we did not identify a precise cut-off for predicting treatment response or cognitive decline that performed better than the cut-off of ≤4.83% which was defined a priori using statistical methods (i.e. using the lowest quartile) in the MAPT trial main analyses. This cut-off requires further validation in different samples.

Theme : Clinical Trials: Cognitive and functional endpoints

P2-15 DIGITAL BIOMARKERS FOR CLINICAL TRIAL USE IN PRE-SYMPTOMATIC TO SYMPTOMATIC ALZHEIMER'S DISEASE AND RELATED DEMENTIAS - BUILDING THE REGULATORY SCIENCE ROADMAP. Stephen P. Arnerić[1], Daniel R. Karlin[2], Maurizio F. Facheris[3], Jesse M. Cedarbaum[4], Mark Forrest Gordon[5], Enrique Avilés[1], Derek L. Hill[6], Lynn D. Hudson[1], Volker D. Kern[1], Klaus Romero[1], Jane Rhodes[4], George Vrandenburg[7], Penny A. Dacks[8], Jeffrey A. Kaye[9] *((1) Critical Path Institute, Tucson, AZ, USA; (2) Pfizer, Boston, MA, USA; (3) AbbVie, North Chicago, IL, USA; (4) Biogen, Cambridge, MA, USA; (5) Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA; (6) IXICO, London, United Kingdom; (7) USAgainstAlzheimer's, Washington, DC, USA; (8) Alzheimer's Drug Discovery Foundation, New York, NY, USA; (9) Oregon Health Science University, Portland, OR, USA)*

Background: Interest in identifying, evaluating and qualifying innovative technologies for use in drug development is growing. While FDA guidance documents exist for pursuing novel Drug Development Tools (DDTs) and Medical Device Development Tools (MDDTs) for Qualification, the specific use of Digital Biomarkers (i.e., measured biological events, patient cognition or function captured through device or sensor technologies) as potential DDTs/MDDTs remains vaguely defined. As a step towards building a regulatory science path forward, FDA issued on October 20, 2015, a Federal Register Notice [Federal Register Docket No. FDA-2015-N-3579] to solicit input from a broad group of stakeholders on the scope and direction of the use of technologies and innovative methods in the conduct of clinical investigations. *Methods:* The Coalition Against Major Diseases (CAMD), a consortium within the Critical Path Institute, aims to accelerate the development of tools that increase the efficiency of delivering innovative treatments for Alzheimer's Disease and related dementias with impaired function. This presentation highlights CAMD consensus views (https://c-path.org/camd-digital-biomarkers-conference/; https://c-path.org/wp-content/uploads/2016/02/FDA-Public-Docket-Technology-Use-in-Clinical-Research-Critical-Path-Institute-Docket-No.-FDA-2015-N-3579-FINAL-receipt.pdf) of the use of digital biomarkers in clinical trials, the challenges faced, and the need for: Data Standards- Consensus on standardized ways to record, structure and report data generated by digital biosensors, employing CDISC (Clinical Data Interchanges Standards Consortium) standards to provide the consistent data model/structure to enable data sharing across technology platforms. Digital Biomarkers as Drug Development Tools- Development of standards for validating the analytic performance of devices or sensor technologies for use in clinical trials. Context-of-Use (COU) Statements- Development of COU statements based on the current state-of-evidence for their application in the drug development process. *Results:* CAMD's perspective supports the use of digital biomarkers in clinical trials for: Function- Electronic monitoring of activities in and outside of home (patterns of sleep, eating, drug adherence, mobility, social interactions, cognitive task assessments, etc.) and motor skills (e.g., typing or mouse movements on computers or smartphones), as well as activities of daily living (ADLs) and instrumental activities of daily living (IADLs). These assessments could be done passively, continuously, and/or activated by the user. Physiological measures- ECG, EEG, movement (actigraphy), speech/voice analysis, etc. Symptoms- Electronically reported diaries of symptoms by patients and caregivers, patient-reported outcomes of mood, quality-of-life (QoL) assessments, and treatment-related side effects. *Conclusions & Recommendations:* 1. Further exploration of digital technologies for safety, efficacy, diagnostic, and enrichment biomarker purposes should be encouraged. 2. Dependent upon COU for clinical decisions, different evidentiary standards will be required for use in drug development. 3. Continuous and passive monitoring of patient outcomes will likely provide greater ecological validity, improve statistical power to facilitate personalized therapeutics, reduce cost of lengthy trials, and enable tailored therapeutic approaches. 4. Digital biosensor assessments may provide a more sensitive measure of changes in the pre-symptomatic stages of AD, which would facilitate clinical trial design and monitoring for preventative therapies. Critically, CDISC standards for these measures need to be developed soon, as the Center for Drug Evaluations and Review (CDER) at the FDA will require all data submissions using CDISC starting in 2017. 5. Having open/frequent dialogue with regulators is critical to shape the development, validation, and clinical relevance of these tools for drug development. 6. Various stakeholders will need to effectively collaborate to develop, validate, and secure regulatory endorsement of the use of digital biomarkers in clinical trials in patients with AD and other neurologic disorders. 7. In the absence of more sensitive, regulatory qualified patient assessment technologies, large, lengthy prevention trials (5-10 years) will be required to progress to MCI stages where existing assessments are available.

P2-16 EARLY- VERSUS LATE-ONSET ALZHEIMER'S DISEASE—DIFFERENCES IN FUNCTIONAL IMPAIRMENT. Carina Wattmo, Åsa K. Wallin *(Clinical Memory Research Unit, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden)*

Background: Persons with clinical onset of Alzheimer's disease (AD) before 65 years of age are diagnosed with early-onset AD (EOAD). The prevalence of EOAD is low, but varies among studies from 6% to 16%. Most individuals with EOAD are still working, have an active social life, and might have children living at home. Therefore, the consequences of being diagnosed early with a disease that implies progressive deterioration of cognitive performance and activities of daily living (ADL), and personality and behavior changes, are enormous. These individuals may also have a decreased average life expectancy of 15–18 years. Some studies suggest that EOAD might be a separate, more severe entity than late-onset AD (LOAD). Neuropathological studies have found that younger patients exhibit a higher burden of AD pathology and a larger, more widespread cholinergic deficit than older patients. A faster cognitive progression among patients with EOAD has also been described. The clinical diagnosis of AD in younger persons can be difficult because of atypical symptoms and/or nonamnestic presentations. The present study aimed to investigate the functional outcomes in EOAD versus LOAD, and potential predictors of nursing home placement (NHP). *Methods:* The Swedish Alzheimer Treatment Study (SATS) is a 3-year, prospective, observational, multicenter study that investigated the long-term effectiveness of cholinesterase inhibitor (ChEI) treatment from various perspectives, e.g., cognition, ADL, and community-based service usage. Among the 1,258 outpatients clinically diagnosed with probable or possible AD, 1,021 had mild-to-moderate AD (Mini-Mental State Examination [MMSE] score, 10–26) at the start of ChEI therapy (baseline). Of these, 143 patients were defined as having EOAD (onset <65 years), 874 as having LOAD (onset ≥65 years), and age at onset was missing for 4; thus, 1,017 patients were enrolled in the present study. Participants were assessed for cognitive ability (MMSE) and functional capacity (Instrumental Activities of Daily Living [IADL] scale and Physical

Self-Maintenance Scale [PSMS]). The NHP date was recorded if this occurred during the study. Binary logistic regression was used to determine the patient characteristics that affected NHP. Potential predictors were investigated, including: sex, apolipoprotein E ε4 carrier status, solitary living, years of education, duration of AD, age at baseline, specific concomitant medications, and cognitive and functional abilities at baseline and their rates of decline. *Results:* A significant difference in mean (95% confidence interval) IADL score at the start of ChEI treatment was observed between participants in the EOAD and LOAD groups, 13.9 (13.0–14.8) vs. 16.3 (15.9–16.7) points, p<0.001. The corresponding PSMS scores were 6.7 (6.5–6.9) vs. 7.6 (7.5–7.8) points, p<0.001. The IADL capacity was already markedly impaired at baseline; about 40–65% of the participants with EOAD and 55–75% of those with LOAD were dependent on assistance to perform these activities (IADL score, 2–5). The percentage of participants with impairment in the individual IADL items was significantly lower at baseline in the EOAD cohort, except for the "ability to handle finances" task. After 3 years, the IADL capacity had deteriorated further; 70–90% of the remaining participants in both groups could not perform these tasks independently. Thus, younger individuals showed a faster decline in some tasks including "ability to use telephone," "shopping," "food preparation," and "housekeeping." However, the participants with LOAD still showed worse capacity in "laundry," "mode of transportation," and "responsibility for own medications." Except for physical ambulation (more than 50% of the individuals with LOAD needed assistance; PSMS score, 2–5), most participants could manage their basic ADL independently at baseline. A significantly larger percentage of the participants with LOAD were impaired in the ADL items: "toilet," "physical ambulation," and "bathing." After 3 years, 35–55% of the remaining participants needed assistance in "dressing," "grooming," and "bathing." The mean time from commencing ChEI therapy to institutionalization for participants with EOAD (n=26) and LOAD (n=205), was 22.3 (18.7–25.8) vs. 19.3 (18.0–20.7) months (p=0.156), and the survival time in nursing homes was 4.6 (3.4–5.8) vs. 4.0 (3.6–4.4) years (p=0.352), which were similar between the groups. In a logistic regression model, NHP risk factors for all participants were solitary living, worse IADL capacity at baseline, and faster IADL decline during the study. In the EOAD cohort, more years of education and use of antihypertensives/cardiac therapy, were independent predictors of a lower risk of institutionalization. *Conclusion:* The present study highlights the clinical importance of functional evaluations for individuals with EOAD. Patients in the LOAD group had significantly worse functional ability at baseline than those with EOAD; however, younger patients deteriorated faster in some individual items. Performance in IADL, but not cognitive ability, predicted NHP in both groups. A similar need for NHP and survival time in nursing homes might be expected for both groups, which is important knowledge for community-based services. Among patients with EOAD, higher education or antihypertensives/cardiac therapy might predict less risk of institutionalization.

P2-17 NEUROPHYSIOLOGICAL EFFECT OF PXT864 IN MILD ALZHEIMER'S DISEASE PATIENTS. Karim Bennys[1], Peter Schmitt[2], Audrey Gabelle[1], Daniel Cohen[2], Jacques Touchon[1] *((1) Memory Research Resource Center for Alzheimer's disease, University Hospital Montpellier, France, Montpellier, France; (2) Pharnext SAS, Issy les Moulineaux, France, Paris, France)*

Background: Cognitive event related potential (ERP) is a useful biomarker for the diagnosis of Alzheimer's disease (AD), even from the preclinical stage. We report here the use of ERP in a phase IIa clinical study to explore in mild AD patients the symptomatic effect of PXT864, an underdevelopment fixed combination of low doses of Acamprosate and Baclofen, which has shown multiple reversions of pathological alteration in cellular and animal models of AD. *Methods:* PLEODIAL is a pilot phase IIa study to assess the safety and preliminary evidence of efficacy on cognitive impairment and function of PXT864 in patients with mild AD. PXT864 was taken in single blind during 4 weeks, followed by placebo during 4 weeks, and then PXT864 during 4 last weeks. With this challenge/de-challenge/re-challenge original design, two doses of PXT864 were tested by two sets of patients. Efficacy was assessed through the 11item Alzheimer's disease Assessment Scale cognitive subscale (11ADASCog). In one of the 6 participating investigational centers, a sub-study was added to assess also PXT864 efficacy with the ERP method. Recordings were performed on Cz, Fz, and Pz at baseline (V1, before first drug administration) and at each 4week visit (V2, V3, and V4). 3 patients under the lower dose and 3 under the higher dose of PXT864 had completed their 4-visit ERP sessions. *Results:* An improvement during the 2 periods under active drug, and a worsening during the placebo period were observed in all cases in terms of latencies and amplitudes of P3b on Cz, Fz, and Pz for both doses tested. This expected challenge, de-challenge, re-challenge pattern was also found in a spatiotemporal principal component analysis performed on ERP raw data. *Conclusions:* These ERP results show first evidence of PXT864 neurophysiological activity to restore the balance between glutamate and GABA signaling disrupted by toxic oligomeric peptides, which seemed also to be coupled to a global cognitive improvement in 4-week treatment periods.

P2-18 BIASED ESTIMATES OF COGNITIVE DECLINE RESULTING FROM VIOLATIONS OF MEASUREMENT INVARIANCE CAN BE EXPECTED, TESTED AND CORRECTED. Luca Kleineidam[1,2], Wolfgang Maier[1,2], Michael Wagner[1,2] *((1) University of Bonn, Department of Psychiatry and Psychotherapy, Bonn, Germany; (2) DZNE, German Center for Neurodegenerative Diseases, Bonn, Germany)*

Background: The optimal measurement of cognitive treatment effects in early Alzheimer's disease (AD) clinical trials requires reliable and valid outcomes that are sensitive to change. Currently, the selection and evaluation of composites is often based on the Mean-to Standard Deviation-Ratio (MSDR) of decline over time. A measure with a high MSDR (i.e. high mean change but small inter-individual variations) is considered as being best suited to track the disease process and to require small sample sizes to detect a treatment effect. However, violations of temporal measurement invariance may bias the estimation of mean and variance of change over time (and finally also the MSDR). Temporal measurement invariance is a mandatory but often overlooked requirement for the meaningful interpretation of change. It indicates that a construct is measured on a constant scale over time. Otherwise outcomes are measured differently at each time point leading to inaccurate parameter estimates. The impact of violations of measurement invariance on outcome measures in early Alzheimer's disease is usually not tested although it may substantially influence the selection of outcomes and sample size calculations. Advanced statistical methods like second order latent growth curve models (SOLGM) now offer the possibility to simultaneously test and correct for potential violations of measurement invariance. Using data from an observational study and simulation methods, we here illustrate the size and removal of this bias with SOLGM. *Methods:* We used data from 494 MCI patients from the German Dementia Competence Network (DCN) memory clinic cohort with longitudinal assessments over three years. We evaluated the impact of measurement invariance violations on the CDR Sum of Boxes and on homologues of some recently proposed composites for MCI samples

(TriAD: ADAS Memory & Orientation + CDR cognition boxes; CFC: ADAS Memory & Orientation + CDR-SoB +FAQ) or for preclinical AD patients (ADCS-PACC). Violations of measurement invariance were assessed using longitudinal Confirmatory Factor Analysis (CFA). First, we evaluated the composites without adjustment for violations of measurement variance, fitting a first order latent growth model (FOLGM) to the composites, which is comparable to a linear mixed model. Next, we used SOLGM to adjust for differences induced by lack of measurement invariance. To clarify whether lack of adjustment for measurement invariance induced the differences between modeling methods we generated 500 data sets at various levels of invariance with known population values in Monte Carlo simulations. We subsequently analyzed the data sets with both modeling methods. We also calculated effect sizes for ApoE4, positive CSF-Biomarker profile (Aß+ & Tau+ VS Aß- & Tau-) and dementia conversion on cognitive-functional decline using both statistical methods. *Results:* Violations of measurement invariance were present in all composites. FOLGM suggested a smaller MSDR for the TriAD (-31%), larger MSDRs for the ADCS-PACC (+309%) and CFC (+66%) but approximately equal MSDRs for the CDR-SoB (-3%). Monte Carlo simulations showed that uncorrected violations of measurement invariance in FOLGM induced bias in mean (ADCS-PACC: +385%; CFC: +156%; TriAD: -48%; CDR-SoB: +3%) and variance estimates (ADCS-PACC: +76%; CFC: +51%; TriAD: -9%; CDR-SoB: +9%) leading to incorrect MSDRs and inappropriate sample size calculations. FOLGM could only recover the generating population values when strict measurement invariance holds. This assumption was not tenable for any composite as indicated by model fit indices. SOLGM recovered the true values in all conditions. In line with the latter finding, in real data we observed higher effect sizes of ApoE4 (on average +27%), AD CSF-Biomarker profile (on average +14%) and dementia conversion (on average +17%) on cognitive-functional decline using SOLGM. The ADCCS-PACC showed the highest associations with biomarkers and dementia conversion regardless of modeling method used. This suggests that the ADCS-PACC may also be valuable to track amyloid related decline in MCI samples despite its MSDR was strongly affected by violations of measurement invariance. *Conclusion:* Violations of measurement invariance occurred for several homologues of recently proposed composites in our large data set and might be expected to occur also in other samples because of the very nature of cognitive composite measures for longitudinal change. Ignoring the necessary adjustment of measurement invariance violations can produce biased MSDR estimates, suggesting either too high or too low sample sizes. This could result in a waste of resources, a possibly serious loss in statistical power, and the selection of suboptimal outcomes. SOLGM produced more accurate estimates of mean and variances of the decline and might be more sensitive to disease progression as indicated by higher associations with biomarkers and dementia conversion. Temporal measurement invariance should be routinely checked and corrected during the construction of novel composites and SOLGM should be considered as a novel analytic strategy for clinical trials.

P2-19 OLFACTORY IDENTIFICATION ABILITY CORRELATES WITH CSF TOTAL-TAU/AB1-42 IN NORMAL ELDERLY AT RISK OF AD. Marie-Elyse Lafaille-Magnan[1,2], Judes Poirier[1,2], Anne Labonté[1], David Fontaine[1], John Breitner[1,2], PREVENT-AD Research Group *((1) Centre for Studies on Prevention of AD, Douglas Mental Health University Institute; (2) McGill University, Faculty of Medicine, Montreal, QC, Canada)*

Background: Olfactory Identification (OI), the ability to identify and name specific odorants, declines with age in cognitively normal individuals (Ship, 1996), and in neurodegenerative illnesses such as Alzheimer's disease (AD). Reduced OI in normal elderly may identify persons who will later develop AD dementia (Stanciu, 2014; Roberts, 2015). Relying on the PREVENT-AD cohort of cognitively intact individuals with a parental history of AD, we previously found preliminary results suggesting that OI correlates with: 1) age; 2) global cognition; 3) HbA1C; 4) systolic and diastolic blood pressure; 5) whole-brain cerebral blood flow (ASL); 6) brain atrophy; and 7) cerebrospinal fluid (CSF) total-tau/aβ1-42 (Lafaille-Magnan, AAIC 2014, 2015). To explore these associations, we constructed models that predict OI based on known risk factors and indicators of AD pathology. The models suggest that the associations of OI with age and with global cognition are explained by the relationship of OI and both the latter with CSF total-tau/aβ1-42, an indicator of AD pathology. *Methods:* Participants were cognitively normal volunteers (clinical dementia rating, or CDR, = 0; Montreal Cognitive Assessment, or MoCA >24) who were at least 60 years old (age 55 ok if within 15 years of parental age at dementia onset). While we enrolled over 200 such persons between 2011 and the present, the current analyses rely on PREVENT-AD data release 2.0 (31 August 2015). The sample was 73% female, with an average age of 63 (Table 1). A subset of 101 participants volunteered for serial lumbar punctures (LP). CSF was collected after an overnight fast, and the Innotest/ Fujirebio ELISA kit (previously Innogenetics) was used to analyze CSF t-tau, P-tau, and Aβ1-42. OI was evaluated using the University of Pennsylvania Smell Identification Test (UPSIT; Doty, 1984). Participants' cognition was evaluated using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998). Analyses excluded people with incomplete test scores or nasal congestion on the day of testing. To avoid skewness, the UPSIT error scores were calculated as log10 (41 – raw UPSIT score) as in (Moberg, 1997). We investigated univariate correlations and constructed multivariate models iteratively adding variables of interest. We used robust-fit linear regression with a tuning constant of 1.205 to downweight outliers. Covariates included: age (in months) at baseline, sex, years of education, APOE ε4 status, RBANS total score for global cognition, and CSF total-tau/β1-42 . Age, education, RBANS total score, and CSF total-tau/Aβ1-42 were mean-centered. *Results:* Table 1 presents a range of demographic variables for the sample. We found that OI error score correlated directly with age and CSF total-tau/Aβ1-42 and inversely with the RBANS total score (Figure 1 A-C). Global cognition also correlated directly with age and inversely with CSF total-tau/Aβ1-42 (Figure 1 D & E). Finally, CSF total-tau/Aβ1-42 increased with age (Figure 1 F). Using step-wise multivariate modeling we assessed these same relationships adding variables in sequence (Table 2). As suggested by the univariate regression graphs in Figure 1, the Table's Models 1, 2, and 3 showed strong association between OI and age, cognitive score, and CSF biomarkers after adjusting for sex, education, and APOE status. Model 4 suggested that the association of OI with RBANS was diminished when age was added to the model. But Model 5 suggested that the association with age itself was no longer evident when CSF total-tau/Aβ1-42 was considered. These findings were made clearer by Models 6 and 7 which suggested that all association of OI with either age or RBANS was explained by its mutual (confounded) relationship of both with CSF total-tau/Aβ1-42. *Conclusion:* In a sample of asymptomatic people at increased risk of AD dementia, OI was correlated with age, global cognitive ability, and a CSF biomarker index of AD pathology. None of these relationships were modified substantially after adjustment for sex, educational attainment, or APOE status. However, models that included various combinations of age, RBANS total score, and CSF total-tau/β1-42 showed that the relationships between OI and either age or RBANS total score appear to be spurious

in that both are explained by their common association with CSF total-tau/β1-42, with the latter appearing to be the real "driver" of these variables' relationship to OI. In the future, we shall investigate whether the correlation of OI with other variables such as atrophy are "driven" extensively by the latter's relationship to total-tau/Aβ1-42. For now, our findings suggest that OI may be a useful indicator of AD pathology in cognitively intact individuals at risk of AD, and should therefore be of interest as a potential marker of advancing AD pathology in prevention trials conducted among such individuals.

Table 1

Study demographics for the StoP-AD Centre participants

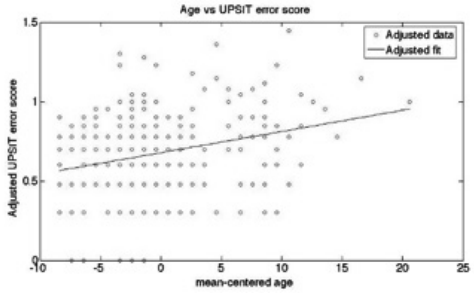
AD8=Dementia Screening Interview, CCSIT=Cross-cultural Smell Identification Test, CDR=clinical dementia rating, MoCA=Montreal Cognitive Assessment, RBANS=Repeatable Battery for the Assessment of Neuropsychological Status, UPSIT=University of Pennsylvania Smell Identification Test

	StoP-AD Centre participants					
Demographics	Average	S.D.	median	min	max	n
Age in years	63.41	5.43	62.00	55.00	84.00	274
Sex, % Female	0.73	0.44	1.00	0.00	1.00	300
% E4 carrier status	0.33	0.47	0.00	0.00	1.00	268
% Caucasian	0.98	0.13	1.00	0.00	1.00	272
% Francophone	0.81	0.39	1.00	0.00	1.00	272
MoCA	28.08	1.52	28.00	23.00	30.00	272
Education in years	15.14	3.47	15.00	7.00	29.00	272
AD8	0.17	0.47	0.00	0.00	3.00	246
CDR	0.00	0.00	0.00	0.00	0.00	272
UPSIT	35.41	3.65	36.00	13.00	40.00	265
CCSIT	10.62	1.28	11.00	4.00	12.00	270
RBANS total index score	101.07	11.35	101.00	72.00	140.00	296
t-tau/$A\beta_{1-42}$	0.28	0.21	0.22	0.11	1.20	101
P-tau/$A\beta_{1-42}$	0.05	0.03	0.04	0.01	0.16	101

Figure 1

A) Robust-fit regression models of UPSIT error score vs. mean-centered age (ε= 0.013368, p= 2.2429e-06, n=265), B) UPSIT error score vs. mean-centered RBANS total score (ε= -0.0066319, p= 1.4654e-06, n= 261), C) UPSIT error score vs. mean-centered CSF total-tau/Aβ1-42 (ε= 0.28568, p= 0.0049429, n=100), D) RBANS total score vs. mean-centered age (ε= -0.83697, p= 2.5751e-12, n=270), E) RBANS total score vs. mean-centered CSF total-tau/Aβ1-42 (ε= -13.801, p= 0.014769, n=98), and F) CSF total-tau/β1-42 vs. mean centered age (ε= 0.0047888, p= 0.005721,n=101). RBANS=Repeatable Battery for the Assessment of Neuropsychological Status, UPSIT=University of Pennsylvania Smell Identification Tes

A)



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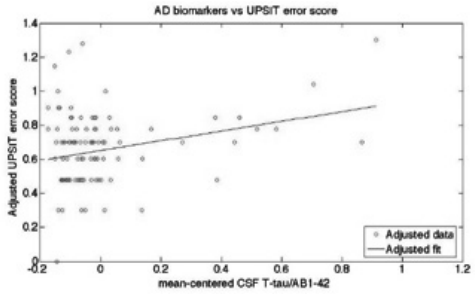
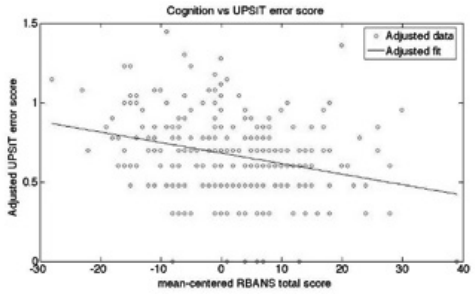


C)



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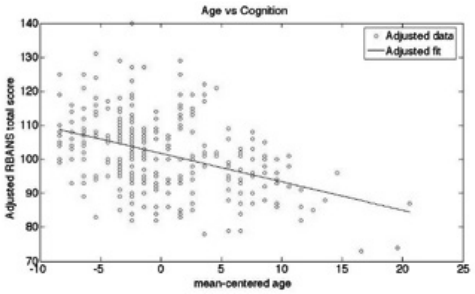

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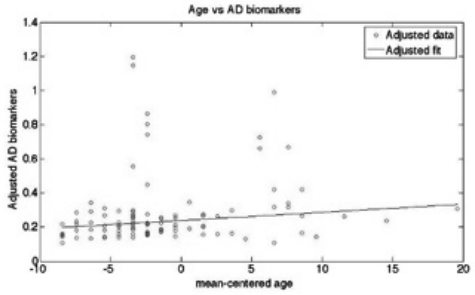

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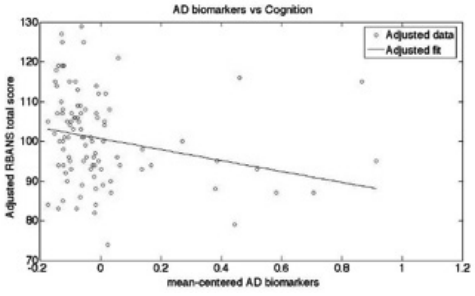


Table 2

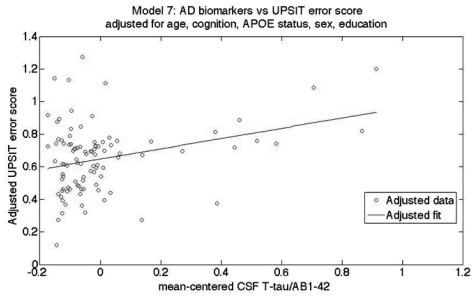
Coefficients from step-wise multivariate modeling to predict UPSIT error score. All Models are adjusted for APOE ε4 status, sex, and education. Because of different metrics used to measure the several variables, the various coefficients shown are not commensurable, but the indicated P-values show the importance of individual variables in the overall model. The coefficient are labeled with a star according to the size of their p-value (*p<0.05,**p<0.01,***p<0.005). RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; UPSIT=University of Pennsylvania Smell Identification Test

Models predicting the UPSIT error score	Coefficients for mean-centered age	Coefficients for mean-centered RBANS total score	Coefficients for mean-centered CSF total-*tau*/β_{1-42}
Model 1	0.011936***	–	–
" 2	–	-0.0051125***	–
" 3	–	–	0.32497***
" 4	0.0094483***	-0.003236*	–
" 5	0.0030887	–	0.30682**
" 6	–	-0.0027262	0.31684***
" 7	0.00020598	-0.0026856	0.31557***

*p<0.05 **p<0.01 ***p<0.005

Figure 2

Model 7: Mean-centered AD biomarkers and UPSIT error score This is a graph of model 7 from Table 2. It shows an increase in the UPSIT error score with an increase in mean-centered CSF total-tau/β1-42 after adjusting for age, RBANS total score, sex, and education. Worse OI ability is correlated with higher levels of AD biomarkers RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; UPSIT=University of Pennsylvania



P2-20 ATYPICAL PRESENTATIONS OF ALZHEIMER'S DISEASE (AD) AND THEIR EFFECT ON DISEASE PROGRESSION AND SURVIVAL. Ajay Sood[1], Eveleen Darby[2], Wenyaw Chan[3], Vallory Pavlik[2], PJ Massman[4], Rachelle Doody[2] *((1) AMITA Health, Alexian Brothers Medical Center, Elk Grove Village, IL, USA; (2) Department of Neurology and Alzheimer's Disease and Memory Disorders Center, Baylor College of Medicine, Houston, TX USA; (3) Department of Biostatistics, University of Texas Health Science Center at Houston, Houston, TX, USA; (4) Department of Psychology, University of Houston, TX USA)*

Background: Typical (symmetric) Alzheimer 's disease (AD) primarily begins with problems with episodic memory. Atypical (asymmetric) presentations of AD, which primarily affect language (dominant hemisphere), visuospatial function (non-dominant hemisphere), or behavior (frontal brain) have been well described but are less common. Using the Alzheimer 's disease and Memory Disorders Center (ADMDC) database at Baylor College of Medicine, we compared visual predominant and verbal predominant AD (asymmetric) to symmetric AD. The aim of this study was to study the effect of asymmetry on disease progression and mortality. *Methods:* We identified 540 right-handed subjects with Probable AD (MMSE ≥ 10) who had at least one year of follow up. Using methods previously described by Alverson et al1. subjects were classified into verbal predominant, symmetric, and visual predominant AD groups. Briefly, normalized data from verbal based tests (WAIS similarities, semantic fluency, naming) and visual-spatial based tests (block design, Rey-copy, Beery) were used to compute composite verbal and visuospatial scores. The verbal composite minus the visual composite constituted the asymmetry index (AI) where an AI of ± 1 indicates one standard deviation between composites. The typical AD group had a composite score in-between these two extremes. The subjects in these groups were then followed over time with MMSE and CDR-SB for disease progression and time to death. We compared baseline characteristics of the three groups (ANOVA and Chi Square). Using Kaplan-Meier survival curve and Cox Proportional hazard model, we compared three time to events: (1) time to increase in CDR-SB by two points from baseline, (2) time to decline in MMSE to below 10 points from baseline and (3) time to death. Covariates included; age at baseline, sex, ethnicity (Hispanic vs. non-Hispanic), education, Clinical Dementia Rating Scale - Sum of the Boxes (CDR-SB) at baseline, baseline Mini Mental status examination (MMSE), pre-progression rate of the disease, Cardiovascular Disease Equivalent (CVDE) and duration of symptoms. For time to death model, CDR-SB was also included as a time-dependent covariate. *Results:* About 27% of all the subjects presented with asymmetric AD (11% verbal, 16% visual). Visual predominant AD patients were 5.2years younger than typical AD and 6.5 years younger than verbal predominant AD (p-value < 0.0001). The verbal predominant group had a lower prevalence of an APOE4 genotype (40.7%) compared to the visual predominant (68%) and symmetric AD groups (65.3%) [p-value=.0003]. There were no significant between-group differences in education, length of follow-up, baseline MMSE,CDR-SB, ethnicity, sex, CVDE, pre-progression rate, or duration of symptoms. The subjects were followed 3.9+/- 2.43 years, with comparable duration of follow up for the three groups. Pre-progression rate and duration of symptoms significantly predicted the time to a two or more point increase in CDR-SB scores: asymmetry, age, education, sex, ethnicity, baseline CDR-SB, CVDE were not significant predictors. Verbal predominant AD subjects declined more rapidly to severe MMSE (score <10) compared to subjects with symmetrical AD (p=.004). In addition, age, baseline MMSE, CVDE and ethnicity were significant predictors of MMSE decline to a severe stage. Analysis of time to death showed no significant effect of asymmetry, however age, sex, ethnicity, baseline MMSE and time dependent CDR decline showed significant effect on mortality. *Conclusion:* Our results suggest that patients who present with visual predominant AD may have earlier onset compared to language predominant and symmetrically presenting patients, and that language predominant AD may have a lower prevalence of APOE4. Asymmetry was not associated with rate of progression on the CDR-SB or with time to death. Verbal predominant patients, as expected, declined more rapidly on the MMSE, which is a heavily language-based assessment. The neuropathological basis for asymmetric presentations is unknown, and our study suggests that it may reflect individual susceptibility factors related to disease onset rather than factors related to disease progression. Reference: 1. Alverson WA, Massman PJ, Doody RS. Prevalence and correlates of cognitive asymmetry in a large sample of Alzheimer's disease patients. Journal of clinical and experimental neuropsychology 2016;38:516-26.

