SYMPOSIA

S1 - PROSPECTIVE READINESS COHORTS, INTERNET-BASED REGISTRIES AND MATCHING SERVICES FOR ALZHEIMER'S DISEASE CLINICAL TRIALS.

MICHAEL WEINER, JESSICA LANGBAUM

The overall goal of this Symposium will be to present updated information concerning the development, use, and progress of based registries and matching services to recruit participants and direct them to participate in Alzheimer's disease clinical treatment trials. There will be four presentations from different programs.

Communications 1: ***Alzheimer's Association TrialMatch.*** Maria C. Carrillo[1], Keith Fargo[1], Beth Kallmyer[1] ((1) Alzheimer's Association National Organization, USA)

The Alzheimer's Association's TrialMatch program is an internet-based matching service that connects people with clinical studies on Alzheimer's disease and other causes of cognitive impairment. The program includes a continuously updated database of clinical trials and observational studies from across the entire spectrum of human-participant studies—including studies for people with disease, their caregivers, and healthy controls of all ages—which includes enrollment criteria and study sites. Currently, the database consists of more than 1,100 study/site combinations. TrialMatch users complete a brief profile (more than 100,000 to date) including demographics and health questions, and the responses are compared to the enrollment criteria and locations of the studies in the database to provide individualized matches, including lay language summaries and contact information for all matched studies.

Communications 2: ***Alzheimer's Prevention Registry.*** Jessica B. Langbaum[1], Nellie High[1], Paul S. Aisen[2], Marilyn S. Albert[3], Meryl Comer[4], Jeffrey L. Cummings[5], Jennifer J. Manly[6], Ronald C. Petersen[7], Reisa A. Sperling[8], Gabrielle Strobel[9], Michael W. Weiner[10], Eric M. Reiman[11], Pierre N. Tariot[1] ((1) Banner Alzheimer's Institute, Phoenix, AZ, USA; (2) Alzheimer's Disease Cooperative Study, University of California San Diego, San Diego, CA, USA; (3) Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA; (4) Geoffrey Beene Foundation Alzheimer's Initiative, Washington, DC, USA; (5) Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA; (6) Department of Neurology, Columbia University College of Physicians and Surgeons, New York, NY, USA; (7) Department of Neurology, Mayo Clinic, Rochester, MN, USA; (8) Department of Neurology, Harvard Medical School, Boston, MA, USA; (9) Alzforum, Cambridge, MA, USA; (10) Department of Radiology and Biomedical Engineering, University of California San Francisco, San Francisco, CA, USA)

The Alzheimer's Prevention Registry (www.endALZnow.org) was launched in 2012 to provide a shared recruitment resource to the scientific community in order to facilitate enrollment in Alzheimer's prevention-related studies and complement and enhance local recruitment efforts. To date, more than 113,000 people have joined, with marketing/advertising/public relations being the primary recruitment methods. Enrollees receive regular email communication to keep them apprised of the latest news in Alzheimer's prevention research, as well as email notifications when study opportunities become available in their communities. Beginning later in 2015, Registry members will be invited to submit a sample of DNA for APOE genotyping as an additional resource to help with recruitment for research studies. Also in 2015, a Researcher Portal will be launched which will allow the Registry to provide additional reporting metrics that assess its impact on accelerating enrollment into studies..

Communications 3: ***Brain Health Registry,*** Michael W. Weiner[1] ((1) University of California San Francisco (UCSF), San Francisco, CA, USA))

The goal of the internet-based Brain Health Registry (BrainHealthRegistry.org) is recruitment, assessment, and longitudinal monitoring of subjects for clinical neuroscience studies of all types, especially Alzheimer's disease studies. The Brain Health Registry is not specific for Alzheimer's disease, but aims to facilitate all types of neuroscience research. Subjects are recruited to the site by a variety of marketing/advertising/public relations methods. Subjects provide informed consent (approved by UCSF IRB). Subjects complete an extensive battery of self-report questionnaires and take on line neuropsychological tests. Subjects who meet specific criteria are informed that studies are taking place at clinics in their area, and are provided with contact information to enroll in studies. Thus far, more than 22,000 have joined and 6-month return rate is approximately 50%.

Communications 4: ***Cognitive Health in Ageing Register: Investigational, Observational and Trial studies in dementia research – Prospective Readiness cOhort (CHARIOT-PRO).*** Michael T. Ropacki[1,2], H. Michael Arrighi[1], Robert Perneczky[3], Josip Car[3], Lefkos Middleton[3] ((1) Janssen R&D, Fremont, CA, USA; (2) Loma Linda University School of Medicine, Neurology, Loma Linda, CA, USA; (3) School of Public Health, Imperial College London, London, UK))

The CHARIOT-PRO program leverages participants from the CHARIOT Registry at Imperial College London. In the first three years, the CHARIOT Registry enrolled approximately 25,000 volunteers over the age of 60 without dementia, recruited from the surgeries of General Practitioners in the London area. CHARIOT-PRO is a single center prospective readiness cohort study of approximately 700 participants self-referred or recruited from the CHARIOT Registry who will be followed for up to 4 years. The goals of CHARIOT-PRO are to better understand the natural history of cognitive and functional changes in participants at risk for mild cognitive impairment due to Alzheimer's disease, as well as to develop a well-characterized, longitudinally followed prospective readiness cohort for future early Alzheimer's disease clinical trials. Participants undergo a series of neuropsychological evaluations to characterize the patterns of cognitive change and their inter-relationship in the earliest stages of cognitive impairment. In addition, how changes relate to the clinical presentation of cognitive impairment of the Alzheimer's type will be evaluated over time. An opportunity is possible to identify and characterize individuals with different likelihoods of progressing along different clinical paths, which may form a framework for the evaluation of interventions. In the first nine months of the study, ~ 500 participants were enrolled in CHARIOT-PRO. Overall, CHARIOT-PRO is designed as the largest head-to-head study of clinical outcome assessments collecting real world information regarding prognostic factors, disease course, functional decline and disease burden on participants in the earliest stage of disease, that also is developing a well-characterized, longitudinally followed prospective readiness cohort for future early AD clinical trials. .

S2 - THE LANCET AND THE LANCET NEUROLOGY SYMPOSIUM ON CLINICAL RESEARCH IN DEMENTIA: INCREASING VALUE AND REDUCING WASTE.

LON S. SCHNEIDER *(University of Southern California, USA)*

Communications 1: ***Towards valuable research design, conduct, and analysis.*** Malcolm Macleod (Professor of Neurology and Translational Neuroscience, University of Edinburgh, UK); *Communications 2:* ***Tackling waste in the regulation and management of clinical trials.*** Rustam Al-Shahi Salman (Professor of Clinical Neurology, University of Edinburgh, UK); *Communications 3:* ***Aims and priorities of the IMI2 Alzheimer's Disease Research Platform.*** Elisabetta Vaudano (Principal Scientific Manager & Coordinator, Innovative Medicines Initiative, Brussels, Belgium)

• ***Panel Discussion***: Lon S. Schneider. *Panelists:* Malcolm Macleod[1], Rustam Al-Shahi Salman[1], Elisabetta Vaudano[1], Rachel J. Schindler[2], Jose Luis Molinuevo[3], Sabine Kleinert[4], Elena Becker-Barroso[2]. ((1) TBC, Innovative Medicines Initiative; (2) Vice-President, Neuroscience Area, Pfizer, New York, NY, USA; (3) Hospital Clinic, Barcelona, Spain; (4) Executive Editor, The Lancet, London, UK; (5) Editor, The Lancet Neurology, London, UK))

Prevention and treatment of age-related cognitive impairment disorders are core challenges for society and governments. Their high prevalence and huge associated burden are driving an unprecedented interest in the biomedical research that could tackle these disorders. However, scientific advances are not keeping pace with the mounting needs driven by the ageing of populations; moreover, about 85% of all biomedical research investment might be wasted (1). As the world economy faces years of low growth, (2) avoiding waste and inefficiency in neurological research becomes imperative. Rooted in the conclusions of a recent Series in The Lancet, (3) our symposium will consider specific ways to increase value and reduce waste when setting research priorities; (4) when designing and conducting clinical trials, and analysing results; (5) and in research regulation and management (6). We will also discuss the factors and incentives that shape the cultural context underpinning neurological research. Prof Malcolm Macleod will describe common pitfalls in study design and evaluation of evidence which is used to make the case for implementing clinical trials; he will reflect on how these issues contribute to a low translational yield and poor reproducibility and reliability of neurological studies, and propose options for improvement. He will also present ongoing institutional initiatives that are trying to limit methodological and analytical weaknesses. Prof Rustam Al-Shahi Salman will consider the unintended inefficiencies associated with the way in which pre-clinical and clinical research is regulated and managed (such as research waste in clinical trials due to slow recruitment or low retention of patients). He will propose recommendations to improve efficiency and monitor progress, and will discuss potential solutions, including the setting of incentives to reward high-quality research. Dr Elisabetta Vaudano (TBC) will bring in the perspective of the funders of dementia research. The Innovative Medicines Initiative (IMI) is the largest public-private partnership between the European Union and pharmaceutical industry, with a total budget of more than $5 billion (7). Dr Vaduano will explain how IMI2 (the second phase of this partnership, launched in 2014) differs from any other initiative in dementia research, and discuss how research sponsors can act to avoid waste and endorse best research practices. After these three presentations and comments from the other members of the panel, the speakers will answer questions from the audience and will engage with the attendees of the symposium in a discussion of the lessons learnt from previous failures and any contentious issues.)1. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. Lancet 2009; 374: 86-89. 2. International Monetary Fund World Economic Outlook, April 2015. Where are we headed? Perspectives on potential output. www.imf.org/external/pubs/ft/weo/2015/01/pdf/c3.pdf (accessed April 15, 2015); 3. Macleod MR, Michie S, Roberts I, et al. Biomedical research: increasing value, reducing waste. Lancet 2014; 383: 101-4. 4. Chalmers I, Bracken MB, Djulbegovic B, et al. How to increase value and reduce waste when research priorities are set. Lancet 2014; 383: 156-65; 5. Ioannidis JPA, Greenland S, Hlatky MA, et al. Increasing value and reducing waste in research design, conduct, and analysis. Lancet 2014; 383: 166-75. 6. Salman RA, Beller E, Kapgan J, et al. Increasing value and reducing waste in biomedical research regulation and management. Lancet 2014; 383: 176-85. 7. Vaudano E, Vannieuwenhuyse B, Van der Geyten S, et al. Boosting translational research on Alzheimer's disease in Europe: The Innovative Medicine Initiative AD research platform. Alzheimer's & Dementia 2015, DOI: http://dx.doi.org/10.1016/j.jalz.2015.02.002

S3 - UTILITY OF MULTI-MODAL BIOMARKER-ENDPOINT TRIALS IN HIGH-RISK PERSONS TO IDENTIFY CANDIDATE AGENTS FOR AD PREVENTION TRIALS.

MARILYN ALBERT *(PhD. Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA)*

Communications 1: ***Study design and cross-sectional analyses of multiple biomarkers in aging persons at high risk of symptomatic AD.*** John C. S. Breitner[1], Judes Poirier[1,2], Pierre E. Etienne[1,2], Pedro Rosa-Neto[1,2,3], Jennifer Tremblay-Mercier[1] ((1) Douglas Hospital Research Centre; (2) McGill University Faculty of Medicine; (3) McGill Centre for Studies on Aging, Montreal, QC, Canada); *Communications 2:* ***Study design and cross-sectional analyses of multiple biomarkers Genetic, CSF and longitudinal results from PREVENT-AD suggest measurable pre-clinical AD progression susceptible to attenuation.*** Judes Poirier[1], John C. S. Breitner[1,2], Pierre E. Etienne[1,2], Pedro Rosa-Neto[1,2,3], Jennifer Tremblay-Mercier[1] ((1) Douglas Hospital Research Centre; (2) McGill University Faculty of Medicine; (3) McGill Centre for Studies on Aging, Montreal, QC, Canada); *Communications 3:* ***Item Response Theory latent variable models may summarize multi-modal biomarker results to measure progress of pre-clinical AD.*** Jeannie-Marie S. Leoutsakos[1], Alden L. Gross[2], Marilyn Albert[3], John C. S. Breitner[1,4,5] ((1) Department of Psychiatry, The Johns Hopkins University School of Medicine, Baltimore, MD, USA; (2) Department of Neurology, Johns Hopkins University School of Medicine; (3) Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; (4) Douglas Hospital Research Centre; (5) McGill University Faculty of Medicine, Montreal, QC, Canada)

Introduction: "Alzheimer's disease" (AD) usually denotes a symptomatic condition. Symptomatic AD is often associated with biochemical or imaging biomarkers. But earlier stages of AD can also be revealed by similar biomarkers, typically in less advanced form. In theory, the trajectories of those markers should track the progression of pre-clinical disease. Preventive treatments that delay the onset of symptoms should slow them. This symposium explores whether attenuation in pre-clinical biomarker trajectories can be used to identify promising candidate AD prevention strategies. This approach is likely best suited to the development of pharmacological preventives (lifestyle interventions, although probably safer, will likely be more difficult to implement outside clinical trial settings.) By analogy one may think of the development of statins for prevention of atherosclerotic cardiovascular disease (ASCVD). These drugs were shown to reduce total and LDL cholesterol and C-reactive protein (example biomarkers) long before they were proven to reduce incidence and mortality of ASCVD. But this sort of drug development for AD prevention is presently impeded by a lack of ways to generate

preliminary data in humans to support a choice among candidate treatments. Instead, we have necessarily relied on animal or cell culture data. Development of a practical method to test an agent's potential for AD prevention in humans would represent a substantial advance in AD prevention science. *Objectives:* We discuss biomarker-endpoint trials of candidate preventive treatments for AD as a method for testing their probable efficacy. Broadly, this approach confronts several questions: • Do the pre-symptomatic biomarkers under study truly predict subsequent disease development (validity)? • Do the markers change fast enough to permit assessment of treatments' ability to modify their longitudinal trajectory? And if so, • Can we measure such change with sufficient precision to detect treatment effects within a reasonable time, say two or three years, using economically defensible sample sizes? • Various biomarkers will probably progress at different stages of the pre-symptomatic AD process; therefore, • Which marker(s) we should measure, and when, to track the progression of pre-symptomatic disease? • If (as seems likely) several markers are suitable for this work, should we not be measuring many of them (not just one) to gain more information about the progression of the pre-symptomatic disease state? But then, • What statistical or analytic methods can we use to deal with the multiplicity of data under study? *Discussion:* The first question (validity) was a central topic of Dr. Marilyn Albert's keynote address at this meeting. Here we address many of the remaining questions by describing and discussing studies of cross-sectional and longitudinal biomarker trajectories in a new cohort for AD PREVention using Experimental or Novel Treatments for AD (PREVENT-AD). Dr. Breitner's talk will address the rationale and design for these studies. The PREVENT-AD cohort includes 270 cognitively "normal" people with a first-degree (>90% parental) family history of AD dementia. On average, these subjects are 9.8 years younger than their parent's age at onset. About 2/3 of them agree to a two-year series of four lumbar punctures for the study of CSF biomarkers. Cognitive abilities are tested using the Repeatable Battery for Assessment of Neuropsychological Status (RBANS), omitting adjustment for age. CSF biomarkers include Aβ42, total-tau (t-tau), 131P-tau, the t-tau/Aβ42 ratio (Innotest technology), while Luminex-based immunoassays (Millipore) are used for apolipoprotein A1, A2, B, C2, C3, and E and for multiple relevant cytokines and chemokines. Genotypes at APOE and other risk-associated polymorphisms are determined using standardized pyrosequencing techniques. Structural MRI metrics include cortical thickness and ventricular and hippocampal volumes, while diffusion imaging yields measures of fractional anisotropy and mean diffusivity of grey and white matter. We use f-MRI to estimate resting state connectivity and task measures, and arterial spin labeling (ASL) to estimate blood flow. Finally, we assess sensori-neural faculties of olfactory identification (University of Pennsylvania Smell Identification Test, or UPSIT) and central auditory processing (two tests of sentence identification in a distractive environment). We describe results from these measures at baseline and their relation to age (a surrogate for the passage of time in vulnerable individuals). The latter shows independent correlation with no fewer than ten of the above metrics. Among 107 subjects who have data on all markers, at least 9 of the measures showed independent inter-correlation ($p<0.05$) in fully saturated models. A subgroup of 150 PREVENT-AD participants have been enrolled in a double-masked randomized placebo-controlled trial of naproxen sodium 220 mg b.i.d. – an intervention that yielded promising biomarker signals and a potentially delayed suppression of cognitive decline in the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT). The PREVENT-AD protocol also prescribes yearly follow-up studies, as well as an interim follow-up assessment at 3 months following initiation of treatment in the naproxen trial. Dr. Poirier will describe the relationship of several of the above markers to APOE status as well as several other genetic polymorphisms including the newly described protective (G-negative) genotype at the HMGCR re3866662 locus.) He will also present longitudinal change in a number of CSF markers, including those from treatment group-pooled results from naproxen trial participants. Other analyses show a relation of longitudinal change in structural and functioning imaging markers and alteration in P-tau at 12 months vs baseline. Two-year time course analyses of tau, P-tau, and Aβ42 indicate strong APOEε4 genotype-driven differences at baseline, and also a clear exacerbation of pathological changes between 12 and 24 months. (The APOE-related elevation in the t-tau/Aβ42 ratio is unapparent, however, in subjects with the G-negative genotype at the HMGCR locus). Surprisingly, the direct correlation of CSF apoE protein level with age is driven exclusively by results from APOEε4-negative subjects ($p<0.002$). Levels of CSF ApoB (derived exclusively from blood) are significantly increased in APOEε4 carriers (vs. non-carriers) at all timepoints ($p<0.01$), suggesting that the APOEε4 allele has important bearing on age-related degradation of the blood brain barrier. fMRI resting state activity connecting precuneus to anterior cingulate cortex correlates inversely with CSF P-tau change between baseline and 12 months. Longitudinal analyses of global cognition (RBANS total score) in 100 persons not participating in the naproxen trial show clear evidence of decline over 24 months (average decline 2.5%/yr; $p<0.001$). The extensive cross-sectional and longitudinal correlation among numerous biomarkers from several modalities suggest that most or all of the markers may be "driven by" a common antecedent. Dr. Leoutsakos will suggest that one can model such an antecedent using latent variable techniques. She will describe how such techniques that may yield a summary indicator of pre-symptomatic AD progression from multiple biomarkers such as those described above. Models that rely on multi-modal data should be advantageous for work on prevention of symptomatic AD, because different markers may reflect different stages of AD progression and because they can provide richer information about disease progression than any single marker. Although this sort of summary indicator would be inappropriate today for use as a primary outcome in Phase III prevention trials, we wish to test its utility (constructed using data from non-trial participants) as a possible secondary outcome for the naproxen trial. We first constructed a summary Alzheimer Progression Score (APS) using data from BIOCARD as described earlier by Dr. Albert. We fit a latent trait Item Response Theory model to CSF, structural MRI, and psychometric test data collected three times over the first five years of BIOCARD. We then estimated every BIOCARD participant's APS at each of the three initial visits. As an indicator of the utility of the APS, we then compared participants' trajectories over the five-year interval, contrasting subjects who remained cognitively normal over the entire follow-up period of BIOCARD (up to 18 years) vs. those who "converted" in that time from normal to Mild Cognitive Impairment (MCI) or dementia. We also calculated sample sizes needed to detect a 50% reduction in the rate of decline in a putative placebo-controlled prevention trial that relied on the various BIOCARD markers. To replicate our findings, we fit similar models to ADNI data. Our simulations also compared composite APS scores constructed via Item Response Theory vs. those constructed using means of the component z-scores. Compared to APS scores for BIOCARD participants who remained cognitively normal, those for participants who converted to MCI or dementia differed significantly in both their intercepts and slopes. For non-converters the APS intercept was 0.07 (s.e. 0.05), whereas those for MCI and dementia converters were 0.55 (s.e. 0.09; $p<0.001$) and 0.80 (0.14; $p<0.001$). Slopes were 0.01 (s.e. 0.01) APS points/yr. for non-converters but 0.04 (s.e. 0.02; $p=0.031$) and 0.08 (0.02; $p<0.001$) for MCI and dementia converters. Sample size requirements were > 50% lower for APS vs. any single marker. A further advantage for the APS over the z-score composite was apparent in models that included non-normally distributed markers. We conclude that combining

multimodal biomarkers into an APS offers advantages of reliance on many markers while avoiding multiple comparisons. The method may have additional strengths when applied to more elaborate datasets such as that in our ongoing PREVENT-AD trial of naproxen. *Conclusion:* Multi-modal biomarker endpoint studies, possibly analyzed using latent variable models, may significantly advance prospects for AD chemo-prevention trials.

S4 - OBSERVATIONAL COHORTS AND GLOBAL INITIATIVES FOR THE PREVENTION OF ALZHEIMER'S DISEASE. JOSÉ L MOLINUEVO[1,2] *((1) Barcelona Beta Research Centre, Pasqual Maragall Foundation, Barcelona, Spain; (2) Alzheimer´s disease and other cognitive disorders unit, IDIBAPS, Hospital Clinic i Universitari, Barcelona, Spain)*

Introduction: An increasing amount of scientific data on the pathogenic events and time-course of Alzheimer's disease (AD) suggest that several years before clinical symptoms appear neuropathological changes are already present. These brain biological changes can now be determined and assessed longitudinally by CSF and neuroimaging markers. The need to study these early events in the time course of the disease has driven the genesis of observational cohorts of healthy middle age subjects potentially at risk. On the other hand, the implementation of biomarkers for identifying AD pathology has created an opportunity to intervene pharmacologically at earlier stages. As a response global worldwide initiatives have emerged to intervene in the preclinical and predementia stages, also aiming to solve several important issues, like the fact that these trials are conducted in cognitively normal people, who are not typically in contact with clinical services for memory problems, and maximize efficiency to obtain a clinical signal and develop sensitive outcomes for tracking early decline through new trial designs. *Objective:* to present the design and emerging data of newly design cohorts aiming to understand the initial physiopathology of AD and of worldwide initiatives intervening to prevent AD. *Discussion:* Regarding observational cohorts, in Barcelona, the ALFA (alzheimer & families) cohort is a long term, longitudinal, prospective, observational study of AD patients' adult children. It is aiming to define the early physiopathological events of AD, to understand the factors that modify its risk and to characterize the markers that predict its progression. The study population, consisting in 2750 middle aged (from 45-74) subjects, is enriched with subjects with increased risk due to their family history. The study started with a screening phase aimed to recruit volunteers complying as much as possible with study selection criteria and perfectly aware of the study needs. The ALFA + study, leveraging from the ALFA parent cohort, will consist of repeated 3-year visits in which the participant will undergo a number of sessions comprising clinical history, cognitive tests, neuroimaging (MRI, AβPET), and samples collection (blood, urine, CSF). In this symposium, we will present cross sectional results from the ALFA parent cohort comprising 2750 subjects. Structural brain characteristics will be presented as a function of the APOE genotype in this large cohort of subjects at risk. In the UK and France, the PREVENT Research Programme has established a cohort of individuals to explore differences in the brain and cognitive function in mid-life (aged 40-59). We will group people into high, mid and low risk based on their family history and APOE status. One of the main aims of the study is to identify the earliest signs of changes in the brain whilst people are still in good health. We will look at biological indicators including markers in blood, saliva, urine and spinal fluid as well as direct imaging of the brain's structure and function. We will then look at how changes in all of these markers develop over (initially) 2 years and develop improved models for probability of decline in a pre-clinical population. Baseline data from the PREVENT Pilot Phase will be presented. Regarding interventional studies, the European Prevention of Alzheimer's Dementia project (EPAD) is a response to the Innovative Medicines Initiative (IMI)-EPOC-AD funding call, with a total of 35 partners from across the private and academic sectors, aiming to deliver a perpetual adaptive trial for the secondary prevention of AD. The US Prevention of Alzheimer's Disease (US-PAD) also share the objective of the secondary prevention of AD dementia and in Canada, the newly formed national Canadian Consortium for Neurodegeneration and Aging (CCNA) network will be supporting studies and prevention trials and there is an initiative to obtain funding for the Canadian Pipeline for AD Therapeutics (CPAD). The aims of EPAD Project are to develop the necessary infrastructure to deliver a standing, adaptive, multi-arm Proof of Concept (POC) study for early and accurate decisions on a candidate compound's (or combination of compounds') ongoing development. This infrastructure has three principal elements: [1] identification of subjects from existing cohorts and registers and recruitment into the EPAD Cohort and then EPAD trial, [2] the development of the necessary data management infrastructure to support disease modeling and adaptive trial decisions and [3] the establishment of a network of EPAD Trial Delivery Centres (TDC's) within collaborating countries. EPAD will establish a virtual register of 24,000 people from across Europe already consented into a cohort or register study. From this, 6,000 people will be asked to join the EPAD Cohort study from which approximately 1,500 subjects will enter the standing, adaptive, proof of concept trial. This approach will ensure we have access to an at-risk population expressing biomarker evidence of disease prior to the development of dementia. All data collected from the cohort and trial will be made available for analysis to improve disease models in the pre-dementia phase of AD leading to more accurate stratification for trial selection, improved measurements of outcomes and a greater understanding of AD processes before dementia develops. The US-PAD efforts are moving forward with several secondary prevention trials actively enrolling and planning to build a large trial ready cohort. The A4 Study, launched in mid 2014 at 60 centers in US, Canada, and Australia, is enrolling 1100 clinically normal older (ages 65-85) individuals with evidence of amyloid accumulation on screening PET amyloid imaging for a 3.25 year Phase 3 registration trial of a monoclonal antibody vs. placebo. The A4 primary outcome is slowing of cognitive decline on a sensitive composite, and also includes multiple biomarkers, including Tau PET imaging in 500 participants. The "A5" trial, which will start in late 2015, will enroll a slightly broader age population to test a beta-secretase inhibitor mechanism to slow AD progression and prevent cognitive decline. The DIAN-TU and API studies are well underway in genetic at-risk populations. The Global Alzheimer Platform (GAP) initiative is working to align with IMI-EPAD, and is planning to build a large Trial Ready Cohort for Prevention of AD (TRC PAD). Planning is also underway for combination trials (COMBAT) to target the multiple pathophysiological processes of AD in prevention trials. The CCNA is creating a national network and research infrastructure for clinical studies including the development of a national cohort across a range of diagnoses of cognitive disorders. One of the CCNA themes is prevention of AD, with the intention of sponsoring prevention clinical trials as the network matures potential treatment approaches. It has the potential to develop to national registry of trial ready individuals. The existing C5R clinical trials network serves as the backbone of sites for the CCNA studies as well as having active sites participating in the DIAN, and A4 studies. CPAD is a current initiative in the planning stages. Its aims include achieving an innovative therapeutic pipeline, of multisourced compounds which can advance to phase 1 and phase 2 POC prevention trials. It will be developed to be interoperable with other international collaborative networks including EPAD, and US-PAD, contributing to the large globally integrated effort. *Conclusion:* emerging cohorts are starting to study the earliest stages of preclinical AD, which will be useful to understand early

pathophysiological changes together with modelling the preclinical stages in order to develop successful trials. Regarding interventional projects, EPAD is a major European proposal aligned to the GAP initiative, including the future USPAD and CPAD. These projects will create a novel environment for testing numerous interventions for the secondary prevention of Alzheimer's dementia, which will increase the likelihood of success through more efficient development, greater number and more diverse compounds being tested, and more rapid back and forward translation of knowledge from lab to clinic.

Communications 1: ***The ALFA and ALFA+ study: cohorts based studies aiming to identify the beginning of AD.*** José L Molinuevo[1,2], Juando Gispert[1], Karine Fauria[1], Nina Gramunt[1] ((1) BarcelonaBeta Brain Research Centre, Pasqual Maragall Foundation, Barcelona, Spain; (2) Alzheimer´s disease and other cognitive disorders unit, IDIBAPS, Hospital Clinic i Universitari, Barcelona); *Communications 2:* ***Moving from PREVENTion cohorts to interventional studies like the European Prevention of Alzheimer's dementia project (EPAD).*** Craig Ritchie[1], Karen Ritchie[2], Katie L Wells[3,4], Isabelle Carriere[5] ((1) Professor of the Psychiatry of Ageing, Centre for Clinical Brain Sciences, University of Edinburgh; (2) Research Director, INSERM Neuropsychiatry (U1061) Montpellier, France; (3) The Centre for Mental Health, Imperial College London, London, UK; (4) West London Cognitive disorders Treatment and Research unit, West London Mental Health NHS Trust, London, UK; 5. Senior Research Assistant, INSERM Neuropsychiatry (U1061) Montpellier, France); *Communications 3:* ***US initiatives for prevention of Alzheimer's disease.*** Reisa Sperling on behalf of the USPAD (Professor of Neurology, Harvard Medical School, Director, Center for Alzheimer Research and Treatment, Brigham and Women's Hospital and Massachusetts General Hospital, Memory Disorders Unit, Boston, MA); *Communications 4:* ***Canadian initiatives to prevent AD.*** Howard Feldman, Howard Chertkow, ((1) Professor of Neurology, University of British Columbia, Director UBC Hospital Clinic for Alzheimer's disease and Related Disorders, Vancouver, British Columbia, Canada; (2) Professor of Neurology, McGill University, Scientific Director, Canadian Consortium of Neurodegeneration and Aging, Jewish General Hospital, Montreal, Quebec, Canada)

S5 - TAU SPREAD, PET TRACERS AND IMMUNOTHERAPY. KHALID IQBAL *(New York State Institute for Basic Research in Developmental Disabilities, Staten Island, New York, USA)*

Communications 1: ***Molecular Mechanism of Tau Spread and Target Regions for Immunotherapy.*** Khalid Iqbalr, Chunling Dai,. Wen Hu, Fei Liu (New York State Institute for Basic Research in Developmental Disabilities, Staten Island, New York, USA)

Background: Neurofibrillary pathology of abnormally hyperphosphorylated tau is a hallmark of Alzheimer disease (AD) and related tauopathies. The density of tau lesions, which are seen as intraneuronal neurofibrillary tangles, neuropil threads and dystrophic neurites surrounding Aβ cores in plaques, correlate with the degree of dementia in AD patients. *Methods:* Non-filamentous aggregates of hyperphosphorylated tau (AD P-tau) were biochemically isolated from AD brains. For in vitro studies the interaction of AD P-tau with normal tau was studied both by overlay and by in vitro microtubule assembly assays. AD P-tau was injected in the hippocampi of human genomic tau mice and the spread of tau pathology was studied 6, 9 and 11 months post injection by immunohistochemical stainings. The clearance of tau with mouse monoclonal antibodies to tau was studied in 3xTg-AD triple transgenic mice. *Results:* AD P-tau interacted with normal tau instead of tubulin, disrupting microtubules. The interaction of AD P-tau with normal tau resulted in the formation of tau filaments. In vivo injection of AD P-tau produced spread of tau pathology both by proximity and by axonal transport of tau seeds from one to another region of the brain. Antibodies 43D to Tau6-18 and 77E9 to tau184-195 both reduced the levels of total and hyperphosphorylated taus and the former also rescued cognitive impairment in 3xTg-AD mice. *Conclusions:* These studies revealed (1) that tau pathology spreads by sequestration and templating of normal tau by AD P-tau; (2) that passive tau immunotherapy can reduce tau pathology and rescue cognitive impairment; and (3) that targeting the amino-terminal region of tau is potentially especially promising for the treatment of AD and related tauopathies. (Supported by the New York State Office for People with Developmental Disabilities.)

Communications 2: ***Characterization and Development of Novel Tau PET Tracers for the assessment of Tau spreading in Alzheimer's disease.*** Andreas Muhs[1], M. Berndt[2], H. Kroth[1], A. Mueller[2], F. Capotosti[1], Felix Oden[2], Y. Varisco[1], S. Nampally[1], Hanno Schieferstein[2], J. Molette[1], E. Gabellieri[1], W. Froestl[1], D. T. Hickman[1], A. Catafau[2], A. Pfeifer[1], A. Stephens[2] ((1) AC Immune, Lausanne, Switzerland; (2) Piramal Imaging, Berlin Germany))

Objective: Tau aggregates represent a critical pathology in Alzheimer's disease (AD) and other neurodegenerative diseases. Indeed, the Braak staging of AD shows a strong association between the spreading of Tau neurofibrillary tangles across specific brain regions, and the observed level of dementia. Positron emission tomography (PET) can be an important tool for the detection of Tau aggregates in the brain. Thus, a Tau PET imaging program was initiated. *Results:* To enable assessment of Tau pathology spreading in AD patients a fluorine-18 labeled Tau PET tracer (PI-2014) was identified as a first candidate within the ongoing program. (18F)-PI-2014 demonstrated specific binding to Tau aggregates on human AD brain sections from Braak I-VI donors and to different Tauopathies. PI-2014 further demonstrated binding to both 3R- and 4R-isoforms of Tau. In addition, PI-2014 did not show off-target binding to beta-amyloid, α-synuclein or TDP-43. The combination of high brain uptake of PI-2014 in mice, rat and non-human primates without de-fluorination and high affinity provided a unique preclinical profile. In addition, an automated radio-synthesis was established and validated. PI-2014 completed IND-enabling toxicity studies and has entered a first-in-man (FiM) study. *Conclusions:* To potentially detect spreading of Tau pathology in AD patients and to enable early diagnosis and clinical management of AD and other Tauopathies, a PET imaging program is currently under development. The first identified candidate, (18F)-PI-2014, demonstrated unique binding specificity to human pathological Tau aggregates and is currently in FiM studies.

Communications 3: ***Two sides of one coin – efficacy and safety in pre-clinical studies on tau immunotherapeutics.*** Michal Novakns (Axon Neuroscience, Bratislava, Slovak Republic)

Neurofibrillary pathology determines the onset and progression of Alzheimer's disease. It is able to spread throughout the brain in a stereotypic, sequential and hierarchical manner. The main constituent of the neurofibrillary tangles is protein tau, which represents one of the most attractive targets for disease modifying treatment of Alzheimer's disease. Several independent studies have demonstrated that pathologic.

ORAL COMMUNICATIONS

OC1: MAGNITUDE OF DELAY IN AB-RELATED MEMORY DECLINE IN APOE E4 NON-CARRIERS: IMPLICATIONS FOR CLINICAL TRIALS IN PRECLINICAL ALZHEIMER'S DISEASE.

PAUL MARUFF[1,2], YEN YING LIM[1], SIMON M. LAWS[3], VICTOR L. VILLEMAGNE[1], DAVID AMES[1], CHRISTOPHER FOWLER[1], CHRISTOPHER C ROWE[1], COLIN L MASTERS[1] *((1) The University of Melbourne, Parkville, Victoria, Australia; (2) CogState Ltd., Melbourne, Victoria, Australia; (3) Centre of Excellence for Alzheimer's Disease Research and Care, Edith Cowan University, Perth, Western Australia, Australia)*

Background: In cognitively normal (CN) older adults, abnormal levels of amyloid (Aβ+) and apolipoprotein E (APOE) ε4 carriage are each associated with increased risk for cognitive decline and Alzheimer's disease (AD). However, the extent to which Aβ+ and ε4 carriage contributes independently or synergistically to cognitive decline in preclinical AD is unclear. Biological studies in humans and transgenic mice show that ε4 can act directly and indirectly to influence AD pathogenesis. Clinical studies of CN older adults followed prospectively up to 54-months show the risk for AD posed by Aβ and ε4 to be related. For example, compared to Aβ- CN ε4 non-carriers, Aβ+ CN ε4 carriers have been found to have substantial cognitive decline, particularly in episodic memory. However, these studies have not observed cognitive decline in Aβ+ CN ε4 non-carriers, suggesting that by themselves, neither Aβ+ or ε4 carriage are sufficient for cognitive decline to occur in preclinical AD. The aim of the current study was to characterize the rate of Aβ-related cognitive decline over a 72-month period in CN older adults and in older adults with MCI who were ε4 carriers and non-carriers. We hypothesized that compared to Aβ- CN ε4 non-carriers and Aβ+ CN ε4 non-carriers, Aβ+ CN ε4 carriers would show greater cognitive decline and higher rates of progression to MCI over 72-months. We further expected that compared to Aβ+ MCI ε4 non-carriers, Aβ+ MCI ε4 carriers would show greater cognitive decline over 72-months. *Methods:* CN older adults (n=423) underwent Aβ imaging with PET, and APOE genotyping. Participants completed comprehensive neuropsychological assessments at baseline, and at 18-, 36-, 54- and 72-months follow-up visits. Rates of change in cognitive domains were compared between groups using linear mixed model. A criterion for clinically meaningful memory impairment was defined as performance 1.5 standard deviation units below the mean of the amyloid negative CN older adults. *Results:* Relative to Aβ- CN ε4 non-carriers, both Aβ+ CN ε4 carriers and non-carriers showed significantly faster decline in memory, executive function and language. However, the rate of decline in memory was significantly more pronounced in Aβ+ CN ε4 carriers than in Aβ+ CN ε4 non-carriers. The rate of memory decline in Aβ+ CN ε4 carriers indicated that a criterion for clinically-significant impairment would be met in 10 years, as opposed to 27 years in Aβ+ CN ε4 non-carriers. *Conclusions:* In CN older adults, Aβ+ is associated with memory decline in ε4 non-carriers; however, the rate of this decline is much slower than that observed in ε4 carriers. Aβ-related memory decline is unaffected by ε4 carriage in MCI groups. These results suggest that the effect of Aβ and ε4 on memory decline in preclinical AD may be ideal targets for therapies that moderate neurodegeneration arising from the interaction between Aβ+ and ε4. They also suggest strongly that clinical trials in preclinical AD should stratify samples according to APOE ε4 carriage.

OC2: THE ACTIVE VACCINE AADVAC1 AGAINST PATHOLOGICAL TAU DISPLAYS AN EXCELLENT SAFETY AND IMMUNOGENICTY PROFILE IN THE PHASE 1 STUDY.

PETR NOVAK[1], MATEJ ONDRUS[1], REINHOLD SCHMIDT[2], STANISLAV KATINA[1], EVA KONTSEKOVA[1], MICHAL NOVAK[1] *((1) AXON Neuroscience SE, Bratislava, Slovakia; (2) Department of Neurology, Medical University of Graz, Austria)*

Backgrounds: Currently, no causal treatment that would influence the progression of Alzheimer's disease is available. Based on extensive preclinical research, we have developed an active vaccine against neurofibrillary tau pathology, AADvac1. The vaccine induces antibodies against a pathological conformation that is in the microtubule binding domain of diseased tau protein. AADvac1 was shown to be efficacious in transgenic models, reducing both neurofibrillary pathology and insoluble hyperphosphorylated tau, and improving the neurobehavioral status and survival of the animals. It was shown to be safe in GLP toxicology studies. AADvac1 has been assessed for safety and tolerability in the first-in-man study Axon CO18700, completed in March 2015. *Methods:* The study consisted of a 3-month double-blind period, followed by a 3-month open label period, and enrolled patients with mild-to-moderate Alzheimer's disease (MMSE 15-26) diagnosed according to the NINCDS/ADRDA criteria. In the double-blind period, the subjects were randomly assigned to one of the two treatment groups, either AADvac1 (n=24) or placebo (n=6). Placebo subjects crossed over to AADvac1 treatment in the open label period. The vaccine was injected subcutaneously once per month, for a total of 6 administrations. The primary objective of the study was to assess safety and tolerability of AADvac1. These 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:* 30 subjects were included into the study, 28 of them completed the planned 6-month investigation period. No safety signals have arisen from this study, including assessments of adverse events, laboratory tests, ECG and MRI results. All patients developed an immune response to AADvac1. Results of cognitive tests showed a large variance and therefore given the limited size of the study sample and duration of observation, a statistical assessment of efficacy would not be meaningful. However, no worsening in cognition was observed over the course of the study, supporting the positive safety assessment. *Conclusion:* Based on the results of preclinical studies and the first-in-man clinical study assessing toxicity, safety and tolerability of AADvac1, there are no safety or tolerability concerns. Combined with the encouraging immunogenicity results, the active vaccine candidate AADvac1 is suitable to enter phase II clinical development. The upcoming studies will be designed aiming to address safety and tolerability objectives, as well as secondary and exploratory efficacy and immunogenicity objectives.

OC3: A PHASE II TRIAL OF AAV2-NGF IN MILD TO MODERATE ALZHEIMER'S DISEASE.

MICHAEL S RAFII[1,2], RONALD G THOMAS[1,2], SARAH WALTER[1,2], MARK TUSZYNSKI[2], PS AISEN[3] FOR THE ADCS *((1) Alzheimer's Disease Cooperative Study (ADCS); (2) Department of Neuroscience, University of California, San Diego; (3) Alzheimer's Therapeutic Research Institute (ATRI) University of Southern California (USC) at San Diego)*

Background: Nerve growth factor (NGF) is an endogenous neurotrophic-factor that prevents the death and augments the functional state of cholinergic neurons of the basal forebrain, a cell population that undergoes extensive degeneration in Alzheimer disease (AD). *Methods:* Forty-nine patients with mild to moderate AD were enrolled in a 24-month, prospective, randomized, double-blind, sham-surgery controlled, multi-center Phase II clinical trial of the genetically

engineered gene-therapy vector adeno-associated virus serotype 2 delivering NGF (AAV2-NGF [CERE-110]). Subjects were randomly assigned to receive six stereotactically-guided intracerebral injections of AAV2-NGF into the Nucleus Basalis of Mynert (NBM) of each hemisphere, or a sham-surgery control procedure (bilateral scalp incision and partial burr holes). The primary analysis assessed the cognitive effects of AAV2-NGF on change in Alzheimer's Disease Assessment Scale-cognitive subscale [ADAS-Cog11] at month 24 as compared to placebo (sham-surgery). Secondary analyses assessed the effect of AAV2-NGF on other outcomes including Mini-Mental State Examination (MMSE), Alzheimer's Disease Cooperative Study Activities of Daily Living scale (ADCS-ADL), Neuropsychiatric Inventory (NPI), volumetric MRI and regional cerebral glucose metabolism on FDG PET. *Results:* Forty-three of forty-nine subjects completed the study (placebo: 23 vs AAV2-NGF: 26). AAV2-NGF did not influence change in ADAS-Cog11 at 24 months (placebo: 9.42+/- 10.14 vs AAV2-NGF 14.91 +/- 10.63, p=0.18). In secondary analyses, AAV2-NGF showed a no difference as compared to sham surgery on change in MMSE (placebo: -4.17+/- 1.36 vs AAV2-NGF: -6.18 +/- 1.11, p=0.42); on ADCS-ADL (placebo: 53.05 +/- 24.03 vs AAV2-NGF: 48.48 +/- 19.23, p=0.11); on CDRSB (placebo: 7.42 +/- 4.24 vs AAV2-NGF: 9.19 +/- 4.16, p=0.16); on CGIC (placebo: 5.33 +/- 0.14 vs AAV2-NGF: 5.59 +/- 0.17, p=0.66) or on NPI (placebo: 17.56 +/- 21.51 vs AAV2-NGF: 14.28 +/- 12.67, p=0.61). At 24 months, AAV2-NGF also did not impact change in hippocampal volume (-0.43+/- 0.07 vs -0.41 +/- 0.08, p=0.31); change in ventricular volume (placebo: 44.84 +/- 9.94 vs 52.16 +/- 5.01, p=0.73) or change in regional cerebral glucose metabolism within cingulate gyrus (placebo: -0.142 +/- 0.02 vs AAV2-NGF -0.15 +/- 0.020.58). No differences were noted in rates of serious adverse events (placebo: 30.43% vs AAV2-NGF 30.77%). There were six deaths, (placebo: 4 vs AAV2-NGF: 2). None were related to study procedures. *Conclusion:* AAV2-NGF delivery to bilateral NBM did not impact clinical or cognitive outcomes in mild to moderate AD. This multicenter study does demonstrate the feasibility of sham-surgery controlled stereotactic gene delivery studies in AD. It remains to be determined, through future pathological examination of brains, whether AAV2-NGF was accurately targeted to the Nucleus Basalis of Meynert and whether NGF spread sufficiently from sites of administration to influence its cholinergic cellular targets. If the target cells were engaged accurately, then the possibility of benefit with earlier intervention could be investigated in further studies. (Clinicaltrials.gov Identifier NCT00876863).

OC4: EFFICACY AND SAFETY OF GANTENERUMAB FROM THE PHASE 3 SCARLET ROAD TRIAL, A STUDY OF GANTENERUMAB IN PATIENTS WITH PRODROMAL AD. ROBERT LASSER[1], SUSANNE OSTROWITZKI[2], PHILIP SCHELTENS[3], MERCÈ BOADA[4], BRUNO DUBOIS[5], ERNEST DORFLINGER[7], BOGDAN BALAS[1], TANIA NIKOLCHEVA[2], DIETMAR VOLZ[1], ELIZABETH ASHFORD[6], SYLVIE RETOUT, CHRIS EDGAR[6], GEORGE GARIBALDI[7], PAULO FONTOURA[1], LUCA SANTARELLI[2] *((1) F. Hoffmann-La Roche Ltd, Basel, Switzerland; (2) Roche Pharmaceutical Research & Early Development, F. Hoffmann-La Roche Ltd, Basel, Switzerland; (3) Department of Neurology and Alzheimer Center, VU University Medical Center, MB Amsterdam, the Netherlands; (4) Memory Clinic of Fundació ACE, Institut Català de Neurociències Aplicades, Barcelona, Spain; (5) Institut de la Mémoire et de la Maladie d'Alzheimer and INSERM, Hôpital La Salpêtrière, UPMC University, Paris, France; (6) Roche Products Limited, Welwyn Garden City, UK; (7) Formerly of F. Hoffmann-La Roche Ltd, Basel, Switzerland)*

Background: Gantenerumab is a fully human, anti-Aβ monoclonal antibody that binds with high affinity to aggregated Aβ. Gantenerumab promotes removal of aggregated Aβ by activating microglial phagocytosis. SCarlet RoAD (NCT01224106; WN25203), a Phase 3, multicenter, randomized, double-blind, placebo-controlled, 2-year study of gantenerumab in prodromal AD, was the first global study using biomarker screening for entry and a single clinical endpoint for outcome. In addition to aMCI, patients recruited to SCarlet RoAD were required to have evidence of amyloid pathology as demonstrated by low levels of Aβ42 in CSF. Dosing in SCarlet RoAD was terminated in December 2014 following a pre-planned futility analysis; patients continue to be followed. Clinical efficacy data for the 2-year completers (n=312) and safety data for the intent-to-treat population (n=797) are presented. *Methods:* Patients eligible for SCarlet RoAD were 50–85 years old, had MMSE scores ≥24 and CDR-Global scores of 0.5 (memory box scores of 0.5 or 1.0). Patients also had abnormal memory function at screening or 1 month prior to screening, based on FCSRT scores (<17 for free recall, or <40 for total recall, or <20 free recall and <42 total recall). Aside from memory impairment, patients had largely preserved levels of general cognition and functional performance such that a diagnosis of dementia could not be made. Patients were further screened using a CSF Aβ assay (INNOTEST® β-AMYLOID1–42, Innogenetics) and patients with CSF Aβ42 levels above the predefined cut-off level were excluded from the study. Patients were randomized to monthly subcutaneous injections of placebo, or 105 mg or 225 mg gantenerumab, depending on their APOEε4 allele status. No patients homozygous for APOEε4 received 225 mg gantenerumab. The primary endpoint for SCarlet RoAD at 2 years was the CDR-Sum of Boxes (SB) total score; secondary endpoints included ADAS-Cog 13, FAQ and MMSE. An exploratory progression analysis was also performed; a model independently developed by Delor et al. based on ADNI data1 was used to identify patients predicted to be fast progressors (n=108). To evaluate treatment exposure effects, fast progressors were grouped by plasma gantenerumab concentration: placebo arm (n=34), low exposure 1.48–5 μg/mL (n=22), medium exposure 5–10 μg/mL (n=29), high exposure 10–26.68 μg/mL (n=19). Biomarker results are presented separately. *Results:* No differences in CDR-SB scores between placebo and gantenerumab treatment groups over 2 years were found in the primary analyses. Results were similar for ADAS-Cog13, FAQ and MMSE. The exploratory progression analysis showed an exposure-dependent trend for treatment effect in patients that were predicted to have a faster rate of progression. About a third of the SCarlet RoAD population was predicted to be fast progressors. Of these fast progressors, those with higher plasma gantenerumab concentration had less clinical decline than those with lower exposure to gantenerumab or placebo. Median change from baseline at Week 104 (±SD) in ADAS-Cog13 in fast progressors: placebo 6 (9.09); low gantenerumab exposure 4.83 (5.97); medium gantenerumab exposure 4 (9.87); high gantenerumab exposure 2.66 (6.1). The total percentage of patients with at least one adverse event was 92.1%, 86.7% and 90.8% in the placebo, 105 mg and 225 mg gantenerumab arms, respectively. Serious adverse events were reported in 19.5%, 17.3% and 16.9% of patients in the placebo, 105 mg and 225 mg gantenerumab arms, respectively. Amyloid-related imaging abnormalities (ARIA) were dose- and APOEε4 allele dependent, with overall incidences of ARIA-E for placebo, 105 mg and 225 mg gantenerumab groups of 0.8%, 6.6% and 12.3%, respectively, and overall incidences of ARIA-H of 10.9%, 19.2% and 13.1%, respectively. Additional exploratory analyses will be presented. *Conclusions:* The SCarlet RoAD study offers one of the larger controlled datasets in prodromal AD patients available to date. Gantenerumab was safe and well tolerated in patients with prodromal AD over the dose range tested. No new safety signals were observed for gantenerumab and the overall safety profile was similar to that seen in Phase 1 studies. No significant differences in efficacy endpoints

between treatment arms were observed in the primary analyses. However, in an exploratory analysis, patients predicted to have greater progression showed an exposure-dependent treatment effect. These data suggest a potential relationship between exposure and clinical effects, and support the exploration of higher doses of gantenerumab. 1. Delor I, et al. CPT: Pharmacometrics & Systems Pharmacol 2013; 2:e78.

OC5: CSF AND AMYLOID PET BIOMARKER DATA FROM THE PHASE 3 SCARLET ROAD TRIAL, A STUDY OF GANTENERUMAB IN PATIENTS WITH PRODROMAL AD. TANIA NIKOLCHEVA[1], ROBERT LASSER[2], SUSANNE OSTROWITZKI[1], PHILIP SCHELTENS[3], MERCÈ BOADA[4], BRUNO DUBOIS[5], ERNEST DORFLINGER[6], DIETMAR VOLZ[2], UDO EICHENLAUB[7], CHRISTINA RABE[7], TOBIAS BITTNER[7], MARKUS SCHMITZ[7], CHRIS EDGAR[8], GEORGE GARIBALDI[6], PAULO FONTOURA[2], LUCA SANTARELLI[1] *(1) Roche Pharmaceutical Research & Early Development, F. Hoffmann-La Roche Ltd, Basel, Switzerland; (2) F. Hoffmann-La Roche Ltd, Basel, Switzerland; (3) Department of Neurology and Alzheimer Center, VU University Medical Center, MB Amsterdam, the Netherlands; (4) Memory Clinic of Fundació ACE, Institut Català de Neurociències Aplicades, Barcelona, Spain; (5) Institut de la Mémoire et de la Maladie d'Alzheimer and INSERM, Hôpital La Salpêtrière, UPMC University, Paris, France; (6) Formerly of F. Hoffmann-La Roche Ltd, Basel, Switzerland; (7) Roche Diagnostics GmbH, Penzberg, Germany; (8) Roche Products Limited, Welwyn Garden City, UK)*

Background: Gantenerumab is a fully human, anti-Aβ monoclonal antibody that binds with high affinity to aggregated Aβ. It promotes removal of aggregated Aβ by activating microglial phagocytosis. Gantenerumab was studied in SCarlet RoAD (NCT01224106; WN25203)—a Phase 3, multicenter, randomized, double-blind, placebo-controlled, 2-year trial in prodromal AD. The optimum time to intervene with anti-amyloid therapies in AD may be before the onset of dementia and prior to advanced neuropathology; SCarlet RoAD tested the efficacy of gantenerumab in patients with prodromal AD. In addition to aMCI, patients recruited to SCarlet RoAD were required to have evidence of amyloid pathology as demonstrated by low levels of Aβ42 in CSF. Following a pre-planned futility analysis in December 2014, dosing was terminated; patients continue to be followed. CSF biomarker data and amyloid PET sub-study results are presented from patients completing 2-year treatment. *Methods:* Patients eligible for SCarlet RoAD were 50–85 years old, had MMSE scores ≥24 and CDR-Global scores of 0.5 (memory box scores of 0.5 or 1.0). Patients also had abnormal memory function at screening or 1 month prior to screening, based on FCSRT scores (<17 for free recall, or <40 for total recall, or <20 free recall and <42 total recall). Aside from memory impairment, patients had largely preserved levels of general cognition and functional performance such that a diagnosis of dementia could not be made. Patients were further screened using a CSF Aβ assay (INNOTEST® β-AMYLOID1–42, Innogenetics) and patients with CSF Aβ42 levels above the predefined cut-off level were excluded from the study. Patients were randomized to monthly subcutaneous injections of placebo, or 105 mg or 225 mg gantenerumab, based on APOEε4 allele status (no patients homozygous for APOEε4 received 225 mg). CSF samples were taken from all patients at baseline, Week 52 (optional) and Week 104. CSF biomarkers were analyzed using Elecsys® β-Amyloid(1–42), tTau and pTau(181P) immunoassays (Roche Diagnostics; these products are in development and not available in the USA or elsewhere). One hundred and fourteen patients were enrolled in a PET sub-study (AmyvidTM) with PET scans carried out at baseline, 20, 60 and 100 weeks. Standardized uptake value (SUVr), normalized to different reference regions including cerebellum grey, whole cerebellum and subcortical white matter, was assessed in a cortical composite volume of interest. In an exploratory analysis to assess treatment–exposure relationships, patients enrolled in the PET sub-study were grouped according to plasma gantenerumab concentration: placebo arm (n=39); low exposure 1.48–5 μg/mL (n=29); medium exposure 5–10 μg/mL (n=27); high exposure 10–26.68 μg/mL (n=19). Clinical results are presented separately. *Results:* No changes in CSF Aβ42 levels were found. A dose-dependent reduction in CSF tau species was observed over 2 years of gantenerumab treatment. CSF P-tau measurements showed a mean % change from baseline at Week 104 (± SD): placebo (n=63) +2.62 (21.89); 105 mg gantenerumab (n=62) –4.85 (12.42), P<0.01 vs. placebo; 225 mg gantenerumab (n=58) –7.52 (9.85), P<0.01 vs. placebo. CSF T-tau measurements showed a mean % change from baseline at Week 104 (± SD): placebo (n=62) +3.11 (21.12); 105 mg gantenerumab (n=60) –1.45 (13.55); 225 mg gantenerumab (n=57) –2.94 (10.37), P <0.01 vs. placebo. Observed mean % change from baseline at Week 100 (± SD) in cortical composite SUVr (using mean cerebellum grey as reference region) on amyloid-PET: placebo (n=20) –1.11 (8.02); 105 mg gantenerumab (n=11) +0.19 (12.70); 225 mg gantenerumab (n=18) –5.37 (7.92). These observations were consistent regardless of reference region used. The exploratory analysis revealed an exposure-dependent effect and those with the highest plasma gantenerumab concentrations (10–26.68 μg/mL) showed a median decrease of approximately 10% SUVr at the Week 100 timepoint. Additional exploratory analyses will be presented. *Conclusions:* Dose-dependent changes in brain Aβ SUVr and CSF P-tau and T-tau were seen following gantenerumab treatment. CSF Aβ42 levels were unaltered, as expected. To our knowledge, this is the first study to show impact of an anti-Aβ treatment on CSF tau species in prodromal AD. Taken together, the findings from the present study are consistent with brain amyloid clearance and subsequent effect on downstream neurodegeneration.

OC6: SEMBRAGILINE IN MODERATE ALZHEIMER'S DISEASE DEMENTIA: RESULTS OF A PHASE 2 TRIAL (MAYFLOWER ROAD). STEPHANE NAVE[1], RACHELLE S DOODY[2], MERCÈ BOADA ROVIRA[3], TIMO GRIMMER[4], JUHA SAVOLA[1], PAUL DELMAR[1], MEIKE PAULY-EVERS[1], TANIA NIKOLCHEVA[1], CHRISTIAN CZECH[1], EDILIO BORRONI[1], BÉNÉDICTE RICCI[1], EMMA MORAN[6], MARIE MANNINO[5], IRENE GERLACH[1], PAULO FONTOURA[1], LUCA SANTARELLI[1], SEMBRAGILINE STUDY GROUP *((1) Roche Pharma Research & Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Switzerland; (2) Alzheimer's Disease and Memory Disorders Center, Department of Neurology, Baylor College of Medicine, Houston, TX 77030, USA; (3) Memory Clinic of Fundació ACE, Institut Català de Neurociències Aplicades, Barcelona, Spain; (4) Department of Psychiatry and Psychotherapy, Klinikum rechts der Isar der Technische Universitaet Muenchen, Munich, Germany; (5) Roche Safety Risk Management, Licensing & Early Development, F. Hoffmann-La Roche Ltd, New York, USA; (6) Roche Products Limited, Roche Innovation Center Welwyn, Welwyn Garden City, UK)*

Background: In Alzheimer's disease (AD), monoamine oxidase B (MAO-B) activity is increased in reactive astrocytes surrounding amyloid plaques in several brain regions from early stages and throughout the course of the disease. Increased metabolism of monoamines by MAO-B leads to the production of toxic reactive oxygen species, thought to contribute to the pathogenesis of the disease (1). MAO-B inhibition may restore brain level of monoaminergic neurotransmitters, decrease formation of toxic reactive oxygen species and reduce neuroinflammation (reactive astrocytosis), potentially leading to neuroprotection. Sembragiline is a potent, selective and reversible inhibitor of MAO-B developed as a potential

treatment for AD. PET studies have shown that doses of 1 mg and 5 mg result in near complete saturation of brain MAO-B in AD patients and elderly controls (2). *Methods*: We randomized 542 patients from 118 outpatient clinical sites in 12 countries to receive sembragiline 1 mg, 5 mg or placebo daily administered for 52 weeks. Patients were 50 years or older, had moderate AD dementia (MMSE score 13-20) and were stably treated with AChEIs with/without memantine for at least 4 months prior to screening. The primary endpoint was change from baseline over 52 weeks on the 11-item Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog11) (MMRM, ITT population). Other efficacy endpoints (ADCS-ADL, Behave-AD-FW, ADCS-CGIC, GDS) were also analysed. This trial is registered at ClinicalTrials.gov (NCT01677754). *Results:* One-year treatment with sembragiline was well tolerated with no difference between treated groups and placebo in treatment emergent adverse events and percentage of randomized patients completing the study. No significant treatment effect was shown on the ADAS-cog11. The estimated difference between groups in the change from baseline was -0.27 (95% CI, -2.03 to 1.48; P=0.76) and 0.82 (95% CI,-0.92 to 2.56; P=0.35), respectively, compared to placebo for the 1 mg and 5 mg doses at endpoint. Of interest, the estimated difference in neuropsychiatric symptoms (BEHAVE-AD-FW) was -2.81 (95% CI, -5.04 to -0.58; P=0.014) and -2.66 (95% CI, -4.87 to -0.44; P=0.019), respectively compared to placebo over 52 weeks. The estimated difference in functioning (ADCS-ADL) was 2.31 (95% CI, -0.35 to 4.97; p=0.089) and 1.77 (95% CI, -0.86 to 4.40; P=0.187), respectively compared to placebo at endpoint. In a post-hoc analysis, stronger effects on behavior and functioning were noted in patients with more severe baseline behavioral symptoms (above the median). *Conclusions:* The MAyflOwer RoAD Phase 2 study of sembragiline in moderate AD patients as add-on to standard of care missed its primary end-point but suggests treatment effect on behavioral symptoms as compared with placebo. 1. Preclinical characterization of RO4602522, a novel, selective and orally active monoamine oxidase type B inhibitor for the treatment of Alzheimer's disease. Borroni et al, AAIC2013; 2. Brain MAO-B inhibition in Alzheimer's Disease patients and elderly controls after oral administration of RO4602522. Ricci et al, AAIC2013.

OC7: PREVENTION OF DEMENTIA BY INTENSIVE VASCULAR CARE (PREDIVA) – PRELIMINARY FINDINGS FROM A RANDOMISED CONTROLLED TRIAL. EDO RICHARD[1,2], ERIC MOLL VAN CHARANTE[3], LISA EURELINGS[1], JAN-WILLEM VAN DALEN[1], SUZANNE LIGTHART[3], MARIEKE HOEVENAAR-BLOM[1], WILLEM A. VAN GOOL[1] *((1) Dept of neurology, Academic Medical Center, University of Amsterdam, the Netherlands; (2) Dept of neurology, Radboud University Medical Center, Nijmegen, the Netherlands; (3) Dept of primary care, Academic Medical Center, University of Amsterdam, the Netherlands)*

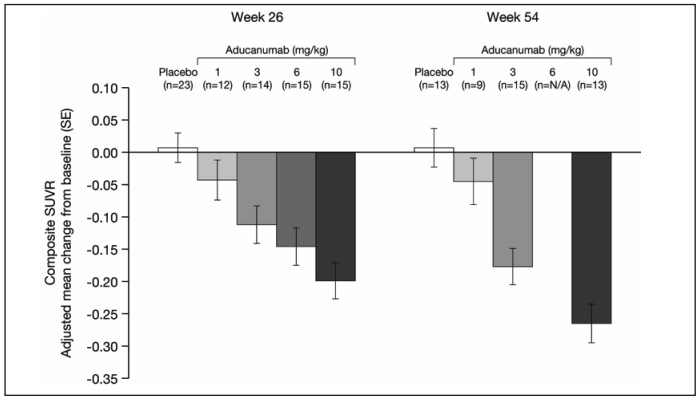
Introduction: Cardiovascular risk factors are associated with an increased risk of dementia. Whether treatment of vascular risk factors can prevent or postpone dementia in older individuals is yet unknown. In the preDIVA trial we test whether a multicomponent intervention targeting all vascular and lifestyle related risk factors could prevent incident dementia. Here we show preliminary findings, including intermediate outcome measures such as on blood pressure. Primary analysis is ongoing. *Methods:* In an open cluster-randomized controlled clinical trial in primary care, 3532 persons (age 70-78 years) were randomized to nurse-led vascular care or care as usual. Sample size was calculated based on age-specific dementia incidence during six years and reported treatment effects of blood pressure reduction on incident dementia. Participants in the intervention group received tailor-made life-style advice during 4-monthly visits to a practice nurse. Medication was started when indicated based on national guidelines. Recruitment took place between May 2006 and March 2009. The intervention and follow-up duration were six years, with an extension to up to eight years for those recruited early in the trial. The primary outcome is incident dementia. Main secondary outcomes are disability, incident cardiovascular disease, mortality, cognitive decline and depression. An independent outcome adjudication committee, blinded to treatment allocation, assessed the main clinical outcomes. For the primary analysis we will use a multilevel Cox proportional hazards model. *Results:* After a total of 21.329 person-years we had complete follow-up on the primary outcome in 3460 persons (98.0%). Follow-up visits were completed by 2789 (79%) at 2 years, 2270 (64%) at 4 years and 1933 (55%) at 6-8 years. During the study 584 (17%) participants died and 251 (7.1%) participants developed dementia. At baseline, 1400 participants (39.6%) had grade II or III hypertension (≥160 mmHg systolic or ≥100 diastolic). Only 13% had no vascular risk factors potentially amenable to treatment. During 6-8 years of follow-up, mean blood pressure decreased significantly in both groups, but more in the intervention group than in the control group (Δ2.5 mmHG, p=0.02). The effect was largest for participants with grade III hypertension (Δ6.2 mmHG, p=0.05). Analyses for clinical outcomes are currently ongoing and results will be presented at CTAD 2015 as available. *Conclusion:* PreDIVA is the largest and longest running RCT ever with incident dementia as primary outcome. PreDIVA has a very high complete follow-up for the primary outcome, in spite of the long duration and high age of participants. Preliminary results indicate a small but consistent beneficiary effect of the intervention on BP. Main results regarding primary and secondary outcomes, including incident dementia and mortality, are expected shortly and will be presented as available.

OC8: RANDOMIZED, PLACEBO-CONTROLLED, PHASE 1B STUDY OF THE ANTI–BETA-AMYLOID ANTIBODY ADUCANUMAB (BIIB037) IN PATIENTS WITH PRODROMAL OR MILD ALZHEIMER'S DISEASE: INTERIM RESULTS FROM A SUBPOPULATION OF PATIENTS WITH EARLY ALZHEIMER'S DISEASE MEETING PHASE 3 STUDY ENTRY CRITERIA. VISSIA VIGLIETTA[1], XIAOPENG MIAO[1], TIANLE CHEN[1], JOHN O'GORMAN[1], LESLIE WILLIAMS[1], YAN LING[1], JEFF SEVIGNY *((1) Biogen, Cambridge, MA, USA)*

Background: Aducanumab (BIIB037) is a human monoclonal antibody against aggregated forms of beta-amyloid (Aβ) being investigated as a potential disease-modifying treatment for patients with Alzheimer's disease (AD). Interim analyses of an ongoing Phase 1b study of aducanumab in patients with prodromal or mild AD have demonstrated target engagement, a pharmacodynamic effect of Aβ reduction, and a clinical effect on exploratory endpoints (change from baseline in Clinical Dementia Rating-Sum of Boxes [CDR-sb] and Mini-Mental State Examination [MMSE]); the most common adverse event (AE) was amyloid-related imaging abnormalities (ARIA). Two Phase 3 trials are planned to assess efficacy and safety of aducanumab in patients with early AD. Here, we report interim data from the ongoing Phase 1b study in a subpopulation of patients with early AD with similar characteristics to those required for entry into the planned Phase 3 trials. *Methods:* In this multicenter, randomized, double-blind, placebo-controlled, multiple-dose study (PRIME; NCT01677572), patients (age 50-90 years) had positive florbetapir (Amyvid) positron emission tomography (PET) scans and met clinical criteria for prodromal or mild AD. Patients were randomized to receive aducanumab or placebo once every 4 weeks for 52 weeks in 9 arms stratified by ApoE4 status in a parallel staggered cohort design at a ratio of 3:1 active versus placebo. The primary endpoint assessed safety and tolerability; secondary endpoints included pharmacokinetic

parameters, anti-aducanumab antibodies, and change from baseline to Week 26 in amyloid PET. Changes in clinical measures of cognitive decline (change from baseline in CDR-sb and MMSE scores) were assessed as exploratory endpoints. A subpopulation of patients with early AD was defined by a CDR global score of 0.5, CDR memory domain score ≥0.5, and MMSE score ≥24. We report interim safety (AEs), Aβ reduction by amyloid PET, and exploratory clinical endpoints (changes from baseline in MMSE and CDR-sb) in the early AD population for treatment arms 1-7 (aducanumab 1, 3, 6, and 10 mg/kg and corresponding placebo arms). PRIME is ongoing; the interim analyses presented here include results to Week 30 for the 6 mg/kg and corresponding placebo arm and to Week 54 for the 1, 3, 10 mg/kg and corresponding placebo arms (Week 54 data for 6 mg/kg are not yet available but will be presented). *Results:* Of 165 patients randomized and dosed in PRIME, 92 (56%; n=14, n=18, n=17, n=18, and n=25 with aducanumab 1, 3, 6, and 10 mg/kg and placebo, respectively) had early AD, including 26 patients with mild AD and 66 with prodromal AD. Consistent with the results in the overall population, dose-dependent reductions in brain Aβ were observed, as measured by changes from baseline in standard uptake value ratio (SUVR) at Week 26 and Week 54 (Figure). Dose-dependent slowing of MMSE and CDR-sb decline was observed at 1 year in this population. Consistent with results in the overall population, the most common AE and serious AE were dose-dependent amyloid-related imaging abnormalities (ARIA; incidence based on MRI: 7%, 11%, 29%, 50%, and 8% with aducanumab 1, 3, 6, and 10 mg/kg and placebo, respectively; serious AEs: 0%, 6%, 6%, 22%, and 0%, respectively). *Conclusion:* Consistent with findings in the overall Phase 1b study population, in the subpopulation of patients with early AD, aducanumab reduced accumulation of Aβ plaques and slowed cognitive decline in exploratory clinical endpoints (MMSE/CDR-sb); dose-dependent ARIA was the main safety finding. Thus, results in the subgroup of patients meeting entry criteria for the planned Phase 3 trials of aducanumab were highly consistent with the results in the overall Phase 1b population. This study is funded by Biogen.

Figure



OC9: FINGER - A MULTIDOMAIN TWO-YEAR RANDOMISED TRIAL TO PREVENT COGNITIVE DECLINE.

MIIA KIVIPELTO[1,2] FOR THE FINGER STUDY GROUP

((1) Chronic Disease Prevention Unit, National Institute for Health and Welfare, Helsinki, Finland Karolinska Institutet Center for Alzheimer Research, Stockholm, Sweden; (2) Institute of Clinical Medicine/Neurology, University of Eastern Finland, Kuopio, Finland Aging Research Center, Karolinska Institutet-Stockholm University, Stockholm, Sweden)

Background: The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) is a proof-of-concept randomised controlled trial for a multidomain approach to prevent cognitive decline in at-risk elderly from the general population. *Methods:* FINGER included 1260 participants aged 60-77 years recruited from previous national surveys. Inclusion criteria were CAIDE Dementia Risk Score>6 points, and cognition at mean level or slightly lower than expected for age. Participants were randomised to a 2-year multidomain intervention (diet, exercise, cognitive training, vascular risk monitoring), or a control group (general health advice). Primary outcome was change in cognition (neuropsychological test battery, NTB z-score). Analysis was by modified intention-to-treat (participants with at least one post-baseline observation). This trial is registered as NCT01041989. *Results:* 2654 individuals were screened, and 1260 were randomised to the intervention (n=631) or control (n=629) group. 591 participants (intervention) and 599 (control) had at least one post-baseline assessment. Mean change (standard error) in NTB total z-score at 2 years was 0·20 (0·01) in intervention and 0·16 (0·01) in control group. Between-groups difference in change of NTB total score per year was 0·022 (95%CI 0·002-0·042), p=0·030. A significant effect was also observed for other cognitive outcomes (executive functioning, processing speed, abbreviated memory score), and risk of cognitive decline and other secondary outcomes (BMI, dietary habits, physical activity, quality of life). Dropout rate was 12·1%, and adverse events rare. Health-related quality of life (HRQoL) was assessed at baseline, 12, and 24 months using RAND-36 which includes 8 scales (domains): Physical Function (PF), Role Physical (RP), Role mental (RM), Vitality (VT), Mental Health (MH), Social Function (SF), Bodily Pain (BP), and General Health (GH). During the 2-year intervention mean scores in all scales decreased in the control group, but increased in the intervention group for VT (12 and 24 months), SF (12 months), and especially GH at both 12 and 24 months. The overall differences between the intervention and control group during intervention period were significant for GH (P<0.01), PF (P =0.03), and RM (P=0.01). A sub-group of FINGER participants (n=48) underwent a [11C]PIB PET scan at baseline and 2 years. Based on a visual PET scan analysis at baseline, participants were divided into two groups (PIB+ and PIB-). Hippocampal atrophy and brain vascular changes on baseline MRI scans were visually graded according to Scheltens and Fazekas scores. 20 individuals (42%) were PIB+. The PIB- group performed better in executive functions than the PIB+ group (Z-score difference p=0.02). The PIB+ group had a higher amount of white matter lesions and hippocampal atrophy (Fazekas score 2-3: 50% in PIB+ vs. 29% in PIB-; Scheltens score 1-3: 40% right, 45% left in PIB+ vs. 29% and 21% in PIB-). *Conclusions:* FINGER is the first large, long-term RCT showing that a multidomain intervention may improve/maintain cognitive functioning in at-risk elderly from the general population. The intervention also had positive effects on health-related quality of life. The high percentage of PIB positive subjects at baseline in the PET sub-group provides evidence of a successful recruitment process of the at-risk population for AD in the FINGER trial. The results suggest an association between early brain amyloid accumulation and lower performance in executive functions, as well as increased vascular changes and hippocampal atrophy in amyloid positive individuals. *Acknowledgements:* This study was supported by Academy of Finland's Responding to Public Health Challenges Research Programme (SALVE) grants 129395, 129397, 129459, 129421, 129416, 129511, 129401, 259615, La Carita Foundation, Alzheimer Association grant (HAT-10-173121), Alzheimer's Research and Prevention Foundation, Juho Vainio Foundation, Novo Nordisk Foundation, Finnish Social Insurance Institution, Ministry of Education and Culture Research Grant, Salama bint Hamdan Al Nahyan Foundation, Axa Research Grant, and EVO grants of University Hospitals of Kuopio, Oulu and Turku, Seinäjoki Central hospital and Oulu City Hospital.

OC10: IMAGING DEMENTIA—EVIDENCE FOR AMYLOID SCANNING (IDEAS): A STUDY TO EVALUATE THE CLINICAL UTILITY OF AMYLOID PET IN U.S. MEDICARE

BENEFICIARIES. GIL D RABINOVICI[1], BRUCE E HILNER[2], RACHEL A WHITMER[3], MARIA C CARRILLO[4], CONSTANTINE A GATSONIS[5], BARRY A SIEGEL[6], JAMES A. HENDRIX[4] *((1) Memory and Aging Center and Dept. of Neurology, University of California San Francisco, USA; (2) Dept. of Internal Medicine, Virginia Commonwealth University, Richmond, VA, USA; (3) Kaiser Permanente Division of Research, Oakland, CA, USA; (4) Alzheimer's Association, Chicago, IL, USA; (5) Department of Biostatistics, Brown University School of Public Health, Providence, RI, USA; (6) Mallinckrodt Institute of Radiology, Washington University School of Medicine, St Louis, USA))*

Background: In its National Coverage Decision on amyloid-beta PET imaging, the U.S. Centers for Medicare & Medicaid Services (CMS) indicated that reimbursement would be considered under coverage with evidence development (CED) as part of research studies to evaluate the scan's impact on patient-oriented outcomes. *Methods:* A U.S. national CED protocol for amyloid PET was developed in response to the CMS decision. The protocol was written under the sponsorship of the Alzheimer's Association and in partnership with the American College of Radiology and the Society for Nuclear Medicine and Molecular Imaging. Key input on the protocol was provided by thought leaders in amyloid PET, CMS and industry stakeholders. *Results:* Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) is an open-label, longitudinal cohort study to assess the impact of amyloid PET in Medicare patients who meet the Appropriate Use Criteria (AUC) for amyloid imaging (Johnson et al. 2013). The primary hypothesis is that, in diagnostically uncertain cases of mild cognitive impairment (MCI) and atypical dementia, knowledge of amyloid status will lead to significant changes in patient management, and this will translate into improved medical outcomes. Approximately 18,500 Medicare beneficiaries will be enrolled in the study from sites across the U.S. Participants will be selected by dementia experts and will undergo imaging at PET facilities qualified to perform and interpret amyloid PET. Aim 1 investigates the impact of amyloid PET on short-term patient management (90 days after the scan) in a cumulative endpoint consisting of Alzheimer's disease drug therapy, other drug therapy, and counselling about safety and future planning. Aim 2 utilizes Medicare claims data to construct a matched control group of amyloid PET-naïve patients and compares 12-month rates of hospitalization and emergency room visits between study participants and controls. Outcomes in both aims will be assessed separately in MCI and dementia. The study will further investigate how the scan impacts health care resource utilization. This population represents a unique research opportunity to consider additional questions not specifically covered in the protocol. *Conclusions:* The IDEAS study was approved by CMS in April 2015, and aims to launch enrollment in early 2016 and complete analysis in 2020. The IDEAS cohort will serve as a foundation for developing further studies in this population.

OC11: A COMBINED MEASURE OF COGNITION AND FUNCTION FOR CLINICAL TRIALS: THE INTEGRATED ALZHEIMER'S DISEASE RATING SCALE (IADRS). ALETTE M WESSELS[1], ERIC R SIEMERS[1], PENG YU[1], SCOTT W ANDERSEN[1], KAREN C HOLDRIDGE[1], JOHN R SIMS[1], YAAKOV STERN[2], DORENE M RENTZ[3], BRUNO DUBOIS[4], ROY JONES[5], JEFFREY CUMMINGS[6], PAUL S AISEN[7] *((1) Eli Lilly and Company, Indianapolis, IN, USA; (2) Department of Neurology, Columbia University Medical Center, New York, NY, United States; (3) Departments of Neurology, Brigham and Women's Hospital, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; (4) Centre des Maladies Cognitives et Comportementales (IM2A), Institut du Cerveau et de la Moelle épinière (ICM), UMR-S975, Université Pierre et Marie Curie-Paris6, AP-HP, Hôpital de la Salpêtrière, 47 boulevard de l'Hôpital, 75013 Paris, France; (5) RICE (The Research Institute for the Care of Older People), Bath, UK; (6) Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, Nevada; (7) University of Southern California, CA, USA)*

Background: There are many industry and academic efforts to develop more sensitive and responsive instruments for measuring treatment effects in early stages of Alzheimer's disease (AD). Strategies applied toward that end include: 1) construction of a composite endpoint to include neuropsychological tests measuring domains known to be impaired at the particular disease stage of interest ("theory driven" approach); 2) mathematical data mining using existing items within a scale(s) to identify, select and weight the most sensitive items to improve performance ("data mining" approach); or 3) a combination of theory and data mining approaches. The integrated Alzheimer's Disease Rating Scale (iADRS) represents a composite that was developed using both a theory-driven approach (incorporating measures of both cognition and function) and a data-mining approach (identifying the most sensitive combination of scales through analysis of data from the Alzheimer's Disease Neuroimaging Initiative, the Baltimore Longitudinal Study of Aging, and the solanezumab EXPEDITION and EXPEDITION2 studies). The iADRS is a simple linear combination of scores from 2 well-established, therapeutically sensitive, widely accepted measures in AD, the ADAS-Cog13or14 and the ADCS-iADL, measuring the core domains of AD. All items of these 2 scales are included without additional weighting of items, yielding face validity and ease of interpretation of the composite relative to its components. *Methods:* The psychometric properties of the iADRS were established through principal component analysis, estimation of the contributions of domain scores to the iADRS total score, and estimation of the contributions of individual item scores to the iADRS total score. Placebo decline and treatment differences by the iADRS were analysed by mixed model repeated measures (MMRM). Data from 5 treatment studies, solanezumab EXPEDITION and EXPEDITION2 and EXPEDITION-EXT, semagacestat IDENTITY, and the donepezil ADCS-MCI (ADCS-008) were used to test iADRS performance. *Results:* Principal :component analyses of placebo baseline and change from baseline data demonstrated that the iADRS can be divided into 2 principal components with factor 1 representing primarily cognitive items and factor 2 representing instrumental ADLs. The dynamic range of each subscale was similar across all studies demonstrating that the iADRS total score reflects approximately equal contributions from both subscales. To assess whether all items in the subscales (ADAS-Cog13 or 14 and ADCS-iADL) needed to be included in the iADRS, item-by-item analyses showed that although every item made a contribution to the total scale score in the assessment of disease progression, the strength of those contributions varied by item and across data sets. Importantly, items that showed the greatest disease progression were not the same items that showed the greatest treatment effect, and items that changed the most and least also differed across data sets. These results suggest that retention of all items is advantageous. When the pooled mild AD (patients with baseline MMSE 20 to 26) data from EXPEDITION and EXPEDITION2 were analysed with MMRM for the ADAS-Cog14 and ADCS-iADL, the solanezumab-treated group showed a statistically significant reduction in decline relative to the placebo-treated group from Week 40 up to and including Week 80 for the ADAS-Cog14 and from Week 64 up to and including Week 80 for the ADCS-iADL. Similarly, iADRS showed statistically significant separation at 40 through 80 weeks. However, when each study was analysed separately, only the iADRS showed treatment separation for both EXPEDITION and EXPEDITION2. Furthermore, the iADRS demonstrated greater robustness of treatment separation for EXPEDITION-EXT compared with either subscale, as demonstrated

by statistical significance and noninferiority at more time points. Notably, iADRS was also able to detect semagacestat treatment-related worsening in the IDENTITY study earlier than either subscale alone. Data from MCI APOE ε4 carriers in the donepezil ADCS-MCI (ADCS-008) study showed that the iADRS was effective in tracking disease progression and effective in detecting early symptomatic treatment benefits that were not maintained over time. Similarly, the iADRS was effective in tracking disease progression in the pooled moderate AD (patients with baseline MMSE 16 to 19) populations from EXPEDITION and EXPEDITION2. *Conclusion :* The iADRS provides an overall measure of AD impairment (total score) and can also provide individual subscores for cognition and function based on standard, accepted instruments. The iADRS demonstrated acceptable psychometric properties and was effective in capturing disease progression and treatment effects (both beneficial and detrimental) across a broad range of the symptomatic disease spectrum – MCI/prodromal, mild AD, and moderate AD populations – allowing its use in studies of mixed-spectrum populations and ensuring its sensitivity to treatment effects as study patients advance in stages of AD severity throughout the long course of disease-modifying studies.

OC12: USING ALL YOUR DATA: COMBINING AREA UNDER THE CURVE AND MULTIDOMAIN COMPOSITE ENDPOINTS IN EFFICACY ANALYSES. ALIREZA ATRI[1,2] *((1) Ray Dolby Brain Health Center, California Pacific Medical Center, and Sutter Health, San Francisco, CA, USA; (2) Harvard Medical School, Boston MA, USA)*

Background: Better longitudinal analytic methods are needed to improve detection and interpretation of treatments effects in clinical trials across the AD clinical spectrum. This talk discusses advantages of area-under-the-curve (AUC) analysis, particularly when utilized with a multidomain composite index (md-CI) that combines several traditional primary and secondary outcome measures (e.g. an equally weighted combination of cognitive, functional, global severity, and behavioral measures). Combining the AUC approach with a md-CI can allow for integration of multiple clinical domains and assessments over time into a single numerical value that utilizes all study data, and which is readily interpretable. *Methods:* Examples using application of the combined AUC-mdCI approach to real clinical trial data are provided; these are compared to results employing traditional analysis of baseline-to-trial-endpoint change score (e.g. last observation carried forward and observed counts utilizing analysis of covariance (ANCOVA) and linear mixed effects regression analysis) for measures of individual domains. *Results:* Assessments based on changes from baseline at a single time point obscure the longitudinal aspects of treatment effects and ignore most of the "history"/information regarding the emergence, onset, duration, and variability of symptoms or disease characteristics. Often, score or score change trajectories over time for primary and secondary AD clinical trial outcome measures are not linear, particularly in the first 3-6 months of study. AUCs are intuitive, straightforward to implement, and maintain the direction of improvement of each individual scale. When calculated at the subject level, they represent each individual's summary of change for a given period of time (as opposed to change at a given time point) and can be treated as raw data for statistical analyses. By simply summing cumulative effect and making no gross linearity assumptions, when non-linear outcome trajectories are present, the AUC method can provide more robust and accurate estimates of treatment effects compared to simple baseline-to-endpoint assessments and linear mixed models. Similarly, use of composite indices is associated with several advantages compared with analyzing data from different clinical domains separately. A pre-specified md-CI could be a more ecologically valid way of capturing change in a condition as complex as AD, and could simplify the problem of choosing one or two primary efficacy parameters from tools designed to assess individual clinical domains. This, in turn, could reduce the need for multiple hypothesis testing: researchers could prospectively create a composite index that best addresses their key experimental question and only perform secondary analyses for questions of secondary importance. *Conclusions:* The AUC method is simple to implement; easy to clinically interpret; can efficiently encapsulate an overall outcome trajectory over a study interval; and can "smooth the data" of subjects whose visit-by-visit scores are prone to variations, thereby increasing efficacy signal-to-noise ratio. Combining the AUC approach with a md-CI extends the smoothing effect across several important clinical domains and allows for integration of various clinical assessments over time into a single numerical value that represents all the salient study data. By potentially lowering noise stemming from variance, such a composite representation, combined with AUC analyses, may have the advantage of capturing treatment-related effects more robustly, and with higher power. AUC md-CI analyses, due to the ability to capture the clinical trajectory and a multi-dimensional picture of illness that uses all available study data, should be investigated as a potential outcome measure-analytics candidate for assessment and interpretation of future AD clinical trials.

OC13: ASSESSMENT OF PLASMA AB MARKERS TO ESTIMATE DICHOTOMIC AMYLOID PET AMONG COGNITIVELY HEALTHY PEOPLE. PEDRO PESINI[1], VIRGINIA PÉREZ-GRIJALBA[1], NOELIA FANDOS[1], SALVADOR OLMOS[2], MATIAS BOSSA[2], COLIN MASTERS[3], VICTOR VILLEMAGNE[4], JAMES DOECKE[5], CHRIS FOWLER[3], ALAN REMBACH[3], MANUEL SARASA[1] AND THE AIBL RESEARCH GROUP[6] *((1) Araclon Biotech, Zaragoza, Spain; (2) Aragon Institute of Engineering Research, University of Zaragoza, Spain; (3) The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, VIC, Australia; (4) Department of Nuclear Medicine and Centre for PET, Austin Health, Heidelberg, VIC, Australia; (5) The Australian E-Health Research Centre, Royal Brisbane and Women's Hospital, Herston, QLD, Australia; (6) http://www.aibl.csiro.au/)*

Background: Currently it is accepted that the development of new Alzheimer's disease (AD) modifying drugs, particularly anti-β-amyloid targeted, should be tried in individuals at early disease stages. In absence of clinical symptoms, this people would have to be recruited based on their biomarker status. However, both amyloid neuroimaging (A-PET) and lumbar puncture for CSF studies present problems that limit their widespread acceptability in global clinical trials. Thus, development of other measures as potential surrogates of brain amyloid positivity should be pursued, particularly for the pre-symptomatic stages of AD. In this work two different cases were considered: i) whether the ratio between the total plasma levels of Aβ42 and Aβ40 (TP42/40) is able to found out PET+ve cases among HC in the AIBL cohort; ii) whether TP42/40 is able to found out the people who is going to increase in A-PET score in the next 18 months. *Methods:* This longitudinal study included 162 healthy controls (HC) at baseline from AIBL dataset. We received plasma samples corresponding to 3 visits, at months 18, 36 and 54. A-PET scans were performed every 18 months on 128 subjects out of these HC individuals at several visits (median 4, min=1, max=5 visits). A-PET measurements were coded using a Becket score to make PIB and flutemetamol scans comparable. Total plasma levels of Aβ42 and Aβ40 were measured with ABtest ELISAs (Araclon Biotech Zaragoza, Spain). Subsequently, we carry out a ROC curve performance assessment of TP42/40 to estimate dichotomic A-PET on healthy control individuals. The results were cross-validated in independent subset of the data to avoid overfitting of the different models explored. *Results:* The TP42/40 ratio has over 75% accuracy when

estimating A-PET positivity. There is an improvement in classification performance (average increments over 0.12 in AUC) when using TP42/40 in each ApoE genotype subgroup, compared to the reference case of ApoE plus demography classifiers (age and gender). On the other hand, the ratio TP42/40 has over 71% accuracy when estimating A-PET progression in the following 18 months. *Conclusions:* The ratio TP42/40 can be developed into a useful first-step screening tool for cohort enrichment in clinical trials recruiting cognitively healthy individuals at increased risk of developing Alzheimer's disease.