P2-21 DETECTION OF NEURODEVELOPMENTAL DIVERSITY IN AN ALZHEIMER PREVENTION COHORT USING A SELF-REPORT SCALE. Alon Seifan[1], Richard S. Isaacson[2], Katherine Hackett[2], Chiashin Shih[2], Jaclyn L. Chen[2], Jessica Shum[2], Matthew W. Schelke[2], Robert Krikorian[3], Eve LoCastro[4], Gloria Chiang[4], Linda Heier[4] *((1) Compass Health Systems / Nova Southeastern University, FL, USA; (2) Weill Cornell Medicine, New York, NY, USA; (3) University of Cincinnati College of Medicine, Cincinnati, OH, USA; (4) Weill Cornell Medicine, Department of Radiology, Imaging Data Evaluation & Analytics Lab)*

Background: Neurodevelopmental Learning & Attention Disorders (NLAD's), such as ADHD or dyslexia, are associated with childhood cognitive susceptibilities in multiple domains. If undiagnosed in childhood or adulthood, NLAD's can cause psychological and cognitive symptoms that persist across the lifespan. Underachievement in work, school, and personal life can, in turn, influence dementia risk via mechanisms that influence brain and cognitive reserve. Intriguingly, atypical neural connectivity in NLAD may also influence the location of onset and spread of neurodegenerative symptoms and pathology. Currently, no validated, objective methods for assessing neurodevelopmental diversity in the adult population at risk for dementia have been validated. This is a critical research gap because these individuals could be at risk of delays in diagnosis. The success of future treatments will rely on early detection. This work is also essential because adults with NLAD are currently largely underrepresented in dementia research. Ultimately, better identification of adults with NLAD could further our understanding of whether childhood cognitive susceptibilities predict neurodegenerative phenotypes. *Methods:* In this retrospective study, we included all patients with MMSE > 26 who presented to the Weill Cornell Memory Disorders and Alzheimer Prevention Programs who had consented to the Comparative Effectiveness Dementia & Alzheimer's Registry (CEDAR) Project. The CEDAR Project is an IRB-approved registry of direct clinical care for patients seeking neurodegenerative disease treatment or risk reduction at Weill Cornell Medicine. All patients routinely answer a comprehensive, childhood cognitive ability self-report questionnaire that was adapted from prior validated scales for assessing NLAD in the adult. Patients with partial missing data were excluded. Prior to CFA, a preliminary exploratory factor analysis (EFA), principle component analysis (PCA), of 226 subjects was performed to identify factors and examine the dimensionality of individual questions. Latent variable modeling methods were used to test convergent and discriminant validity of LDQ. Multiple confirmatory factor analyses were compared to test alternative models for the factors extracted from PCA. Standardized factor loading, factor correlations, and model fit indices were compared to identify the best fitting model. Modification indices were examined to identify cross loadings between questions within the same factor to improve model fit. Standardized residual covariance were also examined for each paired questions. Model estimation was performed with SPSS Amos 23.0 using a maximum likelihood estimator for continuous variables applied to a mean and covariance data structure. A follow-up discriminant analysis was also conducted to assess whether the questionnaire differentiated adults with and without a self-reported formal diagnosis of LD (of any type). *Results:* 227 participants were included. The sample was mostly White/not Hispanic (87.2%), with slightly greater proportion of females (59%). Age ranged from 25 to 95 years, with a mean age of 60 and standard deviation of 14.2 years. More than half the sample reported having a college degree or higher. 14 (6%) reported some sort of prior dx of LD, but 8 of these didn't specify which type. The major majority of subjects(199, or 86%) were classified as Low Risk on the Mid-Life Dementia Risk Index. 61 (26%) of subjects tested for APOE carried a high-risk phenotype (APOE 3/4 or 4/4). A total of 30 question items were included in the analysis. Using PCA, 10 factors were identified. Factors 9 and 10 were excluded from CFA due to low sum of square loadings. Four questions were also excluded due to low factor loading and high standardized covariance residuals. After comparing multiple alternative models, the 8-factor model (Math, Language, Working Memory, Cognitive Control, Motor Planning, Attention, Visuospatial, and Executive Function) presented the best model fit (χ 2 /df=1.746, CFI=.918, RMSEA=0.057, NNFI=0.832, AND SRMR=.0615. The follow-up discriminate analysis revealed one discriminant function which explained 100% of the variances (canonical correlation R2 = 0.44). The discriminant function significantly differentiated the patients with and without a formal diagnosis of learning disability (Wilks' lambda = 0.808, chi-square 14.627a, p= 0.041). The results showed that language factor was loaded the highest (r = 0.972), cognitive control was the second (r = 0.504), executive function was the third (r= -0.421), working memory was the fourth (r = -0.372), then followed by visuospatial (r = 0.272), motor planning (r=.0.265), and attention (r = -0.193). Contrary from CFA, math was loaded the least in the standardized canonical discriminant function and was insignificant to be included in the model, Wilks' lambda=.806, chi-square (14.639), p=.067. In addition, 71.6% of originally grouped cases were correctly classified. Seven variables: language, working memory, cognitive control, motor planning, attention, visuospatial, and executive function, originally identified from CFA, were predictor variables of adult learning disability. *Conclusion:* Institution of effective dementia prevention depends on accurate differentiation of neurodevelopmental from neurodegenerative symptoms. These data suggest that a simple, self-report scale can at least initially identify potential childhood cognitive susceptibilities in a group of middle aged adults seeking memory loss prevention or treatment services. More careful attention to neurodevelopmental diversity can help to identify and engage the full population of adult patients with NLADs. This may foster a deeper understanding of how this unique cohort of individuals should be assessed in longitudinal clinical trials. Research is ongoing to discover whether self-reported childhood susceptibilities correlate with neuropsychological, neuroimaging and neuropathological abnormalities.

P2-22 VALUE OF PERFORMANCE-BASED OUTCOME ASSESSMENTS OF FUNCTION IN EARLY ALZHEIMER'S DISEASE CLINICAL TRIALS. Chris J Edgar[1], Meaghan Krohe[2], Stephen Joel Coons[3], on behalf of the Patient-Reported Outcome (PRO) Consortium's Cognition Working Group *((1) Roche Products Ltd, Welwyn, UK; (2) Adelphi Values, Boston, MA, USA; (3) Patient-Reported Outcome Consortium, Critical Path Institute, Tucson, AZ, USA)*

Background: Both FDA and EMA provide guidance that clinical trials in the dementia stage of AD should use a co-primary endpoint approach in which a treatment should demonstrates efficacy on both a cognitive and ideally a functional measure. However, in the early stages of AD, including prodromal AD (pAD)/Mild Cognitive Impairment (MCI) due to AD, it is recognized that measurement of more mild functional impairments may be challenging, primarily due to a lack of suitable functional assessments, but also rate of progression/length of required observational period. Current approaches to the assessment of function such as Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL) and Functional Activities Questionnaire (FAQ) make use of an observer-reported outcome (ObsRO) assessment approach.

The use of an informant, typically the main caregiver, overcomes issues with level of patient insight, offers an important perspective on the patients' current level of function from a person with a high degree of knowledge, and has strong 'real-world' / ecological validity. However, such assessments may be subject to a number of caregiver biases. Furthermore, the approach is reliant on an activity having been performed and observed within the recall period, and in being retrospective, is not a temporal match with other assessments performed at an in-clinic visit (e.g. cognitive measures). Issues with specific instruments themselves include minimal published content validity, item content which may not be well suited to early AD, or more modern instrumental activities of daily living (iADLs), and items that may mix concepts of differing complexity/difficulty. In addition, in rating and scoring such instruments, it may be difficult to account for differences between 'unable', 'unobserved', 'no recent opportunity' and 'never did'. The purpose of this study was to identify performance-based outcome (PerfO) assessments for use in pAD/MCI due to AD which may have a number of potential methodological advantages in being able to overcome issues with bias, reliance on observation and temporal differences from complimentary clinical outcome assessments, whilst retaining ecological validity and inherent clinical relevance. *Methods:* To inform identification of PerfO measures that could be used in pAD/MCI due to AD, a systematic search of peer-reviewed literature and a targeted Internet search were conducted. Abstracts were reviewed to identify potentially relevant measures, and identified measures were further reviewed/ compared against a set of inclusion/exclusion criteria. Measures were considered for inclusion if they contained items relevant to iADLs in pAD/MCI due to AD and were available in US English. Measures were excluded if a more recent/revised version was available, if there was no information available on the measure, if the measure was not a PerfO, if it did not directly assess iADLs, and/or the measure only assessed one concept/domain/item relevant to patients with pAD/MCI due to AD. Following the selection of measures, articles relevant to the development and evaluation of each were identified and further reviewed to focus on development, structure and scoring (e.g., domains/concepts assessed, items/activities, administration mode, scoring) psychometric performance, and its use in clinical trials. *Results:* In total 102 PerfO measures were identified. Ninety-one were excluded based upon inclusion/exclusion criteria, and 11 selected for targeted review and discussion with neuropsychological experts. Following the experts feedback, three were excluded as they were deemed to not provide adequate conceptual coverage and/or included items focusing on ADLs rather than iADLs. The remaining eight measures were reviewed in-depth, including the: Direct Assessment of Functional Status-Revised (DAFS-R), Everyday Functioning Battery (EFB), Everyday Problems Test for Cognitively Challenged Elderly (EPCCE), Executive Function Performance Test (EFPT), Functional Living Skills Assessment (FLSA), Observed Tasks of Daily Living Revised (OTDL-R), Texas Functional Living Scale (TFLS), and University of California San Diego Performance-based Skills Assessment (UPSA). None of the identified measures met all criteria for immediate clinical trials use (Target Population, Conceptual Coverage, Trial Burden, and Scoring and Administration). However, four instruments were considered suitable for further evaluation (the UPSA, TFLS, EPTCCE, and OTDL-R). Each has feasible administration times (~30 minutes) and evaluates relevant iADL concepts. *Conclusion:* Further work is needed to generate data to support cross-cultural applicability, as well as evidence for reliability, validity, sensitivity to change, and interpretation of change in the target population (pAD/MCI due to AD), for each of these instruments. It is possible that revisions in item content, administration and scoring may also be required to ensure relevance, as well as feasibility and utility for large, long-term, multicentre, multinational clinical trials. Once these important research questions are thoroughly addressed, PerfO measures have the potential to serve as primary endpoints in AD clinical trials.

P2-24 INTELLIGENT CLINICAL INTERVIEWS for ALZHEIMER'S DISEASE: HOW THE ADDITION OF AUDIO REVIEWS TO eCOA SCALE ADMINISTRATION RESULTS IN IMPROVED DATA QUALITY. Todd M. Solomon, Jessica Meyer, David S. Miller *(Bracket, Wayne, PA, USA)*

Background: Prior research has shown that employing enhanced electronic versions of the ADAS-Cog and MMSE in Alzheimer's disease (AD) clinical trials significantly reduces rater error rates compared to when paper versions of these scales are used. Additionally, the implementation of a customized in-study data quality program can further improve study data quality by monitoring scale administration and scoring to identify instances where raters deviate from proper administration guidelines and/or scoring conventions. When deviations occur, raters are remediated resulting in a decrease in error rates over the course of the trial. In this preliminary analysis, we evaluated whether, and to what extent, adding audio reviews of scale administration to the standard review of electronic scale data resulted in additional improvement in data quality. *Methods:* ADAS-Cog and MMSE ratings were evaluated from a multi-national AD clinical trial. Raters were trained and certified on the proper scale administration and scoring. Initial submissions of scale data from the electronic scales administered to each subject were reviewed along with the corresponding audio. All raters' ratings performance was assessed by a calibrated clinician. *Results:* The evaluation of data from MMSE submissions at screening indicated a total of 18% (79/448) of MMSEs contained an error. When reviewing the electronic scale data alone 12% (53/448) of MMSE submissions contained errors. When the corresponding audios were reviewed, an additional 6% (26/448) of MMSE administrations also contained errors. With regard to initial ADAS-Cog submissions, 23% (47/207) contained an error. When reviewing the electronic scale data alone 14% (29/207) of ADAS-Cog submissions contained errors. When the corresponding audios were reviewed, an additional 9% (18/207) of ADAS-Cog administrations also contained errors. *Conclusions:* It is essential that any and all methodologies that could maximize data quality in AD clinical trials be considered. The use of electronic versions of scales that are enhanced beyond their respective paper-pencil versions and coupled with an in-study data quality have proven to reduce rater error. Adding audio reviews of scale administrations enables detection of additional errors that are not apparent on data review alone, thereby further improving data quality over the course of a trial.

P2-25 COULD OBJECTIVE MEASURES OF ACTIVITY AND THE STANDARDISATION OF ENDPOINTS HELP CLARIFY THE VALUE AND IMPACT OF EXERCISE IN PATIENTS WITH AD? Marie Mc Carthy, Bill Byrom, Willie Muehlhausen *(ICON PLC, Dublin Ireland)*

Background: This abstract quantifies the complexity of terminology and methodologies used to assess physical activity (PA) and exercise in Alzheimer 's Disease (AD) patients. We reviewed published research and identified the most common approaches used to assess PA and exercise and identify if any of these approaches are being used in drug development trials. There is a considerable body research into the impact of PA and exercise on AD patients. This is reflected by the number of research articles which is increasing annually. Despite this body of research, there is no definitive consensus on

the type of exercise that is most impactful, the degree of positive impact and in some cases whether any meaningful impact can be derived from an activity or exercise program. Different nomenclature, exercise interventions and assessments have made it difficult to compare studies and draw meaningful conclusions. In addition, the use of patient reported outcomes (PRO) have added to the complexity. In this population, although widespread, the complexity and variability associated with the use of these tools to record and assess exercise and activity levels is well documented. Since the early 2000's accelerometers have been integrated into PA Monitors (PAM) and used to objectively measure free-living activity. Widely used in large scale global community based studies, these devices have been shown to generate a number of outcome measures that can assess both activity and exercise and can generate endpoints such as metabolic equivalents (METs), time spent in moderate to vigorous physical activity (MVPA), energy expenditure (EE) and calories expended as well measures of gross activity and sedentary behaviour. Accelerometers enable these measures to be captured in a precise, reproducible manner with reduced variability. *Methods:* A comprehensive literature search was carried out using PubMed to identify publications on AD and PA, exercise and aerobic exercise. Using the search terms Pub Med "Impact of PA on AD" "Impact of Exercise on AD". 115 unique publications were identified. These articles were data mined and to identify the intervention or assessment used and to further identify if that assessment was subjectively recorded or measured objectively. Similarly ClinicTrials.gov was searched for AD Trials and mined for those trials where PA, and exercise were outcome measures or intervention. *Results:* Research Publications Analysis: A literature search of Pub Med has identified 2226 publications linking PA and AD, with an average of 160 publications a year over the last 10 years. A search for publications using the following search terms "Impact of PA" on AD and "impact of exercise on AD" was carried out. Of these publications 22 very identified where PA or exercise were used either as interventions or means of assessment. 5 papers used the TUG or balance test as an assessment for cognitive decline. 6 studies reported an improvement in behaviour or physical wellbeing when activity or exercise programs were adopted and 10 papers reported an improvement or protective factor for dementia, associated with PA including aerobic activity. However none of the levels of PA assessment included objective measures. Drug Development Clinical Trials Analysis: A review of ClinTrials.gov revealed 1504 AD Trials. A refined search using the following terms Exercise and PA: identified 476 unique trials. The cleaned dataset consisted of 252 trials had an element of activity as an outcome measures. Further refinement of this dataset revealed 31 studies which had PA or exercise as a stated outcome measure, of which 3 were drug development trials. 36 different methods were identified, including 3 different questionnaires, TUG test and objective tests such as Gait, Balance tests, Grip strength tests and accelerometers. *Conclusion:* It is clear from the number of articles that being published activity/exercise is considered and important element in AD assessment. Our review has illustrated the variance in methodologies in measurement and assessment of PA and exercise in AD. PA is important as it has been suggested to reduce the risk or delay the onset of AD, and provide modest improvements in cognitive function in AD patients. However there is considerable debate as to precisely what and how to measure PA and exercise. Removing the subjective assessments and replacing them with objective measurements would assist in bringing clarity to this area, allow a standard approach to be adopted and allow the consolidation and direct comparison of future research. While additional research is needed, we would strongly recommend the use of objective tools such as PAM to generate objective outcome measures. This would facilitate a standard approach for AD drug development trial design, potentially increasing the power of the outcome measures and making a real difference for the success of future trials.

Theme : Cognitive assessment and clinical trials

P2-26 WASURE-NAVI-TO FOR A BETTER DEMENTIA AND MCI PATIENT CARE. Atsushi Iwata[1], Mamoru Yanagimachi[2], Hitomi Sunaga[3], Toji Miyagawa[1], Tatsuo Mano[1], Kazushi Suzuki[1], Yasuhiko Nakamoto[3], Takafumi Watanabe, Rami Suzuki[2], Shoji Tsuji[1] *((1) Department of Neurology, The University of Tokyo, Tokyo, Japan; (2) Eisai Co, Ltd, Tokyo, Japan; (3) Cocokara fine Healthcare, Yokohama, Kanagawa, Japan)*

Background: People with dementia or mild cognitive impairment (MCI) need personalized care, especially because their symptoms arise from their past experience and current relationships with their families and friends. In Japanese outpatient clinic settings, sessions for each patient tend to be very brief owing to the large number of patients visiting hospitals; quite often, sessions are as short as three minutes and can only be held once every three months. Unlike other diseases that physicians deal with, this is not tolerable at all, because it is obvious that under these circumstances it is almost impossible to obtain personal information or give personal advice. Professionals involved in dementia care range from physicians to community volunteers; sharing patient background information or current status among those individuals is extremely important. However, in addition to the previously mentioned limitations, person-to-person or community based approaches are becoming increasingly difficult in urban settings. Thus, better dementia care requires better communication tools that also assure secure information exchange. *Methods:* We plan to develop an information and communication technology (ICT) based communication tool to improve the current situation. *Results:* The Wasure-NAVI-to provides secure information sharing among people involved in dementia care. In this social implementation experiment, dementia or MCI patients and their caregivers are provided with an iPad that allows them to access patients' electric medical records (EMR) obtained at our institution, including cognitive batteries, blood tests, and brain MRIs, through a secure network connection. In addition, the iPad shows them various questions that allow physicians to assess the patients' condition even if they are at home. These questions include E-cog, the Zarit Burden Interview, and the AD-8, and can be added by the physician. The Wasure-NAVI-to has another function that will involve pharmacists. Dementia patients have considerable difficulty adhering to their medication. Due to their symptoms, they easily forget to take their medication regularly. In order to improve adherence, assigned pharmacists will visit patients' home regularly to monitor their adherence and use the Wasure-NAVI-to to report the situation to caregivers. In addition, patients and caregivers can send secure emails through the system to ask the physicians or the pharmacists questions. Through this system, various problems regarding dementia care can be solved simultaneously. *Conclusion:* In this 2-year experiment, we will evaluate our Wasure-(forget not)-NAVI-to system. We expect that it will provide a new dementia care tool through ICT that allows everyone involved in care to fulfill their role to the maximum degree. Wasure-NAVI-to will provide a novel personal health records (PHR) management system for dementia patients and their families.

P2-27 OLFACTORY DEFICITS IN MCI AS PREDICTOR OF IMPROVED COGNITION ON DONEPEZIL: A PRELIMINARY STUDY. D.P. Devanand[1,2], Gregory Pelton[1], Cody Lentz[1], Evan Chunga[1], Karen Bell[2], Jennifer Scodes[3], Adam Ciarleglio[3] *((1) Division of Geriatric Psychiatry, Department of Psychiatry, New York State Psychiatric Institute and Columbia University Medical Center; (2) Department of Neurology and Taub Institute for Research on Alzheimer's disease, Columbia University Medical Center; (3) Division of Biostatistics, Department of Psychiatry, Columbia University Medical Center)*

Background: Cholinesterase inhibitors (CheI) are commonly prescribed in patients with mild cognitive impairment (MCI) though they are not FDA-approved to treat MCI. The olfactory bulb is infiltrated by neurofibrillary tangles early in AD, impairment in odor identification predicts which patients with MCI are likely to transition to AD, and muscarinic cholinergic transmission is prominent in the olfactory bulb and its neuronal projections to secondary olfactory brain regions. Impairment in odor identification may be a useful marker of which patients with MCI are likely to improve with CheI treatment. *Methods:* 41 patients were recruited from the Memory Disorders Center at the New York State Psychiatric Institute for this IRB-approved study. Complete baseline data were available for 37 patients. At baseline, the University of Pennsylvania Smell Identification Test (UPSIT, 40 items) was administered, immediately followed by an atropine (anticholinergic) nasal spray challenge and then a repeat UPSIT. The "squirt system", developed by Scheibe et al. (2008), was utilized to administer the intranasal atropine challenge to the last 29 patients. All patients were treated openly with donepezil 5 to 10 mg per day and followed for 52 weeks, with repeat UPSIT and cognitive testing at 8, 26 and 52 weeks. Alternate AcheIs (galantamine or rivastigmine) were prescribed in 9 patients who could not tolerate donepezil; their data were included in the analyses. The main cognitive outcome measures were the Selective Reminding Test (SRT) total immediate score and the total score from the modified Alzheimer's disease Assessment Scale – cognition (ADAS-cog11). *Results:* Hypothesis 1: The acute change in UPSIT scores from pre- to post-atropine challenge will be associated with cognitive improvement (SRT total recall and ADAS-cog) from baseline to 26 weeks and 52 weeks. The acute decrease in UPSIT score (post-pre) was not associated with change in ADAS-cog from baseline to 26 weeks and 52 weeks on donepezil treatment (F=0.34, p=0.567), and remained non-significant (F=0.68, p=0.418) after adjusting for age, education, sex, APOE e4 allele status, and time. APOE e4 allele positive status was associated with improvement in ADAS-cog scores (decrease in ADAS-cog scores; t=-2.06, p=0.049). The acute decrease in UPSIT score was associated with increase in SRT total recall from baseline to 26 and 52 weeks on donepezil (F=5.41, p=0.027) and remained significant after adjusting for the same covariates (F=4.54, p=0.041). APOE e4 status was not a significant covariate in these analyses. Our model suggests that a one-point decrease in UPSIT score corresponds to a 0.58 increase in SRT total recall on average (p=0.041), adjusting for covariates. Hypothesis 2: Increase in UPSIT scores from baseline to 8 weeks of donepezil treatment will be associated with cognitive improvement (ADAS-cog and SRT total recall) from baseline to 26 and 52 weeks. The change in UPSIT score from 0 to 8 weeks (post-pre) was not associated with change in ADAS-cog from baseline to 26 and 52 weeks on donepezil without covariate adjustment, but there was a trend-level effect (t=-1.74, p=0.092) after adjusting for age, education, sex, APOE e4 status, and time. Our model suggests that a one-point increase in UPSIT score from baseline to week 8 corresponds to a 0.22 decrease in ADAS-cog at 26 and 52 weeks on average, adjusting for age, education, sex, APOE e4 status, and time. The change in UPSIT score from 0 to 8 weeks (post-pre) was not associated with change in SRT total recall score from baseline to 26 and 52 weeks, both with and without covariate adjustment. *Conclusion:* The change in UPSIT from pre to post atropine challenge was associated with increased SRT total recall but not with the ADAS-cog. The results with SRT total recall support the notion that lower UPSIT performance after atropine challenge is caused by decreased cholinergic transmission and that it can be predictive of longer term response to cholinesterase inhibitors like donepezil. The effect size was not large, and a larger sample is needed to confirm the findings before it can be recommended for clinical application to determine which patients are likely to benefit from CheI treatment. For hypothesis 2, the increase in UPSIT scores with 8 weeks of donepezil treatment was associated with improvement in ADAS-cog test performance at trend-level and did not reach significance. The ADAS-cog may not be very sensitive to milder forms of cognitive impairment that do not meet criteria for dementia (Podhorna et al., 2016), and, in our study of patients with mild cognitive impairment (MCI), the impairment on the ADAS-cog was minimal at baseline and throughout the study. The finding of cognitive improvement on donepezil being greater in patients with the APOE e4 allele are consistent with the earlier reported findings in the large-scale donepezil-vitamin E study in MCI (Petersen et al., 2005) and may be worth investigating with odor identification testing in larger samples than reported here in our preliminary study.

P2-28 STABILITY OF BAYESIAN COGNITIVE PROCESS PARAMETERS ACROSS WORDLIST MEMORY TASKS AND STUDY POPULATIONS. William R. Shankle[1,2,3], Junko Hara[1], Dennis Fortier[1], William H. Batchelder[2], Gregory E. Alexander[2], Ronald C. Petersen[4] *((1) Medical Care Corporation, Newport Beach, CA, USA; (2) Dept. of Cognitive Sciences, University of California at Irvine, Irvine, CA, USA; (3) Hoag Neuroscience Institute, Hoag Memorial Hospital, Newport Beach, CA, USA; (4) Mayo Clinic, Rochester, MN, USA)*

Background: Hierarchical Bayesian cognitive process (HBCP) models of wordlist memory (WLM) task performance show great application in drug development and evaluation. Unlike the traditional approach of using total or sub-scores for WLM tasks, the model takes underlying cognitive processes (e.g., encoding, retrieval) into account, and quantifies these processes. In our previous studies, HBCP models have: 1) detected treatment effects in two Alzheimer's Disease (AD) FDA clinical trials that were missed by standard methods; and 2) identified which cognitive processes are differentially affected in normal aging, mild cognitive impairment (MCI), and mild AD dementia. These results have been demonstrated in different WLM tasks and in different patient samples. For a given diagnosis and severity, it would be useful to determine the stability of each cognitive process parameter across different WLM tasks and study populations. If stable, then pooled HBCP analyses across different WLM tasks and study populations could be done to better target putative treatments. *Methods:* The present study applied an HBCP model of 7 cognitive processes (4 for encoding and 3 for retrieval) to predict WLM task item response data of the ADAS-Cog (ADNI sample) and AVLT (Mayo Clinic Alzheimer's Disease Patient Registry) for normal, MCI, and AD dementia subject groups. The encoding and retrieval cognitive processes represented state transitions between unlearned, prefrontal cortical working memory, and hippocampal short-term memory states. The hypothesis was that there was no difference in the relative (rank) ordering of the 7 mean cognitive process values between ADAS-Cog and AVLT WLM tasks. A 2-sample Wilcoxon rank-sum (Mann-Whitney) test was performed to compare the ADAS-

Cog vs. AVLT rank orderings of the 7 mean cognitive process values for all severity conditions combined, and for each condition separately. *Results:* There were no significant differences in the rank orderings of the mean cognitive process values between the ADAS-Cog and AVLT WLM tasks for all severity conditions combined (P = 0.2524), or for each severity condition (Normal Aging: P = 0.3379; MCI: P = 0.4062; AD dementia: P = 0.8480). *Conclusion:* The stability of the HBCP model's cognitive process parameters across different WLM tasks and across studies permits pooling of a variety of WLM tasks and study populations for the purpose of evaluating a common set of cognitive processes involved in WLM task performance at different severities. Such a pooled analysis will help validate which cognitive processes are most responsible for the transition from normal aging to MCI to AD dementia. Treatments can then be targeted to improve the cognitive processes most affected by each stage, which is key to drug development and validation.

P2-29 REPETITIVE TMS OF THE DEFAULT MODE NETWORK: A RANDOMIZED, DOUBLE-BLINDED, CROSS-OVER STUDY TRIAL IN MCI PATIENTS. Giacomo Koch[1], Sonia Bonnì[1], Silvia Picazio[1], Francesco Di Lorenzo[1], Viviana Ponzo[1], Maria Concetta Pellicciari[1], Elias Casula[1], Laura Serra[2], Matteo Mancini[2], Carlo Caltagirone[1], Alessandro Martorana[3], Marco Bozzali[2] *((1) Non-Invasive Brain Stimulation Unit, Santa Lucia Foundation IRCCS, Rome, Italy; (2) Neuroimaging Laboratory, Santa Lucia Foundation, Rome, Italy; (3) Memory Clinic, Department of Neuroscience, Policlinico Tor Vergata, Rome, Italy)*

Objective: Mild cognitive impairment (MCI) has been identified as the earliest clinical condition associated with an increased risk for developing Alzheimer's Disease (AD). The most common clinical presentation of MCI is associated with memory loss as the predominant symptom (amnesic MCI). Recent evidences support strong structural and functional disconnection of the parietal Default Mode Network (DMN) nodes in patients with AD, and less remarkably in those with aMCI. Recent finding suggests that the application of transcranial magnetic stimulation (TMS) over posteromedial cortex including Precuneus (PC) in healthy subjects is able to modulate memory performance. The present double blind randomized cross-over clinical study investigated the efficacy of two weeks of repetitive TMS in modulating cognitive performances in patients with MCI. *Materials:* Eleven MCI patients were enrolled in the study. *Method:* TMS was applied over PC at 20 Hz, in a 10-session course over 2 weeks in a sham-controlled crossover design. Subjects were randomly assigned to real stimulation or control stimulation (sham). A 2-week washout period was applied following which subjects were crossed over to the alternate treatment for an additional two weeks. Neuropsychological tests (cognitive performances), TMS-EEG co-registrations (cortical activity and reactivity), RS-fMRI (functional connectivity), DW-MRI (structural connectivity) acquisition were obtained at baseline and after two weeks of treatment for real and sham condition. RESULTS: The patients demonstrated an improvement in episodic memory performance following real stimulation compared to sham stimulation. CONCLUSIONS: These results support the role of medial parietal region in memory process likely due to modulation of DMN connectivity in aMCI patients these findings suggest that TMS may be a potential effective strategy in treatment of MCI patients for whom, currently, there is no available therapy

P2-30 COGNITIVE COMPOSITES FOR MILD COGNITIVE IMPAIRMENT (MCI): UTILITY OF THE REPEATABLE BATTERY FOR THE ASSESSMENT OF NEUROPSYCHOLOGICAL STATUS (RBANS). Noel Ellison, Suzanne Hendrix *(Pentara Corporation, Salt Lake City, USA)*

Background: The ADAS-cog and MMSE are not optimal for measuring cognitive decline in early Alzheimer's disease stages such as MCI. Sensitive composite scores (composites) have been derived based on existing items from traditional scales. Many of these items have less than optimal psychometric properties in MCI populations. Relevant cognitive domains for MCI are episodic memory and executive functioning. The purpose of this analysis was to explore whether or not composite scores built on newer psychometrically derived measures will yield more sensitivity and clinical meaningfulness in MCI populations. A previous analysis of an optimized RBANS item composite was presented at AAIC 2013 (Hendrix and Ropacki). We compare cognitive composites based on traditional instruments (ADAS-cog and MMSE) in an MCI population to a cognitive composite based on RBANS items. *Methods:* Two databases were pooled for the RBANS analysis: University of Utah database (N=81) and University of Oklahoma database (N=504). MCI patients were defined as patients with a baseline delayed memory index score of 80 or lower, patients who did not fit this criterion were designated as normal controls. Subjects were followed for 1-2 years and were administered the RBANS annually. For the analysis of traditional scale items, the ADNI MCI database (n=325) was used and the ADNI normal population was used as normal controls. Reduced rank regression (RRR) for RBANS and partial least squares (PLS) for traditional scales were used to identify optimized composites for measuring decline over time. Sensitivity to decline of both composites and individual items was assessed by the mean to standard deviation ratio (MSDR) of change scores over 1 year after correction for normal aging and was adjusted to correct for bias. Items from traditional scales and the RBANS are compared within the normal populations and within the MCI populations to assess differences in sensitivity. The composite scores are also compared for sensitivity to progression over time. *Results:* The best composite for tracking decline over time using the RBANS items was a weighted combination of five items. These five items (and percent contribution to the composite) were list recognition (61.4%), list learning (17.8%), figure recall (10.1%), story memory (7.1%) and story recall (3.6%). The combination score was calculated by multiplying each weight by the raw score of the corresponding item and then summing. This composite achieved an MSDR of 0.51 after adjusting for estimated bias. The five items included in the optimal combination were also the five individual items that were most sensitive to decline over time. The five items with the highest individual MSDRs were as follows: list recognition (MSDR=0.54), figure recall (MSDR=0.33), story recall (MSDR=0.29), list learning (MSDR=0.29) and story memory (MSDR=0.29). The next highest MSDR was 0.21 for list recall and was not included in the composite. Coding and semantic fluency had negative MSDRs, -0.04 and -0.05, respectively. The best composite for tracking cognitive decline over time using the ADAS-cog and MMSE items was a weighted combination of 16 items. These items (and percent contribution to the composite) were ADAS-cog word recognition (27.1%), MMSE orientation to time (14.1%), ADAS-cog orientation (13.6%), ADAS-cog word recall (11.3%), ADAS-cog delayed word recall (11.3%), ADSA-cog word finding (5.6%), ADAS-cog comprehension (4.2%), ADAS-cog ideational praxis (2.8%), ADAS-cog recall instructions (2.8%), ADAS-cog spoken language (2.8%), MMSE attention (2.8%), MMSE recall (1.7%), ADAS-cog commands (1.4%), MMSE language (1.1%), ADAS-cog construction

(-1.4%) and MMSE orientation to place (-1.4%). The composite achieved an MSDR of -0.4434 after adjusting for an estimated 8% bias. The five items with the highest individual MSDRs were as follows: MMSE orientation to time (MSDR=-0.2851), ADAS-cog word recall (MSDR=0.1754), ADAS-cog orientation (MSDR=0.1620), ADAS-cog delayed word recall (MSDR=0.1519) and MMSE attention (MSDR=0.1099). All of these items were included in the derived composite. *Conclusions:* The MSDR of 0.51 for the composite is higher than that observed for the best composite of ADAS-cog items and MMSE items in ADNI MCI population, which was -0.44. The additional sensitivity of the RBANS combination is likely to be the result of better sensitivity on the list recognition item. This study suggests that composites derived from psychometrically validated items and measures are more sensitive than items and composites from measures traditionally used in AD research which potentially translates into increased power, smaller sample sizes and shorter clinical trials.

P2-31 COMPARING RATER PERFORMANCE WITH AUDIO-RECORDED VS. MOCK ADMINISTRATIONS OF COGNITIVE ASSESSMENTS IN AN ALZHEIMER'S DISEASE CLINICAL TRIAL. Gladys Valdez[1], Macarena García-Valdecasas Colell[1], Magda Perez[1], Stephen Sainati[2], Manny Lazaro[2], Stephen Brannan[2], Dana Hilt[2] *((1) inVentiv Health, Cary, NC, USA; (2) Forum Pharmaceuticals, Waltham, MA, USA)*

Backgrounds: Central Rating Review (CRR) programs are commonly used in Alzheimer's disease (AD) clinical trials to improve the quality of site data via monitoring rater performance to identify problematic administration and scoring practices, which could compromise the quality of the data. There are multiple methods of monitoring rater performance as part of the CRR process, which may include: manual review of actual source documents; automated computer algorithms that flag atypical data patterns; review of audio- or video-recorded assessments; and review of interview skills via mock administrations of assessments. For this study, we compare the pros and cons of conducting CRR monitoring through the review of in-study audio-recorded vs. mock administrations of cognitive assessments. We propose that different types of administrations and review will highlight different types of rater errors, and each may have a benefit when customizing a CRR program for a particular AD trial. *Methods:* Raters in a global Phase 3 AD Program first attended training for the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), Mini-Mental State Examination (MMSE), Clinical Dementia Rating (CDR), and Disability Assessment for Dementia (DAD). Additionally, rater's completed a certification exercise for the ADAS-Cog, CDR, and DAD. Next, raters were divided into two groups: 1) raters who submitted for review conventional audio-recorded administrations of scales with real subjects at the raters' sites; and 2) raters who completed the administration of scales in a role-playing format with a mock subject. All administrations were conducted in each rater's native language by an external reviewer. Both groups received feedback in their native language on their audio or mock administration performance via teleconference. We examined each group's performance on their respective scales at their initial mock or audio administration by examining the type and quantity of errors each rater group committed. Then we followed each group and examined their performance on manual review at their first administration after receiving feedback on the initial mock/audio administrations. We compared the type and quantity of errors raters made before feedback and after feedback, based on the type of rater group. *Results:* Fifty-one trained and certified raters were included in the analyses – 26 raters were in the Mock group compared to 25 raters in the Audio group. The majority of Mock raters were Spanish-speaking, (mainly from Spain). A small minority of Mock raters were from the U.S. and Argentina, (English and Spanish-speaking, respectively). Audio raters were split between Spanish-speakers from Mexico and French-speakers from France. Results indicate that prior to feedback, Mock raters were more likely to make administration errors while administering the ADAS-Cog and CDR compared to Audio raters. Audio raters made more errors in administration, scoring, and recording (i.e., failure to record a subject's response or write in a score) on the MMSE, as well as had more errors in DAD scoring and administration, compared to the Mock raters. At the first administration after raters received feedback, it was noted that both Mock and Audio raters had a substantial decrease in administration errors across all scales, when compared to their performance prior to feedback. However, both Mock and Audio raters had an increase in recording errors after feedback. *Conclusion:* When the two methods of CRR monitoring of cognitive assessments were compared, mock administrations appeared to be superior to audio-recorded reviews of administrations in detecting administration errors for the ADAS-Cog and CDR. Both methods require a nuanced understanding of the scales and scoring norms in order for the rater to be able to administer and score these scales effectively and consistently. Audio-recording review appears to be more effective in detecting initial administration, scoring, and recording errors on the MMSE than mock administrations. This may be due to the relative ease and clarity of the MMSE administration and scoring manual used in AD trials. Mock MMSE administrations do not appear to provide any additional benefit in detecting inconsistencies or errors in scale administration and scoring. Both methods of initial review and feedback provide overall benefits in reducing administration errors in subsequent administrations. However, it appears that reviewers' focus on administration errors during the feedback session may prime raters to focus on proper administration, while neglecting consistent and accurate recording of subject data. In conclusion, a hybrid model of CRR may be the most beneficial in detecting errors early on in the AD trial, yet ultimately the scales selected to be administered in a trial may help determine the most adequate CRR monitoring method, as both audio and mock reviews appear to have strengths and weaknesses.