OC14: HIPPOCAMPUS VOLUME LOSS IN ALZHEIMER'S DISEASE PATIENTS: EFFECT OF TREATMENT WITH CHOLINE ALPHOSCERATE IN ADDITION TO CHOLINESTERASE INHIBITOR. ENEA TRAINI[1], ANNA CAROTENUTO[1,2], ANGIOLA MARIA FASANARO[1,2], RAFFAELE REA[1,2], FRANCESCO AMENTA[1] *((1) Centre for Clinical Research, Telemedicine and Telepharmacy, University of Camerino, Camerino; (2) Alzheimer Evaluation Unit, National Hospital, "A. Cardarelli", Naples, Italy)*

Background: Cholinergic precursors have represented the first approach to counter cognitive impairment occurring in adult onset dementia disorders. ASCOMALVA [Effect of association between a cholinesterase inhibitor (ChE-I) and choline alphoscerate on cognitive deficits in AD associated with cerebrovascular injury] is a double-blind, controlled, randomized clinical trial investigating if the ChE-I donepezil and choline alphoscerate in combination are more effective that donepezil alone. One of the most important biomarkers for AD is the atrophy of the hippocampus. In this study, MRI from patients were analyzed for the evaluation of the brain atrophy. *Methods:* Participants of the ASCOMALVA trial underwent yearly MRI for diagnostic purposes. In 56 patients who achieved two years of therapy, MRI were analyzed by voxel morphometry techniques to assess if addition of choline alphoscerate to treatment with donepezil had an effect on volume loss characteristic of hippocampus of Alzheimer's disease patients. *Results:* Reference group showed a greater atrophy of the gray matter, white matter ad hippocampus than the group treated with donepezil plus choline alphoscerate. In the reference group a concomitant increase of the volume of the ventriculi and space of the cerebrospinal fluid was noticeable. Neuropsycological tests over the 24-month observation period showed in patients of the reference group a moderate time-dependent worsening in all the parameters investigated. Treatment with donepezil plus choline alphoscerate resulted in better scores of the cognitive and functional items and an improvement in behavioural parameters, superior to that induced by donepezil alone. *Conclusion:* The above results have shown that cholinergic precursor loading strategy with choline alphoscerate counters to some extent hippocampal volume loss occurring in the brain of Alzheimer's disease patients. The observation of a parallel improvement of cognitive and functional tests in patients treated with choline alphoscerate plus donepezil versus donepezil alone suggests that morphological changes observed may have functional relevance.

OC15: SHORT-INTERVAL MRI ATROPHY RATES AND IMPLICATIONS FOR CLINICAL TRIAL DESIGN. ALEXANDER J MCC FOULKES[1], JENNIFER M NICHOLAS[1,2], IAN B MALONE[1], CHRIS FROST[1,2], NICK C FOX[1] *((1) Dementia Research Centre, UCL Institute of Neurology, London, UK; (2) London School of Hygiene and Tropical Medicine, London, UK)*

Background: Good drug trial design is critical to the success or failure of novel therapeutics for Alzheimer's disease, and a key component of this comes from understanding the statistical power of different outcome measures. The ADNI2 dataset (Alzheimer's Disease Neuroimaging Initiative) provides T1 volumetric MRI at baseline, 3 months, 6 months and 12 months, as well as psychometric measures. We used this dataset to determine the population characteristics of participants' brain atrophy rates over these short intervals, and to inform sample size calculations required to power clinical trials, including those with a run-in design. *Methods:* After QC fails were removed (~7%), we analysed a total of 1910 T1 volumetric MRIs from 592 participants in the ADNI2 cohort. 484 had good quality imaging from baseline and at least two other time-points. 348 had good quality imaging from all time-points. There were 172 participants who were cognitively healthy at baseline (age=72.9±10.0; 52%M), 161 diagnosed as early MCI (EMCI; age=70.3±10.5; 44%M), 152 diagnosed as late MCI (LMCI; age=72.1±7.7; 47%M) and 107 diagnosed as Alzheimer's disease (age= 75.0±7.7; 39%M). Annualized% atrophy was measured by calculating boundary-shift integrals for whole brain (BBSI), ventricles (VBSI) and hippocampi (HBSI) between the baseline MRI and each time-point and then normalizing for baseline brain volume and time interval between MRIs. Power calculations were performed for each diagnostic group and each time interval to calculate the sample size required for a randomized control trial with equal numbers of subjects in each arm to detect a 25% reduction in atrophy with 90% power. Bootstrapping was used to calculate 95% confidence intervals. An additional analysis was performed to calculate the sample size required to power a 'run-in' trial design, in which the rate of atrophy over the first 3 months (the run-in period) was used as a covariate in the analysis of the rate of atrophy over the subsequent 9 months (the treatment period). *Results:* The mean (SD) rate of whole-brain atrophy (%/yr) at 12 months was 1.64 (0.89) for participants diagnosed with AD, 1.03 (0.84) for LMCI, 0.70 (0.70) for EMCI and 0.64 (0.67) for normal controls. The sample sizes (95% CI) for 90% power to detect a 25% reduction in atrophy in subjects with AD were 898 (463 – 2084) over 3 months, 245 (119 – 544) over 6 months and 100 (57 – 181) over 12 months. In subjects with LMCI these were 1351 (691 – 3357) over 3 months, 520 (341 – 861) over 6 months and 225 (161 – 333) over 12 months. In subjects with EMCI these were 2143 (1055 – 6372) over 3 months, 1414 (781 – 3178) over 6 months and 331 (217 – 541) over 12 months. Samples sizes required for a 12-month trial with a run-in design were 101 (66 – 166) for subjects with AD, 341 (225 – 573) in LMCI and 522 (320 – 942) in EMCI. *Conclusions:* This is the largest short-interval MRI dataset yet analysed. The mean atrophy rates were reasonably stable across different time intervals, with the standard deviation of the rates reducing by a little under a half for each doubling of time interval. Sample sizes therefore reduce by a factor of nearly four for each doubling of time interval between 3 and 12 months. This is in keeping with previous work on samples sizes based on longer time intervals (Schott et al, 2006, J.Neurol. 253:1147-53). The statistical power of a run-in design (of 3-then-9 months) does not appear to be better than that of a conventional design over 12 months. A number of factors may contribute to this. In particular, the variance when measuring brain atrophy on MRI over 9 months instead of 12 is greater, and there is a negative correlation between atrophy rates over the first and second measurement periods when they share the middle time-point. Thus even though there are advantages of accounting for between-subject heterogeneity by measuring individual baseline rates of atrophy, this is balanced by other factors that erode this theoretical advantage over this time period.

OC16: IMPACT OF A MULTI-DOMAIN INTERVENTION ON BRAIN ATROPHY RATE: THE MAPT MRI ANCILLARY STUDY. CAROLE DUFOUIL[1], JEAN-FRANÇOIS MANGIN[2], ALI BOUYAHIA[3], MICHÈLE ALLARD[4], FRÉDÉRIC RICOLFI[5], DOMINIQUE DUBOIS[6], MARIE PAULE BONCEOUR MARTEL[7], FRANÇOIS COTTON[8], ALAIN BONAFÉ[9], STÉPHANE CHANALET[10], FRANÇOISE HUGON[11], FABRICE BONNEVILLE[12], CHRISTOPHE COGNARD[12],

FRANÇOIS CHOLLET[12], ISABELLE CARRIE[13], S. GILLETTE-GUYONNET[13], SANDRINE ANDRIEU[13], STÉPHANE LEHÉRICY[14], MARIE CHUPIN[3], BRUNO VELLAS[13] *((1) INSERM Center U897, CIC-EC7, Bordeaux University, Department of Public Health of CHU Bordeaux, Bordeaux, France; (2) CATI, NeuroSpin, CEA-Saclay Center, Gif-sur-Yvette, France; (3) Inserm U1127, CNRS UMR 7225, Sorbonne Universités, UPMC Univ Paris 06 UMR S 1127, Institut du Cerveau et de la Moelle épinière, ICM, Inria Paris-Rocquencourt, F-75013, Paris, France; (4) Neuroimaging department, CHU Bordeaux, Bordeaux, France; (5) Neuroimaging department, CHU Dijon, Dijon, France; (6) Neuroimaging department, CH Foix, Foix, France; (7) Neuroimaging department, CHU Limoges, Limoges, France; (8) Neuroimaging department, CHU Lyon, Lyon, France; (9) Neuroimaging department, CHU Montpellier, Montpellier, France; (10) Neuroimaging department, CHU Nice, Nice, France; (11) Neuroimaging department, CH Tarbes, Tarbes, France; (12) Neuroimaging department, CHU Bordeaux, Bordeaux, France; (13) Gérontopôle, Department of Geriatrics, CHU Toulouse, Purpan University Hospital, Toulouse, France; (14) Institut du Cerveau et de la Moelle épinière, Centre de NeuroImagerie de Recherche (CENIR), InstiCRICM, UPMC/Inserm U975, CNRS 7225, Hôpital Pitié Salpétrière, Paris, France)*

Introduction: Neuroimaging studies have shown that, in the cognitively normal individuals, brain is shrinking at a rate of about 0.5% per year. In those with AD (Alzheimer's disease) the rate is accelerated by a factor 5. Several studies have also suggested, that in patients with MCI or in persons with cognitive complaints, brain atrophy predicts future cognitive decline. It has therefore been suggested brain atrophy to be used as a surrogate marker for disease modification in clinical trials. *Objectives:* To assess the impact of the different intervention strategies used in the MAPT trial on the rate of whole brain atrophy and the rate of hippocampal volume atrophy in a large sample. *Results:* Nine centers agreed to participate in the MAPT MRI ancillary study. In total, a baseline MRI scan was performed in 503 participants that were aged 75 years old on average. After a follow-up of up to 3 years, 380 participants had a follow-up MRI. We will compare the atrophy rates (total and hippocampal) in the 3 intervention groups (omega-3 alone, Multi-domain intervention alone, omega-3 plus multi-domain intervention) to those observed in the placebo group. Similarly the impact of the intervention on change in white matter lesions load will be analyzed. Results of sensitivity analyses will be presented that assess the impact of trial attrition on the findings. *Conclusion:* The MAPT-MRI ancillary study is one of the largest neuroimaging trials aiming at studying the impact of prevention strategies on brain shrinkage in frail individuals aged 70 years old and above. Results of the trial will have an impact on the design of future neuroimaging AD prevention trials.

OC17: THE DOWN SYNDROME BIOMARKER INITIATIVE (DSBI) PILOT: PROOF OF CONCEPT FOR DEEP PHENOTYPING OF AD BIOMARKERS IN DS. MICHAEL S. RAFII[1], HANNAH WISHNEK[1], JAMES B. BREWER[1], MICHAEL C. DONOHUE[1], SETH NESS[2], WILLIAM C. MOBLEY[1], PAUL S. AISEN[3], ROBERT A. RISSMAN[1] *((1) Alzheimer's Disease Cooperative Study, Department of Neurosciences, University of California, San Diego, CA, USA; (2) Janssen Research and Development LLC, Titusville, New Jersey - USA; (3) Alzheimer's Therapeutic Research Institute (ATRI) University of Southern California (USC) at San Diego)*

Background: To gain further knowledge on the preclinical phase of AD, we sought to characterize cognitive performance, volumetric MRI, amyloid PET, FDG PET, retinal amyloid, and plasma biomarkers in a cohort of non-demented adults with Down Syndrome (DS). The goal of the Down Syndrome Biomarker Initiative (DSBI) pilot is to test feasibility of this approach for future multicenter studies. *Methods:* We enrolled 12 non-demented participants with DS between the ages of 30-60 years old. Participants underwent extensive cognitive testing, volumetric MRI, amyloid PET 18F-florbetapir, 18F-fluorodeoxyglucose (18F-FDG) PET and retinal amyloid imaging. In addition, plasma beta-amyloid species were measured and ApoE genotyping was performed. *Results:* Consistent with previous autopsy studies, most subjects demonstrated amyloid PET positivity reflecting fibrillar amyloid plaque deposition. Results from our multimodal analysis also suggest greater hippocampal atrophy with amyloid load. One year follow up data indicate reginal atrophy rates consistent with AD. Additionally, we identified an inverse relationship between amyloid load and regional glucose metabolism. Cognitive and functional measures did not correlate with amyloid load in DS but did correlate with regional FDG PET measures. Retinal amyloid imaging demonstrated presence of plaques. Biomarkers of AD can be readily studied in adults with DS as in other preclinical AD populations. *Conclusion:* The data indicate that a large, multicenter longitudinal study is feasible to better understand the trajectories of AD biomarkers in this enriched population.

OC18: TWO PHASE IIB TRIALS OF S 38093 IN ALZHEIMER'S DISEASE PATIENTS AT MILD TO MODERATE STAGE. ROY JONES[1], BRUNO VELLAS[2], SERGE GAUTHIER[3], BÉNÉDICTE COGNET[4], ANTHONY BAURAND[5], HANS-MARTIN SCHNEBLE[4], ANNETTE MERDES[5] *((1) RICE - Research Institute for the Care of Older People, Bath, United Kingdom; (2) C.H.U. Toulouse, France; (3) McGill Centre for Studies in Aging, Montréal, Canada; (4) Institut de Recherches Internationales Servier, Suresnes, France; (5) Servier Forschung und Pharma-Entwicklung, München, Germany)*

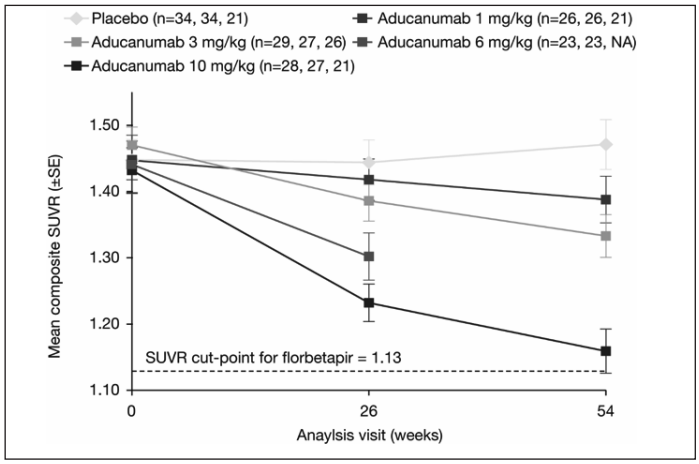
Background: S38093 possesses antagonist properties at Histamine H3 receptors and displays robust cognition-enhancing actions in various preclinical models, together with a good safety profile in healthy young and older volunteers. *Methods:* Two double-blind, randomized, placebo-controlled trials with a 24-week treatment period of 4 parallel groups of S 38093 of 2mg, 5mg or 20mg, or placebo daily were conducted; one in 711 randomized AD patients at the mild to moderate stage (MMSE 15-24) and one add-on donepezil in 806 randomized AD patients at the moderate stage (MMSE 12-20). The primary outcome measure was the score on the 11-item subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog11) and the key secondary outcome measure was the Disability Assessment for Dementia (DAD). Secondary outcome measures included the Mini-Mental State Examination (MMSE), the Neuropsychiatric Inventory (NPI 12 items), the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS CGIC) and the Zarit burden inventory. *Results:* There were no significant between-group differences in the primary outcome. At week 24, in the «pure» placebo study, the between-group differences (S 38093 minus placebo group) in the change from baseline in the ADAS-Cog 11 scores were -0.8 (P=0.47) with the 2mg dose of S 38093, -0.3 (P=1.0) with the 5mg dose and -0.6 with the 20mg dose of S 38093; in the add-on donepezil study, the corresponding differences were 0.7 (P=1.0) with the 2mg dose, 0.5 (P=1.0) with the 5mg dose and -0.04 (P=1.0) with the 20mg dose of S 38093. No significant difference in change from baseline was demonstrated on function (DAD), and no trend was observed on the other secondary outcome measures. Overall, the safety profile was good. The most frequently observed emergent adverse event in patients receiving S 38093 was fall, in the «pure» placebo study 4.5%, 5.1% and 4.4% with the 2mg, 5mg and 20mg dose, respectively, versus 2.2% in patients receiving placebo; in the S 38093 add-on

donepezil study in 3%, 8% and 6.4% with the 2mg, 5mg and 20mg dose, respectively versus 4.5% in patients receiving placebo. Other aspects of these trials of potential relevance to the design and outcome of future trials are currently being evaluated. *Conclusion:* S 38093 did not improve clinical outcomes in patients with Alzheimer's disease in these two clinical trials, despite robust preclinical findings.

OC19: RANDOMIZED, PLACEBO-CONTROLLED, PHASE 1B STUDY OF THE ANTI–BETA-AMYLOID ANTIBODY ADUCANUMAB (BIIB037) IN PATIENTS WITH PRODROMAL OR MILD ALZHEIMER'S DISEASE: INTERIM RESULTS. JEFF SEVIGNY[1], PING CHIAO[1], LESLIE WILLIAMS[1], TIANLE CHEN[1], YAN LING[1], JOHN O'GORMAN[1], CHRISTOPH HOCK[2], ROGER M NITSCH[2], ALFRED SANDROCK[1] *((1) Biogen, Cambridge, MA, USA; (2) Neurimmune Holding AG and University of Zurich, Zurich, Switzerland)*

Background: Aducanumab (BIIB037) is a human monoclonal antibody against aggregated forms of beta-amyloid (Aβ) being investigated as a disease-modifying treatment for patients with Alzheimer's disease (AD). The ongoing Phase 1b PRIME study is evaluating the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple doses of aducanumab in patients with prodromal or mild AD. *Methods:* In this multicenter, randomized, double-blind, placebo-controlled, multiple-dose study (PRIME; NCT01677572), patients (age 50-90 years) had positive florbetapir (Amyvid) positron emission tomography (PET) scans and met clinical criteria for prodromal or mild AD. In a parallel staggered cohort design, patients were randomized to receive aducanumab (1, 3, 6, or 10 mg/kg or dose titration) or placebo (ratio of 3:1 active versus placebo) once every 4 weeks for 52 weeks within 9 treatment arms stratified by ApoE4 status. The primary endpoint assessed safety and tolerability; secondary endpoints included pharmacokinetic parameters, presence of anti-aducanumab antibodies, and change from baseline to Week 26 in amyloid plaque burden, as measured by PET imaging. Changes in clinical measures of cognitive decline (including change from baseline in Clinical Dementia Rating, sum of boxes [CDR-sb] and Mini-Mental State Examination [MMSE] scores) were assessed in exploratory endpoints. We report interim safety, Aβ reduction by amyloid PET, and exploratory clinical endpoints (changes from baseline in CDR-sb and MMSE). PRIME is ongoing; the interim analyses reported here include results to Week 30 (for aducanumab 6 mg/kg and corresponding placebo) and Week 54 (for aducanumab 1, 3, and 10 mg/kg and corresponding placebo; Week 54 data for aducanumab 6 mg/kg not yet available for this interim analysis; updated interim data will be presented). *Results:* Patients (N=166) were randomized to placebo (n=40, pooled), 1 (n=31), 3 (n=33), 6 (n=30), or 10 (n=32) mg/kg aducanumab. The most common adverse events (AE) were amyloid-related imaging abnormalities (incidence of ARIA as detected by MRI: 10%, 16%, 33%, and 47% for 1, 3, 6, and 10 mg/kg aducanumab, respectively, versus 5% for placebo) and headache (16%, 16%, 27%, and 28% versus 5%). The most common serious AE was ARIA (incidence: 3%, 3%, 13%, and 19% versus 0%). Treatment-related dose- and time-dependent reductions in brain amyloid plaque burden (as shown by standard uptake value ratio reduction at Week 26 and further reductions at Week 54) were observed within the doses tested (Figure). Dose-dependent attenuation of cognitive decline was observed with aducanumab in exploratory clinical endpoints. *Conclusion:* Dose-dependent ARIA was the main safety and tolerability finding. Aducanumab reduced amyloid plaque burden as measured by PET imaging in patients with prodromal or mild AD. A clinical signal was observed in exploratory analysis. This study is funded by Biogen.

Figure



OC20: ELND005 FOR AGITATION AND AGGRESSION IN ALZHEIMER'S DISEASE (HARMONY-AD STUDY): PHASE 2/3 DESIGN AND CLINICAL OUTCOMES. ANTON P PORSTEINSSON[1], SUSAN ABUSHAKRA[2], MERCE BOADA[3], IRA GOODMAN[4], GIOVANNI MAROTTA[5], ALEKSANDRA PASTRAK[2], EARVIN LIANG[2], RACHELLE DOODY[6], BRUNO VELLAS[7], CONSTANTINE LYKETSOS[8] *((1) University of Rochester School of Medicine and Dentistry, Rochester, NY, USA; (2) Transition Therapeutics Ireland Limited, Dublin, Ireland; (3) Fundacion ACE, Barcelona Alzheimer Treatment & Research Center, Barcelona, Spain; (4) Compass Research, Orlando, FL, USA; (5) Centre for Memory and Aging, Gerontion Research, Toronto, Canada; (6) Department of Neurology, Baylor College of Medicine, Houston TX, USA; (7) University of Toulouse, Alzheimer's Disease Research Center, Toulouse, France; (8) Department of Psychiatry, Johns Hopkins University, Baltimore MD, USA)*

Background: Agitation and Aggression are the most disruptive neuropsychiatric symptoms (NPS) in AD dementia, and a major reason for psychiatric admissions (Soto et al. 2014). Agitation and Aggression (Agit/Aggr) occur in up to 50% of AD patients, and are associated with increased morbidity, caregiver burden and healthcare cost. Agit/Aggr are likely related to mono-aminergic imbalance and synaptic dysfunction in limbic frontal networks (Lyketsos, 2006, Van Dam et al, 2013), possibly due to amyloid toxicity and disruption of neuronal signaling in AD (Liu et al, 2011). To date, there are no FDA approved drugs for this indication, and few drugs have shown definitive efficacy and acceptable safety in AD patients with Agit/Aggr. Antipsychotics are frequently used "off-label" despite their known safety risks in this population. There is a major need for a drug with a favorable safety and efficacy profile. ELND005 (Scyllo-inositol) has received fast track status designation from the US FDA for its evaluation in this indication. This is based on clinical and biomarker effects in a prior 78-week AD study (Study AD201, Salloway et al, 2011). Similar to lithium, lowering of brain myo-inositol by ELND005 is thought to regulate phospho-inositol signaling in limbic frontal networks, leading to mood stabilizing effects. In Study AD201, the 250mgBID dose showed lowering of CSF Abeta42 at 78 weeks. This dose also showed beneficial trends on NPI-Agit/Aggr at earlier time points (12 and 24 weeks) and ~ 40% reduction of myo-inositol on brain imaging (Abushakra et al. CTAD 2012). The HARMONY-AD program includes a 12-week placebo-controlled study AG201, and a blinded 36-week safety extension (Study AG251). Study AG201 was recently completed, while AG251 is still ongoing. *Objectives:* The primary objective of the study is to evaluate the efficacy of ELND005 treatment compared with placebo in reducing

the severity of agitation and aggression at 12 weeks. *Methods:* This was a randomized, double-blind, placebo-controlled study of 12 weeks duration, with 2 parallel arms: Placebo or Active drug. The dosing regimen included loading (1000mg BID for 4 weeks) and maintenance doses (250mg BID for 8 weeks). Inclusion required screening MMSE between 5-24 inclusive, and at least moderate Agit/Aggr (NPI-Agit/Aggr ≥ 4). The study included subjects residing at home, in assisted living and/or skilled nursing facilities. Primary outcome was summed Agitation and Aggression scores from the NPI-C, which is an expanded form of the original Cummings NPI, and is rated by a trained clinician. The NPI-C Agitation and Aggression domains include 21 items/questions (DeMedeiros et al. 2010). Secondary outcomes included NPI-Agit/Aggr domain (includes 8 items/questions) and ADCS-CGIC as global assessment. *Results:* The study enrolled 350 mild to severe AD patients who received study drug (Safety Set), and 314 patients completed the study. The modified ITT Set included 334 patients (mean age 76 years, 56% female/87% Caucasian). Baseline mean scores were: MMSE 14.6 (5.8), NPI-total 47.3 (25.5), NPI Agit/Aggr 7.2 (2.5), and NPI-C Agitation + Aggression score 18.7 (10.3). At baseline, there was a high prevalence of irritability, apathy, anxiety, depression, and aberrant motor behavior, and approximately 55% were on psychotropic agents. Of the 350 enrolled patients, a total of 157 had baseline MMSE > 15. Of the 314 patients who completed the study, a total of 297 continued in the blinded extension study. Topline efficacy and safety results will be presented. *Conclusion:* Study AG201 is, to date, the largest completed study of Agitation and Aggression in AD. Baseline patient characteristics, including severity of Agit/Aggr, are similar to those from recent positive agitation studies in AD (Porsteinsson et al., 2014), and are consistent with recently proposed criteria for agitation in dementia (Cummings et al., 2014). This is the first intervention trial to use the expanded NPI-C as primary outcome, and includes NPI-Agit/Aggr as a secondary outcome. This will allow comparison of drug effects on the NPI and NPI-C scale. A safe and effective drug for this indication fulfills a major unmet need in AD patients.

OC21: A NEW PLASMA METABOLOMICS PANEL PREDICTS PRECLINICAL TO CLINICAL ALZHEIMER'S DISEASE TRANSITION. MASSIMO S FIANDACA[1,2], XIAOGANG ZHONG[3], AMRITA K CHEEMA[4], MICHAEL H ORQUIZA[2], SWATHI CHIDAMBARAM[5], MING T TAN[3], MIKE A NALLS[6], MARK MAPSTONE[7], HOWARD J FEDEROFF[1,2] *((1) Neurology Department, Georgetown University Medical Center, Washington, DC, USA; (2) Neuroscience Department, Georgetown University Medical Center, Washington, DC, USA; (3) Department of Bioinformatics, Biostatistics and Biomathematics, Georgetown University Medical Center, Washington, DC, USA; (4) Departments of Oncology and Biochemistry, Georgetown University Medical Center, Washington, DC, USA; (5) School of Medicine, Georgetown University, Washington, DC, USA; (6) Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA; (7) Neurology Department, University of Rochester Medical Center, Rochester, NY, USA)*

Background: Lipid dysregulation has been a consistent finding within the brains of individuals succumbing to Alzheimer's disease (AD) since the sentinel description by Alois Alzheimer. We recently discovered and validated reductions in specific plasma lipid species in a longitudinal cohort of healthy septuagenarians that went on to phenoconvert to clinical stages of late-onset AD (LOAD). Ten specific plasma lipids, featuring choline phospholipids and acylcarnitines, were significantly reduced in the cognitively normal seniors that would go on to show significant memory deterioration, with or without functional impairment during the 5-year study. Despite defining a classifier with 90% sensitivity and specificity for risk determination in a preclinical population of seniors, the published plasma lipid panel did not achieve the predictive requirements for utility as a general screening tool, despite signaling the potential for such metabolite panels in helping define preclinical stages of LOAD. A blood-based screening tool may be useful for enriching LOAD clinical trial subject selection for those destined to phenoconvert, potentially reducing the number of subjects and the length of trial required and thereby the limiting trial costs. In the next phase of analysis of our longitudinal cohort's metabolomic dataset, we attempted to further improve our accuracy and predictive capability through the identification of an additional biomarker panel. A more accurate preclinical risk panel would allow increased confidence by physicians (and researchers) regarding the likely clinical trajectory of their patients (or subjects). Such information would allow advanced planning and counseling for patients and allow selection for inclusion in secondary prevention trials of novel or repurposed preclinical therapeutics. *Methods:* We reanalyzed the metabolomic dataset we had put in the public domain as part of our original biomarker publication. Discovery analyses were performed on the metabolomic data from 71 cognitively normal septuagenarians who were all initially neuropsychologically "normal", and a subset of which went on to phenoconvert to prodromal or manifest LOAD by the end of year 3 of the 5-year study. Data from a validation cohort of 30 additional subjects, a subset of which phenoconverted between the end of year 3 and year 5, was similarly analyzed. Normalization of the data and LASSO restriction was carried out, as in our previous report. Liberalization of the type and number of analytes available for inclusion in developing the best predictive classifier, compared to limited selection criteria used for our 10-lipid panel, was hypothesized to improve the accuracy and predictive power of the resulting biomarker set. *Results:* A novel plasma 24-metabolite panel was discovered and validated, featuring 22 lipid species, an amino acid, and a biogenic amine. Seven analytes from our original 10-lipid panel were selected for the novel biomarker set, with the majority continuing to represent phosphatidylcholine species (54%), a larger percentage representing acylcarnitines than in the original panel (41% versus 20%), and the two non-lipid biomarkers known to have associations with cognition and inflammation, respectively. Except for three specific acylcarnitines that were increased in phenoconverters, all other biomarker species in the new panel were consistently reduced in those that would progress to prodromal or manifest LOAD. The 24-metabolite classifier readily differentiated between these two preclinical groups with an ROC AUC of 1.00 for the discovery cohort and 0.995 for the validation cohort. A calculated plasma 24-metabolite index provided 100% accuracy for individual phenoconversion risk prediction. Positive (PPV) and negative (NPV) predictive values were improved from those associated with our previous plasma 10-lipid panel, but especially the PPV remained limited by the disease prevalence in septuagenarians and the conservative statistical methods used. *Conclusion:* Although our past and current metabolomic biomarker panels require external validation in larger and more diverse subject cohorts, including those with different dementias represented, we propose that expansion of our biomarker set, to include additional lipid and non-lipid species, provided greater accuracy and predictive power in determining preclinical risk of phenoconversion to the symptomatic stages of LOAD in our study group. The reduction in specific plasma lipid species in those at risk of phenoconversion remains to be adequately explained, but there is growing evidence of both a central (brain) and peripheral (blood) dysregulation of unique lipid species, that may indicate a shared mechanism of action. Such growing evidence may provide a better appreciation for the etiologic pathobiology of LOAD. Our expanded plasma biomarker panel represents an advance in preclinical risk determination that may further support its use in selecting appropriate

individuals for secondary prevention clinical trials. In addition, the new biomarker panel provides further evidence for significant plasma lipid dysregulation during the preclinical stages of LOAD.

OC22: THE INCREMENTAL DIAGNOSTIC VALUE OF 18F FLORBETAPIR IMAGING IN NATURALISTIC PATIENTS WITH COGNITIVE IMPAIRMENT: FINAL RESULTS FROM THE INDIA-FBP STUDY*. BOCCARDI MARINA[1], ALTOMARE DANIELE[1], FESTARI CRISTINA[1], TARALLO ANNA[1], GUERRA UGO PAOLO[2], PAGHERA BARBARA[3], PIZZOCARO CLAUDIO[2], PASQUALETTI PATRIZIO[4], MUSCIO CRISTINA[1,5], PIEVANI MICHELA[1], PADOVANI ALESSANDRO[6], FRISONI GIOVANNI BATTISTA[1,7], AND THE INDIA-FBP WORKING GROUP *((1) Laboratory of Alzheimer's Neuroimaging and Epidemiology, IRCCS Fatebenefratelli, Brescia, Italy; (2) Department of Nuclear Medicine, Poliambulanza Foundation, Brescia, Italy; (3) Nuclear Medicine, University of Brescia and Spedali Civili di Brescia, Brescia, Italy; (4) Fatebenefratelli Hospital of Isola Tiberina, Roma, Italy; (5) European Foundation Biomedical Research (FERB), Center of Excellence Alzheimer, Ospedale Briolini of Gazzaniga, Bergamo, Italy; (6) Centre for Neurodegenerative Disorders, Neurology Unit, University of Brescia, Brescia, Italy; (7) Memory Clinic and LANVIE - Laboratory of Neuroimaging of Aging, University Hospitals and University of Geneva, Geneva, Switzerland)*

Backgrounds: The 18F-Florbetapir PET (FBP-PET) amyloid tracer, recently approved by the FDA and EMA, has a relatively long radioactive half-life (110-min), making amyloid imaging logistically feasible at clinical centers. However, its added diagnostic value is unclear. We aim to evaluate the incremental diagnostic value of 18F-Florbetapir amyloid PET on top of routine assessment for the diagnosis of cognitive impairment. *Methods:* The study, completed in December 2014, included 227 patients from 20 Italian memory clinics. Patients underwent their diagnostic work-up according to usual local practice and physicians initially formulated a clinical diagnosis, rated their diagnostic confidence (0-100%), and prescribed a therapeutic plan. Inclusion criteria for FBP-PET was a diagnostic probability of Alzheimer Disease (AD) between 15% and 85%. Patients then underwent FBP-PET and all the scans were evaluated by two nuclear medicine physicians specifically trained for the procedure. Diagnoses, diagnostic confidence and therapeutic plan were revised by the physician after FBP-PET results. Changes in diagnosis and therapeutic plan were evaluated by the McNemar's Chi-squared test. Diagnostic confidence change was evaluated by Wilcoxon Signed Rank Test (V). A group of 26 healthy elderly controls (HC) was also included and underwent FBP-PET. *Results:* - FBP-PET visual assessment. Two hundred fifty-three PET scans were evaluated by two nuclear medicine physicians, who showed a good agreement (rate of concordance = 87%; Cohen's Kappa = 0.74). - Diagnosis before FBP-PET. 163 patients were diagnosed with AD, 36 with FrontoTemporal Dementia (FTD), 9 with Vascular Dementia (VD), 4 with Lewy Body Disease (LBD), and 15 with Cortical Basal Degeneration (CBD), Parkinson's Disease Dementia (PDD), or other pathologies. - FBP-PET results. Fifty-three AD (33%) tested negative to amyloid-imaging. Positive scans occurred in 15 FTD (42%), 3 VD (33%), 3 LBD (75%), 6 CBD-PDD-other (40%), and 4 HC (15%). 75% of positive HC were men (Figure 1). - Change in diagnosis. FBP-PET results produced a significant diagnostic change from AD to Non-AD, or vice versa ($\chi 2 = 9.8$, p-value = 0.002; Table 1). In 77% (41/53) of AD Aβ– patients, the diagnosis changed into Non-AD (e.g., 30% VD, 21% FTD, 11% depression, 6% SNAP; Table 2). Among Non-AD Aβ+ patients, diagnostic changes into AD occurred in 87% (13/15) of FTD Aβ+ (Table 3), 67% (2/3) of VD Aβ+, 33% (1/3) of LBD Aβ+, and none of CBD-PDD-other Aβ+ (0/6). - Increase in diagnostic confidence. The diagnostic confidence increased significantly after FBP-PET for both patients with confirmed diagnosis of AD (11% increase; V = 491.5, p < 0.001; Figure 3) and those with confirmed diagnosis of non-AD (10% increase; V = 41, p < 0.001; Figure 4). - Change in therapeutic plan. After the FBP-PET scan, there was a significant change in the prescription of AD-specific medications (acetylcholinesterase inhibitor or memantine; $\chi 2 = 47$, p-value < 0.001; Table 4). In particular, an increase of AD-specific medications occurred in 33% (53/163) patients with a diagnosis of AD before the FBP-PET scan. No change occurred for non-AD-specific medications ($\chi 2 = 2.4$, p-value = 0.120). *Conclusion:* Our data are in line with previous reports showing that amyloid PET has a significant impact on diagnosis, diagnostic confidence and therapeutic plan in memory clinic settings. Contrary to expectations, the use of the positive predictive value of FBP-PET was similarly represented to the use of the negative predictive value. These results support a potential beneficial impact of amyloid PET on patients care. Further studies are needed to assess the cost/benefit ratio of amyloid PET in clinical practice. *Full list of INDIA-FBP participants: http://www.centroalzheimer.org/sito/contenuti/ip_lilly_publications/INDIA-FBP_WORKING_GROUP.pdf. Project link: http://www.centroalzheimer.org/sito/ip_lilly.php

Table 1
Change in patients' diagnosis after FBP-PET exam (green cells).

227 patients	AD diagnosis After FBP-PET	Non-AD diagnosis After FBP-PET
AD diagnosis Before FBP-PET	118	45
Non-AD diagnosis Before FBP-PET	19	45

Table 2
Diagnosis after FBP-PET in 163 patients with a clinical diagnosis of AD before FBP-PET.

163 AD patients	Aβ+	Aβ–
Same (AD)	106 (96%)	12 (23%)
SNAP	0	3 (6%)
FTD	1 (1%)	11 (21%)
LBD	1 (1%)	1 (2%)
VD	1 (1%)	16 (30%)
SMI	1 (1%)	2 (4%)
Depression	0	6 (11%)
Other	0	2 (4%)
Total	**110 (100%)**	**53 (100%)**

Table 3
Diagnosis after FBP-PET in 36 patients with a clinical diagnosis of FTD before FBP-PET.

36 FTD patients	Aβ–	Aβ+
AD	2 (10%)	13 (87%)
Same (FTD)	17 (81%)	2 (13%)
VD	2 (10%)	0
Total	**21 (100%)**	**15 (100%)**

Table 4
Change in the prescription of AD-specific medications (green cells).

227 patients	AD-specific prescribed After FBP-PET	AD-specific NOT prescribed After FBP-PET
AD-specific prescribed Before FBP-PET	55	7
AD-specific NOT prescribed Before FBP-PET	67	98

Figure 1
HC divided by age and amy-PET result. In red HC Aβ+ and in blue HC Aβ-

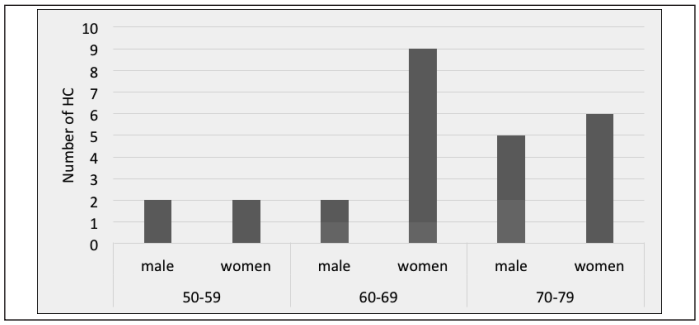


Figure 2
Increase in diagnostic confidence in patients with a confirmed diagnosis of AD. In blue patients resulted Aβ–, in red patients resulted Aβ+

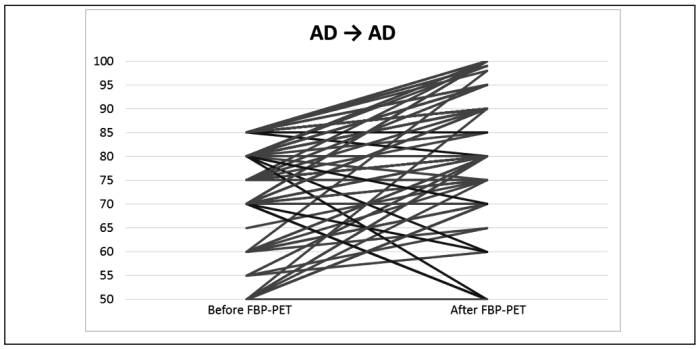
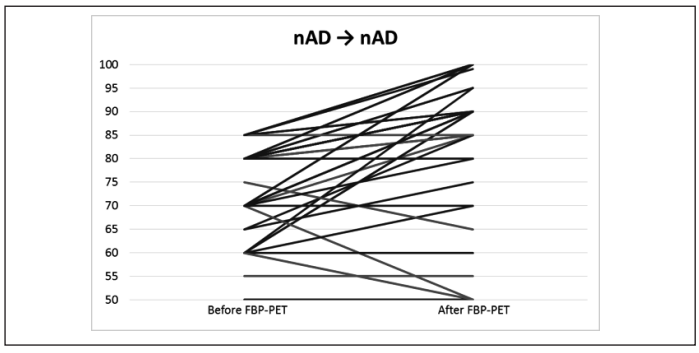


Figure 3
Increase in diagnostic confidence in patients with a confirmed diagnosis of Non-AD. In blue patients resulted Aβ–, in red patients resulted Aβ+



OC23: CSF BIOMARKERS FOR AMYLOID RELATED IMAGING ABNORMALITIES (ARIA) IN IMMUNOTHERAPY TRIALS OF ALZHEIMER'S DISEASE AND CEREBRAL AMYLOID ANGIOPATHY: REPORT FROM THE ICAB INTERNATIONAL NETWORK. FABRIZIO PIAZZA[1] ON BEHALF OF THE INFLAMMATORY CEREBRAL AMYLOID ANGIOPATHY AND ALZHEIMER'S DISEASE BIOMARKERS (ICAB) INTERNATIONAL NETWORK: *Main network co-investigations:* STEVEN M GREENBERG[2], BENGT WINBLAD[3], NICK FOX[4], ALBERTO LLEO[5], FABRIZIO TAGLIAVINI[6], RICARDO NITRINI[7], HIDEYA SAKAGUCHI[8], MASAFUMI IHARA[9], MASSIMO CAULO[10], ANTONINO UNCINI[10], MEHDI TOUAT[11], RICHARD LEVY[11], MARTINA LONGONI[1], JACOPO C DIFRANCESCO[1] *((1) Department of Surgery and Translational Medicine, Milan Center for Neuroscience (NeuroMi), University of Milano-Bicocca, Monza, Italy; (2) Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA; (3) Department of Neurobiology, Care Sciences and Society (NVS), Karolinska Institutet, Center for Alzheimer Research, Division of Neurogeriatrics, Huddinge, Sweden; (4) Dementia Research Centre, Institute of Neurology, Queen Square, London; (5) CIBERNED, IIB-SantPau, Barcelona, Spain; (6) IRCCS Foundation «Carlo Besta» Neurological Institute, Milano, Italy; (7) Department of Neurology, University of Sao Paulo, Sao Paulo, Brazil; (8) Department of Neurology, Kumamoto University, Kumamoto, Japan; (9) Division of Neurology, Department of Stroke and Cerebrovascular Diseases, National Cerebral and Cardiovascular Center; Osaka, Japan; (10) Department of Neuroscience and Imaging, University "G. d'Annunzio", Chieti, Italy; (11) INSERM & Neurology Department, Hospital Saint Antoine, APHP, Paris, France)*

Background: The recent advance in the biomarkers discovery for Alzheimer's disease (AD) and Cerebral Amyloid Angiopathy (CAA) has sensibly accelerated the design of novel disease-modifying therapies (DMT), with different promising anti amyloid-beta (Aβ) therapeutic antibodies already in Phase II and III. The first active and passive immunotherapy strategies tested in clinical trials, i.e. CAD106 or the monoclonal antibody bapineuzumab as well as the subsequent antibodies gantenerumab and solanezumab, however, have been characterized by the occurrence of Amyloid-Related Imaging Abnormalities (ARIA) in more than 17% of the treated patients, probably related to the drug and APOEε4 allele dose. ARIA has generated recent increasing interest because the promising data for the Phase 1b study of aducanumab presented at the 12th AD/PD Meeting in Nice. The enthusiasm for aducanumab may in fact be damped by the even larger occurrence of treatment-related ARIA compared to bapineuzumab or gantenerumab, with an incidence of 55% in the high-dose and ApoEε4 carriers arm, and that 35% of patients discontinued the treatment due to the development of ARIA. In the last decade, ARIA have severely limited the development of immunotherapy, leading to the exclusion of several patients from the opportunity to be treated, and the continuous adjustment of the therapeutic protocols. The discovery of safety biomarkers to avoid, or at least enable, the early detection of ARIA will represent an important challenge to help stratify and personalize treatments, increasing the chances for developing more effective DMT. Biomarkers will have critical implications to predict individuals in a particular disease stage chosen as the therapeutic window for a specific treatment, especially as we move to more large and long duration prevention trials based on the selective enrolment of positive Amyloid-PET patients (and/or CSF), potentially increasing the risk to incur in the same ARIA side-effects of treatment. It is quite clear that without effective biomarkers, we will have the consequence of further unacceptable delays in finding a cure for this devastating disease. Through the iCAβ International Network, we pioneered in showing that CAA-related inflammation (CAA-ri), a rare and aggressive meningoencephalitis affecting CAA, share several similarities with the drug-induced ARIA in AD, suggesting that elevated CSF anti-Aβ autoantibodies, microhemorrhages and vasogenic edema are linked to a transient vascular leakage at the sites of major Aβ removal. ARIA may thus paradoxically represent

a transient but necessary event preceding the downstream beneficial Aβ-clearance effects of treatment, particularly in patients with high degree of CAA, where CSF anti-Aβ antibodies (both therapeutically administered and/or spontaneously produced) may play a key role in the process, causing a shift in CAA accumulation and increased vascular permeability eventually leading to ARIA. These aspects are timely and could provide an important challenge for the field, leading to critical information for the ongoing clinical trials. *Methods:* World-Wide longitudinal study in patients from the iCAβ International Network. By a novel ultra-sensitive technique (patent pending), we evaluated anti-Aβ autoantibody concentration in CSF of CAA-ri, CAA, AD, Multiple Sclerosis and healthy-control. All patients undertaken neuropsychological assessment, T2*/SWI and FLAIR-MRI, Aβ40, Aβ42, tau, P-181 tau and APOE investigation. 15/80 CAA-ri underwent brain biopsy for pathological confirmation, 5/80 Amyloid-PET imaging. *Results:* In CAA-ri, higher amount of anti-Aβ autoantibodies is accompanied by massive drainage of Aβ from the brain and vascular deposits to its soluble pools. Like in immunotherapies, we observed a reduction of both autoantibodies and neurodegenerative markers (tau, P-tau, Aβ40 and Aβ42) in CSF and on Amyloid-PET after clinical-radiological remission, either spontaneously or after immunosuppressive treatment. An increased concentration of autoantibodies in AD carrying the APOEe4 allele has been observed. Diagnostic cut-off for CSF anti-Aβ autoantibodies, by ROC curve analyses, has been determined. *Conclusions:* The correct dosing of the therapeutic drug is a vital challenge to address. This may perhaps explain the lack of efficacy of previous DMT compared to aducanumab, where the dosage has often been limited due to the concerns of ARIA side-effects. Our test for CSF anti-Aβ autoantibody follow-up would allow maintaining a putative "therapeutic window" for the safe clearance of vascular Aβ limiting the occurrence of ARIA, placing the CSF dosage of anti-Aβ autoantibodies as a very promising biomarker currently on the market. The monitoring of CSF autoantibody may allow to personalize treatment for a greater clinical effect, but still minimise the occurrences of the putative side effects (ARIA paradox). This may be particularly true for patients at high risk of ARIA, e.g. high CSF autoantibody titre at the baseline, before treatment, and/or APOEe4 carriers. Cut-off for the early diagnosis/prediction of ARIA will eventually allow a prompt treatment with steroids, thus avoiding the exclusion of these patients from trials, with relevant impacts for the patient outcomes. We strongly believe that the inclusion of CSF anti-Aβ autoantibody as biomarkers for the ongoing immunotherapy trials should be taken in serious consideration, not only in order to avoid the occurrence of ARIA but also to increase understanding of its mechanisms of action and a better interpretation of the trial outcomes.

OC24: RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDIES TO EVALUATE TREATMENT WITH ADUCANUMAB (BIIB037) IN PATIENTS WITH EARLY ALZHEIMER'S DISEASE: PHASE 3 STUDY DESIGN.

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Background: Aducanumab (BIIB037) is a human monoclonal antibody against aggregated forms of beta-amyloid (Aβ) being investigated as a disease-modifying treatment for patients with Alzheimer's disease (AD). Interim analyses of an ongoing Phase 1b study of aducanumab in patients with prodromal or mild AD have demonstrated target engagement, pharmacodynamic effect of Aβ reduction, and an effect on exploratory clinical endpoints (change from baseline in Clinical Dementia Rating-Sum of Boxes [CDR-sb] and Mini-Mental State Examination [MMSE]); the most common adverse event (AE) was amyloid-related imaging abnormalities (ARIA). Here, we describe the design of 2, Phase 3 studies evaluating the efficacy and safety of monthly IV doses of aducanumab in patients with early AD. *Methods:* Two randomized, placebo-controlled, Phase 3 studies (ENGAGE; Protocol 221AD301 and EMERGE; Protocol 221AD302) with identical design will be conducted, each across approximately 150 sites globally. Eligible patients (planned N=1350 in each study) are 50-85 years old, have mild cognitive impairment (MCI) due to AD or have mild AD according to National Institute on Aging-Alzheimer's Association guidelines. In addition, patients must have a CDR-global score of 0.5, Repeatable Battery for Assessment of Neuropsychological Status score ≤85, and MMSE score of 24-30 and have elevated brain amyloid as measured by amyloid position emission tomography (PET) scan (visual read). For the 18-month placebo-controlled period, patients will be randomized (doses based on ApoE4 carrier status) in a 1:1:1 ratio to low-dose or high-dose aducanumab, or placebo, administered every 4 weeks following a dose titration regimen. After completing the placebo-controlled period, patients who meet the extension entry criteria will have the option to enter the 24-month dose-blind long-term extension period, during which all participants receive aducanumab. Patients receiving aducanumab during the placebo-controlled period will continue on the same dose; those randomized to placebo will be re-randomized 1:1 (stratified by ApoE4 carrier status) to low-dose or high-dose aducanumab. The primary endpoint for the placebo-controlled period will assess the efficacy of aducanumab in slowing global decline as measured by changes from baseline in CDR-sb score at Week 78. Secondary endpoints will assess clinical progression as measured by changes from baseline in MMSE score, Alzheimer's Disease Assessment Scale – Cognitive Subscale (13 items) score, and Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (MCI version) score at Week 78. Safety (eg, AEs, brain MRI findings including incidence of ARIA-E and ARIA-H); immunogenicity; pharmacodynamic biomarkers (eg, cerebral amyloid plaque content by amyloid PET); pharmacokinetics; and additional clinical, radiologic, and patient- and informant-reported outcomes will be evaluated as tertiary endpoints. The long-term extension period will evaluate the long-term safety and tolerability of aducanumab and the long-term efficacy as measured by clinical, radiologic, and patient- and informant/caregiver-reported assessments. *Results:* N/A. *Conclusion:* We have designed Phase 3 clinical trials that will determine the clinical efficacy and safety profile of aducanumab in individuals with early AD. This study is funded by Biogen.

OC25: TOLERABILITY AND PRELIMINARY PHARMACODYNAMICS AFTER SINGLE DOSES OF MEDI1814, A BETA-AMYLOID 42 (AB42)-SPECIFIC ANTIBODY, IN MILD-MODERATE ALZHEIMER'S DISEASE.

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MedImmune, UK; (6) Translational Sciences, Gaithersburg, MD, USA)

Background: MEDI1814, a fully human IgG1λ monoclonal antibody, was engineered for selective, high-affinity binding of Aβx-42 (Aβ42) peptides as well as to have a greatly reduced effector function by introducing a triple mutation (TM) into the Fc region. In vitro, MEDI1814 binds specifically all forms of Aβ42 peptides but not Aβ40 peptides. In rats and cynomolgous monkeys, MEDI1814 increases total and decreases free CSFAβ42 levels, but does not affect total CSF Aβ40 levels. *Methods:* Subjects aged 55-85 with mild to moderate Alzheimer's Disease (AD) were randomized into a 2-part, single/ multiple ascending dose study. Key inclusion criteria were a > 6-month history of probable AD, according to National Institute of Aging-Alzheimer's Association (NIA-AA) criteria, and an MMSE score of 16-26 inclusive. In the single ascending dose portion, subjects were administered intravenous doses of MEDI1814 or placebo at 25, 100, and 300 mg (Cohorts 1-3, respectively), with a target of 6 subjects receiving active drug and 2 placebo (saline) per cohort. Safety data, including a 5-week cerebral MRI scan, of at least 5 subjects were reviewed prior to dose escalating to the next cohort. *Results:* For doses of 25 to 300 mg, MEDI1814 was well tolerated with no serious adverse events reported. No cases of amyloid-related imaging abnormalities (ARIA) have been observed. Preliminary CSF pharmacodynamics indicate specific binding to Aβ42 and not Aβ40, similar to results seen in preclinical species. *Conclusions:* To date, MEDI1814 appears safe and well tolerated at single intravenous doses up to 300 mg, with no evidence of ARIA. Suppression of CSF Aβ42 peptides specifically has been demonstrated by MEDI1814. Results of an interim analysis will be presented at the meeting.

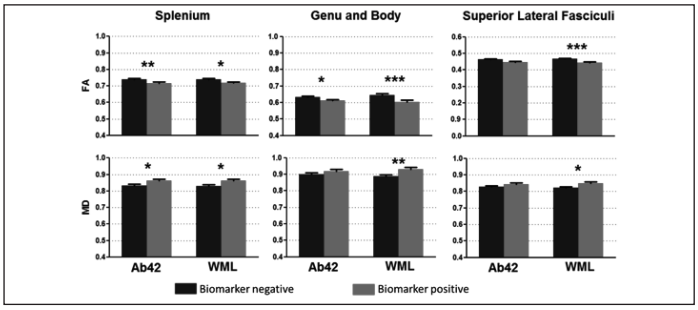
OC26: ADDITIVE AND INDEPENDENT EFFECT OF VASCULAR AND AMYLOID PATHOLOGY ON STRUCTURAL CONNECTIONS IN MILD COGNITIVE IMPAIRMENT. MOIRA MARIZZONI[1], JORGE JOVICICH[2], FLAVIO NOBILI[3], MIRA DIDIC[4,5], DAVID BARTRÉS-FAZ[6], UTE FIEDLER[7], PETER SCHONKNECHT[8], PIERRE PAYOUX[9,10], ALBERTO BELTRAMELLO[11], ANDREA SORICELLI[12,13], LUCILLA PARNETTI[14], MAGDA TSOLAKI[15], PAOLO MARIA ROSSINI[16,17], PHILIP SCHELTENS[18], GIANLUIGI FORLONI[19], REGIS BORDET[20], OLIVIER BLIN[21], GIOVANNI BATTISTA FRISONI[1,22] 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) APHM, CHU Timone, Service de Neurologie et Neuropsychologie, Marseille, France; (5) Aix-Marseille Université, INSERM U 1106, Marseille, France; (6) Department of Psychiatry and Clinical Psychobiology, Universitat de Barcelona and IDIBAPS, Barcelona, Spain; (7) LVR-Clinic for Psychiatry and Psychotherapy, Institutes and Clinics of the University Duisburg-Essen, Essen, Germany; (8) Department of Neuroradiology, University Hospital Leipzig, Leipzig, Germany; (9) INSERM, Imagerie cérébrale et handicaps neurologiques, UMR 825, Toulouse, France; (10) Université de Toulouse, UPS, Imagerie cérébrale et handicaps neurologiques, UMR 825, Toulouse, France; (11) Department of Neuroradiology, General Hospital, Verona, 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 Centre and Department of Neurology, Vrije Universiteit University Medical Center, Amsterdam, The Netherlands; (19) Neuroscience Department, IRCCS Istituto di Ricerche Farmacologiche «Mario Negri», Milano, Italy; (20) Department of Pharmacology, EA1046, University of Lille Nord de France, 59045 Lille Cedex, France; (21) Pharmacology, Assistance Publique-Hôpitaux de Marseille, Aix-Marseille University-CNRS UMR 7289, Marseille, France; (22) Memory Clinic and LANVIE - Laboratory of Neuroimaging of Aging, University Hospitals and University of Geneva, Geneva, Switzerland)*

Background: Amyloid accumulation is useful to identify those MCI who subsequently progress to dementia from those who remain stable (Galluzzi S, 2010). White matter hyperintensities (WMH) cause cognitive decline and are related to the aetiology of dementia (Brickman AM, 2015; Vermeer SE, 2003). Moreover, it was recently hypothesized that WMH, in the presence of significant amyloid load, may provide a second hit necessary for the clinical presentation of AD (Provenzano FA, 2013). Aim of this study is to investigate the effects of amyloid load and vascular pathology (WMH) on structural connections of mild cognitive impairment (MCI) patients. *Methods:* 147 MCI patients were enrolled in WP5 of PharmaCOG (E-ADNI) and underwent CSF collection and high resolution 3T MRI protocol that included DTI and FLAIR sequences. An atlas-based DTI analysis was performed to collect measures of fractional anisotropy (FA) and mean diffusivity (MD) from corpus callosum and from several association tracts (i.e. superior lateral fasciculi) (Jovicich et al., 2014). White matter hyperintensities (WMH) volume was extracted using LesionTOADS software (www.mipav.cit.nih.gov) on intensity inhomogeneity corrected FLAIR. Patients were defined positive for vascular pathology when the WML volume was greater than 0.5% of intracranial volume (Chao LL, 2013) and positive for amyloid when the CSF Ab42 level was lower than 550 pg/mL (Mulder C, 2010). Multivariate analysis of covariance (MANCOVA) was performed considering amyloid and vascular status as independent factors, diffusion estimates as dependent variables and correcting for age, gender and ApoE ε4 genotype. Based on MANCOVA results, a new variable was defined considering the following three groups: biomarker negative (Ab- WML-), amyloid positive only (Ab+), vascular pathology positive only (WML+) and amyloid-vascular pathology positive (Ab+ WML+); post-hoc Tukey's test was applied to compare their diffusion indices estimates. *Results:* Figure 1 summarizes the main effects of vascular and amyloid pathology on the FA and MD extracted from corpus callosum and associations fibers. Vascular positivity was associated with lower FA and higher MD in the corpus callosum (splenium, $p<0.05$; genu-body, $p<0.01$) and SLF ($p<0.05$). Amyloid positivity was associated with diffusion pathological alterations mainly in the splenium (lower FA, $p<0.05$; higher MD, $p<0,01$) of the corpus callosum. No significant interactions between Ab42 and WMH were reported. Diffusion indices comparison among Ab- WML-, Ab+ or WML+ and Ab+ WML+ showed a similar trend of alterations in all the ROI and for all the diffusion metrics considered: Ab+ WML+> WML+ or Ab+> Ab-WML-. Significant differences were reported for: i) lower FA and higher MD from all tracts between Ab+ WML+ and Ab- WML-MCI patients ($p<0.05$ at Tukey's post hoc test), ii) lower FA in all tracts between Ab- WML- and MCI patients positive for at least one marker ($p<0.05$ at Tukey's post hoc test), iii) lower FA in the genu of the corpus callosum between Ab+ WML+ and patients with at least one positive marker ($p<0.05$ at Tukey's post hoc test). *Conclusions:* We found that i) vascular pathology alters diffusion in all the fiber tracts considered, ii) amyloid influences diffusivity mainly in splenium of the corpus callosum, iii) amyloid and vascular pathology act in an independent manner, iv) an additive effects is detected when both coexists. These results suggest that vascular pathology,

as well as amyloid, may play an important role in the connectivity deterioration of MCI patients and it should be taken into account in future prevention strategies aimed at delaying the AD clinical manifestation. Pharmacog is funded by the EU-FP7 for the Innovative Medicine Initiative (grant n°115009).

Figure 1

Effects of amyloid (Ab42) and vascular (WML) pathology on FA and MD from corpus callosum and association fibers. Error bars indicate the standard error on the least square mean. *p<0.05, ** p< 0.001, *** p<0.001 are refered to Ab42 or WML effect



OC27: EFFECT OF INSULIN SENSITIZER METFORMIN ON AD BIOMARKERS (NCT01965756): INITIAL FINDINGS OF A RANDOMIZED PLACEBO CONTROLLED CROSSOVER PILOT STUDY OF METFORMIN EFFECTS ON BIOCHEMICAL, NEUROPHYSIOLOGICAL AND COGNITIVE BIOMARKERS OF AMNESTIC MCI AND MILD AD. STEVEN E ARNOLD[1,2,3], DAVID A WOLK[1,3], DAWN MECHANIC-HAMILTON[1,2], AARON M KOENIG[1,2], SHARON X XIE[4], ANNE R CAPPOLA[5], MARTHA F COMBS[1,2], NATALIA LOUNEVA[2] *((1) Penn Memory Center, University of Pennsylvania, Philadelphia, PA, USA; (2) Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA; (3) Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA; (4) Department of Epidemiology & Biostatistics, University of Pennsylvania, Philadelphia, PA, USA; (5) Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA)*

Background: Epidemiological studies find a robust association between Type II diabetes mellitus and dementia, including Alzheimer's disease (AD), and recent neurobiological studies have shown abnormalities in brain insulin signaling in AD indicating insulin resistance (IR), even in non-diabetics. Our molecular neuropathological studies have found direct evidence of brain IR in MCI and AD as well as abnormal activation of both proximal insulin signaling molecules and downstream components and regulators of neuronal insulin signaling. Preclinical studies have provided evidence for reciprocal relationships of IR with β-amyloid (Aβ) and tau mechanisms. Transgenic Aβ and tau mouse models show neuronal IR while diet-induced brain IR accelerates Aβ accumulation and induces tau phosphorylation. Insulin sensitizing drugs decrease Aβ and inflammatory pathology in transgenic mice and improve long-term potentiation and spatial memory and other studies have shown beneficial effects of insulin-sensitizers on chronic hyperinsulinemia-induced tau phosphorylation. Given the association of brain IR with AD, we hypothesized that CNS-penetrant insulin-sensitizing medications already approved for diabetes may prove beneficial as disease modifying and/or symptomatic therapies for AD. Metformin is a first-line drug for type II diabetes. Its principal mechanism of action is activation of AMP-activated protein kinase (AMPK), which then inactivates the mTOR/p70S6K-mediated negative feedback loop to insulin receptor substrate-1, thus enhancing insulin signaling. To begin a translational evaluation of metformin in human AD, we conducted a brief, efficient pilot clinical trial in subjects with MCI and mild-stage dementia due to AD using high-dose metformin and multi-dimensional biomarker and cognitive outcomes. *Methods:* We conducted a 16-week, randomized double-blind placebo crossover study of metformin in non-diabetic patients with MCI or early dementia due to AD. Essential eligibility criteria included ages 55-80, diagnosis of amnestic MCI or mild-stage dementia due to AD (MMSE>19, CDR 0.5-1) and no history of diabetes. Subjects were randomized to receive either metformin (ascending dose up to 2000 mg/d) for 8 weeks followed by placebo for 8 weeks or vice versa. Cerebrospinal fluid (CSF) was collected at baseline and Week 8 for Innotest ELISA assays (Fujiriebio Europe) of Aβ, total tau and phospho-tau levels in a parallel-design analysis. Pulsed continuous Arterial Spin Label (ASL) MRIs were conducted at baseline, Week 8 and Week 16 to measure regional cerebral perfusion in resting state and during activation using a visual scene encoding memory task. Cognitive testing was conducted at baseline, Week 8 and Week 16 and included selected paper-and-pencil tests and computerized tests from the CANTAB batteries (Cambridge Cognition). Safety and tolerability were monitored via standard assessments and monthly blood work. *Results:* Twenty subjects met eligibility criteria and all completed the 16-week trial. There were 9 women and 11 men, all Caucasian, with a mean age of 70.2 years (SD=6.9), education of 16.7 years (2.8) and screening MMSE of 25.5 (2.7). For CSF AD biomarkers, there were no significant changes from baseline in levels of Aβ, total tau or phospho-tau for subjects treated with either metformin or placebo. For ASL-MRI, data analyses are being performed at the time of abstract preparation and will be described. For cognition, univariate analyses found no significant changes from baseline in either metformin or placebo conditions in tests of attention, motor speed, episodic memory, working memory, executive function, social reasoning or depressive symptoms. Metformin was safe and generally well tolerated. Gastrointestinal adverse effects occurred in 7/20 subjects while on metformin, prompting a reduction in dose in 2 subjects. There were no occurrences of lactic acidosis nor changes in hematologic, hepatic, renal or other safety measures. *Conclusion:* This brief and efficient randomized crossover clinical trial employed a multi-dimensional biomarker panel to obtain deep phenotyping data on the effects of metformin in MCI and AD. While the study procedures and metformin were found to be safe and well-tolerated, treatment did not effect salutary changes in the principal CSF biomarkers for AD nor in cognition. Functional MRI analyses are ongoing and results will be reported. *Acknowledgment:* Funded by the BrightFocus Foundation, a gift from the Allen H. and Selma W. Berkman Charitable Trust and the National Institute on Aging (AG10124)

OC28: A PHASE IB STUDY OF AZD0530 (SARACATINIB) AND THE TRANSITION TO A PHASE IIA PROOF OF CONCEPT STUDY FOR ALZHEIMER'S DISEASE. HAAKON B NYGAARD[1], KEWEI CHEN[2], ERIC M REIMAN[2], STEPHEN M STRITTMATTER[3], CHRISTOPHER H VAN DYCK[3] *((1) The University of British Columbia, Vancouver, BC, Canada; (2) Banner Alzheimer's Institute, Phoenix, AZ, USA; (3) Yale University School of Medicine, New Haven, CT, USA)*

Background: Despite significant progress, a disease-modifying therapy for Alzheimer's disease (AD) has not yet been developed. Recent findings implicate soluble oligomeric amyloid beta as the most relevant protein conformation in AD pathogenesis. We recently described a signaling cascade whereby oligomeric amyloid-beta binds to cellular prion protein on the neuronal cell surface, activating intracellular Fyn kinase to mediate synaptotoxicity. Fyn kinase has been implicated in AD pathophysiology both in vitro models and in human subjects, and is a promising new therapeutic target for the treatment of AD. Herein, we present a Phase Ib trial of the repurposed

investigational drug AZD0530, a Src family kinase inhibitor specific for Fyn and Src kinase, for the treatment of patients with mild-moderate AD. *Methods:* The study was a 4-week Phase Ib multiple ascending dose, randomized, double-blind, placebo-controlled trial of AZD0530 in AD patients with MMSE scores ranging from 16-26. A total of 24 subjects were recruited in 3 sequential groups, with each group of 8 randomized to receive oral AZD0530 at doses of 50mg, 100mg, 125mg, or placebo daily for 4 weeks. The drug:placebo ratio was 3:1. Primary endpoints were safety, tolerability, and CSF penetration of AZD0530. Secondary endpoints included changes in clinical efficacy measures (ADAS-Cog, MMSE, ADCS-ADL, NPI, and CDR-SOB) and regional brain glucose metabolism measured by FDG-PET. *Results:* AZD0530 was generally safe and well tolerated across doses. One subject receiving 125mg of AZD0530 was discontinued from the study due to the development of congestive heart failure and atypical pneumonia, which were considered possibly related to study drug. Plasma/CSF ratio of AZD0530 was 0.4. The 100mg and 125mg doses achieved CSF levels corresponding to brain levels that rescued memory deficits in transgenic mouse models. One-month treatment with AZD0530 had no significant effect on clinical efficacy measures or regional cerebral glucose metabolism. *Conclusion:* These data will be discussed in light of their translation to a recently-launched Phase IIa clinical trial of AZD0530 for the treatment of patients with mild AD. AZD0530 is reasonably safe and well tolerated in patients with mild-moderate AD, achieving substantial CNS penetration with oral dosing at 100-125mg. Some safety and tolerability issues may emerge, particularly at the 125mg dose. However, the tight correlation between plasma and CSF levels of AZD0530 will enable individualized dosing within the 100-125mg range, based on early plasma level monitoring. Individualized dosing may maximize the number of subjects who reach the target CSF drug concentration of 5nM, while minimizing those who encounter safety and tolerability problems. Targeting Fyn kinase may be a promising therapeutic approach in AD.

OC29: A CASE-CONTROL COHORT STUDY TO DEFINE A THRESHOLD FOR THE TAU/ABETA42 RATIO IN CEREBROSPINAL FLUID OPTIMIZED FOR DIAGNOSIS OF ALZHEIMER'S DISEASE. MICHAEL F EGAN[1], YI MO[1], JULIE STROMSWOLD[1], KIMBERLY WILSON[1], DANIEL E HOLDER[1], CYRILLE SUR[1], OMAR LATERZA[1], MARY J SAVAGE[1], ARIE STRUYK[1], PHILIP SCHELTENS[2], CHARLOTTE E TEUNISSEN[2], JAMES BURKE[3], S LANCE MACAULAY[4], GEIR BRÅTHEN[5], SIGRID BOTNE SANDO[5], LINDA WHITE[5], CHRISTY WEISS[6], ARTURO COWES[6], MICHELE M BUSH[6], GANGA DESILVA[6], JOHAN LUTHMAN[1], DAVID MICHELSON[1] *((1) Merck & Co, Inc., Kenilworth, NJ, USA; (2) VU University Medical Center, Amsterdam, Netherlands; (3) Duke Neurology, Duke University, Durham, NC, USA; (4) Commonwealth Scientific and Industrial Research Organization, Parkville, Victoria, Australia; (5) Department of Neuroscience, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway; (6) Luminex, Austin, TX, USA)*

Background: Prior studies have demonstrated that the CSF Tau to Amyloid ß(42) ratio (Tau/Aβ42) can distinguish patients with mild to moderate Alzheimer's disease (AD) from healthy elderly control (HC) subjects. We hypothesized that a cutoff with at least 80% sensitivity and 60% specificity could be identified using Luminex® xMAP® Tau/Amyloid ß(42) assays to discriminate between AD and HC subjects. *Methods:* CSF samples were collected from 188 HC and 155 mild to moderate AD subjects from five sites and assayed using the Tau/Amyloid ß(42) assay. A two-step approach was used to determine cutoff. First, a range of possible cutoff values was determined that distinguish AD from HC subjects with at least 80% sensitivity and 60% specificity. Second, results from amyloid PET imaging were used to select a specific cutoff within this range. Briefly, amyloid deposition status assessed with PET by visual read and CSF Tau/Aβ42 were both obtained from a heterogeneous group of 95 subjects (including HC, mild to moderate AD, amnestic MCI and other subjects). The CSF Tau/Aβ42 value within the window that met sensitivity and specificity criteria and maximized concordance with amyloid PET was chosen as the final cutoff. *Results:* A CSF Tau/Aβ42 ratio value of 0.215 provides an estimated 77.7% (72.3%, 100%) specificity, 94.8% (91.1%, 100%) sensitivity to discriminate AD from HC and maximized concordance with PET. Concordance with PET visual reads was 86.9% (80.7%, 91.9%) in a population that is 50% PET positive [values are given as estimates with (95% CI)]. The Tau/Aβ42 ratio performed better than either Tau or Aβ42 alone. The levels of concordance between tau/Aβ42 and PET SUVR scores using either flutemetamol or PiB were similar to those observed with flutemetamol visual reads. *Conclusions:* In this study, the Luminex xMAP Tau/Amyloid ß(42) assay was used to identify a threshold ratio value of CSF Tau/Aβ42 with acceptable sensitivity and specificity for distinguishing HC from AD. This threshold is highly correlated with the results of PET amyloid imaging, with an estimated concordance rate of 86.9%. Overall, these results indicate that the Luminex xMAP Tau /Aβ42 assay may have clinical utility for identifying subjects with AD.

OC30: AEROBIC EXERCISE REDUCES PHOSPHORYLATED TAU PROTEIN IN CEREBROSPINAL FLUID IN OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT. LAURA D BAKER[1], JEANNINE SKINNER[2], SUZANNE CRAFT[1], BRENNA CHOLERTON[3], MAUREEN CALLAGHAN[4], , ANGELA HANSON[4], KAYCEE M SINK[1], VALERIE M WILSON[1] *((1) Department of Internal Medicine – Geriatrics, Wake Forest School of Medicine, Winston-Salem NC, USA; (2) Vanderbilt School of Medicine, Memory and Alzheimer's Center, Nashville TN, USA; (3) Department of Psychiatry, University of Washington Health Sciences, Seattle WA, USA; (4) Geriatric Research, Education, and Clinical Center, VA Puget Sound, Seattle WA, USA)*

Background: We have shown that in older adults with mild cognitive impairment, aerobic exercise has favorable effects on executive function and plasma levels of beta amyloid, a biomarker linked to Alzheimer's disease pathology. These and similar findings by other investigators suggest that aerobic exercise holds promise as a disease-modifying therapeutic intervention for adults in the earliest stages of the disease. High tau protein levels in the brain predict rate of progression to Alzheimer's dementia. Thus, identifying interventions that can successfully reduce these levels has become a priority in clinical treatment trials. *Methods:* We enrolled 65 sedentary older adults (age range: 55-89 yrs) with amnestic MCI and prediabetes, as per American Diabetes Association blood hemoglobin A1c criteria given the added dementia risk conferred by early glucometabolic disease. Participants were randomized to an aerobic training or a stretching control group, and completed structured exercise under the supervision of a trainer for 45-60 min, 4 times per week for 6 months using community-based facilities. The aerobic group exercised at 70-80% of heart rate reserve (HRR), while participants in the stretching group exercised at an intensity below 35% HRR. At baseline and month 6, participants completed cognitive testing (verbal recall, several tests of executive function), a 400m timed walk test, glucose tolerance test, body fat assessment, and blood and cerebrospinal fluid (CSF) collection for biomarker assay. Forty participants also received structural and functional brain MRI. ANCOVA models are used in the data analyses with adjustments for age and education. *Results:* Adherence to the intervention protocols was 92%, and aerobic exercise improved walk times and glucose

tolerance relative to the control group ($p<0.05$). Six months of structured moderate-to-high intensity aerobic exercise reduced CSF levels of phosphorylated and total tau protein, particularly for adults over the age of 70 years ($p<0.05$). We also report exercise-induced increases in blood flow in the right anteromedial temporal lobe region ($p<0.05$), and favorable effects on a composite measure of executive function ($p<0.05$). *Conclusions:* Six months of aerobic exercise is sufficient to favorably move tau protein levels in older adults at high risk of progression to dementia. These findings provide important evidence to indicate a disease-modifying effect and thus high therapeutic relevance of a readily accessible nonpharmacological intervention for adults with MCI.

OC31: DATA-DRIVEN ENRICHMENT STRATEGIES FOR PREDICTING AB POSITIVITY IN AN OLDER ADULT COHORT FROM THE BRAIN HEALTH REGISTRY. RACHEL L NOSHENY[1], PHILIP S INSEL[1], DIANA TRURAN[1], DEREK FLENNIKEN[1], SHANNON FINLEY[1], MONICA CAMACHO[1], R SCOTT MACKIN[1,2,3], MICHAEL W WEINER[1,2,4] *((1) Center for the Imaging of Neurodegenerative Diseases, San Francisco Veteran's Administration Medical Center; (2) Department of Psychiatry, University of California, San Francisco; (3) Mental Health Service, Department of Veteran's Affairs Medical Center, San Francisco, CA; (4) Department of Radiology, University of California, San Francisco)*

Background: Alzheimer's disease (AD) clinical trials often use brain burden of Aβ as an inclusion criterion. However, identifying Aβ+ individuals by PET scan or lumbar puncture is time consuming, resource intensive, and invasive. Developing a more efficient, less expensive, less invasive screening tool that can predict whether cognitively normal older adults are Aβ+ positive can greatly facilitate subject enrollment into AD secondary prevention trials, which target clinically-normal older adults at risk for developing AD. *Methods:* We developed an enrichment algorithm for predicting Aβ positivity in 362 clinically-normal older adults (CN) from ADNI-2 with normal cognition, with (n=87) or without (n=275) subjective memory complaints. Aβ+ was defined as SUvR of 1.11 or above on Florbetapir PET scan. We estimated the proportion Aβ+ using iterative thresholds for multiple variables, including age, gender, ApoE ε4 genotype, family history of AD, and performance on memory tests. We then applied the algorithm to the Brain Health Registry (BHR) cohort. The BHR is an internet-based registry with over 22,000 participants, 31% within the San Francisco Bay Area (SFBA). BHR collects longitudinal self-report health and lifestyle data, and data from online cognitive tests. We identified BHR participants with self-reported family history of AD who would be eligible for preclinical AD trials based on the absence of commonly-excluded medical conditions and scores on the Cogstate One Card Learning (OCL) online test. We compared the size and composition of subgroups based on two OCL cut scores, and calculated the number of participants in each group who remained "in range" for inclusion based on longitudinal OCL scores. ANDI participants were ranked according to likelihood of being Aβ+, based on age, auditory verbal learning test (AVLT) scores, and family history of AD. In participants ranked 1-250 in their likelihood of being Aβ+ (<250), we measured the proportion who were Aβ+ as a function of their rank. *Results:* In ADNI, variables that predicted Aβ+ were age, gender, maternal family history of AD, and ApoE ε4 genotype. Learning and memory tests added predictive value to the model, with the greatest increase in prediction the proportion of Aβ+ afforded by immediate logical memory, delayed logical memory, and Trails B. Application of the enrichment algorithm increased the predicted proportion Aβ+ from 35% to 74% without including ApoE genotype, and from 35% to 77% including ApoE. In ApoE negative participants (n=262), enrichment was associated with an increase from 27% to 58% of predicted proportion Aβ+. In the BHR cohort (n=22,385), 420 participants completed OCL tests and met medical and enrichment inclusion criteria for a hypothetical preclinical AD trial. Of these participants, 290 (69%) had OCL scores between 1.5 standard deviations (SD) below and one SD above the age-adjusted mean (OCL-Norm), and 46 (11%) had OCL scores between 1.5 and one SD below the age-adjusted mean (OCL-Low). Eighty-seven percent of OCL-Norm participants and 18% of OCL-Low participants with longitudinal OCL data had OCL scores that remained within range at 6-month follow-up. The remainder of participants worsened out of range or improved to within normal or supernormal ranges. In the SFBA BHR cohort (n=6924), 226 participants completed OCL tests and met medical and enrichment criteria. Of these, 153 (68%) were OCL-Norm and 27 (12%) were OCL-Low Seventy-four percent of OCL-Norm participants and 24% of OCL-Low participants had OCL scores that remained within range at 6-month follow up. In the ADNI sample, 90 out of 512 participants (18%) met inclusion and enrichment criteria. Of these, 70 (78%) had AVLT scores within 1 SD of the mean and 8 (9%) had AVLT scores between 1.5 to 1 SD below the mean. In the entire ADNI cohort, 283 had declining and 229 had improving longitudinal AVLT scores. In the ranked ADNI cohort, 10% of the <250 group met enrichment criteria to achieve 75% Aβ+. *Conclusions:* Application of an enrichment algorithm greatly increased the likelihood of correctly predicting Aβ+ in CN ADNI participants. The same algorithm identified a substantial number of BHR participants, including those within the SFBA, likely to be Aβ+ and eligible for preclinical AD trials. Conservative cognitive cut-scores were relatively consistent across the three groups (ADNI, BHR-USA, and BHR-SFBA). Only 10% of ADNI participants ranked as likely to be Aβ+ had a high Aβ+ rate, highlighting the need for a large cohort to accurately predict Aβ+. Preliminary longitudinal BHR data suggested that approximately 25% of the cohort will worsen or improve out of range, which can further enrich the sample. Taken together, the results suggest that application of an enrichment algorithm for Aβ+ can be used to identify participants likely to be Aβ+ without invasive Aβ+ testing, and can therefore lessen screen fail rate and improve power of AD preclinical trials targeting Aβ+, CN participants.

OC32: FORNIX DEEP BRAIN STIMULATION FOR ALZHEIMER[1]S DISEASE: RESULTS OF THE MULTI-CENTER ADVANCE TRIAL. KATHRYN B HOLROYD[1], LISA FOSDICK[2], GWENN SMITH[3], JEANNIE-MARIE LEOUTSAKOS[3], CYNTHIA MUNRO[3], ESTHER OH[3], KRISTEN DRAKE[2], PAUL B ROSENBERG[1,3], WILLIAM S ANDERSON[3], STEPHEN SALLOWAY[9], CARA PENDERGRASS, ANNA BURKE, DAVID A WOLK[7], DAVID F TANG-WAI[4,6], FRANCISCO A PONCE[8], WAEL F ASAAD[10], MARWAN SABBAGH, MICHAEL S OKUN, GORDON BALTUCH, KELLY D FOOTE, STEVE TARGUM[2], ANDRES M LOZANO[4], CONSTANTINE G LYKETSOS[3] *((1) Johns Hopkins University School of Medicine; (2) Functional Neuromodulation Ltd., Minneapolis, MN; (3) Johns Hopkins University Memory and Alzheimer's Treatment Center and Alzheimer's Disease Research Center, Baltimore MD; (4) Departments of Neurology and Neurosurgery, University of Toronto, Toronto, Ontario Canada; (5) Departments of Neurology and Neurosurgery, University of Florida Center for Movement Disorders and Neurorestoration, Gainesville FL; (6) University Health Network Memory Clinic, University of Toronto, Division of Neurology, Toronto ON Canada; (7) Penn Memory Center, Department of Neurology, University of Pennsylvania, Philadelphia PA; (8) Division of Neurological Surgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ; (9) Departments of Neurology, Butler and Rhode*

Island Hospital and the Alpert Medical School of Brown University; (10) Departments of Neurosurgery, Rhode Island Hospital and the Alpert Medical School of Brown University)

Background: There are currently few available treatments and no cure for Alzheimer's disease (AD). Animal models and an open-label human trial have suggested that deep brain stimulation (DBS) directed at cognitive circuits may improve symptoms and possibly slow disease progression. The ADvance trial (Clinicaltrials.gov: NCT01608061) was designed to examine DBS targeting the fornix (DBS-f) as a treatment for mild AD. *Methods:* ADvance is a randomized, double-blind, placebo-controlled, delayed-start, multicenter clinical trial conducted at 6 sites in the US and 1 site in Canada. Forty-two patients with very mild AD who met entry criteria received bilateral DBS implants with leads placed anterior to the columns of the fornix. After being randomized 1:1 in a double-blind fashion to DBS "off" or DBS "on" groups for the initial 12 months, all participants' devices were turned "on" for the remainder of the study. Post-implantation, patients return for 13 follow-up visits over 48 months for cognitive and psychiatric assessments, brain imaging (up to 12 months), and safety monitoring. The primary efficacy outcome measures include: Alzheimer's Disease Assessment Scale (ADAS-cog-13), Clinical Dementia Rating sum of boxes (CDR-SB), and cerebral glucose metabolism measured with positron emission tomography (18FDG-PET). *Results:* Implanted subjects (mean age =68.2 years; 55% male) had baseline mean ADAS-cog-13 and CDR-SB scores of 28.9 (SD 5.2) and 3.9 (SD 1.6), respectively. During the oral presentation, we will present unmasked safety and efficacy results for the 12-month double-blind phase of the study. *Conclusions:* ADvance was successful in enrolling a group of early AD patients for this novel application of DBS. The study is strengthened by rigorous independent subject selection, a double-blind placebo-controlled design, and an extensive open-label follow up period.

OC33: MAPT (MULTI-DOMAIN ALZHEIMER'S PREVENTION TRIAL): CLINICAL, BIOMARKERS RESULTS AND LESSONS FOR THE FUTURE. B VELLAS[1,2,3], T VOISIN, C DUFOUIL, I CARRIE[1], S GILLETTE-GUYONNET[1,2,3], A GABELLE[4], J TOUCHON[4], T DANTOINE[5], JF DARTIGUES[6], MN CUFFI[7], S BORDES[8], Y GASNIER[8], P ROBERT[9], L BORIES[10], O ROUAUD[11], F DESCLAUX[12], K SUDRES[13], M BONNEFOY[14], A PESCE[15], B FOUGERE[1], J DELRIEU[1], C FAISANT[1], F LALA[1], C DUPUY[1,2], C CANTET[1,2,3] N COLEY[2,3], S BELLEVILLE[18], S WILLIS[19], MW WEINER[20], MW PJ OUSSET[1,2,3], S ANDRIEU[1,2,3,21] *((1) Gérontopôle, Department of Geriatrics, CHU Toulouse, Purpan University Hospital, Toulouse, France; (2) INSERM UMR 1027, Toulouse, France; (3) University of Toulouse III, Toulouse, France; (4) Department of Neurology, Memory Research Resource Center for Alzheimer's Disease, University Hospital of Montpellier, Montpellier, France; (5) Geriatrics Department, Memory Research Resource Center, University Hospital of Limoges, Limoges, France; (6) INSERM U897, Memory Research Resource Center for Alzheimer's Disease, University Hospital of Bordeaux, Bordeaux, France; (7) Geriatrics Department, Hospital of Castres, Castres, France; (8) Geriatrics Department, Hospital of Tarbes, Tarbes, France; (9) Memory Research Resource Center, University Hospital of Nice, Nice, France; (10) Geriatrics Department, Hospital of Foix, Foix, France; (11) Memory Research Resource Center, Neurology Department, University Hospital of Dijon, Dijon, France; (12) Geriatrics Department, Hospital of Lavaur, Lavaur, France; (13) Geriatrics Department, Hospital of Montauban, Montauban, France; (14) Geriatrics Department, Centre Hospitalier Lyon-Sud, Lyon, France; (15) Geriatrics Department, Hospital of Princess Grace, Monaco; (16) Institut de Recherche Pierre Fabre, Toulouse, France; (17) Department of Medical Information, CHU Toulouse, Toulouse, France; (18) Research Center, Institut Universitaire de Gériatrie de Montréal, Montréal, Canada; (19) Department of Psychiatry and Behavioral Sciences, University of Washington, Washington, USA; (20) University of California, San Francisco, California, United States; (21) Department of Epidemiology and Public Health, CHU Toulouse, Toulouse, France*

The MAPT trial was designed to assess the efficacy of supplementation with omega-3 fatty acid, multidomain intervention or a combination of the two interventions on the change of cognitive functions in subjects 70 years and older with subjective memory complaints for a period of 3 years. 1680 elderly subjects enrolled by 13 memory clinics, were randomized into one of the four intervention groups. Participants underwent cognitive (MMSE, CDR, COWAT, CNT, Digit symbol substitution test, Trail making test, Free and cued selective Reminding test), functional (SPPB, ADCS-ADL-PI) and biological assessments at M6, M12, M24 and M36 visits. The primary endpoint was a change of cognitive function at 3 years, as assessed by a composite cognitive test Z score. Interventions: 1/ Omega-3: 800 mg docosahexaenoic acid (DHA) per day, for 3 years. 2/ Multidomain intervention: training sessions in small groups (6–8 participants) in twelve 120-minute sessions over the first 2 months, then a 60-mn session per month in the following three areas: nutrition, physical activity, and cognition until the end of the 3 years. Individualized preventive outpatient visits exploring were also performed at baseline, M12 and M24. We will present new analysis from MAPT trials in those with low DHA at entry, those with MCI and those with ApoE4 alleles.