P2-32 PSYCHOMETRIC PROPERTIES OF COGNITIVE ENDPOINTS FROM THE CANTAB NEUROPSYCHOLOGICAL BATTERY IN A PRODROMAL ALZHEIMER'S DISEASE POPULATION. Rosemary Abbott[1], Chris Edgar[2], Francesca Cormack[1], Robert Lasser[3], Elizabeth Ashford[2], Kenton Zavitz[1] *((1) Cambridge Cognition, Cambridge, UK; (2) Roche Products Limited, Welwyn Garden City, UK; (3) F. Hoffmann-La Roche Ltd, Basel, Switzerland)*

Background: Recent research has documented the psychometric properties of neuropsychological tests and primary endpoints commonly used in clinical trials and studies of prodromal Alzheimer's disease (pAD). This research has focused on global and summary measures of cognition such as the CDR and ADAS-Cog using data from the SCarlet RoAD (NCT01224106; WN25203) study, in a population of CSF biomarker confirmed, amyloid positive subjects. Here we extend this analysis to include a broader range of cognitive measures using the CANTAB neuropsychological battery which taps into distinct aspects of cognition. *Methods:* The CANTAB neuropsychological assessment tasks included in this study covered a range of cognitive domains including episodic memory (Paired Associates Learning, PAL), working memory (Spatial Working Memory, SWM), recognition memory (Pattern Recognition Memory, PRM and Delayed Matching to Sample, DMS), sustained attention (Rapid Visual Processing, RVP), processing speed (Reaction Time

task, RTI) and a composite memory score. The psychometric properties of the CANTAB tasks were evaluated using traditional assessment methods, including floor and ceiling effects, test-retest reliability and construct validity, at screening and baseline (8 weeks apart). In addition, assessment of bias and limits of agreement were established using the Bland and Altman method for reliability of measurement. Sensitivity to change was evaluated via the calculation of standardized response means (SRMs) for the change from baseline to Week 104 (mean change divided by standard deviation of change) in subjects randomized to placebo only. Properties of the CANTAB tasks were compared with global measures previously reported (Edgar et al, 2015), including the CDR, ADAS-cog, MMSE, FCSRT, and FAQ. *Results:* Seven hundred and ninety-seven pAD subjects aged between 50-85 years were randomized and received allocated treatment. Minimal ceiling effects were evident for the majority of CANTAB tasks at Screening and Baseline (<1%); the exception being the PRM task for both the immediate (15%) and delayed (3%) sections at Screening, although these had reduced to 8% and 2% respectively by the baseline measurement. Floor effects were recorded in a small proportion of subjects for the PAL task (first trial memory score (<6%) and total errors adjusted (3%). Test re-test reliability ranged from 0.63 for PAL first trial memory score to 0.76 for PAL total errors adjusted. Test-retest was low for DMS (0.47) and PRM (0.37 immediate. 0.29 delayed), the latter partly reflecting the change in performance (ceiling effects) from Screening to Baseline. The majority of the CANTAB measures showed low to moderate inter-task correlations between (0.2-0.4) at baseline, supporting measurement across separate cognitive domains. In relation to external construct validity (non-CANTAB measures) the CANTAB Composite memory score was most strongly correlated with the ADAS-13 (-0.5), and moderately with the MMSE (0.4), FCSRT-IR total recall (0.4) and free recall (0.4). The individual CANTAB domains showed correlations between 0.2-0.4 with the above measures, with the exception of the Reaction time measure where all correlations were low (<0.1). CANTAB measures showed low correlations with the FAQ (< 0.2). The limits of agreement (Bland and Altman) plots confirmed that the proportional differences between screening and baseline measurements across the different CANTAB tests were relatively even across the performance range (from high to low). This means that repeated measurements showed equivalent reliability across levels of performance. Sensitivity to decline as evaluated by the SRM of the change from baseline to Week 104 in the placebo arm (N=104) was variable, with memory measures e.g. PAL total errors adjusted and the CANTAB Composite memory score showing moderate responsiveness (≥0.5), whereas the attention and reaction time measures showed lower levels of responsiveness (~0.2). *Conclusions:* The data supported the reliability and validity of the CANTAB tasks in a biomarker-confirmed pAD population. In relation to floor and ceiling effects, the CANTAB tasks compared favourably to ADAS-Cog, CDR, FAQ and MMSE where a high proportion of subjects were at ceiling. The individual CANTAB tasks showed moderate correlations with summary and global cognitive measures. The CANTAB cognitive memory score showed a relatively high correlation with the ADAS-Cog 13. The CANTAB tasks are a suitable assessment tool for pAD subjects enabling robust measurement across the ability range and sensitivity to early cognitive decline and disease progression. References: Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1: 307-310. Edgar C, Rylands AJ, Volz D, Mertes M, Gruendl E, Fontoura P, Santarelli L, Lasser R. Comparative traditional psychometrics of cognitive and functional endpoints in a prodromal Alzheimer's disease population. J Prev Alzheimers Dis 2015;2(4):314.

P2-33 COMBINING THE INFORMATION FROM MULTIPLE EPISODIC MEMORY TESTS TO OPERATIONALIZE THE DIAGNOSIS OF MILD COGNITIVE IMPAIRMENT.

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Background: Guidance criteria for the diagnosis of prodromal AD (International Working Group 2, IWG2) require significant impairments in episodic memory adjusted for age and education in absence of dementia, but neither the specific test(s) nor the magnitude of deficits are defined. It is possible that a combination of information from more than one test of episodic memory might better characterize variability in performance seen early in the course of AD. Though the free and cued selective reminding test (FCSRT) has been proposed as sensitive to the medial temporal pathology of typical AD, we hypothesized that its accuracy might be optimized by combining it with another wordlist task, in this case the cognitive battery of the Consortium to Establish a Registry for AD (CERAD). *Methods:* Two observational cohorts (from the Institut d'Investigacions Biomediques August Pi i Sunyer and Hospital de Sant Pau, Barcelona, Spain) were pooled to include 134 community-recruited older subjects with normal cognition (NC) and 61 subjects meeting clinical criteria for amnestic MCI that included consideration of performance on FCSRT or CERAD; all had scores for both immediate and delayed recall of the CERAD word list task, and for immediate free and total recall, and delayed free and total recall, of the FCSRT. Scores were standardized (z-score) by linear regression on age, gender, and education, using the NC subjects within the combined cohorts. Linear Discriminant Analysis (LDA) was used to explore the contributions of both tests separately and combined in the prediction of mild cognitive impairment. Balanced priors were used for LDA models to avoid bias in predictions towards the majority class available in this data. Other assessments available for nearly all subjects included the Clinical Dementia Rating scale-Sum of Boxes (CDR-SB), the Mini-Mental Status Examination (MMSE), APOE genotype, and CSF Aβ1-42, and total-tau/phospho-tau. Florbetapir PET was performed on 35 subjects. Biomarker data permitted an IWG-2 diagnosis in 193 of 195 subjects. Model operating characteristics were compared with respect to discrimination of NC and MCI; in addition, baseline biomarkers and clinical characteristics were compared for those subjects classified as MCI or NC by both CERAD and FCSRT models (using the clinical diagnosis as the standard of reference) vs those subjects classified as MCI by one model and not the other. *Results:* MCI subjects were older (68±8 vs 62±9), less educated (13±5 vs 11±5 years), more impaired on MMSE 26.6±2.5 vs 28.8±1.3) and CDR-SB (1.7±1.2 cs 0.1±0.4), and more likely to be ApoE4 carriers (55% vs 25%) and to have an abnormal amyloid (78% vs 31%) or tau biomarker (62% vs 19%). Mean performance on neuropsychological subtests ranged -1.5 to 4.2 sd below the mean of the NC population. Based on IWG2 criteria, 58.3% of MCI subjects had prodromal AD and 10.5% of NC were asymptomatic-at-risk. Based on LDA, the full model with both FCSRT and CERAD tests included yielded the best overall performance (Table 1). Interestingly, the FCSRT-based model yielded high specificity, while the CERAD-based model yielded high sensitivity.

Table 1
Model Performance

Model	Sensitivity	Specificity	Total Error Count*
CERAD+FCSRT	86.89%	94.78%	9.17%
CERAD	85.25%	82.09%	16.13%
FCSRT	72.13%	95.52%	16.17%

*Resubstitution error rates.

An exploration of the importance of each individual memory subtest to the classification of mild cognitive impairment or normal cognition is presented in Table 2. The CERAD delayed recall test had largest coefficient for prediction of MCI whereas the FCSRT delayed free recall test had the largest coefficient for the prediction of NC.

Table 2

Rank order of importance for individual episodic memory subtests

Rank order*	Prediction of MCI	Prediction of NC
1	CERAD delayed	FCSRT delayed free
2	FCSRT immediate total	FCSRT immediate free
3	FCSRT delayed free	CERAD immediate
4	FCSRT immediate free	CERAD delayed
5	CERAD immediate	FCSRT delayed total
6	FCSRT delayed total	FCSRT immediate total

* Discriminant function coefficients

Prediction of clinical diagnosis by the FCSRT and CERAD models was concordant in 155 subjects, achieving an accuracy of 94.8% (95.3% sensitivity, 94.6% specificity). Accuracy was lower when only one model predicted MCI (11/33 subjects for CERAD, and 3/7 for FCSRT, 35% total). *Conclusions:* Our results reveal the importance of combining information from multiple episodic memory tests to improve the diagnostic classification of mild cognitive impairment. Although results need to be confirmed in other cohorts, the FCSRT test proved most important for model specificity (minimizing the false positive rate) while the CERAD test proved most important for model sensitivity (minimizing the false negative rate).

P2-34 VIRGIL PLATFORM HELPS IMPROVE SITE PERFORMANCE AND SIGNAL DETECTION IN AD TRIALS; Christopher Randolph[1,2], Selam Negash[1], Doug Osman[1], Peter Sorantin[1] *((1) MedAvante, Inc., Hamilton, NJ, USA; (2) Loyola University Medical Center, Maywood, IL, USA)*

Backgrounds: Late-phase clinical trials in Alzheimer's disease (AD) typically involve large numbers of sites across different geographic regions. While the multi-site approach is necessary for recruitment, it can pose several challenges, including endpoint measurement variability across investigative sites (e.g., Cummings, et al., 2011). Traditional paper-based administration of clinical outcome assessments (COA) is prone to high error rates and requires an additional step of manual data entry into an electronic data capture (EDC) system, imposing administrative burden on trial sites. The Virgil platform, used for digital outcome administration (eCOA), in addition to enabling electronic source data (eSource) collection, provides real-time clinical guidance to help standardize administration and improve data quality across sites. The goal of the present study was examine site performance in AD trials, and to determine whether the use of eCOA platform can help enhance site performance by reducing scoring errors in the primary and co-primary endpoints. *Methods:* Investigative sites that used paper-based COA administrations in a recent clinical trial of mild cognitive impairment (MCI) were compared against sites that used eCOA administrations of the same scales in separate MCI trials. All studies are phase II/III multinational trials. The same cohort of expert calibrated clinicians reviewed audio recordings and source data to report scoring discrepancies in CDR and ADAS-Cog administrations. The percentage of reviews with two or more scoring errors served as a measure of site performance. *Results:* Analysis of scoring errors by site identified sites with high scoring errors (>40%), and also those that performed well (<10%) while enrolling large number of subjects. Further, Virgil administration significantly improved site performance compared to paper-based administration of both CDR and ADAS-Cog measures. *Conclusion:* Improving site performance is integral to the success of clinical trials and contributes to faster and more efficient trials. Study-specific site metrics can identify sites that require remediation in order to improve data quality in trials. Use of an eCOA platform with real-time clinical guidance, auto-calculation of scores and prompts for missing data and out-of-range errors can standardize measurements, thereby reducing error variance and improving signal detection across investigative sites.

P2-35 A COMPARISON OF AUDIO AND MANUAL REVIEW OF RATER PERFORMANCE IN AN ALZHEIMER'S DISEASE CENTRAL RATING REVIEW PROGRAM. Stephen M. Meyer[1], Dawn Sikich1, Elisa S. Conrad[1], Magdalena Perez[1], Stephen M. Sainati[2], E. Manny Lazaro[2], Stephen Brannan[2], Dana Hilt[2] *((1) inVentiv Health Rater Training Services, Cary, NC, USA; (2) FORUM Pharmaceuticals, Waltham, MA, USA)*

Background: With the goal of enhancing the ability to detect treatment effect via cognitive and functional test assessment, Rater Training Organizations (RTOs) employ several training and data quality methods to ensure raters' adherence to standardized administration and scoring procedures, reduce variance due to scoring errors, and maximize inter-rater reliability. As a component of central rating review (CRR) quality assurance programs, rating scale source document review (SDR: manual review and algorithmic flagging of atypical data patterns) has been common in Alzheimer's disease (AD) clinical trials, and allows RTO assessment experts to identify administration and scoring errors, unusual data trends, improper documentation of subject responses, etc. audio review (AR) of raters' in-study rating scale administrations has become more common and allows RTO assessment experts to assess raters' adherence to standardized administration procedures, which cannot be detected via SDR. The focus of these analyses is to compare AR and SDR evaluations of rater performance. *Methods:* U.S. raters in a global Phase 3 AD program were prequalified, trained, and certified to conduct the Alzheimer's Disease Assessment Scale-Cognitive subscale 13-item (ADAS-Cog), Clinical Dementia Rating (CDR), and Disability Assessment for Dementia (DAD). Raters were required to have previous experience with AD patients and rating scales, complete didactic training on standardized administration and scoring procedures, and demonstrate proficiency on certification rating exercises. The CRR program included SDR (manual and algorithmic review) of all ADAS-Cog, CDR, and DAD assessments. Additionally, most raters submitted an in-study audio recording for review for each scale they were certified to administer. Raters who failed the AR evaluation were requested to submit an additional in-study audio recording. For AR and SDR, administration, scoring, improper documentation, and other errors were documented, and raters were remediated for both SDR- and AR-identified errors. SDR and AR evaluations and remediations were completed by RTO assessment experts. AR pass/fail status was determined using a semi-structured evaluation form. A failing performance was defined as one or more "unsatisfactory" or "fair" ratings for standardized administration (ADAS-Cog, CDR, and DAD) or scoring procedures (DAD). These analyses were based on a subset of raters who submitted audio-recordings. *Results:* Two hundred seventy-three trained and certified U.S. raters submitted for review: ADAS-Cog (AR n=91; SDR n=1,785), CDR (AR n=101; SDR n=2,110), and DAD (AR n=81; SDR n=1,344). Of the raters who participated in AR, 15 (17%) ADAS-Cog, 16 (16%) CDR, and 26 (32%) DAD raters failed their first AR and submitted a second in-study audio-recording for review. The correlations observed between raters' initial AR score and the average number of SDR administration and scoring errors for the

ADAS-Cog, CDR, and DAD were negligible (R2 ranged from .03-.05). When raters were grouped by initial AR pass/fail status, there were no significant differences between groups on the overall number or type (i.e., administration, scoring) of SDR errors for the three scales. For those raters who failed their initial AR evaluation and submitted a second in-study audio-recording, there was a statistically significant improvement on AR performance on all three scales. While only 6% of reviews for each of the ADAS-Cog and CDR included AR, AR-identified errors accounted for approximately one-third (data still under review) of all errors for each scale. For the DAD, only 8% of reviews included AR, but AR-identified errors accounted for 93% of all DAD errors. Sixty-four percent and 51% of SDR-identified errors resulted in score changes for the ADAS-Cog and CDR, respectively. For the DAD, 23% of AR- and SDR-identified errors resulted in score changes. Additional analyses are being conducted for which results were not available at the time of this abstract. *Conclusion:* The present analyses highlight the importance of two methods of CRR monitoring to standardize rater administration and scoring and improve the quality of study data. When the two methods of CRR monitoring of rating scales were compared, the lack of relation between raters' AR and SDR performance suggested that these two methods evaluate different indicators of rating proficiency. AR more readily detects raters' ability to adhere to standardized administration procedures, which often is not evident via SDR; any deviation from standardized administration procedures lessens the reliability of rating scales, even if the impact on the data is not patently evident. SDR is more likely than AR to identify simple calculation errors or deviations from standardized scoring rules, which also decreases reliability if not detected. AR of rater administrations (in-study or as part of training) can identify and remediate raters who do not adhere to standardized administration procedures. On average in this sample, raters who failed their initial AR evaluation improved significantly on their second AR evaluation, demonstrating improved administration procedures. These results indicate that AR and SDR evaluations of rater performance provide two different, but complimentary approaches to rater oversight and data quality. Therefore, it is recommended that both methods be employed for raters involved in pivotal clinical trials.

P2-36 IMPACT OF THE BDNF VAL66MET POLYMORPHISM ON LONG TERM MEMORY IN SUBJECTS WITH AGE-ASSOCIATED MEMORY IMPAIRMENT (AAMI).

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Background: Brain derived neurotrophic factor (BDNF) promotes growth and proliferation of cells in the hippocampus and is important in long-term potentiation and memory formation. A common functional single nucleotide polymorphism (SNP) in the BDNF gene exists, a methionine (Met) substitution for valine (Val) at codon 66 (Val66Met). Individuals homozygous or heterozygous for the Met allele have lower BDNF secretion than Val homozygotes. Increasing age is associated with reduced BDNF levels, smaller hippocampal volumes, and poorer memory performance. Furthermore, the adverse effect of age on memory functioning is reportedly stronger in BDNF Met carriers than for Val homozygotes. However, whether the formation of new long term memories in particular is impacted by the BDNF Val66Met polymorphism is unknown. This analysis compared long term memory between subjects with age-associated memory impairment (AAMI) who are BDNF Val-Val homozygotes and AAMI subjects who are BDNF Met carriers. *Methods:* Design: The data analyzed and presented here were obtained during the Baseline (i.e., pre-randomization), two-week, single-blind, Placebo Run-in Phase of a double-blind, placebo-controlled multicenter investigational treatment study. Subjects meeting diagnostic criteria for AAMI (n = 119) at 18 participating research sites underwent neuropsychological assessment at Screening and collection of a blood sample analyzed for BDNF polymorphism. Eligible subjects then entered the Baseline Phase, which consisted of two visits, one week apart, after which subjects entered a 4-week double-blind placebo-controlled treatment phase (not reported here). At each clinic visit, subjects completed the Name-Face Memory Consolidation Test (NFMCT) and the Cognitive Drug Research (CDR) System battery, which are both computer-based cognitive testing systems that are designed for repeated assessment of long term paired associates and word list memory, respectively, in clinical trials. The long term memory variables (i.e., based on one-week retention intervals) analyzed were 7-Day Delayed Word List Recall and Recognition and 7-Day Delayed Picture Recognition from the CDR Systemsm and 7-Day Delayed Name-Face recall from the NFMCT. Participants: 119 subjects with AAMI (59 M, 60 F; mean age 65.5 yrs), and otherwise normally healthy volunteers enrolled in the study. Subjects were predominantly Caucasian (86.6%), and male (59%), with a mean age of 65.5 years, an estimated premorbid I.Q. of 115.6 and 14.6 years of education. Baseline mental status was intact (MMSE = 28.5), and depressive symptoms were within the normal range (GDS-15 = 2.1). Analysis Methodology: All outcome variables were evaluated by a linear mixed model for repeated measures (MMRM) analysis. Performance on each outcome variable was analyzed as either an accuracy (percent correct) or speed score (speed of making correct responses only). Baseline neuropsychological characterization assessments were analyzed by t-tests. All statistical tests were two-sided and conducted at the 0.05 significance level. *Results:* BDNF genotyping resulted in 78 (65.5%) subjects with Val66Val polymorphism and 37 (31.1%) with Val66Met polymorphism (2 subjects with Met66Met are included), while results of 4 subjects (3.4%) were unknown. The groups were largely similar in their overall cognitive functioning. General fund of knowledge (WAIS-Vocab), nonverbal reasoning (WAIS-Matrix Reasoning), and explicit episodic memory (WMS-VPA) did not differ between the groups. However, statistically significant differences between groups were observed in working memory and immediate recall (WMS-LM I; $p = 0.03$), and short-term (25 min delay) memory (LMII; $p = 0.05$), with the Val66Met group performing worse than Val66Val group in each of those domains. Differences between groups were also observed in long-term memory (7-day Delayed Recall). Performance on the CDR 7-Day Delayed Word Recall demonstrated a trend for Val66Val homozygotes to recall more words on average than Met carriers ($p=0.0874$), and faster reaction times with which they recognized those words ($p = 0.05$). There were no statistically significant differences between the groups on 7-Day Picture Recognition accuracy; however, Met carriers demonstrated significantly slower correct response reaction times for the Original stimuli ($p=0.004$) as well as for the Original plus Distractor stimuli combined ($p=0.0176$). Performance on the NFMCT 7-Day Recall demonstrated no statistically significant differences between the Val66Val homozygotes and Met carriers on percentages of faces correctly recalled on the 1st test trial after a 7-Day delay interval. *Conclusion:* This study compared baseline performance on neuropsychological assessment and various long term memory tests between Val66Val and Val66Met/Met66Met BDNF phenotypes in a population of subjects with AAMI. The proportion of subjects who were Met carriers (31%) was consistent with that reported for the general population. In this study, AAMI subjects who were Met carriers generally demonstrated lower performance on various

7-Day memory testing paradigms than Val66Val homozygotes and in several instances the differences between groups reached, or trended toward, statistical significance. This data adds to the growing body of evidence suggesting that BDNF plays a role in neuropsychological functioning and demonstrates, for the first time, the differential impact the polymorphisms have on long term memory functioning out to 7 day intervals.

Theme: New therapies and clinical trials

P2-37 POTENTIAL OF PROTEOSTASIS-DIRECTED THERAPIES FOR ALZHEIMER'S DISEASE (AD). John Alam[1,2] *((1) EIP Pharma LLC, Cambridge, MA, USA; (2) Alliance for Aging Research, Washington, DC, USA)*

Introduction: Maintenance of physiological and balanced levels of protein synthesis, folding, degradation and trafficking (i.e. "proteostasis") within the neuron is critical to normal neuronal function. Disruption of proteostasis is increasingly recognized as a driver of synaptic dysfunction and loss, which otherwise is a critical early and upstream event in AD pathogenesis. Therefore, the correction of proteostatic defects has emerged as novel potential therapeutic approach for AD. *Methods:* Literature review and integration to understand the therapeutic potential for proteostasis-directed therapies for AD. *Discussion:* Proteostatis processes that have been implicated in AD pathogenesis include: (1) Unfolded Protein Response (UPR); (2) Integrated Stress Response (ISR) (3) macroautophagy (referred to otherwise as autophagy; and (4) endocytic trafficking, There is rich crosstalk between these processes, and with more general stress-activated signaling pathways such as mTORC/AKT and MAPK (mitogen-activated protein kinase). The most direct evidence linking proteostasis with memory formation has been with the ISR/UPR pathways. Constitutive activation in mice of eif2α, a core ISR/UPR, leads to decreased memory function. And, knockout of PKR (a kinase that activates the ISR) improves memory. The link between ISR/UPR and memory is translation (protein synthesis), which is required for efficient synaptic plasticity. ISR upregulation also increases AMPA receptor trafficking and long-term depression. With respect to AD, synaptic dysfunction and the first signs of cognitive deficits occur at 3 -6 months of age in transgenic rodent models; ahead of amyloid plaque accumulation; but a time when intraneuronal proteostasis disruption is evident. Presenilin mutations have also been linked to reduced autophagy-lysosome mediated protein degradation; and APP mutations to defects in endocytic trafficking. The two combined, such as in the APP/PS1 transgenci mouse, would be expected to lead to profound disruption of proteostasis. Genetic approaches that improve lysosomal function have also been shown to be efficacious in AD transgenic mice. The role of disruption of proteostasis in late onset AD is supported by the ISR being upregulated in the Apoe4 mouse; and that inhibition of ISR with PKR inhibitor "rescues" memory deficits in that model. Accumulation of autophagic vacuoles, thought to reflect failure of autophagic processes, is well documented in human AD brain. As well, the genetics of AD increasingly support a major role of protestasis disruption in disease pathogenesis. The mutations in FAD have been linked to defects in endocytic trafficking and autophagy, respectively. For LOAD, aside from Apoe4 the genetics appear to cluster in four broad areas: Aβ processing, inflammation, lipid metabolism and endocytic recycling. The connection to protestasis for all but perhaps lipid metabolism is well established. Specifically for inflammation, it activates the ISR/UPR and impairs autophagy. The therapeutic potential of targeting proteostasis has been documented in preclinical animal models with specific small molecules antagonists. These include: inhibition of PERK (protein kinase RNA-like endoplasmic reticulum kinase; activator of ISR and one arm of UPR), which restores translation in neurodegenerative disease models, leading to improved behavioral and neuropathologic outcomes; ISRIB, which inhibits activation of eif2α and restores memory function in a number of models; rapamycin, which reverses autophagy defects in APP/PS1 mouse model and ameliorates behavioral deficits. In addition, genetic knockout of the stress activated MAPK p38α in neurons in APP/PS1 mice stimulates autophagy, leading to reduced BACE1 enzyme levels and decreased amyloid pathology; while selective chemical inhibitors of p38α reverse spatial learning deficits in APP/PS1 transgenic mice and in aged rats. A major challenge to chronic administration of proteostasis-directed drugs will be finding an adequate safety margin as the targeted processes are part of normal cell physiology and are active in all cell types, not just neurons. One means to address the safety challenge may be to develop drugs that modulate the pathways indirectly, rather than develop drugs that target core components of proteostasis pathways. For example, ISRIB acts on a partner protein that is required for eif2α activation. In doing so, it modulates eif2α in mid-range of activation stimulus, preserving the ability to activate eif2α when it must be activated. As a result, ISRIB through acting on the same general pathway as PERK inhibitors reverses the same translation defects and behavioral deficits in prion disease model as seen with PERK inhibitors, but without the pancreatic toxicity of PERK inhibitors. *Conclusion:* There is consistent biologic evidence across multiple animal models, and in human pathology & genetics, implicating defects in proteostasis as a major pathogenic driver in AD. Therapies directed at correcting protestatic defects have shown significant effects on both pathology and behavioral deficits in animal models. Taken together, the science indicates there is high potential for proteostasis-directed therapies to a treat a fundamental component of Alzheimers pathogenesis; though, the potential must be balanced with the risks of targeting normal physiologic processes.

P2-38 AMYLOID-B OLIGOMER MAY INDUCE NEURONAL IMPAIRMENT VIA DISRUPTING STRUCTURE AND LACTATE TRANSPORT OF OLIGODENDROCYTES. Zhongxiang Yao[1], Mao Zhang[1], Ziyi Ma[2], Haochen Qin[3], Jie Zhang[1] *((1) Department of Physiology, Third Military Medical University, Chongqing 400038, China; (2) Battalion 14 of Cadet Brigade, Third Military Medical University, Chongqing 400038, China; (3) Battalion 10 of Cadet Brigade, Third Military Medical University, Chongqing 400038, China)*

Backgrounds: The aggregation of amyloid-β (Aβ) peptides in extracellular plaques is recognized as a pathological appearance in Alzheimer's disease (AD). In a triple transgenic mouse model of AD (3xTg-AD), myelin disruption occurs at time points preceding the appearance of amyloid and tau pathology. Indeed, myelin integrity is not only indispensable for physiological function of brain, but also required for neuronal survival. Otherwise, the effect of Aβ peptides on myelin and oligodendrocytes (OLs), and its relationship with neuronal damage haven't been extensively discussed. Thus, it might be necessary to explore the change of myelin and OLs directly in response to Aβ attack. *Methods:* Body weight and motor coordination of mice were monitored during 8 weeks, and low concentration of amyloid-β oligomer (AβO) was intracerebroventricularly injected to mice at the 2nd week. Immunostaining was supplied to evaluate neuronal damage, myelin disruption and activation of inflammatory cells (astrocytes and microglias) in vivo followed by AβO injection. In vitro, AβO was administrated to cultured oligodendrocyte precursor cells (OPCs). Subsequently, immunofluorescent staining was supplied

to evaluate the change of oligodendrocyte amount and membrane expansion of OLs under AβO attack. Furthermore, monocarboxylate transporter 1 (MCT1) which is supposed to metabolically support axons in energy supplement via regulating lactate shuttle from OLs to axons, was assessed by immunostaining and western blotting in medial prefrontal cortex (mPFC) in 12 months in vivo. *Results:* (1) AβO suppresses the body weight and motor coordination of mice at the 2nd week, which are still inhibited at the 8th week. (2) AβO results in an obvious decrease of neuronal amount in hippocampus and cortex at the 8th week. Meanwhile, neurofilament loss is developed in corpus callosum (CC). (3) AβO leads to myelin disruption, but not neurofilament injury at the 3rd week, while neuronal impairment becomes evident until the 8th week in accompanying with demyelination. (4) In addition, the amounts of astrocytes and microglias are increased at the 8th week. (5) In vitro, AβO not only reduces the amount of OLs, but also restricts membrane expansion of OLs. (6) MCT1 is changeably expressed around axons but not in neurons in mPFC in vivo in 12 months. But interestingly, MCT1 expressions is highly associated with neuronal amounts in mPFC in vivo in 12 months. (7) MCT1 does actually localize to OLs, and changes in a similar trend as the amounts of OLs in mPFC in vivo in 12 months. Otherwise, the direct effect of AβO on MCT1 expression hasn't been evaluated, which is still waiting for further exploration. *Conclusion:* Currently, it is primarily found here that demyelination takes place prior to neuronal damage followed by AβO administration. Furthermore, it suggested that early demyelination may be the main contributor to continuous deterioration of neuronal damage under AβO attack. Secondary, it displayed here that AβO not only reduces the amount of OLs (differentiated from OPCs), but also restricts membrane expansion of OLs. In particular, it is also found that MCT1 is changeably expressed in OLs, which is highly associated with neuronal amounts in mPFC in vivo in 12 months. Therefore, it is hypothesized here that AβO-induced demyelination is prior to neuronal damage, which should be aggravated by AβO-induced decrease of oligodendrocye amount and restriction of membrane expansion in OLs, and this reaction of OLs and neurons to AβO may be related with the changed expression of MCT1 in OLs. In particular, AβO may possibly inhibit MCT1 expression in OLs, through which OLs become incapable to support enough lactate to neuronal axons. As a result, neurons are even more vulnerable to AβO endangerment.

P2-39 DECONVOLUTION OF NASAL ABSORPTION OF RIVASTIGMINE IN HUMANS AND FUTURE CLINICAL DEVELOPMENT. Timothy Morgan *(Lachesis Biosciences Pty Ltd, Warrnambool, VIC, AU)*

Backgrounds: Whilst the dominant, validated pharmacological strategy for symptomatic treatment of Alzheimer dementia is to raise acetylcholine levels in the brain to improve cognition and function, the EMA Responders data for this class of drugs highlights the unmet need for therapies with improved efficacy, tolerability and convenience. A markedly worse tolerability profile from higher dose formulations (e.g. 20 cm2 rivastigmine patch and 23 mg oral donepezil) confirms that further clinically meaningful effect cannot be achieved at the expense of tolerability. Recent study terminations for the prospective adjuncts, EVP-6124 (NCT01969123/36) and MK-7622 (NCT01852110) also serve to further highlight this relationship; G protein–coupled receptor facilitated increments in acetylcholine levels without concomitant tolerability improvement appear to be incongruent with achieving higher Responder numbers. Toward this latter goal, a written Pre-IND response for Rivastigmine Nasal Spray (WIPO PCT Patent Appl. WO 2016/049700 A1) from FDA has confirmed the suitability of similar rivastigmine pharmacokinetics to reference listed drug (RLD) and open-label safety in AD patients to support a prospective marketing approval. Following both oral and patch administration rivastigmine metabolite (NAP226-90) exposure was previously correlated with adverse events. Logically, there was no requirement to provide similar NAP226-90 levels as this would be detrimental to improving tolerability. The purpose of this study analysis was to determine the inter-individual variability of the nasal absorption rate in humans using Wagner-Nelson deconvolution. This absorption rate modelling will be used to assist with dose selection for the outlined, future clinical development studies of Rivastigmine Nasal Spray. *Methods:* Individual rivastigmine plasma concentration time profiles from a prior absolute bioavailability study (ACTRN12614001313628) where plotted on a log natural scale to verify linear absorption and elimination. Wagner-Nelson deconvolution of individual rivastigmine plasma profiles were calculated with the aid of corresponding intravenous elimination rates. Individual percent absorbed (% Abs) versus time profiles were fitted to an exponential, first-order nasal absorption model (Zhang et al. 2013). Mean (SD) nasal absorption model parameters (A, ka) were used to plot a mean profile for Rivastigmine Nasal Spray in humans for comparison to the individual profiles. To better inform product development, NAP226-90 Cmax was correlated with common adverse events (e.g. vomiting) observed in pivotal trials of rivastigmine oral capsule and transdermal patch. *Results:* Individual plasma profiles on log natural scale confirmed acceptability of Wagner-Nelson deconvolution. A representative, individual plasma profile and corresponding Wagner-Nelson profile visually demonstrates the closeness of the fit to the model. All individual % Abs versus time profiles (n=8) robustly fitted the first-order nasal absorption model ($p<0.0001$) with r2 and F-statistic ranging from 0.95 to 0.98 and 362 to 1020, respectively. The mean (SD, n=8) model parameters, % Abs (A) and nasal absorption rate (ka) of rivastigmine in humans were 93.9 (3.7) % and 1.50 (0.54) h-1, respectively. Linear correlation of oral capsule and transdermal patch NAP226-90 Cmax as the dependent variable with adverse events, such as % vomiting, was highly significant ($p<0.001$, r2=0.98, F=530). This was consistent with past FDA analysis of rivastigmine oral capsule showing that gastrointestinal adverse events (nausea, vomiting, diarrhoea, weight loss and anorexia) were significantly correlated with NAP226-90 exposure (both Cmax and AUC) using logistic regression analysis of Phase 3 clinical study data (n=625). No such correlation was found for rivastigmine exposure. *Conclusion:* Rivastigmine Nasal Spray has good inter-individual variability of nasal absorption rate in humans. Dose selection for future clinical studies will be aided by pharmacokinetic modelling and knowledge of the relationship between rivastigmine efficacy and tolerability. Future clinical studies will confirm single-dose Rivastigmine Nasal Spray bioavailability compared to RLD (e.g. oral capsule) in healthy volunteers, followed by human factors design confirmation, multiple-dose pharmacokinetics and open-label safety in AD patients. By producing lower NAP226-90 exposures at comparable efficacy levels as the oral capsule and transdermal patch, Rivastigmine Nasal Spray has good potential to improve efficacy, tolerability and convenience of cholinesterase inhibitor therapy. Ref. Zhang H. et al. AAPS PharmSciTech 2013. 14(1): 60-63

P2-40 SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL N-METHYLENEBENZENAMINE DERIVATIVES AS SELECTIVE ACETYLCHOLINESTERASE INHIBITORS TO IMPROVE LEARNING AND MEMORY. Sushant Kumar Shrivastava, Pavan Srivastava, TVR Upendra, Prabhash Nath Tripathi *(Department of Pharmaceutics, Indian Institute of Technology (Banaras Hindu University), Varanasi - India)*

Backgrounds: Alzheimer's disease (AD) is the most common cause of dementia and a progressive irreversible neurodegenerative disorder characterized by selective loss of cholinergic neurons and accumulation of β-amyloid protein in the selective brain areas such as cortex and hippocampus. WHO (World Health Organization) reported that 36 million people were suffering from dementia worldwide and estimated to increase to 66 million by 2030 and 115 million by 2050. The discovery development of new drug to treat AD patients is still a big challenge for medicinal chemists. Several approaches and established therapies for the treatment or prevention of Alzheimer disease are still in progress.Various drugs, acetylcholinesterase (AChE) inhibitors (donepezil, rivastigmine, and galantamine) or NMDA receptor antagonists (memantine), are used clinically for symptomatic relief of the disease. Our main strategy is the augmentation of cholinergic neurotransmission at the synapse by selective AChE inhibition in the specific brain region that may escalate the synaptogenesis & up-regulate the memory and learning in aged rats. *Methods:* A series of N-methylenebenzenamine derivatives were synthesized by the nucleophilic addition of an amine to the carbonyl group forming an unstable carbinolamine followed by dehydration in an acidic condition (pH 5-6) to afford an imine (schiff base). 3,5-dimethoxyaniline (3,5-DMA) and PABA acted as the nucleophile for substituted benzaldehydes. All derivatives were purified by column chromatography and characterized by spectral technique (300 MHz NMR, FT-IR, CHN Elemental Analyser). The in-vitro inhibitory activities for all derivatives (IMDA1-5 and IMPA1-7) were evaluated on AChE from electric eel and hBChE from human serum. The IC50 values of derivatives were determined by Ellman's method and compared with standard donepezil. The most active compound was further evaluated for in-vivo Spatial Reference Memory (SRM) and Spatial Working Memory (SWM) assays using Morris water maze model and compared with standard donepezil. Spatial Reference Memory and Spatial Working Memory (SWM) data were analyzed by repeated measure two-way ANOVA. The in-silico docking simulation of active compound was confirmed its consensual interaction with the important active-site gorge residues Phe330 and Trp279. Docking studies were performed on AChE complexed with E2020 (donepezil) (PDB Code: 1EVE) and BChE complexed with N-{[(3R)-1-(2,3-dihydro-1H-inden-2-yl)piperidin-3-yl]methyl}-N (2methoxyethyl) naphthalene-2-carboxamide (3F9) (PDB Code: 4TPK) (Maestro 10.5.014, Glide, Schrödinger, 2016-1). Validation of docking protocol was done by measuring the root mean square deviation (RMSD) between the actual pose and predicted pose of ligand to the protein. Further, the most active compound IMDA4 was subjected for enzyme kinetics study. *Results:* The in-vitro IC50 values of both the 3,5-dimethoxy-N-methylenebenzenamine and 4-(methyleneamino) benzoic acid series were determined, where selective inhibitions of all compounds were observed against acetylcholinesterase. The 3,5-dimethoxy-N-methylenebenzenamine derivation elicited better activity against AChE, indicating the presence of methoxy group modulate the AChE inhibitory potency due to increased lipophilicity of molecule (IMDA4: AChE: IC50 = 0.826 μM, Ki = 0.72 μM; BChE: IC50>50 μM) in comparison with standard donepezil (AChE: IC50 = 0.04 μM, Ki = 0.056 μM; BChE IC50=15.24 μM). Most active compound IMDA4 elicited a considerable decrease in escape latency and was comparable to donepezil via Spatial Reference Memory (SRM) and Spatial Working Memory (SWM) in-vivo models. The in-silico docking simulation of IMDA4 confirmed its consensual interaction with the important active-site gorge residues Phe330 and Trp279 responsible for its high affinity and selectivity for AChE. The lacking of the BChE inhibition can be considered due to a wider gorge binding site and absence of important aromatic amino acids. Further, the enzyme kinetic study of IMDA4 exposed an uncompetitive inhibition of acetylcholinesterase (AChE). All these investigations corroborated the outcomes of the in-vitro and in-vivo evaluation studies. *Conclusion:* We have successfully identified a new class of potent cognition-enhancing chemical entity. Among the identified compounds, compound IMDA4 deserves further studies which can lead to a discovery of a new lead having a potent cognition-memory enhancing property.

P2-41 STUDY DESIGN AND RECRUITMENT IN TWO PHASE II PROOF-OF-CONCEPT CLINICAL TRIALS OF THE PDE9 INHIBITOR BI 409306 IN EARLY ALZHEIMER'S DISEASE. Glen Wunderlich[1], Claus Thamer[2], Michael Roehrle[2], Miguel Garcia Jr.[3], Lutz Froelich[4], Bruno Dubois[5] *((1) Boehringer Ingelheim (Canada) Ltd., Burlington, ON, Canada; (2) Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany; (3) Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA; (4) Department of Geriatric Psychiatry, Central Institute of Mental Health, Mannheim, Germany; (5) Institut de la Mémoire et de la Maladie d'Alzheimer (IM2A), UPMC, Paris, France)*

Background: Prodromal Alzheimer's disease (AD) can be described as a predementia stage of AD, with a slight but noticeable and measureable decline in cognitive abilities, including impairment of memory. There are currently no approved treatments for the prodromal stage of AD. Approved symptomatic treatments for mild-to-moderate AD include acetylcholinesterase inhibitors (AChEIs) and memantine. However, more efficacious treatments are needed that can improve existing cognitive deficits. BI 409306 is a potent and selective phosphodiesterase 9 (PDE9) inhibitor being developed for the symptomatic treatment of AD. *Methods:* Here, we describe the study design, recruitment, and current status of two ongoing Phase II proof-of-concept clinical trials in prodromal AD (NCT02240693; BI study 1289.5) and mild AD (NCT02337907; BI study 1289.7). *Results:* The two studies are randomized, double-blind, placebo-controlled, 12-week treatment trials, with approximately 60 participating sites from 11–12 countries in North America and Europe. The primary objective of both trials is to assess the efficacy, tolerability, and safety of BI 409306 compared with placebo. Patients in each trial are randomized to one of four doses of BI 409306 (10–50 mg) or placebo, in a 1:1:1:1:2 ratio. The primary endpoint in both trials is the change from baseline in total z-score of the Neuropsychological Test Battery (NTB) after 12 weeks of treatment. Secondary efficacy assessments include the change from baseline in Clinical Dementia Rating Scale Sum of Boxes (CDR-SB), Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog11), and Alzheimer's Disease Cooperative Study/Activities of Daily Living scale (ADCS-ADL; mild cognitive impairment [MCI] version for prodromal patients) after 12 weeks of treatment. Safety and tolerability assessments comprise adverse event reporting, monitoring of vital signs, 12-lead electrocardiograms, routine laboratory tests, and Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaires. Both trials aim to randomize approximately 290 patients (48 per treatment group and 96 for the placebo group), with Mini-Mental-State-Examination (MMSE) scores of ≥24 for the prodromal AD trial and between 18 and 26 for the mild AD trial. The mild AD trial initially included an

active-control (donepezil) arm in addition to placebo, and restricted recruitment to treatment-naïve patients. However, this design feature was changed approximately 8 months after initiation to allow enrollment of patients currently taking an AChEI and to remove the active comparator arm. Patient recruitment has subsequently increased in the mild AD trial, and an enhanced recruitment program is planned for the prodromal AD trial. Both trials should complete enrollment in Q1 2017, with study completion expected mid-2017. The efficacy and safety data from these trials will be pooled for analysis, with the combined data to be presented in addition to the results from each individual study. Change from baseline in NTB total z-score and CDR-SB will be analyzed using the restricted maximum likelihood-based mixed-effects model with repeated measurement (MMRM). An analysis of covariance (ANCOVA) model will be used to assess ADCS-ADL (including the MCI version in the prodromal AD trial) and ADAS-cog11 scores. *Conclusions:* The results from the prodromal and mild AD trials are expected in the second half of 2017. The results of these trials will demonstrate whether 12 weeks of treatment with four BI 409306 dosing regimens provides clinical proof of concept in patients with prodromal and mild AD. Funding: Boehringer Ingelheim (NCT02240693 [BI study 1289.5] and NCT02337907 [BI study 1289.7])

P2-42 THE INFLUENCE OF A SHORT COGNITIVE AND MOBILITY TRAINING PROGRAM ON COGNITIVE PERFORMANCE AMONG THE "YOUNG-OLD" AND THE "OLD-OLD". Carine Federspiel[1,2,3], Elisabeth Bourkel[1], Jean-Paul Steinmetz[1,3] *((1) Centre for memory and mobility, Luxembourg; (2) Association Luxembourg Alzheimer, Luxembourg; (3) ZithaSenior, Research&Development, Luxembourg)*

Backgrounds: Cognitive and mobility training both maintain or improve cognitive functioning in elderly people. Thus, cognitive and mobility interventions play an important role in the primary and secondary prevention of dementia. The aim of this study is to further clarify the influence of diverse training programs on cognitive performances in older adults. *Methods:* The participants (N = 60) partook in a 12 week mobility and cognitive training program with two sessions per week. The participant's cognitive abilities were assessed before and after training, using learning and recall memory tests, a cognitive flexibility test, a verbal fluency test and a nonverbal attention test. *Results:* We investigate the effects of cognitive and mobility training on the "young-old" (younger than 80 years) and the "old-old" (80 years or older). Furthermore, we determine which cognitive functions (i.e., memory, cognitive flexibility, fluency and attention) are most influenced by the training. Potential covariates like initial cognitive deficits, gender and social network are considered. *Conclusion:* The discussion of the findings focuses on the necessity of introducing as early as possible structured cognitive and mobility training programs in the primary and secondary prevention of dementia in older adults.

P2-43 PHARMACOKINETICS OF SINGLE DOSES OF BI 425809 IN CHINESE SUBJECTS: A DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL IN HEALTHY VOLUNTEERS. Yasuhiro Tsuda[1], Regina Park[2], Hiroyuki Ugai[3], Michael Desch[4], Sophia Goetz[4], Christina Schlecker[5], Armin Schultz[6], Karl-Heinz Liesenfeld[4], Sven Wind[4], Sun-Young A. Yum[2], Glen Wunderlich[7], Jae-Gook Shin[8] *((1) Nippon Boehringer Ingelheim Co. Ltd, Kobe, Japan; (2) Boehringer Ingelheim Corporation Ltd, Seoul, South Korea; (3) Nippon Boehringer Ingelheim Co. Ltd, Tokyo, Japan; (4) Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany; (5) Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany; (6) CRS Clinical Research Services, Mannheim GmbH, Mannheim, Germany; (7) Boehringer Ingelheim (Canada) Ltd, Burlington, ON, Canada; (8) Inje University Busan Paik Hospital, Busan, Korea)*

Background: Hypofunction of N-methyl-D-aspartate (NMDA) receptors has been implicated in cognitive impairment in Alzheimer's disease and schizophrenia. Glycine is a co-activator of the NMDA receptor; increasing glycine levels through inhibition of glycine transporter-1 (GlyT1) is hypothesized to facilitate NMDA receptor function, enhancing structural plasticity relevant to learning. BI 425809, a potent and selective GlyT1 inhibitor, was generally well tolerated in healthy male Caucasian subjects in a previous Phase I trial, at doses of up to 75 mg twice daily. The objectives of this trial were to investigate the safety, tolerability, and pharmacokinetics (PK) of BI 425809 in Chinese healthy male volunteers. Results for Japanese healthy male volunteers from this trial have been reported previously (ClinicalTrials.gov Identifier: NCT02383888).1 *Methods:* This was a single-center, double-blind, placebo-controlled within dose groups, randomized trial. Chinese healthy male volunteers received single rising doses of BI 425809 in tablet formulation in three dose groups (10, 25, and 50 mg). Safety was assessed with adverse event (AE) monitoring (including clinically relevant findings from the physical examination), safety laboratory tests, 12-lead electrocardiogram (ECG), neurologic examinations, visual tests and ophthalmologic examination, vital signs (blood pressure, pulse rate), and visual analog scales (VAS) to assess subjective psychiatric effects (Bond-Lader and Bowdle). The primary endpoint was the number (%) of subjects with drug-related AEs. The PK profile of single-dose BI 425809 was explored, including area under the concentration-time curve of BI 425809 in plasma over the time interval from 0 to 72 hours (AUC0-72), and over the time interval from 0 extrapolated to infinity (AUC0-∞). Maximum measured concentration of BI 425809 (Cmax), time from dosing to Cmax (tmax), and terminal half-life of BI 425809 in plasma (t1/2) were also determined and results compared with historical data from Phase I trials conducted in Caucasian subjects (ClinicalTrials.gov Identifiers: NCT02068690 and NCT02337283). *Results:* A total of 24 Chinese subjects completed the trial according to protocol (mean age 24.8 years; mean body mass index 22.2 kg/m2); 6 subjects received a single dose of placebo and 18 subjects received a single dose of BI 425809 (6 subjects in each of the 10, 25, and 50 mg dose groups). Only one AE was reported (blood bilirubin increased) in Chinese subjects in the BI 425809 treatment group, and this was not defined as drug-related by the investigator. No severe AEs, deaths, protocol-specified AEs of special interest, or other serious AEs were reported. There were no clinically relevant safety-related findings reported from the ophthalmologic examinations, vital signs, physical examinations, neurologic examinations, VAS or ECGs. Exposure parameters (Cmax and AUCs) increased slightly less than proportionally to the dose following administration of BI 425809. Across dose groups, geometric mean BI 425809 plasma concentrations in Chinese subjects increased and reached peak levels with median

tmax values of 3.5 to 4 hours, and declined with terminal t1/2 values of 29.0 to 41.2 hours (independent of dose). Renal clearance of BI 425809 was low for all dose groups (less than 6.2 mL/min) and cumulative urinary excretion was 4.23–7.34% of the dose. Plasma concentration-time profile and PK parameters in Chinese subjects were comparable to those observed in Caucasian subjects. *Conclusions:* Single doses of BI 425809 10 to 50 mg were generally well tolerated in healthy Chinese male subjects and the results did not indicate any safety concerns for future clinical trials of BI 425809. Single-dose PK of BI 425809 in Chinese subjects demonstrated a slightly less than dose proportional increase in exposure, a long half-life, and cumulative urinary excretion of 4.23–7.34% of the dose. PK characteristics of BI 425809 in Chinese subjects were comparable to historical PK data from Caucasian subjects. The results of this trial support the inclusion of Chinese subjects into global clinical trials. 1Park R, et al. Presented at the American Psychiatric Association Annual Meeting, 2016 (Abstract p8–102). Funding: Boehringer Ingelheim (ClinicalTrials.gov Identifier: NCT02383888).

P2-44 PHASE 3 EFFICACY, SAFETY, AND TOLERABILITY STUDIES OF AVP-786 (DEUTERATED (D6)-DEXTROMETHORPHAN HYDROBROMIDE PLUS QUINIDINE SULFATE) FOR THE TREATMENT OF AGITATION IN ALZHEIMER'S DISEASE (NCT02442765, NCT02442778, NCT02446132). Jeffrey Cummings[1], Sanjay Dubé[2–5], Paul Shin[2], Thomas Megerian[2], Stacy Wu[2], Uyen Nguyen[2], Constantine Lyketsos[6] *((1) Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA; (2) Avanir Pharmaceuticals, Inc., Aliso Viejo, CA, USA; (3) Stanford University School of Medicine, Stanford, CA, USA; (4) Indiana University School of Medicine, Indianapolis, IN, USA; (5) University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; (6) Johns Hopkins Bayview Medical Center, Baltimore, MD, USA)*

Background: Neuropsychiatric symptoms are common in patients with Alzheimer's disease (AD) and are associated with poor patient quality of life, faster progression of dementia, and earlier institutionalization, as well as increased caregiver burden, health care costs, and mortality. No pharmacologic treatments have received FDA approval for AD-related agitation. Nonpharmacologic interventions are often used first-line in patients with mild symptoms, with varying reliability and success. Pharmacologic therapies such as cholinesterase inhibitors and memantine, which are approved for the treatment of AD, are generally considered ineffective for treating agitation. Atypical antipsychotics that are widely used off-label are associated with safety and tolerability issues, such as increased extrapyramidal symptoms, cognitive impairment, and mortality, and have modest efficacy at best. Other medications such as anticonvulsants, benzodiazepines, and antidepressants have shown inconsistent benefits or unacceptable side effects. Thus, there is a significant unmet need for safe and efficacious therapies for agitation in patients with AD. AVP-786 is being developed for the treatment of neurologic disorders, including AD-related agitation. AVP-786 is a combination of (+)-3-trideuteromethoxy-17-trideuteromethyl-(9α, 13α, 14α)-morphinan-hydrobromide monohydrate (referred to as d6-deuterated dextromethorphan hydrobromide monohydrate [d6-DM]), which is an uncompetitive NMDA antagonist, sigma-1 agonist, and serotonin/norepinephrine reuptake inhibitor, plus ultra-low dose quinidine sulfate (Q), a cytochrome P450 2D6 (CYP 2D6) inhibitor that slows the metabolism of d6-DM, thereby increasing its bioavailability. Deuterium is a nontoxic, naturally occurring isotope of hydrogen that when substituted at specific positions in the DM molecule, also significantly reduces CYP 2D6 metabolism of d6-DM. By having a lower rate of metabolism, d6-DM requires an ultra-low dose of Q in the AVP-786 formulation. *Methods:* Two phase 3 studies from the TRial to Improve Agitation in Dementia (TRIAD™) program, TRIAD™-1 (NCT02442765) and TRIAD™-2 (NCT02442778), are currently underway to assess the safety, tolerability, and efficacy of AVP-786 for the treatment of agitation in patients with dementia of the Alzheimer's type. Both are multicenter, randomized, double-blind, placebo-controlled studies, consisting of 12 weeks of treatment of 2 fixed doses (TRIAD™-1) or 1 flexible dose (TRIAD™-2) of AVP-786 administered orally twice-daily after appropriate titration. Eligible patients are aged 50–90 years with a diagnosis of probable AD (based on the 2011 Diagnostic Guidelines for Alzheimer's Disease issued by the National Institute on Aging-Alzheimer's Association workgroups) with clinically significant moderate/severe agitation (meeting the International Psychogeriatric Association [IPA] provisional definition of agitation) at screening and for ≥2 weeks prior to randomization. Patients must also have a Clinical Global Impression of Severity score ≥4 at screening and baseline and a Mini-Mental State Examination score of 6–26 (inclusive) at screening and baseline. Community-dwelling outpatients or residents of an assisted-living facility or skilled nursing home are eligible to participate. In both studies, the following efficacy endpoints are being assessed: Cohen-Mansfield Agitation Inventory Agitation/Aggression score; Neuropsychiatric Inventory (NPI) Agitation/Aggression score, Modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change Agitation score, NPI total score, NPI individual domain scores, NPI Agitation/Aggression Caregiver Distress score, Patient Global Impression of Change score, Dementia Quality of Life score, Alzheimer's Disease Assessment Scale-Cognitive score, and scores on standardized assessments of resource utilization. Standard safety and tolerability measures are also assessed. Recruitment is ongoing for both studies at centers in the United States. Patients who successfully complete TRIAD™-1 or TRIAD™-2 are eligible for entry into a 52-week long-term extension study of AVP-786 (NCT02446132). Novel aspects of the TRIAD™ studies include use of a deuterated compound to minimize certain drug-drug interactions, focus on AD-related agitation, use of the IPA work group definition of agitation, implementation of global ratings of agitation as inclusion criteria, requirement of patients to meet inclusion criteria at screening and baseline, inclusion of patients with relatively severe AD-type dementia, and exploration of the use of a patient-reported outcome measure. These studies will inform the field regarding agitation trial methods as well as providing evidence of potential efficacy of AVP-786. These studies are funded by Avanir Pharmaceuticals, Inc.

P2-45 PHASE 1 PROGRAM OF ALZ-801, A NOVEL PRO-DRUG OF TRAMIPROSATE WITH IMPROVED PHARMACOKINETIC PROPERTIES: BIOEQUIVALENCE STUDIES PROVIDE BRIDGING TO UPCOMING PHASE 3 PROGRAM. J.A. Hey, S. Abushakra, A. Power, J.Y. Yu, P.L. Kaplan, M. Versavel, M. Tolar *(Alzheon, Inc., Framingham, MA, USA)*

Background: ALZ-801 is a novel, orally bioavailable, small-molecule prodrug of tramiprosate with improved pharmacokinetics (PK) and oral tolerability. Tramiprosate, the active agent in ALZ-801, is a β-amyloid (Aβ) anti-aggregation agent that inhibits the formation of Aβ oligomers and neurotoxicity. The tramiprosate Phase 3 program included two studies with >2,000 patients with Mild-to-Moderate Alzheimer's disease (AD). In these studies, ~60% of patients were carriers of the ε4 allele of the apolipoprotein E gene (APOE4), and ~14% were homozygous for APOE4. The completed North American study did not show efficacy on the co-primary outcomes (Aisen et

al. 2011). However, in a protocol-specified analysis, tramiprosate demonstrated compelling efficacy on cognitive and functional co-primary outcomes, ADAS-cog and CDR-SB, in APOE4 carriers; the benefits were related to the number of APOE4 alleles: highest in APOE4 homozygotes, intermediate in heterozygotes, and no benefit in non-carriers (Porsteinsson et al. CTAD 2015). In both Phase 3 studies, tramiprosate also showed a favorable safety profile without vasogenic edema (ARIA-E) in 426 subjects receiving the treatment. The most common adverse events (AE) were nausea and vomiting, likely due to mild GI irritation. PK bioequivalence with a dose of ALZ-801, that achieves tramiprosate exposures similar to that in the tramiprosate Phase 3 studies, supports bridging ALZ-801 safety to the tramiprosate safety database from the prior Phase 3 program. *Methods:* To advance the clinical development of ALZ-801 into Phase 3, we have completed single dose and 14-day multiple ascending dose (MAD) Phase 1 bridging studies in healthy elderly volunteers to evaluate safety, tolerability and PK of ALZ-801 administered as a loose filled capsule. In addition, the PK properties of an immediate release tablet administered as a single ascending dose (171-342 mg) under both fasted and fed conditions were evaluated. *Results:* Compared with oral tramiprosate, oral ALZ-801 delivered an equivalent plasma exposure of tramiprosate with marked improvements in AUC and Cmax inter-subject variability. At steady-state conditions in the MAD study, oral ALZ-801 also prolonged the plasma tramiprosate terminal half-life to ~24 hours. The half-life of the prodrug, ALZ-801, was ~1 hour, and was consistent across dose groups after single dose or multiple doses. In both single and multiple dose studies, administration of ALZ-801 with food markedly reduced the incidence of GI symptoms compared to the fasted state, while maintaining plasma tramiprosate exposure. ALZ-801 and tramiprosate exposure showed excellent dose proportionality over 14 days. An immediate release tablet formulation of ALZ-801 was also developed, which displayed exposure and low PK variability similar to the loose filled capsule formulation. The tolerability of both solid dose formulations was comparable and improved vs. oral tramiprosate. The steady-state plasma AUC exposure of tramiprosate following an oral BID dose of ALZ-801 immediate release tablet has been projected based on the single dose PK of the ALZ-801 tablet, and both single and multiple doses of the capsule in healthy elderly volunteers. The MAD study with the ALZ-801 capsule showed that the AUC exposure of tramiprosate, after administration of ALZ-801, reached steady state within 7 days, without accumulation. The projected ~1.3-fold increase in tramiprosate AUC following administration of the ALZ-801 tablet at steady state aligned well with the observed Day 7 vs. Day 1 AUC ratio for the ALZ-801 capsule. Based on these calculations, the plasma tramiprosate dose/exposure relationship for oral ALZ-801 in tablet form following a single dose administration and at the projected steady state after BID dosing was determined. *Conclusions:* In the present ALZ-801 phase 1 bridging program, we have determined the steady-state plasma exposure of the active drug tramiprosate after oral twice-daily dosing of the ALZ-801 capsule and immediate release tablet, based on single and multiple dose studies. The PK bioequivalence analyses show that 265mg BID of ALZ-801, administered under fed conditions, achieves a steady-state tramiprosate exposure that is equivalent to the target exposures after 150mg BID of the tramiprosate tablet used in the prior Phase 3 trials. These bridging data support the Phase 3 program of ALZ-801 in APOE4 positive AD subjects, with an optimized tablet formulation that shows improved GI tolerability with sustained and consistent plasma drug exposure.

Saturday, December 10

Theme : Clinical Trials Biomarkers including Plasma

P3-1 EVALUATION OF CROSS-SECTIONAL TAU BURDEN AND PRELIMINARY LONGITUDINAL CHANGES IN ALZHEIMER'S DISEASE SUBJECTS USING [18F]GTP1 (GENENTECH TAU PROBE 1).

Sandra Sanabria Bohorquez[1], Thomas Bengtsson[2], Jan Marik[3], Olivier Barret[4], Gilles Tamagnan[4], David Alagille[4], Gai Ayalon[5], Mike Ward[6], Danna Jennings[4], John P. Seibyl[4], Ken Marek[4], Geoffrey A. Kerchner[6], Robby M Weimer[3] *((1) Clinical Imaging Group; (2) Biostats; (3) Department of Biomedical Imaging; (4) Molecular NeuroImaging LLC, 60 Temple Street, New Haven; (5) Department of Neuroscience; (6) Early Clinical Development, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA)*

Background: In Alzheimer's disease (AD), the extent and density of tau pathology (intracellular aggregates of hyperphosphorylated tau) correlates with disease severity and cognitive decline prior to death. [18F]GTP1 is a tau PET tracer that exhibits rapid pharmacokinetics, enabling the use of SUVR60-90min as a surrogate measure of tau specific binding, and robust test-retest reliability. Here, we report preliminary results on the distribution of tau pathology in an AD cross-sectional cohort as well as the changes in tau distribution observed at 6 months in a group of participants enrolled in a longitudinal 18-month natural history study. *Methods:* Subjects were enrolled in an ongoing longitudinal natural history study; enrollment goals: 10 cognitively normal (amyloid-PET positive or negative, MMSE 28-30, CDR 0), 20 prodromal AD (amyloid-positive, MMSE 24-30, CDR = 0.5), 20 mild AD (amyloid-positive, MMSE 22-30, CDR 0.5 or 1) and 10 moderate AD (amyloid-positive, MMSE 16-21, CDR 1 or 2). All subjects are aged 50-80. Neurocognitive evaluations include the MMSE, ADAS-cog-13, CDR, RBANS, and Stroop color word. [18F]GTP1 images are acquired over a 30-minute window starting 60 minutes post-injection. The cerebellum gray is used to calculate SUVR, as it was shown to be an adequate reference region to estimate the non-displaceable component in cortical regions1. *Results:* Consistent with observations from a first-in-human study, visual inspection and quantification of images shows that [18F]GTP1 exhibits a wide dynamic range and allows differentiation between AD and healthy controls, and between regions of predicted high and low tau pathology burden1. The tau burden extent (defined as the percentage of voxels above an SUVR threshold) and tau burden density (SUVR) increase with disease state (prodromal<mild<moderate). A variable distribution between subjects within each cohort was observed. The preliminary data suggests that tau burden extent within an ROI has a larger dynamic range than estimating tau burden by mean SUVR alone. The preliminary longitudinal data showed a 5% increase in both tau extent and density in a moderate AD subject at 6 months (vs. 1% test-retest) and a 18% and 14% increase in tau extent and density, respectively (vs. 2% test-retest), in a mild AD subject at 9 months. In contrast, no increases were observed at 6 months in 4 healthy controls. Additional interim analysis from this ongoing study will be presented. *Conclusion:* [18F]GTP1 is currently under evaluation in a longitudinal natural history study. Preliminary cross-sectional results reveal how the extent of GTP1 uptake relates to clinical cognitive and functional deficits in AD. The preliminary longitudinal results showed evidence of an increase in tau burden over 6 months in two AD patients, but not in healthy controls. References: (1) Sanabria-Bohorquez, 2016 Human Amyloid Imaging.

P3-2 CLUSTERIN IS A POTENTIAL BIOMARKER FOR LATE ONSET ALZHEIMER'S DISEASE. Jordan L. Holtzman *(Environmental Health Sciences, University of Minnesota, Minnapolis, MN)*

Background: Recent clinical trials have indicated that early initiation of monoclonal antibody therapy is associated with a reduced rate of decline in cognitive function. The categorizing of patients with early disease is currently dependent on scanning studies with radioactive abeta. These procedures are expensive and there is some question of concerning their sensitivity. These shortcomings suggests that it would be desirable to examine new biomarkers that might improved identification of potential patients who patients who are at an early stage of the decline. One approach has been to look for genetic markers that could classify patients who could benefit from antibody therapy In line with this approach there have been four large QWAS studies of patients with late onset Alzheimer's disease These studies have identified several genes that may be associated with an increased incidence of the disease. Yet, of most of these genes which were reported to have possible SNP's in all of these trials Only two werei dentified in more than one trial were apoE4 and clusterin, also known as apoJ. Clusterin is an chaperone found in the plasma. Early masspectrographic studies reported by Ghiso et al. (1993) found that when abeta was added to the CSF, it specifically and tightly bound to clusterin, also known as apolipoprotein J. Since then a number of groups have examined the association between clusterin and abeta. Furhtermore Jongbloed (2015) reported that low plasma levels of clusterin were associated with an increase incidence of late onset cognitive decline. This relationship between clusterin levels and cognitive decline is consistent with the amyloid model since clusterin inhibits the nucleation of soluble abeta to form aggregatets. The high affinity of clusterin for abeta has been reported by several groups in more recent studies. *Comment:* The recent observation that the early treatment of patients with at an early stage of cognitive decline has suggested that there is a growing need for inexpensive and sensitive biomarkers which could serve to identify patients who might benefit for early treatmen. Clusterin may fill this niche. It has already shown promise in observational clinical trials. Furthermore it is readily assayed in serum samples. Finally small early clinical studies have shown an association between low levels of plasma clusterin and cognitive decline.

Theme : Cognitive assessment and clinical trials

P3-3 IMPACT OF DIABETES ON CAREGIVER STRESS IN PATIENTS WITH AD: DATA FROM THE ICTUS STUDY. Jun Li *(West China Hospital, Sichuan University, Chengdu, CN)*

Objective: To estimate the impact of comorbid diabetes on caregiver stress in patients from a large sample of community-dwelling older patients with AD. *Methods:* Using the Data from the ICTUS study, DM was recorded at baseline and caregiver burden assessed twice per year using the ZBI scale. And the 3-factorial model of ZBI was adopted. Linear mixed models were used to examine the relation between DM and the scores of ZBI and its different factors. *Results:* The present analyses were conducted on 1,264 subjects. A total of 156 patients (12.3%) had DM. At baseline, the caregivers of patients with DM or without DM had the similar ZBI global scores and the similar scores of the three different factors of ZBI. Unadjusted and adjusted models both indicated that the global score of ZBI increased over a 24-month follow-up without significant effect of the DM. Similarly, the unadjusted models showed that DM was not determining any significant difference in the score of any factor. However, the adjusted model indicated that in the group of diabetic patients, the scores of the effect on the social and personal life of caregivers and the psychological burden increased more slowly than in the group of non-diabetic patients (P=0.04 and 0.01, respectively). *Conclusions:* DM is not associated with the global ZBI score but positively affected the caregivers' daily social and personal life and psychological burden in AD patients. It is necessary for further research. *Key words:* Diabetes mellitus(DM); Caregiver; Stress; Alzheimer's disease (AD);

P3-4 IMPROVED DETECTION OF TREATMENT EFFECTS IN SEVERE ALZHEIMER'S DISEASE: A QUANTITATIVELY-DERIVED SIB-BASED COMPOSITE SCALE. Alireza Atri[1,2], Suzanne Hendrix[3], Noel Ellison[3], Mary Clare Kane[4], John Edwards[5], George Grossberg[6] *((1) Ray Dolby Brain Health Center, California Pacific Medical Center, San Francisco, CA, USA; (2) Center for Brain/Mind Medicine, Department of Neurology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; (3) Pentara Corporation, Salt Lake City, UT, USA; (4) Prescott Medical Communications Group, Chicago, IL, USA; (5) Allergan, Jersey City, NJ, USA; (6) Saint Louis University, Saint Louis, MO, USA)*

Background: The Severe Impairment Battery (SIB) is a multi-domain, reliable, and valid cognitive scale often used in moderate to severe Alzheimer's disease (AD) dementia trials. The SIB has 6 major subscales (attention, orientation, language, memory, visuo-spatial ability, and construction), along with three brief evaluations of praxis, social interaction, and orienting to name. The SIB allows measurement of effects in patients with AD who perform at floor level on other frequently used cognitive scales. It is possible that combining items corresponding to disease severity along the broad spectrum of moderate and severe AD may not be optimal for detecting effects in patients with severe AD. As such, traditional total SIB scoring may lack sensitivity in individuals with severe AD compared with moderate AD. In this study we investigated whether a composite scale based on SIB items could be developed based on a quantitative model, to better detect treatment effects in the most severe patients with AD, compared with the traditional SIB scale. *Methods:* The quantitative-SIB composite score (qSIB-total) was developed using a partial least squares (PLS) regression modeling approach and a model training dataset (Training-dataset), and was tested on a separate and independent test dataset (Test-dataset) utilizing a mixed effect model with repeated measures (MMRM) modeling approach. A second SIB composite (qSIB-severe) was created using the same methodology in only moderate subjects in the training and test datasets. The Training-dataset consisted of pooled data from three 24-week, randomized, double-blind, placebo-controlled, parallel-group studies of memantine in moderate-to-severe patients with AD (Tariot, JAMA 2002; Reisberg, NEJM 2003; van Dyck, Alzheimer Dis Assoc Disord, 2007) in which the SIB was administered at weeks 4, 8, 12, 18, and 24. Utilizing the Training-dataset, a PLS regression analysis was used to derive a summed composite of weighted SIB items, the qSIB-composite scale, with all items having variable importance projection (VIP) of 0.80 or greater. The qSIB-composite was then tested in a Test-dataset consisting of an independent study of memantine in patients with moderate to severe AD (NCT00322153) using MMRM regression analysis. The qSIB-severe was evaluated for severe patients only (baseline Mini-Mental State Examination [MMSE] < 9) and the qSIB-total was evaluated for all patients. *Results:* A total of 966 patients were included in the pooled Training-dataset, with baseline MMSE range between 1-16; mean (SEM) baseline MMSE was 9.57 (0.107); mean (SEM) age was 76.54 (0.267)

years. The Test-dataset included 661 patients, with baseline MMSE range between 3-17; mean (SEM) baseline MMSE was 10.78 (0.113); mean (SEM) age was 76.39 (0.312) years. For all patients, the SIB total score identified significant treatment effects in patients receiving memantine vs placebo at 18 and 24 weeks (P<0.05). The qSIB-total scores did not improve sensitivity when all patients were included in the MMRM. The qSIB-severe composite included 5 items: language, memory, praxis, attention, and orientation. These items had weights of 0.009, 0.003, 0.021, 0.020, and 0.044, respectively. The minimum VIP among these 5 items was 0.8101. For severe patients (baseline MMSE <9), the qSIB-severe score improved sensitivity (lower P-values) vs the SIB total score at 8 weeks (qSIB-composite, P=0.6304; total SIB, P=0.7057), 12 weeks (qSIB-composite, P=0.6305; total SIB, P=0.8403), 18 weeks (qSIB-composite, P=0.0204; total SIB, P=0.0491), and, most substantially, at 24 weeks (qSIB-composite, P=0.002; total SIB, P=0.0241). *Conclusion:* Compared with total SIB score, a quantitative SIB composite (qSIB-severe), which was developed and tested in separate and independent AD clinical trial datasets and which used five SIB items of language, memory, praxis, attention, and orientation, provided additional measurement sensitivity and differentiation between memantine- and placebo-treated patients with severe AD. The qSIB-total did not improve sensitivity to treatment effects over the SIB total score indicating that the SIB total is already optimized for combined moderate and severe patients. Development and utilization of quantitatively optimized composite scales from established clinical trial measures may substantially improve sensitivity to measure state, rate, and treatment effect in subgroups of interest in AD clinical trials, particularly when floor effects are present, such as in severe AD. Funding: Allergan plc (A. Atri did not receive remuneration or funding for this study)