OC34: IMPROVING THE SENSITIVITY OF COGNITIVE COMPOSITE SCORES TO ABNORMAL AMYLOID BURDEN IN PRECLINICAL ALZHEIMER'S DISEASE. PAUL MARUFF[1,2], YEN YING LIM[1], PETER J SNYDER[3], VICTOR L VILLEMAGNE[1], DAVID AMES[1], CHRISTOPHER C ROWE[1], COLIN MATERS[1] *((1) The University of Melbourne, Parkville, Victoria, Australia; (2) Cogstate Ltd., Melbourne, Victoria, Australia; (3) Department of Neurology, Warren Alpert School of Medicine, Brown University, Providence, RI, USA)*

Background: Multiple studies now indicate that in the very early stages of Alzheimer's disease (AD), episodic memory provides the most reliable and sensitive index of amyloid (Aβ)-related cognitive decline. However, the ADCS Preclinical Alzheimer Cognitive Composite (ADCS-PACC) developed for clinical trials of preclinical AD included measures of additional cognitive domains on the basis that their inclusion may provide greater sensitivity to detect Aβ-related cognitive. The ADCS Preclinical Alzheimer Cognitive Composite (ADCS-PACC) also emphasised which cognitive domains were important without specifying the tests to be operationally define those domains. The ADCS-PACC combines measures of episodic memory (e.g., measures of list learning such as the Free and Cued Selective Reminding Test [FCSRT] or the California Verbal Learning Test, Second Edition [CVLT-II], and measures of paragraph recall such as the Wechsler Memory Scale [WMS] Logical Memory delayed recall or New York University Paragraph Recall test), complex attention (e.g., the Wechsler Adult Intelligence Scale-Revised [WAIS-R] Digit Symbol Substitution Test score [DSST]) and a general cognitive screen (e.g., the Mini Mental State Examination [MMSE] total score). While each of the tests used to define episodic memory and complex attention in the ADCS-PACC have demonstrated sensitivity to cognitive decline in early AD, the MMSE has not. Therefore, its inclusion may reduce the sensitivity of the ADCS-PACC because of its sub-optimal metric characteristics when used in CN older adults (i.e., ceiling effects, negative skew, poor test-retest reliability). One additional limitation of the ADCS-PACC is that it does not include

a measure of executive function when substantial Aβ-related decline in this domain is also observed reliably in preclinical AD, often to a greater extent than that observed for attentional function. Thus, cognitive composite scores used in studies of preclinical AD may have increased sensitivity to drug effects and Aβ-related cognitive decline if they also included a measure of executive function rather than the MMSE. The aim of this study was to compare the rate of cognitive decline associated with Aβ in CN adults using the ADCS-PACC, an Episodic Memory composite and a composite score derived from neuropsychological tests of attention, executive function and episodic memory. *Methods:* CN older adults (n=423) underwent Aβ neuroimaging with positron emission tomography and completed neuropsychological assessments at baseline, and at 18-, 36-, 54-, and 72-month follow-ups. Three cognitive composite scores were computed: the ADCS-PACC, an Episodic Memory composite and a composite score that included measures of episodic memory (CVLT, Logical memory), Attention (DSST) and executive function (Controlled Oral Word Association Task [COWAT) and was denoted as the Z-scores of Attention, Verbal fluency and Episodic memory for Non-demented older adults (ZAVEN) composite. *Results:* Compared to Aβ+ CN older adults, Aβ++ CN older adults showed faster rates of decline across all cognitive composites, with the largest decline observed for ZAVEN composite (d=0.70). Similarly, compared to Aβ- CN older adults, Aβ+ CN older adults also showed faster rates of cognitive decline, but only for the EM (d=0.53) and ZAVEN (d=0.50) composites. *Conclusions:* Aβ-related cognitive decline best detected using validated neuropsychological instruments, particularly of episodic memory. Removal of the MMSE from the ADCS-PACC and replacing it with a test of executive function (i.e., verbal fluency) rendered this composite more sensitive even in detecting Aβ-related cognitive decline between Aβ+ and Aβ++ CN older adults.

OC35: NEUROINFLAMMATION IN ALZHEIMER'S DISEASE: ROLE IN PATHOGENESIS AND PROSPECTS FOR THERAPEUTIC INTERVENTION. RICHARD MARGOLIN[1]
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Introduction: Neuroinflammation refers to the collective reactions of the several components of the brain's innate immune system to pathogens and toxic substances. The system's cellular elements — astrocytes and microglia — perform diverse functions including surveillance for "danger signals", recruitment of other types of immune cells, removal of harmful substances, and tissue repair. Astrocytes and microglia interact closely with each other, with neurons, and with the neurovascular unit to preserve brain integrity. Their functions are carried out through the release of a plethora of soluble mediators (classically known as cytokines and chemokines); some cytokines promote inflammation while others are anti-inflammatory. Both cell types undergo phenotypic change in response to danger stimuli, resulting in marked increases in the production of immune mediators. For microglia, these include TNF-α and various interleukins, and activation of the classical complement system. Microglia also undergo dramatic morphologic changes in response to these stimuli that enable them to carry out one of their essential functions, the phagocytosis of dying cells and debris. In addition, microglia are motile, like their corresponding cell type in peripheral tissues, macrophages, and migrate actively to the source of danger stimuli. Though glia were relatively less studied than neurons in years past, their properties are now the subject of intensive research in which molecular genetic, biochemical, and advanced imaging techniques are rapidly elucidating key features of their physiology in health, aging, and neurodegenerative diseases. Early conceptual frameworks, e.g., the pro-inflammatory (M1) and anti-inflammatory (M2) microglial activation states, terms borrowed from classification systems for macrophages, are giving way to a richer and more nuanced understanding as detailed knowledge about physiology accrues. Indeed, whether neuroinflammation is "good" or "bad" is highly context dependent, and in chronic diseases it may have both attributes at different times in the course of disease. A wealth of evidence obtained in the last 20 years implicates dysfunction of the innate immune system as a very important element of the pathogenesis of Alzheimer´s disease (AD). The observation that activated microglia and astrocytes accumulate around amyloid plaques supported the initial view that neuroinflammation was simply a response to late-stage pathology; more recent evidence suggests that it may occur much earlier, e.g., driven by toxic oligomeric amyloid β species and/or other as yet unknown stimuli. Both gain and loss of function have been demonstrated. For example, microglia do not efficiently remove Aβ fibrils or tau aggregates, which presumptively should be recognized as toxic. The associated increases in immune mediator release and oxidative stress likely contribute very substantially to tissue damage and neuronal loss. Aging may also prime glia for susceptibility to other pathogenetic processes operative in AD, and systemic inflammatory disorders may also be important, given evidence for peripheral/CNS signaling and the possible importance of infiltrating monocytes in the expression of neuroinflammation. The recent discovery of risk alleles in several genes associated with microglial physiology, including TREM2, CR1 and CD33, has greatly galvanized interest in the role of innate immunity in AD pathology. Though rare, the protein alternations encoded by these alleles may indicate mechanisms and pathways that might be operative in typical sporadic AD. A by-product of the increasingly intensive study of the innate immune system is the development of translatable biomarkers to aid research. In tandem with classical and molecular genomic investigations, fluid markers of astrocytic and microglial function have been developed, which, together with imaging techniques such as dual photon microscopy, positron emission tomography, and volumetric magnetic resonance imaging, are being used both preclinically and translationally. Important findings are resulting from the application of such techniques, alone and in combination e.g., evidence of cortical thickness changes associated with neuroinflammatory fluid biomarker alterations. Based on epidemiologic evidence suggesting a reduction in the risk of AD associated with premorbid use of anti-inflammatory drugs, trials of a number of such agents were performed in AD and MCI in the early 2000s. Prednisone and multiple non-steroidal agents were explored, with essentially negative results, however. Consequently, for a time, interest in neuroinflammation as a focus for drug discovery and development waned. This is rapidly changing, however, driven by the newly identified genetic risk factors, the rapidly advancing understanding of molecular pathology, and the development of valuable biomarker tools. One drug, CSP-1103, which has been shown to affect both microglial cytokine production and markers of phagocytosis in ways beneficial for the treatment of AD is entering late-stage development, and other agents operating through a variety of approaches are in preclinical discovery or Phase 1. Thus, it is critical to understand the reasons that the early anti-inflammatory drug treatments failed and to appreciate the implications of various factors that may be critical to the success of clinical trials of new neuroinflammation-targeting treatments. These factors include the anticipated timing of biomarker and clinical evidence of effect, and the appropriate disease stage for intervention, among others. Innate immune system dysfunction is increasingly viewed as both a key component of AD pathophysiology and a promising focus of therapeutic intervention. Rapidly increasing knowledge about the genetic and molecular basis of pathology and the development of advanced biomarkers are expected to be potent aids for drug discovery and development in this space. This symposium will clarify current understanding of the biology of the innate immune system, the capability of biomarker tools to serve as potent adjuncts for research, and prospects for strategies to develop effective therapeutics targeting

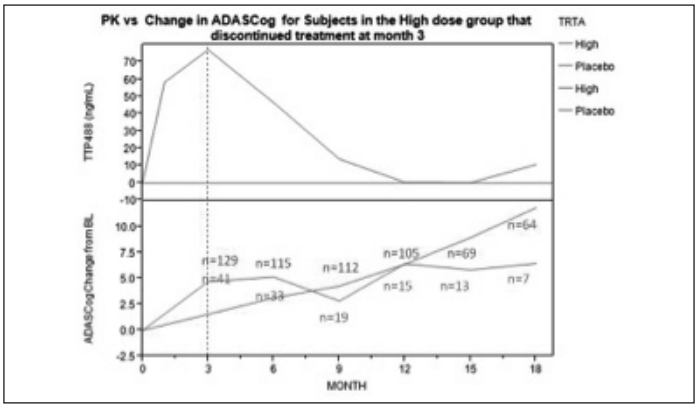
this space.

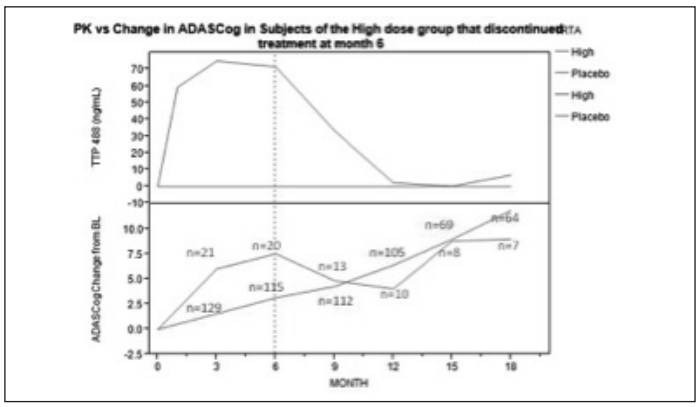
OC36: EVALUATION OF THE PHASE 2B SAFETY OF AZELIRAGON (TTP488) 20MG/DAY AND 5 MG/DAY IN SUPPORT OF PHASE 3 DOSE SELECTION. MARWAN N SABBAGH[1], AARON BURSTEIN[2], IMOGENE GRIMES[2], CARMEN VALCARCE[2], RACHELLE S DOODY[3], LON S SCHNEIDER[4], DOUGLAS GALASKO[5] *((1) Barrow Neurological Institute, Phoenix, AZ, USA; (2) vTv Therapeutics, High Point, NC, USA; (3) Baylor College of Medicine, Houston, TX, USA; (4) Keck School of Medicine of USC, Los Angeles, CA, USA; (5) UC San Diego / VA San Diego Healthcare System, San Diego, CA, USA)*

Background: Azeliragon is an oral antagonist of the Receptor for Advanced Glycation Endproducts (RAGE) currently in Phase 3 testing for mild Alzheimer's disease (AD). Safety and efficacy of azeliragon were previously evaluated in an 18-month Phase 2 study in patients with mild to moderate AD. We evaluated safety data and the relationship between plasma concentration and changes in ADAS-cog to support Phase 3 dose selection. *Methods:* Patients with mild-to-moderate AD (MMSE 14-26) were randomized to receive 60mg/day for 6 days followed by 20mg/day (high dose, n=135) for 18 months, 15 mg/day for 6 days followed by 5 mg/day for 18 months (low dose, n=131) or placebo for 18 months (n=133). An interim analysis for safety was performed when 50% of subjects completed 6 months of treatment. Final evaluation of safety data and analysis of the relationship between plasma azeliragon concentration and change in ADAS-cog was performed following conclusion of the trial. *Results:* At the interim analysis for safety (see table) no concerns were noted for 5 mg/day. Increased incidence of SAEs, falls, confusion, a greater mean decline in ADAS-cog, and a higher percentage of subjects with ≥10 point decline on the ADAS-cog, relative to baseline, in the 20 mg/day group prompted the DSMB to recommend discontinuation of dosing in the 20 mg/day group.

	High Dose N=135	Low Dose N=133	Placebo N=131
SAEs n, %	18, 13.2%	7, 5.3%	11, 8.3%
Falls n, %	14, 10.3%	8, 6.1%	8, 6.1%
Confusion n, %	11, 8.1%	8, 5.3%	6, 4.5%
ADAS-cog mean change	8.0±6.6	3.1±5.4	3.1±5.9
% with 10pt decline from baseline	35.8%	11.7%	11.4%

Subjects were reconsented and the 20 mg/day group was followed off drug for evaluation of safety. Following discontinuation of dosing, plasma concentrations declined with a corresponding reversal of the decline in ADAS-cog. For those subjects followed out to 18 months the magnitude of decline for the 20 mg/day group was numerically less than the decline for placebo treated subjects, but the sample size was small. Azeliragon 5 mg/day appeared safe and well-tolerated following 18 months of dosing with gastrointestinal adverse events occurring more frequently (33.6% vs 22.7%), and psychiatric adverse events occurring less frequently (26.7% vs 39.4%), than placebo. Plasma azeliragon concentrations >46.8 ng/mL were associated with the statistically significant worsening in ADAS-cog relative to placebo at months 3 and 6, whereas values of 7.6-16.8 were associated with statistically significant beneficial treatment related differences in ADAS-cog at 18 months. *Conclusions:* Safety and efficacy results support advancement of azeliragon 5 mg/day to Phase 3. Target concentrations achieved at 5 mg/day dose and associated with efficacy (8-17 ng/mL) provide a 3-fold safety margin relative to concentrations associated with falls, confusion and reversible ADAS-cog decline seen at 20 mg/day (which is not being studied in Phase 3). This therapeutic window should accommodate any pharmacokinetic variability that may be seen in an expanded Phase 3 population and together with vigilance for cognitive decline, falls and confusion may minimize the potential for toxicity in Phase 3. Trial registration: ClinicalTrials.gov identifier NCT00566397





OC37: CRF RECEPTOR 1 ANTAGONISM AS A DISEASE-MODIFYING TREATMENT FOR AD: PRECLINICAL EFFICACY AND SAFETY DATA. ROBERT A RISSMAN, *(Alzheimer's Disease Cooperative Study, Department of Neurosciences, University of California, San Diego, La Jolla, CA)*

Background: Stress and corticotropin-releasing factor (CRF) have been implicated as mechanistically involved in Alzheimer's disease (AD) but agents that impact CRF signaling have not been carefully tested for therapeutic efficacy or long term safety in animal models. Our work in animal models identifies signaling through a major stress mediator, the type 1 CRF receptor (CRFR1) in the development of both AD hallmarks. Prior studies indicates that exposure to potent homeostatic insults (e.g. starvation, etc) can activate tau kinases and induce tau phosphorylation. We extended these finding to include acute exposure to the prototypic emotional stressor, restraint. While acute stress-induced tau phosphorylation was transient, repeated restraint exposure resulted in cumulative increases in phosphorylated tau, a portion of which was sequestered as insoluble pre-pathogenic aggregates. All of these effects were abolished by pharmacologic or genetic ablation of CRFR1. In working to extend these findings into a transgenic model of AD, we find that genetic and pharmacologic blockade of CRFR1 reduces Aβ accumulation and mitigates cognitive impairment independent of stress exposure. *Methods***:** Here we examined whether antagonism of the type-1 CRF receptor (CRFR1) could be used as a disease-modifying treatment for AD, we used a preclinical prevention paradigm and treated 30-day-old AD transgenic (AD) mice with the small molecule, CRFR1-selective antagonist, R121919, for 5 months and examined AD pathological and behavioral endpoints. Our prior work demonstrated that systemic administration of R121919 (20 mg/kg/d) was effective in blocking stress-induced tau phosphorylation. To confirm that this dosage

displayed target engagement with chronic administration in AD mice, the ability of R121919 to disrupt binding of radiolabeled sauvagine, a peptide structurally related to CRF that binds both CRFRs was measured. Reduction in sauvagine binding in AD mice was observed at 20 mg/kg of R121919, while lower doses were much less effective. *Results:* In terms of efficacy, R121919 significantly prevented onset cognitive impairment and reduced cellular and synaptic deficits and Aβ and CTF-β levels in both genders. Also of primary importance in our trial, given the history of CRFR1 antagonist trials, we focused heavily on safety and tolerability. That is, we monitored levels of liver enzymes in AD mice (UCSD Pathology Core). Levels of blood urea nitrogen (BUN), albumin, cholesterol, total bilirubin, alanine transaminase (ALT), and aspartate transaminase (AST) were analyzed in serum samples from male and female WT and AD mice treated with vehicle or drug. No effect of R1291919 was observed on any endpoint. Liver morphology was investigated to complement serum biochemistry. Pathological assessments revealed that both vehicle and drug treated mice were normal, with no signs of toxicity present. Animals were monitored daily for grooming behavior and body weight. Grooming behavior was assessed daily by visual inspection of fur and skin. R121919-treated cohorts (both WT and AD) were indistinguishable from vehicle-treated cohorts in terms of grooming and appearance (data not shown). In terms of body weight, all mice were weighed daily each morning. We found no significant differences were observed with R121919 or vehicle treatment in female WT mice. Conversely, a small but statistically significant effect of R121919 was observed on weight gain in male WT mice. A similar reduction was observed in male AD mice, which was detectible beginning at 3 months of age. Drug-treated female AD mice also had a small but significant reduction in weight gain compared to vehicle-treated cohorts only at the 5-month time point. *Conclusions:* To our knowledge, this study is the first to examine the potential of CRFR1 antagonism as a preventative therapeutic for AD and to demonstrate that chronic administration of a CRFR1 antagonist presents a safe and effective treatment in this context. We find that such a chronic treatment regimen can delay the onset of cognitive impairment and rescue synaptic and dendritic deficits in a mouse model of AD. In terms of pathology, AD mice receiving treatment had greatly reduced accumulation of Aβ plaques and concomitant reduction in APP CTF-β, suggesting that the upstream mechanisms involve modulation of Aβ generation pathways. We find that CRFR1 antagonism presents a viable disease-modifying therapy for AD and recommend advancement to early phase human safety trials. Although clinical trials of R121919 have found isolated instances of liver enzyme elevation, we did not observe this in our rodent model nor has been reported in other studies. As detailed in the results section, the change in weight gain we observed was isolated and not associated with any pathological findings. This observation is also mitigated by the fact that AD animals have tendency to be overweight compared to WT counterparts. Regardless of the possibility of moving forward to translational studies with R121919, we are actively developing high throughput screening assays to pursuing the development of new CRFR1 antagonists.

OC38: MK-8931 TREATMENT SUPPRESSES AMYLOID PLAQUE PROGRESSION IN AGED POST-PLAQUE TG2576 MICE WITHOUT INCREASED MICROHEMMORHAGE. MATTHEW E KENNEDY[1], STEPHANIE VILLARREAL[2], FUQIANG ZHAO[6], LYNN HYDE[3], DANIEL HOLDER[5], THOMAS FOREST[4], MARIE SONDEY[3], XIA CHEN[3], CYRILLE SUR[6], ERIC PARKER[3] *((1) Early Discovery Neuroscience, Merck Research Labs, Boston MA USA; (2) Early Discovery Neuroscience, Merck Research Labs, West Point PA USA; (3) Pharmacology, Merck Research Labs, Kenilworth NJ USA; (4) Safety Assessment and Laboratory Animal Research, Merck Research Labs West Point PA USA; (5) Biostatistics, Merck Research Labs, West Point PA USA; (6) Imaging, Merck Research Labs, West Point PA USA)*

Background: MK-8931, a potent active-site inhibitor of the BACE1 enzyme in clinical development for the treatment of Alzheimer's disease (AD) was tested in a 12-week nonclinical study investigating the potential for MK-8931 to induce cerebral microhemorrhage (MH) in very old (18-22 months) post-plaque Tg2576-APPswemice. *Methods:* Mice treated with either the anti-N-terminal Aβ antibody murine analog of bapineuzimab delivered subcutaneously, a known MH inducer or MK-8931 delivered in-diet along with respective controls were evaluated for the incidence of MH using longitudinal imaging via T2*-MRI and cross-sectional analysis using Prussian blue histochemical detection and quantitative histological analysis. *Results:* MK-8931 was well tolerated at ~110 mg/kg/day in-diet and produced >90% reduction of plasma Aβ1-40 and Aβ1-42 and 62% and 68% lowering of CSF Aβ1-40 and Aβ1-42 respectively. MK-8931 plasma exposures were estimated to be 22x higher than the exposures expected at the maximum dose of 60 mg QD that was examined in a Phase 2/3 trial in mild-moderate AD patients. MK-8931-treated animals displayed the lowest degree of MH of any treatment group at study end irrespective of whether MH was detected by T2*-MRI or by Prussian blue staining. MK- 8931-treated mice displayed a mean of 1.45 new MH events following 12 weeks treatment versus a mean of 2.89 new MH events in control diet treated mice. In contrast, anti-Aβ antibody-treated mice displayed an average of 3.81 new MH events at study end compared to 3.07 new MH events in controls. Consistent with the T2 *-MRI results, the MK-8931 treatment group displayed 30.7% and 40% lower levels of Prussian blue positive objects and area respectively vs. controls although this change did not reach statistical significance. This contrasted with statistically significant increases of 145% and 179% in Prussian blue positive object number and area, respectively in anti-Aβ antibody -treated mice vs. controls. The lack of increases in MH in aged Tg2576 mice treated with MK-8931 was associated with a significant reduction in the accumulation of total brain Aβ1-40 and Aβ1-42 peptide levels and the area occupied by Thioflavine S positive amyloid deposits. Anti-Aβ antibody treatment did not significantly impact the area of Thioflavine S positive deposits. Stereological analysis of plaque load in cortex and hippocampus revealed significantly less area of Aβ immunoreactivity and reduced plaque number in MK-8931-treated animals than vehicle controls while anti-Aβ treatment had no significant effect on plaque status. *Conclusion:* The apparent reduction MH events observed for MK-8931-treated mice versus controls was associated with a significant reduction in the level of accumulated CNS amyloid pathology and Aβ peptides as determined by multiple methods, effects consistent with the desired therapeutic outcome of MK-8931 treatment of AD patients. Given the lack of data on the clinical translation of transgenic APP mouse models of MH, however, it is not known if the results described herein predict the potential for changes in the incidence of MH with MK-8931 treatment in AD patients.

OC39: MODULATING GAMMA-SECRETASE ACTIVITY REVERSES ENDOSOMAL PHENOTYPES INDUCED BY INCREASED APP DOSE IN DOWN SYNDROME MODEL NEURONS. WILLIAM C MOBLEY, MATTHEW PEARN, MARIKO SAWA[1], NISHANT SINGHAL[1], ORLANGIE NATERA, XU CHEN, CHENGBIAO WU, STEVEN WAGNER *(Department of Neurosciences, University of California, San Diego, La Jolla, CA, USA)*

Background: Those with Down syndrome (trisomy 21) uniformly harbor the pathology of Alzheimer disease (AD) by age 40; dementia ensues in most by 60. Studies in partial trisomy 21 show that increased

gene dose for the amyloid precursor protein (APP) is necessary for AD in DS. Studies in mouse models of DS are consistent, demonstrating that increased APP gene dose is necessary for degeneration of neurons of the locus coeruleus and basal forebrain cholinergic neurons. Significantly, APP gene dose also disrupted retrograde axonal trafficking of endosomes carrying neurotrophic factor signals that support these populations; the decrease was highly correlated with neurodegeneration. *Methods:* To decipher the mechanism(s) by which APP gene dose acts we carried out studies in vitro, including studies using microfluidic chambers to isolate the cell bodies of neurons from their axons. Quantum-dot labeled neurotrophins enable real-time imaging studies of endosomal transport. *Results:* Mimicking the case in vivo, neurons from the Ts65Dn mouse model of DS showed that increased APP gene dose was necessary for increased early endosome size and reduced axonal trafficking of neurotrophic factors. In rat neurons, increased levels of the full length APP protein as well as its C-99 and Abeta42 products caused increased activation of Rab5, enlarged early endosomes and disrupted retrograde trafficking and signaling of neurotrophic factors with atrophy of neuron cell bodies. Neither the AICD nor C-83 caused these changes. Interestingly, increased Rab5 activation was found to mediate the endosomal phenotypes, including decreased neurotrophin trafficking and atrophy; expressing dominant negative Rab5 prevented them. Because C-99 and Abeta42 are substrates for gamma-secretase, we reasoned that gamma-secretase modulators (GSMs), which increase that activity of this enzyme complex, would rescue endosomal phenotypes. In vivo and in vitro, GSMs reduced the levels of C-99 and Abeta42 in Ts65Dn neurons, reduced the size of early endosomes and restored axonal trafficking of neurotrophins in endosomes. *Conclusion:* GSMs represent a rational approach for preventing the effects of increased APP gene dose causing AD in DS. The similarity in endosomal phenotypes for AD and DS suggest that GSMs may prevent endosomal dysfunction in AD in those without DS.

OC40: VITAMIN D IMPROVES COGNITION AND NEUROGENESIS, REDUCES AMYLOID BURDEN AND INFLAMMATION IN A MOUSE MODEL OF ALZHEIMER'S DISEASE. P MILLET*[1,2,3], V LANDEL*[1], M MORELLO[1,4], F FÉRON[1] *((1) Aix Marseille Université, CNRS, NICN UMR 7259, Marseille, France; (2) CMRR. G.H. Lariboisière-Fd.Widal, Paris, France; (3) Inserm UMR-S942, Paris, France; (4) University of Rome Tor Vergata, Clinical Biochemistry, Human Nutrition, Faculty of Medicine, Italy; * Equally contributing authors))*

Epidemiological and clinical data indicate that i) high serum vitamin D3 (cholecalciferol) levels associate with better cognitive test performance and ii) vitamin D3 deficiency is found in patients with Alzheimer's disease (AD). Vitamin D has also been shown to i) enhance cerebral clearance of human amyloid β peptide from mouse brain across the blood-brain barrier and ii) prevent amyloid β induced alterations in cortical neurons. In order to assess further the therapeutic benefit of vitamin D supplementation, we performed a dual study with a transgenic mouse model of AD (5XFAD). Male and female transgenic (5XFAD) and wild type C57Bl6 mice were fed with either a vitamin D3-supplemented (7,500 UI/Kg/day) or a control (1,000 UI/kg/day) diet. Two time windows were selected: mice were either treated between 1 and 5 months of age (preventive arm) or between 4 and 8 months of age (curative arm). At the end of the treatment period, we assessed cognition, amyloid burden, neurogenesis and transcript expression. We observed that vitamin D: 1. improved working memory and neurogenesis in male animals, only when delivered during the preventive period; 2. enhanced working memory and amyloid burden in female animals, only when administered during the curative period; 3. reduced immunity- and inflammation-related transcripts. These data confirm that a cholecalciferol supplementation can be of therapeutic benefit for Alzheimer's patients. However, our animal studies highlight a gender issue. Vitamin D seems to be efficient during the asymptomatic phase, in male individuals, and during the symptomatic phase, in female individuals.

OC41: INNOVATIVE MASS SPECTROMETRY QUANTIFICATION OF CEREBROSPINAL FLUID TAU AND PHOSPHO TAU IN ALZHEIMER'S DISEASE PATIENTS. C HIRTZ[1]*, N BARTHELEMY[1], A GABELLE[1,3], F FENAILLE[2], N SERGEANT[4], J VIALARET[1], S SCHRAEN-MASCHKE[3], P BROS[1], L TIERS[1], C DELABY[1], C JUNOT[2], J TOUCHON[3], L BUÉE[A], F BECHER[2], S LEHMANN[1] *((1) CHRU de Montpellier and Université de Montpellier, IRMB, Laboratoire de Biochimie Protéomique Clinique, Montpellier, France; (2) CEA, iBiTec-S, Service de Pharmacologie et d'Immunoanalyse, Gif-sur-Yvette, France; (3) Centre Mémoire Ressources Recherche Languedoc-Roussillon, CHU de Montpellier, hôpital Gui de Chauliac, Montpellier, and Université de Montpellier; Montpellier, France; (4) CHU de Lille, Centre de Biologie Pathologie; Université Lille-Nord de France; INSERM U837; Lille, France)*

Background: Detection of biomarkers in the CSF has proven to be useful to follow and understand the metabolism of molecular actors of Alzheimer's disease (AD), as well as, for diagnosis purposes. Immunodetection is mostly used to detect and quantify these biomarkers but this approach has sometime a poor specify and a limited detection range of the different isoforms of the molecules. Hence, we are often missing the full spectrum of the presence and significance of the biomarkers in the cerebrospinal fluid (CSF). This is particularly true for the tau protein which is present in different isoforms and subjected to many modifications including truncation, hyper-phosphorylation or aggregation. Importantly, the understanding of tau metabolism and implication in AD pathology is a major challenge as this molecule is now a major therapeutic target and a diagnosis biomarker. *Methods:* We developed a sensitive multiplex peptide detection using targeted high-resolution MS (HRMS) on a Q-Orbitrap system and accurate parallel determination of peptide stoichiometry and protein absolute quantification. The method was applied to the full length MS quantification of the tau and to the several phospho tau peptides in human CSF. Without immunoprecipitation, this approach allowed a highly reproducible, sensitive, quantitative follow-up of 18 peptides covering the all tau protein sequence and the detection of 4 phosphopeptides in CSF tau .We applied this new MS tool to the CSF of a cohort of memory clinics patients affected by various neurological disorders including DLFT, DCL or AD. *Results:* We could quantify in these clinical situations the relative presence of the different tau peptides corresponding the N-terminus, the central core, the C-terminus of the protein, some of them being exon (2, 3, 10) - isoform (0N,1N,2N,3R,4R) specific or the subject of phosphorylation. This allowed us to link the presence of truncated/modified tau isoforms to the different clinical diagnosis. The quantification of some specific peptides allowed us to differentiate AD from differential diagnosis even in the context of elevated tau. Concerning phospho Tau peptides, the results showed the evidence of 4 phosphopeptides localizing 6 sites of phosphorylation including Thr175, Thr181, Ser198/199, Ser202, Thr205 and Thr217 that can be quantified. *Conclusions:* The HRMS detection of specific peptides encompassing the all tau protein sequence is a new innovative analytical tool that can include specific phosphopeptides of tau protein. When applied to the CSF of patients it demonstrated its interest to explore the pathophysiology of this protein in neurodegenerative disease and for diagnosis purposes.

OC42: MEASURING COGNITIVE PROCESSES AFFECTED BY ALZHEIMER'S DISEASE USING MARKOV MODELS.

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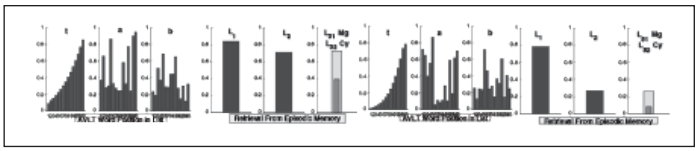
Background: Identifying which cognitive processes sub-serving learning and memory are impaired in Alzheimer's disease (AD) and related disorders is essential for improving early detection, differential diagnosis and treatment. Summary and composite performance scores do not consider these processes, but cognitive models can be formulated that do. In particular, specially formulated Hidden Markov (HM) models can measure latent cognitive processing capacities from memory task data. We previously developed an HM model of wordlist memory (WLM) task performance, which consisted of three memory states – Unlearned (U), Working Memory (WM), and Short-Term Memory (STM) – plus 4 encoding (parameters "a", "r", "v", "b") and 3 retrieval (parameters "t", L1, L2) cognitive processes. This HM model has been used to analyze the 10-item, ADAS-Cog WLM task, which consists of 3 immediate study (learning)-test (free-recall) trials plus a free recall test trial after a 5-minute, delay. This HM model was validated using the ADAS-Cog WLM task data from 465 normal, 985 mild cognitive impairment (MCI), and 225 early AD dementia subjects of the AD Neuroimaging Initiative (ADNI), from 414 amnestic MCI subjects of the AD Cooperative Study (ADCS) trial of donepezil, vitamin E, or placebo, and from 112 normal subjects of the 3-year, ADCS, longitudinal study. The present study examined the generalizability of this HM model to predict underlying cognitive processes of the 15-item, Auditory Verbal Learning Test (AVLT) used by the Mayo Clinic Aging Study, which consists of 5 study-test trials and 2 delayed free recall trials at 5 minutes and 1 hour after learning trials. *Methods:* The HM model derived from the ADAS-Cog WLM task was modified for the new task and used to estimate the posterior distribution of the cognitive processing parameters underlying AVLT WLM task performance. These parameters were then used to generate the posterior predictive distribution of the AVLT WLM task item response data from the initial visits of 178 normal and 131 AD subjects (53% MCI, 47% dementia) from the Mayo Clinic Alzheimer's Disease Patient Registry. *Results:* Having more words and learning trials than the ADAS-Cog, the AVLT required two learning trials before reaching stationary parameter distributions. After adjustment for this difference from the ADAS-Cog WLM task, the AVLT and ADAS-Cog HM model findings were largely in agreement. Lessons learned from the HM model are: 1) HM models accurately estimate cognitive processes common to different clinical WLM tasks; 2) Item retrieval from WM ("t") is similar in all subject groups. 3) Item encoding into WM ("a") is stronger in Normal Aging than in MCI and demented AD. 4) For items recalled during learning trials ("t"), and consequently encoded into STM ("b"): a. Their retrieval strength from STM at that time ("L1") is similar for all subjects. b. However, these items' retrieval strengths from STM 1 hour later ("L31") decline much more in MCI and demented AD than in Normal Aging. 5) Item retrieval strength from STM several minutes after learning trials ("L2") is much weaker in MCI and demented AD than in Normal Aging. 6) Item retrieval strength from STM shows almost no reduction between several minutes after learning ("L2") and 1 hour ("L32") in any subject group. *Conclusion:* This HM model methodology can predict underlying cognitive processes sub-serving different WLM tasks, so the tasks can be compared. A useful discovery of this HM model methodology is the large and rapid (within minutes) reduction in information retrieval strength from STM (hippocampus) that occurs between Normal Aging and MCI. This methodology identified cognitive processes in MCI and dementia AD patients that can be therapeutically targeted to improve patient outcomes. This methodology can also improve meaningful interpretation of clinical trials data, drug development, patient selection, early detection, differential diagnosis and pathophysiological mechanisms.

Figure 1

Some of the cognitive processes estimated by the HM Model of the AVLT WLM task data from Normal (left 2 graphs) vs. MCI and Demented AD patients (right 2 graphs)



OC43: OPTIMIZED COGNITIVE FUNCTION COMPOSITES RELATED TO BIOMARKERS TO LOOK FOR SNAP AND PRODROMAL AD ON AB255 STUDY. ANA ESPINOSA[1], MONTSERRAT ALEGRET[1], PEDRO PESINI[2], SERGI VALERO[1,3], ASUNCIÓN LAFUENTE[1], MAR BUENDÍA[1], VIRGINIA PÉREZ-GRIJALBA[2], ITZIAR SAN JOSÉ , MARTA IBARRIA[1], MIGUEL A TEJERO[4], JOAN GIMÉNEZ[4], SUSANA RUIZ[1], ISABEL HERNÁNDEZ[1], JOSEP MUNUERA[5], JAVIER ARBIZU[6], LLUIS TÁRRAGA[1], AGUSTÍN RUIZ[1], OSCAR SOTOLONGO-GRAU[1], MANUEL SARASA[2], MERCÈ BOADA[1] *(1) Alzheimer Research Center and Memory Clinic. Fundació ACE. Institut Català de Neurociències Aplicades. Barcelona, Spain; (2) Araclon Biotech S.L., Zaragoza, Spain; (3) Deparment of Psychiatry. Hospital Universitari Vall d'Hebron. CIBERSAM. Universitat Autònoma de Barcelona, Barcelona, Spain; (4) Clínica Corachán, Barcelona, Spain; (5) Unitat RM Badalona, Institut de diagnóstic Per la imatge, Badalona, Spain; (6) Clínica Universitaria de Pamplona, Pamplona, Spain)* **Collaborators on AB255 Araclon group:** FRANCESC PUJADAS-NAVINÉS[1], RAFAEL BLESA[12], JORDI PEÑA[3], PEDRO GIL[4], ANA FRANK[5], FÉLIX BERMEJO[6], MIGUEL GOÑI[7], CARMEN ANTÚNEZ[8], MANUEL FERNÁNDEZ[9], FERNANDO PASCUAL[10], MIQUEL AGUILAR[11], JORGE MATÍAS GUIÚ[12], PABLO MARTÍNEZ-LAGE[13], GERARD PINYOL[14], GIOVANNI B FRISSONI[15] *(1) Hospital Universitari Vall d'Hebrón. Barcelona, Spain; (2) Hospital de la Santa Creu i Sant Pau. Barcelona, Spain; (3) Hospital del Mar. Barcelona, Spain; (4) Hospital Clínico San Carlos. Madrid, Spain; (5) Hospital Universitario La Paz. Madrid, Spain; (6) Hospital Universitario 12 de Octubre. Madrid, Spain; (7) Hospital Universitario de Burgos. Burgos, Spain; (8) Hospital Universitario Virgen de la Arrixaca.Murcia, Spain; (9) Hospital Universitario de Cruces. Baracaldo, Spain; (10) Hospital Clínico Universitario Lozano-Blesa. Zaragoza, Spain; (11) Hospital Mútua Terrassa. Barcelona, Spain; (12) Hospital Clínico San Carlos. Madrid, Spain; (13) Fundación CITA-Alzheimer. San Sebastián, Spain; (14) Hospital Santa María de Lleida. Lleida, Spain; (15) IRCCS Centro San Giovanni di Dio FBF.*

Background: Risk factors for conversion to dementia, especially Alzheimer's disease (AD), in patients with Mild Cognitive Impairment (MCI) have been widely studied. The search for biomarkers in the prodromal phase of AD has focused on costly methods, sometimes poorly tolerated by the patients, such as functional and structural imaging, or biochemical tests in plasma and cerebrospinal fluid. However, neuropsychological tests are a cost-effective affordable for a diagnostic unit. In a recent study, we reported in a follow-up of 550 individuals that independently of MCI subtype 45.5% converted to AD (mean follow-up time: 26.6 months; range:6-68 months). Remarkably those patients with probable MCI, with presence of storage memory impairment, multiple domain condition, and presence of at least one ε4 allele had 8.5 times more risk of converting to dementia, especially AD than those Possible non amnestic MCI, with

presence of comorbidities (cerebrovascular disease and/or psychiatric disorders) who displayed the slowest conversion rate to dementia. Recently, individuals with imaging/ biomarker evidence of AD-like neurodegeneration without β-amyloidosis (i.e amyloid PET, and low CSF Aβ42) or at least, a fraction of them, have been labeled "suspected non-Alzheimer's pathology (SNAP). However beyond imaging/biomarkers the core clinical diagnosis of AD must be first satisfied. The main objective of this work was to find the optimized Cognitive Functions Composites (CFC's) related to biomarkers to look for «suspected non-Alzheimer pathology» (SNAP) and Prodromal AD. *Methods:* Two groups of datasets > 64 years old, were analysed: (i) The AB255 study (n=175) with 42 Healthy Aging (HA) and 133 subjects with Probable-amnestic MCI-storage type (MCI from now on); and (ii) The Amyloid substudy (n=59) with 39 HA, and 20 MCI. At baseline, in both datasets, all subjects underwent a neuropsychological assessment including 5 CFC's sensitive to: (1) Learning and (2) Delayed Recall on Memory, (3) Language, (4) Praxis, and (5) Executive functions. They were submitted to a structural MRI, and PET-FDG in the same 30 days window after the baseline visit. The MRI T1-3D of 1x1x1 mm voxel size scans were acquired with a 1.5 T Philips Concerto machine. MRI cortical and subcortical segmentation was carried on with Freesurfer 5.3. The hippocampus volume (HV) was calculated as the mean value between left and right hemispheres and corrected by intracranial volume. The cortex mean thickness (CMT) was calculated as the mean value between left and right hemispheres. PET-FDG imaging were acquired 60 minutes post injection of 370 MBq of [18F]-FDG during 20 minutes. The PET-FDG processing was performed with FSL. Every scan was averaged, corrected, corregistered to MNI standard space and mean value of FDG-PET activity calculated for a composite ROI based on other FDG studies and available in http://adni.loni.usc.edu/methods/research-tools/. The SUVR was normalized by vermis/pons. MRI classified subjects in HV+ or HV- with a cutoff threshold of atrophy value of HV=3.2 cm3, that is, HA+ (n=3), HA-(n=39), MCI+ (n=82), and MCI-(n=50). The HA+ group was excluded from the analysis due to the sample size. Moreover MRI classified subjects in CMT+ or CMT- with a cutoff threshold of atrophy value of CMT=2.3 mm, that is, HA+ (n=13), HA-(n=29), MCI+(n=101), and MCI-(n=30). PET-FDG analyzed according to the Alzheimer's Disease Neuroimaging Initiative (ADNI) methods, classified subjects in FDG+ or FDG- with a cutoff threshold of metabolic value of FDG=1.2 SUVR, that is, HA-(n=42), MCI+ (n=57), and MCI- (n=76). In a subsample, for Amyloid substudy participants, PET-PIB imaging was also acquired in the same 30 days window. PET-PIB was acquired dynamically, immediately after intravenous injection of approximately 555 MBq of the radiotracer. PET-PIB scans were corregistered to subject space. PET-PIB SUVR was calculated taking a cortical composite ROI that included 4 large cortical grey matter regions (frontal, anterior/posterior cingulate, lateral parietal, lateral temporal) and normalizing by the cerebellum grey matter. Subjects were classified in PiB+ or PiB- with a cutoff of PIB=1.5 SUVR, that is, HA+ (n= 2), HA- (n=37), MCI+ (n=12), and MCI- (n=8). The HA+ group was excluded from the analysis due to their sample size. Distance between the CFC's profiles related to biomarkers was calculated as the Kolmogorov-Smirnov (K-S) distance between the corresponding Gaussian distributions. *Results:* On AB255 study dataset, hippocampal volume and cortical mean thickness on MRI, both showed that Learning on Memory (K-S=.26 and K-S=.21, respectively) CFC classified into the HA+, HA-, MCI+ and MCI-. PET-FDG showed that Delayed Recall on Memory (K-S=.28) and Executive (K-S=.17) CFC's classified into the HA, MCI+ and MCI-groups, independently of its APOE- ε4 genotype. On Amyloid substudy dataset, PET-PIB showed that Delayed recall on Memory (K-S=.42), Executive (K-S=.16) and Language (K-S=.11) CFC's, properly classified into the HA, MCI+ and MCI-groups. *Conclusions:* Learning and Delayed Recall on Memory, and Executive functions are the optimal CFC's classifying between SNAP and Prodromal AD. *Keywords:* Cognitive functions composites, Probable amnestic storage type Mild Cognitive Impairment, SNAP, Prodromal Alzheimer's disease, Structural MRI, 18 F-FDG PET, 11C-PET-PIB, ADNI.

OC44: VITAMIN D STATUS PREDICTS RATES OF COGNITIVE DECLINE IN A MULTI-ETHNIC ADC COHORT OF OLDER ADULTS. JOHN M OLICHNEY[1], JOSHUA W MILLER[2,4], DANIELLE J HARVEY[3], LAUREL A BECKETT[3], RALPH GREEN[4], SARAH FARIAS[1], BRUCE R REED[1], DAN M MUNGAS[1], CHARLES DECARLI[1] *((1) Neurology, University of California, Davis, CA (SF, BRR, JMO, DMM, CSD); (2) Nutritional Sciences, Rutgers University, New Brunswick, NJ (JWM); (3) Public Health Sciences, Division of Biostatistics, University of California, Davis, CA (DJH, LAB); (4) Medical Pathology and Laboratory Medicine, University of California, Davis, CA (JWM, RG))*

Background: Vitamin D deficiency is associated with brain structural abnormalities, cognitive decline, and incident dementia. We assessed associations between vitamin D status and trajectories of change in subdomains of cognitive function in a cohort of ethnically diverse older adults characterized by the UC Davis Alzheimer's Disease Center (ADC). *Methods:* We conducted a longitudinal observational study in an outpatient clinic with baseline assessment and yearly follow-up visits (mean follow-up: 4.8±2.5y). Subdomains of cognitive function were assessed using the Spanish English Neuropsychological Assessment Scales. Serum 25-hydroxyvitamin D (25-OHD) was measured by competitive immunoassay with vitamin D status defined as deficient, <12 ng/ml; insufficient, 12 to <20 ng/ml; adequate, 20 to <50 ng/ml; high, >50 ng/ml. *Results:* Subjects (N=382 at baseline) had a mean age of 76±7y; 61.8% were women, 41.4% were White, 29.6% African-American, 25.1% Hispanic, and 3.9% other. Diagnosis at baseline included 17% with dementia, 33% with mild cognitive impairment (MCI), and 50% who were cognitively normal. We found a high prevalence of vitamin D insufficiency in our multi-ethnic cohort (e.g. ~70% prevalence of deficiency or insufficiency in African Americans and Hispanics, ~50% in Non-Hispanic Whites). Overall, mean 25-OHD was 19.2±11.7 ng/ml with 26% deficient and 35% insufficient. 25-OHD levels were significantly lower among African-Americans and Hispanics compared with Whites (17.9±15.8 and 17.2±8.4 vs 21.7±10.0 ng/ml; p<0.05). 25-OHD was lower in the dementia group compared with the MCI and cognitively normal groups (16.2±9.4 vs 20.0±10.3 and 19.7±13.1 ng/ml; p=0.006). Controlling for age, sex, education, ethnicity, BMI, season of blood draw, vascular risk, and apolipoprotein E4, rates of decline were greater for episodic memory (p<0.05) and executive function (p<0.02) in vitamin D deficient and insufficient subjects, compared with those with adequate status. Exclusion of demented subjects did not substantially affect the associations between vitamin D status and rates of cognitive decline. *Conclusion:* Low vitamin D status is associated with accelerated rates of decline in memory and executive function in our cohort of ethnically diverse older adults. Vitamin D insufficiency may be a particularly important treatable risk factor in older African-American and Hispanic populations, who exhibit a very high prevalence of vitamin D insufficiency. These results raise the question of whether vitamin D supplements would slow cognitive decline in elderly populations with vitamin D insufficiency. Randomized clinical trials which address this question could have a major impact on the public health of our aging population. *Study funding:* NIH 5 P30 AG010129 (PI: Charles S. DeCarli, MD). *Disclosure:* The authors report no disclosures relevant to the manuscript.

OC45: REDUCTION OF AMYLOID-B WITH GANTENERUMAB FOR TREATMENT OF PRODROMAL

ALZHEIMER'S DISEASE – POST HOC ANALYSES FROM THE PHASE 3 SCARLET ROAD TRIAL. JUERGEN DUKART[1], FABIO SAMBATARO[2], ROBERT LASSER[2], TANIA NIKOLCHEVA[1], SUSANNE OSTROWITZKI[1], LUCA SANTARELLI[1], DIETMAR VOLZ[2], PAULO FONTOURA[2], ALESSANDRO BERTOLINO[1] *((1) Roche Pharmaceutical Research & Early Development, F. Hoffmann-La Roche Ltd, Basel, Switzerland; (2) F. Hoffmann-La Roche Ltd, Basel, Switzerland)*

Background: SCarlet RoAD (NCT01224106; WN25203), a multicenter, randomized, double-blind, placebo-controlled, 2-year trial, tested the efficacy of gantenerumab in patients with prodromal AD. Following a pre-planned futility analysis, dosing in Scarlet RoAD was terminated. No significant differences in efficacy endpoints between treatment arms were observed in the primary analyses. Different study aspects such as sub-optimal amyloid reduction or potential biases introduced by discontinuing patients (DP) might have contributed to the study outcome. Here, we perform post hoc analyses testing for gantenerumab-induced amyloid reductions (PET imaging) using a more sensitive voxel-wise approach, and for changes in clinical progression rates in all patients including DP. *Methods:* Patients eligible for SCarlet RoAD were 50–85 years old with MMSE ≥24, CDR-Global 0.5 (memory box 0.5 or 1.0), abnormal memory function, no diagnosis of dementia and low CSF Aβ42 levels. Patients were randomized to subcutaneous injections of placebo, 105 mg or 225 mg gantenerumab, based on APOEε4 allele status (no patients homozygous for APOEε4 received 225 mg) every 4 weeks. 799 patients were enrolled in the clinical study and 114 patients in a PET sub-study (AmyvidTM). Main results and more detailed inclusion and exclusion criteria from these studies are reported elsewhere (Lasser et al., AAIC 2015; CTAD 2015; Scheltens et al., AAIC 2015; Nikolcheva et al., CTAD 2015). To test for treatment-related amyloid reductions, voxel-wise general linear models were computed for pre-processed amyloid-PET data using the Statistical Parametric Mapping (SPM12) software with treatment and subject as between- and time (baseline, Weeks 20 and 60) as within-subject factors testing for significant treatment-by-time interactions (P<0.001 voxel level and P<0.05 family-wise error cluster level corrected for multiple comparisons across the whole brain). To test for potential differences with respect to DP, progression rates for all patients including DP were calculated by fitting linear regressions to each subject's individual clinical scores (ADAS-Cog13, MMSE, and CDRSB) from all visits using time as a predictor and extracting the slope of progression. The slope in each treatment arm was compared with placebo in two different analyses of variance: (1) for patients who completed the 2 years' follow-up and (2) for all patients including DP. To further elaborate the effect of DP onto differences between treatment arms, the slopes between DP and completers were separately compared for each treatment arm and between treatment arms using two-sample t-tests at a two-sided P-value of 0.05. *Results:* Voxel-wise analysis of amyloid-PET data identified reduced amyloid binding ratio in anterior, middle and posterior cingulate, insular, medial and lateral prefrontal regions, ventral striatum and precuneus. The precuneus was the region with strongest (peak-voxel) treatment-related reductions in amyloid binding ratio in the 225 mg gantenerumab group of up to 15% relative to baseline and 18% relative to change in the placebo group. Consistent with the primary ANCOVA and MMRM analyses reported elsewhere, comparison of slopes between treatment conditions in patients who completed the 2 years' follow-up evaluation demonstrated no significant difference for any clinical scale tested (all P>0.5). The rate of DP was similar across the three treatment arms (approximately 26%). However, when comparing progression rates in the overall group including DP, significantly less clinical decline was present in the 225 mg gantenerumab arm for both MMSE (P=0.024) and ADAS-Cog13 (P=0.029) compared with placebo; CDRSB changes were not significant (P=0.125). Further, the decline characteristics of the DP were significantly different. In the placebo group, DP had a 3.9-fold faster decline in MMSE (P<0.001), 2.9-fold faster decline in CDRSB (P<0.001) and 2.6-fold faster decline in ADAS-Cog13 (P=0.008) compared with subjects who remained in the trial. In the 105 mg arm, the ratio was 2.6-, 2.3- and 1.9-fold for MMSE (P=0.012), CDRSB (P=0.001) and ADAS-Cog13 (P=0.15), respectively. In the 225 mg arm the ratios were the smallest: 1.7 for MMSE (P=0.172), 1.7 for CDRSB (P=0.029) and 0.95 for ADAS-Cog13 (P=0.918). *Conclusions:* Post hoc analyses of SCarlet RoAD data provided important additional evidence of clinical effects and biological activity of gantenerumab. Voxel-wise analyses of amyloid-PET data showed significant reductions in amyloid depositions across brain regions known to have a high amyloid load in AD. Although the primary analysis reported elsewhere was negative, post hoc progression rate analyses of all patients including DP indicated statistically significant slowing of clinical progression with 225 mg gantenerumab compared with placebo across different clinical scales. These findings are in line with other exploratory analyses of this clinical trial showing an exposure-dependent treatment effect in patients predicted to have greater progression (Lasser et al., AAIC 2015; CTAD 2015). In future studies of gantenerumab, the aim will be to further improve clinical effects of gantenerumab by focusing on expanding the dose range, selecting and maintaining fast progressors in the trials and accounting for different progression rates in DP.

OC46: STATISTICAL MODELING OF BIOMARKER PROFILES FOR THE PREDICTION OF RAPID COGNITIVE DECLINE IN MCI AND MILD AD SUBJECTS. ROBIN WOLZ[1,2], KATHERINE R GRAY[1,2], MARIA ROSA[1], DEREK HILL[1], *((1) IXICO Plc, London, UK; (2) Imperial College London, London, UK)*

Background: Following disappointing results in recent Phase II/III trials in MCI and mild AD populations, more detailed patient stratification protocols play an increasingly important role in trial design. Patient demographics, clinical scores on cognition and function as well as different biomarkers have all been used for defining specific inclusion criteria. Different work was proposed recently for patient stratification (predominantly in MCI populations) that look at individual markers [3] or multi-stage approaches where multiple markers are used sequentially [4,5]. As there is an interplay between the different measurements, a combinatorial approach that considers such relationships is hypothesized to be more powerful than a purely sequential approach where every marker is considered independently. In this work we present preliminary results for using multiple markers in a supervised machine learning model to learn a marker profile that is most predictive for future cognitive decline on a relevant clinical endpoint. *Methods:* Included are the 321 (late) MCI and 179 mild AD subjects from the ADNI I/II cohorts for which an Amyloid marker is available from PET or CSF. Clinical assessment at baseline was required with CDR-SB/ADAS-Cog/FAQ and a follow-up on ADAS-Cog was also required after 12 months. Evaluated were the impact individual / combinatorial biomarkers can have on the identification of subjects rapidly progressing on ADAS-Cog as measured through the effect size (mean change divided by standard deviation). We assessed the impact an application of the following markers (cutpoints) can have when applied sequentially or in a combinatorial machine learning model: (1) FAQ (included with FAQ>0), (2) CDR-SB (included with CDR-SB>0.5), (3) amyloid positivity (cutpoints on PiB PET / CSF A-beta as widely used [1,2]), (4) hippocampal volume, HCV (continuous cutpoints validated). Automated hippocampal volumetry and statistical modeling was performed in a research environment of the CE marked medical device Assessa (www.myassessa.com). *Results:* Table 1 presents for different combinations of measurements

screen failure rates, resulting effect sizes (on 1-year change on Adas-Cog) as well as the required sample size and number of subjects that need to undergo screening (NNS) to obtain this sample size. Both sample sizes are presented relative to the unenriched scenario and are therefore independent of other trial characteristics like the required power or screen failure due to other criteria. Where multiple measurements are combined, results are presented for a Sequential approach with the cutpoints defined above as well as a supervised Machine learning approach. A linear regression model to predict change in Adas-Cog is employed in the supervised approach. In 1,000 runs, models are trained on 80% of data and tested on the remaining data. Results are averaged over all independent runs. Cutpoints on continuous variables (HCV in the sequential approach, output of supervised method) are defined in a way to arrive at the predefined screening failure rates listed below.

Markers	Method	Scr. failure rate		Effect size		Rel. sample size		Rel. NNS	
		MCI	AD	MCI	AD	MCI	AD	MCI	AD
None	n.a.	0	0	-0.21	-0.70	1	1	1	1
Amyloid only	Sequential	0.3	0.1	-0.32	-0.74	0.43	0.89	0.62	0.99
Amyloid / HCV	Sequential	0.5	0.5	-0.33	-0.73	0.40	0.91	0.81	1.84
	Machine learning	0.5	0.5	-0.36	-0.75	0.34	0.87	0.68	1.74
FAQ/CDR-SB/HCV	Sequential	0.6	0.6	-0.32	-0.74	0.43	0.89	1.08	2.23
	Machine learning	0.6	0.6	-0.35	-0.82	0.36	0.73	0.90	1.82
Amyloid/FAQ/ CDR-SB/ HCV/ Demograpics (age / education)	Sequential	0.70	0.7	-0.36	-0.77	0.34	0.83	1.13	2.75
	Machine learning	0.70	0.7	-0.41	-0.94	0.26	0.55	0.87	1.85

Conclusions: The presented results show different approaches for selection of suitable patients into a trial based on multiple measurements. The results show how by modeling the interplay between different measurements through a supervised machine learning approach, an improved prediction of subjects at higher risk of deteriorating on a relevant endpoint can be achieved. Especially continuous clinical scores like FAQ and CDR-SB can be integrated much more efficiently in a statistical modeling approach compared to a sequential approach which leads to significant screen failure rates even at the conservative cutpoints employed here. Statistical modeling also provides a natural means of integrating demographic information like age or education. Combining the relatively easily available measurements of CDR-SB, FAQ and HCV yields the same performance improvement as the significantly more expensive and invasive combination of Amyloid status and HCV. More work will be done to validate more advanced machine learning techniques, other relevant biomarker and patient-demographic data as well as the impact on other trial characteristics like other endpoints and trial cost and -time. *References:* 1. L. M. Shaw et al. Annals of Neurology, 65(4):403-13, 2009; 2. S. D. Weigand, et al. Alzheimer's and Dementia, 7(2):133-41, 2011; 3. P Yu et al. Neurobiology of aging 35 (4), 808-818, 2014; 4. M. Lorenzi et al, Neurob. of Aging, 31:1443-51, 2010; 5. M. Austin et al, CTAD 2014.

OC47: CONSISTENT EFFECTIVENESS OF DEXTROMETHORPHAN/QUINIDINE FOR PSEUDOBULBAR AFFECT ACROSS DIVERSE NEUROLOGICAL ETIOLOGIES.

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Background: Pseudobulbar affect (PBA) is characterized by frequent, sudden, and unpredictable episodes of uncontrollable laughing and/or crying that are exaggerated or incongruent with social context or internal mood state. PBA occurs when various neurologic conditions, such as Alzheimer's disease (AD) or other dementias, or brain injuries, such as TBI or stroke, disrupt brain pathways that regulate emotional expression. Dextromethorphan hydrobromide and quinidine sulfate (DM/Q; NUEDEXTA, Avanir Pharmaceuticals, Inc., Aliso, Viejo, CA, USA), the only approved treatment for PBA in the United States and European Union, was approved without regard to causative condition, based on Phase III trials conducted in patients with ALS or MS. Additionally a Phase IV trial enrolled PBA cohorts with AD, stroke and TBI to obtain additional effectiveness and safety data. Dextromethorphan is the CNS active component of DM/Q; quinidine is a potent inhibitor of cytochrome P450 2D6 and serves to increase CNS bioavailability of dextromethorphan. This analysis evaluates the consistency of DM/Q effect for PBA across trials for patients with these various neurologic conditions. *Methods:* Data are evaluated from 3 randomized, double-blind trials: (1) DM/Q 30 mg/30 mg BID for 28 days (vs. dextromethorphan 30 mg or quinidine 30 mg alone) in patients with PBA secondary to ALS (n=129); (2) DM/Q 30 mg/30 mg BID vs. placebo for 3 months in patients with PBA secondary to MS (n=150); and (3) DM/Q 30 mg/10 mg BID [EU approved dose] or DM/Q 20 mg/10 mg BID [US and EU approved dose] vs. placebo for 12 weeks in patients with PBA secondary to ALS or MS (n=326), and the 3 cohorts of the PRISM II trial: an open-label 12-week study investigating DM/Q 20 mg/10 mg BID in patients with PBA secondary to dementia (n=108), stroke (n=103), and traumatic brain injury (n=120; effectiveness results under analysis). All enrolled patients had clinically diagnosed PBA with a score ≥13 on the Center for Neurologic Study–Lability Scale (CNS-LS range; 7–35). Primary efficacy outcomes were based on change from baseline in CNS-LS scores and reduction in PBA episodes. *Results:* Reduction in CNS-LS score showed consistency across all available double-blind and open-label study cohorts, regardless of the PBA etiology. Mean (standard error) CNS-LS score change from baseline ranged from -7.2 (0.6) to -8.2 (0.6) compared with -3.3 (0.6) to -5.7 (5.3) for control groups in the 3 double blind trials. Reductions in CNS-LS scores with DM/Q corresponded to an average reduction of ~75 % (range 68%–82%) from baseline in weekly PBA episodes across studies. Reductions in PBA symptoms were accompanied by improvements in other study-specific measures of clinical relevance, such as quality of life and global clinical improvements (CGIC/PGIC). *Conclusion:* Data across 4 distinct studies conducted over the past decade that included patients with PBA secondary to 5 different neurologic etiologies (including dementia and stroke), show robust and clearly consistent DM/Q efficacy for treatment of PBA. *Study supported by:* Avanir Pharmaceuticals, Inc.

OC48: UPDATE ON FDA QUALIFICATION OF LOW BASELINE HIPPOCAMPAL VOLUME AS A PROGNOSTIC BIOMARKER IN ALZHEIMER'S DISEASE CLINICAL TRIALS, FOR THE COALITION AGAINST MAJOR DISEASES.

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Development Center Americas, Deerfield, IL, USA; (7) University Hospital of Geneve & University of Geneva; (8) IXICO PLC., London, UK; (9) Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA; (10) Pentara Corporation, Salt Lake City, USA; (11) Pfizer, Groton, CT, USA; (12) University of Trento, Italy; (13) Janssen Research and Development, Titusville, USA; (14) ICON, Lansdale, PA, USA; (15) Coalition Against Major Diseases, Critical Path Institute, Tucson, AZ, USA; (16) Eli Lilly, Indianapolis, IN, USA; (17) BioClinica, Fremont, CA, USA)

Background: The Coalition Against Major Diseases (CAMD), a consortium within the non-profit organization Critical Path Institute, is a public-private partnership aimed at creating new tools and methods to facilitate the development of treatments for Alzheimer's disease (AD) and Parkinson's disease. CAMD seeks FDA qualification for the use of low baseline hippocampal volume (HV) as a biomarker for enrichment in clinical trials of patients with early AD. While considerable evidence links reduced HV in the brains of subjects with cognitive impairment with the presence of underlying pathophysiologic signs of AD and subsequent development of Alzheimer-type dementia, low HV has not been utilized as a biomarker in clinical trials to identify subjects with early AD. Adoption of this biomarker will be facilitated by endorsement from global regulatory authorities. In 2011 The European Medicines Agency issued a Qualification opinion (for regulatory purpose) of low hippocampal volume (atrophy) by MRI for use in clinical trials in pre-dementia stage of AD. Currently, CAMD's imaging biomarker team is at the Consultation and Advice Stage of biomarker qualification with the FDA and will present updates and lessons learned from the regulatory path to date. *Methods and results:* The HV measures proposed for qualification will be applicable independent of the specific drug's mechanism of action or target, the MRI scanner that collected the imaging data, and the algorithm used to measure the HV. Our team has evaluated multiple algorithms in independent clinical cohorts that have longitudinal clinical follow-up, including ADNI. Advances in the field have mitigated concerns regarding repeatability and reproducibility; however, data from relevant clinical trials will be necessary to achieve regulatory success. The ability to acquire usable raw MRI images from clinical trials is significantly delayed by operational factors as well as permission for secondary uses of trial data that were not specified in the protocol or consent forms. Additional work is necessary to achieve formal qualification from the FDA for use of low HV as a prognostic biomarker for enrichment in clinical trials. In early 2015 the FDA issued a Letter of Support that encourages the use of volumetric MRI in AD trials, highlighting the importance of data sharing and use of clinical data standards. *Conclusions:* The development of a robust evidentiary package to support the qualification of the HV imaging biomarker for use in clinical trials of patients with AD requires significant resources and commitment from a wide range of stakeholders. The ability to collaborate efficiently in a pre-competitive environment to benefit the goal of qualifying novel drug development tools requires sharing of data, early anticipation of the necessary processes (e.g., organizing for specimen transfer and/or sharing of de-identified data), permissions (e.g., informed consent approval for sharing of specimen and data) and dedication to achieving a collective goal that aims to benefit the field as a whole.

OC49: RVT-101: REVIEW OF THE PRECLINICAL AND CLINICAL RESULTS AND STATUS OF THE DEVELOPMENT PROGRAM. LAWRENCE T FRIEDHOFF[1], ILISE LOMBARDO[1], GEETHA RAMASWAMY[1], STEPHEN C PISCITELLI[2] *((1) Axovant Sciences, Inc, New York, NY, USA; (2) Roivant Sciences, Inc. New York, NY, USA)*

Backgrounds: RVT - 101 (formerly known as SB-742457) is a potent inhibitor of the 5HT6 receptor in vitro and in vivo. It also inhibits the 5HT2a receptor to a lesser degree. It increases acetylcholine in microdialysis studies and improves performance in a preclinical model of cognitive impairment. These results supported initiation of clinical studies of RVT-101. *Methods:* Internal and published clinical trial results for RVT-101 were reviewed and summarized as was the plan for the further development of RVT-101. *Results:* The results of preclinical pharmacology studies justified initiation of phase I and II clinical trials in Alzheimer's disease. The phase II trials of doses up to 35 mg once daily show evidence of efficacy for RVT-101 when administered as monotherapy to patients with mild-to-moderate Alzheimer's disease. When given against a background of donepezil treatment, 35-mg once-daily doses of RVT-101 were associated with statistically significant superiority to placebo on measures of both cognition and function. RVT-101 was well tolerated among the over 1200 patients and healthy volunteers evaluated so far with high patient retention for up to 48 weeks of treatment. *Conclusion:* These findings justify continuation of development of RVT-101 as a treatment for mild-to-moderate Alzheimer's disease. In particular, initiation of a large Phase III clinical study scheduled to begin in the 4th quarter of 2015. RVT-101 will also be evaluated as a treatment for other forms of dementia.

OC50: NEW EXPLORATORY ALZHEIMER'S DRUG ANAVEX 2-73: ASSESSMENT OF SAFETY AND COGNITIVE PERFORMANCE IN A PHASE 2A STUDY IN MILD-TO-MODERATE ALZHEIMER'S PATIENTS. STEVE MACFARLANE[1], PAUL MARUFF[2], MARCO CECCHI[3], DENNIS MOORE[3], ANASTASIOS ZOGRAFIDIS[4], CHRISTOPHER MISSLING[4] *((1) Caulfield Hospital, Melbourne, Australia; (2) Cogstate, Melbourne, Australia; (3) Neuronetrix, KY, USA; (4) Anavex Life Sciences, Corp., New York, NY, USA)*

Background: Despite major efforts aimed at finding a treatment for Alzheimer's disease (AD), progress in developing compounds that can relieve cognitive deficits associated with the disease has been slow. ANAVEX 2-73 is a sigma-1 and muscarinic receptor agonist that in preclinical studies has shown memory-preserving and neuroprotective effects. In our ongoing phase 2a clinical study we are assessing ANAVEX 2-73 safety in subjects with mild-to-moderated AD, and measuring drug effects on MMSE, EEG and Event Related Potentials (ERP) cognitive measures, and Cogstate test batteries to optimize dosing. *Methods:* Thirty-two subjects that meet NINCDS-ADRDA criteria for probable AD are being recruited at up to seven clinical sites in Melbourne, Australia. Subjects are between 55 and 85 years of age, and have an MMSE of 16 to 28. In PART A of the study, participants are administered ANAVEX 2-73 orally and IV in an open-label, 2-period, cross-over trial with adaptive study design lasting up to 36 days for each participant. In PART B of the study, all participants are administered ANAVEX 2-73 daily orally. MMSE, EEG/ERP (P300) and Cogstate tests are performed at baseline and subsequently at weeks 12, 26, 38 and 52 of the PART B open label extension. *Results:* The primary outcome of the study is safety, and ANAVEX 2-73 was well tolerated. In the secondary outcome endpoints preliminary analysis of data from subjects to date shows an average improvement of the MMSE score at week 12 in PART B (week 17 from baseline). A significant majority of all patients tested so far improved their respective MMSE score. The average EEG/ERP (P300 amplitude) signal also improved and also the average Cogstate test improved across the test batteries. *Conclusions:* Data collected so far indicate that ANAVEX 2-73 is safe and well tolerated. Interim results also show improved cognitive performance after drug administration in subjects with mild-to-moderate AD. The current results seem to justify a prospective comparison with current standard of care in a larger

clinical trial study. A more complete set of results will be available at the time of the conference.

OC51: RATIONALE FOR THE DEVELOPMENT OF LOW DOSES OF ITI-007 FOR THE TREATMENT OF BEHAVIORAL DISTURBANCES ASSOCIATED WITH DEMENTIA. ROBERT E. DAVIS[1], KIMBERLY E VANOVER[12], CEDRIC O'GORMAN[2], JELENA SAILLARD[2], SHARON MATES[2] *((1) 3-D Pharmaceutical Consultants, Inc, San Diego, CA, USA; (2) Intra-Cellular Therapies, Inc, New York, NY, USA)*

Background: Patients with dementia endure neuro-psychiatric symptoms that cause significant distress to themselves and their caregivers. Sleep disturbances, behavioral and depressive symptomatology are well recognized in patients with dementia in addition to the pathognomic hallmarks of the disease, neurodegeneration and cognitive decline. There is a lack of pharmacological options available to clinicians to safely treat these neuro-psychiatric symptoms. Widespread off-label use of existing antipsychotics, despite a lack of supportive clinical evidence, as well as the overuse of benzodiazepines, present substantial health risks for patients. ITI-007 is a first-in-class, investigational new drug that simultaneously modulates serotonergic, dopaminergic, and glutamateric neurotransmission, with differing pharmacology depending on dose. At low doses, ITI-007 fully antagonizes the 5-HT2A receptor (with modest interaction with its other drug targets) and in so doing is believed to confer improvements in sleep as well as provide antidepressant, anti-aggression, anti-agitation and anxiolytic effects. With dose escalation, additional pharmacological interactions play a greater role. This unique pharmacology presents differing therapeutic utility for ITI-007 across a wide dosing range, allowing a dose-dependent pursuit of different neuro-psychiatric indications. In a phase 2 clinical trial, 60 mg of ITI-007 was effective in reducing symptoms of acute schizophrenia. Emerging data suggests low doses of ITI-007 have strong therapeutic potential for the improvement of neuro-psychiatric symptoms including sleep, in patients with dementia and related disorders. *Methods:* A phase 2 clinical trial evaluated low doses of ITI-007 (1–10 mg range) in patients with primary sleep maintenance insomnia. The study's primary objective was to determine the effect of ITI-007 on slow wave sleep time as determined by polysomnography. Secondary objectives were to determine the effect of ITI-007 on objective wake time after sleep onset and other objective sleep parameters (via polysomnography), on daytime functioning (assessed by a cognitive battery), on subjective measures of sleep (evaluated via patient-reported sleep questionnaires, and safety/tolerability. Further, a safety and tolerability study evaluated ITI-007 (7.5, 15.0 and 30 mg, QAM for 7 days) in healthy elderly subjects and evaluated 9 mg of ITI-007 QPM for 7 days in patients with dementia. The primary objectives of this study were to evaluate the safety/tolerability and pharmacokinetics of ITI-007 in the elderly and in the target dementia patient population. Secondary measures were included to explore the effects of ITI-007 on cognition and agitation. The Hopkins Verbal Learning Test-R was used to assess cognition in both groups. *Results:* In a Phase 2 clinical trial of patients with primary insomnia, low doses of ITI-007 significantly and dose-dependently increased slow wave sleep and decreased the duration of wake after sleep onset as measured by polysomnography, meeting the pre-specified primary and key secondary endpoints of the trial. ITI-007 significantly increased sleep duration, with increases in slow wave sleep in the first half of the night and increases in Stage 2 sleep in the second half. Patients treated with ITI-007 showed no next-day hangover effects and no cognitive deficit upon waking. ITI-007, at doses that improved sleep maintenance, did not impair next-morning cognitive measures of memory (measured by the Word Pair Associates Test), attention/vigilance (measured by the Digit Symbol Substitution Test), or psychomotor performance (measured by the Leeds Psychomotor Test). Moreover, ITI-007 had no adverse residual effect on mood (measured by the Bond-Lader Visual Analogue Scale) the morning following treatment. ITI-007 was safe and well-tolerated in a study of healthy geriatric subjects and patients with dementia. Subjects did not exhibit extrapyramidal adverse events or clinically relevant cardiovascular changes. The tolerability and pharmacokinetic profile of ITI-007 in geriatric subjects indicate a wide safety window in the elderly. The trial, designed primarily to measure safety, included cognitive endpoints. The results confirmed no cognitive impairment with ITI-007 and, moreover, demonstrated clinical signals for improved cognition within one week of treatment with ITI-007 in both healthy geriatric subjects and patients with dementia. In these trials, ITI-007 demonstrated favorable efficacy and safety profiles in these patient populations. Based on its pharmacology, ITI-007 is predicted to provide antidepressant, anti-aggression, anti-agitation and anxiolytic effects. As a result of these encouraging results, a clinical study further testing ITI-007 for behavioral symptoms in dementia will be initiated. The design of this study will be described. *Conclusion:* Data generated to date suggests ITI-007 could represent an important and novel therapeutic advance in the treatment of a broad array of behavioral symptoms associated with dementia and related disorders. ITI-007's improvements in sleep, cognition, learning and behavioral disturbances, coupled with its favorable safety and tolerability profile, would make it an important novel and safe treatment option for patients.

OC52: CLINICAL TRIAL IN MCI REDUCING HIPPOCAMPAL OVERACTIVITY: HOPE4MCI. MICHELA GALLAGHER[1,2], MARILYN ALBERT[3], SHARON ROSENZWEIG-LIPSON[2] *((1) Department of Psychological and Brain Sciences, Johns Hopkins University, Baltimore, MD USA; (2) AgeneBio, Inc. Baltimore, MD USA; (3) Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD, USA)*

Background: A novel clinical trial is about to be launched involving patients with mild cognitive impairment (MCI). Previous reports from several laboratories, using functional magnetic resonance imaging (fMRI), have demonstrated that hippocampal hyperactivity is observed in the early-to-middle phase of MCI (Dickerson et al., 2005; Hämäläinen et al, 2007). A basis for hippocampal overactivity detected by fMRI in this phase of AD is supported by evidence of a mRNA expression profile underlying excessive hippocampal excitability in autopsied brains of MCI patients, distinguishing them from older controls and patients with a diagnosis of Alzheimer's dementia (Berchtold et al. 2014). Studies using fMRI have further shown that: (1) this hyperactivity is primarily seen in the medial temporal lobe memory system (Celone et al., 2006) and localized to the CA3/DG subregions of the hippocampus using high-resolution MRI (Yassa et al., 2010), (2) is associated with a greater risk of progression to dementia (Dickerson et al. 2004; Miller et al., 2008), and (3) is correlated with the extent of neuronal injury as measured in structural MRI (Putcha et al., 2011). Moreover, MCI patients who are amyloid positive. (Aβ+) on PET imaging, followed for 3 years, show an increase in hippocampal hyperactivity, greater clinical/cognitive decline and increased hippocampal atrophy, relative to the Aβ- subjects (Huijbers et al, 2015). Our research group has demonstrated that hippocampal hyperactivity can be reduced by low dose administration of the atypical antiepileptic levetiracetam (Bakker et al. 2012; 2015), along with improvements on an episodic memory test administered in the scanner. These findings, which are also supported by animal data (Koh et al., 2010; Sanchez et al., 2012; Shi et al., 2013; Tabuchi et al., 2015), have led to plans for a Phase 3 clinical trial designed to assess the efficacy of AGB101, a low dose extended release formulation of levetiracetam, in patients with MCI

due to AD. *Study Design:* In a multi-site randomized controlled trial (RCT) participants who meet criteria for enrollment with MCI due to AD will be randomized to AGB101 or placebo in a 24-month protocol. The primary objective of the study is to assess the clinical efficacy and safety of AGB101 in the treatment of MCI due to AD, with efficacy assessed utilizing the Clinical Dementia Rating scale sum of boxes score (CDRsb). A secondary objective of the study is to assess the efficacy of AGB101 on slowing neuronal injury in MCI due to AD, with efficacy assessed by entorhinal cortex atrophy using structural MRI. Multiple observational studies were used in the development of the trial design, including ADNI, Biocard, and other longitudinal datasets. The trial size is designed to ensure 250 completers per each enrollment group at 24 months. 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 with a sum of box score not greater than 2.5; (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 conforming to the DFA approved amyvidTM standards. In addition to the screening visit, the protocol will consist of 4 major visits and 6 minor visits during the 24-month study. The use of CDRsb as a sole primary measure for efficacy conforms to current FDA guidelines for the MCI symptomatic phase of disease (Kozauer & Katz 2013). Our analysis of MRI data from ADNI, consistent with analyses of other structural imaging datasets, has guided our selection of EC atrophy as a key secondary outcome measure for neuronal injury. As reported elsewhere, EC atrophy occurs prior to, and predicts, hippocampal atrophy (Desikan et al. 2010; 2013; Eskildsen et al. 2013). Longitudinal EC atrophy can also be detected in individuals with preclinical AD (Miller et al. 2013). Given autopsy evidence for EC neurodegeneration as a signature of AD in its earliest stages and reliable detection of EC atrophy by longitudinal MRI measurement, a therapy that slows or halts disease progression in AD would be expected to decrease EC atrophy. *Conclusion:* The Phase 3 trial of AGB101 represents a novel approach to therapy in the earliest symptomatic phase of Alzheimer's disease, with potential to slow a worsening decline in this population at high risk for AD dementia.

OC53: EFFECTS OF REGULAR AND LONG-ACTING INSULIN ON COGNITION AND AD BIOMARKERS IN MCI AND AD: A PILOT STUDY. SUZANNE CRAFT[1], LAURA D BAKER[1], AMY CLAXTON[2], ANGELA HANSON[2,3], HECTOR HERNANDEZ SAUCEDO[1], DEBORAH DAHL[1], BRYAN NETH[1], JOSEPH MALDJIAN[1] *((1) Department of Internal Medicine-Geriatrics, Wake Forest School of Medicine, Winston-Salem, NC, USA; (2) Geriatric Research, Education, and Clinical Center, VA Puget Sound, Seattle, WA, USA; (3) Department of Medicine-Geriatrics, University of Washington, Seattle, WA, USA)*

Background: Alzheimer's disease (AD) is associated with reduced brain insulin signaling and low CSF insulin levels. These deficiencies may abrogate insulin's role in synaptic maintenance, β-amyloid regulation, and other mechanisms related to AD pathogenesis. Restoring normal insulin function in brain may thus provide therapeutic benefit to adults with AD. Intranasally-administered insulin follows extracellular pathways to the brain, bypassing the periphery and blood brain barrier, and accessing the CNS within minutes. Previously, we showed that cognition, daily function, and cerebral glucose metabolism are enhanced following intranasal treatment with regular insulin, which mimics postprandial insulin release and pharmacokinetics. Insulin detemir is an analogue that provides more prolonged insulin exposure. We present the result of a randomized, double blind pilot study that examine the efficacy of insulin and insulin detemir and discuss the potential mechanisms underlying their effects. *Methods:* Participants with MCI or mild AD (n=36; 3 lost to follow-up) were randomized to receive placebo (n=11, mean age=68.0, mean MMSE=25.3), regular insulin (40 IU; n=11, mean age=69.4, mean MMSE=25.8), or insulin detemir (40 IU; n=11, mean age=66.0, mean MMSE=25.7) daily for 4 months. Cognitive testing and MRI were administered at baseline and 4 months. The primary cognitive outcome was a composite delayed memory score. MRI measures included preselected ROIs of regions most likely to be affected in AD based on a meta-analysis by Wang et al (2015). Post-treatment values were adjusted for baseline values using regression, comparing regular or long-acting insulin to placebo. *Results:* Participants in the regular insulin arm showed improved memory over the 4 month period compared with placebo. No improvement was observed for long-acting insulin. Placebo-assigned participants showed decreased volumes relative to the regular insulin treated group in the following preselected ROIs: right middle cingulate, right parahippocampal gyrus, left cuneus, and left superior parietal lobe. Comparable volume loss was observed in placebo and long-acting insulin groups. For regular insulin treated participants, increased cingulate, cuneus, parietal and frontal volume was correlated with improved memory. No serious adverse adverse events were noted during the study. *Conclusions:* Our results provide strong support for further investigation of intranasal regular insulin as a therapeutic approach for patients with MCI and AD

OC54: NPI AGITATION/AGGRESSION DOMAIN AS A USEFUL CLINICAL TRIAL MEASURE: VALIDITY AND CORRELATION WITH OTHER NPI AND GLOBAL OUTCOMES. JEFFREY CUMMINGS[1], SANJAY DUBÉ[2,3,4,5], HARRY CUI[2], JOAO SIFFERT[2] *((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, Palo Alto, CA, USA; (4) Indiana University School of Medicine, Indianapolis, IN, USA; (5) University of Pittsburgh School of Medicine, Pittsburgh, PA, USA)*

Background: Neuropsychiatric symptoms such as agitation and aggression are common in some patients with Alzheimer's disease (AD), adversely impact patient and caregiver quality of life, and may increase risk for institutionalization. No FDA-approved treatments exist for agitation in AD. In a recently completed phase 2 study, the combination of dextromethorphan and quinidine (DM/Q) was associated with a significant improvement in AD-related agitation as measured by the NPI Agitation/Aggression domain and corroborated by clinician and patient assessed global clinical measures. The current analysis explores the construct validity (convergent and divergent validity) of the change in NPI-Agitation/Aggression domain scores relative to other secondary outcomes assessed in this study. *Methods:* 10-week, multicenter, randomized, double-blind, placebo-controlled, Sequential Parallel Comparison Design (SPCD) study of DM/Q vs. placebo comprised of 2 stages (5 weeks each). Eligible patients had probable AD, presence of clinically meaningful agitation, and Mini-Mental State Examination (MMSE) scores of 8–28. The primary endpoint was change from baseline on the NPI Agitation/Aggression domain (scored from 0 to 12 based on frequency and severity); secondary endpoints included change from baseline in scores for Total NPI, individual NPI domains, NPI Agitation/Aggression Caregiver Distress, Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) Agitation, caregiver-rated

Patient Global Impression of Change (PGI-C), ADCS-Activities of Daily Living (ADCS-ADL), Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog), Caregiver Strain Index (CSI), MMSE, and Cornell Scale for Depression in Dementia (CSDD). Pearson correlation coefficients were calculated between the change from baseline in NPI Agitation/Aggression domain score (from baseline to week 10) and the change score for secondary outcomes. This analysis included only patients who remained in the same treatment assignment (i.e., took only DM/Q or placebo for the entire 10 weeks [n=159]). Missing values were imputed by last observation carried forward. Low correlation was defined as coefficients ≤0.3; moderate correlation, >0.3 to ≤0.5; strong correlation, >0.5 to ≤0.7; and very strong correlation, >0.7. *Results:* 220 patients were enrolled, and 194 (88%) completed the study; 159 (DM/Q N=93; Placebo N=66) remained in the same treatment assignment throughout the 10 weeks of study. The mean (SD) baseline NPI Agitation/Aggression domain scores were 7.1 (2.6) for DM/Q vs. 7.0 (2.5) for placebo and showed clinical and statistically significant improvement for DM/Q vs. placebo in the primary and the majority of secondary endpoints. At week 10, change from baseline in NPI Agitation/Aggression domain score was strongly correlated with change from baseline in ADCS-CGIC Agitation (n=141; r=0.60) and NPI Agitation/Aggression Caregiver Distress (n=159; r=0.65); moderate correlations were observed with NPI Total score (r=0.48), PGI-C caregiver rating (n=140; r=0.45), CSI (n=159; r=0.45), CSDD (n=152; r=0.42) and NPI Irritability/Lability domain (r=0.41). Low correlation was seen with all other individual NPI domains (n=159; range, r=0.06 to r=0.29), ADAS-cog (n=150; r=0.20), MMSE (n=151; r=0.08), and ADCS-ADL (n=152; r=0.06). *Conclusion:* This analysis demonstrated that the reduction in NPI Agitation/Aggression domain score was strongly correlated with improvement in other independent constructs of agitation (ADCS-CGIC Agitation and NPI Agitation/Aggression Caregiver Distress) and was moderately associated with other related measures (caregiver-rated PGIC-C, CSI, and CSDD), providing convergent validity that the NPI Agitation/Aggression domain accurately assesses AD-related agitation. Although there was moderate correlation with the NPI Irritability/Lability domain and the NPI Total score (as expected given the construct underlying the NPI scale itself, and consistent with the common presence of irritability among patients with agitation), the NPI Agitation/Aggression domain appears to capture a unique symptom domain that behaves independently from other NPI domains, and cognitive and ADL measures in patients with AD-related agitation (divergent validity). These data overall support the use of the NPI Agitation/Aggression domain as a valid outcome measure in clinical trials of agitation associated with AD. *Study supported by:* Avanir Pharmaceuticals, Inc.