P3-5 NEUROPSYCHOLOGICAL TESTS VALIDATED BY CSF-BIOMARKERS TO DISTINGUISH BETWEEN COGNITIVE DEFICITS DUE TO OR INDEPENDENT FROM AD IN PATIENTS PRESENTING WITH DEPRESSIVE SYMPTOMS. Oliver Peters, Felix Menne, Manuel Fuentes, Brigitte Haas, Isabella Heuser *(Department of Psychiatry, Charité University Medicine Berlin, Berlin, Germany)*

Background: Depressive symptoms in old age, especially if occurring for the first time, may present independently from underlying neurodegeneration but may also reflect earliest stages of Alzheimer's disease (AD). In daily clinical routine, when depressive symptoms are present, it might be a challenge to differentiate between cognitive impairment due to depression and memory problems as a consequence of early AD. Previously we reported, based on biomarker analyses in the cerebrospinal fluid (CSF), a typical cued recall memory deficit in prodromal AD without depressive symptoms (Wagner et al. 2012). This time, using a very similar approach, we aimed to identify easy-to-apply neuropsychological tests that might help to distinguish cognitive deficits due to and independent from AD in depressed patients. *Methods:* We used the CERAD test-battery, comprising Boston Naming Test (BNT), Mini-Mental Status (MMSE), Word List Recall (WLR), Semantic Fluency (SF), Constructional Praxis (CP), Clock Drawing Test (CDT), and Trail Making Test A and B (TMT A and B), to screen for cognitive impairment in outpatients referred to our memory clinic. Only patients with a MMSE score ≥ 24 were analyzed in this study (n=630) to focus only on those with mild cognitive deficits either due to early AD or due to depression or both. Depressive symptoms were assessed by the long version (30 items) of the Geriatric Depression Scale (GDS). In all patients a spinal tap was performed and Aβ 1-42 as well as total Tau levels were quantified. GDS scores ≤ 10 were regarded as normal. GDS scores ≥ 11 were classified as suspect for depression (Wancata et al. 2006); patients with a moderate (11-20) and high GDS score (21-30) were group-wise analyzed. CSF-biomarkers were regarded as in line with AD pathology when the ratio of t-Tau/Aβ1-42 was 0.58 or higher (corresponding to t-Tau/Aβ1-42 ≥ 350/600 μg/ml). For further analyses we divided the group into patients with more likely positive or negative AD biomarker signature. We then calculated single value ROC curves and determined the best triple of neuropsychological tests to identify typical signs of AD even in depressed patients. *Results:* Our cohort of 630 outpatients (51% female) had a mean age of 68 ± 9.2 years. The mean MMSE score was 27.1 ± 1.8 and the mean GDS score 12.3 ± 7. 251 patients were above the t-Tau/Aβ1-42 ratio cut-off likely for AD, while 379 were classified as non-suspicious for AD. Word List Recall (WLR) performed best with an AUC of 0.71 in the group without depressive symptoms as indicated by a GDS score ≤ 10 (n=285). For patients with moderate and high levels of depressive symptoms (GDS 11-20 (n = 237) and 21-30 (n = 108) respectively) Constructional Praxis Savings (CPS) revealed highest AUCs with 0.72 (medium GDS) and even 0.89 (high GDS), followed by MMSE (0.69 and 0.79). In comparison, in the single item analysis the often recommended CDT reached only 0.64 and 0.76 in our sample. In a multi-parameter analyses we additionally searched for the best combination of two or three screening tests and found that in patients with moderate and high GDS scores beyond CPS adding MMSE and CDT might help to increase discriminability. (AUC varying between 0.735 and 0.888).*Conclusion:* Our analyses reveal the robustness of Constructional Praxis Savings (CPS) as a screening instrument to identify possible underlying AD in depressed patients presenting with a high GDS score. Our findings regarding non-depressed patients are in line with our earlier analyses (Wagner et al. 2012). Meaningful neuropsychological tests to be performed in depressed patients are important to prevent overlooking signs of neurodegeneration when depressive symptoms and cognitive deficits appear in parallel. References: Wancata J, Alexandrowicz R, Marquart B, Weiss M, Friedrich F. The criterion validity of the Geriatric Depression Scale: a systematic review. Acta Psychiatr Scand. 2006 Dec; 114(6):398-410. Wagner M, Wolf S, Reischies FM, Daerr M, Wolfsgruber S, Jessen F, Popp J, Maier W, Hüll M, Frölich L, Hampel H, Perneczky R, Peters O, Jahn H, Luckhaus C, Gertz HJ, Schröder J, Pantel J, Lewczuk P, Kornhuber J, Wiltfang J. Biomarker validation of a cued recall memory deficit in prodromal Alzheimer disease. Neurology. 2012 Feb 7; 78(6):379-86.

P3-6 PRACTICE EFFECTS IN ALZHEIMER'S DISEASE PREVENTION TRIALS: PROOF OF CONCEPT FOR A COGNITIVE TEST RUN-IN. Diane M. Jacobs[1], M. Colin Ard[1], Steven D. Edland[1,2] *((1) Shiley-Marcos Alzheimer's Disease Research Center, Department of Neurosciences, University of California, San Diego, CA, USA; (2) Division of Biostatistics, Department of Family Medicine & Public Health, University of California, San Diego, CA, USA)*

Background: Practice effects (i.e., improved performance over serial cognitive assessments attributed to repeated exposure to test stimuli or procedures) present an important potential confound in clinical trials. Practice effects may be misinterpreted as active drug effects or they may reduce the likelihood of detecting differences between the treatment and placebo arms by masking decline in the placebo group. As the target population for clinical trials in AD continues to move toward the preclinical and prodromal stages of the disease, it will become increasingly important to account for practice effects, since participants whose cognition is intact or subtly impaired are more likely to exhibit robust practice effects. One method to

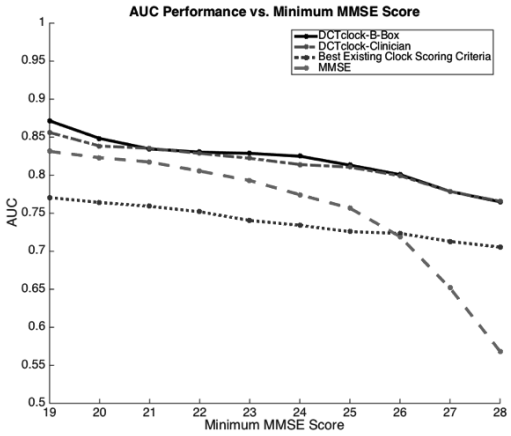
control for practice effects is to use a cognitive test run-in wherein the cognitive outcome measure(s) are administered twice prior to randomization and scores from the second testing are used as the baseline reference. *Methods:* We examined the utility of a cognitive test run-in for AD prevention trials, by performing archival analyses of data from the ADCS donepezil/vitamin E trial in MCI. Participants: The current analyses were restricted to data from participants in the placebo arm. All participants were between the ages of 55 to 90 and met diagnostic criteria for amnestic MCI. The group was comprised of 259 participants with a mean age of 72.9 years (SD=7.6), and an average of 14.7 years of education (SD=3.1); 47% were female, 53% were APOE-ε4 carriers, and the mean score on the MMSE at screening was 27.35 (SD=1.8). Procedure: The modified Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-Cog) is a common primary outcome measure for AD trials. The ADAS-Cog was administered at the screening visit (one month prior to randomization), 3- and 6-months post-randomization, and semiannually thereafter; scores can range from 0-85, with higher scores indicating greater cognitive impairment. Data analyses: Mixed model repeated measures (MMRM) was used to compare change on the ADAS-Cog from screening to 18-month follow-up in two potential trial designs: (1) a 19-month trial using the score from the screening visit as the referent value, and (2) a 15-month trial with a 4-month cognitive test run-in wherein the second administration of the ADAS-Cog (i.e., from the 3-month follow-up visit) was used as the baseline referent. *Results:* At screening, the group mean ADAS-Cog score was 17.40 (SD=6.0). At 3-month follow-up, the group mean score improved slightly to 16.79 (SD=7.0), likely reflecting a practice effect. By 6-month follow-up, the group mean had returned to the baseline level (Mean =17.38; SD=7.0), and scores progressively declined thereafter. The change in ADAS-Cog score between screening and 18-month follow-up was +1.18; however, the change between the 3- and 18-month visits was +1.79. Hence, when the second (i.e., 3 mos.) administration of the ADAS-Cog is used as the baseline referent, the change score at 18-months is greater. This increase in observed change with the cognitive test run-in reduced the required sample size by over 40% when treatment effect size is expressed as percent slowing of progression. For example, N=3846 participants per arm are needed to detect a 50% slowing of progression in ADAS-Cog score without the cognitive test run-in (i.e., when the score from screening is used as baseline), whereas a sample of only N=1692 participants per arm is needed with the run-in (80% power, two-sided alpha = 0.05, with equal allocation to arms). *Conclusion:* Archival analyses of placebo arm data from the ADCS donepezil/vitamin E trial in MCI demonstrates proof of concept for using a cognitive test run-in for AD prevention trials. Using the cognitive test run-in resulted in a greater change score from baseline to study completion and dramatically reduced the requisite sample size to achieve comparable statistical power. If this design were adopted for future trials, the associated decrease in sample size would result in considerable cost savings.

P3-7 IMPROVING COGNITIVE SCREENING ACCURACY AND EFFICIENCY FOR MINIMALLY IMPAIRED INDIVIDUALS. William Souillard-Mandar[1], Randall Davis[1,2], Rhoda Au[3], Dana L. Penney[1,4] *((1) Digital Cognition Technologies, Inc, Waltham, MA, USA; (2) MIT Computer Science And Artificial Intelligence Laboratory, Cambridge, MA, USA; (3) Boston University Schools of Medicine and Public Health, Boston, MA, USA; (4) Lahey Hospital and Medical Center, Burlington, MA, USA)*

Background: Early detection and diagnosis of Alzheimer's disease is critical for quality care and research. Currently, clinical detection depends on complaints of the patient or their family, or impaired performance on a standard cognitive screening task (e.g., the Mini Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA)). But all of these are reliant upon overt cognitive decline and their presence suggests that the pathological burden is significant and irreversible. Biomarkers derived from CSF, imaging, and blood – presumed indices of earliest stage disease – have limited utility because they are costly and invasive; even so their prognostic efficacy still remains unclear. A screening test sensitive to subtle decline in cognitive processes well before traditional metrics detect more severe impairment would have significant financial and scientific utility for large scale studies and for clinical applications. The Clock Drawing Test (CDT) is a frequently used, rapid (under two minutes) and inexpensive cognitive screening tool whose utility is reduced by imprecise measurements and inter-rater unreliability. DCTclock, a novel version of the traditional test, radically improves performance by using novel software and a commercially available digitizing ballpoint pen (Anoto) that reports its position with considerable spatial and temporal precision. As a result DCTclock can analyze both the final drawing and the drawing process. DCTclock automates scoring and improves classification performance by operationally defining variables and by using machine learning (ML) techniques to determine the variables and cut-scores that optimize detection and classification. We previously demonstrated that on a general classification task DCTclock outperforms traditional CDT scoring systems, even when those systems are embodied in code and optimized for best possible performance (1). Here we examine classification accuracy of the MMSE, operationalized CDTs and DCTclock to screen for degradation in general cognitive skills. We also compare two versions of DCTclock, one using an opaque, black box algorithm (B-Box) and another using an algorithm designed for clinician interpretability (Clinician). *Methods:* Subjects are 935 individuals with documented cognitive status from the Framingham Heart Study (FHS) and the Lahey Hospital and Medical Center Neurology service (LC). Cognitive groups consisted of Cognitively Healthy from the FHS (CH, N=443) and Cognitively Impaired (CI, N=492) from FHS and LC. FHS cognitively impaired group classification was based on consensus diagnosis using all available information for each individual including imaging, neuropsychological testing, medical and study record review (including retrospective). Our software automatically categorized the digitized pen stroke data from clock drawings by these subjects, computed approximately 1000 variables that we designed, and used machine learning to build B-Box and Clinician models that classified CH and CI. We compared classification AUC stratified for MMSE scores for three screening tools (optimized CDT; MMSE; DCTclock). *Results:* DCTclock outperformed the MMSE and the optimized traditional CDT on the entire subject population, with AUCs of 0.87 for DCTclock-B-Box, 0.86 DCTclock-Clinician vs 0.83 for optimized CDT and 0.77 for MMSE. We also examined performance at various levels of impairment, restricting our subject population to successively higher levels of MMSE scores: DCTclock outperformed the optimized CDTs and the MMSE at all levels of impairment, maintaining its accuracy in a population of subjects with higher MMSE scores (Fig 1). Over all subjects the MMSE outperformed the optimized existing CDT, with AUCs of 0.83 and 0.77 respectively. In the populations restricted to higher minimum MMSE, accuracy decreased much more significantly for the MMSE than for the optimized CDT: the optimized CDT started to outperform the MMSE in individuals scoring 27 or above (0.72 vs. 0.65). *Conclusion:* While both the MMSE and DCTclock perform well as a general cognitive screener, their classification performance diverges as the population becomes restricted to minimally impaired or healthy appearing: the MMSE performs less accurately compared to both the DCTclock and the optimized CDT. We demonstrate that it is possible to rapidly detect

subtle cognitive impairment in individuals performing in the normal range on a widely used screening tool. This offers opportunity for early detection via accurate widespread, economical cognitive screening. Both B-Box and Clinician classification models performed comparably, demonstrating that with careful variable selection and only a small trade-off in accuracy, opaque algorithms can be made more transparent to the clinician, providing additional useful clinical information. (1) Souillard-Mandar, William, et al. «Learning classification models of cognitive conditions from subtle behaviors in the digital Clock Drawing Test.» Machine Learning 102.3 (2016): 393-441.

Figure 1



P3-8 VALIDATION OF AN AUTOMATED SCORING METHOD FOR WEB CAMERA EYE TRACKING ON A VISUAL PAIRED COMPARISON TASK. Nicholas T. Bott[1,2], Alex Lange[2], Robert Cosgriff[2], Paul Clopton[3], Beth Buffalo[2,4], Dorene M. Rentz[5,6,7], Stuart Zola[2,8] *((1) Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA; (2) Neurotrack Technologies, Inc., Redwood City, California, USA; (3) University of California San Diego School of Medicine, San Diego, California, USA; (4) University of Washington, Seattle, Washington, USA; (5) Massachusetts General Hospital, Boston, Massachusetts, USA; (6) Harvard Medical School, Boston, Massachusetts, USA; (7) Brigham and Women's Hospital, Boston, Massachusetts, USA; (8) Emory University Office of the Provost, Atlanta, Georgia, USA)*

Backgrounds: 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 through comparison of the proportion of time an individual spends viewing a new picture (i.e., novelty preference) compared to a picture they have previously seen. A novelty preference is expected in individuals with normal memory function. By contrast, individuals with memory difficulties are characterized by more equally distributed viewing times between the novel and familiar pictures. The lack of novelty preference suggests impaired declarative memory for what has already been viewed. VPC tasks have been shown to reliably detect memory dysfunction in both primates and humans, and represent a paradigm deployable via devices with web cameras for the rapid assessment of declarative memory dysfunction. This study examined the relationship of a standard eye tracker camera automated scoring procedure at 60 frames per second (FPS), and human and automated scoring procedures from a web-based camera built into a laptop at 30 FPS on a visual paired comparison (VPC) decisional task. *Methods:* This was an observational study of 54 clinically normal older adults. Subjects completed three in-clinic visits with simultaneous recording of eye movements on a 5-minute VPC decision task by a standard eye tracker camera and a built-in laptop-based web camera. Novelty preference was calculated as the ratio of time fixated on the novel image to time spent fixated on either image during each of the 20 test trials. Data from the standard eye tracker camera was scored using the proprietary product software. The web-camera was scored using two methods: an automated scoring and human scoring system. The automated scoring algorithm determined the locations of various landmarks of the participant's face, and then extracted geometric features (e.g., shape of the eyes, relative location of the pupils) from this data to estimate the eye gaze position of each video frame. The human scoring web-camera system evaluated eye gaze on a frame-by-frame basis by 3 independent human coders. *Results:* There were strong relationships on VPC mean novelty preference scores between the 60 FPS eye tracker and the 30 FPS built-in web camera automated scoring algorithm of the same task at each of the three time points (r = 0.89 to 0.96). There were strong relationships on VPC mean novelty preference scores between the 30 FPS human scoring method and the automated scoring algorithm for the built-in web camera at each of the three time points (r = 0.88 to 0.96). *Conclusions:* Automated scoring of a VPC decisional task using a built-in laptop web camera correlated strongly with human-based scoring of the same task. It also correlated strongly with automated scoring of the same task using a standard high frame rate eye tracker camera. Built-in web cameras are a standard feature of most smart devices and can be effectively employed to track eye movements on VPC task paradigms. Brief assessment of declarative memory using such paradigms can be conducted with high accuracy and minimal cost, making them an ideal candidate for use in clinical trials.

Theme : Bevioral Disorders and Clinical Trials

P3-9 ASSOCIATION OF SUBSYNDROMAL SYMPTOMS OF DEPRESSION WITH COGNITIVE DECLINE AND CORTICAL ATROPHY IN INDIVIDUALS WITH MILD COGNITIVE IMPAIRMENT. R. Scott Mackin[1,2], Philip S. Insel[2], Craig Nelson[1], Mitzi M. Gonzales[1,3], Duygu Tosun[2,4], Niklas Mattsson[5,6], Susanne G. Mueller[2,4], Simona Sacuiu[7], David Bickford[1], Michael W. Weiner[1,2,4,8] and the Alzheimer's Disease Neuroimaging Initiative *((1) Department of Psychiatry, University of California, San Francisco, CA, USA; (2) Center for Imaging of Neurodegenerative Diseases, Veterans Administration Medical Center, San Francisco, CA, USA; (3) Department of Mental Health, VA Northern California Health Care System, Martinez, CA, USA; (4) Department of Radiology, University of California, San Francisco, CA, USA; (5) Clinical Memory Research Unit, Faculty of Medicine, Lund University, Lund, Sweden; (6) Department of Neurology, Skane University Hospital, Lund, Sweden; (7) Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden; (8) Department of Medicine, University of California, San Francisco, CA, USA)*

Background: Subsyndromal symptoms of depression (SSD) or depressive symptoms not of the severity or frequency to meet criteria for major or minor depression occur in up to 30% of community dwelling older adults. SSD are also among the most commonly reported neuropsychiatric symptoms in Mild Cognitive

Impairment (MCI) occurring in up to 50% of MCI individuals. As such, both major depression and SSD are often thought to represent prodromal features of incipient dementia. However, despite the prevalence of SSD in MCI, few studies have been conducted to evaluate the impact of chronic SSD on specific domains of cognitive functioning longitudinally. Further, while the etiology of SSD is likely complex, determining the degree to which SSD are associated with cortical atrophy represents a significant avenue to clarify mechanisms contributing to accelerated cognitive decline in individuals with SSD. *Methods:* Data from 149 MCI participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study were analyzed. Participants were evaluated at baseline and 6 to 12 month intervals over four years. SSD were evaluated utilizing Neuropsychiatric Inventory (NPI). Individuals meeting criteria for SSD at each assessment were classified as chronic SSD (n=75) or no chronic symptoms of depression (non-SSD, n=74). Cognitive outcomes were evaluated with mixed effects models adjusting for age, education, gender and ApoE genotype. Primary cognitive outcomes included measures of global cognition, memory, learning, attention and information processing speed (with and without motor speed component), expressive language, and attention. Cortical thickness quantification was conducted using the Freesurfer Version 4.4 longitudinal processing framework (http://surfer.nmr.mgh.harvard.edu/). Cortical thickness was obtained for nine regions of interest: frontal lobe (medial and lateral orbitofrontal, rostral and caudal middle frontal, and superior frontal), anterior cingulate (rostral and caudal regions), precuneus, cuneus, posterior cingulate, temporal lobe, parahippocampus, hippocampus, and entorhinal cortex. Thickness values in the left and right hemispheres were averaged to obtain one measure for each cortical region of interest. CSF measures of total tau were obtained. All p-values were two-tailed and cognitive and cortical atrophy outcomes were adjusted for multiple comparisons using a false discovery rate (FDR) correction. Statistical analyses were conducted with the R Package (v 2.8.1, The R Foundation for Statistical Computing, http:/www.r.project.org/). *Results:* The SSD group demonstrated accelerated decline on measures of global cognition (Alzheimer's Disease Assessment Scale (β=1.580, p=0.003)), memory (Wechsler Memory Scale-Revised Logical Memory II Recall (β=-0.691, p=0.003)), information processing speed (Trail Making Test Parts A (β=4.681, p=0.002) and B (β=12.150, p=0.003)), and semantic fluency (Category Fluency (β=-0.855, p=0.002). No group differences were observed for rate of decline on measures of attention, learning, or confrontation naming. SSD participants also exhibited accelerated frontal lobe (β=-0.020, p=0.008) and anterior cingulate (β=-0.036, p<0.001) atrophy but the two groups did not differ with respect to rate of atrophy in any other regions. Accelerated frontal lobe and anterior cingulate atrophy was associated with cognitive decline on measures of global cognition, information processing speed, and semantic fluency (all p <0.05), but not memory. *Conclusion:* Individuals with chronic SSD may represent an MCI subgroup that is highly vulnerable to decline in multiple cognitive domains resulting from accelerated frontal lobe and anterior cingulate atrophy.

P3-10 CHANGES IN NEUROPSYCHIATRIC SYMPTOMS OVER 3 YEARS BETWEEN EARLY –VERSUS LATE-ONSET AMNESTIC MILD COGNITIVE IMPAIRMENT. Geon Ha Kim[1], Jong-Won Kim[2], Youngshin Yoon[3], Kyoung-Gyu Choi[1], Seong Hye Choi[4], Jee Hyang Jeong[1] *((1) Department of Neurology, Ewha Womans University Mokdong Hospital, Ewha Womans University School of Medicine, Seoul, Korea; (2) Department of Emergency Medicine, School of medicine, Konkuk University, Konkuk University Medical Center, Seoul, Republic of Korea; (3) Department of Neurology, Seoul Metropolitan Seonam Hospital, Seoul, Korea; (4) Department of Neurology, Inha University Hospital, Inha University School of Medicine, Incheon, Korea)*

Background and Objectives: Amnestic mild cognitive impairment (MCI) is regarded as a prodromal stage of Alzheimer's disease (AD). Some researchers arbitrarily classify MCI with a cut-off age of 65 years, into early-onset (EOMCI) and late onset (LOMCI).Several previous studies showed that EOMCI may differ from LOMCI in the patterns of cognitive decline or glucose hypometabolism. However, differences of changes in neuropsychiatric symptoms between EOMCI and LOMCI have seldom been studied. *Methods:* This study was conducted as part of the Clinical Research Center for Dementia of South Korea (CREDOS) study. We enrolled 100 patients with aMCI (27 EOMCI, 73 LOMCI), who were followed up annual neuropsychological tests over 3 years. Neuropsychiatric symptoms were assessed by caregiver-administered neuropsychiatric inventory (CGA-NPI). Group-by-time interaction effects in each 12 neuropsychiatric symptom were analyzed using a linear mixed model. We also compared the baseline and changes of neuropsychiatric symptoms between converters (CV) and non-converters (NCV) within the EOMCI or LOMCI group. *Results:* The LOMCI group increased the scores of disinhibition while EOMCI group decreased those scores over 3 years. Within the EOMCI group, the scores of anxiety in CV were increased whereas those were decreased in NCV group. With regards to the LOMCI group, the scores of delusion and apathy in CV were significantly increased compared to those in the NCV group. *Conclusion:* Our findings may suggest that changes in neuropsychiatric symptoms may differ between EOMCI and LOMCI. Future studies are warranted to elucidate the predictive implication of neuropsychiatric symptoms between EOMCI and LOMCI for conversion to dementia. This research was supported by the Original Technology Research Program for Brain Science through the National Research Foundation of Korea (NRF) funded by the Korean government (MSIP) (No. 2014M3C7A1064752) and by Research Program To Solve Social Issues of the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (No.2015M3C8A8076481)

P3-11 USING ENVIRONMENTAL LIGHT THERAPY TO IMPROVE SLEEP AND NEUROPSYCHIATRIC SYMPTOMS IN DEMENTIA. Sébastien Gonfrier[3], Sawsan Al Rifai[1], Linda Benattar[2], Laurence Merlin[2], Philippe Zawieja[2], Olivier Guerin[3] *((1) EHPAD Les Pastoureaux, Valenton, France; (2) ORPEA group, Puteaux, France; (3) CHU Nice, France)Backgrounds*

Alzheimer's disease and related syndromes (AD) is a disease affecting memory but also the relationship with the environment and empower people. Patients with AD present in 90% of cases of behavioral disorders and of these behavioral disorders include agitation, apathy but also sleep disorders by circadian rhythm impairment. In 2014, the Cochrane published a systematic review of the literature over the last 20 years concerning the use of light

therapy in patients with a AD. No study has shown proven efficacy on the behavior of patients with AD. The main objective of the study was to assess the influence of environmental light therapy (from 5 a.m to 10 p.m) on nighttime sleep of residents. Secondary objectives were the study of sleep time on the day, anxiety by the COVI scale and behavioral disorders by the NPI scale. *Methods:* 12 residents of a nursing home with an integrated light therapy in common areas were studied. , residents was equipped with a actimeter wrist or ankle for 42 days divided into three periods of 14 days with a standard light in period 1 and 3 and light therapy on period 2 . Sleep time was estimated by two algorithms: Cole-Kripke and Sadeth .Neuropsychiatric symptom were assess by the COVI scale for anxiety and the neuropsychiatric inventory (NPI) The modeling results was carried out by a mixed model. *Results:* Average age was 84.2 (SD 6.5) .On the main objective nightsleep time was significantly higher with light therapy (period 2 vs 1 period) of 15.2 and 16.9 minutes on average, but no significant difference were observed with the third period (period 2 vs 3). Of the total sleep time during period 2 was significantly increased with 55.1 and 46 minutes respectively compared to the period 1 without significant difference between period 2 and 3. For the COVI scale there was a significant decrease of 0,7 point and the NPI scale decrease of 4.7 points significantly between period 1 and 2 . For the 2 scales there were no difference between the period 2 and 3. *Conclusion:* The use of environmental therapy shows significant improvement of nocturnal sleep, total sleep, anxiety and behavior. However, this phenomenon did not show reversibility in the third period of the protocol. Ideally a cross-over protocol with longer exposure time could show this phenomenon definitively.

Theme : Epidemiology and Clinical Trials

P3-12 OPERATIONALIZING THE IWG2 AND NIA-AA DIAGNOSTIC CRITERIA IN SIX EUROPEAN COHORTS.

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Background: Both the International Working Group (IWG2) and the National Institute of Aging-Alzheimer Association (NIA-AA) diagnostic frameworks seek to integrate information on the clinical presentation of AD with in vivo biomarker evidence of the underlying disease pathology, with the aim of improving diagnostic accuracy and facilitating the recognition of disease well before the onset of dementia. In this study, we aimed to apply the IWG2 and NIA-AA diagnostic algorithms to cohorts available in the European Medical Information Framework in Alzheimer's Disease (EMIF-AD), i.e. DESCRIPA, Sant Pau, IDIBAPS, EDAR, Antwerp, and Pharmacog, to describe the results of classification, and to summarize the baseline characteristics and disease progression during follow-up across cohorts and diagnostic groups. *Methods:* For each cohort, only subjects with an amyloid or neuronal injury biomarker were included. The level of cognitive function was based on assessment by the investigator (NC=normal cognition, SCI=subjective cognitive impairment but normal cognition, MCI=mild cognitive impairment, AD=Alzheimer's disease, and Other=other dementia). Subjects were further characterized by available biomarkers (CSF Aβ42, t-tau, and p-tau; hippocampal volume). nDescriptive statistics were used to summarize baseline characteristics, including age, sex, years of education, APOE E4 carrier status, and percentage of subjects with abnormal CSF Aβ42 or amyloid PET in the overall population and across cohorts. Analyses were also performed on the subset of subjects with a clinical diagnosis of MCI, including other baseline disease characteristics (MMSE, CDR-SB, and percentage with abnormal t-tau or p-tau) as well as follow-up measurements (progression to any kind of dementia and annualized change in MMSE and CDR-SB). These variables were also analyzed by MCI subgroups generated by the IWG2 and NIA-AA diagnostic algorithms. *Results:* There were 1264 subjects in the pooled sample; 14% NC, 12% SCI, 55% MCI, 14% AD, and 5% other dementia. The distribution of subjects with different clinical diagnoses varied widely across cohorts, as did age, gender, education, percentage of APOE E4 carriers, and percentage of subjects with abnormal CSF Aβ42. To determine whether some of the differences in baseline characteristics among cohorts arose from differences in their proportion of subjects in respective diagnostic categories, analyses were limited to the subset of 700 subjects with MCI. Differences were still observed for age, gender, education, MMSE, percentage with abnormal CSF Aβ42 or amyloid PET, percentage with abnormal t-tau or p-tau, and distribution of subjects with different NIA-AA and IWG2 diagnoses (Table 1), though not for percentage of APOE E4 carriers or CDR-SB. Mean annualized decrease in MMSE (but not CDR-SB), as well as the proportion of subjects that progressed diagnostically (from MCI to any kind of dementia), were greater in subjects meeting NIA-AA criteria for MCI due to AD-high likelihood (both amyloid and neuronal injury biomarkers abnormal) and those with hippocampal atrophy (a "proximity" biomarker) than for those with MCI due to AD-intermediate likelihood (abnormal amyloid/normal neuronal injury biomarker). Disease progression was least in subjects categorized as MCI-SNAP (suspected non-Alzheimer disease pathway) or MCI not due to AD. Similar findings were observed between the IWG2 diagnoses of prodromal AD and MCI not due to AD (Table 2). Across cohorts, there were differences in the proportion of subjects within the various diagnostic subgroups, and in progression to dementia and annualized change in CDR-SB, but not annualized change in MMSE. When the analyses were further restricted to those subjects that had MCI due to AD-high likelihood or prodromal AD, inter-cohort differences progression to dementia remained, though annualized change in CDR-SB was no longer significant. *Conclusions:* There was considerable variability in the 6 analyzed cohorts with respect to baseline clinical diagnoses, demographic and disease characteristics, and disease progression during follow-up. Limiting the analyses to subjects with MCI did not reduce the inter-cohort variability. Nonetheless, both NIA-AA and IWG2-based diagnoses could be assigned in all subjects, and these predicted rate of progression of the disease, validating their utility in diverse populations.

Table 1

Diagnosis (%) by cohort

Framework	Diagnosis	Antwerp	DESCRIPA	EDAR	IDIBAPS	Pharmacog	SanPau
NIA-AA	MCI/AD high likelihood	41	19	30	71	37	44
	MCI/AD intermediate (amyloid+)	12	7	21	23	1	16
	MCI/AD intermediate (hippocampal atrophy)	0	16	0	0	0	0
	MCI low likelihood	22	7	26	3	0	28
	MCI-SNAP	25	12	14	3	61	13
	Inconclusive	1	41	9	0	0	0
IWG2	Prodromal AD	58	18	30	71	37	47
	MCI not AD	41	25	61	29	63	53
	Inconclusive	1	57	9	0	0	0

Table 2
Progression by NIA-AA or IWG2 diagnosis

Framework	Diagnosis	% Progressed	Annualized ΔMMSE	Annualized ΔCDRSB
NIA-AA	MCI/AD high likelihood	42.1	-1.31 (2.89)	0.69 (1.34)
	MCI/AD intermediate (amyloid+)	30.8	-0.79 (4.20)	0.78 (4.60)
	MCI/AD intermediate (hippocampal atrophy)	59.5	-1.08 (1.95)	1.25 (1.74)
	MCI low likelihood	26.9	0.24 (2.58)	0.22 (0.90)
	MCI-SNAP	22.4	-0.22 (2.38)	0.33 (1.71)
IWG2	Prodromal AD	42.0	-1.33 (2.89)	0.65 (1.32)
	MCI not AD	24.9	-0.22 (2.86)	0.45 (2.70)

P3-13 AMYLOID PATHOLOGY IN THE PROGRESSION TO MILD COGNITIVE IMPAIRMENT. Philip Insel[1,2,3], Oskar Hansson[1,5], R. Scott Mackin[2,4], Michael Weiner[2,3], Niklas Mattsson[1,5,6], for the Alzheimer's Disease Neuroimaging Inititaive[7] *((1) Clinical Memory Research Unit, Faculty of Medicine, Lund University, Lund, Sweden; (2) Center for Imaging of Neurodegenerative Diseases, Department of Veterans Affairs Medical Center, San Francisco, CA, USA; (3) Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA, USA; (4) Department of Psychiatry, University of California, San Francisco, CA, USA; (5) Memory Clinic, Skåne University Hospital, Sweden; (6) Department of Neurology, Skåne University Hospital, Sweden)*

Background: Cognitively-normal people with brain β-amyloid (Aβ) pathology are considered to have preclinical Alzheimer's disease (AD), but progression to mild cognitive impairment (MCI) may be seen with or without Aβ pathology. The objective of this study was therefore to identify Aβ-dependent differences among cognitively healthy people who progressed to MCI. n*Methods:* Seventy-five cognitively healthy controls who progressed to MCI during up to 10 years of follow-up were included from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Forty participants were Aβ-positive and 35 were Aβ-negative (tested by cerebrospinal fluid (CSF) biomarkers or positron emission tomography (PET) examination). We tested effects of Aβ on measures of cognition, function, brain structure, brain metabolism, and white matter lesions. *Results:* Aβ-status did not affect time to MCI diagnosis, overall functional decline, or decline in several cognitive tests (including MMSE), but Aβ-positive progressors had greater decline on specific functional items and specific cognitive tests (logical memory immediate and delayed recall, Trails B, and Boston Naming Test), while Aβ-negative progressors had greater frequency of depressive symptoms at baseline. Aβ-status did not influence patterns of brain atrophy or white matter lesions, but Aβ-positive progressors had greater decline of brain metabolism. *Conclusion:* The transition from preclinical to prodromal AD differs from other causes of cognitive decline in terms of baseline depressive symptoms, longitudinal decline in specific functional and cognitive domains, and longitudinal decline in brain metabolism. This may be used to facilitate identification of preclinical AD in screening programs and in clinical trials.