OC55: EFFECT OF ACTIVE AB IMMUNOTHERAPY ON CELLULAR DEATH PATHWAYS IN ALZHEIMER'S DISEASE BRAIN. CLAIRE PAQUET[1,2,3], SETH LOVE FRCPATH[4], JAMES AR NICOLL[5,6], CLIVE HOLMES, JACQUES HUGON[1,2,3], DELPHINE BOCHE[5] *(1) INSERM, U942, F-75010, Paris, France; (2) University of Paris Diderot, Sorbonne Paris Cité, UMRS 942, F-75010, Paris, France; (3) Centre Memoire de Ressources et de Recherche Paris Nord Ile de France AP-HP, Hôpital Lariboisière, F-75010, Paris, France; (4) Department of Neuropathology, Institute of Clinical Neurosciences, School of Clinical Sciences, University of Bristol, Bristol, UK; (5) Clinical Neurosciences, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton UK; (6) Memory Assessments and Research Centre, Moorgreen Hospital, Southern Health Foundation Trust, Southampton UK)*

Background: Alzheimer's disease (AD) patients in Aβ immunotherapy trials have demonstrated amyloid plaque removal but with little evidence of slowed decline in cognitive. We have previously shown a decreased number of neurons. This result could be explain either by an increased activation of neuronal death, or by the disappearance of suffering neurons or both hypothesis. *Methods:* In this paper we have explored in human post mortem tissue, several cellular death pathways to determine if active immunotherapy increase it or not. Thirteen immunized (AN1792, Elan Pharmaceuticals) were compared to 27 non-immunized Alzheimer brains. Immunohistochemistry on sections of temporal cortex were performed for apoptosis pathways (phosphorylated Junk kinase, activated caspase 3, phosphorylated GSK3β, p53, CDK5/p35) and autophagic pathways (LC3II, ATG5) Quantification was performed to obtain proteins load (%). *Findings:* After controlling for age, gender, disease duration and APOE ε4 status, statistical analysis showed that quantification of all apoptotic kinases loads were dramatically decreased in iAD group compare to cAD group (pGSK3β ($p<0.0001$), pJNK (($p< 0.0001$), p53 ($p<0.0001$), p35/CDK5 ($p= 0.0013$), activated caspase3 ($p= 0.0001$). Concerning autophagic pathways, there was no significant difference in ATG5 expression between the two groups ($p=0.13$) while LC3 was significantly decreased ($p< 0.0001$)). In the cAD group, pGSK3β and p53 positively correlated with age at death (respectively $R2=0.438$ $p=0.022$ and $R2= 0.564$ $p=0.003$) while LC3 positively correlated with dementia duration ($R2=0.695$, $p=0.001$). In the iAD (but not the cAD cases), we observed a strong association between p35 and biological results (peak antibody and mean Lab) (respectively $R2=0.840$, $p<0·001$ and $R2=0.829$, $p<0·001$). LC3 negatively correlated with survival time ($R2=-0.568$, $p=0.043$). We found no other correlations between the clinical and neuropathological findings. *Conclusion:* The data are in favor of a beneficial effect of active anti-amyloid immunotherapy on cellular death pathways. *Funding:* Fondation Philippe Chatrier, Alzheimer Research UK (ART/PG2006/4 and ART-EXT2010-1), Medical Research Council UK (G0501033).

OC56: LONGITUDINAL PLASMA BIOMARKER CHANGES IN MIDDLE-AGED INDIVIDUALS AT RISK FOR ALZHEIMER DISEASE. ANNE M FAGAN[1], VIRGINIA PÉREZ-GRIJALBA[2], NOELIA FANDOS[2], PEDRO PESINI[2], SALVADOR OLMOS[3], MATIAS BOSSA[3], MANUEL SARASA[2] AND THE ACS RESEARCH GROUP[1] *((1) Knight Alzheimer's Disease Research Center, Department of Neurology, Washington University, St Louis, MO, USA; (2) Araclon Biotech, Zaragoza, Spain; (3) Aragon Institute of Engineering Research, University of Zaragoza, Spain)*

Background: Individuals in the presymptomatic/preclinical stage of Alzheimer disease (AD) are increasingly being targeted for AD secondary prevention trials. By definition, preclinical AD eludes detection by current clinical measures. Thus, disease-specific biomarkers are necessary to identify individuals prior to the development of clinical symptoms. Knowing how early during the normal life span changes in these biomarkers begin to develop, their patterns of change over time and their relationship with future cognitive decline is crucial for the development of early diagnostic tools and new therapeutic strategies. Recently the within-person trajectories of cerebrospinal fluid (CSF) biomarkers of AD over time and their association with changes in brain amyloid deposition and cognitive decline were described in a cohort of cognitively normal (Clinical Dementia Rating [CDR] of 0), middle-aged (45-75 years at baseline) research volunteers (n = 169) enrolled in the Adult Children Study at Washington University, St Louis, Missouri. This study concluded that longitudinal CSF biomarker patterns consistent with AD are first detectable during early middle age (45-54 years) and are associated with later amyloid positivity by PET and cognitive decline. Such measures may be useful for targeting middle-aged, asymptomatic individuals for therapeutic trials designed to prevent cognitive decline. However, lumbar puncture for CSF collection (as well as amyloid-

PET scans) presents challenges that potentially limit their widespread implementation in global clinical trials or eventually for the screening of the general population. Therefore, in the present work we begin to explore, in a subgroup of the ACS cohort, the possibility of using peripheral blood-based biomarkers based on the quantification of plasma Aβ peptides as potential surrogates of CSF AD biomarkers (Aβ42, tau and ptau). *Methods:* Longitudinal plasma samples obtained from a similar ACS sub-cohort (n=107) were analyzed with ELISAs designed to measure the levels of free (unbound to other proteins) and total (bound plus unbound) Aβ40 and Aβ42 (FP and TP, respectively) (ABtest Araclon Biotech. Zaragoza, Spain). Linear mixed-effect models were used to compare estimated plasma biomarker slopes as a function of AD risk defined by age and family history and their relationship with CSF biomarkers. *Results & Conclusions:* Results and conclusions will be presented at CTAD 2015

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LATE BREAKING COMMUNICATIONS

LB1: EVALUATING THE CLINICAL RELEVANCE OF A COMPOSITE COGNITIVE OUTCOME MEASURE: AN ANALYSIS OF 1414 PARTICIPANTS FROM A 5-YEAR ALZHEIMER'S DISEASE PREVENTION TRIAL. NICOLA COLEY[1,2,3], ADELINE GALLINI[1,2,3], BRUNO VELLAS[1,2,4], SANDRINE ANDRIEU, FOR THE GUIDAGE STUDY GROUP *((1) Inserm UMR1027, Toulouse, France; (2) University Toulouse III, Toulouse, France; (3) CHU Toulouse, Department of Epidemiology and Public Health, Toulouse, France; (4) Gérontopôle, CHU Toulouse, Department of Geriatric Medicine, Toulouse, France)*

Background: Candidate primary outcome measures for Alzheimer's disease (AD) prevention trials include incident dementia, biomarkers and cognitive decline, but all are imperfect: dementia incidence requires large samples and long follow-up periods and may not detect intervention effects earlier in the disease process, biomarkers are not validated as surrogate endpoints, and tests measuring cognitive decline may be insensitive to early cognitive changes and are subject to corrections for multiple comparisons when multiple individual tests are used. Composite scores, which combine the most sensitive measures of cognitive performance into a single measure, have been proposed as a more suitable primary outcome for prevention trials. Their use is supported by drug regulatory authorities, but little is known about the long-term trajectories and clinical relevance of cognitive decline measured by composite scores in a prevention trial setting. *Methods:* We retrospectively analysed data from the GuidAge prevention trial to (i) model trajectories of cognitive decline on a cognitive composite score measuring episodic memory, orientation and executive function in various subgroups; (ii) determine whether the composite score was predictive of AD dementia; and (iii) estimate the composite score's minimal clinically important difference (MCID). GuidAge participants had spontaneously reported memory complaints to their general practitioner prior to inclusion and were randomised to receive standardised Ginkgo biloba extract or placebo for 5 years. At baseline, all were aged 70 or older, were free of dementia and had a MMSE score of 26 or more. Annual cognitive evaluations were performed in expert memory centres throughout France, and dementia diagnoses were validated by an independent committee. The composite score was composed of the following tests: MMSE orientation items, Free and Cued Selective Reminding Test (FCSRT) (free and total recall), Category Fluency and Trail Making Test part B. The Z-scores of each component were summed and the total was divided by 4. Mixed effects models were used to calculate 5-year trajectories of decline, Cox proportional hazards models were used to study the prediction of AD dementia at 5-years, and anchor-based mean changes and ROC curve analysis were used to determine the MCID over 1 year of follow-up (the shortest interval between two consecutive memory centre evaluations). Analyses were restricted to participants randomised in the placebo arm (N=1414). *Results:* Age- and baseline score-adjusted change from baseline to 5 years on the composite measure was significantly different between ApoE Ɛ4 positive and negative subjects (-0.156 vs. -0.026; p=0.003), subjects who developed AD dementia and those who remained dementia-free (-2.118 vs. 0.018; p<0.001), and CDR progressors and non-progressors (CDR 0 at baseline: 0.250 vs. 0.134; p<0.001; CDR 0.5 at baseline: -1.315 vs. -0.015; p<0.001). Decline also differed by age, and learning effects were observed in nearly all subgroups. In a Cox model adjusted for age, sex and education, a 1 point decrease (i.e. an average decline of 1 standard deviation (SD) across the 4 tests) in baseline composite score was associated with a 3.5-fold greater 5-year risk of AD dementia. In comparison, a 1 SD decrease in baseline FCSRT total recall, MMSE and CDR-SB scores were associated with a 2.2-, 1.6- and 1.9-fold greater 5-year risk of AD dementia, respectively. In a preliminary analysis, the unadjusted difference in 1-year composite score change between subjects with a CDR of 0 who remained stable and those who progressed from CDR 0 to 0.5 was -0.28 points, and in a ROC curve analysis, a cut-off of ≤-0.3 points decline over 1 year was considered the optimal cut-off (based on the Youden Index) for distinguishing between CDR progressors and non progressors. *Conclusion:* The composite measure demonstrated criterion validity, distinguishing between subgroups with different expected rates of decline, and predicting future AD dementia. The unadjusted MCID of the composite score, using CDR progression as an anchor measure, was estimated to be approximately -0.30 points over 1 year. This estimate, which will be refined, should help clinicians and researchers to better understand the clinical relevance of changes on the composite score.

LB2: CROSS-CULTURAL VALIDATION AND NORMATIVE STUDY OF A NEUROPSYCHOLOGICAL BATTERY USED IN THE DETERMINATION OF CLINICAL ENDPOINTS TO DELAY ONSET OF MCI DUE TO AD. KATHLEEN A WELSH-BOHMER[1,2], HEATHER R ROMERO[1,2], KATHLEEN M HAYDEN[1,2], BRENDA L PLASSMAN[1,2], ALEXANDRA S ATKINS[3], NICOLE M TURCOTTE[3], RICHARD SE KEEFE[2,3], OKSANA A MAKEEVA[4], NATALIA G ZHUKOVA[4], ANDREAS U MONSCH[5], GIOVANNI B FRISONI[6,7], ZARA MELIKYAN[8], SHYAMA BREWSTER[8], CARL CHIANG[8], YUKA MARUYAMA[8], JANET O'NEIL[9], DOMINIC FITZSIMMONS[9], GRANT RUNYAN[9], STEPHEN CRAWFORD[10], TOYOKO OGURI[10], MARK ATKINSON[10], KUMAR BUDUR[9], DANIEL K BURNS[8], ALLEN D ROSES[1,8], FOR THE TOMMORROW STUDY INVESTIGATORS *((1) Joseph and Kathleen Bryan ADRC, Duke University Medical Center, Durham, NC, USA; (2) Department of Psychiatry, Duke University Medical Center, Durham, NC, USA; (3) NeuroCog Trials, Durham, NC, USA; (4) Center for Clinical Trials, Nebbiolo LLC, Tomsk, RU; (5) University Center for Medicine of Aging Basel, Felix Platter Hospital, Basel, CH; (6) IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, IT; (7) University Hospitals and University of Geneva, Geneva, CH; (8) Zinfandel Pharmaceuticals Inc., Chapel Hill, NC, USA; (9) Takeda Development Center Americas, Inc., Deerfield, IL, USA; (10) Covance Inc, Princeton, NJ, USA)*

Background: Reliable detection of the earliest symptoms of Alzheimer's disease (AD) across multiple countries and languages requires neurocognitive instruments that are cross-culturally valid and normed. In preparation for international site involvement in an ongoing clinical trial (the TOMMORROW Study) to delay the onset of mild cognitive impairment due to AD (MCI-AD), we initiated

an international validation and normative study of a neurocognitive battery in Italy, Switzerland, and Russia. The linguistically and culturally adapted measures will support the systematic application of operationalized criteria to detect MCI-AD in these countries. The criteria for MCI-AD include: 1) decline on the Clinical Dementia Rating Scale from 0 to 0.5, 2) failure on one of two memory tests (–1.5 SD below a normative mean) or failure on two or more tests from separate domains of which one was memory (–1.3 SD below normative mean), 3) exclusion of medical causation, and 4) continued evidence of decline at a 6-month follow-up. To support criterion #2, we sought to determine the reliability, validity, and normative values of a translated battery of eight common neuropsychological tests tapping five cognitive domains affected by MCI-AD. We present the rationale, study design, methods, and results from the study, which concluded in Spring 2015. *Methods:* A total of 675 individuals comprising 200 healthy controls and 25 AD subjects were recruited per language (Italian, German, Russian). Controls represented four age strata (~50/strata/country) ranging from 65-88 years of age, including men and women with a range of low and high education. Healthy subjects repeated the battery 1 month after initial testing to assess test-retest and alternate form reliability. Construct validity was assessed by examining the correlation among measures in healthy controls. Criterion and discriminant validity of the cognitive measures was tested in the entire sample (controls and AD) using logistic regression, discriminant analysis, and Receiver Operating Characteristic analysis. Measure equivalence across countries was examined in relationship to information available in US samples. Age-normed values, adjusted for education and gender when appropriate, were developed for each language to be used for endpoint evaluation in the multi-national TOMMORROW Study. *Results:* Cultural adaptation of the tests across languages was very effective, and the translated tests showed high test-retest reliability as well as construct and criterion validity. Countries varied somewhat in the severity of the AD cases recruited. Switzerland recruited very mild AD cases (mean MMSE = 24.5, SD = 3.2), whereas the cases in Russia (mean MMSE = 19.3, SD = 3.84) and Italy (mean MMSE = 19.2, SD = 3.4) were mild to moderate in severity. Despite these differences, a composite score from the battery distinguished healthy controls from AD across the continuum, with at least 76% sensitivity and at least 97% specificity. Episodic memory performed very well distinguishing cases from controls, with at least 91% sensitivity and 99% specificity. Additionally, the tests performed comparably to the "gold standard" English versions with respect to direction, magnitude, and patterns of the correlations and main effects. Several tests showed some cultural variability. A comparison across the German, Russian, and Italian normative studies revealed that age influenced performance across nearly all tests. Some nuances specific to each language version emerged, underscoring the importance of country-specific norms: For the German language version, gender had an infrequent but strong association on visual naming (men performed better than women) and measures of verbal episodic memory (women performed better than men). These results suggested the use of age-stratified norms with possible correction for gender when the battery is applied in Germany and Switzerland. By contrast, in the Russian-language translation, gender did not have a large effect. However, there were rather striking performance differences across all age groups on Trails B when compared to the English-language normative values, suggesting cultural variation and underscoring the need for language-specific norms. Finally, in the Italian version education effects were seen in some age strata and notable cultural variation on a number of measures, including the BVMT-R, MiNT, Trails A, and Digit Span Total, suggesting the need for Italian norms so as to avoid false-positive errors in diagnostic assignments. *Conclusions:* MCI-AD is a new endpoint in global clinical trials to delay or prevent symptomatic AD onset. An important first step for international trials of this kind is the development of a carefully validated, well-normed MCI-AD outcome battery. The battery reported here has now been translated, culturally adapted, validated, and normed for ages 65-88 in German, Italian, and Russian languages. This neuropsychological tool assesses the key cognitive domains affected in aging and early neurodegenerative diseases. It is psychometrically sound and appropriately sensitive to detecting cases of early AD, making it an appropriate metric for studies in the preclinical stages of the AD continuum.

LB3: ORY-2001, AN EPIGENETIC DRUG FOR THE TREATMENT OF COGNITION DEFECTS IN ALZHEIMER'S DISEASE AND OTHER NEURODEGENERATIVE DISORDERS. TAMARA MAES, ELENA CARCELLER, FERNANDO CAVALCANTI, CRISTINA MASCARÓ, CÉSAR MOLINERO, ALBERTO ORTEGA, DAVID ROTLLANT, CARLOS BUESA *(Oryzon Genomics S.A. Barcelona, Spain)*

Backgrounds: The aging of the Western population is increasing the incidence of neurodegenerative diseases and the burden of patient care and medication on families and on governmental budgets. Current drug treatments are essentially symptomatic, and none is able to prevent, halt or much less reverse the neurodegenerative process. Alzheimer's disease probably has multiple causes. Many reports sustain that epigenetic changes in the brain can have very significant effects on neurodegeneration and it has been shown that epigenetic changes can affect synaptic plasticity in different animals. ORY-2001 is a dual LSD1-MAOB inhibitor. LSD1, Lysine Specific Demethylase-1, is a chromatin modulator that demethylates di- and monomethylated H3K4. In the CNS, LSD1 has been involved in the regulation of expression of neuronal genes and neurogenesis. MAO-B, Monoamino Oxidase B, plays an important role in the catabolism of neuroactive and vasoactive amines in the CNS and in peripheral tissues and is responsible for dopamine degradation. MAO-B is a well known target for Parkinson's Disease and has been explored in AD. LSD1 inhibitors are already in clinical trials in cancer but this is the first time they are promoted to clinical studies in CNS disorders. *Methods:* The regulatory toxicology package of ORY-2001 has been performed using wistar rats and beagle dogs according to guidelines. Novel Object Recognition Test (NORT) were performed on SAMP-8 mice, after 2 and 4 months of oral treatment with ORY-2001. DNA-array analyses were performed using mouse arrays designed by Oryzon and custom synthesized by Agilent, according to manufacturer indications. *Results:* ORY-2001 is a novel brain-penetrable covalent inhibitor of LSD1 and MAO-B with excellent oral bioavailability and PK profile. The compound has shown excellent selectivity for its targets over other FAD containing amine oxidases like MAO-A and LSD2, and did not inhibit other chromatin modulators nor did it inhibit > 100 targets from the CEREP diversity panel. Orally administered ORY-2001 efficiently inhibits brain MAO-B and completely protects mice from MPTP toxicity at doses from 1 mg/kg in mice, while acute administration up to 30 mg/kg in rats did not provoke an increase of blood pressure in the tyramine pressure model; indicating good in vivo MAO-B vs MAO-A selectivity. ORY-2001 efficiently modulates H3K4 methylation status and gene transcription in vitro and in vivo. The regulatory 28d toxicology studies performed in rats and dogs resulted in a clean molecule with no off-target effects and with a robust safety profile. Long term administration in preclinical proof of concept studies confirmed the feasibility of chronic treatments with ORY-2001. Oral administration of ORY-2001 prevented the cognitive impairment as assessed by NORT in the mouse SAMP8 model for accelerated aging and Alzheimer disease. The selective MAO-B inhibitor Rasagiline provided some tendency for improvement in the behavior of SAMP8 mice in the NORT test, but it did not reach statistical significance, underscoring the importance of the LSD1 inhibitory component of ORY-2001 for the beneficial effect on

memory. Microarray analysis on hippocampal samples revealed that ORY-2001 has a limited pleiotropic effect on gene expression. Treatment with ORY-2001 potently down-regulated the expression of a subset of genes related to immune reaction and inflammation including S100A9; and up-regulated genes associated with improved cognitive function, neuroplasticity and memory. S100A9 is emerging as an important contributor to inflammation-related neurodegeneration and was reported to be increased in patients with AD, in postoperative cognitive dysfunction (POCD) and in traumatic brain injury (TBI). In addition, knockout or knockdown of S100A9 has been reported to be beneficial to memory in APP/PS1 and Tg2576 models of Alzheimer's disease. S100A9 is emerging as a possible valuable biomarker. *Conclusion:* A Clinical Trial Application for first-in-human studies for the epigenetic drug ORY-2001 for the treatment of Alzheimer's disease (AD) and other neurodegenerative disorders has been submitted to the Spanish Drug Agency (AEMPS). ORY-2001 is a dual LSD1-MAOB inhibitor. LSD1 is a chromatin modulator that demethylates di-and monomethylated H3K4 and is involved in the regulation of expression of neuronal genes and neurogenesis. MAO-B is a well known target for Parkinson's Disease and has been explored in AD. The drug has demonstrated a good safety profile and has a good Therapeutic Index. ORY-2001 stops/prevents the development of cognitive impairment and memory loss in SAMP8 mice and chronic treatment with ORY-2001 correlates with a decrease in expression of neuroinflammatory genes; opening the possibility of using them as biomarkers in the ORY-2001 Phase I studies foreseen to start by the end of 2015.

LB4: SAPPA IS A POTENT ENDOGENOUS INHIBITOR OF BACE1. VARGHESE JOHN[1], CLARE PETERS-LIBEU[2], JESUS CAMPAGNA[1], PATRICIA SPILMAN[1], KAREN POKSAY[2], DALE E BREDESEN[1,2] *((1) Drug Discovery Lab, Department of Neurology, Mary S. Easton Center for Alzheimer's Disease Research, Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA; (2) Buck Institute for Research on Aging, Novato, CA, USA)*

Backgrounds: Alzheimer's disease (AD) is characterized by the presence of amyloid-β (Aβ) plaques in brain tissue. Aβ is generated by sequential cleavage of full-length amyloid precursor protein (APP) by β and γ secretase. In an alternative pathway, α secretase cleavage of APP produces the protein fragment sAPPα, known to have trophic effects which support synaptic maintenance and memory. Proteolytic cleavage of APP by the β secretase BACE1 (BACE) as the initial step in production of Aβ has been a major target of AD drug discovery efforts. Overproduction of Aβ results in neuronal cell death and accumulation of amyloid plaques in AD and traumatic brain injury (TBI), and is also associated with stroke due to cerebral amyloid angiopathy (CAA). Others have observed in cells that Aβ production is reduced in the presence of increased sAPPα (Obregon et al, Nat. Commun. 2012). We therefore performed studies to determine the mechanism and revealed for the first time that sAPPα is a potent endogenous direct inhibitor of the BACE enzyme, and that this inhibition is likely by an allosteric mechanism. Furthermore, using small-angle x-ray scattering (SAXS), we show that sAPPβ, which is identical to sAβPPα except for a 16-amino acid truncation at the carboxy terminus, adopts a completely different conformational structure than sAPPα and, importantly, does not inhibit BACE. Our data thus reveal a novel mechanistic role played by sAPPα in regulating overproduction of Aβ and restoring neuronal homeostasis and neuroprotection. Identification of sAPPα as a direct BACE inhibitor would lead to design of new therapeutics targeting pathologies associated with overproduction of Aβ. In this regard, we have identified a repurposed drug F03 that increases sAPPα in the brain and is currently in a Phase1b/2a clinical trial in Australia in subjects with MCI due to AD. *Methods:* Inhibition of the BACE enzyme by sAPPα and sAPPβ was determined in a BACE activity assay using both the relatively long MBP-APPC125 substrate and the shorter P5-P5'substrate. For the long substrate, an AlphaLISA-based assay was used, for the short substrate the fluorescence-based BACE assay kit from Sigma was used. The conformational structures of sAPPα and sAPPβ were analyzed by SAXS of recombinant purified proteins. The SAXS analysis was done at the Advanced Light Source (ALS), Lawrence Berkeley National Laboratory. Fluorescence-based protein conformation analysis was also performed to ascertain intrinsic differences in the structural domains of the proteins. *Results:* Our studies show that sAPPα, but not sAPPβ, potently inhibited BACE cleavage of the long MBP-APPC125 substrate with an IC50 ~25nM; but neither sAPPα nor sAPPβ inhibited BACE cleavage of the short P5-P5' substrate. This inhibition profile for sAPPα is similar to that previously seen with an anti-BACE antibody which was shown using co-crystallization studies to bind to an exosite on BACE. As with the anti-BACE antibody, the inhibition of BACE by sAPPα is likely through an allosteric mechanism, that is, by binding to an exosite remote from the enzymatic active-site cleft in such a way that the longer substrate – but not the shorter one – cannot effectively bind the active-site and be cleaved by BACE. SAXS and fluorescent analysis revealed distinct conformational differences between sAPPα and sAPPβ that may account for their differing inhibitory effects on BACE cleavage. *Conclusion:* This study shows for the first time that an endogenous protein produced by neurons - sAPPα - can act as a potent inhibitor of the key enzyme BACE involved in the first step of the cleavage of APP leading to Aβ generation and the amyloid plaques in AD. The inhibition profile of sAPPα is similar to the allosteric anti-BACE antibody. We are currently using X-ray crystallography and other techniques to determine the sAPPα binding-site on BACE. Using the structure-based data, we hope to design and develop sAPPα mimetics with similar effects as the parent protein. In addition, we plan to screen the UCLA small molecule library to identify molecules that can increase sAPPα and thus may reduce Aβ generation. The development of such mimetics represents a new therapeutic approach for Alzheimer's disease and may also have applications in other diseases where Aβ increases are implicated, such as amyotrophic lateral sclerosis (ALS), TBI, and CAA.

LB5: ROBUST AND SUSTAINED EFFICACY OF TRAMIPROSATE IN APOE4/4 HOMOZYGOUS PATIENTS WITH MILD AND MODERATE AD: COMBINED DATA SETS FROM TWO 78-WEEK PHASE 3 TRIALS. A PORSTEINSSON[1], J CUMMINGS[2], M KIPIVELTO[3], JA HEY[4], JY YU[4], A POWER[4], M BAIRU[5], M TOLAR[4], S ABUSHAKRA[1] *((1) University of Rochester, Rochester NY USA; (2) Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, Nevada and Cleveland, USA; (3) Karolinska Institutet Alzheimer Disease Research Center, Stockholm, Sweden; (4) Alzheon Inc., Boston, MA, USA, (5) Serenus Biotherapeutics, Inc., San Francisco, CA, USA)*

Background: Tramiprosate is an inhibitor of amyloid aggregation that has demonstrated a decrease in both soluble and insoluble amyloid aggregation, deposition and neurotoxicity in preclinical studies. ALZ-801 is a novel, oral, small molecule prodrug of tramiprosate with improved pharmaceutical properties over the original compound. The novel ALZ-801 formulation has enhanced gastrointestinal tolerability and oral pharmacokinetic properties, allowing more consistent plasma exposures to tramiprosate, the active moiety. Oral tramiprosate was previously evaluated in two global Phase 3 studies of 78 weeks duration in North America (NA) and several EU countries in approximately 2,000 patients with Mild and Moderate AD (NA study: Aisen et al. 2011). Subgroup analyses of subjects with at least one ε4 allele of the apolipoprotein E gene (APOE4 positive, N= 1,099 in

both studies) were previously reported (Hey et al. ADPD 2015), and showed significant efficacy on cognitive and functional outcomes. We herein report the results of the combined subgroups of patients with two ε4 alleles of APOE gene (APOE4 homozygotes or APOE4/4). APOE4 homozygotes account for ~25% of the APOE4 positive AD patients, and for 10-15% of overall AD patients in population samples. *Methods:* The design and results of the NA study (Alphase study) were previously published (Aisen et al. 2011, Gauthier et al. 2007). This study was a placebo controlled, double blind, 3-arm trial (placebo, 100mg BID, 150mgBID), of 78 weeks duration, and enrolled patients with Mild and Moderate AD, MMSE 16-26. The study allowed stable doses of acetylcholinesterase inhibitors (AChEI) and/or memantine. The EU study was of similar design, but did not allow use of memantine. The co-primary outcome measures in both studies were ADAS-cog and CDR-SB at 78 weeks. *Results:* The baseline demographics of overall population in each study were similar, except for the use of memantine background therapy (NA study 48%, EU study none). Since the initial NA study did not achieve its primary objectives in the overall population, the EU study was terminated early, but most patients had completed at least 52 weeks of treatment, and the study remained blinded until the database lock. In the NA study, there was a total of 141 APOE4/4 homozygous patients (age up to 85 years; placebo 54, low dose 47, high dose 40). Their mean age was 71 years, MMSE= 20.9 +/- 3.3 (~60% Mild, 40% Moderate), 100% were on AChEI and 48% on memantine. In the EU study, the APOE4/4 patients (n= 111) had similar demographics. In the combined APOE4/4 group there was a total of 252 patients (age up to 85 years; placebo 92, low dose 85, high dose 75). Compared to placebo the high dose showed significant cognitive drug effects on ADAS-cog at 52, 65, and 78 weeks in the combined groups: 2.85 ($p= 0.02$); 4.18 ($p<0.001$); and 4.56 ($p <0.001$). The drug effect on ADAS-cog showed a positive trend (delta ~ 1.7, $p= 0.14$) starting at 26 weeks which increased over time. The CDR-SB results with the high dose at 52, 65, and 78 weeks compared to placebo in the combined groups were: 0.64 ($p= 0.054$); 0.86 ($p<0.02$); and 0.60 ($p = 0.1$). The CDR-SB was significant at 26 weeks (delta =0.71, $p= 0.02$). The safety profile in the APOE4/4 population was similar to the overall study population, and was benign as described previously (Aisen et al. 2011). *Conclusion:* The APOE4/4 population is a genetically well-defined population at highest risk of developing amyloid pathology by imaging and of developing AD dementia. A recent meta-analysis of imaging studies reports rates of amyloid positivity ~ 90-95% in APOE4/4 with AD dementia. This population is also at high risk of developing vasogenic edema (ARIA-E) with emerging anti-amyloid immunotherapies. These data from two independent Phase 3 studies, suggest that tramiprosate has efficacy ameliorating AD progression (ADAS-cog effect versus placebo ~ 4.6 points at 78 weeks) with no known risk of ARIA, and a favorable safety profile. These data support further development of the tramiprosate prodrug ALZ-801 with, and suggest an optimal benefit/risk profile in this well-defined APOE4/4 population. ALZ-801 has promise to be a novel, efficacious, and safe treatment for this genetically defined population of AD patients.

LB6: PLASMA EXCHANGE WITH ALBUMIN AND IMMUNOGLOBULIN IN ALZHEIMER'S DISEASE PATIENTS: INTERIM ANALYSIS OF THE AMBAR TRIAL. MERCÈ BOADA[1,2,3], ÓSCAR LÓPEZ[4,5], LAURA NÚÑEZ[6], MIREIA TORRES[6], NATALIA AFONSO[6], ANTONIO PÁEZ[6] AND THE INVESTIGATORS OF THE AMBAR CLINICAL TRIAL STUDY GROUP *((1) Memory Clinic of Fundació ACE. Institut Català de Neurociències Aplicades, Barcelona, Spain; (2) Hospital General Universitari Vall d'Hebron - Institut de Recerca, Universitat Autònoma de Barcelona (VHIR-UAB), Barcelona, Spain; (3) AMBAR clinical trial. National Coordinator of Spain; (4) Departments of Neurology and Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, USA; (5) AMBAR clinical trial. National Coordinator of USA; (6) Clinical Operations Department. Grifols, Barcelona, Spain)*

Backgrounds: Experimental models and clinical studies support the existence of a dynamic equilibrium of Aβ in a bidirectional flow between plasma and brain. Under the assumption that most of the circulating Aβ is bound to albumin, previous results in a Pilot and a Phase II (NCT00742417) studies showed encouraging results in the cognitive status of Alzheimer's disease (AD) patients who underwent plasma exchange with albumin replacement. As a follow up, the AMBAR (Alzheimer's Management by Albumin Replacement) (NCT01561053) study (Phase IIB/III multicenter, randomized, patient- and rater-blinded, controlled, parallel-groups study) is in progress in Europe (Spain) and USA. *Methods:* In the AMBAR study 364 patients with mild to moderate AD are randomly distributed in 4 groups of plasma exchange with albumin replacement treatment according to different doses of albumin (Albutein®, Grifols) plus intravenous immunoglobulin (Flebogamma® DIF) to adjust any possible immune deficit, and a control group (1:1:1:1 proportion), .consisting of a simulated plasma exchange treatment (sham). In a first treatment period (intensive) patients undergo one plasma exchange weekly (2.5-3 L plasma removal/albumin replacement) for 6 weeks. In a second period (maintenance) patients undergo one low-volume plasma exchange monthly (650-880 mL plasma removal/100-200 mL albumin replacement; 10-20 g immunoglobulin) for 12 months. The changes from baseline of scores obtained with the ADAS-Cog and ADCS-ADL tests are the co-primary efficacy endpoints. Secondary efficacy endpoints are assessed through a battery of cognition, functional and behavioral tests such as MMSE, NPB, NPI, CDR-Sb, ADCS-CGIC, CSDD, C-SSRS, QoL-AD, and RUD-Lite®. In addition, changes in the levels of Aβ and tau in plasma and/or CSF, structural and functional changes in areas of interest in the brain by PET and MRI.), safety (monitoring of adverse events, vital signs and laboratory parameters) and treatment feasibility are also assessed. *Results:* Interim results focused on safety and treatment feasibility of the AMBAR study corresponding to 186 patients (approximately half of sample size) are presented at the CTAD Meeting. *Conclusion:* Clinical studies performed so far with plasma exchange plus albumin replacement indicate that this treatment is able to modify Aβ concentration in both plasma and cerebrospinal fluid of AD patients, which has been associated with improvement in cognitive function. The AMBAR study is designed to confirm these previous findings to open new perspectives in the treatment of AD.

LB7: AMYLOID PRECURSOR PROTEIN METABOLISM AND INFLAMMATION MARKERS IN PRECLINICAL ALZHEIMER DISEASE: IMPLICATIONS FOR CLINICAL TRIALS. DANIEL ALCOLEA[1], PABLO MARTÍNEZ-LAGE[2], PASCUAL SÁNCHEZ-JUAN[3], JAVIER OLAZARÁN[4,8], CARMEN ANTÚNEZ[5], ANDREA IZAGIRRE[2], MIRIAN ECAY-TORRES[2], AINARA ESTANGA[2], MONTSERRAT CLERIGUÉ[2], Mª CONCEPCIÓN GUISASOLA[6], DOMINGO SÁNCHEZ RUIZ[4], JUAN MARÍN MUÑOZ[5], MIGUEL CALERO[7,8], RAFAEL BLESA[1], JORDI CLARIMÓN[1], MARÍA CARMONA-IRAGUI[1], ESTRELLA MORENAS-RODRÍGUEZ[1], ELOY RODRÍGUEZ-RODRÍGUEZ[3], JOSÉ LUIS VÁZQUEZ HIGUERA[3], JUAN FORTEA[1], ALBERTO LLEÓ[1] *((1) Department of Neurology, IIB Sant Pau - Hospital Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain; (2) Fundación CITA-alzhéimer Fundazioa, San Sebastián, Spain; (3) Servicio de Neurología, Hospital Universitario Marqués de Valdecilla, Santander, Spain; (4) Servicio de Neurología, Hospital General Gregorio Marañón, Madrid, Spain; (5) Unidad de Demencias, Hospital Clínico Universitario Virgen de la Arrixaca,*

Murcia, Spain; (6) Unidad de Medicina Experimental, Hospital General Gregorio Marañón, Madrid, Spain; (7) Instituto de Salud Carlos III, CIBERNED, Madrid, Spain; (8) Fundación CIEN - Fundación Reina Sofía, Madrid, Spain - Centro de Investigación Biomédica en Red en enfermedades Neurodegenerativas, CIBERNED, Spain. The SIGNAL study)

Backgrounds: Little is known about the changes in cerebrospinal fluid (CSF) biomarkers in the preclinical stages of Alzheimer's disease (AD). The study of biomarkers can help in the characterization of the pathophysiological changes that take place at these stages, and could be of critical importance to select candidates in clinical trials and to monitor the effect of specific treatments. The levels of CSF sAPPβ and β-secretase activity have been previously studied as markers of amyloid precursor protein (APP) processing in patients with mild cognitive impairment and dementia. YKL-40 has been studied as a CSF marker of neuroinflammation in the AD continuum and in other degenerative dementias. It is not known, however, whether sAPPβ levels and β-secretase activity are altered in the preclinical stages of AD, and only a few studies have investigated the role of YKL-40 in preclinical AD. In this study, our objective was to investigate CSF markers involved in APP processing, neuronal damage and neuroinflammation in the preclinical stages of AD and subjects with suspected non-Alzheimer pathology (SNAP). We will also review the implications for AD clinical trials. *Methods:* We collected CSF from 266 cognitively normal volunteers participating in a cross-sectional multicenter study (the SIGNAL study). All participants had a Minimental State Examination (MMSE) score ≥ 24 and normal memory performance, assessed by the Free and Cued Selective Reminding Test (FCSRT, total immediate score ≥ 36 and free immediate recall subscore ≥ 19). Significant impairment in other cognitive domains was excluded through a formal cognitive evaluation. We used commercially available ELISA kits to determine levels of Aβ42 (InnotestTM β-Amyloid1-42, Fujirebio-Innogenetics), t-tau (InnotestTM hTAU Ag, Fujirebio-Innogenetics), p-tau (InnotestTM Fujirebio-Phospho-Tau181P, Innogenetics), sAPPβ (Human sAPPβ-w highly sensitive, IBL) and YKL-40 (MicroVueTM, Quidel) following the manufacturers' recommendations. We also measured CSF β-secretase activity incubating the CSF sample with a fluorogenic β-secretase substrate and measuring fluorescence at different time points. We used CSF Aβ42, t-tau and p-tau levels to classify participants according to the preclinical stages based on NIA-AA classification: stage 0, 1, 2, 3, and SNAP. We applied a cut-off point of 550pg/ml for Aβ42, 350pg/ml for t-tau and 61pg/ml for p-tau. We analyzed the relationship between biomarkers, clinical variables and the APOE genotype, and we compared biomarker levels across the preclinical stages of the NIA-AA criteria. *Results:* The median age in the whole cohort was 58.8 years (range 39.8 – 81.6). Subjects in stages 2-3 and SNAP had higher levels of YKL-40 than those in stages 0 and 1. Subjects with SNAP had higher levels of sAPPβ than subjects in stage 0 and 1. No differences were found between stages 0, 1, 2-3 in sAPPβ or β-secretase activity in CSF. Aβ42 correlated inversely with t-tau in subjects with low Aβ42, but this correlation was positive in subjects with levels of Aβ42 above the cut-off. There were no significant correlations between β-secretase activity and Aβ42 or t-tau. In subjects with Aβ42 levels above the cut-off, sAPPβ showed a significant correlation with both Aβ42 and t-tau. The directionality of the correlation between YKL-40 and Aβ42 differed between subjects that had Aβ42 levels above and below the cut-off point. YKL-40 correlated directly with t-tau regardless of the Aβ42 status. Age correlated with t-tau, p-tau and YKL-40. It also correlated with Aβ42, but only in APOE4 carriers. *Conclusions:* Our findings suggest that inflammation in the CNS is intimately related to markers of neurodegeneration in the preclinical stages of AD and SNAP. sAPPβ and β-secretase activity are not useful diagnostic or staging markers in preclinical AD. Therefore, the role of sAPPβ and β-secretase activity in clinical trials is restricted to measures of target engagement. It remains to be determined if sAPPβ or YKL-40 correlate with the progression of the disease and whether they could be useful prognostic markers for clinical trials. Since the preclinical stages of AD are defined on the basis of biomarkers, it is critical to achieve a better knowledge of the different pathophysiological pathways involved in order to maximize the possibilities of a positive clinical outcome in clinical trials.

LB8: A RATIO OF SYNAPTIC CSF BIOMARKERS AS POTENTIAL CORRELATE FOR COGNITIVE DECLINE IN ALZHEIMER'S DISEASE. ANN DE VOS[1], HANNE STRUYFS[2], DIRK JACOBS[1], ERIK FRANSEN[3], DIRK SMEETS[4], WIM MAES[5], SEBASTIAAN ENGELBORGHS[2,6], EUGEEN VANMECHELEN[1] *((1) ADx NeuroSciences NV, Ghent, Belgium; (2) Reference Center for Biological Markers of Dementia (BIODEM), Institute Born-Bunge, University of Antwerp, Antwerp, Belgium; (3) StatUa Center for Statistics, University of Antwerp, Antwerp, Belgium; (4) icoMetrix NV, Leuven, Belgium; (5) PharmAbs, The KU Leuven Antibody Center, Leuven, Belgium; (6) Department of Neurology and Memory Clinic, Hospital Network Antwerp (ZNA) Middelheim and Hoge Beuken, Antwerp, Belgium)*

Backgrounds: The core biochemical biomarkers for Alzheimer's disease (AD), i.e. cerebrospinal fluid (CSF) tau and CSF Aβ1-42, are clinical relevant as single analyte in the new diagnostic criteria for AD as they reflect the neuropathology of the disease. Yet, there is evidence that a combination of CSF biomarkers, in particular CSF biomarker ratios, such as CSF tau/Aβ1-42 or CSF Aβ1-42/Aβ1-40, might have an improved diagnostic performance in comparison to the single analytes. Nevertheless, their value to predict cognitive decline remains limited as these biomarkers are "state markers". Recent insights suggest that synaptic CSF biomarkers might be relevant from this respect, being candidate "stage markers" for AD. *Methods:* In a small focused clinical study we studied six analytes in CSF, involving the two classical markers, CSF tau and CSF Aβ1-42, and two additional Aβ peptides, CSF Aβ1-40 and CSF Aβ1-38. Also BACE-1 protein levels, a marker of presynaptic structures, and neurogranin (Ng) levels, a postsynaptic component, were quantified. All ELISAs, including the BACE-1 and Ng immunoassays, were based on monoclonal antibodies. Three clinical groups were analyzed: age-matched controls (n=20), patients with MCI due to AD (MCI-AD) (n=38) and 50 AD dementia patients. In a subset of the MCI-AD and AD dementia patients, neuropsychological (MMSE) and structural imaging follow-up for at least one year was available. *Results:* In every CSF sample, quantification of all six analytes was possible within the calibration range, with an intra-assay precision of the sample replicates less than 10%CV. While the single analytes showed statistically significant differences between the clinical groups as expected, we also confirmed that ratios of analytes had a higher diagnostic performance. Furthermore the ratio of CSF Ng/BACE-1 was the only ratio that showed a significant correlation with the yearly decline in MMSE in the MCI-AD group as well as the AD dementia patients. We are currently analyzing the relationship between whole brain atrophy, studied by magnetic resonance imaging with longitudinally follow-up, and the single analytes, as well as the ratios of the analytes. *Conclusion:* This is the first study demonstrating that the ratio CSF Ng/BACE-1, which reflects postsynaptic/presynaptic integrity, correlates with cognitive decline, and possibly brain atrophy. Since the tools are available, i.e. monoclonal based, specific ELISAs with adequate analytical sensitivity, the CSF Ng/BACE-1 ratio can rapidly be confirmed in independent focused clinical studies with large groups of longitudinally followed-up patients. If validated, such a biochemical synaptic profile as a "stage marker" may provide novel

insights into pathophysiological mechanisms. It will be necessary to verify this profile in established clinical consortia cohorts and clinical trials targeting synaptic integrity.

LB9: THE CHALLENGE OF INTERPRETING LONGITUDINAL CHANGE IN CSF TAU IN THERAPEUTIC TRIALS OF AMYLOID POSITIVE SUBJECTS. JOHN R SIMS[1], PENG YU[1], JEFFREY L DAGE[1], YUN-FEI CHEN[1], PETER CASTELLUCCIO[2], ROBERT A DEAN[1] *((1) Lilly Research Laboratories, Indianapolis, IN, USA; (2) Bucher & Christian Consulting, Inc., Indianapolis, IN, USA)*

Background: Recent therapeutic trials have reported cerebrospinal fluid (CSF) tau and p-tau results that may be discrepant with clinical results. Changes in CSF tau and p-tau concentrations reflect multiple processes including alterations in production or clearance and other factors changing the mass of the tau proteins and/or the volume of CSF into which those tau proteins are dissolved. Furthermore, a decrease in production may reflect either reduced degeneration or a loss of the tissue mass generating the signal. This latter case can be seen in end-stage organ disease such as liver, pancreas, or muscle with their respective decline in injury markers, despite progressive disease. We set out to test the hypothesis of whether increasing brain atrophy, as reflected by corrected ventricular volume, is correlated with decreased CSF total tau or p-tau in amyloid positive subjects. *Methods:* We analyzed CSF tau protein data from amyloid positive participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI-1, GO and 2), which includes normal, mild cognitive impairment (MCI), and mild dementia (http://adni.loni.usc.edu/), as well as amyloid positive, mild dementia subjects from placebo arms of two semagacestat IDENTITY and two solanezumab EXPEDITION clinical trials. MRI-derived ventricular volumes were corrected for intracranial volume. We analyzed cross-sectional (baseline) data and longitudinal data (ADNI: 1 year, IDENTITY:76 weeks, EXPEDITION: 80 weeks) for CSF total tau and p-tau (AlzBio3 assay for ADNI and INNOTEST assay for IDENTITY and EXPEDITION). However, p-tau longitudinal data were not available in all ADNI data sets. Spearman correlation analysis was used to explore the relationship of ventricular volume and tau. *Results:* In ADNI, amyloid positive, normal participants at baseline showed small but significant negative correlations of larger ventricular volume and lower CSF tau and p-tau (n=103 and 104, r=-0.230 and -0.212, respectively, $p<0.05$). Longitudinal change in tau for normal individuals showed no significant correlation (n=33). Amyloid positive MCI participants at baseline showed similar negative correlations for both CSF tau and p-tau (n=373 and 390, r=-0.196 and -0.166, respectively, $p\leq0.001$) and no significant correlation for longitudinal change in tau (n=106). Amyloid positive mild dementia participants in ADNI at baseline showed only significant negative correlation for tau (n=191, r=-0.198, $p<0.01$) and there was a negative correlation (but not significant) for longitudinal change (n=52, r=-0.244, p=0.08). Within our placebo trial population of amyloid positive mild dementia patients, there were significant negative correlations for both tau and p-tau (n=86, r=-0.3 and -0.36, respectively, $p<0.01$) at baseline. Furthermore, there was a negative correlation trend for both tau and p-tau for longitudinal changes (n=46 and 44, r=-0.25, respectively, $p<0.1$). *Conclusion:* These data suggest that ventricular volume and CSF injury markers, tau and p-tau, may be inversely correlated in amyloid positive individuals. The implication of increasing ventricular volume with elevated but decreasing injury markers in the setting of disease progression, if replicated, could have major implications on the interpretation of longitudinal tau or p-tau changes. At a minimum, the above data suggest that a more thorough understanding of CSF injury marker changes may need to incorporate ventricular volume. It remains to be tested, but decreasing injury markers in the setting of increasing ventricular volumes may portend Alzheimer's disease progression rather than slowing of neurodegeneration and may replicate decreasing levels of biochemical markers of tissue injury as commonly observed in other chronic organ failure syndromes.

LB10: DISCOVERY, PRECLINICAL DEVELOPMENT, AND CLINICAL TRIAL APPROACH FOR NPT088, A GENERAL AMYLOID INTERACTION MOTIF (GAIM)-IMMUNOGLOBULIN FUSION. RICHARD FISHER[1], RAM KRISHNAN[1], KIM GANNON[1], JONATHAN LEVENSON[1], HAIM TSUBERY[1], MING PROSCHITSKY[1], EVA ASP[1], JENNA CARROLL[1], VALERIE CULLEN[1], MYRA GARTNER[1], SHARON GILEAD[1], MICHAL LULU[1], SALLY SCHROETER[1], JASON WRIGHT[1], CHARLOTTE CHUNG[1], PETER DAVIS[2], JONATHAN WALTHO[2], E ROCKENSTEIN[3], E MASLIAH[3]3, BEKA SOLOMON[4], MICHELLE GRAY[1], FRANZ HEFTI[1], MICHAEL GRUNDMAN[5] *((1) NeuroPhage Pharmaceuticals, Cambridge, MA, USA; (2) Molecular Biology and Biotechnology, University of Sheffield, Sheffield, United Kingdom; (3) Neurosciences, UC San Diego, San Diego, USA; (4) Molecular Microbiology and Biotechnology, Tel Aviv University, Tel Aviv, Israel; (5) Global R&D Partners, San Diego, CA, USA)*

Background: Combinations of brain deposits of misfolded proteins, such as aggregated amyloid-β, tau, and frequently α-synuclein, can occur within a single disease, such as Alzheimer's disease (AD). The multiple pathologies suggest therapeutic strategies that generically target such aggregates, independent of primary protein sequence. NPT088 is a human immunoglobulin (huIgG1)-Fc fusion that displays two copies of the General Amyloid Interaction Motif (GAIM). We have shown that NPT088 has uniquely broad activities, both in vitro and in vivo, against multiple neuropathological aggregates, making it a novel candidate for treating AD and other neurodegenerative diseases with amyloid pathology. *Methods:* NPT088 was measured for amyloid (Aβ, tau, α-synuclein) binding and binding specificity using ELISA and SPR formats. Aggregation inhibition was monitored by ThT fluorescence. Oligomer-induced cytotoxicity, was measured on N2a cells using an adenylate kinase release assay. Aβ aggregate-NPT088 co-precipitation assays used insoluble fractions from aged Tg2576 brain homogenates. Inter-neuronal transmission inhibition of aggregated tau or α-synuclein was measured in primary mouse cortical or hippocampal neuron cell culture and quantified by fluorescent microscopy and imaging. NPT088 was administered to Tg AD and PD model mice weekly i.p., 10-14 weeks: Tg2576,18 m.o.; rTg4510, 3.6 m.o; mThy1-Hα-synuclein, 6 m.o. Cognitive changes were assessed by spontaneous alternation (Y-maze) and novel object recognition. Brain biochemistry for changes in levels of aggregated proteins was measured using Western blot or ELISAs on soluble and insoluble fractions from brain homogenates or CSF. Neuropathology assessed by immuno-histochemistry utilized 40μm fixed brain sections. *Results:* NPT088 specifically and potently binds amyloid fibers of Aβ, tau and α-synuclein (Kds=5-46 nM), but does not bind monomers or natively aggregated proteins. NPT088 binds Aβ oligomers, blocks oligomer-induced cytotoxicity (IC50<10 nM), and prevents Aβ and tau aggregation in vitro. NPT088 recognizes brain homogenate Aβ aggregates from aged Tg2576 mice. NPT088 effectively treats Tg AD and PD mouse models. In the Tg2576 hAPP model, NPT088 significantly improves cognition; reduces brain Aβ(1-42) and Aβ plaque; and reduces Aβ levels in CSF. In rTg4510 tau mice, NPT088 significantly improves cognition, reduces levels of phospho-tau associated with neuropathology and lowers CSF tau. In mThy1-Hα-synuclein mice, NPT088 significantly reduces proteinase-KR α-synuclein and increases tyrosine hydroxylase levels. NPT088 has successfully completed IND-enabling monkey and rat safety studies. *Conclusion:* These results demonstrate that NPT088 is

a first-in-class therapeutic candidate for AD, which targets misfolded proteins generically, including aggregates of Aβ, tau and α-synuclein. Following IND filing in 4Q2015, NPT088 will be tested for proof of activity in AD by measuring for simultaneous reductions of Aβ and tau deposits utilizing PET imaging.

LB11: EVALUATION OF SERUM PLASMALOGENS AND THEIR ASSOCIATIONS WITH COGNITION AND ALZHEIMER 'S DISEASE ACROSS FOUR STUDIES. DAYAN B GOODENOWE[1], VIJITHA SENANAYAKE[1], MITCHEL A KLING[2], JON B TOLEDO[3], TARA SMITH[1], ASUKA MOCHIZUKI[1], JESSICA TENENBAUM[4], EMILY BURKE[4], XIANLIN HAN[5], REBECCA BAILLIE[6], JOSEPH LUCAS[4], MURALI DORAISWAMY[7], JOHN Q TROJANOWSKI[3], LESLIE M SHAW[3], SUNGEUN KIM[8], ANDREW J SAYKIN[8], RIMA KADDURAH-DAOUK[7] AND THE ALZHEIMER DISEASE METABOLOMICS CONSORTIUM *((1) Phenomenome Discoveries Inc., Saskatoon, Saskatchewan, Ca(nada; (2) Department of Psychiatry and (3) Department of Pathology & Laboratory Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; (4) Duke University Medical Center, Durham, NC; (5) Sanford-Burnham Medical Research Institute, Orlando, FL; (6) Rosa & Co. LLC, San Carlos, CA; (7) Duke Institute for Brain Sciences, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC; (8) Indiana Alzheimer Disease Center , Indiana University School of Medicine, Indianapolis, IN)*

Background: Justification of the investment required to develop therapeutics for targets inferred by putative biomarkers of Alzheimer's Disease (AD) identified in small case-control discovery studies requires confidence that the observations are not the results of artifacts specific to the collection and execution of any one particular study. The inter-study translation and reproducibility of the association between serum plasmalogens (PL) and AD was investigated. *Methods:* Four study groups were evaluated: Study 1 (case-control, n=670, PrecisionMed (Pmed)); Study 2 (community cohort, n=1096, Rush University Religious Orders Study and Memory and Aging Project (Rush)); Study 3 (case-control, n=808 with 19 random replicates, Alzheimer's Disease Neuroimaging Initiative (ADNI-1) baseline visit); Study 4 (case-control, n=84, Indiana Memory and Aging Study). To determine the relative and combined contributions of PL levels and PL biosynthesis, the serum levels of PL species containing fatty acids that are precursors (adrenic acid, 22:4), products (eicosapentaenoic acid, 20:5), or both a product and precursor (docosahexaenoic acid, 22:6) of peroxisomal β-oxidation and a corresponding DHA-containing phosphatidylethanolamine (PE). Three product/precursor ratios were used as biomarkers of peroxisomal β-oxidation (PL205/PL224, PL226/PL224 PL205/PL226) and two PL/PE ratios were used as biomarkers PE pool size (PL205/PE226, PL226/PE226). Each ratio was divided by its sex-specific mean, and then log10 transformed to correct for skewness. The overall plasmalogen biosynthesis value (PBV) was created by averaging these values. Ordinal logistic regression was performed to determine the associations with clinical classification (Cognitively Normal (CN), Mild Cognitive Impairment (MCI) or AD). Multiple regression was performed to determine associations with cognition using Mini Mental State Examination (MMSE) scores available for all studies. All models were adjusted for age, and sex. PBV associations are expressed per standard deviation (SD). Analytical reproducibility was determined by linear regression of replicate 1 versus replicate 2 for PBV and each of the component ratios. *Results:* Higher PBV was associated with a lower odds of AD [(Pmed (OR=0.63, p=1.3e-08); Rush (OR=0.67, p=4.3e-08); ADNI-1 (OR=0.71, p=5.1e-07); Indiana (OR=0.62, p=4.2e-02)] and a higher MMSE [Pmed (Coef=1.21, p=9.9e-10); Rush (Coef=0.99, p=2.6e-11); ADNI-1 (Coef=0.60, p=1.2e-10); Indiana (Coef=0.66, p=4.3e-02)] in each of the four studies (meta analytic p=6.7e-29). R-squared value (r2) between the 19 blinded replicates for each of the five ratios ranged from 0.95 to 0.99 and was 0.98 for the PBV. *Conclusion:* The associations between PBV and clinical diagnosis of CN, MCI, and AD and PBV and cognition are stable and reproducible across independent study groups. The analytical determination of PBV and its subcomponents is robust and reproducible. The utility of pharmacologically targeting the biochemical systems underlying these associations as being potentially disease modifying in AD warrants further investigation. Authors wish to acknowledge Rush University, Precision Med, ADNI, including ADNI funding sources and Indiana University for the provision of respective samples and clinical data. Partly funded by the NIA R01 grant: 1R01AG046171.

LB12: KINETIC MODELING OF THE TAU PET TRACER [18F]AV1451. OLIVIER BARRET[1], DAVID ALAGILLE[1], SANDRA SANABRIA[2], ROBERT COMLEY[3], ROBBY WEIMER[2], EDILIO BORRONI[3], NICHOLAS SENECA[4], ABHINAY JOSHI[5], MICHAEL DEVOUS[5], MARK A MINTUN[5], DANNA JENNINGS[1], KEN MAREK[1], JOHN P. SEIBYL[1], GILLES D TAMAGNAN[1] *((1) Molecular NeuroImaging LLC, 60 Temple Street, New Haven, CT, 06510, USA; (2) Genentech Research and Early Development, Genentech, 1 DNA Way, South San Francisco, CA, 94080, USA; (3) Pharma Research and Early Development, F. Hoffmann-La Roche, Konzern-Hauptsitz, Grenzacherstrasse 124, CH-4070 Basel, Switzerland; (4) Product Development, F. Hoffmann-La Roche, Konzern-Hauptsitz, Grenzacherstrasse 124, CH-4070 Basel, Switzerland; (5) Avid Radiopharmaceuticals, 3711 Market St. Philadelphia, PA, 19104, USA)*

Background: [18F]AV1451 (T807) is currently the most widely used of several experimental tau PET tracers. However, the tissue kinetics of [18F]AV1451 differ between brain regions (and subjects), presumably due to differences in tau load. These differing kinetics complicate the task of simplifying the image acquisition and analysis procedures (i.e. avoiding dynamic imaging and blood sampling), which would be desirable if [18F]AV1451 were to be used to assess changes in tau burden in multicenter clinical trials. The objective of this study was to perform tracer kinetic analysis with an arterial input function (for full quantification), and to determine optimal time interval over which to calculate an uptake ratio (SUVR) with minimal bias compared to a measure of specific binding such as the Binding Potential (BPND). *Methods:* [18F]AV1451 PET brain imaging was completed in 14 subjects: 4 young healthy controls (HC) (age 26-37), 4 aged HC (age 52-73) and 6 Alzheimer's Disease subjects (AD) (Age 57-85, MMSE 14-29). Subjects were administered 8.9 ± 0.7 mCi [18F]AV1451 and imaged for 3.5 hours in 3 sessions of 50 min: 0-50 min, 80-130 min and 160-210 min. Arterial blood samples were drawn throughout the 3.5 hours and analyzed by reverse HPLC. Aged HC and mild AD subjects also underwent [18F]Florbetapir amyloid imaging (9.2 ± 0.4 mCi, 50-65 min post injection). [18F]AV1451 PET data were modeled with a 2-tissue compartment model to estimate the distribution volume VT. Binding potential (BPND) was derived using cerebellar cortex as reference region. SUVr curves (relative to cerebellar cortex) were calculated over 210 min and compared to BPND for different time windows: 80-100 min, 110-130 min (currently used in clinical studies), 160-180 min and 190-210 min. BPND and SUVr estimates were also compared between the three groups. *Results:* Two main radiometabolites were observed that were more polar than the parent, with a fraction of intact parent of ~20% remaining at 90 min post injection. VT and BPND estimates were heavily dependent on the acquisition duration, with in particular a reduction of BPND of ~25% for the AD subjects when truncating from 210 min to 130 min of data. VT (130 min) ranged from 5.3±0.9 (across

all subjects) to up to ~18 mL/cm3 in cortical regions of AD subjects. Overall, a good correlation was found between BPND (130 min or 210 min) and SUVr-1 (80-100 min, 110-130 min, 160-180 min or 190-210 min) with R2>0.88. The agreement was however best between BPND (130 min) and SUVr-1 (110-130 min), and between BPND (210 min) and SUVr-1 (160-180 min). SUVr curves for both young and aged healthy controls reached within 80 min of injection a relative plateau around 1.0-1.2 in cortical areas (decrease <10% up to 210 min post injection). For AD subjects, cortical SUVr curves increased throughout the 210 min of acquisition, by up to ~15%, ~30% and ~40% for SUVr (110-130 min), SUVr (160-180 min) and SUVr (190-210 min) relative to SUVr (80-100 min), respectively. SUVr curves were increased in AD subjects compared to HC in regions expected to demonstrate tau pathology, with values up to 2.8 in the inferior lateral temporal cortex compared to around 1.2 for the aged HC for SUVr (80-100 min), while no significant difference was observed between young and aged HC. The separation increased over time, with for instance values up to 3.3 in the inferior lateral temporal cortex compared to still around 1.2 for the aged HC for SUVr (160-180 min). *Conclusions:* Our data suggest that although [18F]AV1451 SUVr curves do not reach a plateau and are continuously increasing in AD subjects, an imaging window of 80-100 min does provide SUVr estimates in good correlation with BPND (130 min), suitable for cross sectional comparisons of tau load. However, this data suggests that later imaging windows may be better suited for longitudinal studies. Also, it will be important to confirm the linearity of the relationship between SUVr and BPND in more subjects, in particular seeing the time dependence of the different measurements (SUVr, VT or BPND). Since both disease progression and treatment will likely influence tracer kinetics, the extent to which measured changes in SUVr correlate with changes in true tau load will likely vary by region and subject. This source of variability should be properly considered in any longitudinal studies designed to detect changes in tau load, particular in response to drug treatment.

LB13: THE IMPORTANCE OF UNDERSTANDING THE VARIABLE RATE OF PROGRESSION AMONG ALZHEIMER'S DISEASE PATIENTS: DATA FROM THE GANTENERUMAB PROGRAM. SYLVIE RETOUT[1], RONALD GIESCHKE[1], CORNELIA WEBER[1], JEAN-ERIC CHAROIN[1], DIETMAR VOLZ[2], ROBERT LASSER[2], NICOLAS FREY[1], CARSTEN HOFMANN[1] *((1) Roche Pharma Research and Early Development, Clinical Pharmacology, Roche Innovation Center Basel, Switzerland; (2) F. Hoffmann-La Roche Ltd, Basel, Switzerland)*

Background: Gantenerumab is a fully human, anti-Aβ monoclonal antibody that binds with high affinity to aggregated Aβ. It promotes removal of aggregated Aβ by activating microglial phagocytosis. Gantenerumab was studied in SCarlet RoAD (NCT01224106; WN25203)—a Phase III, multicenter, randomized, double- blind, placebo-controlled, 2-year trial in prodromal AD. Patients were randomized to monthly subcutaneous injections of placebo, 105 mg or 225 mg gantenerumab, depending on their APOEε4 allele status. Following a pre-planned futility analysis, dosing in SCarlet RoAD was terminated. No treatment effect was detected on the clinical scores CDR-SOB, ADAS-Cog13, FAQ and MMSE in the 2-year completer patients (N=312). Additional exploratory analyses were undertaken to inform the program since another Phase III study (Marguerite RoAD, WN28745) is ongoing in patients with mild AD. *Methods:* An ADNI-based [1] AD progression model [2, 3] describing the time course of CDR-SOB in AD patients was applied to identify patients at study entry that were likely to be slow progressors or fast progressors based on CDR-SOB, FAQ and normalized hippocampal volume values at study entry. Patients were also classified into placebo, low-, medium- and high-exposure groups based on estimated average serum concentrations computed by population pharmacokinetic analysis. Exposure–clinical outcome relationships were then examined in the slow and fast progressor sub-groups. *Results:* One-third (N=108) of the patients were predicted to be fast progressors, and a clear exposure–response relationship for ADAS-Cog13 could be observed in those patients with a median decrease of 3 points at 2 years in the highest exposure category compared with placebo. Similar exposure trends were observed in fast progressors for MMSE and CANTAB scores but not for CDR-SOB. Among slow progressors, no exposure–response relationship could be observed, indicating that the slow disease progression over the 2-year treatment period was probably limiting the detection of a drug effect. *Conclusions:* Identifying Alzheimer's patients at study entry who are likely to progress faster than others permitted the establishment of a potential signal of efficacy for gantenerumab in a failed Phase III study. 1. www.adni.loni.ucla.edu; 2. Delor I, et al. CPT: Pharmacometrics & Systems Pharmacol 2013; 2:e78; 3. Retout S, et al. PAGE 22 (2013) Abstr 2767 [www.page-meeting.org/?abstract=2767]

LB14 : USING RUN-IN DATA IN SECONDARY PREVENTION COGNITIVE ENDPOINT TRIALS. JASON HASSENSTAB[1,2], SUZANNE HENDRIX[3], NOEL ELLISON[3], YAKEEL T. QUIROZ[4,5], DANIEL C. AGUIRRE[4], ELIANA HENAO[4], VICTORIA TIRADO[4], CLAUDIA MUÑOZ[4], JENNIFER SMITH[1], FRANCISCO R. LOPERA[4], JOHN C. MORRIS[1], RANDALL BATEMAN[1] AND THE DOMINANTLY-INHERITED ALZHEIMER NETWORK (DIAN) *((1) Knight Alzheimer's Disease Research Center, Department of Neurology, Washington University in St. Louis, St. Louis, MO USA; (2) Department of Psychology, Washington University in St. Louis, St. Louis, MO USA; (3) Pentara Corporation, Salt Lake City, UT USA; (4) Grupo de Neurociencias, Universidad de Antioquia, Medellín, Colombia; (5) Departments of Psychiatry and Neurology, Massachusetts General Hospital, Boston, MA USA)*

Background: In clinical trials of Alzheimer's disease therapeutics, outcomes are often expressed as a rate of change. Run-in periods, where subjects complete assessments prior to randomization, can provide estimates of that rate of change which can be modeled as covariates in power calculations. Run-in periods typically improve power and reduce the number of subjects required to reach trial goals, however, subjects in secondary prevention trials are by definition asymptomatic and have minimal cognitive decline in the pre-randomization period. Therefore, it is unclear if run-in periods are beneficial for secondary prevention trials with a cognitive endpoint. This study had two main goals: First, to determine if including pre-randomization cognitive data improves treatment effect power calculations in existing datasets from autosomal dominant Alzheimer's disease (ADAD) cohorts and sporadic Alzheimer's disease (SAD) cohorts. Second, to determine the optimal study design that maximizes benefit from run-in periods while maintaining a practically feasible visit structure. *Methods:* Datasets included the Dominantly-Inherited Alzheimer Network observational study (DIAN), the PSEN1 E280A cohort from Colombia followed by the Groupo de Neurosciencias of Antioquia (GNA), and cohorts from the Rush Alzheimer's Disease Center (RADC). From each dataset, a global cognitive performance measure that emphasized episodic memory, executive function, and mental status was chosen as the primary outcome. Follow-up visits were used as proxies for post-randomization visits and initial visits were used as proxies for pre-randomization visits. Using 1000 iterations for each dataset, subjects were randomly assigned to either an "active" or "placebo" group. Simulated treatment effects of 30% and 50% were applied to the active group for each iteration. Linear mixed effects models tested whether including cognitive performance in the pre-randomization period as slopes, intercepts, or averages increased statistical power compared to models excluding pre-randomization data. *Results:* Across all datasets, including slopes and

intercepts from pre-randomization periods as covariates resulted in increased statistical power, reducing the number of subjects required to reach trial goals by 5-20%, depending upon effect size targets and the length of the pre-randomization period. A one-year run-in period with at least two pre-randomization visits provided the most improvement in power; however, simulations indicate that shorter run-in periods with more frequent assessments may provide similar power increases. *Conclusions:* Increasing the number of assessments in a cognitive endpoint secondary prevention trial by incorporating a run-in period or moving some assessments from post-randomization to pre-randomization can significantly enhance the power of the trial. Study designs that include 6 months to 1 year of pre-randomization visits may be an ideal method to increase power, increase compliance, and reduce costs for cognitive endpoint trials.

LB15: SEX DIFFERENCES IN NEUROPSYCHIATRIC SYMPTOMS IN PATIENTS WITH ALZHEIMER'S DISEASE.
CYNTHIA A MUNRO[1], YE TAO[1], MATTHEW E PETERS[1], LEA T DRYE[2], DAVANGERE P DEVANAND[3], JACOBO E MINTZER[4], BRUCE G POLLOCK[5], ANTON P PORSTEINSSON[6], PAUL B ROSENBERG[1], LON S SCHNEIDER[7], DAVID M SHADE[2], DANIEL WEINTRAUB[7], JEROME YESAVAGE[8], CONSTANTINE G LYKETSOS[1] FOR THE CITAD RESEARCH GROUP *((1) Johns Hopkins University School of Medicine; (2) Johns Hopkins Bloomberg School of Public Health; (3) Columbia University Medical Center ; (4) Medical University of South Carolina, Clinical Biotechnology Research Institute-Roper St. Francis Healthcare, Ralph H. Johnson VA Medical Center; (5) University of Toronto; (6) University of Rochester School of Medicine; (7) University of Pennsylvania School of Medicine; (8) Stanford University School of Medicine)*

Background: While cognitive decline is a cardinal feature of AD, the concurrent development of neuropsychiatric symptoms (NPS) during the course of the illness is more often the rule than the exception. It has long been established that the prevalence of AD is higher in women than in men, and more recently, sex differences in the clinical and pathological manifestations of the disease have been described. In this study, we aimed to further characterize the sex differences in the clinical presentation of AD by focusing on NPS. In this secondary analysis of data obtained through a clinical trial for the treatment of agitation in patients with AD, we hypothesized that compared to women, men would exhibit a greater number of physical symptoms of agitation whereas women would be more likely than men to exhibit affective symptoms. *Methods:* This cross-sectional cohort analysis examined baseline data from the Citalopram for Agitation in Alzheimer's Disease (CitAD) clinical trial. The CitAD, a randomized, double-masked, placebo-controlled multicenter clinical trial, recruited patients having probable AD with clinically significant agitation from eight sites across the United States and Canada. The final sample (n = 186) were randomized to receive citalopram (target dose of 30 mg/day) or matching placebo. Agitation was assessed with the short (14-item) Cohen-Mansfield Agitation Inventory (CMAI), the Agitation subscale of the NBRS (NBRS-A), and the Neurobehavioral Rating Scale (NBRS); broader neuropsychiatric symptoms (NPS) were quantified by Neuropsychiatric Inventory (NPI) ratings. Statistical analyses were completed using SAS version 9.2 and R version 2.13.1 Logistic regression was used to model associations between sex and the four CMAI factors, the individual NBRS-A subscales or individual NPI symptoms and the test for significance was a Wald $\chi 2$. The unadjusted models were univariate models of sex versus the CMAI, NBRS-A, or NPI outcome. Adjusted models were multivariate, including control for all potential confounders (demographic variables, caregiver distress, MMSE score, and ADCS-ADL score) that were significant at the 20% level. *Results:* Women were slightly older than men, less likely to be Caucasian, and less likely to live in their own homes compared to men. Women were also less likely than men to be married. Men had higher MMSE scores (for men: mean=16.8, SD = 6.8, for women: mean = 14.5, SD = 6.3) and were more functionally independent than were women as measured by the ADCS-ADL scale. The distribution of the total number of CMAI symptoms that were present was higher in women (median of 7 symptoms [Q1, Q3: 4, 8]) compared to men (median of 5 [Q1, Q3: 4, 7]); Kruskal-Wallis p = 0.01. Women were more likely than men to engage in verbally non-aggressive behaviors (1.9 [1.0, 3.5]) in the unadjusted model, and after adjusting for covariates, the effect size of the difference actually increased, although this difference was no longer statistically significant. Women were more likely than men to engage in pacing or aimless wandering (1.9 [95% CI: 1.1, 3.4]; p=0.03), complaining or refusal to follow directions (2.5 [95% CI: 1.1, 5.7]; p=0.03), and hiding or hoarding things (2.0 [95% CI: 1.1, 3.6]; p=0.02). Adjusting for covariates resulted in only small decreases in effect sizes. The percent of women exhibiting motor manifestations of agitation (NBRS-A) was slightly higher than the percent of men rated as manifesting this symptom (1.8 [0.9-3.4], p=0.07) in the unadjusted model. Adjusting for covariates increased the effect size for the difference. Examination of broader NPS as assessed by the NPI indicated with the exception of elation and hallucinations, each NPS was present in at least 40% of the sample. The distribution of the total number of NPI NPS symptoms that were present did not differ by sex, but women were more likely than men to exhibit delusions (2.3 [95% CI: 1.3, 4.2]; p=0.01) and anxiety (1.9 [95% CI: 1.0, 3.6]; p=0.04) whereas men were more likely to exhibit apathy (0.5 [95% CI: 0.3, 0.9]; p=0.03). After adjusting for covariates, the additional NPS of irritability/lability was more likely in women than men (4.4 [95% CI: 1.4, 14.1]; p=0.01) but no single NPS was higher in men than in women. Effect sizes for the differences between men and women did not change substantially after adjustment, suggesting that a lack of power to detect the differences after adjusting for the covariates was an issue. *Conclusion:* In AD patients enrolled in a clinical trial for agitation, pervasive NPS were common; indeed, in only 2 patients was agitation the sole NPS. Women exhibited a broader range of NPS, and were more likely to exhibit several specific symptoms of agitation, compared to men. Men, in contrast, were more likely to exhibit only apathy. Given sex differences in response to, and pharmacodynamics of, psychoactive medications, studies aimed at further characterizing the nature of sex differences in NPS among patients with AD will be valuable in suggesting targets for treatment.

LB16: CHOLESTEROL-METABOLIZING ENZYME CYTOCHROME P450 46A1 (CYP46A1) AS A NEW THERAPEUTIC TARGET FOR ALZHEIMER'S DISEASE.
IRINA A PIKULEVA, NATALIA MAST, JAMES CONSTANS, ANA VALENCIA-OLVERA *(Department of Ophthalmology and Visual Sciences, Case Western Reserve University, Cleveland, OH, USA)*

Background: Cytochrome P450 CYP46A1 is the central nervous system-specific enzyme catalyzing cholesterol 24S-hydroxylation, the major mechanism for cholesterol elimination from the brain. CYP46A1 also plays a role in higher order brain functions because its activity controls the rate of production of cerebral non-sterol isoprenoids important for learning and memory and the levels of 24OH-hydroxycholesterol, a potent positive allosteric modulator of N-methyl-D-aspartate receptors. Mouse models of Alzheimer's disease (AD) with genetically increased CYP46A1 expression and enzyme activity have improved cognition and a reduction in amyloid pathology. Pharmacologic stimulation of CYP46A1 is, however, a challenge because drugs on the market usually act as enzyme inhibitors rather than activators. *Methods:* Enzyme assay (cholesterol 24-hydroxylation) was used to screen the FDA-approved drugs for

the effect on activity of purified CYP46A1 in vitro. The anti-HIV medication efavirenz was then tested on mice including the 5XFAD strain, a mouse model of Alzheimer's disease. These animals were treated systemically with efavirenz for 4 months using the drug dose >100-times lower than that given to HIV patients. Animals were assessed for the levels of cerebral sterols (by gas chromatography-mass spectrometry) as well as manifestations of Alzheimer's disease pathology (by immunohistochemistry and Western blotting). *Results:* Four pharmaceuticals (efavirenz, acetaminophen, mirtazapine, and galantamine) prescribed for indications unrelated to cholesterol maintenance increased CYP46A1 activity in vitro from 6 to 11-fold. Efavirenz also stimulated CYP46A1 and cerebral cholesterol turnover in vivo in mice. In addition, efavirenz-treated 5XFAD animals had a significant reduction in the number and area of cerebral amyloid plaques (up to 1.8-fold depending on the brain region), the levels of amyloid precursor protein (1.6-fold in mouse brain homogenates) as well as cerebral microglia activation. Ongoing studies include measurements of soluble and insoluble amyloid-beta peptides, behavioral and other animal characterizations, as well as investigation of the mechanism whereby CYP46A1 might reduce Alzheimer's disease pathology features. *Conclusions:* We discovered that CYP46A1 could be activated pharmacologically in vivo in mice via the allosteric mechanism. Our data indicate that CYP46A1 has a potential to be a new anti-Alzheimer's disease therapeutic target and that EFV should be tested further in clinical studies. Only a tiny dose of efavirenz may be required to activate CYP46A1 in humans.

POSTER COMMUNICATIONS

Thursday, November 5th

P1-1: VALIDATING THE PGSA (PLACEBO GROUP SIMULATION APPROACH) USING DATA FROM A COMPANY-SPONSORED MCI DRUG TRIAL. RENÉ SPIEGEL[1], ANDREAS U MONSCH[1], ANDRÉ MISEREZ[2], MANFRED BERRES[3] *((1) Felix Platter Hospital, University Center for Medicine of Aging Basel, Switzerland; (2) diagene Laboratories Inc., Reinach, Switzerland; (3) University of Applied Sciences Koblenz, RheinAhrCampus, Remagen, Germany)*

Background: The PGSA aims at avoiding problems of sample representativeness and ethical issues typical of long-term placebo-controlled prevention trials with MCI patients. The PGSA uses mathematical modeling to forecast the distribution of quantified outcomes of MCI patient groups based on their own baseline data established at the outset of clinical trials (Alzheimers Res Ther 2011, 3:9-20). These forecasted distributions are then compared with the distributions of actual outcomes observed on candidate treatments, thus substituting for a concomitant placebo group. The original PGSA algorithms were developed using data from the aMCI (amnestic MCI) population of ADNI-1. We have subsequently published (J Prev Alzheimers Dis 2014, 1: 99-109) the results of the application of a PGSA algorithm to patient data available from the National Alzheimer Coordinating Center (NACC). Analysis showed that the distributions of empirically observed and simulated data after 1, 2 and 3 years were very similar, with some over-estimation of cognitive decline after 3 years. The most important predictor of cognitive decline as assessed by a neuropsychological test battery (NTB) were the NTB scores established at baseline. Other significant predictors were the MMSE at baseline and the interactions of time with ApoE4 and the score of the functional activities questionnaire (FAQ). The InDDEx study (Lancet Neurol 2007, 6:501-512) assessed the effect of the cholinesterase inhibitor rivastigmine in patients with MCI on the time to clinical diagnosis of AD and the rate of cognitive decline. InDDEx was a double-blind, randomized, placebo-controlled trial of up to 48 months duration. Patients had MCI operationally defined by having cognitive symptoms, a GDS rating stage of 0.5, a score of less than 9 on a delayed paragraph recall test, and by not meeting the diagnostic criteria for AD. Primary efficacy variables were time to clinical diagnosis of AD, and change in performance on a cognitive test battery. 1018 patients aged 55-85 were enrolled at 65 research centers in 14 countries between May 1999 and April 2000, the last patient completed the study in April 2004. No statistically significant difference between the rivastigmine-treated and the placebo-treated subjects with regard to time to diagnosis of AD or the rate of cognitive dysfunction over 4 years was observed. *Methods:* Data from a randomly selected subsample of 660 subjects, i.e., about 65% of the InDDEx study population were analyzed. This included data from the run-in phase, the double-blind phase and the retrieved dropout phase following the double-blind phase. This material was used to assess the validity of the ADNI-1-based PGSA algorithms in a sample of MCI patients recruited and followed within a rigorous drug study protocol. Here we report the results of a comparison between the ADAScog as observed in the InDDEx trial and those modeled using the PGSA algorithm for this scale. Since the ADAScog scores are skewed to the right a square-root transformation was applied before the analysis. After exclusion of interactions and fixed main effects based on an AIC-based procedure, the final model contained the following factors (in descending order of importance): ADAScog score at baseline, a composite neuropsychological score at baseline, gender, MMSE score at baseline, and two interactions with time. *Results:* The distribution of observed and simulated data over all time points shows a high degree of correspondence, with all - means, median values, standard deviations - deviating by only a few percent between observed and simulated values. Graphic representation of the distributions shows that only a few extreme values in the observed data were without correspondence in the simulated data. QQ-plots show that the correspondence between observed and simulated values is rather constant over time, i.e. there is no drift in the quality of the simulation between month 6 and month 48 in the study. These statements apply to the analysis of the observed cases (OC) and to a somewhat lesser extent to the one of the OC plus retrieved dropouts and open-label continuers. *Conclusion:* The InDDEx trial was initiated more than 15 years ago and used inclusion criteria for MCI that differ in several respects from current definitions of aMCI and from those typical of ADNI-1. Regardless of this difference, the PGSA algorithm for the ADAScog that was developed from ADNI-1 data modeled cognitive performance data over 4 years with high accuracy, i.e., with little deviation from the observed data. This finding is of relevance for future drug trials in aMCI patients, as it originated from an international study with a rigorous protocol typical of company-sponsored trials. Comparing simulated scores for one subsample of patients with observed scores from the other subsample opens the perspective of replacing a significant portion of the placebo group by simulated data.

P1-2: COMPARATIVE TRADITIONAL PSYCHOMETRICS OF COGNITIVE AND FUNCTIONAL ENDPOINTS IN A PRODROMAL ALZHEIMER'S DISEASE POPULATION. CHRIS EDGAR[1], ANGELA J RYLANDS[1], DIETMAR VOLZ[2], MICHAELA MERTES[2], ELISABETH GRUENDL[2], PAULO FONTOURA[2], LUCA SANTARELLI[2], ROBERT LASSER *((1) Roche Products Limited, Welwyn Garden City, UK; (2) F. Hoffmann-La Roche Ltd, Basel, Switzerland)*

Background: Psychometric properties of outcome measures commonly used in Alzheimer's dementia have not been well established in prodromal AD. SCarlet RoAD (NCT01224106; WN25203) is a Phase 3, multicenter, randomized, double-blind,

placebo-controlled, 2-year study in patients with prodromal AD. In addition to aMCI, subjects recruited to SCarlet RoAD are required to have evidence of amyloid pathology as demonstrated by low levels of Aβ42 in CSF. Here we describe traditional psychometrics of cognitive and functional assessments in this population. *Methods:* Subjects eligible for SCarlet RoAD were 50–85 years old with MMSE ≥24, CDR-Global 0.5 (memory box 0.5 or 1.0) and abnormal memory function based on FCSRT (<17 for free recall, <40 total recall, or <20 free recall and <42 total recall). Subjects did not meet a diagnosis of dementia and were further screened for low CSF Aβ42 levels, using a CSF Aβ assay (INNOTEST® β-AMYLOID1–42, Innogenetics). Psychometrics of ADAS-Cog, CDR, FAQ, FCSRT and MMSE at screening and baseline were evaluated by assessment of floor and ceiling effects, test–retest reliability, (intra-class correlation coefficients), internal consistency of summary scores (Cronbach's α) and construct validity (Spearman correlation coefficients and t-tests). In addition, sensitivity to change was evaluated via calculation of standardized response means for the change from baseline (mean change divided by standard deviation of change) to Week 104 in subjects randomized to placebo only. *Results:* Seven hundred and ninety-nine subjects were randomized. All measures showed ceiling effects (subjects with no impairment at baseline) at the individual item level, with some items also displaying floor effects (maximal impairment). However, ceiling and floor effects were much less pronounced for total/summary scores. Test–retest reliability was good for all measures (≥0.67). Internal consistency was variable and inter-correlation of tests modest to good, supporting hypothesized differences in the domains covered by each instrument. Both cognition and function declined over 2 years in untreated patients, with the different measures exhibiting differing degrees of sensitivity to decline. *Conclusions:* The data support traditional psychometrics of these instruments in prodromal AD, but suggest that in some instances, specific items may lack sensitivity to very early cognitive and functional impairment. Differences in the domains of assessment covered by each instrument are important to guide the selection of screening and assessment batteries for clinical trials and the iterative development of these tools. Whilst cognition and function are declining in this population, different rates of change are observed dependent on the measure used. This may reflect differences in the sensitivity of assessments, including their ability to measure changes and variability, as well as variations in disease course, dependent on the specific domains of assessment.

P1-3: DESIGNING A FIRST INTERVENTIONAL PHASE 2A TRIAL IN FTD-GRN WITH AN HDAC INHIBITOR (FRM-0334). HANS J MOEBIUS[1], NANCY DGETLUCK[1], GORDON LOEWEN[1], HOLGER PATZKE[1], ADAM L BOXER[2], DANA C HILT[1] *((1) FORUM Pharmaceuticals Inc, Waltham, MA, USA; (2) Neurosciences Clinical Research Unit, University of California, San Francisco, CA, USA)*

Background: Frontotemporal dementia with progranulin gene mutation (FTD-GRN) is a rare, autosomal dominantly inherited neurodegenerative disorder with a peak onset in the fifth decade and an average survival after diagnosis of about 6 years. Many described mutations of the GRN gene lead to haploinsufficiency resulting in lowered progranulin (PGRN) concentrations. PGRN function is not fully elucidated but has been connected to neuroinflammation, microglial function and neuronal survival. *Methods:* Interventional placebo-controlled trials in FTD-GRN have never been done; there is a dearth of information on optimal design and endpoints to assess pharmacologic benefit in these patients. Trial methodology was only finalized after an international, systematic feasibility study at selected sites. *Results:* The present study was designed to obtain rapid elucidation of the safety/tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of a selective, blood-brain-barrier penetrant HDAC inhibitor (FRM-0334) in this orphan population. Based on preclinical human cell models assessing PGRN induction, a target plasma/brain drug concentration was defined and a sequential, parallel, placebo-controlled, group-wise dose-escalating, adaptive design was selected. The sample size estimation was based on previous observations of intra- and inter-individual variability of plasma and CSF PGRN (co-primary pharmacodynamic outcome variables). Additional assessments include other fluid biomarkers both in blood (PGRN mRNA) and CSF (Abeta1-42, t-tau, p-tau181, NfL, TDP43), and FDG-PET change, as well as exploratory psychometric endpoints. Each dose escalation is to be preceded by a favorable safety assessment of the Safety Review Committee. *Conclusion:* While FTD-GRN shows a wide spectrum clinical phenotypes, a flexible Phase 2a clinical trial design optimized for safety/tolerability, PK and PD readouts was defined. The study is currently being implemented on an international basis in the US and Western Europe.

P1-4: CAUSAL ANALYSIS WITH TRUNCATION BY DEATH IN RANDOMIZED AND NON-RANDOMIZED CLINICAL TRIALS. XIAO-HUA ZHOU[1,2,3], LINBO WANG[1] *((1) Department of Biostatistics, University of Washington, Seattle, WA, USA; (2) National Alzheimer's Coordinating Center (NACC), University of Washington, Seattle, WA, USA; (3) Biostatistics Unit, U.S. Department of Veterans Affairs Seattle Medical Center, Seattle, WA, USA)*

Background: In clinical trials and observational studies, researchers are often interested in evaluating risk factors for a non- mortality outcome such as memory decline. However, the non-mortality outcome may be truncated by death if some subjects die before the follow-up assessment, leaving their non- mortality outcomes to be undefined. For example, suppose we are interested in estimating effects of smoking on memory decline in an aged population. If a participant dies before the follow-up memory test is administered, then his/her memory score at the follow-up visit is undefined. Direct comparisons between smokers and non-smokers among observed survivors are subject to selection bias as nonsmokers are more likely to survive to the follow-up assessment. More fundamentally, direct comparisons among observed survivors are not causally interpretable as they compare outcomes from different subpopulations at baseline. Alternatively, Rubin (2000) proposed to estimate the average causal effect in the always-survivor group, the group of subjects who would survive if they choose to receive either exposure at baseline. The resulting estimand is termed survivor average causal effect (SACE). *Methods:* In this talk, we introduce some new non-parametric approaches, based on a baseline substitution variable whose distribution is informative of the membership of the always-survivor group to estimate SACE. We will present the methods for consistently estimating SACE in both randomized and non-randomized clinical trials. We first introduce the definition of a substitution variable, which is similar in idea to the conditions for an instrumental variable. We then show that under the existence of a substitution variable and other commonly made assumptions in causal inference literature such as the mono- tonicity assumption and the strong ignorability assumption, SACE is non-parametrically identifiable. We also propose a non-parametric method to estimate SACE under our identifiability conditions. We finally apply our method to estimate the effect of smoking on memory decline with data from the Health and Lifestyle Survey (HALS), a population-based prospective cohort study conducted in England, Scotland and Wales. *Results:* Under some regularity conditions, we show the proposed estimator for SACE is consistent and asymptotically normally distributed and also enjoys good finite-sample properties. Application of the new method to HALS for assessing how smoking affects memory decline over a 7-year period between study follow-ups shows that no effect

of smoking on memory decline within always-survivors can be detected from HLS data. *Conclusion:* It is very common that in both randomized and non-randomized clinical trials, the outcomes are truncated by death. Restricted analysis in observed survivors is subject to both selection bias and confounding bias. To deal with the selection bias, we propose to use a substitution variable for the latent survival type. To deal with the potential confounding bias, we propose to use propensity score methods. We show that under our assumptions our new non-parametric estimators are consistent estimators of SACE. Our analysis on HLS shows that smoking does not affect cognitive decline among always-survivors.