P3-14 UTILIZING ADMINISTRATIVE CLAIMS DATA TO IDENTIFY SEVERITY IN PATIENTS WITH ALZHEIMER'S DISEASE: CHALLENGES AND OPPORTUNITIES. Fanta W Purayidathil[1], Sarah Cadarette[2], Amanda Forys[2], Trent McLaughlin[2], Manasee Shah[2], Myrlene Sanon Aigbogun[3] *((1) Health Economics and Outcomes Research, Avanir Pharmaceuticals, Inc.; (2) Health Economics and Outcomes Research, Xcenda; (3) Health Economics and Outcomes Research, Otsuka Pharmaceutical Development & Commercialization, Inc.)*

Background: Qualifying disease severity informs treatment decisions, prognosis evaluation, and comparative analysis of patient populations. The economic burden of Alzheimer's Disease (AD), resulting from associated declines in cognition and function and the onset of behavioral symptoms, such as agitation, is substantial. Understanding costs associated with AD management, stratified by severity, may further qualify the burden on patients and on the healthcare system. While US administrative health claims data are widely available and include information on diagnosis, therapies, laboratory tests and procedures, they inherently lack important clinical markers of severity. Additionally, diagnosis codes are not structured to indicate level of severity for AD patients. A review of previously-developed severity algorithms in AD using claims data to identify variables which could serve as proxies for AD severity was undertaken. *Methods:* A systematic literature review of indexed articles published between January 1995 and February 2016 was performed using MEDLINE, EMBASE, and the Cochrane Central Library of Controlled Trials. Additionally, hand searches of gray literature relevant to AD were conducted. Study designs included retrospective database analyses, observational studies, and economic evaluations. Outcomes of interest included surrogate measures of severity/stage of AD, clinical outcomes, resource utilization, changes in living situation, and direct medical costs. *Results:* Of 21 full-text articles identified, 12 were included in the assessment. Two studies focused on deriving AD stage using claims data and three linked claims and survey data encompassing clinical staging. Specific methods for determining severity from claims included comorbidities (decubiti, malnutrition, aspiration pneumonia) and cholinesterase or memantine prescriptions. Additional methods for qualifying disease severity included medical complications and procedures (transitions in sites of care, insertion of a feeding tube), use of comorbidity indices, cognitive performance scores, and estimation of activities of daily living). Severity staging categories were either mild/moderate/severe or early- vs. late-stage. *Conclusion:* Review of previously-developed severity algorithms in AD using claims data corroborates previous understanding that few algorithms have been attempted. Continued research into the development of an algorithm using administrative claims data may help to identify patients in managed care and understand patterns and opportunities related to disease management.

Theme : Animal Model and Clinical Trials

P3-15 AMELIORATION OF GASTRO-INTESTINAL MICROBIOTA FOLLOWING STEM CELL TREATMENT IN A MOUSE MODEL OF CEREBRAL ABETA AMYLOIDOSIS. Tristan Bolmont[1,2], Taoufiq Harach[2], Alexei Lukashev[1], Nikolai Tankovich[3] *((1) Stemedica International, Lausanne, Switzerland; (2) Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland; (3) Stemedica Cell Technologies, San Diego, CA, USA)*

Background: Alzheimer's disease (AD) is a severe and ever-growing socio-economic burden to western societies. Despite all research efforts there is currently no treatment for AD, and currently approved therapies only provide symptomatic treatments for this disease. A growing body of clinical and experimental evidence suggests that gut microbiota may contribute to aging and influence brain disorders. In particular, a new connection between gut microbiota and Parkinson's disease has been reported in humans. In mouse models, studies report a role for the microbiota in the modulation of stress-related behaviors relevant to psychiatric disorders. Recent research has revealed that microbiota may impact

the development of autism spectrum disorders (ASD) as Bacteroides fragilis improved defects in communicative and sensorimotor behaviors following maternal immune activation in mice, a mouse model exhibiting ASD features. In a mouse model of multiple sclerosis, gut microbiota strongly contributes to pathology. While such findings strongly suggest that the gut microbiota may impact a wide range of brain functions, the role of intestinal microbes on AD pathogenesis is largely overlooked and far from being understood. To this end we have studied the role of the microbiota in a commonly used mouse model of cerebral β-amyloidosis and we demonstrated that intravenous injection of human adult mesenchymal stem cells reduces amyloid pathology while ameliorating the composition of gastro-intestinal microbiota. *Methods:* Since microbial dysbiosis has been associated with many diseases we sought to determine whether conventionally-raised transgenic APPPS1 mice (CONVR-APPPS1) develop age-related changes in the intestinal microbiota. Thus, we sequenced bacterial 16S rRNA genes extracted from fecal samples of pre-depositing and Aβ-depositing CONVR-APPPS1 and compared it to wild-type littermates control mice (CONVR-WT). To address the role of the gut microbiota in AD, we next generated a mouse model of AD without gut microbiota, referred to axenic, or germ-free (GF-) APPPS1 mice. We compared GF-APPPS1 mice with conventionally-raised APPPS1 mice (CONVR-APPPS1). Bacteriological evaluation of the GF-APPPS1 animals was regularly performed for their germ-free status by aerobic and anaerobic culture, DNA and gram staining of cecal content to detect uncultivable contamination. In addition, serological testing for known viruses and pathogens was performed periodically by ELISA, PCR or IFA tests. To evaluate the impact of stem cells on gastro-intestinal microbiota, CONV-APPPS1 mice received a single intravenous injection of adult human mesenchymal stem cells. *Results:* To address whether the microbiome may be altered in Alzheimer´s disease, we sequenced bacterial 16S rRNA from fecal samples of conventionally-raised Aβ precursor protein (APP) transgenic mice and found a remarkable shift in the gut microbiota as compared to healthy, wild-type mice. We then generated germ-free APP transgenic mice and found a drastic reduction of cerebral Aβ amyloid pathology when compared to control mice with intestinal microbiota. Importantly, re-colonization of germ-free APP transgenic mice with microbiota from conventionally-raised APP transgenic mice increased cerebral Aβ pathology, while re-colonization with microbiota from wild-type mice was much less effective in increasing cerebral Aβ levels. We also performed gut colonization studies in these APPPS1 mice that underline the importance of the nature of the donor from which microbiota is harvested for the promotion of AD. Our results indicate a microbial involvement in the development of Alzheimer's disease pathology, and suggest that microbiota may contribute to the development of neurodegenerative diseases. Most notably, following a single intravenous hMSC delivery, the gastro-intestinal microbiota composition of the APPPS1 mice was restored towards the level of that in healthy WT mice. *Conclusion:* Our pre-clinical results using an axenic mouse model of AD demonstrate that the absence of microbiota retards substantially the progression of AD-like pathology. The association of bacterial taxa with cerebral Aβ pathology observed in conventionally raised APPPS1 mice indicates that specific microbes may be involved in progression of AD pathology. The gut colonization studies underline the important role of microbiota harvested from a diseased versus healthy model for the promotion of AD. Thus, our study strongly argues for a role of gastro-intestinal microbes in the development of cerebral Aβ amyloidosis. Importantly, the composition of gastro-intestinal microbiota was ameliorated following a single intravenous injection of human adult mesenchymal stem cells, strongly suggesting that the development of cerebral Aβ amyloidosis which is amenable to stem cell therapeutic intervention. Obviously, the clinical translation of these preclinical results bears the potential for opening a new area for the treatment and prevention of AD pathology.

P3-16 BI 425809, A NOVEL GLYT1 INHIBITOR, INCREASES GLYCINE LEVELS IN CEREBROSPINAL FLUID (CSF): RESULTS FROM PRECLINICAL AND CLINICAL TRANSLATIONAL PROOF-OF-MECHANISM STUDIES.

Holger Rosenbrock[1], Viktoria Moschetti[2], Oliver Kleiner[1], Michael Desch[1], Christina Schlecker[2], Sophia Goetz[1], Karl-Heinz Liesenfeld[1], Sun-Young A. Yum[3], Gwenaelle Fillon[1], Glen Wunderlich[4], Sven Wind[1] *((1) Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany; (2) Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany; (3) Boehringer Ingelheim Corporation Ltd, Seoul, South Korea; (4) Boehringer Ingelheim (Canada) Ltd, Burlington, ON, Canada)*

Background: N-methyl-D-aspartate (NMDA) receptor hypofunction is associated with cognitive impairment in Alzheimer's disease (AD) and schizophrenia. Cognitive function therefore may be improved by enhancing glutamatergic neurotransmission in patients. This may be achieved by increasing the synaptic cleft levels of glycine, a co-agonist of the NMDA receptor. Inhibition of the glycine transporter 1 (GlyT1) is hypothesized to increase glycine levels within the synaptic cleft. BI 425809 is a potent and selective GlyT1 inhibitor being developed for the treatment of cognitive impairment in AD and schizophrenia. The preclinical study described here characterized the effects of BI 425809 on glycine levels in rat cerebrospinal fluid (CSF) in order to demonstrate central target engagement, ie, GlyT1 inhibition in the brain. To translate this preclinical proof-of-mechanism study into humans, BI 425809 was further evaluated in healthy volunteers and the glycine levels in CSF were measured after oral administration of single and multiple doses. *Methods:* Preclinical: In rats, glycine levels in the CSF were determined from samples collected through the cisterna magna under anesthesia at the time of maximum concentration since dosing (tmax, 90 minutes), after single, oral administration of BI 425809 0.2, 0.6, and 2 mg/kg. Clinical: A single-center, non-randomized, open-label trial assessed multiple doses of BI 425809 in sequential groups. Healthy male volunteers, 18–55 years old, received oral doses of BI 425809 (5, 10, 25, or 50 mg) once daily for 14 days. CSF was serially collected through a lumbar catheter for 14 hours after the first dose and through single lumbar puncture before the last dose on day 14. Glycine levels as a curve over the time interval of 0–14 hours were expressed as percent change from baseline. Plasma and CSF BI 425809 exposures, including area under the concentration-time curve over the time interval of 0–14 hours (AUC0-14), and maximum concentration (Cmax) after first dose and steady state concentration (312 hours before the last dose of BI 425809, Cpre,ss), were measured (primary endpoints). Safety and tolerability were assessed throughout the study by adverse event (AE) reporting, clinical laboratory assessments, vital signs, 12-lead electrocardiogram (ECG), physical examinations, ophthalmologic tests, and suicidality assessments. The secondary endpoint was the number (%) of subjects with drug-related AEs. CSF glycine levels from preclinical and clinical samples were determined by high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). *Results:* Preclinical: Oral administration of BI 425809 dose-dependently increased glycine levels in the CSF of rats. BI 425809 0.2, 0.6, and 2 mg/kg increased CSF glycine concentrations by 30%, 61% ($p<0.05$), and 78% ($p<0.01$), respectively, relative to vehicle. Clinical: Consistent with preclinical data, oral administration of BI 425809 in 25 healthy volunteers (22 completers) resulted in an overall dose-dependent increase from baseline in CSF glycine levels at steady state, with a mean 50%

increase at doses as low as 10 mg. BI 425809 (5, 10, 25, and 50 mg) caused a dose-dependent increase in BI 425809 exposure in plasma and CSF, though concentrations were generally lower in CSF. The Cmax of BI 425809 was achieved earlier in plasma than in CSF (tmax 3.0–5.0 vs 5.5–8.1 hours, respectively) and steady state was reached in plasma after 6 days. At steady state, there was a moderate correlation between the CSF glycine percentage change from baseline and CSF BI 425809 concentration (Spearman's correlation coefficient of 0.66). In general, BI 425809 was safe and well tolerated at all doses tested with only one subject (4.0%) reporting a drug-related AE in the BI 425809 25-mg group. Overall, 22 out of 25 subjects (88.0%) reported at least one AE, which were mostly related to the lumbar puncture. Two subjects (8.0%) discontinued due to non-drug-related AEs (moderate procedural headache and moderate headache, nausea, and vomiting), and one subject (4.0%) reported a severe AE (neck pain) in the 10-mg group. There were no AEs of special interest, deaths, or other serious AEs. *Conclusions:* In rats, systemic administration of BI 425809 led to a dose-dependent increase in glycine levels in the CSF, indirectly demonstrating functional engagement of the target (ie, GlyT1 inhibition in the brain). This outcome was further explored in a translational clinical study aiming to demonstrate functional target engagement in the human brain. The clinical study was conducted in healthy volunteers; oral administration of BI 425809 led to a dose-dependent increase in CSF BI 425809 exposure, which was accompanied by an increase in CSF glycine levels. These data provide evidence for GlyT1 inhibition by BI 425809 in the human brain and therefore a potential therapeutic mechanism for cognitive improvement in AD and schizophrenia. Funding: Boehringer Ingelheim (Study 1346.3; NCT02362516).

P3-17 REVERSIBLE AND SPECIES-SPECIFIC DEPIGMENTATION EFFECTS OF AZD3293 ARE RELATED TO BACE2 INHIBITION AND CONFINED TO SKIN AND HAIR. Gvido Cebers[1], Magnus Soderberg[2], Evan W. Ingersoll[1], Robert C. Alexander[1], Samantha Budd Haeberlein[1], Alan R. Kugler[1], Bassem Attalla[3], Thyphaine Lejeune[3], Stefan Platz[2], Clay W. Scott[4] *((1) Neuroscience iMed, AstraZeneca, Cambridge, MA, USA; (2) Drug Safety and Metabolism, AstraZeneca, Cambridge, UK; (3) Charles River Laboratories, Montreal ULC, Sonneville site, Canada; (4) Drug Safety and Metabolism, AstraZeneca, Waltham, USA)*

Background: AZD3293 is a brain-permeable inhibitor of human beta-site amyloid precursor protein-cleaving enzyme1 (BACE1) in Phase 3 clinical development for Alzheimer's disease. AZD3293 inhibits both BACE1 and BACE2 with nearly equal potency. BACE2-dependent premelanosome protein (PMEL) processing is necessary for correct eumelanin synthesis and packaging and BACE2 knockout mice have less pigmented fur than wild-type mice. Non-selective pharmacological inhibition of BACE enzymes has also been shown to induce seemingly irreversible depigmentation in mice (Shimshek et al., 2016). Here we report depigmentation-related data of AZD3293 effects in laboratory animals, in vitro systems, and a clinical study (using human skin biopsy samples). *Methods:* Observations of animal skin and fur color changes were made in chronic non-clinical safety studies of AZD3293 in pigmented Long-Evans rats and beagle dogs treated with AZD3293 or AZD3839 (a BACE-1-specific inhibitor; only used in dogs). Further, skin samples from these studies were also analyzed using immunohistochemistry (to visualize melanocytes), and/or with electron microscopy. Further, human skin biopsies collected before and after 13 days of dosing up to supratherapeutic doses in a Phase 1 study (NCT01795339) were analyzed histopathologically, including special staining to determine melanin distribution. In addition, a series of in vitro studies were carried out to determine AZD3293 effects in human melanocytes and reconstituted human skin and compare them with effects of AZD3839. *Results:* AZD3293-induced depigmentation was animal age- and dose-dependent occurring after 6 weeks, and readily reversible following 4- or 13-week treatment-free (recovery) periods. The reversibility of these findings differs from previously reported in vivo depigmentation effects of BACE inhibition in mice (Shimshek et al, 2016) where no reversibility was seen. Depigmentation did not affect pigmented tissues other than hair-less skin, hair, and oral mucosa (in the dog) and was not accompanied by any degenerative or inflammatory changes in these tissues in either species. The appearance of the animals correlated with marked decrease of melanin in the epidermal and hair follicle keratinocytes and changes in the morphological appearance of melanocytes. Importantly, only eumelanin was affected while production of pheomelanin (the red-brown pigment) was unchanged, as evidenced by the lack of depigmentation of the tan-colored fur in beagle dogs. Dogs were more sensitive to the depigmentation effects than rats as effects in dogs occurred at about 5-fold lower plasma AZD3293 exposures compared to rats. Depigmentation clearly depended on BACE2 inhibition, as BACE1 inhibition alone was insufficient to produce depigmentation either in vitro or in vivo. AZD3293 did not cause any effects in human primary melanocytes and reconstituted human epidermis. Furthermore, AZD3293 did not cause any significant changes in melanisation or the appearance of melanocytes in skin biopsies taken from human subjects treated daily with supra-therapeutic doses of AZD3293 for 13 days. Plasma AZD3293 exposures in human subjects were similar to the exposures in the animal studies at which depigmentation at the cellular level was clearly present after just one week of treatment (and some of the hair pigmentation changes in dog were observed even after a single dose). *Conclusions:* Our data show that BACE2 inhibition is sufficient to cause clearly reversible depigmentation (in contrast to data reported by Shimshek et al (2016)) in laboratory animals by interfering with the processing of PMEL, a primary component of protein scaffolding necessary for correct packaging of newly synthesized eumelanin in melanosomes. As a result, the melanosomes cannot mature normally thus precluding their transfer from melanocytes to keratinocytes in the epidermis or the hair shaft in the hair follicle, which produces gradual depletion of eumelanin levels in these structures. No depigmentation effects were noted in skin biopsy material from a Phase 1 clinical study following daily AZD3293 administration for up to 13 days. These data suggest poor human translatability of depigmentation findings observed in animals. Various animal species and humans are not equally sensitive to BACE2 inhibition with respect to eumelanin production, with dogs being the most sensitive and humans the least sensitive species. Reasons for this apparent species-specific sensitivity are not clear but could be related to subject age and species differences in hair cycles, hair follicle morphology, and melanocyte function.

P3-18 APP GENE DOSE MEDIATED NEURODEGENERATION IN MOUSE MODELS OF DOWN SYNDROME. Mariko Sawa, Cassia Overk, Eliezer Masliah, Ann Becker, Xu Chen, Chengbiao, Wu, William Mobley *(Department of Neurosciences, University of California San Diego, San Diego, CA, USA)*

Backgrounds: DS (trisomy 21) impacts cognition throughout the lifespan. We address the age-related emergence of the neuropathological hallmarks of Alzheimer disease (AD) and dementia in the vast majority of adults with DS. Recently reviewed1, 2 evidence supports the designation of AD in DS (AD-DS). Our goal is to discover a treatment(s) that prevents and/or reverses AD-DS. This effort is informed by evidence that increased dose for

the amyloid precursor protein (APP) gene on human chromosome (HSA21) is necessary for AD-DS1-4. To confirm APP dose effects on neurodegeneration and explore the underlying mechanism(s), we examined DS models in vitro and in vivo, focusing on early endosomes, whose structure is disrupted very early in AD-DS and AD5, phosphorylation of Tau, and neuronal atrophy and loss. *Methods:* In vivo studies employed immunohistochemistry to examine endosome structure, p-Tau and neurodegeneration in various brain regions of a DS mouse model; we selectively reduced APP dose to determine what role was played. To deduce which APP products were responsible for these phenotypes, we carried out in vitro studies in which APP products were overexpressed. In addition, we examined the activity of Aβ species present in the conditioned medium of cells expressing human APP V717F. *Results:* The Dp16 mouse model of DS showed enlarged endosomes, increased p-Tau and degeneration of neurons of the superficial entorhinal cortex, locus coeruleus and medial septal cholinergic complex. Normalization of APP dose eliminated each of these phenotypes. In vitro, C99 and Aβ42 induced hyperactivation of Rab5, endosomal enlargement, increased p-Tau and impaired axonal trafficking and neurotrophin-mediated signal transduction with atrophy of basal forebrain cholinergic neurons. *Conclusion:* Drawing an important parallel with AD-DS, cellular and mouse models of DS show that increased APP dose is necessary for degenerative phenotypes. Increased APP dose acts via increased levels of C99 and Aβ42. Therapeutically targeting increased APP dose offers a rational approach to treat AD-DS. Targeting Aβ by vaccination, reducing Aβ42 and C99 via modulation of γ-secretase, and use of antisense oligonucleotides to suppress APP expression are suggested. 1. Wiseman, F.K. et al. A genetic cause of Alzheimer disease: mechanistic insights from Down syndrome. Nat Rev Neurosci 16, 564-574 (2015). 2. Ballard, C. et al. Impact of Antipsychotic Review and Nonpharmacological Intervention on Antipsychotic Use, Neuropsychiatric Symptoms, and Mortality in People With Dementia Living in Nursing Homes: A Factorial Cluster-Randomized Controlled Trial by the Well-Being and Health for People With Dementia (WHELD) Program. Am J Psychiatry 173, 252-262 (2016). 3. Korbel, J.O. et al. The genetic architecture of Down syndrome phenotypes revealed by high-resolution analysis of human segmental trisomies. Proc Natl Acad Sci U S A 106, 12031-12036 (2009). 4. Prasher, V.P. et al. Molecular mapping of Alzheimer-type dementia in Down's syndrome. Ann Neurol 43, 380-383 (1998). 5. Cataldo, A.M. et al. Endocytic pathway abnormalities precede amyloid beta deposition in sporadic Alzheimer's disease and Down syndrome: differential effects of APOE genotype and presenilin mutations. Am J Pathol 157, 277-286 (2000).

P3-19 TRANSLATIONAL APPROACH TO NEURODEGENERATIVE DISEASES: A SMALL PEPTIDE DERIVED FROM NEURONAL CELL CYCLE KINASE (CDK5) PREVENTS NEURODEGENERATION. Harish C. Pant, *(Chief, Cytoskeletal Protein Regulation Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA)*

During our studies on the compartment specific phosphorylation of cytoskeletal proteins in the neurons, we discovered a novel kinase, Cdk5, a Cell Cycle dependent like kinase in the brain. Though it binds with cyclins, however, its activity is primarily restricted to neurons due to its binding and regulation by neuron specific molecules p35 and p39 (35 KDa and 39 KDa molecular weight respectively). Cdk5, by virtue of its tightly regulated, multifunctional role in neuronal development, migration, synaptogenesis, synaptic activity, memory / learning and survival. It targets a large number of different types of neuronal proteins and has emerged as a major player in nervous system function in health and disease. However, due to neuronal insults and stress (e.g., A-beta, glutamate, oxidative, mutational, neuroinflammation and intra / extra cellular stresses, Cdk5 is hyperactivated and deregulated induces a number of neurodegenerative disorders. Although our studies continue to unravel the role of Cdk5 in neurogenesis and synaptic function but our most exciting recent results have been related to its role in neurodegeneration and our success in developing compounds that protect neurons from deregulated Cdk5 pathology, neuro-inflammation, and apoptosis in vitro and in AD and other neurodegenerative disease (ALS, PD) model mice. Hence, our current and future work include a major emphasis on the efficacy of our newly modified peptide TFP5 (carrying a fluorescent marker at the N-terminal end and a TAT PTD sequence at the C-terminal (to facilitate penetration into tissues) and pass blood brain barrier, as a therapeutic candidate for AD, ALS and PD using model mice. Currently, most therapeutic approaches targeting the deregulated Cdk5/p25 complex and other kinases in neurodegenerative disorders have focused primarily on drugs like roscovitine that inhibit kinase activity by interfering with the ATP binding domain of the kinase. Most of these drugs, however, lack sufficient specificity, since all kinases including cell cycle Cdks, are vulnerable at the ATP binding site targeted by roscovitine. We identified a 24 residue truncated modified peptide (TFP5), derived from the p35 activator, that specifically inhibited hyperactive Cdk5/p25 and rescued cortical cells in vitro from abnormal AD-like phenotypes. It did this without affecting the function of the normal Cdk5/p35 and toxicity. In addition, the Intraperitoneal injection (IP) of TFP5 ameliorated ALS and PD phenotypes in model mice. This talk will focus on the role of TFP5 peptide as a therapeutic reagent to prevent AD, ALS and PD phenotypes in model mice.

P3-20 PRECLINICAL STUDIES OF SAK3, A T-TYPE CALCIUM CHANNEL STIMULATOR IN APP23 MICE AND RATS. Kohji Fukunaga, Hisanao Izumi, Yasuharu Shinoda, Yasushi Yabuki *(Department of Pharmacology, Graduate School of Pharmaceutical Sciences, Tohoku University, Sendai, Japan)*

Backgrounds: As Alzheimer disease therapeutics candidate, we have developed SAK3 (PCT/JP2013/051388). SAK3 stimulates T-type voltage-gated (T-type) calcium channels in Cav3.1 and Cav3.3 transfected neuronal cells. The single administration of ST101, a prototype T-type calcium channel stimulator (J Neurochem 2012;121:44-53) is relatively low efficacy in human clinical study (J Alzheimers Dis 2015;48:473-481). Therefore, we decided to develop SAK3 as more effective derivatives of ST101 and conducted preclinical studies. SAK3 markedly stimulates acetylcholine release and promotes long-term potentiation in mouse hippocampus (Neuroscience 2014 abstract 265.21). We here tested whether SAK3 reduced amyliod beta (1-42) accumulation in Alzheimer model (APP23) mice and confirmed reasonable pharmacokinetics in rat serum after administration with its therapeutic doses. *Methods:* APP23 mice aged 6 and 9 months were treated for two or three months with SAK3 (0.5mg/kg, p.o.) and measured amyliod beta (1-42) levels in both soluble and insoluble fractions from APP23 mouse cortex. The amyloid plaques were also assessed by thioflavin staining. Pharmacokinetics was analyzed in rat after oral and intravenous injection of SAK3. *Results:* Chronic administration significantly reduced amyliod beta (1-42) levels in APP23 cortex. Consistent with the reduced amyliod beta (1-42) levels, the numbers of amyloid plaques assessed by thioflavin staining were significantly reduced by chronic SAK3 treatment. Furthermore, the cognition assessed by novel object recognition task was improved by the chronic administration.

Using LC/MS/MS system, we established high sensitivity quantification system for SAK3 in rat serum to obtain its proof-of-concept of safety. *Conclusion:* The novel T-type calcium channel stimulator SAK3 restored cognitive ability in APP23 mice and reduced amyliod beta (1-42) accumulation/aggregation in the cortex. SAK3 transiently stimulated hippocampal ACh release peaked at 20 min. Likewise, pharmacokinetic analyses revealed transient elevation of SAK3 concentration within 30 min and rapid clearance within 8 hours in rat serum levels. Taken together, AD therapeutic candidate SAK3 has attractive potentials to reduce amyliod beta accumulation and to improve cognition in AD model mice. We will finish all preclinical studies by 2016. This work is supported by Project of Translational and Clinical Research Core Centers from AMED, Japan. The authors declare no conflict of interests.

Theme : New Therapies and clinical Trials

P3-21 SUVN-502: A PURE 5-HT6 ANTAGONIST FIRST-IN-CLASS TRIPLE COMBINATION PHASE-2 POC STUDY. A PROMISING THERAPEUTIC STRATEGY FOR SYMPTOMATIC TREATMENT OF AD. Ramakrishna Nirogi, Koteshwara Mudigonda, Devender Reddy Ajjala, Vijay Benade, Renny Abraham, Ramasastry Kambhampati, Anil Shinde, Venkat Jasti *(Discovery Research, Suven Life Sciences Ltd, Hyderabad, India)*

Background: SUVN-502 is a pure 5-HT6 antagonist with more than 1200 fold selectivity over 5-HT2A receptor. It has shown robust efficacy in various animal models of cognition and produced significant increase in hippocampal acetylcholine levels. SUVN-502 demonstrated excellent margin of safety in all long term non-clinical safety studies. In the clinical studies, SUVN-502 was well tolerated after single or repeated administration. No gastro-intestinal side effect or liver toxicity was seen in healthy elderly subjects. Food, gender and age had no effect on the pharmacokinetics of SUVN-502. SUVN-502 has excellent pharmacokinetic profile suitable for once a day treatment. Current medications used for the symptomatic treatment of AD are marred with poor efficacy and have swathe of cholinergic side effects (dose limiting central and peripheral side effects). One way of addressing these limitations is to combine the existing treatment options with new drugs acting through different mechanisms. *Methods:* Preclinical efficacy of "triple combination" viz. "SUVN-502, donepezil and memantine" were evaluated in the object recognition task, brain microdialysis and electroencephalography. The exposures required for SUVN-502 to potentiate the procognitive effects of donepezil and memantine in AD patients was projected based on the concentrations of SUVN-502 in animal models. *Results:* Co-treatment of SUVN-502 with memantine and donepezil significantly potentiated the procognitive effects of memantine and donepezil. These effects were also seen after repeated treatments for 14 days indicating lack of tachyphylaxis. Triple combination of SUVN-502, donepezil and memantine significantly enhanced the effects on hippocampal acetylcholine levels and brain neuronal activity. No significant difference was observed in the exposures of SUVN-502, donepezil or memantine in triple combination treatment. Exposures of SUVN-502 projected to potentiate the procognitive effects of donepezil and memantine were achieved in elderly healthy subjects. *Conclusions:* The enhanced procognitive effects seen in the group co-treated with SUVN-502, memantine and donepezil can be attributed to the augmentation of the cholinergic neurotransmission in the brain. Thus, combination of SUVN-502 with memantine and donepezil may offer a promising new therapeutic strategy for the symptomatic treatment of Alzheimer's disease. SUVN-502 is being evaluated in moderate AD patients currently treated with donepezil and memantine. A total of 537 subjects aged between 50 to 85 years are being enrolled for phase-2 study in USA.

P3-22 SUVN-G3031: A POTENT AND SELECTIVE H3 RECEPTOR INVERSE AGONIST - SAFETY, TOLERABILITY AND PHARMACOKINETICS IN HEALTHY ADULT MEN. Ramakrishna Nirogi, Koteshwara Mudigonda, Nageswararao Muddana, Rajesh Kumar Boggavarapu, Ranjith Kumar Ponnamaneni, Pradeep Jayarajan, Anil Shinde, Venkat Jasti *(Discovery Research, Suven Life Sciences Ltd, Hyderabad, India)*

Background: Histamine 3 receptors (H3R) play a critical role as neuromodulators through their widespread distribution in the central nervous system. Blockade of this receptor augments the pre-synaptic release of histamine and other neurotransmitters including acetylcholine from cholinergic neurons, which plays an important role in learning and memory. SUVN-G3031, a potent H3R inverse agonist, is being developed for the treatment of cognitive deficits associated with Alzheimer's disease (AD). SUVN-G3031 demonstrated cognitive enhancement and relevant neurochemical changes without affecting sleep signature in rodent models. *Methods:* SUVN-G3031 was studied in a single-center phase-1 clinical trial (US IND) to evaluate its safety, tolerability, and pharmacokinetics after single and multiple ascending doses in healthy adult male subjects. SUVN-G3031 was quantified in plasma and urine using a validated LC-MS/MS method. Safety was evaluated based on assessments of adverse events, physical examinations, laboratory tests, vital signs, 12-lead ECGs, continuous telemetry, and C-SSRS. *Results:* SUVN-G3031 was well tolerated up to the highest tested single dose of 20 mg and multiple doses of 6 mg in healthy adult subjects. There were no clinically relevant or serious adverse events observed at any of the doses tested. SUVN-G3031 has shown excellent pharmacokinetic profile with no sleep disturbances even at doses several folds higher than the projected therapeutic exposure. SUVN-G3031 achieved the projected efficacy concentrations and attained steady state on day 7 in the tested population. *Conclusions:* SUVN-G3031 has excellent safety and pharmacokinetic profile after single and multiple dose oral administrations for 14 days in healthy adult subjects. Following single or multiple oral administrations, SUVN-G3031 exposures were dose proportional across the tested doses. SUVN-G3031 is well tolerated in humans with adequate plasma exposure for efficacy and excellent pharmacokinetics suitable for once a day oral administration. Effects of food, age and gender on pharmacokinetics of SUVN-G3031 are currently being evaluated in healthy human volunteers. Phase-2 enabling long term safety studies for is currently ongoing. The Phase-2 proof-of-concept study is being planned in 2017.

P3-23 SUVN-D4010: A POTENT AND SELECTIVE 5-HT4 RECEPTOR PARTIAL AGONIST - SAFETY, TOLERABILITY AND PHARMACOKINETICS IN HEALTHY ADULT MEN. Ramakrishna Nirogi, Koteshwara Mudigonda, Gopinadh Bhyrapuneni, Veera Raghava Chowdary Palacharla, Rajesh Kumar Boggavarapu, Devender Reddy Ajjala, Abdul Rasheed Mohammed, Venkat Jasti *(Discovery Research, Suven Life Sciences Ltd, Hyderabad, India)*

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder and AD patients have impaired cognitive skills. Abundance of 5-HT4 receptors (5HT4R) both in hippocampus and frontal cortex suggests the role of this receptor in memory and cognition. 5-HT4R ligands have the ability to induce neurogenesis in various brain regions such as hippocampus which eventually replace the degenerated neurons. 5-HT4R partial agonists offer both symptomatic and disease-modifying effects, hence may be beneficial

for treatment of AD. SUVN-D4010 is a potent, selective and orally bioavailable 5-HT4R partial agonist. Efficacy of SUVN-D4010 has been proved in various preclinical models of cognition where it improved all the three facets of memory (episodic, working and emotional). SUVN-D4010 increased cortical acetylcholine and sAPPα levels and simultaneously decreased the amyloid-β protein levels in the rat brain. SUVN-D4010 is being developed for the treatment of cognitive deficits associated with AD. *Methods:* Safety, tolerability and pharmacokinetics of SUVN-D4010 were assessed in a single-center phase-1 clinical trial (US IND) following single and multiple ascending doses in healthy adult male subjects. In single dose evaluation, subjects were dosed orally with 5, 15, 30 and 45 mg of SUVN-D4010. For multiple ascending dose evaluation, SUVN-D4010 (10, 25 and 40 mg) was administered orally once a day for 14 days. SUVN-D4010 was quantified in plasma and urine using a validated LC-MS/MS method. Safety was evaluated based on assessments of adverse events, physical examinations, laboratory tests, vital signs, 12-lead ECGs, continuous telemetry and C-SSRS. *Results:* SUVN-D4010 was well tolerated in healthy male subjects up to the highest tested dose (single or multiple) and there were no clinically relevant or serious adverse events reported. Absorption of SUVN-D4010 is rapid and exposures (Cmax and AUC) were dose proportional at the tested doses. SUVN-D4010 has an excellent pharmacokinetic profile. SUVN-D4010 achieved the projected efficacy concentrations and attained steady state on day 3 in the tested population. *Conclusions:* SUVN-D4010 has excellent safety and pharmacokinetic profile following single and multiple administration in healthy male subjects. SUVN-D4010 exposures were dose proportional following single or multiple oral administrations. SUVN-D4010 is well tolerated with adequate plasma exposures for efficacy and excellent pharmacokinetics for once a day oral administration. Long term non-clinical safety studies are in progress. Effects of food, age and gender on pharmacokinetics of SUVN-D4010 are currently being evaluated in healthy human volunteers. Phase-2 proof-of-concept study will be initiated in 2017.