P1-5: EXPERIENCES AND PERSPECTIVES OF STUDY PARTNERS INVOLVED IN DEMENTIA RESEARCH. BETTY S BLACK[1], HOLLY A TAYLOR[2], PETER V RABINS[3], JASON KARLAWISH[4] *((1) Department of Psychiatry & Behavioral Sciences, Johns Hopkins School of Medicine and the Johns Hopkins Berman Institute of Bioethics, Baltimore, MD, USA; (2) Department of Health Policy & Management, Johns Hopkins School of Public Health and the Johns Hopkins Berman Institute of Bioethics, Baltimore, MD, USA; (3) Department of Psychiatry & Behavioral Sciences, Johns Hopkins School of Medicine and the Johns Hopkins Berman Institute of Bioethics, Baltimore, MD, USA; (4) Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA)*

Background: Clinical trials on Alzheimer disease and other dementias that include cognitively impaired participants usually require the involvement of a study partner. Typically, study partners are family members—most often spouses serving as informal caregivers—who know the participant well and can accompany the patient to study visits. Study partners usually participate in the decision to join the study and respond to questions about the patient participant throughout the trial. While researchers expect study partners to be knowledgeable informants, dependable and adherent to a study's protocol, little is known about the experiences of and any challenges faced by study partners who are needed for the successful conduct of dementia research. Determining why and how study partners enable research participation can inform participant recruitment and retention strategies. This prospective qualitative study examined the experiences and perspectives of caregivers involved in dementia research to understand their motivations, responsibilities, burdens and perceived benefits of serving as study partners. *Methods:* Semi-structured interviews were conducted with 62 study partners involved in 12 dementia studies at two academic research sites. The studies included 9 clinical trials, 2 natural history studies and 1 imaging study. Up to three interviews were completed with each study partner during their involvement in a dementia study, totaling 133 qualitative interviews. The audio-recorded interviews were transcribed verbatim; transcripts were verified; and textual data were coded, organized and analyzed to identify themes and sub-themes in the data. Demographic data were collected to describe the study sample. *Results:* The majority of study partners in this sample were white (91.9%), the patient's spouse/partner (80.7%), females (61.3%) and many (46.8%) were employed. On average, they were age 64.9 (±11.6; range 26-86) and had 16.6 (±3.3) years of education. Their primary motivations for joining research included seeking a direct benefit for the patient participant, contributing to scientific advancement (altruism), taking action to address the patient's illness, pursuing hope, or participating because of limited treatment options available for dementia. Responsibilities of study partners were often viewed within the context of their role as caregivers. Their tasks included being a proxy decision-maker, an advocate or comforter/encourager for the patient, scheduling and ensuring study visits, monitoring medication use and the patient's fasting, responding to study questions, providing feedback on the patient's status, dealing with adverse events and serving as a liaison to other family members and the patient's health care providers. While some study partners viewed their duties as adding no burden to their role as caregiver, others described a range of challenges. The most common burdens were the time commitments required for sometimes frequent and often long study visits, particularly when study procedures were delayed, and the travel time to study visits that involved dealing with heavy traffic in urban environments and associated expenses if long travel distances were required. Some partners were distressed by study questions that implied what the future may hold for the patient, by spending time in waiting areas with other dementia patients or by disappointment if study outcomes were not as they had hoped. Others struggled to get the patient to take the study drugs or to get dressed and ready for study visits on time. Navigating the study sites or managing the logistics of monitoring pill-taking, scheduling study visits or adhering to a protocol were burdensome for some partners. While some felt that research participation was of no benefit to the study partner, most identified ways in which they personally benefitted from the experience. The most common benefits noted for study partners were knowledge about the patient's illness, about dementia or about the research process and the emotional support or advice they received from the study team. Other benefits were positive feelings derived from the opportunity to be proactive in addressing the patient's illness, the opportunity to contribute to science and hope drawn from pursuing an effective treatment. *Conclusions:* This study demonstrates that study partners of participants in dementia research experience both challenges and rewards. Their role may be complex, burdensome and laden with hope; and it can add to the study partner's responsibilities as a caregiver. Rewards include obtaining information about dementia and the care of the participant. Investigators, institutional review boards and caregivers (as potential study partners) should be aware of the responsibilities, potential challenges and interests of study partners and recognize that some caregivers are unable to fulfill this role. Ensuring that study team members can provide some measure of caregiver education and support may help compensate study partners for their role in dementia research. Study partners should be recognized as legitimate stakeholders in the assessment of risks, burdens and benefits of research and in the development of recruitment and retention strategies.

P1-6: FUNDACIÓ ACE HEALTHY BRAIN INITIATIVE (FACEHBI): A LONGITUDINAL STUDY OF BIOMARKERS AND COGNITION IN INDIVIDUALS WITH SUBJECTIVE COGNITIVE DECLINE. O RODRÍGUEZ-GÓMEZ[1], A SANABRIA[1], A PÉREZ-CORDÓN[1], S RUIZ[1], M TARRAGONA[1], D SÁNCHEZ-RUÍZ[1], S MORENO-GRAU[1], J PAVÍA[2], F CAMPOS[2], A VIVAS[3], M GÓMEZ[3], M TEJERO[3], M ALEGRET[1], A ESPINOSA[1], G ORTEGA[1], C ABDELNOUR[1], M ROSENDE-ROCA[1], A MAULEÓN[1], L VARGAS[1], E MARTÍN[1], S VALERO[1], O SOTOLONGO-GRAU[1], A RUIZ[1], I HERNÁNDEZ[1], J GIMÉNEZ[3], F LOMEÑA[2], L TÁRRAGA[1], M. BOADA[1] *((1) Alzheimer Research Center and Memory Clinic, F ndació ACE, Institut Català de Neurociències Aplicades, Barcelona, Spain; (2) Servei de Medicina Nuclear, Hospital Clínic i Provincial. Barcelona, Spain; (3) Departament de Diagnòstic per la Imatge. Clínica Corachan, Barcelona, Spain)*

Background: The natural history of Alzheimer´s disease (AD) seems to begin some time before the onset of cognitive symptoms; during this preclinical phase, key pathophysiological features of AD can be shown through different biomarkers. Positron emission tomography (PET) with amyloid ligands such as florbetaben (FBB), is useful to detect the in vivo amyloid burden of the brain. Plasmatic levels of amyloid peptides could also be related to brain amyloidosis. Magnetic resonance imaging (MRI) allows detection of the brain

atrophy present in some individuals with preclinical AD and several studies have reported alterations in brain metabolites quantified through magnetic resonance spectroscopy. Moreover, a certain degree of disruption of white matter integrity measured by diffusion tensor imaging (DTI) has been reported in the preclinical phase of AD. Subjective Cognitive Decline (SCD) has been proposed as a marker of neurodegenerative pathology in cognitively normal subjects. This idea is supported by the growing evidence that SCD is associated with AD biomarkers and increases the risk of future cognitive impairment. Thus, including subjects with SCD in a cohort of individuals without objective cognitive impairment may enhance the prevalence of preclinical AD in the sample. SCD due to AD occurs in the later stages of the preclinical phase, when a subtle cognitive decline that does not reach the MCI threshold is likely to be present. New, more sensitive neuropsychological tests are required in order to detect these subtle cognitive changes. The recently developed Face Name Associative Memory Exam (FNAME) has rendered scores found to be correlated with amyloid burden in individuals without cognitive impairment. The present study, Fundació ACE Healthy Brain Initiative (FACEHBI), is a clinical trial (EUDRACT 2014-000798-38) embedded in a longitudinal study of cognition, biomarkers, risk factors and lifestyle designed to capture the cognitive changes and early pathophysiological events present in individuals with SCD due to AD. *Methods:* To conduct the FACEHBI trial, two hundred participants are to be recruited at Fundació ACE, Barcelona, Spain. The primary objective is to determine whether elevated basal levels of brain β-amyloid detected by PET-FBB are associated with a greater decrease in cognitive performance based on the FNAME score after two years of follow up. Inclusion criteria are: age >49 years; subjective cognitive complaints defined as a score of ≥ 8 on MFE-30, a Spanish validation of Memory Failures in Everyday Life questionnaire; MMSE ≥27; Clinical Dementia Rating=0; performance in a comprehensive neuropsychological battery Fundacio ACE Neuropsychological Battery (NBACE) within the normal range according to age and education; literate. Exclusion criteria are: evidence of impairment of daily living activities; relevant anxiety or depressive symptoms defined as a score of ≥11 on the Hospital Anxiety and Depression scale; any other psychiatric disease; severe auditory or visual abnormalities; known renal or liver failure; previous or current history of alcoholism or epilepsy. There will be 2 years of follow up with 3 visits: basal, intermediate (at 1 year) and final (at 2 years). At the basal and final visits all subjects are to undergo a complete physical and neurological examination, a comprehensive neuropsychological assessment with NBACE, Trail Making Test A and B, RBANS visual memory subtest, Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) vocabulary subtest, FNAME (Spanish version), Action Naming Test and Rule Shift Cards subtest of the Behavioral Assessment of the Dysexecutive Syndrome (BADS). Within 30 days of the neurological evaluation all individuals are to undergo FBB-PET (Neuraceq©) 80 minutes post injection of 300 Mbq of the radiotracer, a structural MRI including a T1-3D MPRAGE scan of 1x1x1 mm voxel definition for a later automatic segmentation and quantification, magnetic resonance spectroscopy, and DTI. Blood samples are to be collected for DNA banking and APOE genotyping. ABtest 40 and ABtest 42 of Araclon Biotech© will be used to quantify plasmatic amyloid Beta species. At the intermediate visit all subjects will undergo a complete physical and neurological examination and a neuropsychological assessment with NBACE. *Results:* FACEHBI has been registered as a clinical trial by the Spanish agency and received the approval of local ethics committee. Of note, following local ethics committee recommendation, PET amyloid results cannot be communicated to the SCD volunteers. Recruitment began in December 2014 and by April 2015, 70 participants had been enrolled and undergone all the basal visit procedures. Mean age of these participants was 65.8 (7.5) years and 43% were male. *Conclusions:* The identification of subjects with preclinical AD is becoming a research topic of major interest in order to develop clinical trials and secondary prevention strategies. SCD can be understood as an opportunity to identify individuals at high risk of developing cognitive impairment. FACEHBI is an ambitious longitudinal project intended to study risk factors, multimodal biomarkers and cognition in a sample of individuals with SCD. *Funding:* Funds from Fundació ACE. Institut Català de Neurociències Aplicades, Grifols ®, Piramal ® and Araclon Biotech® are supporting FACEHBI. *Keywords:* Subjective cognitive decline, Amyloid deposition, Amyloid PET, Neuroimaging, Biomarkers, Preclinical Alzheimer´s disease

P1-7: DEVELOPMENT OF A COGNITIVE SAFETY INDEX FOR MONITORING ADVERSE EVENTS IN INDIVIDUALS TAKING PART IN CLINICAL TRIALS OF ANTI-AMYLOID DRUGS. PAUL MARUFF, YEN YING LIM[1,2], PETER J SNYDER[2], VICTOR L VILLEMAGNE[1,6,7], DAVID AMES[8,9], CHRISTOPHER C ROWE[6,7], ROBERT PIETRZAK, COLIN L MASTERS[1] (*(1) The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, Victoria, Australia; (2) Department of Neurology, Warren Alpert School of Medicine of Brown University & Lifespan Hospital System, Providence, RI, USA; (3) Centre of Excellence for Alzheimer's Disease Research and Care, Edith Cowan University, Joondalup, Western Australia, Australia; (4) Sir James McCusker Alzheimer's Disease Research Unit, Hollywood Private Hospital, Perth, Western Australia, Australia; (5) Co-operative Research Centre for Mental Health, http://www.mentalhealthcrc.com; (6) Department of Nuclear Medicine and Centre for PET, Austin Health, Heidelberg, Victoria, Australia; (7) Department of Medicine, Austin Health, The University of Melbourne, Heidelberg, Victoria, Australia; (8) Academic Unit for Psychiatry of Old Age, St. Vincent's Health, The University of Melbourne, Kew, Victoria, Australia; (9) National Ageing Research Institute, Parkville, Victoria, Australia; (10)CogState Ltd., Melbourne, Victoria, Australia)*

Background: In clinical trials, the effectiveness and safety of drugs on the central nervous system (CNS) are often determined from comparing performance at the end of the trial between placebo and active treatment groups; that is at the level of the population. However it may be possible to utilize the presence of changes in cognitive function at the level of individual patients to assist with decisions about acute adverse events in clinical trials of disease modifying drugs in mild cognitive impairment (MCI) or early AD. The first aim of this study was to develop a method and analyses for identifying acutely meaningful cognitive decline in individual older adults by challenging them with drug known to cause acute and reversible cognitive decline The second aim was to determine the rate of the classification of meaningful cognitive decline in adults with MCI who were assessed repeatedly but who were not undergoing treatment with anti-amyloid drugs. *Methods:* To develop the rule for identifying meaningful cognitive decline a group of 30 healthy older adults completed a double blind parallel groups study of the effects of alprazolam 1mg (per oral,) where cognitive function was measured using the four tasks from the Cogstate brief battery (CBB) immediately before and one hour after drug administration. Acute cognitive change was defined initially as a change of >1.65 SD on two or more of the four tasks from the CBB. Proportions of classifications of abnormal change was compared between the alprazolam and placebo treatment conditions. To determine the extent to which the rule for acute cognitive change identified abnormal change in individuals with MCI, the rule was applied to data from 30 amyloid negative (AB-) cognitive normal adults (CN) 30 amyloid positive (AB+) adults with MCI who were in the Australian Imaging and Biomarkers (AIBL) rate of change sub-study (ROCS) where they had undergone assessment on the CBB at baseline and then five occasions over 12 months (baseline 3, 6, 9

& 12 months) and who remained medically healthy across the study period. The proportions of classifications of abnormal change using the rules developed in the first study were computed for the ROCs subjects. *Results:* At the group level, and relative to placebo, 1mg alprazolam induced a cognitive decline at hour of greater than 1 for the four CBB tasks (Detection d=1.2, Identification d = 1.2, One Back d =1.5 , One Card Learning d = 2). At the individual level significantly more ($p<0.01$) of the alprazolam group (86%) than of the placebo group (16%) were classified as showing acute cognitive change. At the group level performance on the CBB tasks did not change over 12 months in the NC group but did show significant decline on the One Back and One Card Learning tasks in the MCI group. At the individual level, one of the HC and none of MCI subjects were classified as showing acute cognitive change on at least one of the five post-baseline assessments. *Conclusions:* Cognitive decline of a meaningful levels can be detected acutely in older adults. Application of this same rule to older NC and MCI individuals who were not undergoing drug treatment assessed across multiple intervals showed the method and rule to have a high specificity. These data suggest that it is possible to use cognitive tests to monitor cognitive function acutely in individuals enrolled in clinical trials.

P1-8: 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: The SIMaMCI dementia prevention trial started in 2009 as a multicenter randomized controlled trial to test the hypothesis, that daily administration of 60 mg/d simvastatin for at least 2 years significantly reduces the progression rate to Alzheimer´s dementia in patients with amnestic MCI as compared to those receiving placebo. Epidemiological studies point to a link between cholesterol metabolism and the prevalence of dementia. Further, experiments in cell cultures and transgenic animals as well as exploratory clinical trials in patients with Alzheimer´s disease demonstrated that treatment with cholesterol-lowering 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 humans, especially in the very early stages of the disease; simvastatin was chosen because of its generally excellent tolerability. *Methods:* Patients with a diagnosis of amnestic mild cognitive impairment are recruited in 16 memory clinics in Germany based on scoring in the CERAD (Consortium to Establish a Registry for Alzheimer`s Disease) neuropsychological test battery and CDR (Clinical dementia rating). Basic activities of daily living must be normal and general cognitive function other than memory impairment must be preserved. Presence of overt neurodegenerative diseases (e.g. Parkinson's disease) or disorders where cognitive impairment is regularly part of the syndrome (e.g. major depression) and current or previous use of antidementia drugs were excluded. As primary efficacy endpoint the change in CDR-SOB at 24 months of treatment is chosen. Key secondary endpoint(s) are: 1. Change in ADAS-Cog and FCSRT score; 2. Length of conversion-free interval, starting at the time of randomization, with conversion being defined as an increase of the CDR score beyond 0.5 3. Change in ADCS-ADL score 4. Change in volumetric brain measures (structural MRI) 5. Changes in CSF and blood measures of beta-amyloid peptides, total and phosphorylized TAU proteins. *Results:* 260 amnestic MCI patients fulfilling in- and exclusion criteria have been randomized to the SIMaMCI prevention trial so far. Since the start of the study in 2009, prescription of cholesterol lowering drugs, especially statins, has increased substantially in Germany (>200%) therefore the recruitment of "statin-naïve" patients to the trial as required by the original protocol became increasingly difficult. Hence, we recently amended the trial to also enrol additionally a second cohort of 260 patients, who were included if they had received no more than 20 mgs of simvastatin for no more than 2 years (low statin group); they were than randomized to either stay on this dose (placebo-controlled) or to receive 60 mgs of simvastatin. This was done because several findings from clinical and preclinical trials support the reasoning that only high doses of statins have an effect on cognition in early, prodromal stages of dementia. While the recruitment of the original "no-statins" group was completed in spring of 2015, it was decided to postpone the analysis of results in favour of collecting new data from the "low-statins" cohort, which better reflects the current population with respect to intake of cholesterol-lowering drugs. *Conclusion:* This pragmatic change of protocol will not only provide information about the potential of simvastatin to prevent the transgression of MCI patients to Alzheimer's disease but will generate additional data on dose-effect relationship.

P1-9: ANALYSING TIME TO EVENT DATA IN DEMENTIA PREVENTION TRIALS: THE EXAMPLE OF THE GUIDAGE STUDY OF EGB761®. B SCHERRER[1], S ANDRIEU[2,3,4,5], PJ OUSSET[2,3,4], G BERRUT[1], JF DARTIGUES[7], B DUBOIS[8], F PASQUIER[9], F PIETTE[10], P ROBERT[11], J TOUCHON[12], P GARNIER[13], H MATHIEX-FORTUNET[13], B VELLAS[2,3,4] AND THE GUIDAGE STUDY GROUP* *((1) Bruno Scherrer Conseil, Saint-Arnoult en Yvelines, France; (2) INSERM, U1027, F-31073 Toulouse, France; (3) University of Toulouse III, F-31073, Toulouse, France; (4) Gerontopole, Toulouse University Hospital, Toulouse, France; (5) Department of Epidemiology and Public Health, Toulouse University Hospital, Toulouse, France; (6) Clinical Gerontology Department, Nantes University Hospital, Nantes, France; (7) INSERM U897, University of Bordeaux II, Bordeaux, France; (8) Department of Neurology and Alzheimer Institute, Salpetrière University Hospital, Paris, France; (9) University Lille Nord de France, UDSL EA1046, Centre Hospitalier Universitaire, Lille, France; (10) Gerontology Department, Charles Foix Hospital, Pierre and Marie Curie University, Ivry-sur-Seine, France; (11) Memory Center–EA CoBTeK Centre Hospitalier Universitaire, University of Nice Sophia Antipolis, Nice, France; (12) Neurology Department, INSERM U1061, Montpellier University Hospital, Montpellier, France; (13) Ipsen, Boulogne, France*

Rationale: Time-to-event analysis is frequently used in medical research to investigate potential disease-modifying treatments in neurodegenerative diseases. Potential treatment effects are generally evaluated using the logrank test, which has optimal power and sensitivity when the treatment effect (hazard ratio) is constant over time. However, there is generally no prior information as to how the hazard ratio for the event of interest actually evolves. In these cases, the logrank test is not necessarily the most appropriate to use. When the hazard ratio is expected to decrease or increase over time, alternative statistical tests such as the Fleming-Harrington test, provide a better sensitivity. *Method:* An example of this comes from a large, five-year randomised, placebo-controlled prevention trial (GuidAge) in 2854 community-based subjects making spontaneous memory complaints to their family physicians, which evaluated whether treatment with EGb761® can modify the risk of developing AD. The primary outcome measure was the time to conversion from memory complaint to Alzheimer's type dementia (Figure 1). Although there was no significant difference in the hazard function of conversion between the two treatment groups according to the preplanned logrank test, a significant treatment-by-time interaction for the incidence of AD was observed in a protocol-specified analysis, suggesting that the hazard ratio is not constant over time. For this reason, additional

post hoc analyses were performed using the Fleming-Harrington test to evaluate whether there was a signal of a late effect of EGb761®. *Results:* Applying the Fleming-Harrington test, the hazard function for conversion to dementia in the placebo group was significantly different from that in the EGb761® treatment group (p = 0.0054), suggesting a late effect of EGb761®. Since this was a post hoc analysis, no definitive conclusions can be drawn as to the effectiveness of the treatment. *Conclusion:* This post hoc analysis illustrates the interest of performing another randomised clinical trial of EGb761® explicitly testing the hypothesis of a late treatment effect, as well as of using of better adapted statistical approaches for long term preventive trials when it is expected that prevention cannot have an immediate effect but rather a delayed effect that increases over time.

P1-10: INFLAMMATORY MARKERS IN ALZHEIMER'S DISEASE WITH VARIOUS DEGREES OF DEMENTIA SEVERITY. TATYANA KLYUSHNIK, LYUBOV ANDROSOVA, NATALIA MIKHAYLOVA, SVETLANA ZOZULYA, ALEXANDER DUPIN, SVETLANA GAVRILOVA *(FSGI "The Mental Health Research Centre", Moscow, Russia)*

Background: There is much evidence, suggesting an important role for systemic inflammation in the pathogenesis of Alzheimer's disease and a close connection between systemic and central innate immune systems. The main objective of the study was to investigate the peripheral inflammatory immune responses in various degrees of dementia severity (mild, moderate, severe). Material and methods The activity of human leukocyte elastase (LE), α1-proteinase inhibitor (α1-PI), the level of IL-6 and C-reactive protein (CRP) were determined in plasma of 75 AD patients and 39 healthy controls. Alzheimer's disease was diagnosed according to the ICD-10 and NINCDS-ADRDA criteria. The severity of dementia was determined by using the clinical method, applying Clinical Dementia Rating (CDR) and MMSE scores. The patients were examined at various stages of dementia (19 subjects with mild dementia, 30 subjects with moderate dementia, and 26 patients with p severe dementia). *Results:* The LE activity was significantly lower in the total group of AD patients ($p<0.0001$), but the activity of α1-PI, level of IL-6 and CRP were significantly higher as compared with the controls ($p<0.00001$, $p<0.01$, $p=0.05$, accordingly). Patients with mild AD were only characterized by a significant increase of α1-PI activity. The reduced LE activity and increased activity of α1-PI, level of IL-6 were revealed in moderate dementia. The reduced LE activity and increased activity of α1-PI, level of IL-6 and concentration of CRP, were revealed in severe dementia. LE activity positively correlated with the total score of evaluation of cognitive functions according to the MMSE ($r=0.28$, $p=0.017$). Direct correlation between the disease severity and IL-6 and CRP levels ($r=0.25$, $p=0.036$, $r=0.24$, $p=0.046$, correspondingly) was revealed. *Conclusion:* Thus inflammatory mechanisms are involved in the progression of the disease: α1-PI increased functional activity is only noticed in mild dementia, while in moderate and severe dementias LE reduced activity and increased activity/level of α1-PI, IL-6, and CRP are detected. *Key words:* Alzheimer's disease; dementia severity; inflammatory markers; leukocyte elastase

P1-11: STATISTICAL PROPERTIES OF COMPOSITE SCALES. HONG LIU-SEIFERT[1], SCOTT ANDERSEN[1], MICHAEL CASE[1], JONDAVID SPARKS[1], SUZANNE HENDRIX[2], PAUL AISEN[3], ERIC SIEMERS[1] *((1) Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA; (2) Pentara Corporation, Salt Lake City, UT, USA; (3) Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, CA, USA)*

Background: Composite outcome measures have been used more frequently in clinical trials, especially composites that combine multiple clinical events. These composite measures have been studied extensively and have been shown to capture the net benefit of the investigative treatment and potentially increase study efficiency in detecting treatment effects, but could also lead to challenges in interpretation and potential diluting of the true underlying treatment effect. Another type of composite measures, which combines continuous outcome measures of several component items or subscales, has also received recent attention in the Alzheimer's disease (AD) area due to the need to develop new outcome scales, especially for patients with earlier stages of the disease. However, there has been little literature on these continuous composite scales regarding their performances relative to the individual components. In this study, we evaluate the statistical properties of continuous composite scales and how they are impacted by the individual components. For illustration purposes, we focus on a composite of a simple summation of two normally distributed individual scales, X+Y. The approach and implications of this study can be applied to more general forms of composites involving weights and multiple components. *Methods:* We derived the mathematical expressions for the effect size of the composite X+Y, ES(X+Y), in terms of the effect sizes of the components, ES(X) and ES(Y). The effect size is defined as the treatment difference divided by the standard deviation. The statistical properties of the composite X+Y are proven based on these expressions. Two case studies are included to demonstrate the properties using real-world randomized controlled trials. The first is the solanezumab studies EXPEDITION/2 with mild AD subpopulation, and the second is the Donepezil+Vitamin E study. In both case studies, we compare the performance of two scales, Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-cog) and ADCS instrumental Activities of Daily Living (ADCS-iADL), to the composite ADAS-cog+ADCS-iADL (for simple notation; adjustments are made for the differential directions of the two scales that comprise the composite). *Results:* Based on the mathematical derivation of the effect size of X+Y, ES(X+Y) is greater than the smaller of ES(X) and ES(Y). Further, ES(X+Y) may or may not outperform the larger of ES(X) and ES(Y), depending on the relative magnitude of ES(X) and ES(Y), the variances and correlation of the two components. For any given correlation of X and Y, a specific threshold for the relative magnitude of ES(X) and ES(Y) can be calculated to determine if ES(X+Y) is greater than the maximum of ES(X) and ES(Y). The case studies confirm these statistical properties. Various examples within the case studies representing different scenarios are presented. *Conclusion:* To our knowledge, this is the first time the treatment effect of a continuous composite X+Y has been expressed relative to the individual components mathematically. Regarding power to detect treatment difference, the composite always outperforms the component with the lower effect size. In the situation where both scales X and Y are required to have statistical significance, this implies the composite X+Y provides greater power than the co-primaries. Furthermore, the composite may or may not have better power than the component with greater effect size depending on the components' variances and correlation and relative magnitudes of the treatment effects of the components. This finding is intuitive in that the power of the composite is strengthened when the components all contribute with consistent treatment effects. Similar conclusions have been made regarding composites that include discrete clinical events, such as death and/or hospitalization. Numerous publications have pointed out that composites may dilute the treatment effect when some of the components/events have considerably different treatment effects. In such instances, combining the components into one composite may also create challenges for clinical and regulatory interpretation. Besides the treatment effect of a composite, the mathematical derivations and discussions in this study can also be applied to the concept of signal-to-noise ratio of a composite in relation to its components. In the field of AD where much interest

and research centers on developing new primary endpoints, better understanding of the properties of composites as illustrated in this study will provide guidance for future development of new scales. Of particular significance, these findings can be applicable to fields other than AD. Mathematical expressions of ES(X+Y) in terms of ES(X) and ES(Y). Let SD(X) and SD(Y) be the standard deviations of X and Y, respectively, and r = (SD(Y))/(SD(X)). Let ϱi be the correlation between X and Y in treatment i, i=1, 2. Assume ϱi 0. Then it can be derived that ES(X+Y) = (ES(X)+ rES(Y))/√(1+r²+r(ϱ1+ϱ2))

P1-12: APPLICATION OF NEUROCIRCUITRY-BASED ASSESSMENTS USING EEG/ERP AND FMRI TO ASSESS NOVEL MOLECULES IN EARLY PHASE CLINICAL DEVELOPMENT FOR BEHAVIOURAL AND PSYCHIATRIC SYMPTOMS ASSOCIATED WITH DEMENTIA. BRETT A ENGLISH[1,2], JACK JOHNSTONE[3], ALEX KORB[4], LEV GERTSIK[5], LOVINGLY Q PARK[5], NIKI OSIMO[1], LARRY ERESHEFSKY[1,6] *((1) PAREXEL International Glendale, CA; (2) Dept. of Pharmacology, Vanderbilt University Medical Center, Nashville, TN; (3) Q-Metrix, Glendale, CA; (4) Department of Psychiatry, University of California, Los Angeles; (5) California Clinical Trials Medical Group, Glendale, CA; (6) University of Texas College of Pharmacy, Austin, TX; Glendale, CA. 91206)*

Background: Pharmaceutical research into Alzheimer's disease (AD) and related dementias has largely focused on development of novel molecules that alter the neuropathology, enhance cholinergic neurotransmission or modulate glutamate. These treatments target primarily cognitive symptoms associated with the disease. However, AD is also associated with a number of behavioral and psychological symptoms (BPSD) associated with higher rates of institutional care and a more rapid cognitive decline (1). These neuropsychiatric symptoms of AD include psychosis, agitation, apathy, anhedonia, depression, sleep disturbances; are typically persistent, fluctuate with the stage of the illness, and are often resistant to 'standard therapies' which work in psychiatric populations (2,3,4). Second generation antipsychotics (SGAs), despite explicit regulatory warnings, are currently the most commonly used medications to treat BPSD. However safety issues and a lack of clear benefit over risk, i.e., cerebrovascular events and death, underscore the need for novel molecules now in development to manage these problems.5 For BPSD, methodologies to accelerate the screening of promising drug candidates in smaller populations of patients, and potentially in non-dementia volunteers is critically needed. Recently, the National Institutes of Mental Health (NIMH) introduced a research framework, Research Domain Criteria (RDoC), for studying mental disorders drawing upon recent developments in neuroscience and technologies that permit the characterization of the effects of novel molecules on neurocircuitry of relevance for specific domains of function and symptoms (6). We suggest that the application of an RDoC-based strategy in early phase clinical development is applicable for AD and other neurodegenerative disorders, and can be built on the same assumptions as in psychiatry, i.e., dysfunction in neural circuits can be measured by electrophysiology (quantitative, qEEG; event related potentials ERP) and functional neuroimaging (fMRI). We illustrate the use of technologies and methodologies employed during Phase 1 (Ph1) clinical development that may aid in characterizing effects of novel molecules on neurocircuits associated with phenotypes (ex. Apathy, psychosis) of relevance to BPSD. *Methods:* The study implementation of EEG and fMRI paradigms was conducted in 2 separate subject Cohorts conducted at the PAREXEL Early Phase unit in Los Angeles. Subject Cohort 1 consisted of patients with stable, chronic schizophrenia receiving clinically stable doses of SGAs for at least 1 month. Cohort 1 was further subdivided into subgroups consisting of those who remained on their SGA (Group A, n=25) or were washed out of their medications for at least 5 half-lives (Group B, n=18) prior to baseline qEEG recordings. Resting state EEG was recorded for 10 minutes with eyes closed using 19-scalp electrodes. Signals were digitized and manually reviewed for artifacts that were removed prior to power spectral analysis. Frequency ranges included were: delta (1-4Hz), theta (4-8Hz), alpha1 (8-10Hz), alpha (10-12Hz), beta1(12-15Hz), beta2(15-18Hz), beta3(18-25hz), high beta (25-30Hz), gamma1 (30-35hz), gamma2 (35-40Hz) and high gamma (40-50Hz). To investigate circuitry associated with reward processing and motivation, potentially two constructs contributing to apathy and depressive symptoms in dementia, we used the monetary incentive delay (MID) task in the fMRI which measures anticipation and consumption of reward incentives by use of rapid presentation stimuli (anticipation) followed by feedback contingencies (ie. performance) (outcome).7 Subject Cohort 2 consisted of male, right handed healthy normal volunteers (HNVs, n=10) between 18-50 years of age. After providing written informed consent, subjects underwent MRI safety screening and were trained on the monetary incentive delay task (MID).7 Using their dominant hand, subjects were presented 3 shapes and instructed to respond as quickly as they could to gain or avoid losing money.8 fMRI data was collected on a Siemens 3T Skyra MRI using a 32-channel head coil. Each subject underwent sagittal T2-weighted, three-dimensional (3D), non-contrast enhanced, echo planar imaging (EPI) sequence measuring changes in the blood oxygen level dependent (BOLD) contrast with the following acquisition parameters: 3x3x3.2mm resolution, repetition time (TE) 750ms, echo time (TE) 30ms, flip angle 52deg, # of slices 44. Behavioral data for participant performance was also recorded. *Results:* For Subject Cohort 1, preliminary t-tests were computed to evaluate possible group differences at baseline between patients who were washed-out of their antipsychotic vs patients who continued to take their usual SGA medication. There were a number of statistically significant differences in EEG frequency ranges between medicated and the medication washed out patients. The largest differences were seen in the alpha1 (t=3.14, df=33, P<0.01) and theta (t=3.04, df=34, p<0.01) frequency ranges at the anterior and posterior temporal regions bilaterally. These differences were due to higher amplitudes in the alpha1 and theta frequency ranges in the patients on SGAs. In contrast, higher beta activity was observed in the frontocentral leads for those patients off of SGAs. *Conclusions:* A neurocircuitry-based approach that utilizes technologies such as EEG/ERP and fMRI can improve our understanding of novel CNS compounds in early phase clinical development. Quantitative EEG and reward-related fMRI tasks such as the MID are examples of circuitry based assessments that can be readily employed during Phase 1 studies in healthy volunteers, healthy elderly and in patients with dementia to aid in the characterization of novel compounds targeting BPSD. In our pilot work, there were different baseline qEEG frequencies between patients receiving SGAs vs those who were washed out of their antipsychotic. Recognizing the qEEG differences in patients with behavioral issues receiving antipsychotics may aid in characterizing novel molecules in future studies with dementia patients. Similarly, our HNVs exhibited significantly significant increased BOLD signal in the left ventral striatum (p<0.05, 2-tailed; cluster corrected) when comparing "hits" (gains) vs "misses" (loss), consistent with reports in the literature. Applying the MID task to patients with MCI and milder dementia could be part of a more comprehensive neurocircuitry and behavioral characterization of apathy/anhedonia patient populations. *Disclosures:* BAE, NO, and LE are employees of PAREXEL International that receives financial compensation from numerous pharmaceutical companies for the conduction of clinical trials. 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P1-13: ENHANCING CLINICAL TRIAL RECRUITMENT IN ALZHEIMER'S DISEASE RESEARCH THROUGH MOBILE CLINICAL TRIAL UNIT. JILL SMITH, AMANDA SMITH, DAVE MORGAN *(USF Health Byrd Alzheimer's Institute, University of South Florida, Tampa FL 33613 USA)*

Background: There are presently no long lasting disease-modifying treatments for Alzheimer's disease. Clinical trials for Alzheimer's disease presently involve long enrollment 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 on the 5, 6 and 7 of 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. This unit will offer potential benefits including: A) increasing the availability of clinical trials to Florida's older adults, B) taking advantage of the superb clinical diagnosis provided by MDCs for clinical trial recruitment and C) increasing the number of clinical trial participants evaluated by the same individuals. This mobile unit could travel to retirement communities, neighborhoods and/or MDCs that lack established clinical trial facilities to conduct clinical drug trial research. In addition to facilitating enrollment, the increased accessibility may increase retention by enhancing access. 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. Since the workshop, the USF Health Byrd Alzheimer's Institute research team and administration has continued to discuss this opportunity with individuals throughout the clinical trials industry, as well as potential communities who are very eager to have a reputable, university-based research group come to their area. *Results:* Our facility has acquired funding from the State of Florida in July 2015. As of September 2015, the design specifications for the unit were sent out for bid by potential manufacturing companies. Manufacturing is expected to begin in Fall 2015 be completed shortly after new year. The current 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. Mobile unit will include 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 equal activity in a minimum of 5 clinical research centers. It also offers 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 capability on this mobile unit for a clinical trial to be 75-100 participants, in phased enrollment across multiple locations over a period of time. 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, FL as well as Orlando, FL which offers a high concentration of Hispanic Americans.

P1-14: A METHODOLOGY FOR EVALUATING CLINICAL TRIAL SITES AND RATERS BASED ON PERFORMANCE DATA. D MILLER, T FEASTER, S ALLEN, H GRATKOWSKI, 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. In this study, a methodology was developed to evaluate historical experience and clinical outcome administration performance data as a mechanism to enhance site and rater selection. *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." Once sites were categorized, a clinical review was conducted of the data and rankings based on experience with sites and raters as well as overall performance. Sites in the "Recommended" category were those that had overall positive scores contributing and were in the top 56% of sites evaluated. Sites in the "Moderately Recommended" group had lesser positive weighting and contributed to 40%. Sites in the "Not Recommended" category had scores that were in the lower 5% of sites. *Results:* Data were evaluated for 13,600 unique raters covering 2,195 research sites in 49 countries and across 21 different clinical trials. Certification and experience data were evaluated for every rater. Performance data included 27,277 scale administrations resulting in 10,188 rater contacts for potential quality assurance issues. Of those issues that required contact with the site rater, 4,352 resulted in a remediation (re-training or targeted review of potentially problematic data). Sites and raters were required to complete a minimum number of trials and ratings to be weighted and evaluated. A total of 2,198 sites were given a final classification based on those criteria. 1,223 (56%) were classified as "Recommended", 873

(40%) were classified as "Moderately Recommended", and 102 (5%) were classified as "Not Recommended." From the pool of evaluated sites, one site that was classified as "Not Recommended" was included in the trial. 77 sites classified as "Recommended" were selected, and 20 sites classified as "Moderately Recommended" were selected. 25 sites that were not previously evaluated were also selected. *Conclusions:* CNS clinical trials almost always rely on subjective, clinician-rated outcomes as primary endpoints. The importance of training those raters and monitoring their subsequent performance is well understood. Systematic tracking and evaluation of experience and performance data is routinely utilized to assist in clinical trial site feasibility processes. This data frequently relies heavily on past patient recruitment and site data monitoring outcomes, and rarely proactively references past clinical ratings performance data. Utilizing this data may be useful in identifying the highest quality clinical trial sites and raters to conduct future research programs. *Disclosures:* This poster is financially supported by Bracket. The authors report no conflicts of interest for this work.

P1-15: EFFICIENCY OF TELEPHONE PRESCREENING FOR THE A4 TRIAL. KRISTINE LIPOWSKI[1], OKKES KUYBU[1], CARLY OBOUDIYAT[1], RAJ C SHAH[2], NEELUM T AGGARWAL[2], SANDRA WEINTRAUB[1] *((1) Northwestern University Cognitive Neurology and Alzheimer's Disease Center, Chicago, IL; (2) Rush Alzheimer's Disease Center, Chicago, IL)*

Background: The screening process for clinical trials is the essential first step to ensure fidelity of the results of the trial. This process, however, is time-consuming and expensive. The Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease Trial (A4 Trial) is a landmark effort to prevent the cognitive decline associated with amyloid accumulation in the brain, a risk for dementia of the Alzheimer type. This trial has stringent inclusion/exclusion criteria, which can result in many screen fails during the 5 in-person screening visits conducted for this study. *Methods:* Two Chicago study sites, one at Northwestern University and one at Rush University, developed a pre-screening telephone questionnaire to identify those who might fail in-person study screening. The questionnaire focused on potential participants who had contacted our centers after learning of the A4 trial via a variety of sources. They were contacted over the phone prior to an on-site visit and were asked 34 questions covering inclusion/exclusion criteria for the trial. *Results:* From August 2014 through August 2015, 81 telephone pre-screens were conducted at Northwestern and 30 at Rush. Of the 81 Northwestern individuals screened, 25 were male (31%) and 56 (61%) were female. The average age of the sample was 71.5 years (71 years for males, 72 for females). The majority of our sample, 73 individuals, was Caucasian (90%), 4 were Hispanic (5%), and 4 were African-American (5%). The screening resulted in the exclusion of 26 participants (32%). Telephone screen fails were subdivided by reason for failure, which included logistical problems (i.e. unwillingness to undergo infusions, no study partner), the presence of exclusionary medical conditions, and inability to undergo study procedures, for example, MRI ineligible due to metal. Half of those excluded by the phone screen were excluded by a single criterion, while the other half were excluded for multiple reasons. We calculated that the exclusion of 26 participants who may have otherwise been scheduled for an on site visit resulted in savings of approximately 104 hours of staff time, and at least $19,500 dollars for screen study costs. Data from Rush will be analyzed in the similar manner to highlight similarities and differences in findings and will also be presented. *Conclusions:* A relatively brief telephone screening questionnaire was useful in eliminating 32% of potential participants for the A4 clinical trial who would have failed the first in-person screening visit. This method can save staff time, reduce costs and prevent unnecessary visits of participants likely to fail screening at a later time.

P1-16: ASSESSING ELIGIBILITY FOR PRODROMAL AND PRECLINICAL AD TRIALS USING THE LUMOSITY BRAIN PERFORMANCE TEST AND THE BRAIN HEALTH REGISTRY. RACHEL L NOSHENY[1], DEREK FLENNIKEN[1], PHILIP S INSEL[1], R SCOTT MACKIN[1,2], SHANNON FINLEY[1], MONICA CAMACHO[1], DIANA TURAN[1], GLENN MORRISON[3], NG NICOLE[3], DANIEL STERNBERG[3], MICHAEL W WEINER[1,4] *((1) Center for Imaging of Neurodegenerative Diseases, San Francisco Veteran's Administration Medical Center, San Francisco, CA; (2) UCSF Department of Psychiatry, San Francisco, CA; (3) Lumos Labs. Inc. San Francisco, CA; (4) UCSF Department of Radiology and Biomedical Imaging, San Francisco, CA)*

Background: The high cost of recruiting, screening, and longitudinally monitoring participants for Alzheimer's disease (AD) clinical trial is a major obstacle to developing effective treatments. Many AD clinical trials target cognitively-normal older adults at risk for AD or those with prodromal AD, two groups that are especially difficult to identify and recruit because they are often not treatment-seeking. The Brain Health Registry (BHR) is an internet-based registry designed to reduce costs and accelerate completion of clinical trials for AD by facilitating recruitment and screening. *Methods:* After registration and online consent, BHR participants complete health and lifestyle questionnaires and neuropsychological tests (NPTs), including the Lumosity Brain Performance Test (BPT), online with no supervision. Receiver operator curve analysis using a longer, 8-item BPT was previously found to discriminate self-reported MCI (AUC=0.745) and self-reported AD (AUC=0.8824) from cognitively-normal participants in a large cohort of older adults. We analyzed the eligibility of BHR participants, both nationally and within the San Francisco Bay Area (SFBA), for prodromal and preclinical AD clinical trials based on multiple inclusion and exclusion criteria. Inclusion criteria included age, BPT scores, and self-reported memory concerns. Exclusion criteria included history of neurological disease and other medical condition, recent drug or alcohol abuse, and use of anti-AD or antipsychotic medications. We hierarchically applied a set of lax and strict criteria to determine the differential effects of criteria on the size of the potential participant pool. We also considered the effect on cohort size of applying option enrichment criteria such as a family history of AD and the ability to identify someone who could serve as a study partner. Receiver operator curves (ROC) were used to assess the accuracy of an 8-item BPT to distinguish self-reported. *Results:* The BHR has over 26,000 subjects, with 33% residing in the SFBA. The average age is 57±14.6 years; 59% of participants (n=15,426) are age 55 and over. Two percent of older adults report having AD or another form of dementia, 76% report a first degree relative with AD, and 45% endorse a memory problem. To date 49% of participants have returned for 6-month follow-up, and 37% have returned for one-year follow up. Ninety-six percent of older adult participants agree to be contacted for future studies, and 66% indicated that they have someone who can serve as a study partner for future studies. Over 13,567 participants have taken the BPT at baseline, and 4341 have longitudinal BPT scores. Depending on whether lax or strict exclusion criteria were used, between 56-87% percent of participants over age 55 passed a mock AD clinical trial screening process that excludes those with medical conditions, recent drug or alcohol abuse, and use of anti-AD and antipsychotic medications. In the general older adult BHR cohort, as well as in the SFBA cohort, a large number of participants can be identified whose BPT scores and self-reported memory concerns make them good candidates for prodromal and preclinical AD studies. *Conclusion:* The BHR cohort contains a significant number of participants who would be eligible for prodromal and preclinical AD trials, including a large cohort residing

in the SFBA. Hierarchical application of inclusion, exclusion, and enrichment criteria identifies the impact of specific criteria on the size of the potential subject pool for clinical studies. In the future, criteria can be differentially applied to recruit for specific trials and minimize screen fail rates. This data demonstrates the feasibility of using an internet-based registry, the Brain Health Registry, to identify and recruit participants for AD clinical trials.

P1-17: DEVELOPMENT OF AD CLINICAL RESEARCH: EXAMPLE OF THE NORTH OF FRANCE MEMORY CLINICS NETWORK "MEOTIS3RC". CATHERINE ADNET-BONTE[1], LAETITIA BREUILH[2,3], FLORENCE PASQUIER[2,3] *((1) Meotis, Centre Hospitalier Regional Universitaire de Lille, France; (2) Neurology Department, Centre Hospitalier Regional Universitaire de Lille, France; (3) Excellence Laboratory DISTALZ)*

Background: Settled in the French region Nord-Pas-de-Calais, the Lille Resources and Research Memory Centre (RRMC) was founded in 1991. Headed by Professor Florence Pasquier, its multidisciplinary team performs a wide range of activities including clinical research. It is one of the three most active clinics in France. It develops translational research and is currently involved in 20 academic clinical studies and 8 clinical trials (phases 2 or 3) of innovative treatments or new radiotracers sponsored by pharmaceutical companies. More than 500 patients are included in a study: 70 in an industrial trial and 440 in an academic study. Since 1995, the RRMC currently coordinates a network of 24 memory clinics throughout the region, with the precious help of the Meotis team which is a hospital-private office network created in 2002 (http://www.meotis.fr/). This network uses standardized procedures for diagnosis and follow-up and keeps up-to-date a database recording patients' medical profiles, allowing statistical analysis as well as clinical research feasibilities. Among the 4 millions inhabitants living in this region, around 7 000 patients have been diagnosed with Alzheimer's disease (AD), but only 15% of them receive care in the RRMC and thus have access to clinical trials. The RRMC communicates regularly with the Memory Clinics network about its clinical research activities and some centres have been invited to participate in some academic clinical studies. Despite their motivation and their patients' active lists, several centres failed in the recruitment process mainly due to lack of medical time, lack of nurse time, logistical issues and inefficient patients identification process. *Methods:* In order to facilitate access to clinical research for all AD patients of the region, we created in August 2013 a professional mobile clinical research team which is dedicated to the development of clinical research activities in all interested memory clinics of the network. This AD experimented team involves 1 neurologist and 3 study nurses who have been trained by RRMC staff on all clinical trials related aspects. Their actions include prescreening, information to the patients and their carers, scheduling, support during screening, baseline and follow-up visits, CRF and/or eCRF data entry... Moreover, the team offers the possibility for home visits. In parallel, Meotis3RC is implied in global awareness and training actions about clinical research for patients and carers, general public and healthcare professionals. *Results:* To date, Meotis team provides its services in 8 investigator sites of the region which are implied in 2 academic interventional studies: - COVARAD (NCT01423396) which is funded by the French Clinical Research Hospital Program; - NILVAD (NCT02017340), a FP7 project funded by European Commission. In only 22 months, 8 sites benefitted from this support, 56 patients have been successfully enrolled in the 2 studies. We also noticed empowerment of several investigator sites. In 2014, Meotis team met 15 other regional Memory Clinics in order to extend this regional clinical research network, now called «Meotis3RC». These new investigator sites have been trained for Good Clinical Practise and will be soon involved in clinical studies with the precious support of the mobile team. Moreover, the regular meetings with the Memory Clinics' staffs are key moments to disseminate new concepts in AD research such as clinical trials targeting presymptomatic patients (memory complaints, MCI) or asymptomatic persons. Finally, awareness among professionals raised in turn awareness among patients and their carers. As a result, motivated patients from all over the region have been referred to the RRMC for complex clinical trials. *Conclusion:* The recruitment results exceeded our expectations for the first years of operation and it is clear that the mobile team is a driving force for clinical research in our region. This AD clinical research network and its mobile team are operational for pharmaceutical companies sponsored clinical trials, allowing faster and better recruitment. With around 2200 MCI patients followed in the Meotis3RC network in 2014, they will be key actors for coming clinical trials.

P1-18: EFFECTS OF MULTIMODAL COGNITIVE ENHANCEMENT THERAPY (MCET) FOR PEOPLE WITH MILD COGNITIVE IMPAIRMENT AND EARLY STAGE DEMENTIA: A RANDOMIZED, CONTROLLED, DOUBLE-BLIND, CROSS-OVER TRIAL. JI WON HAN[1], HYEONGGON LEE[2], JONG WOO HONG[1], KAYOUNG KIM[1], TAE HYUN KIM[1], HYE JIN BYUN[1], JI WON KO[1], JONG CHUL YOON[3], SEUNG-HO RYU[4], NAM-JIN LEE[5], KI WOONG KIM[1,6,7] *((1) Department of Neuropsychiatry, Seoul National University Bundang Hospital, Seongnam, Korea; (2) Department of Neuropsychiatry, Seoul National University Hospital, Seoul, Korea; (3) Department of Neuropsychiatry, Kyunggi Provincial Hospital for the Elderly, Yongin, Korea; (4) Department of Psychiatry, School of Medicine, Konkuk University, Konkuk University Medical Center, Seoul, Korea; (5) Department of Psychiatry, Jeonju City Welfare Hospital for the Elderly, Jeonju, Korea; (6) Department of Brain and Cognitive Science, Seoul National University College of Natural Sciences, Seoul, Korea; (7) Department of Psychiatry, Seoul National University College of Medicine, Seoul, Korea)*

Backgrounds: There are many nonpharmacological interventions proven to be effective in improving cognition, behaviors or function of dementia patients. We developed the Multimodal Cognitive Enhancement Therapy (MCET) that consists of cognitive trainings, cognitive stimulations, reality orientation, physical therapy, reminiscence therapy, and music therapy, and evaluated its' efficacy. *Methods:* This study was a multi-center, double-blind, randomized, placebo-controlled, two-period cross-over study (8 weeks of treatment separated by one wash-out period of 4 weeks). Sixty four participants with mild cognitive impairment (MCI) or dementia whose Clinical Dementia Rating (CDR) was 0.5 or 1 were allocated to the active therapy (MCET) group or the placebo (mock-therapy) group, and 55 completed the study. Diagnoses of MCI and dementia were made according to the International Working Group on MCI criteria and the Diagnostic and Statistical manual of Mental Disorders, 4th Edition (DSM-IV) criteria, respectively. Primary outcome measures were the Mini Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog). Secondary outcome measures were the Subjective Memory Complaints Questionnaire (SMCQ), Revised Memory and Behavior Problems Checklist (RMBPC), Geriatric Depression Scale (GDS), Disability Assessment for Dementia (DAD) and Quality of Life-Alzheimer's Disease (QoL-AD). All measures were administered at baseline, week 9 and week 21. *Results:* The MCET was more effective in improving the MMSE score (effect size 0.47, p=0.009), ADAS-cog (effect size 0.35, p=0.038), RMBPC positive items (Effect size 0.42, p=0.020), RMBPC frequency score (effect size 0.38, p=0.038) and QoL-AD (effect size 0.39, p=0.040). *Conclusion:* The results suggested that the MCET may be effective in improving cognition, behavioral and

psychological symptoms, and quality of life of the people with MCI or early stage dementia. (ClinicalTrials.gov Identifier: NCT02350738). *Keywords:* Multimodal Cognitive enhancement therapy, Mild Cognitive Impairment, early stage dementia, randomized clinical trials

P1-19: AN INTELLIGENT SYSTEM FOR MONITORING PEOPLE WITH DEMENTIA. ÉDGAR BATISTA, FREDERIC BORRÀS AND ANTONI MARTÍNEZ-BALLESTÉ AND AGUSTI SOLANAS *(Smart Health Research Group, Universitat Rovira i Virgili, Tarragona, Catalonia, Spain)*

Background: Our society will face important challenges in the years to come as a result of the steady increase of life expectancy. One of the most formidable challenges will be the delivery of efficient health services to the growing number of elderly people. Mild Cognitive Impairments (MCI) and other dementias, that cause memory and disorientation problems, might be considered one of the major problems of our ageing society. Patients suffering from MCI might refrain from freely carrying out their everyday activities and, hence, their quality of life might deteriorate. Moreover, relatives and caregivers step into patients' lives to look after them and, in consequence, patients see how their privacy is diminished. In turn, relatives that take care of patients might see their stress levels increased, which also diminish their quality of life. Current technology for monitoring patients with MCI and other dementias focuses on controlling where patients are so as to raise alarms in simple situations (e.g. when patients are at a certain distance from home). This limits the leeway of patients, who even might prefer not to use monitoring technology so as to avoid surveillance. Within the SIMPATIC project (Catalan acronym for Intelligent System for Private and Autonomous Monitoring based on Information and Communications Technologies), funded by the RecerCaixa programme, we have designed, developed and tested a system aiming at detecting abnormal behaviours, complex alarm situations and wandering. This system, which consists of a mobile application and a web server, analyses patients' locations in real time and raises alarms upon a variety of conditions, informing caregivers whenever necessary. *Methods:* The system comprises a mobile application that runs on the patient's smartphone. It has been designed to be lightweight and it can be run on low-budget smartphones (e.g. the same device that patients might use to make phone calls or to send instant messages). In this way, the system does not require specific devices that might stigmatise patients. The smartphone sends the location of the patient and other data to a remote server. Next, the server analyses this information and, using artificial intelligence techniques, it decides whether to raise and alarm or not. This alarm will be received in the caregiver's or relative's mobile phone. In addition, alarms are logged in the system's website. It is worth emphasising that the location of the patient is only disclosed in case of specific alarms. Caregivers are allowed to configure alarms by using a website interface. A variety of alarms can be detected. For instance, zone alarms (patients are not at home when they are supposed to, patients are walking outside a secure zone) and movement alarms (patients are on a car or a train, patients are wandering, patients are not moving for a period of time, etc.). Regarding movement alarms, we focus on typical situations and behaviours for MCI and other similar cognitive impairments. A unique feature of our system is the ability to detect wandering behaviours (i.e. erratic movements), which is important since this might occur inside zones considered secure (e.g. in a park). *Results:* We have conducted a seven-month pilot test in the area of the city of Tarragona (Catalonia, Spain), aiming at validating our software. Sixteen volunteer patients, mainly with GDS (Global Deterioration Scales) degrees 3 and 4, took part in the test and utilised our technology. Thanks to these tests, our algorithms have been fine-tuned and, currently, the application is working accurately in a real scenario with real users. We have had to face several challenges, namely loss of coverage, lack of GPS precision, battery drainage, etc. that were overcome with slight modifications in the application and the server. Moreover, we checked that alarms were generated in a precise manner and reached the caregiver's application. Finally, during the pilot test, we studied the mobility patterns of patients. Although our project is mainly technological, it also has a clear human and social dimension. Hence, we have conducted several interviews and questionnaires with caregivers to obtain first hand information about their feelings about the SIMPATIC technology. During pilot tests, we were in touch with patients and caregivers, aiming at controlling every aspect of the process. It is worth mentioning that in several patients it was the daughter or son, and not the wife or husband, who was in charge of managing the configuration of the system and receiving alarms in their smartphone. This situation has proven to be positive, since it has strengthened the relationship between the son or daughter and the patient who suffers from MCI. *Conclusions:* The SIMPATIC project does not offer solutions to avoid MCI, but it influences positively in the life of patients and caregivers. Due to the reduced number of volunteers, we still do not have statistically relevant results, but from the pilot test data we can infer that the majority of volunteers were engaged and felt comfortable with the technology. We might conclude that our solution pave the way for a wider use of technology and mobile health related applications, focusing on the quality of life elderly people.

P1-20: PHASE I STUDIES EVALUATING THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF MULTIPLE-RISING DOSES OF BI 409306 IN YOUNG AND ELDERLY HEALTHY VOLUNTEERS. GLEN WUNDERLICH[1], WOLFGANG TIMMER[2], GRIT ANDERSEN[3], ANJA HOCH[4], VIKTORIA MOSCHETTI[5], KATJA BOLAND[4], HEIKE ZIMDAHL-GELLING[4], ANDREAS BORTA[4], MICHAEL SAND[6] *((1) Boehringer Ingelheim (Canada) Ltd, Burlington, ON, Canada; (2) CRS Clinical Research Services Mannheim GmbH, Mannheim, Germany; (3) Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany; (4) Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany; (5) Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany; (6) Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA)*

Background: BI 409306 is a phosphodiesterase 9A inhibitor, being developed for the symptomatic treatment of Alzheimer's disease. The primary objective was to investigate the safety and tolerability in young subjects and elderly healthy volunteers. The secondary objective was to characterise the pharmacokinetics (PK) of multiple rising doses of BI 409306. *Methods:* Two randomised, double-blinded, placebo-controlled, within-dose group, multiple rising dose, single-centre phase I trials were conducted in healthy male and female volunteers. In study 1, young and elderly subjects were allocated to 25, 50, or 100 mg dose groups. In study 2, young CYP2C19 poor metabolisers (PM; defined as carrier of *2 and/or *3 alleles) and elderly subjects not stratified for CYP2C19 genotype were allocated to 25 or 50 mg dose groups. In both studies, subjects were randomised to BI 409306 or placebo (3:1) once daily for 14 days. Additionally, 50 mg was given twice daily in young subjects of study 1. *Results:* In study 1, 46/48 young and all 35 elderly subjects, with a mean age of 42 and 68.7 years, respectively, completed the trial as planned. In study 2, all 16 young CYP2C19 PM and 24 elderly subjects with a mean age of 30.5 and 69.5 years, respectively, completed the trial as planned. Demographic and baseline characteristics were comparable between the different treatment groups. At least 1 adverse event (AE) was reported in 31/48 (64.6%) young and 22/35 (62.9%) elderly subjects in study 1, and 9/16 (56.3%) young CYP2C19 PM and 14/24 (58.3%) elderly subjects in study 2. AEs considered to be related

to the trial medication by the investigator were seen in 24 (50%) young and 17 (48.6%) elderly subjects in study 1, and 9 (56.3%) young CYP2C19 PM and 12 (50%) elderly subjects in study 2. The majority of AEs were of mild intensity. The incidence of possibly drug-related AEs increased with dose for both young and elderly subjects. No deaths, severe or serious AEs or AEs of special interest were reported. In study 1, the most frequently reported AEs were photophobia and headache in 18.8% young subjects each; in the elderly, these were photopsia (17.1%), blurred vision and fatigue (14.3% each). In study 2, the most frequently reported AEs were photophobia (41.7%), dizziness (33.3%) and somnolence (16.7%) in young CYP2C19 PM subjects. In the elderly of study 2, these were dizziness (22.2%), photophobia (16.7%), headache (16.7%) and chromatopsia (16.7%). All AEs were of short duration and resolved without sequelae. There were no clinically relevant findings from electrocardiogram recordings, vital sign measurements, and physical examination. Generally, the PK of BI 409306 was characterised by a very rapid absorption followed by a rapid monophasic to biphasic elimination. The plasma-concentration profiles were very similar following single and multiple dose administration. Accumulation was minor with gMean accumulation ratios of AUC ranging from 0.964 to 1.26 and 1.05 to1.41 in young and elderly subjects, respectively, in study 1; 1.14 to1.27 in young CYP2C19 PM subjects, and 1.10 to1.22 in elderly subjects in study 2. Steady-state was achieved by Day 2. The gMean maximum BI 409306 concentrations (Cmax,ss) on Day 14 ranged from 348 nmol/L to 1260 nmol/L and 444 nmol/L to 2150 nmol/L in young and elderly subjects, respectively, in study 1. In study 2, Cmax,ss ranged from 694 to1740 nmol/L in CYP2C19 PM subjects and 516 to 872 nmol/L in the elderly. The gMean AUCτ,ss ranged from 747 h·nmol/L to 1960 h·nmol/L and from 621 h·nmol/L to 3990 h·nmol/L in young and elderly subjects, respectively, in study 1. In study 2, gMean AUCτ,ss ranged from 1800 h·nmol/L to 3410 h·nmol/L in CYP2C19 PM subjects and from 682 h·nmol/L to 1250 h·nmol/L in the elderly subjects. The systemic exposure of elderly subjects in study 1 was similar to study 2. The highest exposure upon multiple dosing was observed in the elderly administered with 100 mg BI 409306 once daily in study 1. *Conclusion:* Overall, good safety and tolerability were observed after administration of multiple doses of 25, 50 and 100 mg BI 409306 in young and elderly subjects and up to 50 mg in young CYP2C19 PM. In all treatment groups, drug elimination was rapid, thus accumulation was minor with once daily and twice daily dosing. The systemic exposure of elderly subjects was similar in study 1 and 2.

P1-21: CUMULATIVE CLINICAL EFFICACY OF IDALOPIRDINE, A 5-HT6 ANTAGONIST IN ADVANCED DEVELOPMENT FOR TREATMENT OF ALZHEIMER'S DISEASE. ALIREZA ATRI[1], KRISTIAN WINDFELD[2], BENOÎT RIVE[3] *((1) Ray Dolby Brain Health Center, California Pacific Medical Center, San Francisco, CA; Dept. of Neurology, Massachusetts General Hospital; and Harvard Medical School, Boston MA, USA; (2) H. Lundbeck A/S, Valby, Denmark; (3) Lundbeck SAS, Issy-les-Moulineaux, France)*

Background: A 24-week, double-blind, placebo-controlled phase II clinical trial demonstrated a pro-cognitive effect of idalopirdine in patients with moderate Alzheimer's disease (AD) dementia (MMSE 12-19), and observed potential beneficial trends in activities of daily living and global clinical status (Wilkinson et al 2014). Area-under-the-curve (AUC) analysis of the individual clinical domains, that assessed cumulative efficacy over the entire 24-week period, was compared to mixed-effects model for repeated measures (MMRM) analysis of changes from baseline to primary endpoint at week 24. *Method:* AUC analyses for measures of cognition (Alzheimer's Disease Assessment Scale, cognitive subscale – ADAS-Cog), function (Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory – ADCS-ADL 23), and global clinical status (Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change – ADCS-CGIC) were performed by applying the trapezoidal rule to the estimated visit-wise means from the MMRM analyses used in the primary analysis of changes from baseline. This provided an approach to handling missing values (e.g due to early withdrawal) in an analysis of cumulative effects. Since the ADCS-CGIC assesses changes in patient health state, analyses on this scale were performed on the score at each visit minus 4, such that no change in health state corresponds to a score of 0. Cumulative effects of treatment over time in the different domains were estimated and contrasted with the visit-wise results from the MMRM analysis. *Results:* The estimated cumulative effect on ADAS-Cog (i.e. the mean idalopirdine-placebo difference in the area under curve for ADAS-Cog changes from baseline) over the 24 weeks of treatment was 31.7 points x weeks in favour of idalopirdine (p=0.0046) while the point estimate at week 24 was 2.16 points in favour of idalopirdine (p=0.0040). For the ADCS-ADL 23, the estimated cumulative effect of idalopirdine was an increase of 25.4 points x weeks (p=0.14) over 24 weeks versus a point estimate of 1.72 points (p=0.12). The cumulative effect on the ADCS-CGIC over 24 weeks was 3.84 points x weeks and significantly in favour of idalopirdine (p=0.033); this contrasted to the point estimate at week 24 which was 0.22 and not statistically significant (p=0.12). *Conclusion:* This area-under-the-curve analyses of the 24-week cumulative efficacy of idalopirdine versus placebo in the treatment of moderate AD dementia supports previous results from MMRM baseline-to-24-week change score analyses for a significant treatment effect on cognition, and a possible signal for treatment trend on daily function. AUC analysis additionally revealed a significant effect, not observed in past bascline-to-24-week change score analysis, on global clinical status in favor of idalopirdine treatment. These results provide convergent and further support for the potential efficacy of idalopirdine in AD; this is currently under investigation in a large Phase III clinical trial program.

P1-22: THE ROSAS STUDY: A LONG-TERM, LONGITUDINAL, MULTI-PARAMETRIC AND COMPARATIVE EVALUATION OF ALZHEIMER'S DISEASE PROGRESSION IN A UNIQUE COHORT OF PATIENTS. PIERRE-JEAN OUSSET[1], MARIA PUEYO[2], MARIA SOTOMD[1], VERA KIYASOVA[2], ISABELLE GUIGNOT[2], EVA BOUGUEN[2], STÉPHANIE GALTIER[2], FABRICE BONNEVILLE[1], FRANÇOISE LALA[1], NATHALIE SASTRE[1], JULIEN DELRIEU[1], BRUNO VELLAS[1] *((1) Gerontopôle, INSERM U 1027, Alzheimer's Disease Research and Clinical Center, Toulouse University Hospital, France; (2) Institute de Recherches Internationales SERVIER, Suresnes, France)*

Background: Numerous studies have been performed on the natural course of Alzheimer Disease (AD) in different countries and settings. The ROSAS (Research Of biomarkerS in Alzheimer's diseaSe) study is a monocentric observational study performed at Gerontopôle in Toulouse, France. It aimed to analyze the cognitive and behavioral evolution, identify biochemical, imaging and protein biomarkers of AD Progression in a unique French cohort. This abstract will focus on longitudinal evaluation of cognitive and behavioral symptoms. *Methods:* Four hundred eight (408) subjects aged 65 years and older were enrolled in the study, were divided into 3 groups and followed for 4 years: 110 normal controls (NC; MMSE≥26, CDR =0); 100 patients with memory impairment without dementia (MCI; MMSE≥24, CDR=0.5, memory impairment RAVLT, but not DSM IV criteria for AD) and 196 patients with dementia of the Alzheimer's type (AD; 12≤MMSE≤26, CDR≥0.5, DSM IV criteria). Clinical examination, cognitive and behavioral evaluation (MMSE, ADAS Cog, CDR, RAVLT, TMT A and B, ADCS-MCI-ADL, NPI),

laboratory assessment of blood and urine were performed every 6 months; MRI was undertaken at 3 time points (inclusion, 12 and 48 months). *Results:* Baseline characteristics of ROSAS cohort were presented at Alzheimer's Association International Conference 2015. Longitudinal evaluation of participants showed different patterns of progression. A sub-group of MCI patients (44%) progressed to dementia, whereas the 52 subjects (56%) remained relatively stable in the course of the study. Cognitive function of AD patients (MMSE, ADAS-Cog) declined linearly, but at different rate (number of point per year) in mild compared to moderate patients. After 24 months in moderate AD and at 42 months in mild AD cognitive decline rate stabilized for MMSE measures and continued progression for ADAS Cog evaluation. AD patients who performed all the study visits were subdivided into clusters according to decline rate, based on MMSE change. Analyses of socio-demographic characteristics of these patients revealed that slow decliners were older (77.7 vs.75.6 years old), with higher level of education (8.4 vs.7.4 years) than fast decliners. Slow decliners presented a longer disease duration (18.8 vs. 9.6 months). In a group of fast decliners 61.5% of patients were ApoE carriers, whereas in slow decliners group it was only 38.1% of patients. In the MCI group, the progression of cognitive decline was linear during the study (MMSE, ADAS Cog), whereas the incidence of neuropsychiatric symptoms differed greatly between subjects with stable MCI and those who progressed to AD. Neuropsychiatric symptoms were classified in 4 clusters: affective (depression, anxiety), apathy (apathy, appetite and eating change), hyperactivity (delusions, hallucinations, sleep and night time behavior change) and psychosis (agitation, disinhibition, irritability, aberrant motor behavior, euphoria) and analyzed separately for subgroups within MCI population; in mild and moderate AD. Three clusters (affective apathy, hyperactivity) score increased in the MCI group that progressed to AD but not in stable MCI participants. Apathy and psychosis have been already described in the literature as predictors of faster cognitive decline in mild and moderate AD patients; however their role in MCI has been less well explored. In this ROSAS cohort cognitive phenotype change from MCI to AD occurred in most patients between month 12 to 24 of study participation (MMSE) and this transition was correlated with progressive score increase in affective, apathy and hyperactivity clusters in these sub-group of patients. *Conclusion:* To our knowledge, this is the first observational European cohort, demonstrating the predictive value of several neuropsychiatric sub-syndromes on the rate of cognitive decline in MCI patients. In patients with AD compared to subjects displaying MCI, differential patterns of cognitive decline were observed. In addition it was shown that the worsening of neuropsychiatric symptoms in MCI patients correlated with their rate of cognitive decline. Ongoing multi-variant analyses should clarify the relationship and contribution of specific neuropsychiatric to the clinical trajectory of the disease.

P1-23: PHARMACOKINETICS AND TARGET ENGAGEMENT PROFILE OF RESVERATROL IN HUMAN BLOOD: IMPLICATIONS FOR AD CLINICAL TRIALS. LOUISE MONTE[1,2], DARREN INSKO[1,2], PAULA DESPLATS[2], PAUL S AISEN[1,2], R SCOTT TURNER[3], ROBERT A RISSMAN[1,2] *((1) Alzheimer's Disease Cooperative Study; (2) Department of Neurosciences, University of California, San Diego, La Jolla, CA, USA; (3) Department of Neurology, Georgetown University, Washington, DC, USA)*

Background: The major risk factor for Alzheimer's disease (AD) is aging - even in individuals with high genetic risk – but molecular mechanisms linking aging to AD pathogenesis are unclear. Resveratrol (trans-3,4',5-trihydroxystilbene) treatment decreases age-dependent cognitive decline and neuropathologies in animal models of aging and AD. This effect may be mediated by activation of sirtuins - a highly-conserved family of deacetylases that are regulated by NAD+/NADH levels and thus link energy metabolism to gene expression. The Alzheimer's Disease Cooperative Study (ADCS) recently completed a trial of resveratrol - taken orally with a dose increase every 13 weeks (from 0.5 to 2 g daily) for 1 year. The trial was a randomized, placebo-controlled, double-blind, multicenter 52-week phase 2 study of resveratrol in individuals (n=119) with mild to moderate Alzheimer's disease (AD). The main objectives were to examine its safety and tolerability and effects on AD biomarkers - Aβ40 and Aβ42 in plasma and cerebrospinal fluid (CSF), tau and phosphoTau181 in CSF, and volumetric MRI (primary outcomes) - and clinical (secondary) outcomes. A subpopulation of the subjects also participated in a 24h study of the pharmacokinetic profile of resveratrol and its metabolites in blood. *Methods:* For the pharmacokinetic analysis a LC-MS method was developed and validated according to the FDA's Guidance for Industry: Bioanalytical Validation. The method measures the levels of Resveratrol and its metabolites trans-resveratrol-3-O-β-D-Glucunoride (3G-RES), trans-resveratrol-4-O-β-D-Glucunoride (4G-RES) and trans-resveratrol-3-Sulfate Sodium Salt (S-RES) in plasma (n=119) and cerebrospinal fluid (CSF) (n=75). The pharmacokinetic analysis was performed on an AB Sciex QTRAP 5500 and Shimadzu UFLC XR rack changer LC-MS system and data acquisition and analysis was made using Analyst 1.6. To examine target engagement, RNA was extracted from blood samples and the gene expression of sirtuin 1, 2, 3 and 5 was determined using q-PCR. This was done with samples taken from the 24h pharmacokinetics (n=13) sub-group and from the larger study (n=94). *Results:* The plasma tmax (ng/ml) was 90 min for RES and S-RES and 120 min for 3G-RES and 4G-RES. The half-life of RES and its metabolites ranged from 10 h to 20 h. There was a great deal of inter-individual variation in drug and metabolite levels that was unrelated to the time between last dose and blood draw. The most prominent metabolite was S-RES and 3G-RES was the least abundant. The pharmacokinetics of the CSF samples also demonstrated significant levels of resveratrol and its metabolites. This demonstrates that RES can penetrate the blood brain barrier to have CNS activity. At the end of the trial, by week 52, transcription of sirtuins 1, 2 and 3 was decreased at 2h after drug dose, in comparison to baseline levels. Sirtuin 5 expression did not appear to be affected by resveratrol treatment. *Conclusion:* We demonstrate target engagement - namely altered transcription of sirtuins 1, 2 and 3, but not sirtuin 5 - in blood samples from RES treated individuals with AD. We also find significant levels of RES and its major metabolites in plasma and CSF. The altered gene expression of sirtuins 1-3 may mediate the significant changes in some AD biomarkers found with RES treatment (Turner et al., submitted). These data will inform the design of a planned Phase 3 trial of RES in individuals with mild cognitive impairment or mild dementia due to AD.

P1-24: COGNITIVE AND FUNCTIONAL EFFICACY OF TRAMIPROSATE IN APOE4+ PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE: SUB-GROUP ANALYSES OF THE PHASE 3 NORTH AMERICAN AND EUROPEAN TRIALS. JOHN A HEY[1], JEREMY YU[1], MARTIN TOLAR[1], MENGHIS BAIRU[2], JOHN SAMPALIS[3] *((1) Alzheon, Inc., Framingham, MA, USA; (2) Serenus Biotherapeutics, Inc., San Francisco, CA, USA; (3) JSS Medical Research, Inc., St. Laurent, QC, Canada & McGill University, Montreal, QC, Canada)*

Background: Current therapeutic options for Alzheimer's disease (AD) provide limited long-term efficacy. The apolipoprotein E4 (APOE4) genotype is the most significant known risk factor for the development and progression of late-onset AD, through a possible increase in β-amyloid (Aβ) deposition. APOE4 positive (APOE4+) subjects, which comprise up to 60% of AD patients, display more aggressive course as well as more homogenous progression and

severity of the disease, and are significantly less likely to be misdiagnosed of AD than the general population. Tramiprosate, a small molecule inhibitor of Aβ aggregation, has been shown to prevent amyloid deposition and protect against Aβ-induced neurotoxicity, as well as to significantly reduce CSF Aβ42 in AD patients. Tramiprosate was evaluated in two independent multicenter, double-blind, placebo-controlled Phase 3 trials in AD patients conducted in North America and Europe, respectively. We report a subgroup analysis of the merged data from both trials, with the goal to evaluate the efficacy of tramiprosate in APOE4+ patients with AD. This study summarizes the cognitive and functional efficacy data of tramiprosate 100 mg BID and 150 mg BID on the co-primary endpoints ADAS-Cog and CDR-SB. Based on the promising efficacy and safety findings with tramiprosate, Alzheon is developing ALZ-801, a novel, orally available valine conjugate prodrug of tramiprosate with improved pharmaceutical properties, oral absorption and gastrointestinal tolerability. *Methods:* A total of 909 APOE4+ patients (i.e., with either one or two APOE4 alleles) were included in this analysis. Patients were ≥ 50 and < 80 years of age at enrollment, with mild-to-moderate AD (MMSE 16–26), and on a stable dose of acetylcholinesterase inhibitors, alone or with memantine. Patients were randomly allocated to 78-week treatment with placebo (n = 320), tramiprosate 100 mg BID (T100) (n = 307) or 150 mg BID (T150) (n = 282). The primary clinical efficacy endpoints were the changes from Baseline to Week 78 in ADAS-Cog and CDR-SB scores. General Linear Repeated Measures Mixed Effects models adjusting for baseline ADAS-Cog or CDR-SB, site, age, baseline MMSE, race, education, cardiovascular comorbidity, use of antidepressants and vitamin E were used to assess between group differences with respect to the study outcomes. *Results:* For placebo, T100 and T150, respectively, baseline mean (SD) for ADAS-Cog was 21.4 (8.5), 22.1 (8.6) and 21.8 (8.0), for CDR-SB 5.5 (2.6), 5.2 (2.5) and 6.0 (2.6), and for MMSE 21.0 (3.0), 21.0 (3.0) and 21.0 (3.0). For ADAS-Cog, the results showed a significant treatment group (F = 5.29, P = 0.0051) and group x time effect (F = 1.77, P = 0.0614). Significant adjusted differences vs. placebo (i.e., ADAS-Cog delta improvement vs. placebo) were observed for T150 at Week 78: delta = +2.17, P = 0.0009; Week 26: delta = +1.22, P = 0.0248; Week 52: delta = +1.89, P = 0.0014; and Week 65: delta = +1.98, P = 0.0015 and overall slope: delta = +8.64, P = 0.0012. A trend was observed for the T100 at Week 78: delta = +1.13, P = 0.0985. For CDR-SB, a significant group effect (F = 3.98, P = 0.0190) was observed. Significant adjusted differences vs. placebo (i.e., delta improvement vs. placebo) were observed for T150 at Week 78: delta = +0.63, P = 0.0015; at Week 65: delta = +0.53, P = 0.0053 and overall slope: delta = +1.74, P = 0.0422. The incidence of adverse events (AEs; mild gastrointestinal) and drop-out rates due to AEs were similar for the three groups, with AE rates 7.5% for placebo, 14.1% for T100 and 15.0% for T150, respectively. Also, the incidence of observed serious AEs (SAEs; any causality) was the same for the three groups: 9.4% for placebo, 9.7% for T100 and 8.7% for T150, respectively. *Conclusion:* The subgroup analysis of the merged North American and European cohorts of the Phase 3 tramiprosate North American and European trials showed that, in the population of APOE4+ patients < 80 years of age, tramiprosate displayed sustained and significant efficacy in AD patients on top of standard of care treatment with acetylcholinesterase inhibitors and/or memantine. The observed efficacy of the top dose of tramiprosate (150 mg, BID) was sustained over the 78-week treatment. In addition, tramiprosate was very well tolerated at both dose strengths and the tolerability and drop-out rate were similar to placebo. The data of this analysis, in combination with the demonstrated high safety and tolerability profile of tramiprosate, support progression of the optimized tramiprosate prodrug ALZ-801 into confirmatory Phase 2/3 program in the APOE4+ Alzheimer's disease population in the near future. ALZ-801 has the promise to be a new, oral, small molecule amyloid-targeting treatment for AD that extends the efficacy of the current standard of care therapy.

P1-25: DISEASE-MODIFYING EFFECT OF B-VITAMINS ON BRAIN ATROPHY AND COGNITIVE DECLINE IN MCI IS ENHANCED BY OMEGA-3 FATTY STATUS. A.D. SMITH[1], A OULHAJ[2], F JERNEREN[1], H REFSUM[1,3], CA DE JAGER[4] *((1) OPTIMA, Department of Pharmacology, University of Oxford, Oxford, United Kingdom; (2) Institute of Public Health, College of Medicine and Health Sciences, United Arab Emirates University, United Arab Emirates; (3) Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway; (4) Division of Geriatric Medicine, Department of Medicine, University of Cape Town, Cape Town, South Africa)*

Background: Elevated concentrations of plasma total homocysteine (tHcy) are a strong risk factor for cognitive impairment and dementia, while eating fish rich in omega-3 fatty acids appears to be protective (1). The VITACOG trial showed that lowering tHcy by B-vitamin treatment in mild cognitive impairment (MCI) slows the rate of global brain atrophy (2) and of cognitive decline (3). The effect is especially marked in the regions of the brain susceptible to AD: gray matter atrophy rate in these regions was slowed by 90% upon B-vitamin treatment in subjects with high baseline tHcy (4). We have now investigated whether baseline plasma omega 3 fatty acid concentrations (docosahexaenoic acid, DHA; eicosapentaenoic acid, EPA) modify the treatment effect of B-vitamins on the rate of brain atrophy and on cognitive decline in this placebo-controlled trial. *Methods:* This study from the VITACOG trial included 266 older persons (≥70 y) with MCI, randomly assigned either to placebo (n = 133) or to daily high-dose B-vitamin supplementation (folic acid, 0.8 mg; vitamin B6 , 20 mg; vitamin B12, 0.5 mg) (n = 133) for 2 y. The participants all underwent cognitive testing at baseline and 2 y later, with some tests (HVLT with delayed recall [DR] and the TICS-M) repeated more frequently. A subset of this cohort volunteered for volumetric MRI scans at the start and end, so that the rate of global brain atrophy could be assessed (n = 83, placebo; n = 85 B-vitamins). The effects of the intervention on brain atrophy and on cognitive performance were analyzed according to baseline omega-3 fatty acid concentrations (EPA+DHA), adjusted for age, gender, APOE4, education, and were stratified for plasma homocysteine (tHcy) at baseline. *Results:* Brain atrophy rates: We found an interaction (P =0.024) between B-vitamin treatment and baseline plasma concentration of omega-3 fatty acids (EPA+DHA) on brain atrophy rates. In subjects with high baseline omega-3 fatty acids (>590 μmol/L), B-vitamin treatment slowed the mean atrophy rate by 40.0% compared with placebo (P = 0.023). B-vitamin treatment had no significant effect on rate of atrophy in subjects with low baseline omega-3 fatty acids concentrations (<390 μmol/L). A striking effect was found in subjects with tHcy ≥ median (11.3 μmol/L) at baseline: those with high baseline omega-3 fatty acids experienced a 68% slowing of brain atrophy upon B-vitamin treatment (P < 0.001), whereas those with low omega-3 experienced no slowing of atrophy. These results have been reported in detail (5). *Cognition:* There were significant interactions between B-vitamin treatment and baseline plasma omega-3 fatty acids and several cognitive tests. In general, there was no beneficial effect of B-vitamin treatment on cognition in those with low omega-3 levels, but at high omega-3 levels (upper tertile), those treated with B-vitamins showed either no cognitive decline or even improvement, compared with the placebo group; the latter showed cognitive decline. The omega-3 status also influenced the final CDR score: the proportion of subjects with a CDR score > 0 was not affected by B-vitamin treatment in those with low baseline omega-3, but in those with high omega-3 it fell to 33%, compared with 59% in placebo. The interactions were stronger for participants with high baseline tHcy: those with high baseline tHcy on B-vitamin

treatment and with high omega-3 levels, had improved HVLT-DR scores after 12 months and then maintained scores at baseline performance, while the placebo group showed a marked decline by 24 months, with a 4 point difference in HVLT-DR score between the groups at the study end. *Conclusion:* The disease-modifying effect of B-vitamin treatment in MCI, as revealed by assessment of brain atrophy rates and cognitive test performance, is markedly enhanced in subjects with good omega 3 fatty acid status. These results highlight the importance of considering several risk factors when designing clinical trials. A trial of a combination of B-vitamins and omega-3 fatty acids in MCI is clearly needed. *References:* 1. Beydoun MA et al. BMC Public Health. 2014;14:643. 2. Smith AD et al. PLoS ONE. 2010;5:e12244. 3. de Jager CA et al. Int J Geriatr Psychiatry. 2012;27:592-600. 4. Douaud G et al. PNAS. 2013;110:9523-8. 5. Jerneren F et al. Am J Clin Nutr. 2015. DOI: 10.3945/ajcn.114.103283

P1-26: HEALTHY AGEING THROUGH INTERNET COUNSELING IN THE ELDERLY (HATICE) – A LARGE PREVENTION TRIAL. E RICHARD, S ANDRIEU, H SOININEN, C BRAYNE, N COLEY, J GUILLEMONT, F MANGIALASCHE, T NGANDU, C BEISHUIZEN, Y MEILLER, A VD GROEP, E MOLL VAN CHARANTE, WA VAN GOOL, M KIVIPELTO *(Academic Medical Center, dept of Neurology, Amsterdam; INSERM U1027, University of Toulouse III; Dept. of Epidemiology and Public Health and Gerontopole , Toulouse University Hospital; Dept. of Neurology, University of Eastern Finland, Kuopio; Dept. of Public Health and Primary Care, Institute of Public Health, Cambridge, UK; NOVAPTEN; Aging Research Center, Dept. of Neurobiology, Health Care Sciences and Society, Karolinska Institute, Stockholm; Dept. of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki; VitalHealth Software; Academic Medical Center, dept of primary care, Amsterdam)*

Background: Cardiovascular risk factors are common in the elderly and increase the risk of cardiovascular disease and dementia. Internet-based interventions are a potentially powerful and scalable solution for large-scale prevention programs for both cardiovascular disease and dementia. Collaboration of research groups performing RCTs to prevent dementia in the 'European Dementia Prevention Initiative' (EDPI) has led to the HATICE project. *Methods:* The HATICE project consist of three phases: 1) evaluation of three ongoing trials to prevent cognitive decline and dementia (preDIVA, MAPT and FINGER), including the development of a shared data platform for pooled analyses; 2) development of an interactive internet intervention to reduce the risk of cardiovascular disease and dementia; 3) Evaluation of the efficacy of the platform in a RCT. The multinational randomized controlled trial (RCT) to evaluate the efficacy of the interactive internet-based intervention targeting vascular and lifestyle-related risk factors has started among 4250 persons aged >65 with >= 2 cardiovascular risk factors or manifest cardiovascular disease. The interactive internet intervention is based upon national and European guidelines for cardiovascular risk management. Participants in the intervention group get access to an interactive internet platform supported by a coach to improve their lifestyle and cardiovascular risk profile by encouraging self-management. Participants in the control condition get access to a platform with static health information. Primary outcome is a composite score of systolic blood pressure, BMI and cholesterol. Main secondary outcomes are individual risk factors, incident cardiovascular disease, cognitive decline and dementia. Intervention and follow-up are 18 months. *Results:* The interactive internet platform was tested in a pilot study among 38 persons (26 intervention, 12 control). During the pilot software bugs and inconsistencies were encountered and solved. Participants in the intervention group actively used the platform (average of 22 log-ins per month). 85% of participants set a goal for lifestyle improvement and entered health data on the platform. Variables that were measured by participants were blood pressure, BMI, physical activity, nutrition and smoking behaviour. Recruitment in the full RCT has started in the Netherlands, Finland and France and is scheduled to be complete by March 2016. *Conclusions:* After preDIVA, MAPT and FINGER, HATICE will be the fourth large RCT investigating a multi-domain intervention to prevent cognitive decline and dementia. The web-based and generic character of the intervention will allow for implementation throughout Europe (and beyond) if proven effective.

P1-27: PHARMACOKINETIC AND PHARMACODYNAMIC (PK/PD) ASSESSMENT AND COVARIATE ANALYSIS FOR ADUCANUMAB (BIIB037) IN PATIENTS WITH PRODROMAL OR MILD ALZHEIMER'S DISEASE: INTERIM RESULTS OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 1B STUDY. YAMING HANG, PING CHIAO, JEFF SEVIGNY, LESLIE WILLIAMS, XIAOPENG MIAO, JOHN O'GORMAN, ALVY MIKULSKIS, KATE LEITERMANN, JAMES FERRERO *(Biogen, Cambridge, MA, USA)*

Background: Aducanumab (BIIB037), a human IgG1 monoclonal antibody that binds selectively to aggregated forms of Aβ, is being investigated in a Phase 1b study as a disease-modifying treatment in patients with prodromal or mild AD. The objective is to assess the pharmacokinetic and pharmacodynamic (PK/PD) relationships and the possible covariates associated with amyloid removal and cognition following 12 months of treatment of aducanumab in a Ph1b study. *Methods:* In a staggered, parallel-group design, treatment arms included: 1, 3, 6, and 10 mg/kg, and placebo. Sparse samples from the multiple ascending dose study and intensive sampling from an earlier single ascending dose study were combined to construct a Population PK model. Cumulative AUC up to month 12 was estimated for each individual and used as the exposure variable for the assessment of PK/PD relationship. The relationship between BIIB037 exposure, amyloid PET SUVR and cognition change (MMSE and CDR-sb) from baseline, and covariates were evaluated using the Analysis of Covariance (ANCOVA) method. *Results:* Cumulative BIIB037 exposures and baseline SUVR levels were found to correlate with SUVR change from baseline at month 12. APOE4 carrier status (carriers vs non-carriers), stage of AD (mild vs prodromal) did not correlate with change in SUVR. A dose-dependent slowing of cognitive decline, represented as change from baseline in both MMSE and CDR-sb relative to placebo was demonstrated. *Conclusions:* Aducanumab treatment for 12 months resulted in a dose-dependent removal of brain amyloid plaques in prodromal and mild AD patients as well as a dose-dependent slowing of cognition decline. There was a significant correlation between aducanumab exposures and degree of change in SUVR. Change in SUVR was not significantly different between APOE4 carriers and non- carriers or between prodromal and mild AD patients.

P1-28: COMPARATIVE EFFICACY AND SAFETY OF ANTIDEPRESSIVE MONO- AND MULTIMODAL THERAPY IN ELDERLY PATIENTS WITH DEPRESSION IN PSYCHOGERIATRIC HOSPITAL. YB KALYN, TP SAFAROVA, VS SHESHENIN, SI GAVRILOVA *(FSGI "The Mental Health Research Centre", Moscow, Russia)*

The aim of the study: comparative evaluation of the efficacy and safety of a multimodal antidepressive therapy with venlafaxine plus Cerebrolysin and monotherapy with the same antidepressant for the treatment of elderly patients with depression in the psychogeriatric hospital. *Material and methods:* The two groups of patients were included in the study (20 patients in each group) aged 60 years and older (60 to 79 years), comparable to the main clinical characteristics

(mean HAMD17 - ¬ 23,01±1,89 and MMSE ¬- 26,56±2,37). All the patients in both groups had minimal organic dysfunctions and MRI signs of cerebrovascular and neurodegenerative disorders. Patients of the first group were treated with venlafaxine (75-150 mg/day) and patients of the second group – with venlafaxine and intravenous infusions of Cerebrolysin: 20 infusions (20.0 ml in 100 ml isotonic sodium chloride solution daily) during 4 weeks. Cerebrolysin is a medication with the proved neuroprotective and neurotrophic activity. The main mechanisms of Cerebrolysin actions include antiapoptopic activity, neuroplasticity and neurogenesis stimulation and protection of neurons. *Results:* The multimodal therapy allowed to get more rapid and pronounced therapeutic response as well as the significant reduction of adverse events compared to monotherapy with venlafaxine. *Conclusion:* The data obtained allow to recommend a multimodal antidepressive therapy with inclusion of cerebrolysin course for the treatment of elderly depressive patients for reduction the risk of adverse effects of antidepressants and shortening of hospitalization period. *Keywords:* elderly, minimal organic dysfunctions, cerebrovascular and neurodegenerative disorders, depression, therapy, venlafaxine, cerebrolysin.

P1-29: COGNITIVE RESPONSE TO METFORMIN IS ASSOCIATED WITH PRE-TREATMENT CSF AB1-42 LEVELS: SECONDARY ANALYSIS OF DATA FROM PILOT STUDY OF METFORMIN'S EFFECTS ON BIOMARKERS OF ALZHEIMER'S DISEASE. AARON M KOENIG[1,2,5], DAVID A WOLK[1,3], DAWN MECHANIC-HAMILTON[1,2], SHARON X XIE[4], MARTHA F COMBS[1,2], STEVEN E ARNOLD[1,2,3,6] *((1) Penn Memory Center, University of Pennsylvania, Philadelphia, PA, USA; (2) Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA; (3) Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA; (4) Department of Epidemiology & Biostatistics, University of Pennsylvania, Philadelphia, PA, USA; (5) Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA (Current affiliation); (6) Department of Neurology, Massachusetts General Hospital, Boston, MA, USA (Current affiliation))*

Background: Epidemiological studies have identified a robust association between Type II Diabetes Mellitus and Alzheimer's disease (AD), and recent neurobiological studies have suggested the presence of CNS insulin resistance in individuals with AD (even among non-diabetic individuals). Furthermore, preclinical studies have provided evidence for the existence of a reciprocal relationship between CNS insulin resistance and amyloid and tau disease pathways. Given this relationship, we hypothesized in a recent pilot clinical trial that the CNS-penetrant insulin-sensitizing medication metformin would be beneficial as a disease modifying and/or symptomatic therapy for AD. The primary outcomes of this trial—in which high-dose metformin was administered to subjects with MCI and mild dementia due to AD—suggested that metformin had no salutary cognitive effects over placebo. A subsequent review of the data, however, suggested that cognition improved among some patients taking metformin and worsened among others. To explore potential differences between responders and non-responders to metformin, we examined baseline characteristics of two groups: metformin responders (defined broadly as demonstrating a positive change on the Montreal Cognitive Assessment (MoCA) over 8 weeks of double-blinded treatment with metformin) and metformin non-responders (demonstrating no change or worsening on the MoCA over 8 weeks of treatment). *Methods:* We used data from a 16-week, randomized, double-blind, placebo-controlled crossover pilot study of metformin for disease-modifying effects in AD. Eligibility criteria included age 55-80, diagnosis of amnestic MCI or mild dementia due to AD (MMSE>19, CDR 0.5-1), and no history of diabetes. Subjects were randomized to receive placebo followed by metformin for 8 weeks or vice versa. For the current analyses, we pooled data from the metformin (MET) and placebo (PBO) phases of the trial, irrespective of treatment sequence. We classified each subject as a metformin responder (improvement in MoCA) or non-responder (no change or worsening in MoCA), and compared demographic characteristics and CSF levels of β-Amyloid1-42 (Aβ1-42), total tau (t-Tau), and hyperphosphorylated tau (p-Tau) prior to treatment. Categorical characteristics were summarized using means and percentages, and differences across groups were tested using paired t-tests. Exploratory analyses utilized logistic regression to examine the relationship between baseline CSF biomarkers (Aβ1-42, t-Tau, p-Tau levels) and response to treatment (%ΔMoCA) during the MET and PBO phases of the study. *Results:* Twenty subjects completed the 16-week pilot study, including 9 women and 11 men, all Caucasian, with a mean age of 70.2 years (SD=6.9) and education of 16.7 years (2.8). At baseline, cognition was mild to moderately impaired, with a mean MoCA of 19.9 (SD 3.3, range 11-25). MoCA scores declined for 8 subjects (loss of 1 to 8 points, representing 4-38% decline from baseline), remained stable for 6 subjects, and improved in 6 subjects (gain of 1 to 5 points, representing 5-25% improvement from baseline). Responders and non-responders did not differ significantly in age (t=-0.527, df=18), education (t=-0.31, df=18), ethnicity (t=0.65, df=18), gender (t=-0.66, df=18), or mean MoCA score (t=0.96, df=18) at baseline. Baseline levels of Aβ1-42(t=-1.73, df=18), t-Tau (t=1.68, df=18), and p-Tau (t=1.87, df=18) did not differ significantly among responders and non-responders at baseline. However, an exploratory analysis suggested that baseline Aβ1-42 levels were significantly associated with improvement on the MoCA during the MET (t=2.99, p<.01) but not PBO (t=-0.55) phase of the study, and that baseline t-Tau and p-Tau scores were not associated with changes on the MoCA during either phase (MET: t-Tau (t=-0.56), p-Tau (t=-0.63); PBO: t-Tau (t=-0.06), p-Tau (t=-0.51)). *Conclusion:* This secondary analysis found that baseline CSF Aβ1-42 levels correlated with response to metformin, but not placebo, in individuals with MCI and mild dementia due to AD. More precisely, higher pre-treatment Aβ1-42 levels were associated with subsequent improvement on the MoCA, while lower pre-treatment levels were associated with decline on the MoCA. Given that CSF levels of Aβ1-42 may correlate with the neuropathological severity of AD (with higher CSF levels seen in pre-clinical and early stages of the disease), it appears that the beneficial cognitive effects of metformin were more likely to be experienced by individuals at earlier stages of the disease. Results of this exploratory analysis suggest that further study of the effects of metformin on cognitive dysfunction due to AD should focus on individuals at earlier stages of AD, with a particular focus on the mechanism of action of any putative salutary effects.

P1-30: PREVENTION OF COGNITIVE DECLINE AND IMPROVEMENT OF INNATE IMMUNITY IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT BY OMEGA-3 FATTY ACID AND ANTI-OXIDANT SUPPLEMENTATION. M. FIALA *(Surgery Department, UCLA, Los Angeles, CA, USA)*

Background: Preventive therapy of mild cognitive impairment (MCI) patients is based on repairing the innate immunity centered on macrophages. Therapeutic antibodies are helpless in repairing innate immunity. The macrophages of MCI patients are deregulated to either inflammatory M1 or pro-resolution M2 type, but macrophages of all AD and MCI patients are defective in phagocytosis and degradation of amyloid-beta1-42 (Abeta). Cellular defects of macrophages include defective migration, subcellular transport, and propensity to apoptosis from fibrillary Abeta related to transcriptional, genetic, epigenetic, and metabolomic mechanisms in individual patients. Exogenous Abeta increases inflammation in peripheral blood mononuclear cells

(PBMCs) of patients in comparison to controls. The lipid modulator from docosahexaenoic acid (DHA) called resolvin D1 (RvD1) and the hormonal form of vitamin D3 termed 1,25dihydroxyvitamin D3 (1,25D3) promote Aβ1-42 phagocytosis and regulate inflammatory genes in macrophages and PBMCs. Omega-3 fatty acids DHA and EPA are precursors of the lipid modulators resolvins, protectins and maresins that resolve inflammation. *Methods:* Prospective study of 18 MCI patients (up to 2 years) supplemented with omega-3 antioxidant drink "Smartfish" (Oslo, Norway), which is stabilized against oxidative degradation by botanical additives (pomegranate, chookberry and transresveratrol; curcumin in select patients) and vitamin D3 ; Flow cytometric test of Abeta phagocytosis (mean fluorescence intensity (MFI) units; mRNA testing by PCR; M1M2 testing of macrophages using anti-CD54, anti-CD80, anti-CD163, anti-CD206 (M1M2 ratio = CD54+CD80/CD163+CD206); Minimental state examination (MMSE); RvD1 (pg/ml) EIA assay. *Results:* MCI patients were separated according to the initial M1M2 ratio into non-inflammatory (M1M2 ratio <1) and inflammatory (M1M2 ratio>1) patients. On nutritional supplementation by the Smartfish drink, MMSE (Mean (M) ~26) was maintained in non-inflammatory but decreased in inflammatory patients. MFI increased in both groups. The M1M2 ratio increased in the non-inflammatory patients to 2.7 and marginally increased in inflammatory patients to 3.55. Transcription of inflammatory genes increased in the non-inflammatory patients and was not changed in the inflammatory patients.

Category	duration (months)	MMSE		MFI		M1M2	
		initial	final	initial	final	initial	final
A. Noninflammatory							
(n=6)	M=14.8	M=25.83	26.00	496.68	1272.17	0.79	2.70
		S.D.1.84	4.43	321.28	408.30	0.31	0.91
B. Inflammatory							
(n=5)	M=10	M=27.00	26.20	584.60	1943.40	3.40	3.55
		S.D.4.24	5.93	389.29	869.53	0.98	1.65

Conclusions: Nutritional supplementation of MCI patients by omega-3 and antioxidants maintained or improved cognition in Apo E3/E3 genotype patients but failed in 3 of 6 Apo E3E4 genotype patients. The supplementation improved Abeta phagocytosis and regulated macrophage type to M1/M2 pro-phagocytic, mildly inflammatory type in both groups. Therefore, omega-3/antioxidant supplementation is beneficial in individual MCI patients who are observed and treated in a personalized fashion. Large studies of MCI patients fail due to heterogeneity of patients and lack of effective therapy of innate immunity.

P1-31: ACCELERATING PATIENT RECRUITMENT IN EARLY ALZHEIMER'S DISEASE. HANS CHR HOECK[1], METTE SKAKSEN[2], TUE K RASMUSSEN[2], PETER ALEXANDERSEN[3], LINE M LINDGREN[4], ANTHONY FRANKLAND[1], ROGER BULLOCK[1] *((1) CCBR, Stans, NW, Switzerland; (2) CCBR, Aalborg, Denmark; (3) CCBR, Vejle, Denmark; (4) CCBR, Copenhagen, Denmark)*

Background: The disappointing effects of treatments targeting patients with more advanced stages of Alzheimer's Disease (AD) has prompted a paradigm shift towards the development of drugs targeting the very early stages of the disease. This generates several new challenges for the traditional investigator sites. The majority of the target population for the very early stages are not patients yet and as such not in contact with specialist clinics. In addition, both the number of subjects that needs to become pre-screened and the total number of patients included per study has increased. CCBR has over the last 18 month built a dedicated cross functional research team with the objective not only to meet all requirements needed in this therapeutic area but also to optimize recruitment and research performance in trials in AD disease. The aim of this study is to present CCBR's recruitment performance in our first trial in patients with mild to moderate AD. CCBR was included as one of the rescue sites in order to achieve the total number of patients needed in Europe (EU). The Study closed four weeks after CCBR's commencement and contributing to having the end date brought forward. The average enrolment per site per month in the EU participating sites was 0.75 patient screenings per site per month and 0.25 randomizations per site per month. The average SF rate for the EU participating sites was 33 %. *Methods:* Three CCBR sites were engaged to take part. The sites had established capacity in the conduct of clinical trials and further investment in training in specific knowledge and technical capabilities such as cognitive rating assessment was already in place through a well-recognized global vendor in the field. The training was supplemented with study specific training provided in a fast track manner through very close working relationships with the local sponsor representatives as well as the sponsor's third party training provider. A range of material needed for the different recruitment technologies was prepared in advance and submitted for approval by the Ethic Committee. This included material used for recruitment through: Facebook; Newspapers; Alzheimer's magazines; Cooperation with GP´s and ophthalmologist; Cooperation with dementia nurses; Posters and brochures. In parallel all logistics and preparations were implemented and the sites were ready to recruit patients from day one of the approval of the study. *Results:* The 3 sites were initiated in august, 2015 and were only active for 4 weeks as the study achieved the target. A total of 49 patients were screened averaging 16.3 patients per site/month. The SF rate is currently 28% and may increase as not all patients are currently randomized. *Conclusion:* The ability of sponsors to achieve the aims of their clinical research programs in AD in the coming years is going to depend on finding a solution to the challenges of finding participants, successfully engaging with them and their partners in order to enroll them into studies and having the capacity to manage the high burden of work associated with the activities of running the protocol. The data from the present study may point the way how to manage the paradigms and help the industry to achieve the aims of their huge research programs scheduled for the coming years in the early stages of AD.

P1-32: EFFICIENCY OF COGNITIVE REHABILITATION IN ALZHEIMER'S DISEASE: A ONE YEAR FOLLOW-UP STUDY. SOPHIE GERMAIN[1,2], VINCIANE WOJTASIK[1], FRANÇOISE LEKEU[1], ANNE QUITTRE[1], CATHERINE OLIVIER[1], VINCIANE GODICHARD[1], ERIC SALMON[1,3] *((1) Memory Clinic, Department of Neurology, C.H.U. Liège, Belgium; (2) Neuropsychology Unit, Department of Psychology : Cognition and Behavior, University of Liège, Belgium; (3) Cyclotron Research Centre, University of Liège, Belgium)*

Backgrounds: For now, the efficacy of medications for the treatment of Alzheimer disease (AD) is limited to delaying the progression of symptoms. Therefore, it remains necessary to develop non pharmacological treatments to help people to deal with cognitive and functional impairments due to AD. This study focuses on one specific non-pharmacological intervention: the cognitive rehabilitation (CR), referring to an individualized approach that helps people with cognitive impairments by improving functional ability, and enabling patients to attain personally relevant goals. The general procedure of the present revalidation program starts with the identification by participants of some activities of interest, followed by the choice of a limited numbers of realistic activities on which to work. A first observation of the activity (at baseline) allows defining strategies for progressive interventions that may be adapted. After evaluation, the knowledge about the optimal strategies is explained to patients'

relatives. A key aspect of this intervention is to thoroughly evaluate the functional level of the patient. During the rehabilitation, errorless progressive adaptation (Kessels & Hensken, 2009) and spaced retrieval are frequently used for progressive acquisition of a new ability or a new procedure (Thivierge et al, 2008), written instructions are provided with step by step procedure and exercises are given where each step had to be mastered by the patient before moving to the next one (Lekeu et al, 2002). Furthermore, an adaptation of the external environment is frequently required. This study aimed at determining whether CR would improve patients' autonomy and reduce caregivers' burden immediately after the intervention and in the long term (one year follow-up), even when global cognition is deteriorating. *Methods:* Design. The CR program consists in 90-minute weekly individual sessions during a 3 months period. Initial (T1), post intervention (T2; 3 months), 6-month follow-up (T3) and 12 month follow-up (T4) assessments were carried out. *Participants:* 119 patients were involved (mean age = 73.21 ± 8.4). Initial MMSE was 23.7 ± 3.69. At 12 month follow-up, MMSE was 20.63 ± 5.58. Main diagnosis was AD (51.26%). Caregiver was spouse in 70%. To date, 52 patients have completed the 12 months follow-up. *Measures:* The Profinteg scale. This tool focused specifically on impairment in instrumental activities of daily living IADL (currently 98) that is due to cognitive deficits, in order to efficiently guide cognitive rehabilitation of IADL (Anselme et al, 2013). The scale is composed of two parts: the patient and the caregiver's part. Both are asked to identify and to evaluate the degree of severity of each problematic activities, patient determine the importance of this activity in daily live and caregiver determine the burden both objectively (number of hours spent to palliate patient deficit) and subjectively (arduousness to assume the task). The Zarit burden scale was also administered as a global burden measure. *Results:* (1) Patient's dependence. Results showed an significant effect on the global patient's dependence [$F(3,153)=7.17$, $p<.001$]. Planned comparisons showed a significant reduction of the global dependence immediately after the end of the revalidation program [$F(1,51)= 23.51$, $p<.001$]. However, this reduction is followed by an increase of the dependence over one year. Analyses demonstrated a significant effect of the time of evaluation on dependence for adapted activities [$F(3,153)=39.88$, $p<.001$]. The decrease occurred between T1 and T2 [$F(1,51)= 100.51$ $p<.001$]. This reduction faded slightly between T2 and T3 [$F(1,51)= 6.77$, $p<.05$], but remained stable subsequently (T1 versus T4: $F(1,51)= 29.54$, $p<.001$]. (2) Objective charge. We also observed an significant effect of time of evaluation on relatives' objective charge [$F(3, 153)=5.32$, $p<.005$]. Specifically, a decrease in the score of objective charge was revealed between T1 and T2 [$F(1,51)=8.99$, $p<.005$]. However, this reduction dimmed with time. (3) Subjective charge. Analyses demonstrated a significant effect of the time of evaluation on subjective charge [$F (3, 153)=10.943$, $p<.001$]. Interestingly, results of the planned comparison indicated that the decrease was marked between T1 and T2 [$F(1,51) =20,72$, $p<.001$] and stayed at a low level after one year. (4) Zarit score No significant effect was found. *Conclusion:* While global cognitive performance decreased over one year, our results demonstrated a positive impact of CR with an increase in patients' autonomy for adapted activities and a reduction in caregivers' burden. Interestingly, we found no effect on the Zarit score. One explanation could be that the Zarit scale is too general for detecting the effect of such a specific program tailed to patients' specific needs. This finding highlights the importance of a specific and detailed evaluation of the patient's functional level when the efficiency of CR is assessed. So, individualized and specific CR, based on a detailed functional evaluation, can offer benefits for people with AD and their caregivers. These results are encouraging in conducting more CR programs in order to help people confronting to cognitive disorders. *References:* Anselme, P., Poncelet, M., Bouwens, S., Knips, S., Lekeu, F., Olivier, C., Quittre, A., Van Heugten, C., Warginaire, S., Wojtasik, V., Verhey, F., Salmon, E., & Majerus, S. (2013). Profinteg: A tool for real-life assessment of activities of daily living in patients with cognitive impairment. Psychologica Belgica, 53(1), 3-22. Kessels, R. P., & Hensken, L. M. (2009). Effects of errorless skill learning in people with mild-to moderate or severe dementia: a randomized controlled pilot study. NeuroRehabilitation, 25, 307-312. Lekeu, F., Wojtasik, V., Van der Linden, M., & Salmon, E. (2002). Training early Alzheimer patients to use a mobile phone. Acta Neurol Belg, 102, 114-121. Thivierge, S., Simard, M., Jean, L., & Grandmaison, E. (2008). 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P1-33: CLINICAL CORRELATES OF COGNITIVE SCALES USED AS PRIMARY ENDPOINTS IN PRODROMAL ALZHEIMER'S DISEASE CLINICAL TRIALS. STEVEN D EDLAND[1,2] *((1) Department of Neurosciences, University of California San Diego, La Jolla, CA, USA; (2) Division of Biostatistics, Department of Family & Preventive Medicine, University of California San Diego, La Jolla, CA, USA)*

Background: The primary outcome measures for recently initiated trials in preclinical and prodromal Alzheimer's disease are novel composite cognitive scales composed of linear combinations of subscales and items from existing cognitive scales most sensitive to the earliest stages of disease. Only limited normative data are available for these composite endpoints, limiting our ability to describe the practical relevance of change in scores and, in particular, treatment efficacy in the event of a positive trial. This paper explores methods of describing the potential clinical significance of treatment effects observed in trials using novel cognitive scale primary endpoints. *Method:* Logistic regression analysis was applied to cross-sectional data from large-scale pilot studies to characterize the probability of loss of specific clinically meaningful endpoints as a function of scores on the cognitive scales. Graphs and tables listing the probability of crossing clinically meaningful thresholds of functional performance are used to characterize clinical function across the range of cognitive performance measured by the cognitive scales. Two examples are presented. Data from 398 subjects with mild cognitive impairment (MCI) enrolled in the joint NIH/pharmaceutical industry funded Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort study were used to characterize the probability of meeting a range of clinically meaningful milestones as a function of performance on the Cognitively Boosted Clinical Dementia Rating Scale (CB-CDR). Similarly, data from 103 cognitively normal elderly with genetic predisposition to Alzheimer's disease enrolled in the Alzheimer's Disease Cooperative Study "Prevention Instrument" protocol were used to characterize the probability of meeting clinically meaningful milestones as a function of performance on the ADCS-Preclinical Alzheimer Cognitive Composite (ADCS-PACC). *Results:* Subjects with high scores on the CB-CDR retained most instrumental activities of daily living (ADLs), but approximately 25% had trouble managing personal finances and 50% failed to remember appointments. Conversely, among subjects in this population with low scores on the CB-CDR, approximately 75% had trouble managing finances and 85% failed to remember appointments. Subjects with high scores on the ADCS-PACC retained most instrumental ADLs. An estimated 90% of subject at one standard deviation above mean performance on the PACC retained the ability to manage personal finances; this percentage reduced to 75% among subjects one standard deviation below mean performance on the ADCS-PACC. *Conclusions:* We have used data from two large studies implemented expressly to inform the design of preclinical and prodromal Alzheimer's disease clinical trials to demonstrate a method for characterizing the

probability of maintaining activities of daily living as a function of scores on cognitive scales. Change on composite cognitive scale clinical trial endpoints may have little meaning to relevant stakeholders, including FDA regulators, prescribing physicians, and patients. The methods present here may be one approach to attaching «clinical meaningfulness» to the novel cognitive composite outcome measures used in these Alzheimer trials. Nonetheless, post-marketing surveillance will likely be required to confirm the functional effects of treatment.

P1-34: DAILY FUNCTIONING BENEFITS OF ADDING MEMANTINE TO STABLE CHOLINESTERASE TREATMENT IN PATIENTS WITH MODERATE TO SEVERE ALZHEIMER'S DISEASE: A POST HOC POOLED FACTOR ANALYSIS. GUSTAVO ALVA[1], NOEL ELLISON[2], BIPLOB DASS[3], SUZANNE HENDRIX[2] *((1) ATP Clinical Research, Costa Mesa, CA, USA; (2) Pentara Corporation, Salt Lake City, UT, USA; (3) Prescott Medical Communications Group, Chicago, IL, USA)*

Backgrounds: In Alzheimer's disease (AD), daily functioning is a key determinant of patients' well-being and caregiver burden. Individuals with moderate to severe AD are frequently treated with a combination of a cholinesterase inhibitor (ChEI; usually donepezil) and memantine. Two similarly designed, 24-week, randomized, placebo-controlled trials of memantine in patients with moderate to severe AD receiving stable ChEI treatment have been conducted: MEM-MD-02 (N=403, donepezil) and MEM-MD-50 (N=676, any ChEI [donepezil: 69%]). In both trials, memantine was numerically superior to placebo on the 19-item Alzheimer's disease Cooperative Study – Activities of Daily Living scale (ADCS-ADL19), a measure of daily functioning; however, the effect was statistically significant in one trial only. In order to better ascertain the effects of memantine on daily functioning in this patient population and assess potential clusters of functional tasks that improved together, we performed a pooled post hoc analysis of the ADCS-ADL19 scores. *Methods:* Patient-level data were pooled from trials MEM-MD-02 and MEM-MD-50, to allow comparison between treatment groups (placebo/ChEI, n=525; memantine/ChEI, n=531). Factors were derived using a principal components analysis based on change-from-baseline item values (placebo and memantine groups combined), a varimax rotation, maximum loading for each item, and eigenvalues of ≥1 for each factor with a designated maximum of 4 factors. Between-group comparisons of item and factor score changes across the entire trial duration were conducted using a mixed-effects model with repeated measures (MMRM) analysis using a compound symmetric covariance structure that included terms for treatment group, visit, treatment-by-visit interaction, baseline score, baseline-by-treatment interaction, and center as a random effect (α=0.05). Baseline-to-Endpoint changes were estimated using both observed cases (OC) and last observation carried forward (LOCF) approaches for handling missing data. No adjustments for multiple comparisons were made. *Results:* At week 24, significant advantages of memantine/ChEI treatment over placebo/ChEI were observed for the items of grooming (P<0.001), conversing (P=0.010), and finding belongings (P=0.002). No other ADL items demonstrated significant between-group differences. The factor analysis identified 4 subscales: basic ADLs (eating, walking, toileting, bathing, grooming, dressing; loading value range: 0.41-0.71), higher-level ADLs requiring communication/comprehension skills (using the telephone, watching television, conversing, finding belongings, traveling, being left alone; loading value range: 0.37-0.58), simple praxis (turning faucet on, turning faucet off, turning light on; loading value range: 0.53-0.80), and praxis items requiring visuo-spatial and memory skills (clearing the table, obtaining a beverage, disposing of litter, turning light off; loading value range: 0.35-0.63). The MMRM analysis revealed that at week 24 the memantine/ChEI group declined less than the placebo/ChEI group on each factor subscale: basic ADLs (least squares difference [LSDiff]=0.376; P=0.017), higher level ADLs requiring communication/comprehension skills (LSDiff=0.265; P=0.156), simple praxis (LSDiff=0.077; P=0.043), and praxis items requiring visuo-spatial and memory skills (LSDiff=0.300; P=0.017). The Baseline-to-Endpoint change analyses (OC and LOCF) largely corroborated these findings. *Conclusion:* In this post hoc analysis, the addition of memantine to stable ChEI treatment was associated with significant improvements over placebo for the items of grooming, conversing, and finding belongings. The factor analysis identified 4 subscales, and significant advantages of memantine/ChEI treatment over placebo/ChEI were observed on the subscales for basic ADLs, simple praxis, and praxis items requiring visuo-spatial and memory skills.

P1-35: IMPROVEMENT IN VISION, COGNITION, AND NEUROPSYCHIATRIC SYMPTOMS FOLLOWING CATARACT SURGERY IN SUBJECTS WITH DEMENTIA. ALAN J LERNER[1,4], SARA M. DEBANNE[2], JULIE K BELKIN[3,4], JONATHAN H LASS[3,4], PAULA K OGROCKI[1,4], TATIANA M RIEDEL[6], SUSIE A SAMI[4], THOMAS L STEINEMANN[3,5], GROVER C GILMORE[6] *((1) Department of Neurology, Case Western Reserve University, Cleveland, OH, USA; (2) Epidemiology and Biostatistics Case Western Reserve University, Cleveland, OH, USA; (3) Department of Ophthalmology and Visual Sciences, Case Western Reserve University, Cleveland, OH, USA; (4) Department of Neurology, University Hospitals Case Medical Center, Cleveland, OH, USA; (5) Department of Ophthalmology, MetroHealth Medical Center, Cleveland, OH, USA; (6); Jack, Joseph and Morton Mandel School of Applied Social Sciences, Case Western Reserve University, Cleveland, OH, USA)*

Background: Elderly people frequently suffer from multiple diseases, and multi-morbidity often disproportionately adversely affects their health. Alzheimer's disease (AD) and cataracts are both aging-related diseases, and often co-occur. Cataract removal in a dementia patient should improve visual function, although dementia may affect visual pathways, but has not been well studied. Since memory is perception dependent, improvement in vision may improve cognitive status and other symptoms of dementia. There is oft-expressed concern that safety risks and potential surgical complications of cataract surgery on dementia patients may be sufficiently great to warrant withholding treatment. The present study is evaluating the impact of cataract surgery on the vision, cognition and neuropsychiatric status of dementia patients enrolled in a clinical trial. *Methods:* The study is an on-going NIH sponsored clinical trial with two cohorts suffering from co-morbid dementia and visually significant cataracts (best corrected acuity≥ 20/40). 47 participants have been randomized into either the intervention (cataract surgery) group (N = 32) or the control (no surgery for 6 months) group (N = 15) and followed longitudinally for 6 months. Primary outcome measures are visual acuity (Early Treatment Diabetic Retinopathy Study Chart (ETDRS, Snellen-equivalent), cognitive function (Mini Mental Status Exam), and Neuropsychiatric Inventory (NPI). Subjects were tested at baseline and at 6-months post-baseline. Subjects were recruited from Neurology and Ophthalmology clinics at University Hospitals Case Medical Center and Metro Health Medical Center. Participants were included if diagnosed with dementia (CDR 0.5-3.0) and at least 1 visually significant cataract and excluded if they have Down syndrome, advanced macular degeneration or other possible confounding optical abnormality, or contraindication to cataract surgery. Subjects were stratified according to dementia severity using the Clinical Dementia Rating Scale (CDR) and visual acuity in the better eye (ETDRS Snellen-equivalent <20/70 = moderate impairment, >20/70 = severe impairment). ETDRS Far Visual Acuity

testing was performed in the typical clinical setting (at 4 meters), using the ETDRS chart. Analyses were conducted on both logMAR and Snellen-equivalent denominator values. A decrease in the logMAR and/or the Snellen denominator value indicates an improvement in visual acuity. *Results:* Baseline mean MMSE and CDR scores in the intervention group were 19.1 and 1.5 respectively, and in the control group, 16.4 and 1.7. ETDRS far visual acuity: Mean changes in the right eye (OD) and left eye (OS) logMAR values for the intervention group are -0.26 and -0.24 respectively, indicating improvement. The control group did not show a change in vision with logMAR (OD mean change = -0.03, OS mean change = 0.00). The corresponding Snellen-equivalent denominator values indicate a change of -5 lines in both eyes in the intervention group while the control group values remain static (OD change = -2 lines, OS change = -1 line. Mean MMSE score change was +0.17 points while the control group showed a six-month MMSE change of -2.21points. This compares to a meta-analysis of the expected annual rate of MMSE change (Han et al., 2000) which produced a pooled estimate average rate of a -3.3 point decline. NPI scores of intervention group subjects improved (mean change = -4.6) and worsened in the control group (mean change = +4.0). Caregivers for the intervention group showed a reduction in NPI caregiver distress ratings with mean change = -2.47; NPI caregiver distress rating of caregivers for control group subjects had a mean change of = 0.87; *Conclusion:* Preliminary results of an ongoing study demonstrate that cataract removal positively affects visual acuity, cognitive scores and behavioral indices while lowering caregiver distress over 6 months. Results and challenges of recruitment will be discussed in detail. Cataract removal should be studied in a larger Phase 3 clinical trial, and clinically considered regardless of dementia status. (NCT: 00921297)

P1-36: THE ADAS-COG NAME ITEM: MORE TROUBLE THAN IT IS WORTH? SELAM NEGASH[1], CHRISTOPHER WEBER[1], LORI GARZIO[1], CHRISTOPHER RANDOLPH[1,2]
((1) MedAvante, Inc; (2) Loyola University Medical Center)

Background: The Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) is the most widely used primary endpoint in AD trials. The high error rates in administration and scoring of this scale, however, have lead to the increased use of centralized oversight, including recording and review of these assessments. This quality control practice is complicated by the Name item on the Orientation subtest, which requires the subject to provide his/her own name. This has implications with respect to release of personal health information, which can occur even in the absence of recording, if the rater mistakenly writes down the name on source documentation. The Coalition Against Major Diseases (CAMD), a public-private-partnership program at Critical Path (C-Path), has launched C-Path Online Data Repository (CODR) in an effort to accelerate advances in AD therapeutic development. The database contains data from placebo arm of over 20 clinical trials of AD and MCI. The ADAS-Cog data from this database were reviewed to examine the Name item from the Orientation subscale. These data were also augmented with assessments from two double-blind, placebo-controlled AD clinical trials that underwent central review by MedAvante clinicians. Our goal was to examine the error rates on the name item of the ADAS-Cog, and the extent to which a score on this item contributes to the orientation score and also the total score. *Methods:* There were four studies in the CODR containing ADAS-Cog data, which generated a total of 6,185 responses to the name item question. Assessments were reviewed to determine the percentage of responses to the name question that were scored as 'incorrect'. The correlations between the name item score and the orientation score (and total score) were examined. *Results:* In the CODR, 28 out of 6185 (0.45%) responses to the name item were scored as 'incorrect'. The name item showed weak correlation with the total score (r = 0.215). Further, Chronbach's alpha for the 8 orientation items was 0.97, and removing the name item did not affect the alpha value. *Conclusions:* The name item in the ADAS-Cog has a very low error rate; as a result, it does not contribute to the variance in the total score and also has weak internal consistency with the other orientation items. Further, it creates central oversight issues, conflicting with protected health information disclosure. Thus, it is recommended that the ADAS-Cog instrument be modified to eliminate the name item from the orientation subscale, and simply providing credit for that item in calculation of the total score. This will enable centralized oversight of the administration of this scale without the potential exposure of personal health information.

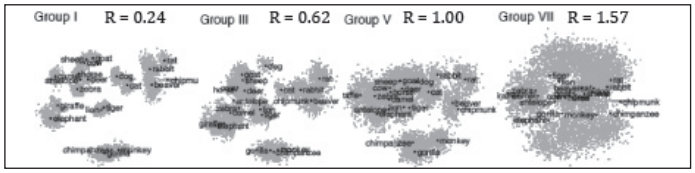
P1-37: MEASURING EXECUTIVE FUNCTION USING A SIMPLE, CULTURE- AND EDUCATION-FREE TASK. MICHAEL D LEE[1], MELINEA ABRAMYAN[1], WILLIAM R SHANKLE[1,2,3] *((1) Dept. of Cognitive Sciences, University of California at Irvine, Irvine, CA, USA; (2) Medical Care Corporation, Irvine, CA, USA; (3) Hoag Neuroscience Institute, Hoag Memorial Hospital, Newport Beach, CA, USA)*

Background: Executive function is impaired in the mild cognitive impairment (MCI) and pre-MCI stages of Alzheimer's disease (AD). Measuring executive function often requires complex tasks with detailed instructions that confound test interpretation and scoring, thus increasing measurement signal noise. Anthropological research on human behavior identified a simple, 2-to-4 minute, executive function task - triadic comparisons of animals – with minimal cultural, educational, and linguistic bias. Graphical Bayesian modeling of this task was used to assess judgment and semantic organization in groups and individuals. *Methods:* The first visit of 2,712 subjects was assessed using the MCI Screen (MCIS). One task of the MCIS consists of 12 triadic comparisons of 9 animals, randomly selected from 21 animals, in which each animal appears in four triads. The task instruction per triad is, "which animal is most different from the other two?" 8 severity groups were defined in terms of subjects' delayed free recall performance. For each group, Bayesian methods were applied to the triad task data to construct a 2-dimensional representation of underlying processes of semantic organization and judgment. The Bayesian methods resulted in assigning each of the 21 animals a 2-dimensional Euclidean coordinate. Applying spatial statistics (Dry et al. 2012) to the distribution of the 21 animals in each severity group afforded a quantitative and visual measure of their semantic clustering and judgment. This method was also used to study 2,216 individuals, consisting of 8 severity groups with 277 individuals per group. The semantic organization of animals is largely universal for all humans because it is relatively independent of culture, ethnicity, language and education (Romney & Moore, 1998). Individuals who are less impaired were assumed to use this universal representation whereas more impaired individuals were assumed to deviate from it. This assumption was implemented as a Luce-choice rule, in which the similarities between animals are affected by an individual-level "response determinism parameter" in the Bayesian model. *Results*: Figure 1 shows that semantic organization becomes more random with increasing memory impairment as does the spatial statistic, R (from Groups I to VII). Figure 2 shows the response determinism parameter's distribution of the subjects in each group (black), superimposed on its distribution over all groups (gray). From groups 1 VIII, the reponse determinism shifts progressively to the left (greater deviation from the universal representation of semantic organization). *Conclusion:* Triadic comparisons of animals are a relatively universally represented executive function task of judgment and semantic organization that becomes more randomly represented with increasing severity of episodic memory. Individual differences

are measurable as memory severity increases. This executive function task is the distracter part of the MCI Screen, an 8-10 minute test that also assesses working memory, episodic memory, delayed recognition memory, associative memory, and is 96-97% accurate in discriminating between normal aging and MCI.

Figure 1

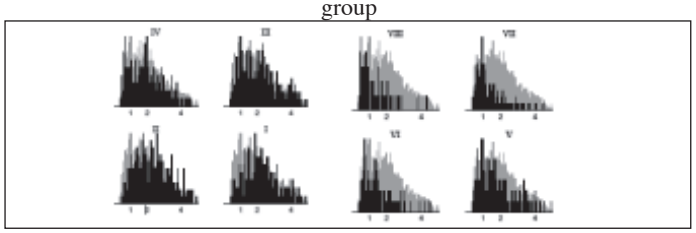
Semantic clustering of animals per severity group



R: Spatial clustering statistic

Figure 2

Distribution of response determinism for individuals in each severity group



P1-38: AN INNOVATIVE COGNITIVE INTERVENTION GROUP PROGRAM FOR PATIENTS WITH MILD COGNITIVE IMPAIRMENT: TRAIN YOUR BRAIN. YANHONG DONG[1,2], KIM A GRANLAND[2,3] *((1) Psychological Medicine, National University Hospital, Singapore; (2) Memory Ageing and Cognition Center, Pharmacology, National University Health System, Singapore; (3) James Cook University, Singapore Campus, Singapore)*

Backgrounds: An innovative cognitive intervention group program is required for patients with Mild Cognitive Impairment (MCI) due to the lack of pharmaceutical treatments for this population. The «Train Your Brain» (TYB) cognitive intervention group program customized for Asian patients and is currently under development to remediate cognitive impairments, promote psychological well-being and memory self-efficacy, as well as maintain independent functioning in older adults with MCI. The TYB program has recently been delivered as a clinical service and was well received with good patient attendance. We aimed to evaluate the efficacy of TYB program using various measures such as cognition, psychological wellbeing, memory self-efficacy and daily functioning. This study aims to discuss the contents of TYB program and study design of a pilot feasibility and program efficacy evaluation study for TYB intervention. Additionally, the adaptation of culturally and linguistically appropriate assessment measures for the TYB program evaluation will be discussed. *Methods:* The pilot program evaluation study has two phases. In Phases 1, the TYB group will attend a nine-session psycho-education intervention group program which will provide information on the role of diet, exercise and mental stimulation in healthy brain functioning. The intervention will also provide practical cognitive training for participants to practice in session and for weekly homework tasks. For example learning and practicing face-name strategies to help improve their functional memory. The control group will be waitlisted. Both groups will be assessed on pre/post measures of cognition, psychological wellbeing, memory self-efficacy and daily functioning. Cognitive functioning will be measured by brief tests including the Mini-Mental State Exam and Montreal Cognitive Assessment. While a formal neurocognitive battery consisting of Digit Span Forward and Backward, Rivermead Behavioural Memory Test and Brixton Spatial Anticipation Test will be used to assess attention/working memory, functional verbal and visual memory, as well as executive function. Self-report measures of memory include Cognitive Failures Questionnaire and Memory Self-Efficacy Questionnaire. Psychological wellbeing and moods will be assessed using the Depression, Anxiety and Stress Scale, Quality of Life Scale and the Scale of Psychological Wellbeing. Patient's daily functioning will be assessed by their informant answering the AD8 Dementia Screening Interview and the Bayer Activities of Daily Living Scale (B-ADL). In Phase 2, the TYB group will attend a computerised brain training program comprising nine sessions using cognitive training software (e.g. Lumosity). The control group will remain on a waiting list. The feasibility of the computer training program will be assessed by measuring frequency, satisfaction, usability and acceptability after training is completed. *Results:* The randomized control trial design, contents of TYB program, culturally and linguistically appropriate measures for program efficacy evaluation will be discussed. *Conclusion:* The findings will provide evidence for the feasibility of a cognitive intervention group program, including computerised training, and will assist in the implementation of an evidence-based cognitive intervention service for MCI patients.

P1-39: IMPACT OF EXPERT DATA REVIEW AND CENTRALIZED SCORING ON TESTRETEST RELIABILITY OF THE ADASCOG. ALEXANDRA S ATKINS[1], IOAN STROESCU[1], VICKI G DAVIS[1], TINA TSENG[1], TIFFANY WILLIAMSON[1], KELLEY BOYD[1], LYN HARPER MOZLEY[2], TIFFINI VOSS[2], KERRY BUDDMCMAHON[2], RICHARD SE KEEFE[1,3] *((1) NeuroCog Trials, Durham, NC, USA; (2) Merck & Co, Inc., Kenilworth, NJ, USA, (3) Duke University Medical Center, Durham, NC, USA)*

Background: The Alzheimer's Disease Assessment Scale Cognitive Subscale (ADASCog) is the primary neurocognitive outcome measure in many clinical trials for mildmoderate Alzheimer's disease (AD). Despite wide use, variations in administration and scoring are well-documented (1), and may reduce reliability and sensitivity of the measure (2). Clinical trials devote considerable effort and resources to rater training and quality assurance of ADAS-Cog endpoints. To examine the efficacy of these efforts in improving ADASCog reliability, we evaluated the impact of central data review on ADASCog testretest reliability in an ongoing, multicenter, placebo-controlled treatment trial (NCT01852110). *Methods:* Data included 3 pretreatment ADASCog12 assessments for 152 randomized subjects with a diagnosis of mildmoderate AD. Tests were administered and scored by trained, certified raters at investigational sites. In order to qualify for rater training and certification, potential raters were required to submit credentials for review and approval. Once approved, raters completed all training and certification activities prior to testing. Following each ADAS-Cog administration in the trial, source documents and video media were submitted for central review by expert data monitors. Testretest reliability of sitereported and central scores was assessed with intraclass correlation coefficients (ICCs) across 2 pretreatment testretest intervals. Discrepancies between sitereported and central scores were described using the average sum of absolute differences (ASAD). The impact of central scoring on rates of missing data was also examined by comparing the rates of missing data for site-reported and central scores. *Results:* ICCs for both testretest intervals were improved for central scores compared to sitereported scores. Using all available data, Screening to RunIn ICCs were .78 for site reported scores and improved to .83 for central scores. RunIn to Baseline ICCs were .75 for site-reported scores and improved to .80 for central scores. Missing or invalid data

were present in 28% (42/152) of sitereported baseline assessments and impacted the total score in 22% (33/152) of tests. The baseline ASAD for the remaining 119 assessments was 2.2 (SD=3.56). Total ADASCog scores were recovered by central reviewers for all but 1 assessment. An additional 7 assessments were deemed invalid due to egregious errors in administration detected during central review, resulting in a final missing/invalid data rate of 5% (8/152). *Conclusions:* Central review by expert data monitors can improve testretest reliability of the ADASCog and substantially reduce the rate of missing data in clinical trials for mildmoderate AD. These findings suggest inclusion of central data review within a trial can improve the integrity of data collection of cognitive endpoints. *References:* (1) Connor & Sabbagh (2008). J Alzheimers Dis. 15(3): 461–464. (2) Schafer et al.(2011). Curr Alzheimer Res. 8(4):3736. *Disclosures:* AS Atkins is a full-time employee of NeuroCog Trials, Durham, NC, USA, and has received support from National Institute of Mental Health. I Stroescu, V Davis, T Tseng, T Williamson and K Boyd are employees of NeuroCog Trials. L Harper Mozley, T Voss and K BuddMcMahon are employees of Merck & Co, Inc., Kenilworth, NJ, USA. RSE Keefe currently or in the past 3 years has received investigator-initiated research funding support from the Department of Veteran's Affair, Feinstein Institute for Medical Research, GlaxoSmithKline, National Institute of Mental Health, Novartis, Psychogenics, Research Foundation for Mental Hygiene, Inc., and the Singapore National Medical Research Council. He currently or in the past 3 years has received honoraria, served as a consultant, or advisory board member for Abbvie, Akebia, Amgen, Asubio, AviNeuro/ChemRar, BiolineRx, Biogen Idec, Biomarin, Boehringer-Ingelheim, Eli Lilly, EnVivo/FORUM, GW Pharmaceuticals, Janssen, Lundbeck, Merck, Minerva Neurosciences, Inc., Mitsubishi, Novartis, NY State Office of Mental Health, Otsuka, Pfizer, Reviva, Roche, Sanofi/Aventis, Shire, Sunovion, Takeda, Targacept, and the University of Texas South West Medical Center. Dr. Keefe receives royalties from the BACS testing battery, the MATRICS Battery (BACS Symbol Coding) and the Virtual Reality Functional Capacity Assessment Tool (VRFCAT). He is also a shareholder in NeuroCog Trials, Inc. and Sengenix.

P1-40: CREATION OF A MOBILE RESEARCH TEAM TO ALLOW EQUAL OPPORTUNITY FOR PATIENTS WITH ALZHEIMER DISEASE. EMILIE CHRÉTIEN, JING XIE, CHRISTELLE MOUCHOUX, PIERRE KROLAK-SALMON *(CRC VCF, Hôpital des Charpennes, Villeurbanne, France)*

Distance from research reference center proposing clinical trials is a major barrier to patient's participation to research, involving a loss of opportunity. We develop a mobile research team to allow eligible and willing patients to participate to clinical research, by going out to them in their nearest hospital center. The mobile research team is composed of a sub-investigator, neuropsychologists, a nurse and a clinical research assistant. It goes to Hospital Centers to 1) inform patients previously identified by local healthcare team as eligible to participate to the study, about ongoing clinical trials at the Centre de Recherche Clinique « Cerveau, Vieillissement, Fragilité » in the field of Alzheimer Disease (AD), 2) perform on site all screening, inclusion and follow-up visits associated to clinical trials. Among requested hospital centers, centers of Villefranche and Vienne promptly showed their willingness for a partnership in the interest of patients. With the support of a pharmaceutical company, we can now propose two clinical trials targeting AD to patients. A physician and a pharmacist from each center will be declared as responsible for patient's pre-screening and follow-up of experimental medicines dispensation, respectively. In terms of feasibility, we are expected approximately 15 patients per month to be eligible to participate. The research mobile team allows patients of remote hospital centers to access new therapeutic treatment and research strategies. This action will be reinforced by deploying our activities to other centers and through the support of other pharmaceutical companies, to propose diverse types of clinical trials. We will further communicate with private doctors about the existence of a potential local research network for their patients. Overall, the research mobile team will facilitate the access to clinical trials by providing equal opportunity to all Alzheimer patients.

P1-41: EFFECT OF CIRCADIAN RHYTHM ON COGNITION TESTING IN A PHASE 2B MILD/MODERATE ALZHEIMER'S DISEASE (AD) STUDY. DANA C HILT, NANCY DGETLUCK, STEPHEN SAINATI, HANS J MOEBIUS *(FORUM Pharmaceuticals, Waltham MA, USA)*

Background: Cognition is affected by a variety of factors including circadian fluctuations over the course of the day. Most people have optimal cognition early in the day with variation, typically a decrease in cognition, as the day and evening progress. Additionally, patients with AD may have sleep disturbances or other alterations of their circadian rhythms. These factors may contribute to variation and challenges for signal detection in assessing cognition in patients with AD. *Methods:* We examined the impact of time-of-day cognition testing in a large (n=409) multinational (US and Eastern Europe) placebo-controlled Phase 2b mild/moderate 6-month AD study. The primary cognition measure in the study was the ADAS-Cog-13. Overall, 409 patients with mild/moderate AD (MMSE 14-24 and CDR-SB >2) were enrolled and treated with placebo or Encenicline 0.27, 0.9, or 1.8 mg/day. *Results:* The 1.8 mg/d Encenicline group [n=100 vs n=104 placebo] showed the largest treatment effect on the ADAS-Cog-13 [cohen's d ES at 6 months vs placebo of d=0.39, p=0.019 after multiplicity correction]. In order to assess the effect of variation in time-of-day cognition testing performance, patients who completed the 24 week study were analyzed according to the consistency of time-of-day ADAS-Cog-13 cognition testing. Patients in the 1.8 mg Encenicline treatment group whose ADAS-Cog-13 at 6 months was administrated at the same time of day (+ one hour) (n= 46, 1.8 mg Encenicline, n=40, placebo) at 6 months as compared to baseline had a treatment effect of d=0.5, p=0.039 vs those who did not: d=0.16, p=0.708 (n=37, 1.8 mg Encenicline, n=48, placebo). *Conclusion:* These results suggest that circadian rhythm effects on the assessment of cognition are a significant source of variability in interventional mild/moderate AD clinical trials. Taking this factor into consideration by assuring that cognition testing occurs in each specific patient at the same time of day (+ one hour) may decrease variability, enhance the ability to detect a procognitive signal, and more accurately measure the procognitive effects of a drug.

P1-42: THE IMPACT OF ELECTRONIC ADMINISTRATION OF THE ADAS-COG, MMSE AND CDR ON CLINICAL TRIAL DATA QUALITY. DAVID MILLER[1], TODD FEASTER[1], ANTONIO HERNANDEZ[1], JESSIE HE,[2] ALAN KOTT[3] *((1) Bracket, Wayne, PA, USA; (2) F. Hoffmann-La Roche, Shanghai, China (3) Bracket, Prague, Czech Republic)*

Background: The Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog), the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating Scale (CDR) are among the most commonly used inclusion and primary efficacy measures in Alzheimer's disease (AD) clinical trials. Earlier research has demonstrated considerable variability in how raters have been trained to administer and score the ADAS-Cog, MMSE and CDR in clinical trials. Moreover, prior research has also demonstrated error rates among clinical trial raters occurring upwards of 32% for the ADAS-Cog, 23% for the MMSE and 25% for the CDR on initial administration when using the paper-pencil version of

these scales. The impact of technology on society is unquestionable. Technological advancements are being incorporated into the conduct of AD clinical trials more so today than ever. One example is the use of electronic versions of assessment scales. The impact of an enhanced electronic version of the ADAS-Cog, MMSE and CDR on overall data quality was assessed when used in the WN28745 Marguerite RoAD study, a multi-national clinical trial in subjects with mild AD. *Methods:* After being trained and certified to rate the ADAS-Cog, MMSE and CDR, all raters' performance regarding accuracy in scale administration and scoring was assessed by a calibrated clinician at the initial Screening visit. The electronic versions of the ADAS-Cog (eADAS-Cog), MMSE (eMMSE) and CDR (eCDR) used in this trial were designed to be equivalent to the paper version of the scale. Additionally, the eADAS-Cog, eMMSE and eCDR were augmented with internal logic, standardized instructions and scoring conventions taken directly from the scale manuals and study specific training curriculum. These enhancements were intended to increase the likelihood the scales would be consistently administered and scored according to standard conventions. *Results:* All eADAS-Cog, eMMSE and eCDR scales at Screening were reviewed by a calibrated clinician to assess the accuracy of rater administration and scoring. 1009 eADAS-Cogs were reviewed and 101, or 10%, required a contact with the rater due to an error noted in scoring. Pearson's chi-square was performed and noted a significant reduction ($p < 0.001$) in error rates compared to the previously reported 32% found with the paper-pencil version of the scale. 1097 eMMSEs were reviewed and 107, or 9.8%, required a contact due to an error noted in scoring. This represents a significant reduction ($p < 0.001$) in error rates compared to the previously reported 23% found with the paper version of the scale. Finally, 886 eCDRs were reviewed and 38, or 4.3%, required a contact due to issues noted in administration and/or scoring. This also represents a significant reduction ($p < 0.001$) in error rates compared to the previously reported 25% found with the paper version of the scale. *Conclusions:* The use of an eADAS-Cog, eMMSE and eCDR designed with enhancements beyond the paper-pencil version, coupled with an in-study ratings surveillance program to identify errors in scoring and administration, can significantly improve data quality by reducing rater error, enhancing standardized administration/scoring and minimizing rater drift.

P1-43: THE INFLUENCE OF THE SUBCORTICAL ISCHEMIA AND COGNITIVE PATTERNS AND THEIR CHANGES IN NORMAL HOSPITAL VISITED ELDERLY. SANG JOON AHN[1], BON D KU[2], HYE-YOON KIM[2], MIN SUNG KOO[3] *((1) Neurology Department, Seoul National University, Seoul, South Korea; (2) Neurology Department, Catholic Kwandong University, Incheon, South Korea; (3) Psychiatry Department, Catholic Kwandong University, Incheon, South Korea)*

Backgrounds: Recent studies on the cognitive changes of normal elderly showed diverse results due to the variety of the methodology and the participants. The cognitive changes during normal aging related to the white matter ischemia showed two distinct patterns such as generalized cognitive decline and inhibitory dysfunction. The domestic longitudinal studies of the normal aging, however have been performed rarely and limited in South Korea. We performed a short term longitudinal study related to the normal cognitive changes who had visited university affiliated hospital for the cognitive evaluation. *Methods:* Participants were consecutively recruited from January 2008 to June 2012. On magnetic resonance imaging (MRI), deep white matter (DWM) ischemic lesions were classified into D1 (the longest diameter of DWM lesion <10 mm), D2 (10mm≤DWM≤24mm), and D3 (25mm <DWM). Likewise, perventricular white matter (PVWM) ischemic lesions were classified into P1 (caps or rim <5 mm), P2 (between P1 and P2), P3 (10 mm <caps or rim). The subcortical ischemia were divided into three groups according to combinations of DWM and PVWM ischemic lesions: Group I (mild ischemia: D1P1, D1P2, D2P1), Group III (severe ischemia: D3P3), and Group II with ischemia of remaining combinations. Seoul neuropsychological screening battery, blood tests and MRI were performed in all participants. Participants were divided into three groups according to the subcortical ischemia (minimal, moderate and severe). The three groups were matched in age, education and general cognition level. Follow up protocol and neuropsychological tests were analyzed in comparison with the initial examination. And follow-up neuropsychological tests and protocol were analyzed depending on the severity of subcortical ischemia. The three groups were matched in age, education and general cognition level. *Results:* A total of 95 Participants were recruited (76 in minimal, 15 in moderate and 4 in severe). Mean age were 62.0±11.7and female was predominant. Mean score of Korean version of mini-mental status examination (K-MMSE) was 27.1±2.7 and that of clinical dementia rating some of boxes (CDR-SOB) was 0.9±0.8. In clinical profiles, hypertension, hyperlipidemia, cardiac disease, stroke were common. Depending on the subcortical ischemia focal neurological sign ($p=0.015$) and Hachinski ischemic score ($p=0.004$), hypertension ($p=0.015$), cardiac disease ($p=0.027$) and stroke ($p=0.016$) were increased. By the increasing of subcortical ischemia, complex cognitive abilities such as multiplication and division of claculation were affected. Rey-Osterreith complex figure test (RCFT) recognition test of true positive ($p = 0.014$) and Korean color word stroop test (K-CWST) word reading correct ($p = 0.012$) were also affected according to the ischemic burden. In the follow-up cognitive function test practice effects was prominent in the K-MMSE place orientation. CDR-SOB score suggest the possibilities of the useful clinical tool in the longitudinal study of the normal cognitive function ($p = 0.009$). *Conclusion:* These results suggest that in the frontal and some parietal areas are sensitive cognitive domains in normal elderly. By the increasing of the subcortical ischemia the frontal inhibitory function and some parietal functions required complex cognitive abilities are more likely affected. During the course of normal aging, CDR-SOB score has the possibility of useful clinical tools of the longitudinal study of the normal cognition. The ischemia sensitive cognitive domains during normal cognition are frontal inhibitory dysfunction and visual memory recognition tests. *Keywords:* Subcortical ischemia, Normal cognition. Clinical profiles, Neuropsychological profiles, Longitudinal study

P1-44: RELATIONSHIP BETWEEN SUBJECTIVE AND OBJECTIVE MEMORY IMPAIRMENT IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT AND NORMAL AGING. MONTSERRAT ALEGRET[1], OCTAVIO RODRÍGUEZ[1], ANA ESPINOSA[1], GEMMA ORTEGA[1], ANGELA SANABRIA[1], SERGI VALERO[1,2], ISABEL HERNÁNDEZ[1], MAITÉE ROSENDE-ROCA[1], LILIANA VARGAS[1], CARLA ABDELNOUR[1], ANA MAULEÓN[1], ANNA GAILHAJANET[1], ELVIRA MARTÍN[1], LLUÍS TÁRRAGA[1], DORENE M. RENTZ[3,4], REBECCA E. AMARIGLIO[3,4], AGUSTÍN RUÍZ[1], MERCÈ BOADA[1] *((1) Alzheimer Research Center and Memory Clinic of Fundació ACE. Institut Català de Neurociències Aplicades, Barcelona, Spain; (2) Psychiatry Department. Hospital Universitari Vall d'Hebron, CIBERSAM. Universitat Autònoma de Barcelona, Spain; (3) Center for Alzheimer Research and Treatment, Department of Neurology, Brigham and Women's Hospital, Boston, MA, USA; (4) Department of Neurology, Massachusetts General Hospital, Boston, MA, USA)*

Background: Subjective cognitive decline (SCD) has been proposed as a risk factor for progression to Alzheimer's Disease (AD) dementia. Specifically, subjective memory impairment (SMI) refers to subjective awareness of initial memory decline undetectable with

existing standardized cognitive tests. The Face Name Associative Memory Exam (FNAME) was created to detect memory deficits in individuals with preclinical AD. We reported normative data of a Spanish version of FNAME (S-FNAME) in cognitively normal (CN) Spanish-speaking subjects older than 49 years. The aim of the present study was to determine whether higher SMI (measured with the Spanish modified version of the Memory Failures Everyday questionnaire, MFE-30) was related to worse memory performance (S-FNAME) or associated with greater affective symptoms in subjects older than 49 years; and whether MFE-30 and FNAME were able to discriminate between CN and MCI subjects. *Methods:* The Fundació ACE Memory Clinic attends routine outpatients on a daily basis and organizes an annual "Open House Initiative" (OHI) as a contribution to the World Alzheimer's Day. This initiative enables any individual older than 49 years of age to come to a Memory Clinic for free cognitive screening, with follow-up, if desired, facilitating access to complete neurological and neuropsychological assessments, including a reliable diagnosis to subjects who probably would not be referred by their primary care physician. From the 512 subjects examined in the OHI, 317 subjects were included in this analysis because they were older than 49 years, had preserved global cognition (MMSE≥ 27), were literate and without any sensory losses (CN= 196, Mild Cognitive Impairment (MCI)= 121). All subjects received S-FNAME, MFE-30 and the Hospital Anxiety and Depression Scale, and a comprehensive diagnostic assessment. A subset of CN participants was included in Fundació ACE Healthy Brain Initiative (FACEHBI), a longitudinal study of cognition, biomarkers, risk factors and lifestyle (cohort of 200 individuals with SCD). *Results:* MFE-30 scores were associated with affective symptoms but not with S-FNAME performances. S-FNAME scores were related to performance on memory variables of the NBACE: verbal long-term memory (r= 0.43) and learning (r= 0.44) of the Word List of WMS-III. Discriminability values between CN and MCI groups of MFE-30 and S-FNAME were similar (Sensitivity: 49.6, 52.9; Specificity: 85.1, 83.6, respectively). *Conclusions:* SMI was more related to depressive symptoms than to S-FNAME memory variables; and S-FNAME scores were related to other episodic memory test performances, but neither to affective symptoms nor to SMI. MFE-30 and S-FNAME were not optimal for discriminating between CN and MCI groups at baseline in this cohort. Longitudinal follow-up will determine if lower S-FNAME and higher SMI are related to increase risk of AD. *Keywords:* preclinical Alzheimer's disease, episodic memory, FNAME, subjective memory impairment, neuropsychology.

P1-45: REGIONAL WHITE MATTER DISRUPTIONS OF CINGULUM IN MILD COGNITIVE IMPAIRMENT DEFINED BY FUNCTIONAL AND COGNITIVE CRITERIA. YU-LING CHANG[1,2], YU-SHIUAN YEN[1], PEI-CING CHEN[1], CHIA-HUA LIN[1], YI-YUAN ZHUO[1], TA-FU CHEN[3], SUI-HING YAN[4], WEN-YIH ISAAC TSENG[2,5,6,7] *((1) Department of Psychology, National Taiwan University, Taipei, Taiwan; (2) Neurobiology and Cognitive Science Center, National Taiwan University, Taipei, Taiwan; (3) Department of Neurology, National Taiwan University, Taipei, Taiwan; (4) Section of Neurology, Renai Branch, Taipei City Hospital, Taipei, Taiwan; (5) Graduate Institute of Medical Devices and Imaging System, National Taiwan University, Taipei, Taiwan; (6) Graduate Institute of Brain and Mind Sciences, National Taiwan University, Taipei, Taiwan; (7) Department of Medical Imaging, National Taiwan University Hospital, National Taiwan University, Taipei, Taiwan)*

Backgrounds: The study of Alzheimer's disease (AD) has advanced, enabling earlier detection and diagnosis. Mild cognitive impairment (MCI) is well established as a risk state for the development of Alzheimer's disease (AD). Current diagnostic criteria for MCI highlight the need for evidence of cognitive decline which has been documented using either direct performance based measures or clinical interview based measures. This study investigated the putative changes in regional gray matter and cingulum bundle segments in mild cognitive impairment (MCI) using two different MCI diagnostic criteria. *Methods:* Participants comprised 50 individuals with MCI and 22 healthy controls (HC). Based on their global Clinical Dementia Rating (CDR) scores and performances on neuropsychological tests (NPT), the MCI participants were further divided into two groups (CDR MCI and CDR/NPT MCI). Tract-specific analysis derived from diffusion spectrum imaging (DSI) was performed to investigate the integrity of three segments (i.e., anterior, posterior, and inferior) of the cingulum bundle. DSI is sensitive to intravoxel heterogeneities in diffusion directions caused by crossing fiber tracts and thus enables more accurate mapping of axonal trajectories compared with other diffusion imaging approaches. *Results:* Comparable regional gray matter integrity was observed among the three groups. However, the two MCI groups exhibited reductions in right inferior segment of cingulum bundle compared to the HC group, and the CDR/NPT MCI group showed additional disruption in left inferior cingulum bundle. There were also significant brain-behavior associations between the integrity of cingulum and cognitive function. *Conclusion:* The findings emphasize the utility of informant rating scales in detecting high-risk individuals even before objective cognitive impairment is evident. It also highlights a prominent role of white matter measurement as a biomarker for early detection. The findings can be a reference for developing an enrichment approach for drug or behavioral intervention during stages where objective cognitive impairment is not yet clinically evident.

P1-46: Δ SCORES PREDICT AD CONVERSIONS FROM MCI. CASE-SELECTION FOR EARLY INTERVENTIONS. DONALD R ROYALL[1-4], 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") accurately diagnoses dementia, and has been associated with atrophy in the Default Mode Network (DMN), AD neuropathology, AD-specific CSF biomarkers, certain serum inflammatory proteins, hippocampal atrophy, and with concurrent and future CDR scores. Here, we examine δ's ability to predict prospective conversion to AD from "Mild Cognitive Impairment" (MCI). *Methods:* We constructed an ethnicity equivalent δ homolog ("dEQ") among n = 1113 Mexican-American and n = 1958 non-Hispanic White participants in the Texas Alzheimer`s Research and Care Consortium (TARCC). dEQ was indicated by COWA, LMII, VRI, and DST, targeted IADL, and was adjusted for age, education, and gender. After assessment of its factor determinancy, dEQ was validated by its correlation with CDR-SB, and output as a composite "dEQ-score". The dEQ composite's validity was confirmed by ROC. Cases adjudicated as MCI at visit 1 (n = 611) were followed annually for up to 6 years [ṁ = 4.7(0.6)]. The ability baseline dEQ to predict conversion was tested by logistic regression. Baseline g' (i.e., dEQ's residual in Spearman's general intelligence factor "g"), age, education, GDS, APOE e4 burden, gender and ethnicity were tested as independent predictors. *Results:* dEQ's model fit well ($\chi 2$/df = 181/24, $p < 0.001$; CFI = 0.97; RMSEA = 0.05). It achieved factor determinancy, and ethnicity equivalence for all indicators. dEQ correlated strongly with CDR-SOB ($r = 0.99$, $p<0.001$) and achieved a high AUC for AD v. NC (= 0.95). n = 106 (17.3%) of MCI converted to "AD". In a logistic regression model, each quintile increase in

the dEQ scores of MCI cases increased the odds of conversion to AD eighteen-fold [OR = 18.07 (8.84 - 36.91)], independently of g', APOE, age, gender and GDS scores. Education and gender did not enter. *Conclusions:* Baseline δ scores predict AD conversions from MCI in MA and NHW. δ score recruitment thresholds can be specified in advance that will select MCI cases at high risk of conversion. This approach has many additional advantages for clinical trial design. δ homologs allow the recruitment of identically demented subjects across sites or investigators, regardless of cultural or linguistic barriers. Additionally, effecting change in δ scores ensures functionally salient cognitive benefits.

P1-47: DIFFERENTIAL EFFECTS OF VASCULAR AND AMYLOID PATHOLOGY ON COGNITIVE FUNCTIONS IN MILD COGNITIVE IMPAIRMENT. ELENA ROLANDI[1], MOIRA MARIZZONI[1], SAMANTHA GALLUZZI[1], JORGE JOVICICH[2], FLAVIO NOBILI[3], MIRA DIDIC[4,5], DAVID BARTRÉS-FAZ[6], UTE FIEDLER[7], PETER SCHONKNECHT[8], PIERRE PAYOUX[9,10], ALBERTO BELTRAMELLO[11], ANDREA SORICELLI[12,13], LUCILLA PARNETTI[14], MAGDA TSOLAKI[15], PAOLO MARIA ROSSINI[16,17], PHILIP SCHELTENS[18], GIANLUIGI FORLONI[19], REGIS BORDET[20], OLIVIER BLIN[21], GIOVANNI BATTISTA FRISONI[1,22] ON BEHALF OF THE PHARMACOG CONSORTIUM *((1) Laboratory of Neuroimaging and Alzheimer's Epidemiology, IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy; (2) Center for Mind/Brain Sciences, Dept. of Cognitive and Education Sciences, University of Trento, Trento, Italy; (3) Department of Neuroscience, Ophthalmology, Genetics and Mother–Child Health (DINOGMI), University of Genoa, Genoa, Italy; (4) APHM, CHU Timone, Service de Neurologie et Neuropsychologie, Marseille, France; (5) Aix-Marseille Université, INSERM U 1106, Marseille, France; (6) Department of Psychiatry and Clinical Psychobiology, Universitat de Barcelona and IDIBAPS, Barcelona, Spain; (7) LVR-Clinic for Psychiatry and Psychotherapy, Institutes and Clinics of the University Duisburg-Essen, Essen, Germany; (8) Department of Neuroradiology, University Hospital Leipzig, Leipzig, Germany; (9) INSERM, Imagerie cérébrale et handicaps neurologiques, UMR 825, Toulouse, France; (10) Université de Toulouse, UPS, Imagerie cérébrale et handicaps neurologiques, UMR 825, Toulouse, France; (11) Department of Neuroradiology, General Hospital, Verona, 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 Centre and Department of Neurology, Vrije Universiteit University Medical Center, Amsterdam, The Netherlands; (19) Neuroscience Department, IRCCS Istituto di Ricerche Farmacologiche «Mario Negri», Milano, Italy; (20) Department of Pharmacology, EA1046, University of Lille Nord de France, 59045 Lille Cedex, France; (21) Pharmacology, Assistance Publique-Hôpitaux de Marseille, Aix-Marseille University-CNRS UMR 7289, Marseille, France; (22) Memory Clinic and LANVIE - Laboratory of Neuroimaging of Aging, University Hospitals and University of Geneva, Geneva, Switzerland)*

Background: Amyloid and vascular pathology could act independently in producing cognitive impairment in elderly or could interact sharing several vascular risk factors (Villeneuve 2015). Investigation of the effect of white matter hyperintensities (WMH) in the context of Alzheimer's Disease pathology could be of great interest to further elucidate the aetiology of cognitive impairment and possibly explore adjunctive therapeutic strategies (Prins & Scheltens 2015). Aim of this study is to investigate the independent effect of cortical amyloid pathology and WMHs on cognitive performance persons with Mild Cognitive Impairment. *Methods:* 147 MCI patients were enrolled in WP5 of PharmaCOG (E-ADNI) and underwent CSF collection and high resolution 3T MRI protocol that included FLAIR sequences. White matter hyperintensities (WMH) volumes were extracted from intensity inhomogeneity corrected FLAIR scans using LesionTOADS (www.mipav.cit.nih.gov). Patients were defined positive for vascular pathology (WMH+) if WML volume was greater than 0.5% of intracranial volume (Chao LL, 2013) and positive for amyloid (Ab42+) if CSF Ab42 level was lower than 550 pg/mL (Mulder C, 2010). Patients with available both baseline CSF Ab42 measure and MRI-FLAIR sequence were included in the present study, resulting in a total sample of 142 MCI. A series of univariate analyses of covariance (ANCOVA) were performed to explore main and interactive effects between amyloid and vascular status on individual neuropsychological tests raw scores, with age and years of education as covariates. *Results:* MCI Ab42+ and Ab42- (N=54 and N=88) were comparable for age, years of education, functional status, depressive and behavioural symptoms. WMH+ compared to WMH- (N=94 and N=48) were significantly older (67.9 VS 72.0 years, p=.00). CSF-Ab42 positivity was associated with lower performance in Auditory Verbal Learning Task (AVLT) immediate recall (p=.01) and Logical Memory delayed recall (p=.00), while WMH pathology was associated with lower performance in Trail Making Test Part A (p=.02) and Part B-A (p=.02) and Letter fluency (p=.01). The interaction between Ab42 and WMH status was not significant for any test. *Conclusions:* Amyloid and vascular pathology affect different cognitive domains in MCI patients. In particular, CSF-Ab42 positive MCI showed decreased learning abilities and episodic memory, while vascular pathology was associated with lower performance in attention and executive functions. Pharmacog is funded by the EU-FP7 for the Innovative Medicine Initiative (grant n°115009).

	Ab42 -		Ab42 +		Effects		
	WMH - N=61	WMH + N=27	WMH - N=33	WMH + N=21	Ab42	WMH	Ab42 x WMH
Memory							
AVLT immediate recall	32.4 ± 11.1	32.1 ± 8.8	30.4 ± 8.0	25.7 ± 9.5	**.01***	.46	.21
AVLT dealyed recall	4.6 ± 3.4	4.5 ± 3.1	3.7 ± 2.9	3.5 ± 3.1	.14	.98	.77
Logical Memory immediate recall	9.9 ± 7.1	7.9 ± 5.0	9.8 ± 13.3	5.1 ± 4.7	.32	.06	.39
Logical Memory delayed recall	5.9 ± 3.8	5.3 ± 3.1	4.7 ± 3.4	3.0 ± 3.1	**.00***	.34	.38
Attention and Processing Speed							
Trail Making Test part A	60.6 ± 28.4	83.0 ± 45.8	54.4 ± 21.0	70.5 ± 33.5	.23	**.02***	.45
Digit Symbol Substitution Test	30.2 ± 14.0	24.3 ± 10.7	31.0 ± 12.7	25.0 ± 11.8	.82	.19	.87
Digit Span Forward	5.4 ± 1.2	5.3 ± 1.2	5.5 ± 1.2	5.3 ± 1.0	.83	.80	.95
Digit Span Backward	3.7 ± 1.0	4.0 ± 1.3	3.8 ± 1.0	3.9 ± 0.9	.54	.14	.87
Language							
Boston Naming Test	22.4 ± 5.5	20.2 ± 5.6	23.7 ± 3.8	20.9 ± 4.6	.38	.11	.75
Category Fluency	37.0 ± 44.2	31.7 ± 13.4	35.2 ± 10.9	38.2 ± 45.4	.66	.91	.58
Executive functions							
Trail Making Test part B-A	124.6 ± 79.0	140.9 ± 70.5	109.6 ± 59.3	172.9 ± 54.6	.22	**.02***	.08
Letter fluency	31.1 ± 12.7	26.4 ± 11.0	35.9 ± 11.6	27.6 ± 9.7	.38	**.01***	.53

P1-48: ACEMOBILE – UTILIZING AN APP PLATFORM TO SUPPORT DEMENTIA RESEARCH VIA PARALLELED SUPPORT AND DATA ACQUISITION: AN UPDATE. CRAIG NEWMAN[1], JOHN HODGES[2], STEPHEN PEARSON[3], RUPERT NOAD[4] *((1) Plymouth University Peninsular Schools of Medicine and Dentistry, Plymouth, UK; (2) Neuroscience Research Australia, New South Wales, Australia; (3) Devon Partnership Trust, Devon, UK; (4) Plymouth Hospital NHS Trust, Plymouth UK)*

Background: The paper-based Addenbrooke's Cognitive Examination-III (ACE-III) is one of the most widely used assessments in specialist dementia assessment clinics in the UK (Larner, 2012). It is a 100-point paper-based cognitive assessment which takes 15–20 minutes to complete. ACEmobile is an iPad version of ACE-III which has been designed to support the clinician in all areas of administration. ACEmobile is provided for free, maintaining the persistent ethos of the ACE brand, for clinical use both within and outside of the NHS on a worldwide scale. The tool, and its

sustainability, is built on the framework of a research endeavour. It brings with it the ability to effortlessly collect anonymised data relating to the assessment of dementia sub-types. The development of this method of cognitive assessment, available at no cost to the administrator, with automatic collection of anonymised data via the internet, could facilitate the development of extremely large datasets. These data could then become the focus for instrument evaluation and development during routine clinical use, as well as having potential for use in clinical trials.

P1-49: THE SKT SHORT COGNITIVE PERFORMANCE TEST: A REGRESSION-BASED SCALING OF A PROVEN NEUROPSYCHOLOGICAL TEST ESPECIALLY FOR PRE-CLINICAL STAGES OF NEUROCOGNITIVE DISORDERS.

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Backgrounds: The SKT is a short cognitive performance test for assessing deficits of memory and attention. The test was developed in Germany and first published in 1977 by Hellmut Erzigkeit (1944-2010). Consisting of nine subtests, the SKT is designed like a challenging game. Three of the subtests assess different aspects of memory (i.e., immediate recall, delayed recall and recognition), the remaining six subtests refer to attention in the sense of speed of information processing (with some of the tasks including an executive component). The diagnostic aim of the SKT is the quantification of cognitive impairment in patients suffering from major neurocognitive disorders. *Methods:* Based on a sample of N = 1056 healthy German speaking elderly, aged between 60 and 91 years, a regression-based scaling of the nine subtests was applied. Each subject was tested with the SKT in addition to test procedures assessing crystallized intelligence (i.e., at least two subtests of the German adaptation of the WAIS; Petermann, 2012). Individual scores for each subtest were calculated based on age, gender and intelligence. Regression equations enable the calculation of an individual predicted score. Deviations of the obtained scores from the predicted scores were analyzed using Crawford's methods of the standard error for a new case (Crawford and Garthwaite, 2007). *Results:* Multiple regression analyses were applied to eight out of nine subtest; the data of a highly skewed subtest was simply transformed into percentile ranks. Age was a significant predictor in all eight subtests with higher age resulting in worse performance. Intelligence and gender were significant in seven subtests indicating on average better results for women; higher intelligence was positively correlated with better performance. The explained variance ranged from R2 = 0.05 to 0.27. With the help of an easy to use EXCEL program it is possible to sum up deviations from the predicted scores across all subtests. Making use of the colours of traffic lights, the sum of all deviations indicates whether the subject's cognitive performance is equivalent to healthy aging (i.e., green), equivalent to mild cognitive impairment (i.e., yellow) or equivalent to pathological cognitive decline (i.e., red). Cut-offs for the different stage of cognitive performance were based on multiple correspondence analyses. *Conclusions:* Preliminary results suggest that the new standardization provides a higher sensitivity for detecting cognitive decline even in preclinical or MCI stages of neurocognitive disorders. While the new standardization focuses the early detection of cognitive decline, the traditional standardization of the SKT (Erzigkeit 2001) still applies for patients already diagnosed with mild to moderate dementia.

P1-50: NORMATIVE STUDY OF THE GERMAN LANGUAGE TOMMORROW NEUROPSYCHOLOGICAL BATTERY.

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Background: Global clinical trials are increasingly focused on the presymptomatic phase of Alzheimer's disease (AD) with the goal of delaying the onset of AD symptoms. These trials require a comprehensive neuropsychological battery capable of detecting subtle cognitive change as individuals transition from normal cognition to Mild Cognitive Impairment due to AD (MCI-AD). However, few neuropsychological tests have been validated or normed for use in non-English speaking countries. For use in global clinical trials, neuropsychological tests need to be shown to be valid, reliable and culturally sound in different languages. The TOMMORROW Study is an international trial using MCI-AD as the primary endpoint. In preparation for initiating the TOMMORROW Study in German-speaking countries, we conducted a validation and normative study of the TOMMORROW neuropsychological battery in Basel, Switzerland. *Methods:* The TOMMORROW neuropsychological battery is comprised of measures of episodic memory, executive function, visuospatial function, attention/concentration, and language. Linguistic and cultural adaptation of the neuropsychological battery was completed in High German. This was done in accordance with International Society for Pharmacoeconomics and Outcomes Research (ISPOR)guidelines, including forward and backward translation, pilot testing, cognitive debriefing interviews, in-country expert review, and review by lead neuropsychologists. As part of the validation and normative study, the battery was then administered to cognitively healthy controls (controls, n=198) and patients with AD (n=25), aged 65-88. Controls had Mini Mental State Examination (MMSE) scores >24 and were clinically determined to be without cognitive disorder. Approximately 50 controls were sampled from each of four age strata (65-69, 70-74, 75-79, 80-88). Each age strata included both men and women, and individuals with high and low education. AD patients met NINCDS-ADRDA criteria for AD and had mild disease severity, as evidenced by MMSE scores of 17-28. *Results:* The California Verbal Learning Test-II (CVLT-II) long delay free recall showed the best discrimination between the AD group and controls with a sensitivity of 96% and specificity of 97%. A composite score derived from four cognitive domains (episodic, executive, attention, and language) did not improve the discrimination between the AD group and controls (76% sensitivity and 97% specificity), though the contribution of each domain was as expected given the mild severity of AD cases. Criterion validity was demonstrated by the finding that the AD group was more impaired on all tests compared to controls (Cohen's effect size range: 0.33-3.21). CVLT-II long delay free recall (Cohen's effect size 3.21) and CVLT-II short delay free recall (Cohen's effect size = 2.65) had the largest effect sizes. Construct validity was supported by high correlations among related domains (0.41-0.87). Test-retest reliability was >0.60 for most tests and alternate-form reliability for memory tests was >0.55. Compared to the psychometric properties of these tests in U.S. samples, results from Switzerland were in the same direction and of similar magnitude, though with

variability for some tests. *Conclusions:* The current study has shown the German translation and cultural adaptation of the TOMMORROW neuropsychological battery is psychometrically sound and performs comparably to English test versions with few exceptions. However, the variability in performance on some tests observed between the English version in the U.S. and the German version in Switzerland highlights the need for region-specific norms. Based on these findings which demonstrate adequate reliability and validity, age-corrected normative values were developed for use by German-speaking participants in the TOMMORROW study. The use of High German translations means that these norms can be applied in other German speaking regions. The normative data for this standardized battery will support valid interpretation of cognitive performance in German speaking individuals and assist in detecting cases of early mild cognitive impairment in clinical trials. *Disclosures:* Funding for this study was provided by Takeda Pharmaceutical Company Limited, Zinfandel Pharmaceuticals, Inc.

P1-51: NORMATIVE STUDY OF THE RUSSIAN TOMMORROW NEUROPSYCHOLOGICAL BATTERY. HEATHER ROMERO[1,2], OKSANA MAKEEVA[3], KATHLEEN A.WELSH-BOHMER[1,2], BRENDA L PLASSMAN[1,2], KATHLEEN M HAYDEN[1,2,4], KUMAR BUDUR[5], GRANT RUNYAN[5], STEPHEN CRAWFORD[6], MARK ATKINSON[6], TOYOKO OGURI[6], ALEXANDRA ATKINS[7], NICOLE TURCOTTE[7], RICHARD KEEFE[7], SHYAMA BREWSTER[8], DANIEL K BURNS[8], YUKA MARUYAMA[8], NATALI ZHUKOVA[3], IRINA ZHUKOVA[3], VALENTINA MARKOVA[3], LARISA MIHAYCHEVA[3], STEPAN BUIKIN[3], ZARA MELIKYAN[8], ALLEN D ROSES[8] FOR THE TOMMORROW STUDY INVESTIGATORS *((1) Joseph and Kathleen Bryan ADRC, Duke University Medical Center (Durham, NC); (2) Department of Psychiatry, Duke University Medical Center (Durham, NC); (3) Center for Clinical Trials, Nebbiolo LLC (Tomsk, RU); (4) Department of Social Sciences and Health Policy, Wake Forest School of Medicine (Winston-Salem, NC); (5) Takeda Development Center, Americas, Inc., (Deerfield, IL); (6) Covance Inc (Princeton NJ); (7) NeuroCog Trials Inc. (Durham, NC); (8) Zinfandel Pharmaceuticals, Inc. (Chapel Hill, NC))*

Background: Culturally sound neuropsychological metrics are required for global clinical trials that are designed to delay the progression of Alzheimer's disease (AD) from normal cognition to fully expressed disease. A validated neuropsychological battery with normative data in a target language is needed to detect subtle cognitive change in the presymptomatic phase of AD. However, few neuropsychological tests have been validated and normed for use with non-English speaking populations. The TOMMORROW Study is an international clinical trial that uses the NIA-AA 2011 criteria for Mild Cognitive Impairment due to AD (MCI-AD) as the primary endpoint. The trial requires validation of a neuropsychological battery both to detect MCI-AD in each language as well as to evaluate cognitive decline and response to treatment. In preparation for initiating the TOMMORROW Study in Russia, we conducted a validation and normative study of the TOMMORROW neuropsychological battery in Tomsk, Russia. *Methods:* The TOMMORROW neuropsychological battery was comprised of measures of episodic memory (California Verbal Learning Test-II (CVLT-II), Brief Visuospatial Memory Test-R (BVMT-R)), executive function (Trails B and Digit Span Backward), visuospatial function (BVMT-R copy and Clock Drawing Test), attention/concentration (Trails A and Digit Span Forward), and language (Multilingual Naming Test (MiNT), lexical fluency, and semantic fluency). In preparation for the validation study, linguistic and cultural adaptation of the neuropsychological battery was completed in accordance with International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines, including forward and backward translation, pilot testing, cognitive debriefing interviews, in-country expert review, and review by lead neuropsychologists. The battery was then administered to normal controls (NCs, n=195) and patients with AD (n=23), aged 65-88. Controls had Mini Mental State Examination (MMSE) scores >24 and were clinically determined to be without cognitive disorder. Approximately 50 NCs were purposively sampled in each of four age strata (65-69, 70-74, 75-79, 80-88), including men and women with high and low education. AD patients had MMSE scores of 13-28 and met NINCDS-ADRDA criteria for AD. Normal control subjects returned for a second visit one month later to determine test-retest and alternate-form reliability. *Results:* A composite score derived from four cognitive domains (episodic memory, executive function, attention, and language) discriminated AD cases from NCs, with >82% sensitivity and >97% specificity. The CVLT-II long delay free recall subtest performed better than the composite at discrminating between cases and controls (91.3% sensitivity and 97.9% specificity), which is consistent with the mild severity of AD cases. Criterion validity was supported by the finding that the AD group was more impaired on all tests compared to NCs, (Cohen's effect size range: .45-3.55); the CVLT-II long delay, CVLT-II short delay, and MiNT had the highest effect sizes. Criterion validity was supported by high correlations among tests in related domains (.43-.87). Test-retest reliability was >0.55 for all tests, alternate-form reliability was >0.61 for memory tests. Compared to psychometric properties of these tests in samples from the United States, results from Russia were in the same direction and of similar magnitude, though with variability for some tests. Specifically, time to completion for Trails B was slower in Russia compared to U.S.-based normative data, perhaps due to differences between U.S. and Russia in the use of over-learned alphabetical sequences. *Conclusions:* The Russian translation/adaptation of the TOMMORROW neuropsychological battery is psychometrically sound and performs comparably to English test versions with few exceptions. Variability between U.S. and Russia on some tests highlights the need for region-specific norms. Given adequate reliability and validity, age-corrected normative data were developed for use with Russian-speaking participants in the TOMMORROW study. The use of this standardized battery and normative data will enhance precision for measuring cognition and treatment effects in Russia and will facilitate the detection of cases of mild cognitive impairment in AD continuum clinical trials. *Disclosures:* Funding for this study was provided by Takeda Pharmaceutical Company Limited, Zinfandel Pharmaceuticals, Inc.