P3-24 A RANDOMIZED DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO TEST THE EFFICACY AND SAFETY OF S 47445 IN PATIENTS SUFFERING FROM ALZHEIMER'S DISEASE AT MILD TO MODERATE STAGE WITH DEPRESSIVE SYMPTOMS. Pueyo Maria, Bernard Katy, Bretin Sylvie, Gouttefangeas Sylvie, Picarel-Blanchot Françoise *(Pôle Innovation Thérapeutique Neuropsychiatrie, Institut de Recherches Internationales Servier, Suresnes, France)*

Background: Alzheimer's disease (AD) is the most common type of dementia with an incidence increasing with age. There were 44 million of people with dementia worldwide in 2013 and the prevalence augments due to population aging and a better diagnosis. By 2030, the number of people living with dementia is estimated to reach 75 million. Patients with Alzheimer's disease present with memory impairment and other cognitive disorders leading to an alteration of functionality and dependence. These patients also present neuropsychiatric symptoms, which have a negative impact on cognition, functionality, quality of life and caregiver burden. There is a strong medical need of new treatments in AD since efficacy of treatments on the market is moderate and systematically questioned. Specific treatments for patients with neuropsychiatric symptoms (i.e.: depressive symptoms) are also needed. S 47445 is a potentiator of AMPA receptors that demonstrated both procognitive and antidepressant-like properties in various animal models. Further, S 47445 modulates synaptic plasticity by enhancing Long Term Potentiation and by increasing neurotrophic factors expression as BDNF. Based on these observations, S 47445 has emerged as a favourable candidate for the treatment of memory deficits, depressive symptoms and synaptic dysfunction associated with Alzheimer's disease. Eleven phase I studies have been conducted in healthy volunteers showing a good safety and suitable PK of the drug. Pharmacodynamic effects have also been observed in healthy elderly volunteers. In particular,S 47445 increases plasma BDNF and enhances functional connectivity between brain networks and augments glutamate concentration in posterior cingulate cortex (Ciuciu et al, CTAD 2016). *Study design and main criteria:* The current study, is a 24-week international, multi-centre, randomized, double-blind, placebo-controlled phase II, 4-arm study in monotherapy followed by an optional 28-week extension period in co-administration with donepezil. Five hundred patients are planned to be included in 80 centers across 12 countries and will be randomized (1:1:1:1) to S 47445 (5, 15 or 50 mg/day) or placebo. The primary objective of this trial is to demonstrate the superiority of at least one dose of S 47445 versus placebo after 24 weeks of treatment on the 11-item ADAS-Cog total score (cognition). The key secondary objective of this trial is to demonstrate the superiority of at least one dose of S 47445 versus placebo after 24 weeks of treatment on the DAD total score (functionality). Other secondary endpoints includes efficacy on cognition, depressive symptoms, neuropsychiatric symptoms, global clinical impression of change and gait velocity as well as safety criteria. Patients entering in the study must fulfill the following main selection criteria: - Male of female out-patients aged between 55 and 85 years old with a school education level of at least 4 years, able to perform neuropsychological tests. - DSM-IV-TR criteria for Dementia of the Alzheimer's Type. - Mini-Mental State Examination (MMSE) total score between 15 and 24, both inclusive. - National Institute of Mental Health (NIMH) provisional criteria for depression in AD (NIMH-dAD). - Cornell Scale for Depression in Dementia total score ≥ 8. - Patients who have never been treated with AD treatments (acetylcholine esterase inhibitor and memantine) or patients who have stopped AD treatment whatever the reason (Wash-out period: 8-week before inclusion). - Patients either not currently treated with an antidepressant or patients being treated with an antidepressant at the recommended dose for at least 8 weeks without clinical efficacy, who can stop this treatment according to the investigator's opinion. *Results:* To date 463 patients have already been included and the study is progressing well. *Conclusion:* This study will provide information on the efficacy and the safety of the S 47445, a new potentiator of AMPA receptors, in patients with Alzheimer's disease and depressive symptoms. It will also allow to better understand the characteristics of this population and to assess the tools to evaluate these patients. The study population characteristics will be presented in 2017 and the study results are expected by the end of 2017.

P3-25 THROMBIN: A VASCULAR-DERIVED NEUROTOXIN AND NOVEL TARGET FOR AD THERAPY. Paula Grammas, *(George and Anne Ryan Institute for Neuroscience, University of Rhode Island, Kingston, RI, USA)*

Background: The global societal burden of Alzheimer's disease (AD), a neurodegenerative dementing disorder, is staggering. Current estimates suggest that 5.4 million Americans and 36 million people world-wide have AD. Identification of new therapeutic targets is a critical barrier to progress in the AD field. Pathologic processes in the cerebrovasculature are likely important targets for AD therapeutics, as supported by observations that vascular perturbations in AD are widespread and occur early in the disease process. Brain microvessels derived from AD patients have been shown to release a diverse array of inflammatory proteins. Expression of these diverse mediators is

consistent with the process of vascular activation and reflects the transition of brain endothelial cells from a quiescent to a highly synthetic phenotype. We propose vascular activation as a heretofore unexplored target for AD therapeutics. Vascular activation in the AD brain likely has deleterious consequences for neuronal health as many of these vascular-derived factors are neurotoxic and therefore important to disease pathogenesis. The idea that vascular activation contributes to pathogenic events in the AD brain is strongly supported by our recent study showing that treatment of AD mice with a vascular activation inhibitor not only reduced endothelial activation and expression of inflammatory/neurotoxic proteins but also improved cognitive performance. Identifying the stimuli triggering vascular activation as well as the key mediators of this pathologic process could lead to novel therapeutic approaches. We consider thrombin (an inflammatory protein upregulated in AD) and hypoxia to be two critically important and interrelated mediators of vascular activation. Thrombin expression is increased in the cerebral vasculature and plaques in AD, is known to have potent pro-inflammatory effects on endothelial cells and other cell types and is inherently neurotoxic. In addition, a recent community-based study found that use of the thrombin inhibitor dabigatran was associated with a lower risk of new-onset dementia. Hypoxia is likely an important factor in vascular activation as inflammation and hypoxia are mechanistically linked and hypoxia has been implicated in the pathogenesis of dementia. The objective of this study is to investigate the role of thrombin as a mediator of cerebrovascular inflammation and oxidative stress in AD transgenic mice and in hypoxia induced proinflammatory changes (i.e. vascular activation) of brain endothelial cells in vitro. *Methods:* Endothelial cell cultures were obtained from rat brain microvessels and cell survival assessed by MTT assay. Hypoxia was induced by exposure to 1% O2 conditions for 6 h. Reactive oxygen species (ROS) in endothelial cell cultures were assessed using dihydroethidium (DHE) and inflammatory protein expression in culture measured by RT-PCR. Adult wild-type 3xTgAD—LaFerla (control) and 3xTgAD—LaFerla mice were treated daily with the direct thrombin inhibitor dabigatran etexylate (Pradaxa®, Boehringer Ingelheim, Germany) (100 mg/kg) beginning at 18 weeks of age and continuing for 34 weeks. Mice were euthanized and brain tissue fixed. Oxidative stress was determined by DHE staining and inflammatory protein expression was assessed by immunofluorescence. *Results:* Immunofluorescent analysis of the cerebrovasculature in AD mice demonstrates significant ($p < 0.01–0.001$) increases in thrombin, hypoxia inducible factor-1α (HIF-1α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), matrix metalloproteinases (MMPs), and ROS compared to controls. Administration of the thrombin inhibitor dabigatran (100 mg/kg) to AD mice for 34 weeks significantly decreases expression of inflammatory proteins and ROS. Exposure of cultured brain endothelial cells to hypoxia for 6 h causes an upregulation of thrombin, HIF-1α, MCP-1, IL-6, and MMP2 and ROS. Treatment of endothelial cells with the dabigatran (1 nM) reduces ROS generation and inflammatory protein expression ($p < 0.01–0.001$). The data demonstrate that inhibition of thrombin in culture blocks the increase in inflammatory protein expression and ROS generation evoked by hypoxia. Also, administration of dabigatran to transgenic AD mice diminishes ROS levels in brain and reduces cerebrovascular expression of inflammatory proteins. Taken together, these results suggest that inhibiting thrombin generation could have therapeutic value in AD and other disorders where hypoxia, inflammation, and oxidative stress are involved. *Conclusion*: Thrombin inhibitors block the effects of hypoxia on brain endothelial cells and reduce vascular activation in transgenic AD mice. Based on evidence that reducing vascular activation in AD mice is associated with improved cognition, we propose thrombin inhibitors could prove useful for improving cognition in AD patients. Next generation AD therapeutics should not focus on single target drugs but rather employ a multi-component cocktail approach. We propose thrombin inhibitors be considered as potential contributors to the dementia therapy pharmacopeia. The urgent need for disease-modifying drugs in AD demands new thinking about disease pathogenesis and exploration of novel drug targets.

P3-26 MULTIPLE ASCENDING DOSE STUDY WITH A PRODRUG OF GALANTAMINE: EVIDENCE OF DIMINISHED SIDE EFFECTS. D.G. Kay[1], E t'Hart[2], C. Bakker, J. van der Aart, G.J. Groeneveld[2], A. Maelicke[1,3] *((1) Neurodyn Cognition Inc., Charlottetown, PE, Canada; (2) Centre for Human Drug Research (CHDR), Leiden, the Netherlands); (3) Galantos Pharma, Nieder-Olm, Germany)*

Background: Cholinesterase inhibitors (ChEIs) have been shown to enhance cognitive functioning in patients with Alzheimer's disease (AD). The use of ChEIs and their maximum dose is limited by side effects, largely gastrointestinal, such as nausea, vomiting and diarrhoea. These side effects are known to be caused by stimulation of peripheral acetylcholine receptors. Memogain® is a pharmacologically inactive prodrug of galantamine, a ChEI and allosteric potentiating ligand (APL) of nicotinic acetylcholine receptors (nAChR). Due to the much enhanced lipophilicity of Memogain, as compared to galantamine, it has one order of magnitude higher bioavailability in the brain than oral galantamine . Administration of Memogain is by way of an intranasal spray. After entering the brain, Memogain is enzymatically cleaved to active galantamine, accordingly enhancing the bioavailability of the active drug in the target organ brain. Evidence from an extensive pre-clinical development program and a single ascending dose (SAD) human clinical trial [Baakman et al. (2016) Alzheimer's & Dementia: Translational Research & Clinical Interventions 2 13-22] has demonstrated Memogain to have reduced peripheral side effects and a higher safety margin than galantamine, with evidence of improved cognitive enhancement. Additionally, in pre-clinical animal models of AD, Memogain has been demonstrated to both, diminish plaque burden (via enhanced microglial removal of plaques), and to promote increased neurogenesis leading to restored cognitive function. Thus Memogain has the potential of being disease modifying. The aim of this Phase Ib multiple ascending dose (MAD) clinical trial was to assess safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of increasing doses of Memogain repetitively administered over a seven day period, in comparison to oral galantamine. *Methods:* The present study was conducted at Center for Human Drug Research (CHDR), Leiden (The Netherlands) and was a randomized, double blind, placebo controlled, sequential cohort, multiple ascending dose study in 48 healthy elderly subjects (>65 yrs). Each cohort consisted of 12 subjects who were administered two doses of Memogain b.i.d for 7 consecutive days. Thus, cohort 1 received 2 x 5.5 mg [11 mg] of Memogain per day, cohort 2 received 2 x 11 mg [22 mg] of Memogain per day, plus a cross-over administration of a single dose of 16 mg oral galantamine (for CSF PK determination of drug concentrations), and cohort 3 received 2 x 22 mg [44 mg] of Memogain per day. Safety assessments included incidence and severity of adverse events (AEs) and abnormalities or changes in laboratory measurements, vital signs and ECG. Standard PK parameters were derived from non-compartmental analysis. For PD the NeuroCart, a computerized test-battery of CNS tests designed for repeated measurements, was used. CNS domains tested included attention, episodic and working memory, executive functioning as well as pharmaco-EEG, eye movements and visual analogue scales (VAS) for mood and drug effects. *Results:* Administration of

Memogain was well tolerated and safe. All AEs were either mild or moderate, and transient. The most prevalent side effect observed was nausea, however even at the highest dose tested (22 mg b.i.d.), was restricted to the first day of dosing. Hematology, blood chemistry, blood pressure and pulse rate, body temperature, urine analysis, ECG, including QT interval, were all in normal ranges for all doses of Memogain tested. Finally, dose dependent improvements in cognitive performance, e.g. in the adaptive tracking test, the N-back test and the Visual Verbal Learning Test (VVLT) were seen. These results are consistent with the initial PD data obtained in the SAD study. *Conclusion:* Memogain was well tolerated and found to be safe in elderly men and women in the dose range investigated. This drug candidate remained safe, tolerable and clearly advantageous with respect to the classical AE profile observed for galantamine (and other cholinesterase inhibitors).

P3-27 NO DOSE ADJUSTMENT REQUIRED FOR E2609, A NOVEL BACE1 INHIBITOR, FOR JAPANESE SUBJECTS, BASED ON PHARMACODYNAMIC AND PHARMACOKINETIC COMPARISONS WITH WHITE COHORTS. Robert Lai[1], Bruce Albala[2], Peter Boyd[1], June Kaplow[2], Satish Dayal, Min-Kun Chang[2], Nozomi Hayata[3], Kenya Nakai[3], Sanae Yasuda[3], Bhaskar Rege[2] *((1) Eisai Co. Ltd., London, UK; (2) Eisai Inc., Woodcliff Lake, NJ, USA; (3) Eisai Co. Ltd., Japan)*

Background: Alzheimer's disease (AD) affects more than 5 million people in the United States and 4.6 million people in Japan. Beta-amyloid converting enzyme 1 (BACE1) is a key enzyme responsible for production of amyloid β (Aβ) peptides and plaque formation in AD. E2609 is a small molecule BACE1 inhibitor being investigated as a treatment for AD. Previous single ascending dose and multiple ascending dose studies have shown that E2609 doses were well tolerated for single doses up to 800 mg, and multiple daily doses up to 200 mg, which resulted in reductions in plasma Aβ(1-x). Phase 2 studies are currently underway investigating once daily doses ranging from 5 mg to 50 mg for up to 18 months duration. Pharmacokinetic studies have demonstrated that the PK of E2609 is linear in predominantly white study populations. To enable enrollment of Japanese subjects in global clinical studies, it is common practice and a regulatory requirement to carry out bridging studies comparing pharmacokinetics and safety and, in some cases, pharmacodynamics as well between Japanese subjects and other racial groups. Here, we investigated plasma Aβ(1-x) levels in response to E2609 as well as the pharmacokinetics of E2609 and selected metabolites in a Japanese population and compared these with a reference white population. Safety was also assessed and compared. *Methods:* This was a Phase 1, randomized, double-blind, placebo-controlled study investigating the pharmacokinetics and pharmacodynamics of a single oral dose of E2609 in adult Japanese and white males. Healthy Japanese subjects were enrolled in 3 cohorts of 8 subjects each. Six subjects in each cohort received a single, oral doses of E2609 at 5 mg, 50 mg, and 200 mg, respectively, with the remaining 2 subjects in each cohort receiving placebo. Cohort 4 enrolled 8 white subjects who were age and BMI-matched to the Japanese 50 mg cohort (Cohort 2). These subjects were randomized 6:2 to 50 mg E2609 or placebo. Plasma Aβ(1-x) levels were determined from blood samples taken prior to Day 1 dosing at various time points (-24, -22, -20, -18, and -12 hours), predose on Day 1 (0 hours) and post-dose (2.0, 4.0, 6.0, 8.0, 12, 24, 48, 72, 96, 144, and 216 hours). For pharmacokinetic assessments, blood samples were collected at predose and 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12, 24, 48, 72, 96, 144, and 216 hours postdose. Plasma concentrations of E2609 and its metabolites were determined using liquid chromatography with tandem mass spectrometry. Safety assessments included hematology, blood chemistry, and urinalysis, vital signs and adverse events. Race comparisons of pharmacokinetic parameters used an ANOVA model. *Results:* A total of 32 male subjects were enrolled (24 Japanese, 8 white) with a mean age range of 40.0 to 47.5 years. Pharmacodynamic assessments showed that the mean maximum reduction of plasma Aβ(1-x) from baseline after a single oral dose of E2609 occurred between 5 and 12 hours after dosing. Peak response as well as total response increased with increasing dose from 5 to 200 mg in Japanese subjects; the percent reduction from baseline suggested a saturation of response between 50 mg and 200 mg, a finding similar to that previously found in a predominantly white study. Similar reductions in plasma Aβ(1-x) were seen between the Japanese and white 50 mg cohorts. Pharmacokinetic assessments also demonstrated that the Japanese and white cohorts had similar pharmacokinetic profiles. A single dose of E2609 resulted in a tmax at 1.5 h for the 5 and 50 mg dose cohorts, 2.5 h for the 200 mg cohort, and 2.0 h for the 50 mg white cohort. Overall, plasma pharmacokinetic parameters (Cmax and AUCs) of E2609 and its metabolites M1 and M2 were dose proportional in Japanese subjects from 5 to 200 mg. Plasma E2609 concentrations declined over time across the 3 doses. The geometric mean CL/F was consistent across the doses indicating dose linearity, a finding similar to that found previously in white subjects. The pharmacokinetic parameters of E2609, M2, and M5 metabolites following administration of a single 50-mg dose were comparable between Japanese and white subjects. M1 exposure was slightly lower (~12%) in Japanese subjects, a finding not considered clinically meaningful. E2609 was well tolerated in all cohorts. Safety findings were similar between Japanese and white subjects. *Conclusion:* Pharmacokinetic and pharmacodynamics parameters were similar between Japanese and white subjects. E2609 was well tolerated. Overall, the results support the conclusion that Japanese and white subjects can be dosed equivalently.

P3-28 DOSE-RELATED REDUCTIONS OF CSF AMYLOID B (1-X) BY E2609, A NOVEL BACE INHIBITOR IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S DISEASE (AD) AND MILD-MODERATE AD DEMENTIA. Oneeb Majid[1], Michelle Gee[1], Bruce Albala[2], Robert Lai[1], Satish Dayal[1], June Kaplow[2], Ziad Hussein[1], Jim Ferry[2], Bhaskar Rege[2] *((1) Eisai Co. Ltd., London, UK; (2) Eisai Inc., Woodcliff Lake, NJ, USA)*

Background: Phase 1 clinical studies have demonstrated robust dose and exposure-related effects of E2609, a novel BACE inhibitor, on plasma Aβ1-x and CSF Aβ1-x, Aβ40, Aβ42, and BACE1 activity in a dose range of 25 mg to 400 mg administered once daily (QD) for 14 days to healthy elderly subjects. The present integrated data analysis evaluated the population pharmacokinetic (PK), PK/PD, and dose-response of E2609 in subjects who had confirmed positive levels of brain amyloid, based upon PET and were clinically staged with Mild Cognitive Impairment (MCI) due to AD, or mild to moderate dementia due to Alzheimer's disease (AD). The patients were dosed QD with placebo, 5, 15 or 50 mg E2609 in this double-blind clinical trial. *Methods:* For pharmacodynamic (PD) assessment, Aβ1-x [IBL ELISA] was analysed (versus Aβ40 or Aβ42 alone) enabling measurement of total amyloid isoforms cleaved at the N termini by the BACE enzyme. PK/PD models were developed using integrated data from studies in healthy elderly subjects and AD patients describing the relationships between E2609 exposure and CSF Aβ1-x (PD) reduction, and between E2609 dose and CSF Aβ1-x reduction. Based on the plasma and CSF PK of E2609, steady state levels were achieved within 2 weeks, hence, for both analyses, PD data after 4 weeks of dosing were pooled with the 2 week data from a

study in healthy elderly subjects receiving daily E2609 doses ranging from 25 to 400 mg QD for 14 days. For population PK analysis, a total of 288 plasma PK concentrations, collected at Weeks 2, 4, 12, 26 and 52 following the start of treatment were available pre-dose and 4-8 h post-dose for 54 AD subjects. PK data from this study were pooled with E2609 plasma concentration data (full profiles) from 3 studies completed in healthy subjects. Model-derived E2609 average concentration (Cav,ss [ng/mL]) values for each subject were used to describe the PK/PD relationship between E2609 exposure and CSF Aβ1-x reduction. PK and PK/PD modelling were conducted using NONMEM v7.2. *Results:* In patients, multiple-dose administration of E2609 at doses ranging from 5 to 50 mg administered once daily resulted in dose-related reductions in CSF Aβ1-x at Week 4. The relationships between the plasma exposures or dose of E2609 and CSF Aβ1-x were best described by inhibitory Emax models with baseline fixed to 100%. Both models predicted maximum reduction in CSF Aβ1-x on average to be approximately 99%. The E2609 average steady state plasma concentration resulting in a mean 50% reduction in CSF Aβ1-x (IC50) was approximately 17 ng/mL. The corresponding dose of E2609 for a QD regimen to result in approximately 50% reduction in CSF Aβ1-x (IC50) based on the dose-response model was approximately 20 mg. Overall, PK/PD analysis of data from subjects with MCI due to AD and mild-moderate AD demonstrated reduction of CSF Aβ1-x for all three doses which substantially overlapped with corresponding data in healthy subjects. The population PK analysis demonstrated that E2609 exhibited linear pharmacokinetics within the dose range studied, similar to prior findings from healthy subject studies. The PK profiles were described by a 2-compartment model with simultaneous first and zero order absorption and linear elimination, parameterized for absorption rate constant (Ka), duration of absorption (D1), lag time in absorption, apparent clearance (CL/F), apparent central volume (V1/F), inter-compartment clearance (Q) and apparent peripheral volume (V2/F). Overall, the E2609 PK was similar in healthy subjects and AD subjects with MCI due to AD and mild-moderate dementia. *Conclusion:* The integrated PK/PD analysis for the novel BACE inhibitor, E2609, exhibited robust dose- and plasma exposure-related effects in CSF Aβ1-x in both healthy subjects and AD patients with MCI due to AD and mild-moderate dementia. The overall 90% prediction intervals from the integrated PK/PD analysis overlapped substantially with healthy volunteer data suggesting a similar relationship. The PK of E2609 in MCI due to AD and mild to moderate Alzheimer's subjects was also comparable to healthy subjects. The use of such modelling permits the collection of small amounts of difficult to obtain data, such as CSF sampling in special populations like AD and thereby facilitates the clinical advancement of novel drugs such as E2609 by allowing dose selection earlier in development.

P3-29 ADVANCING THERAPEUTICS FOR NEUROINFLAMMATION IN ALZHEIMER'S DISEASE: CLINICAL DEVELOPMENT CONSIDERATIONS. Richard Margolin[1], Lon Schneider[2], Gary Cutter[3], John Breitner[4], Gary Landreth[5], Daniel Chain[1] *((1) CereSpir, Inc., New York, NY, USA; (2) Keck USC School of Medicine, Los Angeles, CA, USA; (3) University of Alabama, Birmingham School of Public Health, Birmingham, AL, USA; (4) Douglas Mental Health University Institute - Research Centre, McGill University, Montreal, PQ, Canada; (5) Case Western Reserve University, School of Medicine, Cleveland, OH, USA)*

Background: Substantial epidemiologic evidence associates chronic anti-inflammatory drug use with reduced AD risk; equally substantial biomarker and neuropathological evidence implicates neuroinflammation in AD pathophysiology. However, clinical trials of various anti-inflammatory drugs conducted from 1993-2008 were neutral or negative, reducing interest in inflammation-targeting therapeutics thereafter. Recent genetic research findings have strongly connected the CNS innate immune system (IIS), particularly microglia, to both increased and decreased risk of AD, though, which has galvanized resurgent interest in neuroinflammation as a therapeutic focus. In parallel, a massive amount of information about the biology of the central and peripheral IIS in recent years, as well as and its role in various inflammatory disorders. As a result, a new generation of therapeutic agents targeting this system in AD is anticipated, and it is important that trials evaluating them be optimally designed. Thus, careful review of the methodology of the early trials may explain their negative results and provide useful insights. Relevant 'Omics and biomarker research findings, and experience with IIS-active treatments for systemic disorders should also be considered. *Methods:* We reviewed published reports of past trials of anti-inflammatory drugs and interacted with study leaders when possible. Drug class (steroid, NSAID, other), population (age, disease stage, APOE4 status), sample size, entry criteria, allowed concomitant medications, clinical and biomarker endpoints, and treatment duration were considered. Performance characteristics of established inflammatory biomarkers (eg, Ifn-γ, IL-6, TNF-α) and emerging biochemical measures (eg, YKL-40, sCD40L) in blood and CSF were also reviewed, as was TSPO PET imaging, to gauge readout quality. The potential that systemic factors (eg, inflammatory disorders and/or their treatments, GI tract microbiome) might influence the outcome of IIS-targeting treatment trials for AD was likewise considered. *Results:* Seventeen trials testing 13 drugs were identified; 16 were conducted in MCI or AD, 1 in at-risk elderly. Treatments included a glucocorticoid, several NSAIDs (both nonselective COX inhibitors and COX-2-selective antagonists), and a PPAR-γ agonist. Sample sizes ranged from 20-2981; treatment duration was from 3 mos-3.5 yrs. Biomarkers use was fairly limited. Temporal variability of classical cytokines is high; properties of newer markers are incompletely established but show promise. Systemic inflammatory disorders and even non-BBB-penetrant treatments for them might influence CNS IIS biology and affect treatment trial results; the impact of the microbiome is unknown. *Conclusions:* The reasons for failure of early anti-inflammatory trials remain uncertain, but carefully evaluating their design features can significantly inform trial strategies for novel agents targeting brain innate immunity. Future trials must address the potential influence of peripheral immune factors. Potential biomarkers need thorough validation, and clinical development plans should include robust bioinformatics/pharmacogenomic strategies.

Theme: Clinical trials: recruitment and pre-screening

P3-30 PATIENT SELECTION FOR CNS CLINICAL TRIALS: FINDINGS FROM A 23,800-PATIENT ELIGIBILITY REVIEW DATABASE AND SUB-ANALYSIS OF ALZHEIMER DISEASE TRIALS? Robin C. Hilsabeck, Jennifer Murphy, Nadia Yakovleva, Claire K. Reinhold, Katya Miloslavich, Jeffrey Holleran, Kari R. Nations *(INC Research, Austin, TX, USA)*

Background: Quality patient selection is one of the most critical elements of a successful clinical trial. The many recent drug failures in Alzheimer disease (AD) and clinical "improvement" in placebo groups when none would be expected create a cautionary tale for all AD trialists. A growing body of evidence suggests that high CNS trial failure rates, including those in AD trials, are partly attributable

to inappropriate patient selection. CNS protocols are universally complicated, with the number of eligibility criteria ranging up to 70 in many trials. The level of complexity is magnified in AD trials due to the older age of most subjects and their many comorbid medical and psychiatric conditions. Investigators, while clearly dedicated to quality and compliance, interpret protocol criteria differently and have varying levels of tolerance for risk. The diversity may be even more significant in international clinical studies involving sites with somewhat different diagnostic and rating approaches. The subjectivity when interpreting vascular load, variability in cognitive scale administration, and judgment driven decisions about co-morbid medical safety naturally translates to compromised internal validity of AD trials in the absence of careful oversight of incoming subjects. Fortunately, centralized review is both operationally feasible and acceptable to Investigators, when conducted collaboratively, leaving final eligibility decisions in the hands of the treating physicians. *Methods:* Eligibility Review is a process conducted at INC Research by a centralized, global team of physicians and doctoral-level clinical scientists. Key screening data in select trials are collected from sites and vendor portals by project management personnel, then compiled and reviewed in a team discussion format. Resulting eligibility concerns and questions are thereafter discussed with Investigators. In the majority of cases, Investigators are able to provide additional clinical history that supports subject eligibility; however, in those cases where Investigators agree the subject is unsuitable, the site proceeds to screen fail the subject. The full process and dialogue takes place within the screening period so that no ineligible patient is randomized inappropriately. *Results:* A total of 23,858 subjects were reviewed for eligibility by a central medical/clinical team, covering 46 trials in 48 countries over a 6-year period, 25 in psychiatric indications, 12 in neurology, and 9 in analgesia. Although the submitting Investigators considered all subjects to be eligible to randomize, the review team identified approximately 2160 (9%) who did not meet eligibility criteria and were ultimately considered unsuitable to enter the trials. Findings did not differ significantly between therapeutic area: 8.4% of subjects reviewed were considered ineligible in psychiatry trials, 9.5% in neurology trials, and 10.4% in analgesia trials [$F(2,43)=1.41$, $p=0.26$]. With regard to AD trials specifically, 133 of 813 subjects (approximately 16%) were considered unsuitable for participation by Investigators after consultation with the central medical/clinical review team, which was not significantly different from all other indications combined [$t(44)=0.977$, $p=0.33$]. Reasons subjects were considered ineligible were broad (some for more than one reason): 45% were ineligible for reasons related to medical history, 38% for laboratory or ECG findings, 26% for treatment history or prohibited medications, 15% due to findings related to primary diagnostic validity, and 11% for psychiatric history or psychosocial reasons. All subjects considered ineligible after review were screen failed following collaborative discussions with Investigators. Additional data about AD trials, including regional differences in findings rates and most common findings will be presented. *Conclusions:* The current analysis demonstrates that CNS trials, including AD trials, are highly susceptible to penetration by unqualified/unsuitable subjects and that eligibility issues are wide-ranging and not limited to issues of diagnostic validity. Importantly, these data show that no therapeutic area is immune to unwanted heterogeneity in the study sample. Light intervention at the time of screening can homogenize the patient sample to align with protocol criteria, rendering trial efficacy and safety results both interpretable and actionable.

P3-31 EVALUATING CORRELATIONS BETWEEN RECRUITMENT RATES AND SITE RATINGS QUALITY. D. Miller, X. Wang, S. Allen, H. Gratkowski, T. Feaster, A. Butler *(Bracket, Wayne, PA, USA)*

Background: The selection of investigative sites to participate in clinical trials is often focused on evaluation of historical therapeutic experience, past subject recruitment and regulatory compliance records. The evaluation of clinical outcome performance criteria could be an important component of improving study execution, and a methodology for this evaluation has previously been presented. In this study, we look to identify possible correlations between recruitment rates and clinical outcome performance criteria. *Methods:* A proprietary database of sites and raters who had participated in recent clinical trials (trailing 3 years) was compiled. The database included historical experience with ratings scales, performance data on certification programs, and performance data based on quality assurance programs implemented to ensure quality ratings were performed during a clinical trial. Quality assurance measures included blinded review of audio/video ratings, worksheet reviews assessing accuracy of scoring, and rater scoring analytics. Each rater's experience, certification and quality assurance measures were assigned weighted numerical values. Each rater at a site contributed to the site's overall score. Each site was classified as "Recommended", "Moderately Recommended" or "Not Recommended." These same sites were subsequently analyzed to identify the number of patients recruited in each historical program. A Spearman correlation was used to determine the relationship between the site quality classification and number of patients recruited. *Results:* Both recruitment and site quality data were available for 691 sites. The mean number of patients recruited across the sites was 12.4, but the majority of the sites (478) recruited less than 10 patients. Sites that recruited no patients were not included in the analysis. A weak, positive, linear association of 0.14 with a p value of 0.0001 was identified. Due to the skewness of both variables, the Spearman correlation is used. Of the sites that were in the highest 20% of recruitment rates, 82 had a site quality classification of "Recommended", 18 sites had a site quality classification of "Moderately Recommended", and 5 had a site quality classification of "Not Recommended." *Conclusions:* Clinical trial site feasibility analysis requires evaluation across a number of factors. Relying on site recruitment rates alone could expose a sponsor to poor- or lower-quality data. But relying on prior site quality rankings alone is also unlikely to provide a comprehensive picture. In addition, simply increasing the number of times a site rater administers a clinical outcome assessment does not ensure that the quality of that assessment will increase. While there was a weak linear association between recruitment and quality, the distribution of high enrollers and high quality sites is still variable enough that careful, individual evaluations should be conducted during site feasibility. Disclosures: This poster is financially supported by Bracket. The authors report no conflicts of interest for this work.

P3-32 RECRUITMENT PRACTICES FOR ENABLING RAPID PRECLINICAL ALZHEIMER'S DISEASE CLINICAL TRIALS ENROLLMENT: EXPERIENCE FROM THE TOMMORROW STUDY. Kathleen A. Welsh-Bohmer[1], Stephen Haneline[2], Brenda L. Plassman[1], Heather R. Romero[1], Kathleen M. Hayden,[1] Meredith Culp[3], Ryan Walter[3], Patrick Harrigan[3], Daniel K. Burns[1], Ferenc Martenyi[3], Oksana Makeeva[4], Allen D. Roses[1,2] for the TOMMORROW investigators *((1) Duke University Bryan ADRC, Durham, NC, USA; (2) Zinfandel Pharmaceuticals, Inc., Durham, NC, USA; (3) Takeda Global Research & Development Center, Inc., Deerfield, IL, USA; (4) Nebbiolo, LLC | Center for Clinical Trials, Tomsk, Russia*

Background: A major challenge in conducting clinical trials that investigate the delay or prevention of the onset of Alzheimer's disease (AD) is the identification of large numbers of appropriate subjects. Unlike recruiting memory impaired patients in treatment trials, it is a daunting task to find ready populations of cognitively healthy individuals both interested and eligible to participate in a clinical trial of an experimental agent that may last several years. The TOMMORROW Study is a global, Phase 3, multicenter, double-blind, randomized, placebo-controlled clinical trial designed to simultaneously: (1) qualify a genetic biomarker risk algorithm for assigning 5-year risk for developing Mild Cognitive Impairment due to Alzheimer's disease (MCI-AD), and (2) evaluate the efficacy of low-dose pioglitazone as a treatment to delay onset of MCI-AD in cognitively normal, high-risk individuals, as identified by the genetic risk algorithm. Enrollment began in August 2013 and completed 29 months later in December 2015, resulting in 24,235 cognitively normal subjects screened (ages 65 to 83) and a total of 3494 study subjects ultimately enrolled in the study at 58 participating global sites. To determine how the sites were able to ramp up quickly to meet the enrollment demands, we surveyed the sites to identify the most successful recruitment processes. We report the characteristics and recruitment procedures of the most successful enrolling sites for the TOMMORROW study. *Methods:* Site surveys were sent to the 58 active sites at the close of enrollment. The questionnaire queried recruitment practices and their overall relative yield. Four items assessed initial recruitment targets, success in reaching these goals, and reasons contributing to lower than expected performance. Seven items assessed methods employed to recruit subjects. If sites used subject registries, two additional items captured information about registry characteristics (e.g. including detailed assessments or biosamples). Information received from the sites was then abstracted, summarized, and analyzed in relationship to performance metrics (number screened and enrolled in study). Controlling for length of time that each site was enrolling subjects into the study, the characteristics of the top recruiting sites were compared to those that were less successful over the same enrollment interval. *Results:* Thirty-nine sites completed the survey, accounting for 84% of all subjects enrolled and 83% of all subjects screened. Over half of the sites (56%) reported using either an existing local subject registry or a registry specifically designed for prevention studies. Twenty-three percent reported drawing subjects from national registries such as Trial Match or Join Dementia Research UK. There were 13 high performing sites, enrolling over 75 subjects. Of these, 62% indicated use of a registry or having access to large electronic data bases. Nearly all sites did some form of telephone prescreening to lower screen/enrollment failures. Interestingly, although subject registries were very common, of the two particularly very high enrolling sites (over 200 subjects each), only one used a local subject registry that was not specific to the trial. In common among the top two enrolling sites was that they enrolled subjects through large local outreach events and with flyers and other print advertisements. *Conclusions:* Rapid enrollment of cognitively healthy subjects into a delay of MCI-AD trial was facilitated at sites by the availability of large subject registries for healthy aging and AD prevention trials. However, registries were not always required in order to achieve rapid enrollment success. Commercial trial operations, experienced in finding and recruiting participants into trials were among the top performers. In population areas enriched for retirees, the need for a pre-existing participant registry was unnecessary. Outreach events, word of mouth, and advertisement were all effective in recruiting interested participants in this scenario. Consequently, it appears that there is not a single "one size" fits all for recruitment into delay of AD onset/prevention studies. Rather, a combination of approaches can be effective. A key ingredient of rapid enrollment whether accomplished with well-resourced, commercial groups or through academic partners, is ready access to a large number of individuals within the right age demographic who are willing to participate in AD clinical research.