P1-52: SOLCOS BASED-MODEL INDIVIDUAL REMINISCENCE FOR OLDER ADULTS WITH MILD TO MODERATE DEMENTIA IN RESIDENTIAL CARE: AN SECOND PILOT STUDY. PETER VAN BOGAERT, ROEL EERLINGEN, DAISY CARVERS *(Division of Nursing and Midwifery Sciences, Centre for Research and Innovation in Care (CRIC), Faculty of Medicine and Health Sciences, University of Antwerp, Belgium)*

Aim: To investigate the effect of a standardized individual intervention based on the SolCos transformational reminiscence model on cognition, well-being, depressive symptoms, and behaviour for older people with mild to moderate dementia. *Background:* Because of limited pharmacological treatment options for older adults with dementia relevant physical, sensory, psychological or social interventions with an effect on depressive symptoms and cognitive and affective functions offers alternative opportunities. In a first pilot study 82 elderly were divided over an intervention and control group. We detected positive effects associated with individual thematically based reminiscence performed by one facilitator offering 8 sessions during 4 weeks. The positive effects consisted of increased well-

being, including improvement of depressive symptoms and cognition of participants. *Design:* A randomized controlled intervention study. *Methods:* Random control trial was set up in two residential aged facilities with 29 and 31 residents in the intervention and the control group, respectively. Eighteen nursing home volunteers were trained to perform the individual reminiscence therapy based on the SolCos model offering 16 sessions during 8 weeks. Various assessment scales were measured pre- and post-sessions. These volunteers assessed each session through a 10-item survey about residents' attention and participation and an 11-item survey about session conditions and facilitators' experiences. *Results:* Delta scores on the Cornell Scale for Depression in Dementia (CSDD) were significant improved post-session in the intervention group compared with the control group. Linear regression controlled for memory games and antidepressant use showed a significant effect of the reminiscence therapy on the CSDD delta scores. Better post-session Mini Mental State Examination (MMSE) delta scores in the intervention group were detected compared with pre-session, but not significant. Facilitators experienced the sessions as useful, pleasant and performed in sufficient conditions and study participants were in general attentive, open and collaborative. *Conclusion:* The effect of the standardized individual reminiscence therapy on depressive symptoms in the second pilot study was confirmed. In comparison with the first study, the effect on cognition was unclear and not confirmed in this study. Study results showed that organizing standardized individual reminiscence therapy with nursing home volunteers in residential aged care was feasible and study participants' attention and participation was overall good. Further study initiatives to explore the potential of individual reminiscence therapy are recommended. We suggest to combine described standardized individual intervention based on the SolCos transformational reminiscence model with a broader person centred framework that underpins the nursing home culture as suggested in previous studies. Through the reminiscence therapy staff will learn systematically more about each participant's aspects of his or her life, personality and preferences and these insights can be used within the person-centred framework to deliver more a supportive and individualized care plan for each resident with a strong involvement of family members. In turn the person-centred framework and staff' communication skills can support and optimize the reminiscence therapy achieving better and sustained outcomes.

P1-53: ALZHEIMER'S DISEASE PREVENTION INTO PRIMARY CARE. BERTRAND FOUGÈRE[1,2], BRUNO CHICOULA[1], JULIEN DELRIEU[1], NÉDA TAVASSOLI[1,4], CHRISTINE LAGOURDETTE[1], JULIE SUBRA[3], STÉPHANE OUSTRIC[2,3], BRUNO VELLAS[1,2,4] *((1) Gérontopôle, Centre Hospitalier Universitaire de Toulouse, Toulouse, France; (2) Inserm UMR1027, Université de Toulouse III Paul Sabatier, Toulouse, France; (3) Département de médecine générale, Université de Toulouse, France; (4) Equipe Régionale Vieillissement et Prévention de la Dépendance, Centre Hospitalier Universitaire de Toulouse, France)*

Backgrounds: Most old adults receive their health care from their General Practitioner (GP); as a consequence, as the population ages, the manifestations and complications of cognitive impairment and dementia impose a growing burden on providers of primary care. Current guidelines do not recommend routine cognitive screening for older persons by primary care physicians, although the vast majority recommends a cognitive status assessment and neurological examination for subjects with a cognitive complaint. The identification and management of elderly with memory complain are clinical priorities nowadays that can no longer wait. It is essential to continue to develop other memory centers at the national level. However, as memory centers are necessarily linked to hospital centers, other evaluation structures may be proposed in order to make more accessible to everyone. In this context, another care model has been developed in primary care: implementing a nurse already trained in geriatric assessment of older person with memory complain in primary care. *Methods:* Patients with memory complain in GP consultations are assessed by a Geriatric Evaluation Nurse (GEN) within GP's office. This assessment helps the GP to propose recommendations to the patient with the support of a hospital geriatrician if necessary, and to coordinate the implementation of the recommendations. In this case, memory centers are specialized in the management of more complex situations. *Results:* 109 patients in 14 GP's offices around Toulouse have been assessed in 3 months with an average age of 81.3 (± 5.92) years. More than half of the study group is female (66%). The participants live alone in 35 cases (32%) and with a home support in 41%. Their average ADL and IADL are respectively 5.77/6 (± 0.36) and 6.77/8 (± 1.69). The average MMS is 25.2/30 (± 4.23) and 27% of participants have a score lower than 24/30. The Mini-GDS is greater than or equal to 1/4 in 53%. We have assessed the patients with MMS greater than or equal to 24/30 with the Wechsler Memory Scale (WMS). The results highlight 16% of MCI including 53% of early MCI and 47% of late MCI. *Conclusion:* Prevention is now increasingly highlighted as the main therapeutic goal to tackle dementia. GP have to play a role to better focus those who can benefit from multi-domain interventions or targeted therapies. Presently, we must target those with memory complaints, monitor cognitive functions and increase the participation of older adults in drug trials and other intervention studies. As important is the need to implement preventative strategies for Alzheimer's disease into everyday clinical practice.

P1-54: NORMATIVE STUDY OF THE ITALIAN-LANGUAGE TOMMORROW NEUROCOGNITIVE BATTERY. BRENDA L. PLASSMAN[1,2], SAMANTHA GALLUZZI[3], CARLO DE LENALENA[4], KATHLEEN A. WELSH-BOHMER[1,2], HEATHER ROMERO[1,2], KATHLEEN M. HAYDEN[1,2,5], KUMAR BUDUR[6], GRANT RUNYAN[6], JANET O'NEIL[6], STEPHEN CRAWFORD[7], MARK ATKINSON[7], TOYOKO OGURI[7], ALEXANDRA ATKINS[8], NICOLE TURCOTTE[8], RICHARD KEEFE[2,8], SHYAMA BREWSTER[9], DOMINIC FITZSIMMONS[10], DANIEL K. BURNS[9], MAURA PARAPINI[3,11], LETIZIA IMBRIANO[4], GIOVANNI B. FRISONI[3,11], ALLEN D. ROSES[9] FOR THE TOMMORROW STUDY INVESTIGATORS *((1) Joseph and Kathleen Bryan ADRC, Duke University Medical Center, Durham, NC, USA; (2) Department of Psychiatry, Duke University Medical Center, Durham, NC, USA; (3) IRCCS Fatebenefratelli, Brescia, Italy; (4) Department of Neurology and Psychiatry, Sapienza University of Rome, Italy; (5) Department of Social Sciences and Health Policy, Wake Forest School of Medicine, Winston-Salem, NC, USA; (6) Takeda Development Center Americas, Inc., Deerfield, IL, USA; (7) Covance Inc, Princeton, NJ, USA; (8) NeuroCog Trials, Durham, NC, USA; (9) Zinfandel Pharmaceuticals, Inc., Chapel Hill, NC, USA; (10) Takeda Development Centre Europe Ltd, London, UK; (11) University Hospitals and University of Geneva, Geneva, Switzerland)*

Background: Global clinical trials are increasingly focused on the presymptomatic phase of Alzheimer's disease (AD), with the goal of delaying the onset of AD symptoms. These trials require a comprehensive neurocognitive battery capable of detecting subtle cognitive change as individuals transition from normal cognition to mild cognitive impairment due to AD (MCI-AD). However, few neuropsychological tests have been validated or normed for use in non–English-speaking countries. For use in global clinical trials, neuropsychological tests need to be valid, reliable, and culturally sound in different languages. The TOMMORROW Study is an international trial using conversion to MCI-AD as the primary

endpoint. We conducted a validation and normative study of the TOMMORROW neurocognitive battery in Italy. The study was conducted at two sites, one in Rome and another in Brescia, to facilitate enrollment of the desired number of participants representative of those expected to enroll in future clinical trials. *Methods:* The TOMMORROW neurocognitive battery comprises measures of episodic memory, executive function, visuospatial function, attention/concentration, and language. Linguistic and cultural adaptation of the neurocognitive battery was completed in Italian. This was done in accordance with International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines, including forward and backward translation, pilot testing, cognitive debriefing interviews, in-country expert review, and review by neuropsychologists. As part of the validation and normative study, the battery was then administered to cognitively healthy controls residing in the community (n= 215) and patients with AD (n=25), aged 65-88 years, inclusive. After screening and careful clinical evaluation, 27 controls were excluded due to medical conditions that could impact cognitive performance. Controls had Mini Mental State Examination (MMSE) scores >24 and were clinically determined to be without cognitive disorder. Approximately 47 controls were sampled from each of four age strata (65-69, 70-74, 75-79, 80-88). Each age stratum included both men and women, and individuals with high and low education. AD patients met National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD and had mild to moderate disease severity, as evidenced by MMSE scores of 14-27. *Results:* The California Verbal Learning Test-II (CVLT-II) long-delay free recall discriminated well between the AD group and cognitively healthy controls, with a sensitivity of 92% and a specificity of 98%. A composite score derived from four cognitive domains (episodic memory, executive function, attention, and language) did not improve the discrimination between the AD group and controls (79% sensitivity and 97% specificity). In fact, the CVLT-II long-delay free recall subtest alone performed better than did the composite at discriminating between cases and controls. Criterion validity was demonstrated by the finding that the AD group was more impaired on all tests compared with controls (Cohen's effect size range: 0.66-2.97). Trail Making Test Part A (Cohen's effect size = 2.97) and CVLT-II long-delay free recall (Cohen's effect size = 2.49) had the largest effect sizes. Construct validity was supported by high correlations among related domains (0.53-0.90). Test-retest reliability was >0.60 for most tests and alternate-form reliability for memory tests was ≥0.64. Compared with the psychometric properties of these tests in U.S. samples, results from Italy were in the same direction and of similar magnitude, though with variability for some tests. *Conclusions:* The current study demonstrates that the Italian translation and cultural adaptation of the TOMMORROW neurocognitive battery is psychometrically sound and performs comparably to English test versions with a few exceptions. The variability in performance observed between the English version in the U.S. and the Italian version on some tests highlights the need for region-specific norms. Based on these findings demonstrating adequate reliability and validity, age-corrected normative values were developed for use by Italian-speaking participants. The normative data for this standardized battery will support valid interpretation of cognitive performance in Italian-speaking individuals and assist in detecting cases of early MCI-AD in clinical trials. *Disclosures:* Funding for this study was provided by Takeda Pharmaceutical Company Limited.

P1-55: CULTURAL ADAPTATION OF THE TOMMORROW COGNITIVE BATTERY IN RUSSIA, SWITZERLAND, AND ITALY. ALEXANDRA S ATKINS[1], ADAM W VAUGHAN[1], NICOLE M TURCOTTE[1], OKSANA A MAKEEVA[2], ANDREAS U MONSCH[3], GIOVANNI B FRISONI[4,10], MAURA PARAPINI[10], IRINA ZHUKOVA[2], ZARA MELIKYAN[5], SHYAMA BREWSTER[5], KUMAR BUDUR[6], JANET O'NEIL[6], HEATHER R ROMERO[8], BRENDA L PLASSMAN[7,8], KATHLEEN M HAYDEN[7,8,9], KATHLEEN A WELSH-BOHMER[7,8], RICHARD SE KEEFE[1,8] *((1) NeuroCog Trials, Durham, NC, USA; (2) Neuropsychology Testing Center, Nebbiolo, LLC, Tomsk, RU; (3) University Center for Medicine of Aging Basel, Felix Platter Hospital, Basel, CH; (4) IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, IT; (5) Zinfandel Pharmaceuticals Inc., Chapel Hill, NC, USA; (6) Takeda Development Center Americas, Inc., Deerfield, IL, USA; (7) Joseph and Kathleen Bryan ADRC, Duke University Medical Center, Durham, NC, USA; (8) Dept. of Psychiatry, Duke University Medical Center, Durham, NC, USA; (9) Dept. of Social Sciences and Health Policy, Wake Forest School of Medicine, Winston-Salem, NC, USA; (10) University Hospitals and University of Geneva, Geneva, CH)*

*Background: Cultural adaptation of cogn*itive assessments improves the quality of translated instruments by ensuring tasks, stimuli, and instructions are understood and are appropriate for use in populations of interest. Successful adaptation for clinical trials ensures cultural appropriateness of performance-based tests while maintaining the construct validity and integrity of the original instruments. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) provides guidelines for adapting patient-reported outcomes (Wild et al., 2005, 2009). Building on this guidance, we present methods and results from a comprehensive linguistic and cultural adaptation of the TOMMORROW cognitive battery, designed to detect transition from normal aging to mild cognitive impairment due to Alzheimer's disease (MCI-AD) in multi-national clinical trials. For all languages assessed, changes were incorporated to improve the quality of adapted instruments and account for cultural and linguistic differences. *Methods:* Linguistic and cultural adaptation of the cognitive battery was completed in Russia, Switzerland (German), and Italy. Cognitive measures included the Mini-Mental State Examination (MMSE), Brief Visuospatial Memory Test-Revised (BVMT-R), California Verbal Learning Test, Second Edition (CVLT-II), Animal Fluency, Lexical Fluency, WAIS-III Digit Span, Trail Making Test, Parts A and B (TMT), Clock Drawing Test (CDT), and a relatively new measure, the Multilingual Naming Test (MINT). After obtaining permission from copyright holders, each measure underwent formal forward and back translation by a professional translation vendor. Cognitive debriefing interviews were then conducted in Russia, Switzerland (German), and Italy in accordance with ICH guidelines for Good Clinical Practice. Each country sample included 10 participants, ages 65-86. Cognitive debriefing interviews included administration of all instructions and test items from each measure by a trained tester. All stimuli were reviewed to determine cultural appropriateness. Subjects and testers in each country provided feedback regarding clarity of test instructions and items, identified any difficult or unclear wording, and provided suggestions for improved language. Each adapted measure and cognitive debriefing questionnaire received formal review by three independent in-country psychologists who provided feedback regarding construct validity, appropriateness for the target population, and potential performance differences. Input from expert reviewers, testers, and subjects led to revision of adapted measures to account for cultural and linguistic differences. *Results:* Final recommendations for revisions to translated cognitive tests were based on feedback from all sources, including in-house psychologists, expert reviewers, testers, and subjects engaged in cognitive debriefing. In all countries, alternative wording was recommended to clarify task demands and increase understanding by the target population (42% of all comments). Significant adaptations to the MINT were requested (25% of comments received) to account for regional differences

in stimuli, improvements in picture quality, and incorporation of alternate culturally acceptable responses for specific items. In response to feedback, regional responses were incorporated and improved pictures were provided by the test's author. The picture of one naming item, the "plug," was adapted for each region. For Russian-language measures, several changes to initial translations were made to achieve cultural equivalency in the presentation of task instructions. These included removal of phrases such as "do the best you can," which were considered insulting (indicating that one would not do this unless asked) in the Russian culture. In addition, Russian feedback indicated potential differences in speed of processing tasks due to a strong cultural emphasis on accuracy, reduced exposure to alphabetical sequencing (TMT-B), and relative unfamiliarity with timed testing. A significant change to the Italian-language MMSE included revision of the "No ifs, ands, or buts" equivalent from the literal translation "Nessun se, e o ma" to "Non c'è se né ma che tenga" to improve construct equivalency and maintain consistency with common practice. Additional notable changes included revision of the TMT-B to remove letters J and K, which are not included in the Italian alphabet, and substitution of letters for the lexical fluency task. Regarding the German language, Swiss reviewers expressed a preference for Swiss German over High German words (eg, Lastwagen vs LKW, Heugümper vs Grashüpfer). To facilitate more widespread use of the final adapted measure, the decision was made to adhere to High German vocabulary. Suggestions regarding revisions of CVLT-II categories were beyond the scope of the present project. As such, recommendations for improved translation of items were incorporated, but alternate words and word lists were not. Although cultural differences in CVLT-II category frequency have the potential to influence raw scores, collection of region-specific normative data completed following cultural adaption can mitigate the impact of these differences by allowing for normalization of raw scores relative to a culturally appropriate standard. *Conclusions:* Linguistic and cultural adaptation activities contributed to the development of improved, culturally appropriate versions of the TOMMORROW cognitive battery for use in German, Russian, and Italian. Results suggest proposed methods for cultural adaptation of performance-based assessments can identify and correct errors prior to use in clinical trials, yielding potentially widespread gains in the reliability and validity of translated instruments.

P1-56: INTERNATIONAL NOMENCLATURE CONSENSUS WORKING PARTY: PERIOPERATIVE NEUROCOGNITIVE DISORDERS (PREVIOUSLY KNOWN AS POSTOPERATIVE DELIRIUM AND POSTOPERATIVE COGNITIVE DYSFUNCTION). LIS EVERED[1,2], STEVEN DEKOSKY[3], ROD ECKENHOFF[4], DAVID SCOTT[1,2], ESTHER OH[5], GREG CROSBY[6,7], BRENDAN SILBERT[1,2] AND THE INTERNATIONAL NOMENCLATURE CONSENSUS WORKING PARTY *((1) St Vincent's Hospital, Melbourne; (2) University of Melbourne; (3) University of Florida; (4) University of Pennsylvania; (5) Johns Hopkins Medicine; (6) Brigham and Women's Hospital, Boston; (7)Harvard Medical School)*

Background: Cognitive change affecting patients after anesthesia and surgery has been recognized for over one hundred years. Research into cognitive change after A&S accelerated in the 1980s when multiple publications utilized detailed neuropsychological testing for assessment of cognitive change following cardiac surgery. This body of work consistently documented decline in cognitive function in elderly patients in the immediate (seven days) and intermediate (three months) postoperative periods. The natural history of these changes requires further investigation, but there is evidence supporting cognitive changes as long as 5 years afterwards. Importantly, other studies have identified that the incidence of cognitive change is similar after non-cardiac surgery. Interestingly, research into these cognitive changes in the perioperative period has been undertaken in isolation from cognitive studies in the general population. The aim of this work is to encourage people to use language and diagnostic criteria which is consistent with the terminology used in the wider clinical community. The use of consistent and relevant nomenclature with direct clinical interpretation will allow future translational research directed toward understanding the impact of anesthesia and surgery on outcomes, care and management for the elderly. *Methods:* The publication of the DSM-5 is an opportune time to align cognitive change detected after anesthesia and surgery with cognitive change in other medical disciplines; with the definition of decline/impairment and meaningful clinical interpretation; and nomenclature. We believe formal classification is critical because:-The numbers of patients aged > 60y undergoing anesthesia and surgery has increased significantly and is projected to further increase. -The cognitive changes identified in this period cannot, and should not, be differentiated from neurocognitive disorders observed in the general population. -The terminology should be aligned with other neurocognitive disorders. - Considering the high prevalence of neurocognitive disorders in the community many individuals will have these disorders before they undergo anesthesia and surgery; using different terminology to classify individuals purely because they are having an operation is counterintuitive and counterproductive at many levels. - It is timely to unify this terminology and most appropriate to unify it with current classifications of neurocognitive disorders. Furthermore, delirium following A&S should be specifically labelled as such (postoperative) to recognize it as a significant clinical event. *Results:* It is understood that two major classification guidelines (DSM-5 and NIA-AA) are currently used more or less synonymously outside of anesthesia and surgery. Mild neurocognitive disorder (mild NCD) and major NCD defined in the DSM-5 map onto Mild Cognitive Impairment (MCI) and dementia (NIA-AA) respectively, and can therefore be effectively used as interchangeable terms. We hope to align POCD with both the DSM-5 and NIA-AA nomenclature. We therefore plan to recommend that the nomenclature be changed from postoperative cognitive dysfunction (POCD) to: - mild NCD (DSM-5) as mild NCD. Mild NCD/MCI may be used for research purposes. - major NCD (DSM-5) as major NCD. Major NCD/dementia may be used for research purposes. Each will also include appropriate specifiers and time-frames. No specific tests are to be recommended as specific tests are not prescribed in psychiatry, neurology or geriatrics. The current recommendations for clinical criteria will not specify individual neuropsychological tests nor the number of tests required in a battery. Further discussion is required around recommendations for research criteria. Norms or controls must be used and cut-points are acceptable. Depending on the circumstance, this may range from a healthy control group to a group with the prevalence of disease expected in the population. Comparable age is always important. Control groups must be appropriate comparators to the population being studied and appropriate to address the questions being asked. *Conclusions:* Including a history which incorporates cognitive concern would allow alignment of cognitive assessments previously termed POCD with DSM-5 and NIA-AA. 'Postoperative' becomes a specifier similar to other specifiers in DSM-5, such as traumatic brain injury or substance abuse. The term POCD will therefore no longer be used. We plan to revise the nomenclature from postoperative cognitive dysfunction (POCD) to: - 'mild NCD (postoperative)' [mild neurocognitive disorder – postoperative]; and - 'major NCD (postoperative)'; [major neurocognitive disorder – postoperative]. In line with both DSM-5 criteria, and with appropriate specifiers and time-frame. The 'Postoperative' specifier should refer to a period from anesthesia and surgery to 30d, 3 or 12 months follow-up. Criteria for cognitive impairment preoperatively or cognitive decline postoperatively will conform to the 3 pillars of diagnosis for NCD/MCI/dementia: -

Subjective complaint (participant, informant, clinician); - Objective impairment / change (Mild: 1 to 2 SD below norms or controls; Major: > 2SD below norms or controls - see 'Criteria'); - Change to instrumental activities of daily living (for Major NCD/dementia)

P1-57: COMPREHENSIVE COGNITIVE TRAINING IN LATER ADULTHOOD LEADS TO A REDUCTION IN ANNUALIZED AGE-RELATED COGNITIVE DECLINE. DANIEL STERNBERG, MICHAEL SCANLON, GLENN MORRISON *(Lumos Labs. Inc. San Francisco, CA)*

Background: The current literature on healthy aging highlights a gradual decline in key cognitive domains including memory, learning, language, and processing speed. These 'fluid' cognitive abilities are important for carrying out everyday activities, living independently and leading a fulfilling life. Although several studies have now established strong and independent links between engagement in cognitively stimulating activities throughout the lifespan and enhanced late-life cognition and reduced risk of cognitive impairment and dementia, there still remains some uncertainty regarding the specific contribution of many common cognitively stimulating leisure activities to overall cognitive health during aging. Recently, Hardy et al. (2015) presented a large randomized active-controlled trial of an online cognitive training program for healthy adults. The study included 4,715 fully evaluable participants between the ages of 18 and 80 years old. Participants in the training group improved significantly more on an aggregate measure of neuropsychological performance than did the control group. Participants in the training group also showed significantly greater improvements in speed of processing, working memory, problem solving, fluid intelligence, and on a number of survey questions related to their real-world ability to concentrate. Hardy and colleagues did not specifically evaluate the effects of cognitive training in older adults, where positive effects on enhanced cognition may be more relevant. *Methods:* The Hardy et al. (2015) cohort included 1,328 fully evaluable participants who were between 50 and 80 years old (Ntreatment = 758, Ncontrol = 570). After providing informed consent, participants were given a neuropsychological test battery and a survey of real-world cognitive performance. Following the battery, participants were randomized into either the computerized cognitive training condition, which consisted of full access to Lumosity, or into an active control condition that consisted of daily crossword puzzles. Participants were instructed to train for ten weeks, and at the end of this period were invited to take the neuropsychological test battery and the real-world cognitive performance survey a second time. Performance on the neuropsychological assessments was scaled using a rank-based inverse normal transformation with five-year age bins, and the sum of scaled assessment scores was used to generate an overall scaled score (the Grand Index) using the same rank normalization procedure without age bins. *Results:* Fully evaluable participants in the cognitive training group were marginally older than those in the crosswords control group according to a Kolmogorov-Smirnov test ($d = 0.75$, $p = .053$). Education and gender differences were non-significant. The mean change from baseline on the Grand Index score in the Lumosity group was 5.48 points (sd = 12.00), and the mean increase in the control group was 2.29 points (sd = 10.50). An ANCOVA model measuring the effect of group revealed that aggregate cognitive performance improvement in the Lumosity group was significantly greater than in the control group ($t(1325) = 4.28$, $p < 0.0001$, $d = 0.24$) Significantly larger improvements for Lumosity relative to the control group were found for Forward Memory Span, Progressive Matrices, and Arithmetic Reasoning. An ANCOVA model measuring the effect of group on the change in average survey score also revealed a main effect of group on change score, indicating that cognitive training with Lumosity resulted in larger increases in self-reported cognition and emotional status scores compared to the crossword puzzles control ($t(1317) = 3.94$, $p < 10\text{-}4$, $d = 0.218$). Annualized age-related cognitive decline was estimated via linear models predicting baseline score from participants' ages. The reduction in age-related decline for the Lumosity group compared to the control ranged from 3.61 to 6.37 years depending on the assessment, while the Lumosity group showed an improvement of approximately 3 years over the control group on the Grand Index. *Conclusions:* The results indicate that cognitive training with Lumosity was more effective than crossword puzzles for improving cognitive performance as measured by a standardized assessment battery, and specifically, significantly larger improvements were found for three assessments: Forward Memory Span, Progressive Matrices, and Arithmetic Reasoning. The findings in this cohort of older adults was similar to those reported in Hardy et al (2015) and demonstrate that Lumosity training improves cognitive abilities that generalize beyond the actual trained tasks to untrained cognitive tasks. The clinical relevance of these effects is that they translate into a reduction of 3.6 to 6.4 years in annualized age-related cognitive decline for the three assessments or a reduction of 3 years on the full standardized battery. This reduction is similar to Wolinsky et al (2013), who reported between 1.5 and 5.9 years of protection against normal age-related cognitive decline following 10 hours of visual speed of processing training in adults older than 50.

P1-58: DEMENTIA IN LONG TERM CARE FACILITIES; TELEMEDICINE FOR THE MANAGEMENT OF NEUROPSYCHIATRIC SYMPTOMS: THE DETECT STUDY. METHODS OF A CLUSTER RANDOMIZED CONTROLLED TRIAL. MARIA SOTO[1], ANTOINE PIAU[2], ADELAIDE DE MAULÉON[1], PIERRE RUMEAU[1], ALSANE SENE[2], PPASCAL SAIDLITZ[1], BENOIT LEPAGE[3], MARYLINE DUBOUÉ[1], BRUNO VELLAS[1], FATI NOURHASHÉMI[1] *((1) Gerontopôle, INSERM U 1027, Alzheimer's Disease Research and Clinical Center, Toulouse University Hospital, France; (2) Gerontopôle, Cand University, France; (3) Department of Epidemiology and Public Health, CHU Toulouse University Hospital, France, INSERM U 1027)*

Background: Management of people with dementia (PwD) in long-term care facilities (LTCF) is under the spotlight, given the rapidly growing prevalence of such condition in ageing populations. Neuropsychiatric symptom (NPS) are frequent and associated with a number of adverse outcomes for the patient including progression from early dementia to severe dementia, greater disability, worse quality of life or earlier death. Moreover, NPS have serious consequences for professional caregivers and higher health care costs. Management of NPS needs a comprehensive assessment of the resident in his/her environment of daily life (which is usually not possible in a classic/usual memory consultation office). Thus, Telemedicine (TM) may facilitate adequate treatment of NPS by identifying underlying causes and tailoring a treatment plan (pharmacological or non-pharmacologic treatments including provision of staff education and support, training in problem solving, and targeted therapy directed at the underlying causes for specific behaviors). However, scarce work has been done with dementia and telemedicine in LTCF and there is no previous interventional study that assessed efficacy of TM in the management of NPS in institutionalized demented patients. The DETECT study aims to examine the feasibility and acceptability of Telemedicine in addition to standard support and treatment, in the management of PwD with disturbing NPS in LTCF. The secondary aims are to asses and compare in both arms (intervention with TM vs. usual care): 1) the rate of non-programmed hospitalizations and/or consultations due to disrupting NPS, 2) the psychotropic drugs and physical restraints use, 3) the quality of life of PwD and 4) the estimation of health care costs. *Methods:* Study design: it is a multicenter prospective cluster

randomized controlled open label two arms study: a control arm (usual care) and an intervention arm (TM). The unit of randomization was the LTCF. Twelve months of inclusion period and a 2-month period of participation of each patient in both arms. Population studied: 200 patients aged 65 or more living in LTCF will be recruited (100 in each arm). Patients must suffer for a dementia diagnosed by a specialist or the general practitioner and present a disrupting NPS that require a specialist consultation based on the LTCF staff judgment. Primary outcome: is based on the acceptability of the TM among the LTCF staff which will be assessed in the intervention group by: a) Quantitative indicators: 1) the proportion of the solicitation of the TM solution among patients with disrupting NPS, 2) the delay to obtain a TM consultation and, 3) the number of the staff participants at each TM consultation. b) Qualitative indicators: staff global satisfaction will be evaluated by focus groups and interviewing. *Results:* The DETECT study is currently running in two French regions. Inclusions started in June 2015. In total 20 LTCF currently participate in the study. Ten intervention LTCF received a package of telemedicine equipment, in addition to the standard health care services available in their area. Their staffs were trained to the TM procedure with a normalized training addressing regulations, deontology, practice, a special training on the use of a dedicated telemedicine information system and included a telemedicine conditions videoconferencing practical training. In the intervention arm, as a patient presents a disruptive NPS, a TM consultation will be planned (inclusion=T0). At this consultation both, the LTCF and Memory Centre medical and nurse staffs will participate. A full record will be elaborate containing the pharmacological and non-pharmacological strategies proposed for the management of NPS. A second follow-up TM consultation will take place at 1 month (T1) with similar characteristics. Controls LTFC manage PwD with NPS with usual health care. *Conclusion:* Currently, the DETECT study is the first interventional study assessing Telemedicine in the management of NPS in PwD living in a LTCF. From previous clinical, uncontrolled, practice we are expecting this study to show that TM is well accepted by the LTFC staff and could be an emerging and effective way to provide consultation and care to LTCF residents displaying disrupting NPS that may not have an easy access to specialist services in a short delay of time. TM might show, as en extra benefit, a reduction in health care costs in comparison to usual care.

P1-59: RATIONALE AND PRELIMINARY DATA FOR THE ADCS MULTICENTER TRIAL: PRAZOSIN FOR AGITATION IN ALZHEIMER'S DISEASE. MURRAY A RASKIND[1,2], ELAINE R PESKIND[1,2] *((1) VA Puget Sound Health Care System, Mental Illness Research, Education and Clinical Center (MIRECC), Seattle/ American Lake, WA, USA; (2) University of Washington, Department of Psychiatry and Behavioral Sciences, Seattle, WA, USA)*

Background: Agitation (irritability, anger outbursts, pressured motor activity) is a major source of distress to patients and caregivers, and is a common precipitant of long term care placement. Paradoxically high CNS noradrenergic responsiveness of the alpha-1 AR in AD may contribute to the pathophysiology of agitation. Prazosin is a CNS active alpha-1 AR antagonist that we evaluated as a treatment for agitation in AD. *Methods:* Participants with AD complicated by frequent disruptive agitation were randomized to prazosin or placebo in two pilot studies. Prazosin was titrated to a maximum dose of 6 mg/day for 8 weeks in study 1 (n=22) and 8 mg/ day for 12 weeks in study 2 (n=20) and change in agitation quantified with the Neuropsychiatric Inventory (NPI). In a subgroup, motor activity was measured by actigraphy at baseline and at the end of drug treatment. Orthostatic change in systolic blood pressure (BP) was evaluated as a potential predictor of response within subjects randomized to prazosin. *Results:* Pooled results from the two studies demonstrated a significantly greater improvement in NPI scores with prazosin than with placebo. Among participants randomized to prazosin, those who improved on the Clinical Global Impression of Change had a mean increase in systolic blood pressure (134 to 138 mmHg) from supine to standing position whereas those who were unchanged or worsened had a mean decrease (134 to 119 mmHg). Actigraphy demonstrated a substantial reduction in motor activity with prazosin treatment. *Conclusion:* These results provide rationale for the ADCS multicenter trial of prazosin for agitation in AD beginning Spring 2015. They also suggest that lack of orthostatic blood pressure drop may predict therapeutic response, and that actigraphic change may provide an objective outcome parameter of response to prazosin in this population. This material is the result of work supported by the Department of Veterans Affairs and Career Development Award Project 3125.

P1-60: APATHY AS A DRUG TARGET AND A SURROGATE MARKER IN AD CLINICAL TRIALS. ANTON ALVAREZ[1,2] *((1) Medinova Institute of Neurosciences, Clinica RehaSalud, A Coruña, Spain; (2) Clinical Research Department, QPS Holdings, A Coruña, Spain)*

Backgrounds: Apathy is the most common neuropsychiatric symptom in Alzheimer's disease (AD). It has been found that the presence of apathy was associated with more pronounced cognitive and functional impairment, to more severe behavior disorders, and with an increase in the prescription of psychotropic medications in AD patients. However, the influence of apathy on clinical outcome measures, and the association between changes in apathy and in efficacy parameters were not consistently evaluated in AD clinical trials. *Methods:* First we assessed the influence of apathy severity scores (no apathy; mild apathy; clinically significant apathy) as evaluated with the neuropsychiatric inventory (NPI) on cognitive performance (ADAS-cog+ scores), on functioning in activities of daily living (ADL), rated with the Disability Assessment for Dementia scale (DAD), and on other neuropsychiatric symptoms (NPI) in 176 mild-to-moderate AD patients without clinically significant depression (122 female). Then, we investigated the associations of apathy scores and scores of change from baseline with the therapeutic responses (ADAS-cog, ADL, NPI) to anti-dementia drugs in 448 mild-to-moderate AD patients (330 female) enrolled in two different randomized-controlled clinical trials (RCTs). *Results:* When assessing the associations of apathy with other neuropsychiatric symptoms, cognition and functioning in ADL in mild to moderate AD out-patients without clinical depression, we found that AD patients with mild apathy ($p<0.05$) or relevant apathy ($p<0.01$) had reduced DAD scores as compared to patients without apathy. Partial correlation analysis also demonstrated a significant correlation between apathy and DAD scores ($r=-0.345$; $p<0.001$). Apathy was associated with significant impairments in instrumental ADL, initiation, and planning and organization DAD subscales, but not in basic ADL and effective performance subscales. No significant differences were found between apathy-related groups for cognitive performance. The influence of apathy on the therapeutic response to anti-dementia drugs (donepezil and Cerebrolysin) was also evaluated in patients enrolled in RCTs. Overall, patients with apathy at baseline showed smaller cognitive improvements after treatment ($p<0.05$) than patients without apathy. A worsening of apathy during the trial period was associated with significant impairments ($p<0.01$) in cognition, functioning and behavior; whereas a reduction in apathy scores was accompanied by cognitive, functional and behavioral improvements. *Conclusion:* These results indicate that: (1) apathy seems to influence disability even more than cognitive performance in mild to moderate AD outpatients without clinical depression; (2) changes in apathy scores are associated with the clinical response to anti-dementia drugs. Our

findings suggest that apathy has a significant impact on the rate of functional deterioration and on the degree of therapeutic response in AD patients. Therefore, apathy seems to be a relevant drug target and to constitute a reliable surrogate marker for clinical trials in AD.

P1-61: RELATIONSHIP BETWEEN «CAREGIVER'S STRESS» AND BPSD IN NURSING HOME. ALBA MALARA, FRANCESCO BETTARINI, FRANCESCO CERAVOLO, SERENA DI CELLO, FRANCESCO PRAINO, VINCENZO SETTEMBRINI, GIOVANNI SGRÒ, FAUSTO SPADEA, VINCENZO RISPOLI *(Scientific Committee of National Association of Nursing Home for Third Age (ANASTE) Calabria, Lamezia Terme (CZ), Italy)*

Backgrounds: The Behavioural and Psychological Symptoms of Dementia (BPSD) are the biggest predictors of stress experienced by caregivers, they are correlated with high levels of burden of care. The level of stress is a multidimensional construct observable and expressed by physical, psychological, social and economic variables. The Relative Stress Scale (RSS), an early assessment tools stress associated with the caregivers of dementia patients, proved to be very well applied in many different situations including the residential care. It was conducted an observational study in six nursing homes of National Association of Nursing Home for Third Age (ANASTE) Calabria, to detect the load experienced by the multidisciplinary èquipe in relation to behavioral and psychological aspects of residential population with dementia. *Methods:* The analysis was conducted on 169 health workers of which 4.70% were doctors (mean age of 38.8 ± 19.7),18:34% were nurses (average age 40.9 ± 5.6,) 50.8% were social health operators (average age of 40.9 ± 5.6), 8.87% were therapists of rehabilitation (average age 42.08 ± 7.67), 8.8% professional educators (average age 37.5 ± 2.5), the social workers were 3.55% (average age 46.33 ± 2.5), finally 5.32% were psychologists (average age 40.8 ± 5.6). The load subjectively experienced by caregivers has been detected by the self-administration of the RSS: an ordinal scale 15-item with 5-mode of answers (0 to 4). It was defined the shape and intensity of the general stress which develops in a caregiver assisting an elderly person with dementia. The scale includes three components that measure the personal distress of the caregiver (personal distress), the upheaval in his life (life upset) and the presence of negative emotions (Negative feelings). The prevalence, frequency and duration of BPSD was evaluated according to the Cohen-Mansfield Agitation Inventory (CMAI) and the Neuropsychiatric Inventory (NPI). The analysis of the results is given as media ± standard deviation , the relationship of linearity was evaluated according to the Pearson's correlation index. *Results:* The sample consisted of 216 residential patients (36.57% Male of average age 79.27 ± 1.76 and 63.42 Female of average age 82.33 ± 5.17). 81.30% of these suffer from dementia of various types and severity, in particular the 18.30% meets the diagnostic criteria for dementia of Alzheimer's and and 63.90% for Vascular dementia according to DSMIVR. 25.70% corresponded to the criteria of National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ ADRA) for diagnosis of Alzheimer's disease (AD), and 43.06% corresponded to the criteria of National Institute for Neurological Disorders and Stroke- Association Internationale puor la Recherche et Enseignement en Neusoscience (NINCDS-AIREN) for diagnosis of vascular dementia. 75.90% of patients with dementia, assessed with NPI, showed a slight behavioral disorder (NPI> 1≤48), 19.80% showed a behavior disorder moderate (NPI> 49≤96), 1.9% a severe behavioral disorder (NPI> 97≤144). According to cruteria of CMAI, the patients with dementia were classified in the following profiles: 8.70% had an aggressive behavior (F1), 29.16% had a physically aggressive behavior (F2), finally 42.59% had a Behaviour Verbally Agitated (F3). The development of the RSS was conducted both on the sample as a whole and for each structure. The overall score has identified three categories of intensity of stress: absent (score: 0-15), moderate (score: 16-30) and severe (score: 31-60). 55.02% of the sample presents a level of moderate stress, while the 45.56% presents a serious stress level. Severe stress correlates with the behavioral disorder moderate in NPI ($\varrho = 0.44$), and with profiles CMAI F1 ($\varrho = 0.61$) F2 ($\varrho = 0.66$) and F3 ($\varrho = 0.88$). Compared to the individual areas of the NPI, stress correlates positively with irritability ($\varrho = 0.30$) and anxiety ($\varrho = 0.30$), while negatively correlated with depression ($\varrho = -0.58$) and Apathy ($\varrho = -0.13$). *Conclusions:* The BPSD have a high interindividual variability in the different types of dementia, the type, severity and age of onset, resulting in not only the quality of life for patients, but also influencing the entire process of caregiving. In such a complex scenario it is fundamental to intervene with measures of protection, education and specific training. Recognition and support needed to deal with stress-related assistance, will allow for both the morale and welfare of the patient with dementia to that of the entire equipe care.

P1-62: DEPRESSION AND COGNITIVE DECLINE: FACTORS RELATED TO DEMOGRAPHICS AND PSYCHO PHARMACOTHERAPY ON ELDERLY IN NURSING HOMES. EDVALDO SOARES, PATRÍCIA DE SOUZA ROSSIGNOLI *(Laboratory of Cognitive Neuroscience-LaNeC, Sao Paulo State University, São Paulo, Brazil)*

Objectives: To identify the prevalence of neuropsychiatric disorders, especially DP and CD, on a sample of nursing home residents, relating this prevalence with some aspects of the demographics and psycho pharmacotherapy. *Methods:* 48 elders from two different nursing homes were selected. The collection of demographic and pharmacological data was made utilizing medical records. The medication was classified according to the Anatomical Therapeutic Chemical Code (ATC) criteria. The Geriatric Depression Scale (GDS 30) and the Mini Mental State Examination (MMSE) tests were utilized to determine the prevalence of DP and CD. *Results:* It was observed in the sample a high incidence of DP and CD among the researched elders. More schooling individuals tend to present less CD. Individuals with less CD indicatives present less symptomatology for DP. Of all the researched elders, 54,2% are submitted to psycho pharmacotherapy. Of all the consumed medicine, 16,5% belonged to the class of neuropsychiatric medicine. The medicated elders present, in average, a larger symptomatology for DP (12 points/ average/GDS) than the non-medicated elders (9,9 points/average/ GDS). The inverse occurs in relation to the CD indicatives. The use of psychotropics, especially in association, can have negative effects related to depression and cognition. *Discussion:* The pharmacotherapy, characterized for the polymedication and chronicity, especially of neuropsychiatric medicines, deserves special attention among elders, because the data suggest a significant relation between the utilization of medicines, singly or in association, and the increase of CD and DP. In addition, the data suggest that DP is a risk factor for CD and DM. *Keywords:* Cognitive decline; Depression; Elderly; Nursing home; Psycho pharmacotherapy

P1-63: PROTEOTOXIC CONTROL IN ALZHEIMER'S DISEASE MAY BE ATTAINED BY BUBR1: A POSSIBLE TARGET FOR THERAPY? VLADAN BAJIC[1], BILJANA SPREMO-POTPAREVIC[2], LADA ZIVKOVIC[2], BOBAN STANOJEVIC[3], MARTINA BRUCKNER[4], THOMAS ARENDT[4] *((1) Department of Radiobiology and Molecular Genetics, ''Vinca'' Institute; Belgrade, Serbia; (2) Department of Physiology, Faculty of Pharmacy, University of Belgrade, Serbia; (3) Department of Endocrinology and Molecular Biology, ''Vinca'' Institute; Belgrade, Serbia; (4) Paul-Flechsig-Institute for Brain Research, University of Leipzig, Medical Faculty, Leipzig, German)*

Background: Aneuploidy has been seen as a culprit of process leading to Alzheimer's Disease (AD). It affects, primarily gene dosage of proteins (proteotoxicity) that are regulators of the APP metabolism but also may affect the protease and autophagy machinery in the AD cell. Bub R1, Mad 2 and Mad 2B proteins are inhibitors of the anaphase promoting complex thus regulating the anaphase cell cycle checkpoint control ensuring proper chromosome segregation and separation. Bub R1 is essential for maintaining genomic balance and is found that its overexpression leads to reduction in chromosome mis-segregation and hence aneuploidy. Also, knowledge that a number of proteins that regulate cell division have secondary roles in maintaining the postmitotic status of a neuron has led to question of how are these protein/s affected in Alzheimer's Disease. Here we wish to elucidate the possible role of BubR1 protein in Alzheimer's Disease (AD) brain versus age matched control. *Methods:* Immunohistochemical analysis and Western blot were used to evaluate the levels and expression patterns of BubR1 protein in the hippocampal region of AD brains compared to age matched controls. *Results:* Our results show that BubR1 protein is differentially expressed, i.e. we found a decreased expression of BubR1protein in AD brains compared to age matched controls. *Conclusion:* It is conceivable that BubR1 protein plays a role in the control of the APC activity in post-mitotic neurons. Our results show changes in expression in the AD brain which may lead us to the possible role of BubR1 in neuronal cell cycle re-entry by increasing proteotoxicity leading to apoptosis. By using BubR1 as novel target may present a novel strategy for AD treatment.

P1-64: EFFICACY AND SAFETY OF A NOVEL ACETYLCHOLINESTERASE INHIBITOR OCTOHYDROAMINOACRIDINE IN MILD TO MODERATE ALZHEIMER'S DISEASE: A PHASE II MULTICENTER RANDOMIZED CONTROLLED TRIAL. SHIFU XIAO[1,2], TAO WANG[1,2], XIA LI[1,2], ZHONGXIN ZHAO[3], XUEYUAN LIU[4], XIAOPING WANG[5], HENGGE XIE[6], QINPU JIANG[7], LI SUN[8], BENYAN LUO[9], LAN SHANG[10], WEIXIAN CHEN[11], YAN BAI[12], MUNI TANG[13], MAOLIN HE[14], KAIXIANG LIU[15], QILIN MA[16], ZHI SONG[17], YINGYI QIN[18], XIUQIANG MA[18], JIA HE[18] *((1) Department of Geriatric Psychiatry, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China; (2) Alzheimer's Disease and Related Disorders Center, Shanghai Jiao Tong University, Shanghai, China; (3) Department of Neurology, Shanghai Changzheng Hospital, Second Military Medical University, Shanghai, China; (4) Department of Neurology, the 10th People's Hospital, Tongji University, Shanghai, China; (5) Department of Neurology, Shanghai General Hospital, Shanghai Jiao Tong University, Shanghai, China; (6) Department of Geriatric Neurology, Chinese PLA General Hospital, Beijing, China; (7) Mental Health Center of Hebei Province, Baoding, Hebei Province, China; (8) Department of Neurology, the First Hospital of Jilin University, Changchun, Jilin Province, China; (9) Department of Neurology, First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang Province, China; (10) Beijing Hui-Long-Guan Hospital, Peking University, Beijing, China; (11) Department of Geratology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, China; (12) First Affiliated Hospital of Kunming Medicine University, Kunming, Yunnan Province, China; (13) Guangzhou Psychiatric Hospital, Guangzhou, Guangdong Province, China; (14) Department of Neurology, Beijing Shijitan Hospital, Capital Medical University, Beijing, China; (15) Affiliated Hospital of Guilin Medical School, Guilin, Guangxi Province, China; (16) Department of Neurology, the First Affiliated Hospital of Xiamen University, Xiamen, Fujian Province, China; (17) Neurological Department, the Third Xiangya Hospital of Central South University, Hunan Province, China; (18) Department of Health Statistics, Second Military Medical University, Shanghai, China)*

Background: The octohydroaminoacridine, a new humanized acetylcholinesterase inhibitor, is a potential treatment for Alzheimer's disease. *Method:* We conducted a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 2 clinical trial to investigate the effects of octohydroaminoacridine in patients with mild-to-moderate Alzheimer's disease. 284 patients were randomized to receive placebo thrice-daily (TID), octohydroaminoacridine 1 mg TID (low dose group), or to titrate up to 2 mg TID (middle dose group) in two weeks, or to titrated up to 4 mg TID (high dose group) in four weeks. Changes from baseline to week 16 were assessed with the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog), Clinician's Interview-Based Impression of Change Plus (CIBIC+), Activities of Daily Living (ADL) and the Neuropsychiatric Inventory (NPI). A 2-way analysis of covariance and least squares mean (LSM) t-test were used. (ClinicalTrials.gov Identifier: NCT01569516). *Results:* In this study, 71, 70, 71 and 72 patients were randomized to low dose group, middle dose group, high dose group, and placebo group, respectively. At week 16, the between-group differences of the change from baseline in the primary outcome of ADAS-cog (octohydroaminoacridine groups minus placebo group) were 3.16, 3.27 and 5.01 for low, middle, and high dose groups, respectively ($p<0.0001$ for all these tests). For secondary outcomes, the patients in three drug groups had better performance in CIBIC-plus score and ADL score, but there were no significant between-group differences in NPI score. There was not any evidence for more adverse events occurred in different drug groups than placebo group. *Conclusions:* Octohydroaminoacridine significantly improved cognitive function and behavior among these patients with mild-to-moderate Alzheimer's disease. *Disclosures and acknowledgments:* Supported by Changchun Huayang High-science and Technology Co.,Ltd, Clinical Trial Approval No. 2010L00161 and the National Natural Science Foundation of China project 81201030, the Funds for International Cooperation and Exchange of the National Natural Science Foundation of China-NSFC project 61210001 and the China Ministry of Science and Technology grants 2009BAI77B03 and 2012ZX09303 and the Shanghai Science and Technology Committee grants 134119a2600, 10ZR1425800 and 14411965000. The authors declare no relevant conflicts of interest.

P1-65: COMBINATION TRIALS WITH AMYLOID MODULATING AGENTS. A QUANTITATIVE SYSTEMS PHARMACOLOGY PERSPECTIVE. HUGO GEERTS[1,2], ATHAN SPIROS[1] *(1) In Silico Biosciences, Berwyn, PA; (2) Perelman School of Medicine, Univ of Pennsylvania, Philadelphia, PA)*

Background: With the large number of monotherapy amyloid trials failing to generate a significant clinical response, there is an increasing interest in combination therapies. However, based on preclinical biochemistry and clinical SILK data, it becomes clear that many non-linear processes play a role and that for instance combining different doses of BACE-inhibitors and antibodies against either monomers or aggregated forms might likely result in quite different outcomes. For instance, BACE inhibition or gamma-secretase modulation (GSM) does not address the formation of possible toxic oligomers derived from aggregated Abeta plaques subject to a changed equilibrium state, possibly determined by antibody-mediated clearance of specific Abeta peptide forms. Furthermore testing such combinations in preclinical animal models is very costly, takes a long time and has its own legal and organisational challenges. *Methods:* We have developed a mechanism-based Quantitative Systems Pharmacology computer model of Alzheimer's disease, based on preclinical (differential aggregation rates for Ab1-40 and Ab1-42) and clinical (SILK) data on

Abeta synthesis in the human brain. The differential dose-dependent effect of Ab1-40 and Ab1-42 on glutamate neurotransmission and a7 nAChR physiology on cortical pyramidal and GABA interneurons is introduced in a biophysically realistic neuronal network that is calibrated with historical trial data on ADAS-Cog changes. Antibody mediated clearance of specific Abeta peptides is modeled using a saturatable Michaelis-Menten description of microglia dependent uptake. This humanized platform that formalizes existing domain expertise is different from correlative analysis based on large –omics databases and has shown practical value in pharmaceutical R&D by correctly and prospectively predicting actual clinical trials outcome at three occasions (1 in AD, 2 in schizophrenia). Because of the mathematical nature of the model, we could identify reasons for translational disconnect, suggesting that it captures human physiology and pathology better than preclinical animal models. We believe that this a good complementary approach for supporting design of clinical trials with regard to dose selection, patient baseline choices and the impact of comedications and common genotypes on functional cognitive readout. *Results:* Because of the different synthesis rates of Ab1-40 and Ab1-42, clearance of monomers, oligomers and aggregated forms after passive vaccination or synthesis inhibitors follow very different time-courses for different disease states (MCI to moderate AD) and baseline amyloid loads. The model captures the experimentally observed faster aggegration rate of Ab1-42 versus Ab1-40 and keeps tracks of the oligomer level derived from breakdown of larger Abeta aggregated forms. The parameters of the model are constrained by available clinical data on cognitive outcomes and amyloid imaging while the outcome quantitatively recapitulates the clinical outcomes in terms of ADAS-Cog or equivalent changes for bapineuzumab, solanezumab after 72 weeks and aducanamab after 52 weeks with regard to the different clinical stages of AD pathology. Interestingly the model is able to provide a possible rationale for the unexpected opposite changes in CSF free unbound Ab1-40 and Ab1-42 with solanezumab treatment. The model furthermore provides biological rationales for the differential effect of amyloid load on cognitive performance in the absence of clear neuropathological effects of the beta-amyloid peptide in the human Alzheimer brain. *Conclusion:* Although the computer model, like any other model of AD suffers from a number of limitations (changes and physiological effects of only two Abeta isoforms, no detailed modeling of microglia-dependent processes involved in the clearance of Abeta peptides, only effect of Abeta peptides on glutamate and nAChR neurophysiology); it is a good first approximation that can be iteratively improved and probably represents the best next approach for optimizing clinical trial design. For instance, one could test the digital equivalents of antibodies (based on the affinity for the respective epitopes) with varying doses of a BACE inhibitor or a GSM in a humanized environment for different disease states and patients with different comedications or genotypes without having to perform the actual physical testing and in a relatively short time. Providing additional knowledge from this 'virtual human patient' platform can help identify and mitigate possible problems and issues associated with expensive clinical trials of combination therapies.

P1-66: RAMCIP PROJECT: ROBOTIC RESEARCH DEVELOPMENT TO HELP ALZHEIMER´S DISEASE PATIENTS AT HOME. CARLA ABDELNOUR, NATALIA TANTINYÀ, JOAN HERNÁNDEZ, ELVIRA MARTÍN, SILVIA GARCÍA, JOAN CARLES RIBES, ASUNCIÓN LAFUENTE, ISABEL HERNÁNDEZ, MAITEE ROSENDE, ANA MAULEÓN, LILIANA VARGAS, MONTSERRAT ALEGRET, ANA ESPINOSA, GEMMA ORTEGA, DOMINGO SÁNCHEZ, OCTAVIO RODRÍGUEZ, PILAR CANYABATE, MARIOLA MORENO, SILVIA PRECKLER, ÁNGELA SANABRIA, ALBA PÉREZ-CORDÓN), LLUIS TÁRRAGA, AGUSTÍN RUIZ, MERCÉ BOADA, RAMCIP GROUP *(Research Center and Memory Clinic of Fundació ACE, Institut Català de Neurociències Aplicades, Barcelona, Spain)*

Backgrounds: There is an increased interest in novel solutions for the supervision and help in activities of daily living in patients with Alzheimer´s disease (AD), since caregiving consumes significant material and human resources. Robotic technologies have potential to support and assist patients with cognitive impairment. Robotic Assistant for MCI Patients at home (RAMCIP) is a three-year research project within the HORIZON2020 programme funded by the European Commission, which started in January 2015 with the aim of research and develop a novel robot that can provide assistance to elderly people with (AD) in early stages (mild cognitive impairment or mild dementia) at their homes, allowing them to maintain independence and quality of life. *Methods:* Eight partners will collaborate in the RAMCIP project that will comprise the following innovative aspects: 1) cognitive skills based on advanced user and home environment modelling and monitoring, allowing the robot to decide when and how to assist the user; 2) novel adaptive multimodal human robot communication interfaces with strong emphasis on emphatic communication and augmented reality displays, and 3) advanced, dexterous and safe robotic manipulation capabilities, for the first time applied in service robots for assisted living environments, enabling grasping and manipulation of a wide variety of home objects, as well as safe physical human-robot interaction (HRI), introducing assistance activities that involve physical contact, all with special emphasis on safety. *Results:* By the end of the RAMCIP project, the RAMCIP robot is anticipated to be capable of: 1) understand actions, complex activities and behavior of multiples persons in the user´s home; 2) provide proactive, discreet and optimal assistance to the user; 3) allow communication between user and the robot, 4) establish advanced physical interaction between robot and the home environment and 5) establish assistance activities involving physical interaction between the robot and the user. Finally, the RAMCIP robot will be demonstrated and evaluated in pilot trials that shall designed to test and validate the efficacy of the robot in real-life scenarios, taking into account the technological challenge this implies. *Conclusions:* The RAMCIP project vision is of future service robots that will be able to assist in significant aspects of the user's daily life, ranging from food preparation, eating and dressing activities, through to managing the home and keeping it secure. Also, the robot should help the user maintain a positive outlooks and also to exercise their cognitive and physical skills. Coverage of these aspects will preserve an independent daily living and quality of life in patients with AD in mild stages. Rigorous evaluation of these novel technologies by using controlled trials is warranted.

P1-67: SAFETY AND PHARMACOKINETICS OF ANTI-PROTOFIBRILLAR MAB SAR228810 IN FIRST-IN-MAN STUDY AFTER SINGLE AND MULTIPLE ASCENDING IV AND SC DOSING IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE. BRUNO VELLAS[1], RAPHAEL DAHMEN[2], OLIVIER NICOLAS[3], VALERIE MARTIN[4], CAROLINE COHEN[4], LAURENT VERMET[3], JÉROME BARAKOS[5], JOYCE SUHY[5], ANNE BÖRJESSON-HANSON[6], HENRIK ÖSTLUND[7], GEERT JAN GROENEVELD[8], NIELS PRINS[9], PHILIP SCHELTENS[9], KAJ BLENNOW[10], NIELS ANDREASEN[11] *((1) Gérontopôle, CHU Purpan, Toulouse, France; (2) Sanofi-Aventis R&D, Frankfurt, Germany; (3) Sanofi-Aventis R&D, Montpellier, France; (4) Sanofi-Aventis R&D, Chilly-Mazarin, France; (5) BioClinica, Medical Imaging, Newark, CA, USA; (6) Department of Neuropsychiatry, Sahlgrenska University Hospital, Gothenburg, Sweden; (7) Memory Clinic, Skanes University Hospital, Malmö, Sweden; (8) Centre for Human Drug Research, Leiden, the Netherlands; (9) Alzheimer Center, VU University Medical Center,*

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Backgrounds: SAR228810 is a humanized monoclonal antibody (mAb) that binds specifically to pathological forms of Aβ: high molecular weight oligomers and fibrils. SAR228810 was designed with an engineered IgG4 framework to reduce the risk of Amyloid-Related Imaging Abnormalities (ARIA). *Methods:* SAR228810 was assessed in this double-blind, randomized, placebo-controlled (ratio active:placebo was 3:1) first-in-human study (NCT01485302) for its safety and tolerability and pharmacokinetic properties after escalating single and multiple IV and selected SC doses of SAR228810 in mild to moderate Alzheimer's Disease. 50 to 85 years old patients with probable Alzheimer's Disease according to the NINCDS-ADRDA criteria and an MMSE score between 16 and 28 were eligible for this study. Their Alzheimer's pathology had to be confirmed by CSF Aβ1-42 or brain amyloid PET scanning before entry into the study. Patients received a single IV dose of 100mg, 300mg, 450mg, or 600mg, or a single SC dose of 100mg or 450mg SAR228810 or placebo. After a complete wash-out, patients with good overall tolerability were carried forward into one of the 6-months multiple dosing regimens with 100mg, 200mg, or 400mg IV every 4 weeks, or 450mg SC every 3 weeks SAR228810 or placebo. Few patients were directly enrolled into the multiple dosing part. Safety was assessed by means of collecting adverse events (AEs), serial MRI scanning including FLAIR and GRE T2* sequences, inflammatory parameters in CSF, and local tolerability. Plasma PK profiles of SAR228810 were taken after a single dose in both study parts and in steady state after multiple dosing. CSF concentration of SAR228810 was assessed at selected time points in both study parts. Validated enzyme-linked immunosorbent assays (ELISA) were used to determine plasma and CSF concentrations of SAR228810, with a lower limit of quantification (LLOQ) of 0.06 μg/mL for plasma and a LLOQ of 4 ng/mL for CSF samples. *Results:* 44 patients were included in the single dosing part and 48 patients in the multiple dosing part of the study. SAR228810 was overall well tolerated in both study parts, a maximum tolerated dose was not reached. There were no deaths and no on-treatment SAEs in the study. The percentage of patients with treatment emergent AEs was comparable between the treatment groups in both study parts. There were no ARIA-E (brain vasogenic edema) in this study. One patient was detected to have a solitary new ARIA-H (cerebral microhemorrhage) in the MRI scan 2 days after a single IV dose of 600mg SAR228810, which remained stable in all further follow-up MRI scans. Local tolerability was good for both routes of administration with no patient reacting with a local tolerability score higher than 2. Single dose and steady state SAR228810 plasma exposure after IV and SC administration increased with dose and showed no deviation from dose proportionality. After single dose, SAR228810 mean absolute SC bioavailability was around 66%. The mean accumulation ratio for AUC was 1.4 to 2.0 for the IV treatment regimens and 2.3 for SC regimen. Steady state was reached within 3 months for all repeated IV and SC dose regimens and the mean steady-state t1/2 ranged from 21 to 25 days. In CSF, SAR228810 concentrations increased with dose after single and repeated IV or SC dosing without major deviation from dose proportionality and steady-state was reached by 3 months of treatment. *Conclusion:* SAR228810 was well tolerated when given up to single doses of 600mg IV and 450mg SC, as well as in multiple dosing regimens up to 400mg IV every 4 weeks and 450mg SC every 3 weeks over 6 months. A maximum tolerated dose was not reached. There were no ARIA-E in this study. One solitary new ARIA-H was detected 2 days after a single IV dose of 600mg SAR228810. Plasma and CSF concentrations increased dose proportionally and reached steady state after 3 months with a plasma half life of 21 to 25 days.

P1-68: SAFETY OF THE 5-HT6 ANTAGONIST, RVT-101 IN PATIENTS WITH ALZHEIMER'S DISEASE: SUMMARY OF PHASE 2 CLINICAL TRIALS. ILISE LOMBARDO[1], GEETHA RAMASWAMY[1], STEPHEN C PISCITELLI[2], LAWRENCE T FRIEDHOFF[1] *((1) Axovant Sciences, Inc., New York, NY; (2) Roivant Sciences, Inc., New York, NY)*

Background: RVT-101 (formerly known as SB-742457) is an orally administered, 5-hydroxytryptamine 6 (5-HT6) serotonin receptor antagonist. RVT-101 was well-tolerated by subjects in 13 clinical trials completed to date. The safety of RVT-101 was evaluated across four Phase 2 program in patients with mild to moderate Alzheimer's disease including three monotherapy double-blind studies of 24 week duration, and a double-blind study as adjunctive use with donepezil for 48 weeks. *Methods:* RVT-101 was evaluated in four Phase 2 trials; three as monotherapy and one as an adjunctive therapy with donepezil. The dose in monotherapy ranged from 5 to 35 mg QD and studies were 24 weeks in duration. In combination with donepezil, doses were 15 mg or 35 mg; subjects completed 24 weeks of treatment and were offered a blinded extension for an additional 24 weeks. *Results:* Monotherapy studies safety database included 330 patients on placebo and 591 patients on RVT-101. The proportion of patients who withdrew from the studies was 19% in the placebo group and 15% in RVT-101 groups. A similar proportion (approximately 5%) withdrew due to adverse events (AE). The incidence of the most common AEs were similar across groups and there were no apparent dose related trends. The incidence of on-treatment serious AEs (SAE) was similar in the groups (placebo 5% vs. RVT-101 4%). The adjunctive therapy study 48 week safety database included 221 patients at 15 mg, 236 at 35 mg and 225 on placebo. The incidence of the most common AEs were similar across groups and there were no apparent dose related trends. Drug related AEs were similar between RVT-101 15 mg (11%), 35 mg (7%), and placebo (13%). The incidence of falls (2%) was numerically lower in the 35 mg group compared to placebo (6%). The proportion of subjects reporting SAEs over 48 weeks was 8%, 12% and 11% for placebo, SB742457 RVT-10115mg and SB742457 RVT-101 35mg, respectively. Drug related SAEs were <1%, (need 15mg data here) and 0% at 24 and 48 weeks for placebo, RVT-101 15mg and RVT-101 35mg, respectively. No significant changes in laboratory AEs were observed; the incidence of ALT > 3X ULN was < 1% in both RVT-101 dosing groups. *Conclusion:* RVT-101 was well tolerated as monotherapy and in combination with donepezil in Phase 2 studies with an incidence of AEs comparable to placebo. These data support the initiation of a Phase 3 study as an adjunct to donepezil.

P1-69: STEM CELLS FOR ALZHEIMER'S DISEASE: TRANSITION TO CLINICAL TRIALS. TRISTAN BOLMONT[1,2], THEO LASSER[1], ALEXEI LUKASHEV[2], NIKOLAI TANKOVICH[3] *((1) Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland; (2) Stemedica International, Epalinges, Switzerland; (3) Stemedica Cell Technologies, San Diego, CA, USA)*

Background: Adult human stem cells constitute a promising therapeutic approach for the treatment of various neurodegenerative disorders including Alzheimer's disease (AD). However, FDA-approved clinical trials currently evaluating the impact of human stem cells on AD remain marginal. Therefore, a stem cell based AD therapy represents a large untapped potential. Several pre-clinical research laboratories have reported a beneficial effect of human stem cells on cerebral Abeta amyloidosis, adult neurogenesis or memory impairments in transgenic models of AD. However, the majority

of these therapeutic initiatives rely on the direct delivery of stem cells into the brain through intracerebral or intracerebroventicular injection. These routes of administration entail a major hurdle for clinical applications due to their invasiveness and possible complications. This difficulty has certainly to a large extend hampered the clinical translation of these positive pre-clinical findings. In contrast, intravenous delivery is fast, easy and complications are rarely observed. A few preclinical studies have evaluated intravenous delivery of stem cells and its impact on neurodegeneration or cognitive impairments in mouse or rat models of AD, however to the best of our knowledge none has evaluated the impact of intravenous stem cell administration on cerebral Abeta amyloidosis. *Methods:* We have investigated the impact of intravenous human stem cell delivery on cerebral Abeta amyloid pathology in a mouse model of AD. The cells used in the study were human mesenchymal stem cells (hMSC), bone marrow derived, ischemia-tolerant and cultured under a controlled, low physiological level of oxygen. Furthermore, these hMSC were manufactured under cGMP conditions and currently used in FDA-approved clinical trials in the US. Importantly, these hMSC express negligible levels of human leukocyte antigen-D related (HLA-DR) cell surface receptor. The Alzheimeric model used in this study is the APPPS21 mouse. Cerebral amyloidosis starts in these mice by 6-8 weeks of age and the number of Abeta amyloid plaques increases steadily thereafter. Both young pre-depositing mice (1 mon. age) as well as aged (15 mon. age) mice were used in experiments with either single or repeated intravenous delivery of hMSC. An injection of Lactated Ringers Solution (LRS) in age-matched APPPS21 mice were used as controls. *Results:* Intravenous delivery of hMSC safely reduced cerebral Abeta pathology in APPPS21 animals analyzed one week after the last injection. Both aged and young APPPS21 mice exhibited significantly decreased Abeta amyloidosis following the hMSC treatments. Concomitantly, microglial activation was diminished in aged and young hMSC-treated APPPS21 mice. No increase of vascular amyloid or manifestation of microhemorrhages was observed following the repeated intravenous hMSC delivery. Quantitative RT-PCR biodistribution analysis revealed that intravenously delivered hMSC migrate to the brain and could be detected in this organ with the highest value at 1 hour post-delivery, decreasing by 1 day and subsequently dropping below detection level at 1 week after the injection. The results of this study on the hMSC safety and efficacy in an animal model were used to substantiate an investigational new drug (IND) application with FDA to commence a clinical trial in US in 2015: A Phase IIa, multi-center, randomized, single-blind, placebo-controlled, crossover study to assess the safety, tolerability, and preliminary efficacy of a single intravenous dose of allogeneic human mesenchymal stem cells to subjects with mild to moderate dementia due to AD. *Conclusion:* 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 of their application for this devastating disease.

P1-70: PHARMACOGENETICS SUPPORTED CLINICAL TRIAL TO DELAY ONSET OF MCI DUE TO AD USING PIOGLITAZONE 0.8 MG SR: TOMMORROW STUDY.

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Background: A number of lines of evidence suggest that pathology associated with Alzheimer's disease is apparent many years before clinical symptoms are evident. This has fostered interest in attempts to delay symptom onset. A number of clinical trials are underway that are recruiting cognitively normal subjects and follow the course of cognitive decline to mild cognitive impairment (MCI) and AD. In order to conduct a trial of this nature, several methodological challenges need to be addressed. The first is the need for a mechanism to enrich the trial population for subjects at elevated risk for developing symptoms during the course of the trial. Second, a battery of neuropsychological instruments is needed that provides sufficient sensitivity to detect early signs of cognitive impairment. Third, the therapy to be investigated for delaying the onset of MCI due to AD must have a well-established safety and tolerability profile in cognitively healthy adults. *Methods:* TOMMORROW is a phase 3, global, multicenter, double blind, placebo controlled, parallel group, registration study. The dual aims are to qualify the biomarker risk assignment algorithm (BRAA) for assigning near term risk for developing MCI due to AD and to evaluate the efficacy of pioglitazone 0.8 mg SR to delay the onset of MCI due to AD in cognitively normal, high risk individuals. All low-risk subjects are assigned to placebo; high-risk subjects are evenly randomized to either pioglitazone 0.8 mg SR or placebo. The study will eventually enroll approximately 5,800 subjects. The BRAA used to assign risk in the TOMMORROW study is composed of age at enrollment (from 65 to 83 years) and genotype at loci in two genes, TOMM40 and APOE. Length variation of a polyT tract (rs10524523), (chr19:44,899,792-44,899,826, human genome reference assembly GRCh38/hg38) located within intron 6 of the TOMM40 gene, which encodes an essential mitochondrial import protein has been associated with LOAD age of onset. TOMM40 is adjacent to, and in linkage disequilibrium with, the APOE gene, which encodes apolipoprotein E, a cholesterol transport protein. Variation in the epsilon allele of APOE is a well-recognized genetic risk factor for age of LOAD onset. The BRAA will identify individuals at highest risk for developing MCI due to AD during the course of the study. Both preclinical and clinical evidence suggest that thiazolidinedione drugs may be effective in enhancing cognitive function and forestalling cognitive decline, and that they represent a fresh approach to easing the burden of AD. Pioglitazone (at doses significantly higher than the dose used in the TOMMORROW study) was approved for the treatment of type 2 diabetes in 1999 and has over 26 million patient-years of exposure data. This study targets a non-amyloid treatment approach, focusing instead on the hypothesis that synaptic energetics and mitochondrial function affect the disease process. TOMMORROW operationalizes the clinical criteria for MCI due to AD [Albert et al. Alzheimers Dement.2011;7(3):270-9],which is a novel primary endpoint . The trial is designed as a time to event study and has an anticipated treatment period of 4 years. The Clinical Dementia Rating scale and a battery of 12 neuropsychological measures representing 5 key cognitive domains affected in early AD are key assessments that enable diagnoses. To support global recruitment, a separate neuropsychological instrument validation/normative study to ensure that test measures perform consistently across cultures and languages has been completed. These data are presented separately. *Results:* The study was initiated in August 2013 and is currently recruiting in the US, UK, Australia, Germany, and Switzerland. To date, over 19,200 subjects have been screened and over 2,300 subjects randomized. Italy will start recruitment soon, and Russia is expected to begin recruitment in mid to late 2015. *Conclusion:* The study was designed with input from international experts and finalized following discussions with US and EU regulatory authorities. It represents a unique opportunity to qualify the BRAA to stratify risk of developing MCI due to AD in the next 5 years, to standardize and validate sensitive cognitive assessment panels, and to explore therapeutic intervention in the earliest phase of the AD

continuum.

Friday, November 6th

P2-1: CORTICAL THINNING PATTERNS IN PATIENTS WITH SUBJECTIVE COGNITIVE DECLINE. EUN YE LIM[1], JUNG HEE CHO[1], YONG SOO SHIM[1], YUN JEONG HONG[2], BORA YOON[3], DONG WON YANG[1] *((1) Department of Neurology, College of Medicine, The Catholic University of Korea, Seoul, Korea; (2) Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; (3) Konyang University College of Medicine, Daejeon, Korea)*

Background & Objective: Subjective cognitive decline (SCD) may be the first changes corresponding to a very subtle alteration at the pre-MCI(mild cognitive impairment) stage of AD (Alzheimer disease). But, The SCD is very heterogeneous state, so it is important to identify of individuals with SMI who will convert to dementia. Measurements of cortical thickness based on MRI are highly sensitive to small structural changes across the cortex. And previous studies showed that cortical thickness can predict MCI group who will progress to AD. In this study, we investigated whether different anatomical patterns of cortical atrophy distinguish SCD patients who progressed to aMCI or AD from SCD patients who didn't. *Patients and Methods:* We conducted a retrospective cohort study of recruited from SCD patients who visited memory clinic of the neurology department of Seoul St. Mary's hospital from Jan, 2010 to Dec, 2013 and who had been to be observed through outpatient clinic until Dec, 2014. We divided them into two groups, SCD patients who progress to aMCI or AD (pSCD; n=12), and who remained stable (sSCD; n=20), according to their follow up neuropsychological test. And we recruited healthy controls(NC; n=20) by advertisements. Structural 3D-T1 weighted MRI was performed on single 1.5 Tesla scanner (Signa Excite 11.0, General Electric Medical Systems). Freesurfer software was used to obtain maps of cortical thickness for group comparisons. *Results:* Cortical thickness analysis revealed that the pSCD patients had focal cortical thinning in the precentral, superior parietal, lingual and middle temporal areas compared with sSCD patients. Compared with NC, pSCD patients had focal cortical thinning in the parietal, orbito frontal and entorhinal cortex areas. And sSCD patients had diffuse thinning patterns involving parietal, occipital and middle frontal areas compared with NC. *Conclusion:* We observed pSCD showed greater similarity to an AD gray matter patterns compared with sSCD and NC. This suggests the possibility that cortical thinning patterns in patients with SCD can be useful imaging biomarkers considering who will progress to Alzheimer dementia.

P2-2: GRAY MATTER VOLUMES AND TREATMENT RESPONSE OF PSYCHOTIC SYMPTOMS TO RISPERIDONE IN ANTIPSYCHOTIC-NAÏVE ALZHEIMER'S DISEASE PATIENTS. YOUNGMIN LEE, JE-MIN PARK, BYUNG-DAE LEE, EUNSOO MOON, HEE-JEONG JEONG *(Department of Psychiatry, School of Medicine, Pusan National University, Busan, Korea)*

Objective: The purpose of this study was to determine whether gray matter volumes are associated with treatment response of psychotic symptoms in Alzhemer's disease patients. *Methods:* Risperidone which is commonly used as atypical antipsychotic drug was administered to antipsychotic-naïve 25 AD patients with psychosis for 6 weeks. Psychotic symptoms were rated with Korean version of the Neuropsychiatry Inventory (K-NPI) at baseline and after 6 weeks, and treatment response was defined as the change in K-NPI score from baseline to 6 weeks. Gray matter volumes were measured with magnetic resonance imaging and voxel-based morphometry at baseline. Age, gender, years of education, total intracranial volume, apolipoprotein E genotype, dosage of risperidone, the baseline Korean version of the Mini-Mental Status Examination scores, the baseline K-NPI psychotic and non-psychotic scores were measured as covariates of no interest. *Results:* We found that treatment response of psychotic symptoms to risperidone, in antipsychotic-naïve AD patients, was positively associated with both putamen, left parahippocampal gyrus and left amygdale volume after controlling covariates of no interest ($P < 0.001$, uncorrected, KE > 100 voxels). *Conclusion:* Therefore, we conclude that gray matter volumes such as putamen, parahippocampal gyrus and amygdale are associated with the treatment response of psychotic symptoms after 6 weeks of treatment with risperidone in antipsychotic-naïve AD patients with psychosis. These results suggest that gray matter volumes in AD patients with psychosis might be a biomarker for treatment response to antipsychotic medication. *Key Words:* Alzheimer's disease, psychotic symptoms, gray matter volumes, treatment response.

P2-3: WHITE MATTER MICROSTRUCTURE DISRUPTION IS CORRELATED WITH AMYLOID BURDEN IN SUBJECTS WITH SUBJECTIVE COGNITIVE DECLINE. FUNDACIO ACE HEALTHY BRAIN INITIATIVE. O RODRIGUEZ-GOMEZ[1], A SANABRIA[1], A PÉREZ-CORDÓN[1], D SÁNCHEZ-RUÍZ[1], S RUIZ[1], M TARRAGONA[1], J PAVÍA[2], F CAMPOS[2], A VIVAS[3], M GÓMEZ[3], M TEJERO[3], M ALEGRET[1], A ESPINOSA[1], G ORTEGA[1], C ABDELNOUR[1], I HERNÁNDEZ[1], A RUIZ[1], J GIMÉNEZ[3], F LOMEÑA[2], L TÁRRAGA[1], O SOTOLONGO-GRAU[1], M BOADA[1] *((1) Alzheimer Research Center and Memory Clinic, Fundació ACE, Institut Català de Neurociències Aplicades, Barcelona, Spain; (2) Servei de Medicina Nuclear, Hospital Clínic i Provincial. Barcelona, Spain; (3) Departament de Diagnòstic per la Imatge. Clínica Corachan, Barcelona, Spain)*

Background: The natural history of Alzheimer´s disease (AD) seems to begin several years before the onset of clinical symptoms. In this preclinical phase of the disease imaging biomarkers can detect some of the key pathophysiological features of AD. Amyloid deposition is an early event that can be detected using positron emission tomography (PET) with amyloid tracers such as Florbetaben (FBB). Magnetic resonance imaging (MRI) can show some degree of brain atrophy in more advanced stages of preclinical AD. Recently, several studies have found that alteration of the white matter microstructure measured by diffusion tensor imaging (DTI) could be an early phenomenon in the pathophysiology of AD. Subjective cognitive decline (SCD) has been proposed as a marker of neurodegeneration in cognitively normal elderly individuals. Thus, population with SCD could be an appropriate target for research studies and clinical trials of preclinical AD. Fundació ACE Healthy Brain Initiative (FACEHBI) is an ongoing longitudinal cohort study of individuals with SCD. FACEHBI has been registered as a clinical trial (EUDRACT 2014-000798-38). *Methods:* FACEHBI inclusion criteria were: 1) age older than 49 years; 2) subjective cognitive complaints defined as a score ≥8 in the Spanish validation of Memory Failures in Everyday Life Questionnaire (MFE-30); 3) MMSE ≥ 27; 4) Clinical Dementia Rating (CDR) =0 ; 5) performance in a comprehensive neuropsychological battery (NBACE) within the normal range according to age and education; 6) absence of relevant anxiety or depressive symptoms defined as a score <11 in Hospital Anxiety and Depression Scale (HAD). Structural MRI, DTI and FBB-PET were acquired for every subject of the study in a 30 days window after the baseline visit. The MRI T1-3D of 1x1x1 mm voxel size and DTI scans were acquired with a 1.5T Siemens© Magneton Aera. FBB-PET scans were acquired in a Siemens© Biograph molecular-CT machine. Four FBB-PET scans of 5 minutes were acquired after 80 minutes post injection of 300 Mbq of Florbetaben(18F) radio tracer

(NeuraCeq©). MRI cortical and subcortical segmentation was carried on with Freesurfer 5.3. Hippocampus volume, cortex mean thickness and white matter hypointensities (WMH) were determined from the segmentation. FBB-PET scans were processed with FSL 5.0 suite. The FBB-PET images were coregistered onto structural images. Standard uptake value ratio (SUVR) were determined as the mean value of the cortical regions segmented on MRI and normalized by the cerebellum. A cutoff of SUVR = 1.45 was selected as amyloid positive criteria. DTI images were also processed with FSL. The images were eddy corrected, skull stripped, fitted to a diffusion tensor model for each voxel and coregistered in the standard space template FMRIB58. Fractional anisotropy (FA) and mean diffusivity (MD) was calculated for the regions of the white matter John Hopkins University (JHU) Atlas. The hippocampus volume was calculated as the mean value between left and right hemispheres and corrected by intracranial volume (aHV). The cortex mean thickness was calculated as the mean value between left and right hemispheres. Statistical treatment of the data was carried on with R statistical software. Pearson regressions for FBB SUVR were made for age, WMH, hippocampus volume, cortex mean thickness and mean diffusivity of JHU regions of interest (ROI) in order to check if relevant relationships exist between those variables. A second attempt of Pearson regressions was made for FBB cortical retention and mean diffusivity of some promising JHU ROIs (body of corpus callosum, splenium of corpus callosum) taking age, gender, education and WMH as covariates. *Results:* The aim of the present work is to explore the relationship between amyloid burden and other neuroimaging measures such as DTI and MR volumetry in FACEHBI study. Seventy subjects were included in this analysis. The mean age was 65.8 (7.5) years and 43% were men. Four subjects were classified as FBB+ (~6%). There was no correlation of FBB SUVR with WMH (r=0.002, p-value=0.3). Besides, amyloid burden neither correlated with hippocampal volume (r=-0.01, p-value=0.8) nor with cortical mean thickness (r=-0.002, p-value=0.4). FBB SUVR significantly correlated with mean diffusivity in body (r=0.41, p-value=0.0008) and splenium (r=0.30, p-value=0.02) of corpus callosum using age, gender, education and WMH as covariates. *Conclusions:* Mean diffusivity in the corpus callosum was significantly correlated with amyloid burden in the context of SCD whereas hippocampal atrophy and mean cortical thickness were not correlated with SUVR in our study. This finding suggests that white matter integrity disruption of interhemispheric connection tracts could be an early phenomenon in the pathophysiology of Alzheimer's disease, even in the absence of significant grey matter atrophy. Further studies are needed to confirm this finding. *Funding:* Funds from Fundació ACE. Institut Català de Neurociències Aplicades, Grifols ®, Piramal ® and Araclon Biotech® are supporting FACEHBI.

P2-4: PET STUDIES WITH RVT-101 IN HEALTHY VOLUNTEERS DEMONSTRATE HIGH OCCUPANCY OF THE 5HT6 RECEPTOR. ILISE LOMBARDO[1], GEETHA RAMASWAMY[1], STEPHEN C PISCITELLI[2], LAWRENCE FRIEDHOFF[1] *((1) Axovant Sciences, Inc.; (2) Roivant Sciences, Inc.)*

Background: RVT-101 (formerly known as SB742457) is an orally administered, potent antagonist of the 5-hydroxytryptamine 6 (5-HT6) serotonin receptor. Nonclinical and clinical data support a complementary mechanism of action with cholinesterase inhibitors. *Methods:* Positron emission topography (PET) was used to assess occupancy of the 5HT6 and 5HT2A receptors following repeat doses of RVT-101 in healthy subjects. Specific ligands for each receptor were administered by IV infusion followed by a PET scan to establish baseline receptor binding. Volunteers then received loading doses followed by repeat doses of 3, 15, and 35 mg for 21 to 28 days. The magnitude and timecourse of receptor occupancy was assessed by conducting additional PET scans at various timepoints (between 7 and 28 days) following initiation of the repeat dose regimen of RVT-101. Plasma concentration time-course pharmacokinetics of RVT-101 were also assessed. *Results:* Eight subjects completed the repeat dose study. At all doses studied, a demonstrable maximal steady state occupancy of the 5-HT6 receptors was achieved in the CNS by Day 7 days. The relationship between plasma RVT-101 concentrations and 5-HT6 receptor occupancy at steady state were described by a sigmoid Emax model with an IC50 of 2.6 ng/ml. Repeat dosing at 35 mg/day is predicted to result in > 90% receptor occupancy in 97.5% of the subjects. Receptor occupancy for 5-HT2A increased with escalating doses of RVT-101, reaching levels of 59% following repeated daily dosing of 35 mg per day. *Conclusions:* RVT-101 penetrates into the brain and binds to 5HT6 receptors with high occupancy at doses of 3 to 35 mg once daily. RVT-101 also binds to the 5HT2A receptor but occupancy is lower at doses of 35 mg/day or less.