P3-33 COMPUTERISED TESTING: APPLICATIONS IN RECRUITMENT AND MONITORING OF PATIENTS IN CLINICAL TRIALS. Francesca Cormack[1], Nick Taptiklis[1], Jack Curtis[2], Rosemary Abbott[1], Jennifer H Barnett[1,3] *((1) Cambridge Cognition, Cambridge, UK; (2) Department of Physiology Development & Neuroscience, University of Cambridge, UK; (3) Department of Psychiatry, University of Cambridge, UK)*

Background: Computerised cognitive assessments have been used in research of patients with Alzheimer's disease for nearly thirty years. New technological developments provide novel platforms for the assessment of cognition. These have the potential to widen access to cognitive assessment and to enable high-frequency testing in between clinic visits. This can help to address the need for the detection of increasing numbers of patients (?) in the prodromal phase of Alzheimer's disease, and enable monitoring of fluctuation and deteriorations in cognitive function with disease progression. In this paper we present data on two technological approaches to these challenges: web-based testing and wearable devices. Web-based testing has the potential to widen recruitment into clinical trials. Assessments such as the computerised Paired Associates Learning (PAL) task have repeatedly been associated with Alzheimer's disease biomarkers, such as levels of Aβ and hippocampal volumes. Assessing subject PAL performance early in the recruitment process therefore has the potential to enrich samples for biomarker-positive patients, reducing costs, site and patient burden. Wearable technology can enable older adults with cognitive concerns to monitor their cognition on a daily basis, and provide clinicians and researchers with information at a higher temporal resolution than previously possible. There are considerable challenges surrounding the implementation of such technologies in practice. Firstly, there is the issue of comparability of these assessment methods to data obtained by standardised assessment, and secondly is the usability of these methods, and the impact of age on this. *Methods:* Here we describe the development and testing of two approaches to cognitive assessment: web-based remote testing and wearable technology. Six hundred participants between 18 and 70 were recruited for web-based testing, and were matched to 94 participants assessed in a supervised setting on age and gender. Participants completed an adaptive test of episodic memory (Paired Associates Learning - PAL) from Cantab, alongside other tests of memory (Delayed Match to Sample), or working memory (Spatial Span, Spatial Working Memory). Demographic data (e.g. age, education) were also recorded. Participants in the supervised testing were assessed on iPads, whereas in online testing participants used a variety of systems, including desktop computers, laptops and tablet devices. Data from reaction times and software use was used to quantify participant engagement. Statistical data analysis focused on 1) the comparison of web-based to in-person testing 2) the factor structure of the web-based testing data, compared to in-person testing 3) the effect of age on task engagement. Wearable assessments of cognition were carried out using an N-back paradigm on a Microsoft Band2. Thirty trials were presented each testing session, with participants responding to a two-back match. We assessed the accuracy and timing of responses. Participants also completed a battery of cognitive tests from the Cantab battery. Analysis of the results focused on 1) the patterns of performance on the N-back, modelling learning effects 2) the relationship between performance on the N-back and performance on standard Cantab

tests 3) the relationship of age with N-back performance. *Results:* There was no difference in PAL errors between supervised and web-based testing. Within the web-based testing, there was no difference between hardware platforms or browser. However, trial-by-trial timing data showed highly variable and slow reaction times in a number of participants during web-based testing, outside the bounds seen on supervised testing. This was associated with more PAL errors (r=.35), and younger age (r=.-21). Web browser activity monitoring revealed whether participants tabbed to a different browser window during task performance (n=200). This behaviour was associated with poorer PAL performance (t = -2.09, df = 161.5, p-value = 0.03), greater RT variability (t = -3.48, df = 119.6, p-value < 0.01) and younger age (t = 3.4157, df = 192.9, p-value <0.01). Factor analysis showed the expected structure, with tests of visual episodic memory loading onto the same factor, separate from tests of working memory. This supports the validity of these methods of measurement. Assessment of performance on cognitive tests on wearable technology showed that participants demonstrated learning over the course of the two-week trial. Performance on the N-back micro-testing was significantly correlated with performance on Cantab tests of working memory and attention switching. There was a significant effect of age on performance on the n-back tests, with older adults showing overall lower levels of performance than younger participants. Compliance and acceptability of wearable testing was good. *Discussion:* Our initial research has shown meaningful assessment of cognitive performance is possible using both remote web-based testing and high frequency protocols on wearable devices. Wearable cognitive test data can be combined with mobile technology, that that can be linked to monitoring of physiological and movement parameters, providing a rich picture of daily fluctuations in state. These data have implications for detection and monitoring of subtle changes due to a variety of conditions and may provide new means of lower cost and more effective patient recruitment, sample enrichment, and personalised treatment protocols.

P3-34 RETHINKING INSTITUTIONAL REVIEW BOARD SUBMISSIONS FOR ONLINE CLINICAL TRIAL RECRUITMENT. Shannon Finley[1], Derek Flenniken[1], Aaron Ulbricht[1], Monica Camacho[1], Juliet Fockler[1], R Scott Mackin[1,2], Rachel L Nosheny[1,3], Diana Truran[1], Michael W Weiner[1,3] *((1) Center for Imaging of Neurodegenerative Diseases, San Francisco Veteran's Administration Medical Center, San Francisco, CA, USA; (2) UCSF Department of Psychiatry, San Francisco, CA, USA; (3) UCSF Department of Radiology and Biomedical Imaging, San Francisco, CA, USA)*

Background: As Alzheimer's disease (AD) clinical trials pivot toward a larger online presence to conduct studies, it is essential to redefine the Institutional Review Board (IRB) approval process for online research. The Brain Health Registry (BHR), an online study for recruitment, screening, and longitudinal monitoring for clinical trial recruitment, has gained considerable experience in this arena. This presentation aims to describe interactions with the University of California San Francisco (UCSF) and other IRBs concerning 1) online informed consent and 2) referral of BHR participants to clinical trials and research studies who hold their own IRB. *Methods:* IRB granted BHR a waiver of signed consent and collects consent via an online information sheet. This sheet, modeled after classic informed consent, requires participants to agree or decline participation but not physically sign a document. This waiver was obtained for the unfeasibility of procuring signed consent on thousands of participants located worldwide. Furthermore, since the only risk to participants is loss of privacy (due to hacking), this research is considered minimal risk. UCSF IRB approved BHR to share participant contact information and identifiable data to facilitate research of collaborating investigators via an IRB approved "Modular Consent Form" (MCF). The MCF is a template that provides a "plug and play" approach - pertinent information needed to share data with collaborating studies is completed on open fields. Completed MCF's do not require separate IRB approval, which increases flexibility of our referral programs by allowing BHR to move quickly without approaching IRB for individual data sharing requests. BHR participants are presented with a MCF to elect to share their BHR data when introduced to a study opportunity. Referrals to outside clinics: BHR currently offer two IRB approved referral programs to facilitate clinical trial recruitment: Direct Site Referral (DSR) and BHR Referral Program (BRP). Collaborating investigators must obtain local IRB approval to receive referrals from online registries like BHR. This is usually accomplished administratively without full IRB committee review and requires minimal effort for collaborating studies. Once local IRB approval is received, BHR emails potentially eligible registrants about study opportunities in their area. BHR obtained IRB approval for recruitment emails sent on behalf of collaborating studies by submitting templated recruitment letters that utilize the same "plug and play" approach as MCFs. The DSR utilizes online advertising strategies designed to drive traffic to the BHR website or landing pages that highlight BHR and associated partnerships for particular online campaigns. These webpages host registration forms that collect contact information and zip code. This information is used to geo-locate trials in the referral's area that are participating in the DSR program and, depending on IRB approval, passes the referral's information to the trial or sends referral emails on the trial's behalf. A referral does not need to be an enrolled BHR participant to be referred to studies, however, little information is known of the referrals and MCF cannot be employed to share data. The BRP goes further by identifying enrolled BHR participants who may be eligible to participate in clinical trials based on data they provided BHR. Trial investigators work with BHR to determine what data to use to assess eligibility for their research study. BHR emails selected referrals and either provides the study contact information to the referral, or obtains permission via MCF to share contact information and/or selected study data with collaborating trial staff. Trial staff report back on the success of the referrals. The entire process - from advertisement, to registration, to referral, to enrollment at clinic site - is tracked electronically under IRB approved methods. *Results:* 18 collaborators are utilizing DSR or BRP and 6977 participants have been referred. 1544 (22%) responded to referral emails with 1030 (15%) declaring interest in the study opportunity. Of those interested, 474 (46%) were eligible, and 418 (41%) enrolled in outside studies. 100 have signed a MCF allowing sharing of identifiable data with outside collaborators. Templated recruitment emails and MCF's have saved countless hours dealing with individual submissions to involved IRB's – either UCSF or collaborators. *Conclusion*: Preliminary data demonstrates proof of concept: BHR can recruit, identify, and refer individuals that are willing and eligible for trials in an IRB approved environment. The methods BHR developed are scalable and become increasingly cost effective as larger numbers of participants enroll. We continue to refine our referral programs to ensure they are helpful and easy for investigators and participants alike. As our referral programs grow, we expect increased referral successes in the months and years to come.

P3-35 THE BRAIN HEALTH REGISTRY CAREGIVER AND STUDY PARTNER PORTAL TO FACILITATE ALZHEIMER'S CLINICAL TRIALS. R.L. Nosheny[1,3], D. Flenniken[1], M. Camacho[1], A. Ulbricht, J. Fockler[1], P.S. Insel[1,3], R.S. Mackin[1,2], D. Truran[1], S. Finley[1], K. Mckenzie[1], M.W. Weiner[1,3] *((1) Center for Imaging of Neurodegenerative Diseases, San Francisco Veteran's Administration*

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Background: Facilitating recruitment, screening, and longitudinal monitoring for Alzheimer's disease (AD) clinical trials is crucial for accelerating the development of new treatments. Study Partner (SP)-reported information is used frequently to assess cognitive and functional status in AD and provides many unique benefits. Unlike neuropsychological tests (NPTs), SP-report captures cognitive decline, including premorbid levels of ability, which are crucial to AD diagnosis. SP-report can sensitively measure instrumental activities of daily living (IADL), complex functional activities that decline in preclinical AD; and SP-report can outperform self-report as a marker of cognitive function and AD pathology. However, no methods exist for efficiently obtaining SP data remotely from a large cohort, without clinician involvement. Development and validation of such methods have great potential for accelerating AD drug development and can also be used for widespread screening of age-related cognitive decline in healthcare settings. *Methods:* We recently developed and publically launched an innovative, web-based tool called the Caregiver and Study Partner Portal (CASPP) within the Brain Health Registry (BHR). BHR is a public online registry currently with over 47,000 participants that collects longitudinal cognitive, health, and lifestyle data through self-report questionnaires and NPTs and is actively referring participants to multiple AD clinical studies. The CASPP allows all BHR participants to identify a potential SP. The SP is then invited by email to join the CASPP. SPs register, consent, and answer questions about the participant, including measures of change in cognitive function and IADLs, which are based on well-validated measures. SPs also answer questions about themselves, including their experience as caregivers. We analyzed the demographic profile of SPs and used multivariable linear regression to analyze associations between participant cognitive function and the following SP-reported variables: memory concerns (SP-SMC), recent changes in cognition (SP-RCC), and recent changes in IADL function (SP-IADL). Participant cognitive function was assessed using scores on online NPTs across cognitive domains, as well as by participant self-reported memory concerns. We also compared SP-reported variables in BHR participants likely to be eligible for preclinical, prodromal, and dementia trials. *Results:* Since August 2016, 1300 BHR participants have invited a study partner to join. Of those, 316 (24%) of potential SPs enrolled in BHR. The average age of SPs is 58 ±15, and 149 (48%) are female. The average age of their associated participant is 60 ± 13. The majority of SPs are participant spouses (71%), followed by children (9%), friends (8%), parents (4%), and siblings (4%). Eighty percent of participants and SPs live together. Forty-two SPs (16%) are the primary caregiver for their associated participant. Thirty-three percent of SPs report memory concerns or recent changes in cognition for their associated participant, while 48% of participants self-report a memory concern or recent change. Eighty-one (26%) of participant-SP dyads agree that the participant has a memory or IADL problem. In univariable regression models, there were significant associations between SP-reported variables and both participant age and participant education. SP-SMC ($p < 0.001$), SP-RCC ($p < 0.001$), and SP-IADL ($p = 0.01$) all significantly predicted participant self-reported memory concerns, both in univariable models, and in multivariable models accounting for participant age, education, and gender. For online NPT memory scores, we found significant associations between scores and SP-RCC ($p = 0.03$), but not SP-SMC or SP-ADL, in univariable and multivariable models. There were no significant associations between scores on other cognitive domains (attention, processing speed) and any SP-report variable. Of those BHR participants who were identified as "possibly impaired" based on low NPT scores and self-reported memory concerns (n=60), 28 (47%) also had SP-reported cognitive or IADL problems, whereas only 36% of participants identified as "cognitively normal" (n=265) had a SP who reported a memory or IADL problem or concern. *Conclusions:* This data proves the feasibility of collecting SP-reported data online from a large cohort online, which can be used to identify and prescreen participants for AD trials. Our results of significant associations between SP-reported cognitive function and participant self-reported memory concerns demonstrate the convergent validity of CASPP data. Likewise, the associations between NPT memory scores and SP-RCC are evidence of convergent validity; such associations appear to be cognitive domain-specific to memory function. Participant self-report memory concern, but not participant NPT memory scores, are significantly associated with SP-IADLs, suggesting that decline in IADLs that occurs in the absence of objective memory impairment is evident in both SP- and participant self-report. Longitudinal analyses are needed to determine whether such IADL decline precedes objective memory impairment, and can therefore be used as an early indicator of preclinical AD. If CASPP data can be validated, the CASPP has great potential to facilitate AD clinical trials.

Theme : Others

P3-36 REPRESENTATIVENESS OF WESTERN EUROPEAN CLINICAL TRIAL POPULATIONS IN MILD ALZHEIMER'S DISEASE DEMENTIA – A COMPARISON OF 18-MONTH OUTCOMES WITH REAL- WORLD DATA FROM THE GERAS OBSERVATIONAL STUDY.

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Background: We previously compared patient and caregiver outcomes in mild Alzheimer's disease (AD) dementia in the placebo groups of two international randomised controlled trials (RCTs; pooled data from EXPEDITION and EXPEDITION 2) with those for patients in the real-world GERAS observational study in three European countries. Baseline-adjusted differences in functional and behavioural symptoms at 18 months were small and may have been due to multi-country or culture-specific variations. As practice patterns and healthcare systems are likely to be different between Western European (W-EU) countries and the rest of the world, this analysis compared W-EU EXPEDITION patients with patients in the EU-focused GERAS study. *Methods:* The EXPEDITION and EXPEDITION 2 trials were 18-month, international, randomised, double-blind, placebo-controlled trials of solanezumab in patients with mild and moderate AD dementia. The W-EU region included France, Germany, Italy, Spain, Sweden and the UK. GERAS was a prospective, 18-month, non-interventional study of community-dwelling patients with AD dementia of all severities in France, Germany and the UK presenting within the normal course of care. All patients were aged ≥55 years, had probable AD dementia (NINCDS-ADRDA criteria) and an informal caregiver, and the majority were receiving standard of care treatment(s). Data collected in all studies included: demographics; medical history; acetylcholinesterase inhibitor (AChEI)/memantine use; measures of cognition (MMSE and ADAS-Cog14), function (ADCS-ADL), behavioural symptoms (NPI-12) and health-related quality of life (HRQoL [EQ-5D]); and caregiver time (hours/month) spent on basic and instrumental activities

of daily living (bADL and iADL) and supervision. For this analysis, pooled data from the subgroups of placebo patients with mild AD dementia (MMSE score 20–26) from the two EXPEDITION RCTs (W-EU countries only) were compared with those from patients with mild AD dementia from GERAS (MMSE score 21–26). A sensitivity analysis compared W-EU and North American (W-EU/NA) EXPEDITION patients with GERAS patients. Demographics and baseline characteristics were summarised using descriptive statistics based on non-missing observations. Differences between the EXPEDITION RCTs and GERAS for changes in outcomes over 18 months were analysed using repeated measures models (where more than one post-baseline visit was recorded). Models included the following covariates: patient age, patient receiving AD medication (Yes/No), propensity score (based on patient age, gender, number of comorbidities, time since diagnosis of AD dementia, years of education, AD medication and baseline MMSE score) and baseline outcome score. *Results:* W-EU EXPEDITION patients (n=168) were slightly younger (mean [standard deviation] 72 [7.4] versus 77 [6.9] years; p<0.001) than GERAS patients (n=566); approximately half of both populations were female (51% in EXPEDITION versus 48% in GERAS; p=0.54). Time since diagnosis was also similar in both populations (1.68 [1.50] EXPEDITION versus 1.66 [2.00] years GERAS; p=0.90). Use of any AD treatment (at least one AChEI and/or memantine) and combination AD treatment (AChEI + memantine) were both higher in EXPEDITION than in GERAS (95% versus 85% [p<0.001] and 11% versus 5% [p=0.003], respectively). Cognitive performance was similar at baseline (mean [standard deviation] MMSE score 23.1 [1.96] in EXPEDITION versus 23.3 [1.62] in GERAS; p=0.15), although GERAS patients showed slightly greater functional and behavioural impairment, and lower HRQoL. No significant differences in characteristics or baseline outcomes were observed after propensity score stratification. Eighteen-month data were available for 133 EXPEDITION patients (79%) and 417 GERAS patients (74%). Least squares mean [standard error] change in MMSE score from baseline was similar for both groups (–3.6 [0.44] in EXPEDITION and –3.1 [0.26] in GERAS; p=0.79). No significant differences between groups were observed for changes in other cognitive, functional, behavioural or HRQoL outcomes. Although change in caregiver time (hours/month) spent on bADL did not differ significantly between groups (18.7 [4.29] in GERAS versus 9.3 [6.50] in EXPEDITION; p=0.14), time spent on iADL (29.2 [5.12] versus 3.2 [7.68]; p=0.001), supervision time (66.6 [9.73] versus 3.0 [14.5]; p<0.001) and overall caregiver time (87.9 [10.89] versus 12.9 [16.31]; p<0.001) all showed greater increases over 18 months in the GERAS versus EXPEDITION populations. Results based on comparing the W-EU/NA EXPEDITION population with GERAS patients were similar to those based on the W-EU-only EXPEDITION population in terms of cognitive, functioning and time measures, but changes in NPI-12, NPI distress and EQ-5D scores, and caregiver time spent on bADL, were also significantly greater for GERAS than W-EU/NA EXPEDITION patients. *Conclusion:* Compared with our previous analysis, cognitive and functional score changes from baseline to 18 months did not differ when the comparison between GERAS and EXPEDITION was restricted to W-EU or W-EU/NA EXPEDITION patients. The large differences in change in caregiver time measures (particularly apparent for supervision time) may be due to baseline functional differences and/or unmeasured confounders. Significant differences in NPI and EQ-5D score changes, identified when more diverse regions (W-EU/NA) were included in the EXPEDITION cohort, indicate the importance of using similar regions when comparing real-world data with RCT results. Sponsored and funded by Eli Lilly and Company.

P3-37 THERAPEUTIC LINKS BETWEEN ANTI-CANCER DRUGS (BEXAROTENE) AND ALZHEIMER'S DISEASE. Krishna Prasad Pathak[1], Tara Gaire[2], Magda Tsolaki[3] *((1) Macedonia of University, Thessaloniki, Greece; (2) Star Hospital, Lalitpur, Nepal; (3) Department of Neurology, Aristotle University of Thessaloniki)*

Background: Cancer is a disease which affects the elderly, just like Alzheimer's Disease (AD) which is also a common disease affecting older people. Most of the symptoms are related with both these diseases, therefore there may be therapeutic link between anticancer drugs and AD. Little is known (by the way of support of animal model studies) whether anticancer drugs may help to reduce cognitive impairment, reduce Aβ protein, decrease amyloid plaques and promote neuroprotection. There is not sufficient evidence cognitive dysfunction impacts quality of life and compliance for treatment, so assessing the elderly cancer affected population is a challenge in clinical practice for distinguishing between AD symptoms and cancer and its proper treatment. *Design:* To identify potential new treatment possibilities we applied the systematic searches of key electronic databases, supplemented by hand searches of reference lists. Relevant articles were searched for on the following databases: PubMed, Psych Info, Medline, Scopus, Google Search engine, Cochrane library. The inclusion criteria were; (1) Studies aimed at improving cancer and anticancer therapies with human model (2) Peer-reviewed and written in English without any searching limitation on the basis of published date (3) Studies of drugs related to cancer treatment that were relevant to AD. (4) We did not include the clinical news, case report and animal trial studies. *Results:* We yielded 45,366 papers. These papers were reduced after filtering titles, abstract, references published in English into one study that has been condensed into one volume of literature. There is very hard to find studies aimed at therapeutic links between Alzheimer's disease and Anti-cancer drugs in human model. However, sufficient studies are conducted with animal model (mice) and indicating the positive benefits to the AD patients. Bexarotene is useful for the reduction of cholesterol, loss of function associated with APOE ε4, peripheral thyroid hormone metabolism and athyreotic and amyloid beta that is a key cofactor of Alzheimer's disease. Also, Bexarotene has been shown to restore cognitive functions. Bexarotene is a compound chemically related to vitamin A that activates Retinoic X Receptors (RXR) found everywhere in the body and rapidly cleared amyloid plaques from the brains of Alzheimer's model mice. *Conclusion:* This review discusses the emerging role of anticancer-drugs-Bexarotene in a clinical trial of Alzheimer's dementia with the support of animal model successful results and their effectiveness. Cancer drugs are not a miracle cure for AD- dozens of questions have been raised, however, Bexarotene (chemotherapy) improves cognition and other symptoms that appear with AD patients and will be a significant drug in the coming decades. Key words: Anti-cancer therapy, Alzheimer's disease (AD), dementia

P3-38 A NEW PARTNERSHIP TO CREATE A NATIONAL IRB FOR CLINICAL TRIALS IN DEMENTING ILLNESS. David S. Knopman[1], Eli T.S. Alford[2], Rebecca A. Ballard[3], Kaitlin E. Tate[2], Ara S. Khachaturian[4] *((1) Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA; (2) Schulman IRB, Research Triangle Park, North Carolina, USA; (3) Schulman IRB, Cincinnati, Ohio, USA; (4) National Biomedical Research Ethics Council, Las Vegas, Nevada, USA)*

Background: Since the later half of the twentieth century, national and provincial governments across the globe have insisted on the development of rigorous systems to assure human safety in the conduct of clinical research. The most visible component

of these systems has been the development of the institutional review boards (IRB), research ethics board (REB), and independent ethics committees (IEC). In North America, local IRB and REB oversight has been a key feature of research ethics reviews. However, increasing sophistication in the design, conduct and analysis of clinical research— now often involving multiple research sites and extending over large geographical distances—are complicating the ethics review process and purely local ethical oversight may confound and delay execution of large studies. These problems are particularly relevant for neurodegenerative disease clinical research. In 2012, the National Institutes of Health (NIH) Alzheimer's Disease Summit recommended that to overcome these challenges there was an imperative to establish a centralized Institutional Review Board for neurodegenerative diseases. The development of a special-purpose ethical oversight panel would enhance patient/volunteer safety, increase the efficiency in the conduct of large-scale multi-site trials and serve as an international model for global prevention studies. Recently, the NIH announced that after May 25, 2017 it is expected "that all sites participating in multi-site studies involving non-exempt human subjects research funded by the NIH will use a single Institutional Review Board." This abstract describes the recently launched joint program of the National Biomedical Research Ethics Council (NBREC) and Schulman IRB to provide a single IRB of record (sIRB) that conducts scientific and ethical review for participating sites of North American multi-site studies. The enterprise will provide services to all phases of clinical drug, device, and biologics development requiring multi-center studies. *Methods:* The NBREC-Schulman Alliance will extend and enhance Schulman's central IRB review of prevention trials of neurodegenerative diseases. The Alliance aims to provide highly customized review support services to study sponsors, participating research institutions, principal investigators, and co-investigators and project staff in two serial steps. First, the Alliance will provide scientific review of submitted research protocols. The review will be conducted by a Scientific Review Committee (SRC), an expert panel of senior researchers in the field, who will evaluate protocols based on the scientific merit and significance of the study, the feasibility of the project, and the likelihood of its producing meaningful results, among other criteria. The SRC will vote to approve, disapprove, or recommend revisions for reconsideration. After SRC protocol approval, the second step will be the IRB's regulatory and ethics review focused on the rights and welfare of research subjects. The IRB will apply appropriate regulatory criteria for approval including minimization of risks to subjects and risks reasonable in relation to anticipated benefits, equitable subject selection, informed consent, protections for vulnerable populations, and application of local context considerations, among others. The SRC and IRB reviews are complementary and mutually supporting, in particular affording the IRB benefit of expert scientific review to inform IRB assessment of risks and benefits to human subjects. *Results:* There is a steady demand for scientific, ethical and regulatory review of planned neurodegenerative disease studies. As of September 15, 2016, using data from clinicaltrials.gov, there are nearly 400 open studies, Phase II and III, industry and NIH sponsored trials on disease indications affecting memory, movement and mood in the US. This includes 42 studies on Alzheimer's disease and dementia, 46 studies of cognition (exclusive of memory, dementia and AD), and 47 studies of memory (exclusive of dementia, Alzheimer's disease and cognition). Since 2010, Schulman has approved 371 CNS/Neurology studies including 92 in Alzheimer's disease. With technology and infrastructure designed to support large multi-site studies, Schulman is currently overseeing Alzheimer's studies with 200 to 400 participating sites. The workflow and communication between the SRC and IRB will enable studies to be submitted, reviewed and approved within 3-4 weeks unless there are approval issues that need to be addressed. *Conclusion:* The NBREC-Schulman Alliance will initially accept protocols for studies of Alzheimer's disease, dementia, and related disorders effecting memory, movement and mood. The next phase of development will focus on a broader group of neurodegenerative diseases including neuropsychiatric syndromes. The project team will also evaluate the possibility of providing scientific review and, where applicable, regulatory and ethical review in an international context outside North America with sites possibly planned for Asia, Europe and Australia.

P3-39 LONGITUDINAL ANALYSIS OF [18F]THK5351 TAU PET IMAGES IN PATIENTS WITH ALZHEIMER'S DISEASE.

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Backgrounds: Recent progress in the development of tau tracers for positron emission tomography (PET) has enabled the visualization of neurofibrillary tangles in the human brains. The inhibition of abnormal tau deposition appears to be a promising therapeutic strategy in Alzheimer's disease (AD). Thus, tau PET is expected to facilitate the monitoring of the efficacy of drugs, and also the initial identification of suitable subjects to receive anti-tau drugs. In this study, we performed a longitudinal PET study using tau-selective PET tracer, [18F]THK-5351, in order to investigate the sequential changes in the spatial distribution of neurofibrillary tangles. *Methods:* A total of 18 participants, including 7 patients with mild or moderate AD (mean MMSE score 19), 6 patients with mild cognitive impairment (MCI) (mean MMSE score 25) and 5 age-matched healthy controls (HCs), participated in this study. The studies consisted of serial [18F]THK-5351 PET and MRI scans. Diagnosis of probable AD was based on the criteria outlined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease Related Disorders Association. Diagnosis of MCI was based on the Petersen criteria. All of the patients with AD and MCI had amyloid deposition on their PiB-PET scans at baseline. One healthy control subject also had amyloid deposition on PiB-PET scan. Participants were followed for 1.1 years (range: 0.8–1.3 years) and then re-examined. These examinations were performed under the regulations of the Ethics Committee of Tohoku University Hospital. PET imaging was performed using Shimadzu Eminence STARGATE scanner. After injecting 185 MBq of [18F]THK-5351 or 296 MBq of [11C]PiB, dynamic PET images were obtained for 60 min or 70 min, respectively. MR scans were performed in all subjects. T1-weighted MR images were obtained using GE SIGNA 1.5-Tesla machine. The PNEURO module in the PMOD software (version 3.7) was used to place and evaluate the volumes of interest. Regional [18F]THK-5351 standardized uptake value ratio (SUVR) value at 40-60 min post injection was calculated using pons as a reference region. *Results*: The annual change in the [18F]THK-5351 SUVR in HCs was within 2-3% in the neocortex. Preclinical AD case showed greater annual change in the [18F]THK-5351 SUVR than amyloid-negative HCs. Patients with MCI showed greater annual changes in [18F]THK-5351 retention in the parahippocampal gyrus and in the hippocampus than HCs. Patients with moderate AD showed greater SUVR changes in the frontal and parietal cortices than HCs. Higher baseline [18F]THK-5351 SUVRs in the parahippocampal gyrus and inferior temporal cortex were

associated with greater annual changes in [18F]THK-5351 retention in the patients with MCI and AD. *Conclusion*: [18F]THK-5351 PET can detect the progressive accumulation of tau deposits in AD. The spatial pattern of [18F]THK-5351 accumulation is consistent with the postmortem observation of tau pathology in the different stages of AD.

P3-40 THE USE OF CONVERSATION ANALYSIS FOR INTERACTIONAL DESIGN WITHIN A LIVING LAB FRAMEWORK. Giovanni Carletti[1], Pierre Wargnier[2], Samuel Benveniste[2], Pierre Jouvelot[2], Anne-Sophie Rigaud[3] *((1) LIAS - Institut Marcel Mauss, CNRS-EHESS, France; (2) MINES ParisTech, PSL Research University, France; (3) Broca Hospital, Assistance Publique - Hˆopitaux de Paris, France)*

Backgrounds: The use of an embodied conversational agent (ECA) for managing people health has been tested from the Expert Center for Cognitive Stimulation of Paris (CEN STIMCO). Conversation analysis (CA) is a discipline which aim is to study the use of language in interaction. This approach was used in comparison to an iterative computer science and medical approach in order to build the interactional design of an ECA. The target of the ECA was to make people living with Alzheimer's disease (AD) drink a glass of water in order to ensure their hydration. The tests were performed in a living lab framework (LLF). LLF tries to improve the ecological conditions of experiments building a familiar and scientifically equipped environment around the tester. *Methods:* Eight, ten and three sessions have been video-recorded with respectively CS, MCI and AD's individuals interacting with an ECA. A comparative conversation analysis has been performed focusing on the use of presuppositions in two task-oriented experimental conditions. In the first condition (A) the main question was: what are people living with dementia capable to understand? Drawing on experts' (MD) focus groups, a computer scientist built an automatized conversational scenario driven by an attention estimator in order to guide a person with AD through the targeted activity: drinking a glass of water. In the second condition (B), the main question was: how do mutual understanding is built in natural everyday interaction? Drawing from conversation analysis a linguistic anthropologist designed a manually triggered scenario to stimulate conversational production and drink a glass of water. Both automatized machine measures and interaction analysis have been used in order to assess ECA efficacy. *Results:* Despite an 86% of successful task completion for A, the comparative results show: 1) the impossibility of automatizing natural conversational interaction; 2) the central role of conveyed presuppositions for the creation of efficient interactional scenarios; 3) the radical difference between A and B main presuppositions: How do we get the person drink? Versus: How do mutual understanding is achieved in natural occurring situations? 4) Factors highly differentiating the three populations: question forms, silences, number of uttered words, number of new topics introduced, speed of talk. *Conclusion:* It is showed how conversation analysis overcomes protocol structure bias at an interactional level and its potential for the early detection of Alzheimer's disease.

P3-41 ELABORATION OF A TOOL AIMING TO IDENTIFY SUBJECTS AT RISKS OF FRAILTY AND TO EVALUATE THE IMPACT OF PREVENTION MEASURES. Michel Noguès[2], Valérie Bruguière[2], Justine Millot-Keurinck[2], Gabrielle Onorato[2], Sébastien Teissier[3], Jacques Touchon[1], Jean-Claude Reuzeau[2], *((1) University of Montpellier, France; (2) Caisse Assurance Retraite et Santé Au Travail (Carsat) Languedoc-Roussillon, Montpellier, France; (3) Resilient Innovation)*

Backgrounds: Frailty could be associated with higher risk of developing dementia (Bilotta C, 2010; Gray SL, 2013) and covers several fields: biophysical, psychological and cognitive, social and environmental. Studies (FINGER, MAPT) have demonstrated that multidomain interventions had a positive impact on cognition. Through a global approach, the French Retirement and Occupational Health Insurance Agency of Languedoc-Roussillon (Carsat LR) supports frailty prevention by targeting psycho-social and environmental components. Over 80% of the population of the Languedoc Roussillon has a pension from the Carsat LR, representing more than 500,000 beneficiaries. Among them, close to 1000 elderly people have been welcomed and accompanied since 2014 through the "concerted service window", an innovative device supporting prevention pathways. The "frailty risks star" research project has been implemented since 2015 through Carsat call for proposal, as a dynamic assessment tool to help demonstrating multidomain interventions impact. It has been administrated to 100 people in several exploratory studies. *Methods:* The "Frailty risks star" is a questionnaire that was built to provide a regular follow-up of people benefiting from prevention actions. It is a 4 sections- 20 question grid (somatic, cognition, psychosocial, nutrition). This grid was tested through 3 cohorts of community-dwelling elderly people between February 2015 and June 2016. The first phase, from February to July 2015, involved two groups. The first group was composed of elderly people, mean age 77, benefitting from home care services. The second group was composed of elderly people with a mean age 62, identified as being at risk of frailty through the Carsat frailty observatory. This group participated in prevention workshops held in a Carsat facility dedicated to seniors. The interventions consisted in 14 physical activity sessions and 4 nutrition sessions. For these two cohorts, 6 questionnaires were administered by professionals each month between February and July 2015. The third group (phase 2 from autumn 2015 to spring 2016) was composed of elderly people living in an assisted-living facility, mean age 76. This group was invited to participate in 22 prevention workshops held next to their residence, to see if the proximity of interventions would foster participation. This time the questionnaires were self-administered at the beginning of the interventions and every 3 months. *Results:* Between the two phases, the frailty star grid was partly rephrased based on the professionals' feedback. The results of phase 1 also allowed to review the questionnaire frequency administration, from 1 to 3 months, to better measure the impact. Despite having been encouraged to participate, people from Group 1 (the older of the 3 groups) did not participate in any prevention workshop. That could raise the hypothesis that elderly people would not easily participate to a workshop if they have to move far from their homes. From Group 2, 52% participated in physical activity workshops and 39% in nutrition workshops, while 30% participated to at least half of the total sessions (physical activity and nutrition together). From Group 3, 75% participated both in physical activity and nutrition workshops. All the participants followed at least half of the physical activity workshops, compared to 55% for nutrition. It is difficult to compare those 3 heterogeneous groups (mean age, autonomy). When self-administrated, some items of the frailty risk star are not filled out, forbidding from generating a spider. *Conclusion:* Further studies and analysis are needed to demonstrate how a simple tool could allow evaluating multidomain interventions for populations at risk of socio-environmental frailty. Even if clinical trials have proven results on high socio economic level population, the main issue is to find the right methodology to reach the more isolated, older and vulnerable ones. In order to get additional relevant information, data will be collected from memory workshops, as from September 2016. The questionnaires will be self-administered at the beginning of the interventions and every 3 months by the 18 elderly people already identified. For those suffering from anxiety, a personalized follow-up might be foreseen.