P2-5: FIRST CLINICAL APPLICATION OF THE AUTOMATIC SEGMENTATION METHOD OF HIPPOCAMPAL SUBFIELDS (ASHS) IN PRODROMAL ALZHEIMER'S DISEASE: A POTENTIAL BIOMARKER? ESKE CHRISTIANE GERTJE[1], JOHN PLUTA[2], SANDHITSU DAS[2], LAUREN MANCUSO[3], DASHA KLIOT[3], ANDREAS ENGELHARDT[1], PAUL YUSHKEVICH[2], DAVID WOLK[3] *((1) Department of Neurology, University of Oldenburg, Oldenburg, Germany; (2) Penn Image Computing and Science Laboratory, Department of Radiology, University of Pennsylvania, Philadelphia, USA; (3) Penn Memory Center, Department of Neurology, University of Pennsylvania, Philadelphia, USA)*

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder with no known cure. Therefore, a better understanding of its onset and progression is very important. Medial temporal lobe (MTL) structures, such as the hippocampus, entorhinal cortex (ERC), and perirhinal cortex (PRC), play an important role in memory and are thought to be affected early by AD. Automatic segmentation of magnetic resonance images (MRIs) can be used to detect evidence of neurodegeneration in these hippocampal subfields and cortical structures, and helps discriminate prodromal AD from healthy controls (HC). This study aimed to demonstrate the first application of the automatic segmentation method of hippocampal subfields and extrahippocampal MTL structures (ASHS) in a clinical population of prodromal AD patients. *Methods:* Clinical subjects were recruited from a database of the Penn Memory Center of the University of Pennsylvania. All subjects had clinical MRI scans. Scans were rated by an experienced rater, and subjects were included in the study based on MRI scan quality. An automatic segmentation method of hippocampal subfields (ASHS) was applied to clinical high-resolution T2-weighted MRI scans of prodromal AD patients and healthy controls (HC). Hippocampal subfields Cornu Ammonis 1 (CA1), dentate gyrus (DG), subiculum (SUB), and cortical structures ERC and PRC (Brodmann area 35 and 36) were automatically labeled, and volumes were calculated. Differences in subfield atrophy were compared between and within groups. *Results:* Clinical scan quality, relative to research scan quality, was lower due to frequent motion artifacts, and about one-third of scans were excluded based on their quality. Volume measurement results showed significant volume reductions in all hippocampal subfields and cortical regions in prodromal ADs compared to HCs, most prominently in CA1 and ERC. *Conclusion:* Clinical scan quality was not always sufficient for the application of the ASHS method and needs to be improved. But, this study's results demonstrate that the automatic segmentation method can be successfully applied to the scans of clinical subjects and can help discriminate between groups. The major finding of this clinical approach was significant group discrimination in CA1 and ERC subfields in prodromal AD similar to pathology results. *Keywords:*

Alzheimer's disease, mild cognitive impairment, biomarker, subfield volumetry, automatic segmentation

P2-6: INTEGRATION OF FLORBETAPIR PET AND CEREBROSPINAL FLUID AB42 TO DEFINE AMYLOID BURDEN IN ALZHEIMER'S DISEASE. GERALD NOVAK[1], LISA FORD[1], MAHESH SAMTANI[1], MARK FORREST GORDON[2], FOR THE ALZHEIMER'S NEUROIMAGING INITIATIVE AND THE EUROPEAN MEDICAL INFORMATION FRAMEWORK ALZHEIMER'S DISEASE *((1) Janssen Pharmaceuticals, LLC, Titusville, NJ, USA; (2) Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA)*

Background: Increased florbetapir PET standard uptake value ratio (SUVr) and decreased CSF Aβ42 concentrations reflect cerebral amyloid deposition. While concordance is high and the overall diagnostic accuracy of both biomarkers is comparable, a greater sensitivity for CSF and specificity for PET have been described (Mattsson, Ann Clin Transl Neurol, 2014). We sought to determine if a combination of biomarkers improved diagnostic and prognostic performance in preclinical AD and MCI due to AD. *Methods:* The analysis included ADNI-GO and ADNI-2 subjects who had florbetapir PET and CSF obtained within the same visit window, analyzed by previously described methods (Landau & Jagust, http://adni.loni.usc.edu, 2014; Shaw, Ann Neurol, 2009). Three criteria for increased amyloid burden were compared: liberal (either PET SUVr > 1.11 or CSF Aβ42 < 192 pg/mL abnormal), conservative (both PET and CSF abnormal as above), and a two sub-population joint mixture model based on PET and CSF. The performance characteristics of each criterion of amyloid burden were first compared for the ability to discriminate cognitively normal (CN) from demented subjects. Then, for each criterion, subjects with and without increased amyloid burden (A+ and A-, respectively) were compared for (a) baseline and rate of change in composite measures of memory and executive function (Crane, Brain Imag Behav 2012), (b) prevalence of the ApoE ε4 allele and biomarkers of neuronal injury (adjusted hippocampal volume (HV) z-score < -1, fluorodeoxyglucose (FDG) PET SUVr < 1.21, and CSF tau > 93 pg/mL), and (c) diagnostic outcome to 2.5 years , using 2-sample t-tests, chi-square, and Kaplan Meier survival plots, respectively. Bonferroni-corrected $\alpha = 0.003$ accounted for multiple comparisons within each criterion. *Results:* At the time of first biomarker assessment, 262 of the 737 included subjects were CN (± subjective memory concerns), 155 had "early" mild cognitive impairment (EMCI), 172 had "late" MCI (LMCI), and 148 had dementia (of these, 20 initially had LMCI and 1 was CN). The conservative criterion for A+ was met in 395 subjects (53.6%) and the liberal criterion by 495 (67.2%). The latter included subjects some abnormal only for CSF (73) or abnormal only for florbetapir PET (22). The mixture model classified 406 (55.1%) subjects as A+. The model's post hoc estimate of sub-population assignment included some subjects with abnormalities only for CSF (22) or florbetapir PET (3), but excluded 14 subjects with abnormalities in both biomarkers who were close to the cutoff values. Discriminating demented from CN subjects, the conservative criterion had a sensitivity of 87.8%, specificity 71.4%, positive predictive value (PPV) 63.4%, and negative predictive value (NPV) 91.7%. The liberal criterion increased sensitivity slightly (91.2%), while sacrificing specificity and PPV (50.8% and 50.9%, respectively). The mixture model increased sensitivity to 90.5% while maintaining the same specificity as the conservative model. In the CN group, A+ subjects had significantly worse baseline executive function ($p<0.0005$) than A- for all criteria, but there were no significant differences for baseline memory or rate of change in memory or executive function. In EMCI, A+ subjects defined by the conservative criterion or the mixture model had worse baseline memory ($p=0.001$ and $p< 0.0005$, respectively), but there were no significant differences for baseline executive function or rate of change in memory or executive function. In LMCI, both baseline memory and executive function were significantly worse in A+ than A- subjects,for all criteria($p<0.0005$), and there was a significantly greater rates of change in memory for A+ defined by the liberal criterion, and in executive function for A+ defined by the conservative criterion ($p<0.0005$) and the mixture model ($p=0.001$). Overall, only 12.1% of CN and 8.6% of EMCI subjects progressed to MCI or dementia (2.5y K-M estimate), and there were no significant differences for any criterion of amyloid burden. However, in the LMCI group, a significantly higher proportion of A+ than A- subjects progressed to dementia based on the conservative criterion (66.2% vs 34.5%, $p=0.001$) and the mixture model (73.7% vs 27.2%, $p < 0.0005$); this did not reach statistical significance for the liberal criterion. A+ subjects had a higher proportion of Apo E ε4 carriers and abnormal CSF tau (for all criteria in all groups). In the LMCI group, A+ subjects defined by the conservative criterion and the mixture model had a higher proportion of abnormal FDG, and those defined by the liberal criterion had a higher proportion with hippocampal atrophy. *Conclusions:* When both florbetapir PET and CSF Aβ42 are available, a conservative criterion of amyloid burden (requiring abnormalities in both) has greater specificity than a liberal criterion (satisfied by abnormality in either). A mixture model provides additional sensitivity and comparable specificity to the conservative criterion, suggesting that information from both biomarkers can be combined independent of the cutpoints derived from analysis of either one alone. Both the mixture model and the conservative criterion had greater prognostic sensitivity to progression in LMCI than a liberal criterion.

P2-7: DIFFERENTIATING THE EFFECTS OF DOWN SYNDROME AND ALZHEIMER'S DISEASE UPON NEURONAL FUNCTION AND BRAIN VOLUME. DAWN MATTHEWS[1], ANA LUKIC[1], RANDOLPH ANDREWS[1], BORIS MARENDIC[1], JAMES BREWER[2], LISA MOSCONI[3], STEPHEN STROTHER[1,4], MILES WERNICK[1,5], MARK SCHMIDT[6], MICHAEL RAFII[2], FOR THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE *((1) ADM Diagnostics, Chicago, Illinois, USA; (2) University of California San Diego School of Medicine, San Diego, California, USA; (3) New York University, New York, USA; (4) Baycrest Hospital, Toronto, ON, Canada; (5) Illinois Institute of Technology, Chicago, Illinois, USA; (6) Janssen Research and Development, Beerse, Belgium)*

Backgrounds: Down Syndrome (DS) is associated with a high incidence of dementia concomitant with the presence of the amyloid plaques and tangles found in AD. Adults with DS may provide an enriched population for the study of AD-targeted treatments in preventative trials. However, to initiate therapy at a well-defined point in disease development, and to longitudinally monitor clinical effects arising from AD progression, it is necessary to dissociate the contributions of DS and AD to the overall phenotype. The objective of our work was to discriminate between effects attributable to DS vs. AD pathology, and to quantify the degree of predementia AD progression within-subject. We evaluated 18-F fluorodeoxyglucose (FDG) PET, structural MRI, and florbetapir PET imaging biomarkers, and relationships among imaging markers and between imaging and clinical endpoints. We hypothesized that although standard methods of image analysis would not be able to dissociate effects attributable to DS vs. AD, application of advanced multivariate methods could identify the relative contributions of these syndromes to overall effect. *Methods:* We evaluated the baseline FDG PET and structural MRI data of 12 nondemented adults with DS (age 32 to 61 yrs, 83% female, 50% ApoE e4 carriers) while blinded to amyloid burden and cognitive status. FDG scans were scored using a previously developed AD Progression Classifier that quantifies the degree to which an

individual subject expresses a pattern of relative hypometabolism reflecting progression from Normal (NL) amyloid negative (Am-) status to amyloid positive (Am+) AD dementia. Separately, we applied NPAIRS multivariate analysis software (Strother 2002, 2010) to identify patterns characterizing similarities and differences between the DS group and four pre-defined, previously processed groups of ADNI subjects characterized by clinical diagnosis, amyloid status, and age: (1) Am- NL, (2) Am+ AD, (3) Am+ early MCI (EMCI), and (4) Am+ late MCI. NPAIRS was used to compare DS, NL, and AD groups (FDG, MRI), and DS, NL, EMCI, LMCI, and AD (FDG). We further included a set of age-matched Am- NLs from New York University for confirmation of DS-NL results. AD-related apriori regions of interest were also measured on the FDG PET scans and compared across groups. After unblinding to amyloid, cortical cerebellar SUVRs were calculated for the florbetapir PET scans of the DS subjects, and a threshold of 1.11 was used to define Am+. Relationships were evaluated between FDG and MRI CV scores and age, amyloid burden, and clinical endpoints. *Results:* The FDG AD Progression scores of DS subjects were distributed across a spectrum from values comparable to independently tested ADNI Am- NL subjects to those of Am+ AD subjects. All Am- or threshold DS had scores in the NL range, whereas Am+ DS exhibited a range of progression scores. The FDG NPAIRS comparing DS, NL, and AD produced two patterns of glucose metabolism whereby the first pattern characterized the difference between DS and all other subjects (FDG-CV1 $p<0.00001$) and the second pattern characterized the difference between NL and AD (FDG-CV2 $p<0.00001$). FDG-CV1 did not correlate with age or amyloid burden, whereas FDG-CV2 scores correlated with both. DS FDG-CV2 scores were highly correlated to AD Progression scores ($R2 = 0.89$, $p<0.00001$). The FDG CV1 and CV2 patterns had some overlap in posterior cingulate and hippocampus, but FDG-CV1 involved distinctive regions of relative hypo- and hyper-metabolism not typical of AD, while FDG-CV2 was highly similar to the AD Progression pattern. Five-class NPAIRS results were consistent with 3 class results, and ROI results were supportive of NPAIRS findings. The structural NPAIRS also resulted in two distinctive patterns whereby MRI-CV1 distinguished DS from NL and AD ($p<0.00001$) and was not related to amyloid burden, while MRI-CV2 differentiated NL and AD ($p<0.0005$), and correlated with amyloid burden. MRI-CV1 included volumetric reductions in cerebellum and hippocampus consistent with young DS study findings, while MRI-CV2 was consistent with AD-related atrophy. FDG-CV2 and MRI-CV2 were highly correlated ($R2 = 0.88$, $p<0.00001$). FDG CV scores correlated with several clinical endpoints (p-value range 0.004 to 0.05); MRI scores correlated with some endpoints ($p<0.05$) including Delayed Memory and Daily Living Skills. While amyloid negative vs. positive status interacted with clinical endpoint scores, amyloid burden did not correlate with clinical endpoints within the Am+ DS subset. *Conclusion:* We have demonstrated for the first time the dissociation of functional and structural effects of DS from those due to AD pathology, and that the degree of Alzheimer's-type neurodegeneration can be quantified in nondemented DS subjects. Findings suggest that AD pattern expression varies greatly within Am+ DS subjects, as do clinical symptoms, underscoring the importance of characterization. We have also shown that the CV scores correlate with cognitive and functional endpoints. By dissociating effects related to DS and AD, and quantifying AD pattern expression, it becomes possible to predict trajectory of decline and monitor treatment response in a disease-specific manner.

P2-8: INCREASED UTILIZATION OF IMAGING IN ALZHEIMER DISEASE (AD) TRIALS: IMPACT ON PATIENT RECRUITMENT, RETENTION AND LOGISTICS. KOHKAN SHAMSI *(Principal at RadMD LLC, Pipersville, PA - USA)*

Background: Imaging is extensively utilized in AD clinical trials for patient's eligibility, efficacy evaluation and safety evaluations. Patient's eligibility, efficacy and safety are evaluated by Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET). MRI is used for structural imaging and PET is used for functional imaging and molecular imaging. The learning objectives of this presentation are: • To understand the role of current MRI and PET techniques utilized in clinical trials. • To understand Amyloid Related Imaging Abnormalities (ARIA) and FDA requirements for ARIA monitoring, assessment and patient management. • To understand the impact of imaging on patient recruitment logistics and retention. *Methods:* Two imaging methods, MRI and PET are commonly used in AD trials. MRI is extensively used for patient eligibility, safety and efficacy evaluations. In multicenter trials, standardization of MRI methodology across the sites is essential to reduce variability and loss of data. This requires prospective site qualification, evaluation of phantom data, training and continuous monitoring through rigorous quality control of both ongoing subject and phantom data. Phantom imaging and standardization is especially important for estimation of brain volumes and comparison of pre- and post-therapy volumes. Discussion of PET in AD trials will include FDG-PET and Amyloid PET imaging. PET has been utilized to evaluate both eligibility evaluations and therapeutic response by measuring FDG activity in the brain. Recently, amyloid burden has been incorporated into Phase 2-3 anti-amyloid clinical therapeutic trials to assess both subject eligibility for enrollment and longitudinal changes in brain amyloid. Site qualification including phantom imaging, image standardization and image acquisition is crucial for the success of PET evaluations. *Results and Discussion:* Evaluation of Patient Eligibility: Many neurological diseases that could either have presentation similar to AD or could be confounding factors in the assessment of drug therapy have to be excluded to evaluate therapeutic effect of a drug on AD patient population. These include vascular dementia, multiple sclerosis, vascular pathology, neoplasms etc. Inclusion of the wrong patient has serious ethical and legal implications. More importantly, these patients could be excluded from the analysis, thereby reducing the sample size and impacting the power of the study and the study results. Patient eligibility can be evaluated either at the site or at a central facility. In this presentation, the pros and cons of various strategies of eligibility evaluation and optimization of the eligibility read process will be discussed. Evaluation of Amyloid Related Imaging Abnormalities (ARIA): Initially these abnormalities were observed in monoclonal antibody against amyloid-β (Aβ) trials. These MRI findings include vasogenic edema (ARIA E), micro and macro hemorrhages (ARIA H) and superficial siderosis. Based on these findings FDA had recommended that patients must be followed by frequent MRI scans in all AD trials, and if ARIA are observed, the patient should be discontinued and should be followed by MRI more frequently till the finding is resolved or stabilized. Efficacy Evaluation: MRI is utilized to evaluate total brain volume and/or hippocampal and ventricular volume. FDG-PET has been used to measure metabolic activity of brain. Recently, Amyloid imaging agents have been approved and are being utilized for drug evaluations. *Impact on Patient Recruitment, Logistics, and Retention:* Although imaging is a critical component of the trial, the imaging sites' evaluation is usually not a part of the site selection process. Evaluation of the imaging facility is performed at a later stage. This is even more important for AD patients, as poor image quality mandates that the patient return for repeat imaging. This is additional burden on both patients and caregivers. Quality and other logistical issues related to site selection process will be discussed. Eligibility reads are time sensitive as all screening evaluations have to be completed within the baseline period. Prospective consideration of MRI/PET turnaround times is essential for appropriate patient recruitment. If patients are

not scanned at the appropriate time, re-screening may be required, which is additional burden on both patients and caregivers (as well as cost to the Sponsor). Occasionally there are discordant site and central assessments. These disagreements have to be actively managed for correct patient recruitment. We will discuss adjudication processes that can be performed within the baseline period. There are multiple post-recruitment imaging time points in the protocol. This creates several logistical issues for patients and caregivers as imaging facilities are located away from the investigator sites. Patients and caregivers have to travel for imaging as well as for post-therapy clinical evaluations. We will present our experience in conducting imaging evaluations and suggest best practices to minimize logistic issues.

P2-9: HIPPOCAMPUS VOLUME LOSS IN ALZHEIMER'S DISEASE PATIENTS: EFFECT OF TREATMENT WITH CHOLINE ALPHOSCERATE IN ADDITION TO CHOLINESTERASE INHIBITOR. ENEA TRAINI[1], ANNA CAROTENUTO[1,2], ANGIOLA MARIA FASANARO[1,2], RAFFAELE REA[1,2], FRANCESCO AMENTA[1] *((1) Centre for Clinical Research, Telemedicine and Telepharmacy, University of Camerino, Camerino; (2) Alzheimer Evaluation Unit, National Hospital, "A. Cardarelli", Naples, Italy)*

Background: Cholinergic precursors have represented the first approach to counter cognitive impairment occurring in adult onset dementia disorders. ASCOMALVA [Effect of association between a cholinesterase inhibitor (ChE-I) and choline alphoscerate on cognitive deficits in AD associated with cerebrovascular injury] is a double-blind, controlled, randomized clinical trial investigating if the ChE-I donepezil and choline alphoscerate in combination are more effective that donepezil alone. One of the most important biomarkers for AD is the atrophy of the hippocampus. In this study, MRI from patients were analyzed for the evaluation of the brain atrophy. *Methods:* Participants of the ASCOMALVA trial underwent yearly MRI for diagnostic purposes. In 56 patients who achieved two years of therapy, MRI were analyzed by voxel morphometry techniques to assess if addition of choline alphoscerate to treatment with donepezil had an effect on volume loss characteristic of hippocampus of Alzheimer's disease patients. *Results:* Reference group showed a greater atrophy of the gray matter, white matter ad hippocampus than the group treated with donepezil plus choline alphoscerate. In the reference group a concomitant increase of the volume of the ventriculi and space of the cerebrospinal fluid was noticeable. Neuropsycological tests over the 24-month observation period showed in patients of the reference group a moderate time-dependent worsening in all the parameters investigated. Treatment with donepezil plus choline alphoscerate resulted in better scores of the cognitive and functional items and an improvement in behavioural parameters, superior to that induced by donepezil alone. *Conclusion:* The above results have shown that cholinergic precursor loading strategy with choline alphoscerate counters to some extent hippocampal volume loss occurring in the brain of Alzheimer's disease patients. The observation of a parallel improvement of cognitive and functional tests in patients treated with choline alphoscerate plus donepezil versus donepezil alone suggests that morphological changes observed may have functional relevance.

P2-10: PRESUBICULUM VOLUME CHANGES IN MILD COGNITIVE IMPAIRMENT PATIENTS WITH AD PATHOLOGY. MOIRA MARIZZONI[1], JORGE JOVICICH[2], ELENA ROLANDI[1], SAMANTHA GALLUZZI[1], FLAVIO NOBILI[3], MIRA DIDIC[4,5], DAVID BARTRÉS-FAZ[6], UTE FIEDLER[7], PETER SCHONKNECHT[8], PIERRE PAYOUX[9,10], ALBERTO BELTRAMELLO[11], ANDREA SORICELLI[12,13], LUCILLA PARNETTI[14], MAGDA TSOLAKI[15], PAOLO MARIA ROSSINI[16,17], PHILIP SCHELTENS[18], GIANLUIGI FORLONI[19], REGIS BORDET[20], OLIVIER BLIN[21], GIOVANNI BATTISTA FRISONI[1,22] ON BEHALF OF THE PHARMACOG CONSORTIUM *((1) Laboratory of Epidemiology, Neuroimaging and Telemedicine, 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) APHM, CHU Timone, Service de Neurologie et Neuropsychologie, Marseille, France; (5) Aix-Marseille Université, INSERM U 1106, Marseille, France; (6) Department of Psychiatry and Clinical Psychobiology, Universitat de Barcelona and IDIBAPS, Barcelona, Spain; (7) LVR-Clinic for Psychiatry and Psychotherapy, Institutes and Clinics of the University Duisburg-Essen, Essen, Germany; (8) Department of Neuroradiology, University Hospital Leipzig, Leipzig, Germany; (9) INSERM, Imagerie cérébrale et handicaps neurologiques, UMR 825, Toulouse, France; (10) Université de Toulouse, UPS, Imagerie cérébrale et handicaps neurologiques, UMR 825, CHU Purpan, Toulouse, France; (11) Department of Neuroradiology, General Hospital, Verona, 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 Centre and Department of Neurology, Vrije Universiteit University Medical Center, Amsterdam, The Netherlands; (19) Neuroscience Department, IRCCS Istituto di Ricerche Farmacologiche «Mario Negri», Milano, Italy; (20) Department of Pharmacology, EA1046, University of Lille Nord de France, 59045 Lille Cedex, France; (21) Pharmacology, Assistance Publique-Hôpitaux de Marseille, Aix-Marseille University-CNRS UMR 7289, Marseille, France; (22) Memory Clinic and LANVIE - Laboratory of Neuroimaging of Aging, University Hospitals and University of Geneva, Geneva, Switzerland)*

Background: Hippocampal atrophy and amyloid accumulation are useful biomarkers able to identify MCI who progress to dementia from those who remain stable (Galluzzi S, 2010). Previous studies have shown differential hippocampal subfields atrophy in MCI compared to healthy controls (Hanseeuw BJ, 2011; Lim HK, 2012). Our aim is to compare subfields hippocampal volumetry between Aβ-negative and Aβ-positive MCI patients (based on CSF Aβ42 levels) in order to i) identify specific patterns of atrophy in those who have the high likelihood to progress to dementia and ii) investigate the relationships between memory impairment and hippocampal subfields atrophy. *Methods:* 147 MCI patients were enrolled in WP5 of PharmaCOG (E-ADNI) and underwent neuropsychological evaluation (memory, language and executive functions), CSF collection and high resolution 3T MRI. 115 MCI further performed MRI at 6 and 12 months from baseline. Hippocampus and its subfileds volumes were obtained using the longitudinal pipeline of Freesurfer v5.1.0 (Reuter M, 2012; Jovicich J, 2013) on the neuGRID platform (https://neugrid4you.eu/) and were normalized with intracranial volume before to proceed with further analysis. Statistics: analysis of covariance (baseline), general linear model for repeated measures (longitudinal). Models were corrected for age, gender, education and MMSE. Baseline correlations were computed using the Pearson's R test. *Results:* Baseline comparison showed lower volumes in the presubiculum of both hemispheres (right: -10.0%, p=.01; left: -7.2%, p=.05) of Aβ-positive relative to Aβ-negative MCI patients. A similar trend, although not significant, was reported for the other subfields evaluated (CA1, CA2-3, CA4-DG, subiculum) and for the whole hippocampus. Moreover, presubiculum volume was significantly associated with long term memory and naming performance (Pearson R ranging from 0.20 to

0.43, all p<.001). Preliminary longitudinal analysis reported greater volume reduction in the left hemisphere only, in the presubiculum (ΔT12-T06Aβ-negative= -0.5%, ΔT12-T06Aβ-positive= -3.1; p= .03) and in the hippocampus (ΔT12-T00Aβ-negative = -1.8%, ΔT12-T00Aβ-positive = -3.5; p=.01) of Aβ-positive relative to Aβ-negative MCI patients. *Conclusions:* These preliminary data highlight the validity of presubiculum atrophy assessment to increase the accuracy and the sensitivity of total hippocampal atrophy in diagnosing MCI who progress to dementia. Indeed, presubiculum is more specific than whole hippocampal volume to discriminate MCI patients with high amyloid load at baseline and its volume reduction correlated with lower performance at verbal memory test, a domain typically impaired in prodromal AD patients. Finally, left presubiculum atrophy in Aβ-positive MCI patients became evident in 6 months while that of the whole hippocampus in 12 months. Pharmacog is funded by the EU-FP7 for the Innovative Medicine Initiative (grant n°115009).

P2-11: ROBUSTNESS OF 18F-FLORBETABEN SUVR CUTOFF QUANTIFICATION ACROSS REFERENCE REGIONS AND STANDARDS OF TRUTH. SANTIAGO BULLICH[1], SUSAN DE SANTI[2], JOHN SEIBYL[3], ANA M CATAFAU[1] *((1) Piramal Imaging GmbH, Berlin, Germany; (2) Piramal Pharma Inc, Boston, MA, USA; (3) Molecular Neuroimaging, New Haven, CT, USA)*

Background: Thresholds of 18F-florbetaben (FBB) standardized uptake value ratios (SUVRs) of 1.45 (Ong et al. Alzheimer's Research & Therapy 2013, 5:4) and 1.39 (Barthel et al. Lancet Neurol 2011; 10: 424–35) have been reported using cerebellar grey matter (GCER) as the reference region (RR) and clinical data as the standard of truth (SoT). The aims of this study were: 1) to generate FBB SUVR cutoff values for different RRs using a histopathology SoT, and 2) to validate them across different clinical populations and SoTs. *Methods:* 1) SUVR cutoff generation: FBB scans from end-of-life subjects (n=78, 80.1±10.4 yrs; n=56 Alzheimer's Disease (AD), n=9 non-demented volunteer, n=13 other dementia) who underwent autopsy after death were included. Histopathological confirmation of the presence or absence of neuritic beta-amyloid plaques was performed using Bielschowsky silver stain and immunohistochemistry. A composite SUVR (mean of frontal, occipital, parietal, and posterior and anterior cingulate regions) was calculated for different RRs: cerebellar gray matter (GCER), whole cerebellum including white and grey matter (WCER), pons (PONS), and subcortical white matter (SWM). A SUVR cutoff value for each RR was generated using Receiver Operating Characteristic (ROC) analysis, histopathology as the SoT, and highest accuracy as the selection criteria. 2) SUVR cutoffs for each RR were validated in two different samples and SoTs: a) the same n=78 end-of life subjects described above, using both histopathology and visual assessment (VA) results from 8 readers as SoTs; and b) n=233 additional subjects (72.5±7.1 yrs; n=118 healthy volunteers, n=115 AD) using clinical diagnosis as SoT. Sensitivity, specificity and accuracy (and their 95% confidence intervals (CI)) were used as performance metrics for the SUVR cutoff validation. Further, the percent agreement and 95% CI between SUVR cutoffs and VA results from 5 different readers was calculated in this second sample. *Results:* Composite SUVR cutoff generated values for each RR were 1.47 (GCER); 0.99 (WCER); 0.76 (PONS); 0.76 (SWM). Sensitivity, specificity and accuracy for each SUVR cutoff, VA, and SoTs are provided in table 1. Accuracy values were high and very consistent across SUVR cutoffs and VA methods and SoTs (range 87-95% for histopathology, 82-85% for clinical diagnosis). No significant differences in the diagnostic performance were found between VA and SUVR cutoff for any of the RRs, or across RRs. No significant differences in the percentages of agreement between VA and SUVR cutoff values for different RR were found (89 (85-93)% (GCER), 93 (89-96)% (WCER), 93 (90-96)% (PONS), 91 (87-94)% (SWM)). *Conclusion:* These results indicate the robustness of 18F-Florbetaben SUVR cutoff quantification. SUVR cutoff performance was high for all RRs, independently of the SoTs, and was consistent with VA. The lack of differences across RR support the use of the cerebellum as the most biologically appropriate for 18F-Florbetaben scan quantification.

Table 1
Sensitivity, specificity and accuracy (and their 95% CI) for each SUVR cutoff, VA, and SoTs

	Sample a), SoT: Histopathology (n=78)			Sample b) SoT: Clinical diagnosis (n=233)		
RR or VA	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)
CGER	86	92	88	80	83	82
	(77-95)	(81-100)	(81-95)	(73-87)	(76-90)	(77-87)
WCER	93	100	95	79	90	85
	(87-100)	(100-100)	(91-100)	(72-87)	(84-95)	(80-89)
PONS	93	96	94	81	89	85
	(87-100)	(88-100)	(89-99)	(74-88)	(83-95)	(80-90)
SWM	93	72	87	69	97	83
	(86-100)	(54-90)	(79-94)	(60-77)	(95-100)	(78-88)
VA	96*	83*	92*	77+	88+	83+
	(94-98)	(73-93)	(89-95)	(74-80)	(85-92)	(82-84)

* mean from 8 readers; + mean from 5 readers

P2-12: CLASSIFICATION OF POSITIVE AND NEGATIVE 18F-FLORBETABEN SCANS: COMPARISON OF SUVR CUTOFF QUANTIFICATION AND VISUAL ASSESSMENT PERFORMANCE. SANTIAGO BULLICH[1], SUSAN DE SANTI[2], JOHN SEIBYL[3], ANA M CATAFAU[1] *((1) Piramal Imaging GmbH, Berlin, Germany; (2) Piramal Pharma Inc, Boston, MA, USA; (3) Molecular Neuroimaging, New Haven, CT, USA)*

Background: Classification of 18F-florbetaben (FBB) PET scans as positive or negative for brain beta-amyloid can be made by either visual inspection of the images or quantification using standardized uptake value ratios (SUVRs) cutoff values. However, comparative data on these two methods are limited. Moreover, the use of different reference regions (RR) adds complexity to SUVR result interpretations. The aim of this study was to compare the performance of the FBB scan visual assessment (VA) and the SUVR cutoff with different RRs, for classifying positive and negative FBB scans. *Methods:* FBB scans from end-of-life subjects (n=78, 80.1 ± 10.4 yrs; diagnosis: n=56 AD, , n=9 non-demented volunteer, n=13 other dementia) who underwent autopsy after death were included. Histopathology confirmation of the presence or absence of neuritic beta-amyloid plaques was performed using Bielschowsky silver stain and immunohistochemistry. FBB scans were visually assessed using the FBB training methodology by 5 independent readers blinded to clinical diagnosis. Visual classification into positive or negative was based on the majority read results (i.e. same result in at least 3/5 readers). A composite SUVR (mean of frontal, occipital, parietal, and posterior and anterior cingulate regions) was calculated for different RRs: cerebellar gray matter (GCER), whole cerebellum including cerebellar white and grey matter (WCER), pons (PONS), and subcortical white matter (SWM). A SUVR cutoff value for each RR was generated using Receiver Operating Characteristic (ROC) analysis and the histopathology assessment as standard of truth. Highest accuracy was used as criteria for SUVR cutoff selection for each RR. The number of correctly or incorrectly classified scans according to pathology results using VA and SUVR cutoffs for each RR was compared. *Results:* The number of scans correctly classified was consistently higher using VA than using SUVR cutoff across RRs,

although not significantly different (p-values: 0.09 (VA vs. GCER), 1.00 (VA vs WCER), 0.73 (VA vs. PONS) and 0.06 (VA vs SWM) (table). A range of 66-71 cases were correctly classified by both SUVR cutoff (across RRs) and VA, while 0-4 cases (across RRs) were incorrectly classified by both SUVR cutoff and VA. SUVR cutoff method misclassified more cases than VA except when using WCER, which misclassified the same number of cases as VA. *Conclusion:* VA and SUVR cutoff quantification perform similarly in classifying FBB scans as positive or negative for brain beta-amyloid. However, the use of SUVR cutoff did not improve VA classification of FBB scans independently of the RR used. These results indicate that VA is a robust method for the correct classification of FBB scans, and suggest limited additional contribution of SUVR cutoff for the detection of presence or absence of neuritic beta-amyloid plaques.

Table

Number of correctly or incorrectly classified scans according to pathology results using VA and SUVR cutoffs for different RR

Classification	GCER (n=78)	WCER (n=78)	PONS (n=78)	SWM (n=77)
Correct VA	74	74	74	73
Correct SUVR cutoff	68	74	73	66
Correct VA and SUVR cutoff	66	70	71	66
Incorrect VA, correct SUVR cutoff	2	4	2	0
Correct VA, incorrect SUVR cutoff	8	4	3	7
Incorrect SUVR cutoff and VA	2	0	2	4

P2-13: SINGLE-CASE VOXEL-BASED ANALYSIS OF FLORBETAPIR-PET. ALTOMARE DANIELE[1], BOSCO PAOLO[1], GUERRA UGO PAOLO[2], PAGHERA BARBARA[3], FESTARI CRISTINA[1], PASQUALETTI PATRIZIO[4], MUSCIO CRISTINA[1,5], PIEVANI MICHELA[1], PADOVANI ALESSANDRO[6], FRISONI GIOVANNI BATTISTA[1,7], BOCCARDI MARINA[1]
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Backgrounds: Amyloid-PET scans with ligands like 18F Florbetapir (FBP) are commonly evaluated through visual reading into a dichotomic positive (Aβ+) or negative (Aβ–) response. This method required specific training and its reproducibility may be low in ambiguous cases. Automated or semi-automated methods for quantitative group comparison were proposed, using voxel based- or standard uptake value ratio- analyses (Kemppainen et al., 2006, Kemppainen et al., 2007, Saint-Aubert et al., 2013, and Ziolko et al., 2006). In our previous study on the incremental diagnostic value of FBP-PET, two indipendent expert nuclear medicine physicians (NPs) read visually 253 FBP-PET scans, showing good overall agreement (rate of concordance=87%). However the NPs disagreed on 32 cases. Therefore in these cases a third more expert NP was involved to give the final report. Aim of this study is to: i) replicate previous results obtained with group analyses; ii) define a fully automated voxel-based procedure for single-case analyses that may detect differences in cerebral amyloidosis for Aβ+ patients versus Aβ– ones. This method may possibly help in disambiguate or discordant cases (replicating the third NP final report) and may make evaluations on large samples effective and reliable. *Methods:* Subjects: From a larger set of FBP-PET scans evaluated by two NPs, we extracted: _11 "Alzheimer's Disease (AD)-Aβ+++" patients with diagnosis of dementia due to typical AD both before- and after- FBP-PET, diagnostic confidence≥70, and agreement among NP in the visual reading. Patients in this group were evaluated as cases of great certainty of amyloidosis by the first NP; _7 "AD-Aβ++" patients with diagnosis of Mild Cognitive Impairment (MCI) or dementia due to atypical-typical-mixed AD both before- and after- FBP-PET, diagnostic confidence≥60, and agreement among NP. The first NP evaluated these cases as intermediate certainty of positivity; _8 "HC-Aβ–", healthy elderly controls with negative scans; readers agreed for all but one subject. Image preprocessing: Before running the group- and single-case- analyses, FBP-PET images were spatially normalized in MNI space (exploiting the structural information provided by the CT acquired in the same session) and intensity normalized (dividing the whole brain voxels intensity by the 90% of the mean intensity of the pons). Finally, we created a customized template (used for spatial normalization during the analyses) averaging scans of 7 HC-Aβ–, 4 AD-Aβ++ and 3 AD-Aβ+++. Group analyses: We performed group analyses contrasting both AD-Aβ+++ and AD-Aβ++ versus HC-Aβ–, and AD-Aβ+++ versus AD-Aβ++. Images were compared with a 2-sample t-test (unequal variance). Threshold for significance was set at $p<0.05$ corrected for multiple comparisons with the family-wise error (FWE). Moreover, we run these analyses with a more lenient threshold $p<0.001$ with false discovery rate (FDR) correction. Minimum cluster size: 200 voxels. Single-case analysis: We compared individual AD-Aβ+++ and AD-Aβ++ patients versus the control sample of 8 HC-Aβ–. Furthermore, we compared each HC-Aβ– with the rest of the control sample as an empirical test for false positive findings. These comparisons were performed with a 2-sample t-test (equal variance). Running single-case analyses we do not apply corrections, setting an uncorrected threshold at $p<0.001$. Minimum cluster size: 200 voxels. *Results:* Group analyses: _AD-Aβ+++ versus HC-Aβ–. AD Aβ+++ subjects displayed wide significant clusters (both with FWE and FDR corrections) including: precuneus/posterior cingulate, and orbito-frontal, parietal and lateral-temporal cortices (Figure 1a and 1b). _AD-Aβ++ versus HC-Aβ–. AD-Aβ++ subjects displayed higher uptake circumscribed in the precuneus/posterior cingulate (Figure 1c) with the FWE correction. With FDR correction, also the orbito-frontal, head of caudate, and inferior-temporal gyrus were significantly positive (Figure 1d). _AD-Aβ+++ versus AD-Aβ++. No difference was found both at FWE and FDR corrected threshold. Single-case analyses: In the single-case analyses, we found a mean of 6.3 clusters for the subjects of the group AD-Aβ+++, 4.3 for AD-Aβ++ and 0.1 for HC-Aβ– (illustrative examples are reported in Figure 2). AD-Aβ+++ patients showed a widespread abnormal uptake in several areas, while AD-Aβ++ showed a more limited differences (always involving the posterior cingulate/precuneus). One HC-Aβ– with uncertainty in the experts' visual reading was the only HC showing one significant suprathreshold cluster compared with the other controls ($p=0.001$ uncorrected). *Conclusion:* Our voxel-based group-analysis was consistent with results already reported in literature, both in AD-Aβ++ and AD-Aβ+++ patients. At an FWE-corrected threshold, AD-Aβ++ invariably had abnormal uptake in the posterior cingulate, an area considered of primary relevance in the evaluation of the FBP-PET scans. FDR-corrected comparisons denoted however additional significant regions, consistently with the visual reading procedure for FBP-PET scans that requires more than one positive area. AD-Aβ+++ exhibited much wider regions of significant uptake both with FWE and FDR corrections. Our fully automated single-case analysis was able to reproduce the experts' visual assessment, showing amyloid positivity in AD-specific regions. Fine tuning of this method may provide an effective and reliable tool for quantification and localization of cerebral amyloidosis, providing more information than the dichotomic response. *References:* Kemppainen,

N. M., Aalto, S., Wilson, I. A., Någren, K., Helin, S., Brück, A., ... & Rinne, J. O. (2006). Voxel based analysis of PET amyloid ligand [11C] PIB uptake in Alzheimer disease. Neurology, 67(9), 1575 1580. Kemppainen, N. M., Aalto, S., Wilson, I. A., Någren, K., Helin, S., Brück, A., ... & Rinne, J. O. (2007). PET amyloid ligand [11C] PIB uptake is increased in mild cognitive impairment. Neurology, 68(19), 1603 1606. Saint-Aubert, L., Barbeau, E. J., Péran, P., Nemmi, F., Vervueren, C., Mirabel, H., ... & Pariente, J. (2013). Cortical florbetapir-PET amyloid load in prodromal Alzheimer's disease patients. EJNMMI Res, 3, 43. Ziolko, S. K., Weissfeld, L. A., Klunk, W. E., Mathis, C. A., Hoge, J. A., Lopresti, B. J., ... & Price, J. C. (2006). Evaluation of voxel-based methods for the statistical analysis of PIB PET amyloid imaging studies in Alzheimer's disease. Neuroimage, 33(1), 94-102.

Figure 1

Group analyses. Row 1: AD-Aβ+++ versus HC-Aβ– (FWE (a) and FDR (b) corrections). Row 2: AD-Aβ++ versus HC-Aβ– (FEW (c) and FDR (d) corrections). Threshold of significance: p<0.05 for FWE and p<0.001 for FDR corrections. Minimum cluster size: 200 voxels

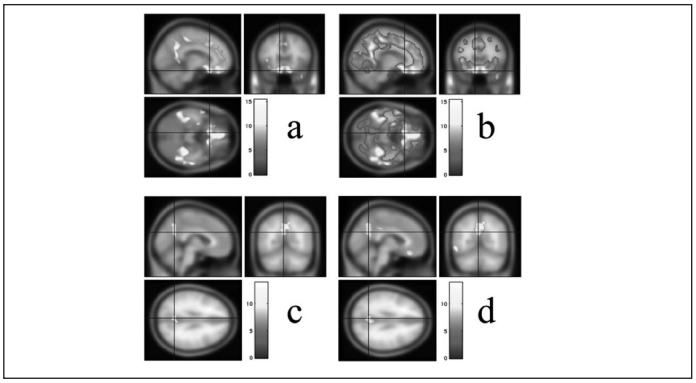
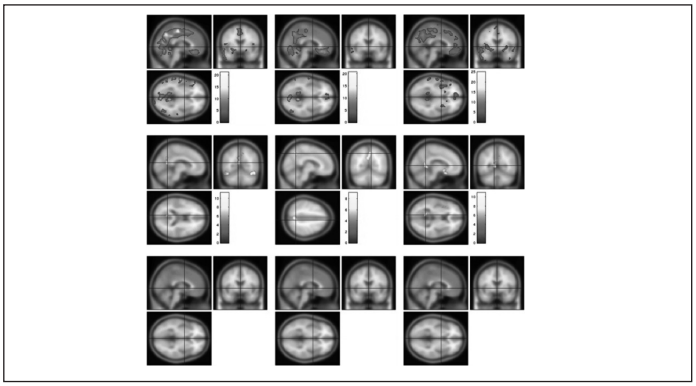


Figure 2

Examples of single-case analyses output. Row 1: 3 AD Aβ+++ subjects, Row 2: 3 AD Aβ++ subjects, and Row 3: 3 HC Aβ–. Uncorrected threshold of significance p<0.001. Minimum cluster size: 200 voxels



P2-14: RELATIONSHIPS BETWEEN COGNITIVE ASSESSMENTS AND SPATIAL DISTRIBUTION OF NEUROPATHOLOGICAL TAU AS ASSESSED BY 18F AV-1451 PET SCANNING. MICHAEL D DEVOUS, MICHAEL NAVITSKY, IAN KENNEDY, ABHINAY D JOSHI, MING LU, MICHAEL J PONTECORVO, MARK A MINTUN *(Avid Radiopharmaceuticals, Inc., Philadelphia, PA, USA)*

Background: The neuropathologic literature suggests that the density and distribution of neuropathologic tau deposits correlates with overall cognitive impairment. 18F-AV-1451 is a PET tracer being developed for tau imaging with potential application as a biomarker for tracking neurodegeneration. This preliminary work explores relationships between spatial distribution of 18F-AV-1451 and a range of cognitive functions as assessed by neuropsychological measures. *Methods:* We analyzed 18F-AV-1451 PET scans in 86 amyloid-positive subjects including healthy controls (n=5), and those with clinical diagnoses of mild cognitive impairment (MCI; n=47) or Alzheimer's disease (AD; n=34). PET scans were acquired 80-100 min after the injection of approximately 370 MBq 18F-AV-1451. SUVr was calculated for each voxel relative to a cerebellar reference region. Cognitive assessments included MMSE, ADAS-cog (as well as its subscores) and a neuropsychological test battery that included the Wechsler Memory Scale-Revised Logical Memory (WMS-R), Trail Making Test, Boston Naming Test, Digit Symbol Substitution Test, Animal List Generation, WMS-R Digit Span (Forwards and Backwards), American National Adult Reading Test, Clock Drawing Test, Judgment of Line Orientation and WMS-R Logical Memory II (Delayed Recall). Pearson correlation analyses comparing voxel-wise SUVr images to cognitive scores were conducted. *Results:* Subjects were an average age of 73.7 ± 9.4 years with mean MMSE and ADAS-cog scores appropriate for their clinical diagnoses; controls (MMSE =30; ADAS =6), MCI (MMSE =27; ADAS =11) and AD (MMSE=21; ADAS =21). Correlation patterns differed across the cognitive domains (see Fig 1) and appeared to follow known spatial distributions of relevant functional neuroanatomy (e.g., impairment of working memory domains associated with increased left temporal lobe tau, spatial processing with right parietal tau, executive function with frontal tau). Strong correlations (p<0.0001) were seen relative to ADAS total (max r>0.6) as well as ADAS subscales including assessments of executive function (Comprehension of Spoken Language, max frontal lobe r>0.6), and in neuropsychological evaluations of executive function (Trails, Digit Symbol Substitution), spatial processing (Trails A, max right parietal r>0.6), and working memory (WMS-R immediate or delayed recall, max left temporal r>0.5). *Conclusions:* Voxel-wise SUVr values correlated with cognitive scores such that greater intensity of 18F AV-1451 uptake was associated with worse performance in a domain-dependent spatial distribution. This supports the hypothesis that PET imaging of neuropathologic tau deposits may reflect underlying neurodegeneration in AD. Further work to understand whether such correlations relate to progression is required.

P2-15: LOW DOSE WHOLE BRAIN IRRADIATION AS A POTENTIAL TREATMENT OF ALZHEIMER'S DISEASE. JAMES FONTANESI[1], DANIEL B MICHAEL[1], BRIAN MARPLES[2], GEORGE D WILSON[2], ALVARO A MARTINEZ[3], SCOTT E BOWEN[4] *((1) Department of Neurosurgery, William Beaumont Hospital/Oakland University School of Medicine, Royal Oak, Michigan USA; (2) Department of Radiation Oncology, William Beaumont Hospital/Oakland University School of Medicine, Royal Oak, Michigan USA; (3) Department of Radiation Oncology, 21 Century Oncology, Farmington Hills, Michigan USA; (4) Department of Psychology, Wayne State University, Detroit, Michigan USA)*

Background: The use of fractionated external beam irradiation has a well-documented history of successful use in the treatment of non CNS Amyloidosis. There are numerous peer reviewed articles which have demonstrated that low dose fractionated external beam irradiation has the ability to not only retard development of the new amyloid deposits but reduce and eliminate existing amyloid which often can cause compromising symptomology. Not only does the radiation provide a near immediate improvement in most cases but there is also long term evidence which suggests lack of recurrence following treatment. It is noteworthy the mechanism related to these non CNS sites is not well been established. Based on this information our group has previously reported our experience with both single fraction and

fractionated hemi and whole brain irradiation in a genetically altered animal model. However, even with our documentation of total amyloid plaque number/volume reductions associated with external beam irradiated we have not previously demonstrated differentiation in neuro cognitive testing. We present our most recent series of animals treated and report on our neuro cognitive findings. *Method:* 16 month old B6. Cg-Tg (APPswePSEN1dE9) 85Dbo/J mice were treated using 5 X 200 cGy (n=19) and compared to non-treated animals (n=14n). Neuro cognitive testing was administered using the Morris Water Maze prior to treatment and at 8 weeks post treatment, animals were then sacrificed. Mice were trained in three trials/day (90 second maximum) with a 30 minute inter-trial interval for 5 At sacrifice amyloid number, volume and various stains were performed in the necropsy material to evaluate the effects of irradiation. Pair sample statistical methods (student T test) were used. *Results:* Latency period for pretreatment controls were 58 seconds (SD+/-23) and 48 seconds (SD+/-13n) for the "to be treated" animals (P=0.39). At initial testing there were no differences in swimming velocity or baseline ambulatory velocity. At 8 weeks post treatment latency period was 60 seconds (SD+/-15) for controls and 31 seconds (SD+/-17n) for the treated animals (P=0.03). The treatment group located platforms significantly faster on the final day of trial were compared to the control group. Treatment animals had a statistical lower number of plaques and there was a trend towards significant of volume of residual plaque. When evaluating special stains differences between the irradiated control animals were evident for IL10, IL-1β ,and IBa-1. Most significant changes were noted for IBa-1 (P=0.001). In addition notable changes were identified in the reduction of Plakophilin (Pkp4) (1.48-Fold, P=0.004), a component of desmosomal plaque and other adhesion plaque which was thought to be involved in regulating junctional plaque organization in canhederan function with a reduction in micro tubular associated protein tau. *Conclusion:* This data confirms our previous animal studies in which we were able to identify with both single fraction and fractionated regiments a statically significant reduction of up to 78% of plaque number and volume. What we have previously lacked was any neuro cognitive testing data. These results showed at least a stabilization of the neuro cognitive decline that is associated with these animals by the intervention of low dose whole brain irradiation. When compared to untreated control animals. Based on these findings we have been given clearance by the FDA to initiate a Phase 1 human clinical trial looking at the use of fractionated whole brain irradiation in the treatment of Alzheimer's disease.

P2-16: SNP PROFILING AS AN APPROACH TO RISK STRATIFICATION FOR FUTURE COGNITIVE DECLINE IN MILD COGNITIVE IMPAIRMENT (MCI). VALENTINA ESCOTT-PRICE[1], RICHARD PITHER[2], HARALD HAMPEL[3], JULIE DAVIS[2], JOHN HARDY[4] *((1) Cardiff University, Cardiff, United Kingdom; (2) Cytox Ltd, UK, Oxford, United Kingdom; (3) Université Pierre et Marie Curie, Paris, France; (4) UCL Institute of Neurology, London, United Kingdom)*

Background: Clinically, Mild Cognitive Impairment (MCI) is a condition of subtle cognitive change which often, but by no means always, represents the first manifestation of Alzheimer's Disease (AD). Since we believe that we need to treat AD very early and we need to assess whether such early treatments work in slowing progression, we need to get better both at diagnosing those within the MCI cohort who have early AD and also identifying the variables which determine their rate of conversion to full blown disease. In both cases, genetic analysis is a promising route to this important clinical dissection. *Methods:* Our aim in this work is to identify genetic risk variants, or single nucleotide polymorphisms (SNPs), which can be used ultimately, in the definition of an algorithm to predict AD progression. In turn, this would be expected to facilitate AD clinical trials by reducing both misdiagnosis rates and enabling better prediction of expected disease progression rates. We are carrying out whole genome association analysis (testing genetic variants across the genome) using novel technologies developed over the last five years, in highly selected and characterised clinical samples. *Results:* The output of our preliminary statistical analysis and modelling of data from cross-sectional AD and control subjects, has identified a SNP panel and associated algorithm which is performing to 90% accuracy (AUC) to distinguish these two groups. *Conclusions:* Additional work in larger, well-characterised cohorts is ongoing to assess whether sufficient sensitivity and specificity performance consistent with potential clinical utility, could be achieved.

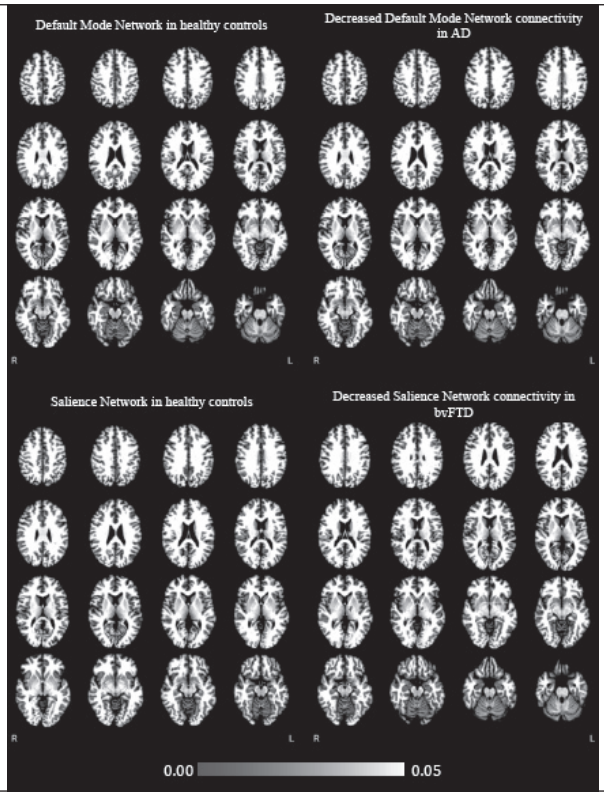
P2-17: IDENTIFICATION OF POTENTIAL TARGETS FOR BRAIN STIMULATION IN AD AND BVFTD: A META-ANALYSIS OF FMRI STUDIES. MICHELA PIEVANI[1], LORENZO PINI[1], CLARISSA FERRARI[2], MARIA COTELLI[3], ROSA MANENTI[3], GIOVANNI B FRISONI[1,4] *((1) Lab Alzheimer's Neuroimaging & Epidemiology, IRCCS Fatebenefratelli, Brescia, Italy; (2) IRCCS Fatebenefratelli, Brescia, Italy; (3) Neuropsychology Unit, IRCCS Fatebenefratelli, Brescia, Italy; (4) University Hospitals and University of Geneva, Geneva, Switzerland)*

Background: Brain stimulation techniques such as transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) are emerging as noninvasive approaches to treat neurological diseases (Schulz et al., 2013; Cotelli et al., 2011). Brain stimulation is only effective when it targets the intended area and a recent study suggested that resting-state fMRI (rs-fMRI) might help in identifying potential targets for effective noninvasive brain stimulation (Fox et al., 2014). In Alzheimer's disease (AD) and behavioral variant frontotemporal dementia (bvFTD), two specific networks are affected by pathology, i.e. the default mode (DMN) and the salience (SN) network, respectively (Pievani et al., 2014). These circuits might be potential targets for noninvasive treatments, however their specific location has never been systematically addressed. The aim of this meta-analysis is to identify consistent coordinates of DMN and SN in healthy and pathological conditions from rs-fMRI studies. *Methods:* A systematic search of rs-fMRI studies reporting the coordinates of the DMN or SN, published in PubMed between January 2005 and March 2015, was conducted. Inclusion criteria were: (1) studies reporting DMN coordinates in healthy adults (HC); (2) studies reporting coordinates of reduced DMN connectivity in AD patients; (3) studies reporting SN coordinates in healthy adults; (4) studies reporting coordinates of reduced SN connectivity in bvFTD patients. Exclusion criteria were: (1) task-fMRI studies; (2) studies reporting only a-priori coordinates; (3) rs-fMRI studies testing pharmacological treatment effects. Coordinate-based meta-analysis was performed to identify spatially consistent coordinates across studies with GingerALE (v2.3.1) and the activation likelihood estimation (ALE) method (BrainMap Project, http://www.brainmap.org/ale/). Four separate analyses were conducted to identify (i) DMN and (ii) SN coordinates in healthy, and (iii) DMN and (iv) SN reductions in patients. Results were thresholded at $p<0.05$ corrected for multiple comparisons using cluster-based correction with a cluster-forming threshold of $p<0.01$ and 1000 permutations (Eickhoff et al., 2012). The meta-analysis was conducted in Montreal Neurological Institute (MNI) space; coordinates in Talairach space were transformed to MNI using Lacadie non-linear transformation (Lacadie et al., 2007). *Results:* We identified 21 studies reporting DMN coordinates in HC (516 subjects and 277 foci), 17 studies reporting DMN reductions in AD patients (475 AD, 452 HCs and 135 foci), 13 studies reporting SN coordinates in HC (366 subjects and 134 foci) and 4 studies reporting SN reductions in bvFTD (60 bvFTD, 72 HCs and 36 foci). Consistent DMN coordinates in HC mapped to the posterior cingulate

cortex (BA 23/31), medial anterior cingulate and frontal cortex (BA 24/32/9/10), and bilateral angular gyrus (BA 39) (Figure 1, top left). Further smaller clusters mapped to the temporal cortex (lateral - BA 21 - and parahippocampus - BA 28), and the lateral superior frontal cortex (BA 6) bilaterally. In AD, these regions consistently showed reduced connectivity, except for the angular gyrus, which did not survive multiple correction (Figure 1, top right). SN coordinates in HC mapped to the medial anterior cingulate cortex (BA 32), bilateral insula, bilateral supramarginal gyrus (BA 40) and right anterior prefrontal cortex (BA 9/10) (Figure 1, bottom left). In bvFTD, clusters of reduced SN connectivity were considerably smaller and mapped to similar regions (anterior cingulate cortex - BA 32 - and bilateral insula) but also to the basal ganglia (Figure 1, bottom right). *Conclusion:* This systematic coordinate-based meta-analysis identified consistent clusters of DMN and SN connectivity. Taking into account the properties of brain stimulation techniques, which cannot reach deep subcortical areas, the candidate target for DMN non-invasive brain stimulation in AD might be the angular gyrus (BA 39) and for SN non-invasive brain stimulation in bvFTD the supramarginal gyrus (BA 40) or the right anterior prefrontal cortex (BA 9/10).

Figure 1

Meta-analysis for the identification of (i) default mode network (DMN) and salience network (SN) regions in Healthy Controls (HC) and (ii) regions of reduced DMN and SN connectivity in patients. Color bar indicates ALE likelihood values



P2-18: DOES HIPPOCAMPAL VOLUMETRY IMPACT ON DIAGNOSTIC CONFIDENCE IN ALZHEIMER'S DISEASE? AN EADC STUDY. PAOLO BOSCO[1], ALBERTO REDOLFI[1], MARTINA BOCCHETTA[1,2], CLARISSA FERRARI[3], SAMANTHA GALLUZZI[1], MARK AUSTIN[4], LOUIS COLLINS[5], ANDREA CHINCARINI[6], ALEXIS ROCHE[7], FRANCESCO SENSI[6], ROBIN WOLZ[4], MONTSERRAT ALEGRET[8], MIRCEA BALASA[9], CHRISTINE BASTIN[10], ANASTASIA BOUGEA[12], DERYA DURUSU EMEK-SAVAŞ[12,13], SEBASTIAAN ENGELBORGHS[14,15], TIMO GRIMMER[16], NTOVAS KONSTANTINOS[17], MILICA G KRAMBERGER[18], BRIAN LAWLOR[19], GORANA MANDIC STOJMENOVIC[20], PATRIZIA MECOCCI[1], JOSE LUIS MOLINUEVO[9], RICARDO MORAIS[22], ELLIS NIEMANTSVERDRIET[14], FLAVIO NOBILI[23], SARAH O'DWYER[11], GEORGE P. PARASKEVAS[11], LUCA PELINI[20], AGNESE PICCO[23], ERIC SALMON[10], ISABEL SANTANA[24], OSCAR SOTOLONGO-GRAU[8], ELKA STEFANOVA[20,25], KATARINA SURLAN POPOVIC[26], MAGDA TSOLAKI[17], GÖRSEV G. YENER[12,13,27], GIOVANNI B FRISONI[1,28]

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Background: Many different tools and metrics have been developed so far to evaluate medial temporal lobe atrophy in Alzheimer's disease (AD). Among them, the measurement of the hippocampal volume has shown promising diagnostic value in patients at the mild cognitive impairment (MCI) stage. We aimed at investigating the impact of hippocampal volumetry on the diagnostic confidence for MCI due to AD in the clinical practice. *Methods:* Nineteen EADC (European Alzheimer's Disease Consortium) centres took part to this study and enrolled 24 patients with MMSE>20, suspected AD with initial diagnostic confidence between 15% and 85%, and an available 1.5T or 3T T1-weighted volumetric MRI scan in digital format. Diagnostic confidence is based on usual local assessment and practices. EADC clinicians upload volumetric MRIs on an ad hoc web platform and automated volumetry is carried out with one of six algorithms at random (AdaBoost [1], Freesurfer [2], LEAP [3], GDISegmenter [4], TPMD [5] and MorphoBox [6]). Clinicians are then fed one volumetric report, including a graph showing left and right hippocampal volumes contrasted with the normative distribution. Based on the volumetric measurement included in the report, clinicians provide a final rating of confidence in diagnosis of AD, and report on

the perceived impact of volumetry on diagnosis by a 4-level Likert scale. *Results:* The first 182 subjects were 44% men, age was 64 (SD 10) years, and MMSE was 24.4 (SD 3.0). In addition to MMSE and MRI, 98% had neuropsychological assessment, 43% visual rating of medial temporal atrophy 37% an FDG-PET scan, 9% a SPECT scan, and 27% Aβ1-42 and tau measured in the cerebrospinal fluid. Initial diagnostic confidence was not associated with hippocampal volume (Pearson's r= -0.05, p=0.4), while final confidence was (Pearson's r= -0.38, p=1.3 x 10-7). In seventy-six percent of the cases clinicians reported a slight to strong impact of hippocampal volumetric information on diagnostic confidence. *Conclusion:* Hippocampal volumetry impacts on diagnostic confidence in European academic memory clinics. Future work will assess the differential impact of the six algorithms. [1] Morra et al, NeuroImage 2008;43(1):59–68. [2] Fischl et al, Neuron 2002; 33(3):341–55. [3] Wolz et al, Neuroimage 2010;49(2):1316-25. [4] Chincarini et al, NeuroImage 2011;58(2):469–80. [5] Collins et al, NeuroImage 2010;52(4):1355-66. [6] Roche et al, Medical Image Analysis 2011;15(6):830-39. [7] Scheltens et al, J Neurol Neurosurg Psychiatry 1992;55:967–72.

P2-19: INABILITY OF THREE FUNCTIONAL MRI CONNECTIVITY ENDPOINTS TO DETECT PROGRESSION IN CLINICAL TRIAL PATIENTS WITH ALZHEIMER'S DISEASE. ALEXANDRE COIMBRA[1], DAVID CLAYTON[1], FARAJI FARSHID[1], LEE HONINBERG[2], ROBERT PAUL[2], ALEX DECRESPIGNY[1] *((1) Genentech, gRed Clinical Imaging Group, South San Francisco, California, USA; (2) Genentech, gRed ITGR, South San Francisco, California, USA)*

Background: Single-center studies on resting-state fMRI (RS-fMRI) have suggested that brain functional connectivity endpoints are altered in patients with AD when compared with healthy controls. Exploratory RS-fMRI was included in two global Phase II multicenter clinical trials of a novel AD drug (NCT01343966, NCT00997919). We report here on (1) execution and data quality control of a harmonized multicenter RS-fMRI data-acquisition protocol, (2) assessment of variability, and minimal detectable difference of three commonly used functional connectivity metrics (FCMs) and (3) assessment of sensitivity of FCMs to detect group-level disease progression over time in the placebo arm of the clinical trial population. *Methods:* A total of 572 scans were acquired from 111 patients across 19 sites in N. America and Europe. Patients had mild–moderate AD (MMSE 18-26) and were selected from the placebo arms of two Phase II studies. Seven sites used 1.5T and the remaining 12 sites used 3T magnets from three major manufacturers—Philips, Siemens and GE. Patients were scanned prior to initiating therapy and then at Weeks 7, 15, 23, 35, 47, 59 and 73. Consecutive pairs of RS-fMRI datasets acquired at 7-week time intervals were assumed to be equivalent to "test–retest" data sets and pooled for analysis of FCM variability. The RS-fMRI protocol consisted of a 2D, single-shot, GRE-EPI sequence, and an anatomic 3D, high-resolution T1. Sites were allowed to use a locally established fMRI scan protocol with the exception of the following required parameters: TR=3000 ms, 140 time points, 64x64 matrix, 224x224 mm FOV, slice thickness 3.5 mm, ~160 mm SI coverage, TE =30/50 ms with flip angle 90°/80° at 1.5T/3T, local fat saturation method, and high-order shimming, if available. Subjects were asked to rest awake with eyes closed. EPI data were brain-extracted, motion-corrected, spatially and temporally filtered and signal-intensity normalized, registered to the brain extracted anatomical T1 scans, and subsequently to MNI152 standard space using non-linear registration algorithms. Mean CSF, WM, global brain signal and 6 motion correction parameters were regressed out of the EPI data by general linear model (GLM) fitting. Raw SNR was defined as the ratio between GM signal and the standard deviation of background. Coefficient of variation (CoV) in gray matter was defined as the average of voxelwise temporal standard deviation/mean. Head motion was assessed with FSL/mcflirt. The following 3 FCMs were computed: goodness-of-fit (GOF) for the Default Mode Network, following independent component analysis using FSL/melodic with automatic dimensionality estimation; average gray matter z-score of GLM regression (SEED) with the mean posterior cingulate cortex (PCC); and correlation coefficients (CORR) between mean PCC and precuneus signals. Intra-class correlation (ICC) for test–retest scan pairs were calculated. Sample size curves were derived to infer minimal detectable FCM changes. Groupwise annualized rates of change (ARC) were also computed. *Results:* Deviations from the prescribed imaging protocol were observed at 10 sites. Most were minor (e.g. deviations in TE/TR) and occurred consistently per site. Significant variation in raw GM SNR was observed across sites, but was highly consistent between 'test–retest' pairs of scans from any specific site. GM CoV showed much less inter-site variation than SNR. Median CoV was 1.0, decreasing to 0.75 after regressing out nuisance variables, decreasing to 0.25 after temporal/spatial filtering. The ICC=0.55 calculated for test–retest pairs was moderate. Sample size calculations for detecting specific % changes with 80% power at 0.05 significance level for GOF and CORR show that 40–80 patients are needed to detect 20–30% change. For SEED, 20–40 patients are sufficient to detect a 7–10% change. This is due to the fact that the standard deviation of SEED test–retest difference is small relative to the mean. The ARCs in the pooled placebo cohorts were: GOF=0.03 ± 0.56/year, CORR=0.05 ± 0.27/year, SEED=-0.14 ± 0.64 /year. No ARC was significantly different from zero. Significant ARC for ADAS-Cog12 score (-7.2 ± 8.7 points/year, $p<0.001$) and whole brain volume (-2.0 ± 1.0 %/year, $p<0.001$) was observed for this cohort of patients. *Conclusion:* In two global Phase II multicenter clinical trials, RS-fMRI data acquisition protocol was established, data of good verified quality were acquired and variability of FCMs was assessed. Of the three FCMs tested, none showed significant progression associated with disease in placebo treated patients, indicating that any actual changes in functional connectivity in this narrowly defined AD population were less than the measurement precision of the investigated metrics. Meanwhile, significant cognitive decline and atrophy were observed. The test–retest precision of FCMs after pre-processing steps was similar to that reported by other single-center test–retest studies of RS-fMRI. Aside from a marked increase in image SNR, which may be difficult to achieve in a multicenter trial, a significantly more sensitive analysis approach will be needed if RS-fMRI is to prove to be a useful tool for the development of novel drugs in mild–moderate AD.

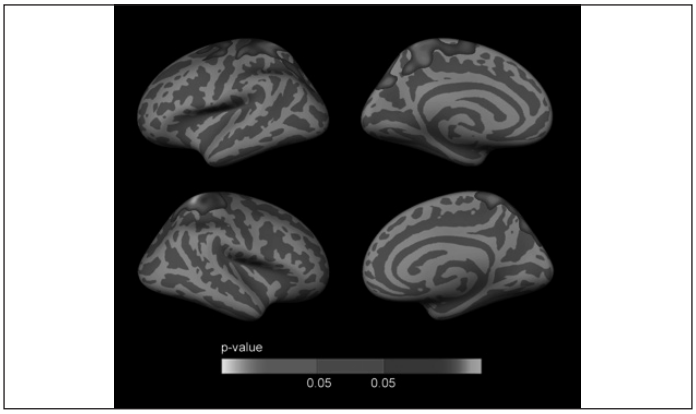
P2-20: CORTICAL THICKENING AND DIFFUSIVITY CHANGES IN PRECLINICAL ALZHEIMER'S DISEASE. JUAN FORTEA[1], VICTOR MONTAL[1], EDUARD VILAPLANA[1], DANIEL ALCOLEA[1], JORDI PEGUEROLES[1], FREDERIC SAMPEDRO[1,2], MARÍA CARMONA-IRAGUI[1], JORDI CLARIMÓN[1], SOFÍA GONZÁLEZ[3], PABLO MARTÍNEZ-LAGE[4], PASCUAL SÁNCHEZ-JUAN[5], RAFAEL BLESA[1], ALBERTO LLEÓ[1] *((1) Department of Neurology, IIB Sant Pau - Hospital Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain; (2) Department of Nuclear Medicine, IIB Sant Pau - Hospital Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain; (3) Department of Radiology, Hospital del Mar, Barcelona, Spain; (4) Fundación CITA-alzhéimer Fundazioa, San Sebastián, Spain; (5) Servicio de Neurología, Hospital Universitario Marqués de Valdecilla, Santander, Spain)*

Backgrounds: According to the amyloid hypothesis, accumulation of ß-Amyloid 1-42 (Aß) in the brain is the primary influence driving AD pathogenesis (Hardy & Selkoe 2002, Science). However, the relationship between amyloidosis and brain structure remains unclear. Recently, we have proposed a 2-phase phenomenon model in preclinical AD (Fortea et al. 2014, Annals of Neurology) that consists

of pathological cortical thickening in relation to decreasing CSF Aß levels followed by atrophy once CSF phospho-tau becomes abnormal. We hypothesized that this 2-phase phenomenon would be driven by the inflammatory process associated to the Aß accumulation (Fortea et al 2010, Journal of Alzheimer's Disease). In this previous small pilot study in familial AD (PSEN1 mutation carriers) we showed that decreases in cortical mean diffusivity (MD) measured by diffusion tensor imaging could be a biomarker for the pathological cortical thickening as it would reflect the increase in both cell volume and cell number due to an inflammatory response to Aß (Fortea et al 2010, Journal of Alzheimer's Disease). The objective of this work was to study the relationship between CSF Aß, brain structure and grey matter MD in a large cohort of cognitively normal controls, based on the hypothesis that a decrease in CSF Aß levels is related to pathological cortical thickening associated with inflammation. *Methods:* In this cross-sectional study, 229 healthy controls underwent structural 3T diffusion weighted (DWI) magnetic resonance imaging (MRI) and lumbar puncture. CSF Aß levels were measured in CSF by enzyme-linked immunosorbent assay (Innotest® ß-amyloid1-42; Fujirebio Europe). Participants were classified as Aß+ (CSF Aß < 550 pg/ml) or Aß- (CSF Aß >= 550 pg/ml) using the internal published cutoff (Alcolea et al 2015, Neurology). Cortical thickness (CTh) was measured with Freesurfer software package (v5.1; http://surfer.nmr.mgh.harvard.edu). CTh difference maps between Aß+ and Aß- groups were extracted by a linear modeling of the thickness maps as implemented in Freesurfer including age, gender and center as covariates. Only results that survived family-wise error correction (FWE) at p<0.05 are presented. DWI was analyzed using FSL (v5; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) and ANTs (http://stnava.github.io/ANTs/) tools. Individual MD maps were computed from each subject, normalized to MNI152 space and smoothed. Results are presented at p<0.005 (uncorrected) and minimum cluster size k=20. Comparisons in demographic variables between groups were performed using SPSS (SPSS Inc, Chicago, IL).

Figure 1

Cortical thickness (CTh) group analysis. Aß+ group show two extensive clusters of increased CTh compared to Aß- subjects (p< 0.05 FWE)



Results: From the initial 229 subjects with available structural MRI, 166 also had a valid diffusion weighted MRI (DWI); 202 were classified as Aß- and 27 as Aß+. The Aß+ group was older (p=0.002) than the Aß- group. In the structural analysis, the Aß+ group showed two extensive clusters (p<0.05 FWE) of increased cortical thickness compared to the Aß- group. These clusters included precuneous and superior parietal regions on the right hemisphere and precuneous, superior parietal, precentral, postcentral, paracentral and superior frontal regions on the left hemisphere (Figure 1). In the DWI analysis, the Aß+ group showed widespread clusters of decreased MD compared to the Aß- group (Figure 2). Only two isolated clusters of increased cortical MD were found (Figure 3). *Conclusions:* Our results provide further evidence supporting the aforementioned two-phase phenomenon model in preclinical AD, in which an Aß-related cortical thickening precedes the volume loss in the disease course. The cortical MD would mirror these changes with decreases in MD associated with cortical thickening. These results have potential implications in AD clinical trials, both when selecting patients and when using MRI as a surrogate marker of efficacy. Moreover, they support the use of cortical DWI as a surrogate marker of neuroinflammation. Centro de Investigación Biomédica en Red en enfermedades Neurodegenerativas, CIBERNED, Spain. The SIGNAL study

Figure 2

DWI analysis. Aß+ group show widespread clusters of decreased mean diffusivity compared to Aß- subjects (p< 0.005 uncorrected, k=20)

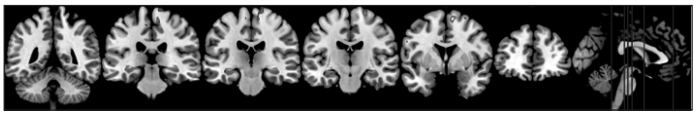
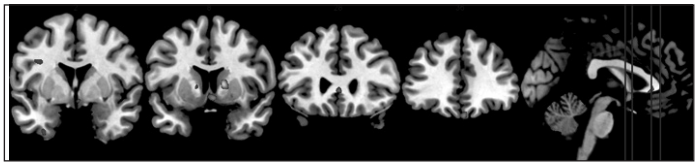


Figure 3

DWI analysis. Aß+ group show two isolated clusters of increased mean diffusivity compared to Aß- subjects (p< 0.005 uncorrected, k=20)



P2-21: IDENTIFICATION AND FIRST-IN-HUMAN EVALUATION OF GENENTECH TAU PROBE 1 ([18F] GTP1). SANDRA SANABRIA BOHORQUEZ[1], OLIVIER BARRET[2], GILLES TAMAGNAN[2], JEFF TINIANOW[3], ANNIE OGASAWARA[3], SIMON WILLIAMS[3], ALEX DE CRESPIGNY[1], GAI AYALON[4], GEOFFREY KERCHNER[5], WILLIAM CHO[5], DANNA JENNINGS[2], JOHN P SEIBYL[2], KEN MAREK[2], ROBBY WEIMER[3], JAN MARIK[3] *((1) Clinical Imaging Group; (2) Molecular NeuroImaging LLC, 60 Temple Street, New Haven, CT, 06510, USA; (3) Department of Biomedical Imaging, (4) Department of Neuroscience and (5) Early Clinical Development, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA)*

Background: In Alzheimer's disease (AD), the extent of postmortem tau pathology, consisting of paired helical tau fibrils, correlates with cognitive deficits, suggesting that tau pathology is closely linked to the pathophysiology of dementia. Positron Emission Tomography (PET) utilizing small molecule radiotracers specific for tau pathology could enable in vivo cross-sectional and longitudinal assessment of tau pathology. Here, we present preclinical validation and first-in-human clinical evaluation of a novel tau-specific PET probe, Genentech Tau Probe 1 ([18F]GTP1). *Methods:* [18F] GTP1 was identified from a library of candidate small molecules by autoradiographic screening using human brain tissues from AD patients that contain tau and Aβ plaque pathology, or Aβ plaque pathology alone. The pharmacokinetic properties of [18F]GTP1 was assessed preclinically by in vivo PET imaging in mouse and rhesus monkey. To assess the properties of [18F]GTP1 in humans, a first-in-human study was conducted consisting of two healthy volunteers (HV) and three probable AD subjects. Dynamic PET scans were acquired in a single exam over 180 minutes following [18F]GTP1 injection (HV, 0-90 and 150-180 minute imaging segments; AD, 0-60, 90-120 and 150-180 minute imaging segments). Quantification of [18F]GTP1 uptake and clearance was performed using the simplified reference

tissue model (binding potential BPND) and target to cerebellum gray standardized uptake value ratio (SUVR). A brain MRI was obtained as part of the screening visit. PET and MRI images were aligned and normalized into the Montreal Neurological Institute (MNI) space. The regions in the Anatomical Automatic Labeling (AAL) template were used to define subject specific regions of interest (ROI) using the MRI gray matter segmentation and the 0-10 min summed PET image. All analysis were performed in Matlab® with SPM12 and in-house developed software. *Results:* [18F]GTP1 exhibited high affinity (KD = 14.9 ± 4.3 nM) and selectivity for tissues containing tau neurofibrillary tangles. In preclinical PET imaging experiments, [18F]GTP1 exhibited high initial brain uptake, rapid washout and low non-specific binding, in particular in the white matter. Similar results were observed in clinical imaging studies of HV. In AD subjects, however, [18F]GTP1 exhibited elevated retention specifically in regions predicted to contain tau pathology: in the temporal (up to 3 SUVR90-120min), parietal (up to 2.4 SUVR90-120min), fusiform (up to 2.7 SUVR90-120min) cortices. The pattern of uptake varied between AD patients and between hemispheres, consistent with known heterogeneity of tau pathology in AD. SUVR and BPND were linearly correlated, SUVR90-120min=1.55*BPND(120min)+0.95 (r2=0.99, 24 cortical regions/subject), suggesting that SUVR is an appropriate estimate of specific tracer binding to tau. Furthermore, comparison of SUVR values between HV and AD subjects and between regions of [18F]GTP1 retention and background within AD subject suggests [18F]GTP1 provides a large dynamic range for detecting tau pathology in vivo. *Conclusions:* The high selectivity and specificity of [18F]GTP1 for tau deposition observed in the pre-clinical evaluation and the results of the FIH study strongly suggest this tracer can detect tau pathology in AD and has excellent pharmacokinetic properties that could provide the dynamic range needed for quantitative measurements of tau pathology burden. Test-retest imaging with arterial blood sampling to measure the tracer input function and dosimetry studies are on going to further characterize [18F]GTP1 and optimize the imaging procedure.

P2-22: INTEGRATION OF EADC-ADNI HARMONISED HIPPOCAMPUS LABELS INTO THE LEAP AUTOMATED SEGMENTATION TECHNIQUE. KATHERINE R GRAY[1,2], HOI KIN KWAN[1], ROBIN WOLZ[1,2], DEREK LG HILL[1] *((1) IXICO plc., London, United Kingdom; (2) Biomedical Image Analysis Group, Imperial College London, United Kingdom)*

Background: Hippocampal volume provides an established supportive marker for the diagnosis of Alzheimer's disease (AD), which can be measured in vivo by segmentation on structural magnetic resonance images (MRI). An EADC-ADNI effort to harmonise the available segmentation protocols has resulted in a consensually defined harmonised protocol for manual hippocampus segmentation (http://www.hippocampal-protocol.net/) [1]. As part of the EADC-ADNI effort, 135 ADNI MRI have been manually labeled according to the harmonised protocol (2). We have previously presented results from integration of a preliminary release of these harmonised labels into the automated segmentation algorithm LEAP (learning embeddings for atlas propagation) (3), the algorithm incorporated in the Assessa® CE-marked medical device. We now present initial results from integration of the final harmonised labels. *Methods*: LEAP is a multi-atlas segmentation technique that is specialised for the diverse populations typically found in AD studies. An iterative propagation scheme is employed to transfer labels from a set of manually segmented atlas images to a large heterogeneous reference dataset, and an intensity-based correction is then applied to refine the label boundaries. As an initial experiment, we have employed a leave-one-out approach within the 135 manually labeled images, such that each image is automatically labeled using LEAP with the remaining 134 manually labeled images as atlases. *Results*: Pearson product-moment correlation coefficients between automated and manual volumes are 0.951 and 0.942 for the left and right hippocampus, respectively. Mean dice overlaps between automated and manual segmentations are 0.875 (95% CI 0.871-0.879) and 0.875 (95% CI 0.872-0.879) for the left and right hippocampus, respectively. Intra-class correlation coefficients (ICC) for absolute agreement between automated and manual volumes are 0.969 (95% CI 0.950-0.980) and 0.963 (0.929-0.978) for the left and right hippocampus, respectively. ICCs for consistency between automated and manual volumes are 0.972 (95% CI 0.961-0.980) and 0.969 (0.957-0.978) for the left and right hippocampus, respectively. For the five tracers involved with manual segmentation of the 135 ADNI images, the ICCs for absolute inter-rater volume agreement (in a different dataset) were 0.953 and 0.975 for the left and right hippocampus, respectively (3). *Conclusions:* The harmonised protocol provides a mechanism for training automated algorithms such as LEAP to provide results that are consistent with one-another. Agreement between automated LEAP volumes and manually segmented volumes is encouraging compared with the inter-rater variability across manual tracers using the harmonised protocol. We plan to extend the experiments presented here by using LEAP to propagate harmonised hippocampus labels from the 135 manually labeled images to a heterogeneous dataset of 1,387 MRI, and then further assessing the performance of LEAP automated segmentation by propagating labels back from this reference database to the atlas images for which manual labels exist. We then plan to incorporate the harmonised labels in a future version of Assessa®, the CE-marked decision-support platform for dementia diagnosis. *References*: [1] Boccardi et al., Delphi Definition of the EADC-ADNI Harmonized Protocol for Hippocampal Segmentation on Magnetic Resonance. Alzheimer's & Dementia 11(2):126–138, 2015. [2] Boccardi et al., Training labels for hippocampal segmentation based on the EADC-ADNI harmonized hippocampal protocol. Alzheimer's & Dementia 11(2):175–183, 2015. [3] Gray et al., Integration of EADC-ADNI Harmonised Hippocampus Labels into the LEAP Automated Segmentation Technique, Alzheimer's & Dementia 10(4):S555, 2014.

P2-23: LONGITUDINAL FDG-PET CHANGES IN COGNITIVELY NORMAL ADNI SUBJECTS USING TEMPORAL CORRELATION ANALYSIS. SEPIDEH SHOKOUHI *(Vanderbilt University Institute of Imaging Science, Nashville, TN, USA)*

Background: The National Institute on Aging and the Alzheimer's Association proposed 3 ordered stages of preclinical AD based on the presence of abnormal Aβ, neurodegeneration and subtle cognitive decline. While standard PET techniques are applied to set discrete cut-points to stratify these stages, the rate of change in Aβ and neurodegeneration in preclinical AD is not yet fully understood by experimental means and is currently presented mainly by hypothetical trajectories. Common PET image analysis tools are not optimal for tracking subtle longitudinal changes. Our proposed PET imaging methods are optimized for detecting subtle longitudinal changes. This research is significant for a better understanding of the pathophysiological processes in preclinical AD, a phase that is emerging as a new target for testing therapeutic interventions, which seem to fail at advanced stages of AD. The results of this study could help identify the best subject group for preventive clinical trials or serve as primary outcomes to test the drug response when clinical symptoms are absent. *Methods:* We download FDG-PET imaging data from 27 cognitively normal ADNI (Alzheimer's Disease Neuroimaging Initiative) subjects who had baseline and follow-up FDG-PET scans with at least two years between the baseline and the last follow-up. All ADNI FDG-PET scans were acquired at

participating ADNI cites following the standardized ADNI protocols. ADNI FDG-PET images preprocessed at "level 2" were downloaded. These images were not normalized. We also downloaded the subject's structural MRI volumes acquired at closest time points to each FDG-PET image. These 3D T(1)-weighted volumes were used for defining anatomical regions and were scanned following the standard ADNI protocols. The gray matter fraction of 12 anatomical regions were extracted and used for the ROI analysis. For each subject, the T1-weighted MRI volume was used to define ROI of 12 regions [left and right frontal lobes, anterior and posterior cingulate cortices, occipital lobe, left and right parietal lobes, left and right temporal lobes, sub lobar region (corpus callosum, caudate, putamen, globus pallidus, thalamus), midbrain, and pons]. Each brain volume was also segmented into cerebral spinal fluid (CSF), gray matter (GM), and white matter (WM) with Fuzzy C-means and a gray matter mask was created for each of the 12 anatomical regions. The longitudinal FDG-PET images were coregistered with the subject's T1weighted MRI volume using SPM8 (Wellcome Department of Cognitive Neurology, London, UK). The mean intensity of each region on the PET image was calculated as a vector of length 12, which we refer to as FDG vector. For each subject, the Spearman's rank correlation between the subject's baseline FDG vector and those from the follow-up scans was calculated and displayed as a function of the time (Fig.1). We used a linear mixed-effects model to see whether a faster rfTC decline of a subject can predict its cognitive decline as measured by ADAS_cog and whether the decline is faster in normal subjects who were also APOE carriers. *Results:* APOE carriers had a significantly faster rFTC decline (p= 0.028) than their age-matched non-carriers (Fig.2). We were not able find similar associations from this cohort using any of the regional SUVR mean values (posterior cingulate, parietal, temporal, frontal, mid brain). We also found that the rFTC declined significantly faster (p= 0.0089) in normal subjects who also had minor decline in their ADAS_cog. *Conclusion:* This is the first FDG-PET image analysis that is based on static scans (short scan time and no arterial input function) that can capture longitudinal changes without reference region normalization. Applied on cognitively normal ADNI subjects we found that faster rFCT decline could be linked to both subtle cognitive decline and the presence of APOE e4 allele in a relatively small cohort.

Figure 1

rFTC trajectory from 27 cognitively normal subjects. Blue line indicate subjects with stable rFTC and red lines indicate subjects with decline

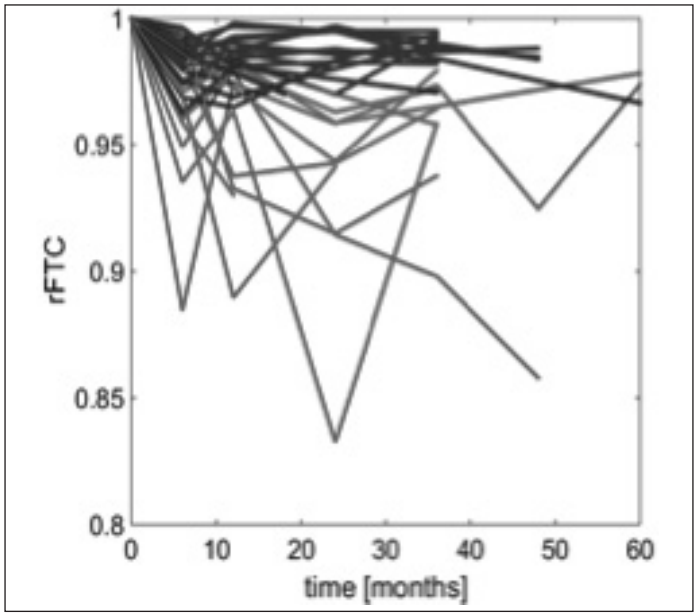
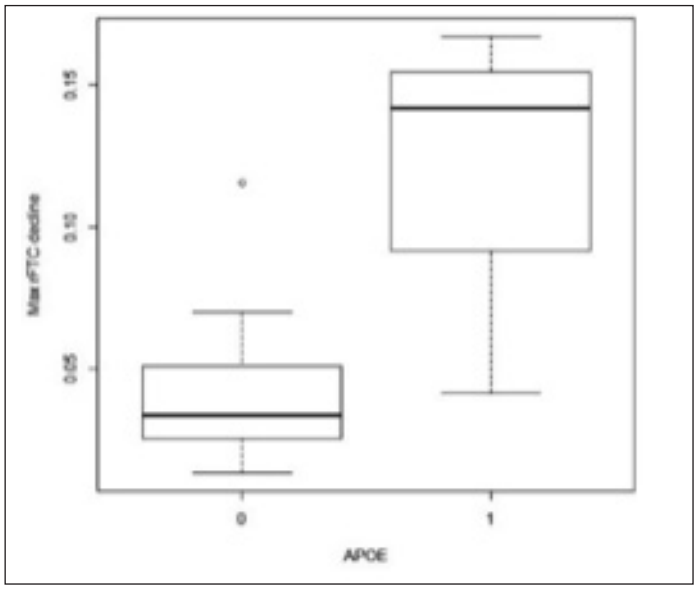


Figure 2

Box plot of the rFTC decline in APOE carriers (right) and non-carriers (left)



P2-24: TEST-RETEST REPRODUCIBILITY OF CSF BIOMARKER MEASUREMENTS IN ADNI. WEINING ROBIESON[1], DELI WANG[1], YUNZHI[1] LIN, DAVIS RYMAN[1], NUNO MENDONCA[2], LAURA GAULT[1] *((1) AbbVie Inc., North Chicago, Illinois, USA; (2) AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany)*

Background: With the recent incorporation of cerebrospinal fluid (CSF) biomarkers into updated research diagnostic criteria for Alzheimer's disease (AD), a detailed understanding of the sources and extent of CSF assay variability is becoming increasingly important. The Alzheimer's Disease Neuroimaging Initiative (ADNI) has greatly contributed to the standardization of CSF assays in AD, and the ADNI Biomarker Core has accumulated a substantial body of data from test-retest analyses. To assess the current state of data on AD CSF assay performance characteristics, we analyzed the reproducibility of ADNI-derived CSF measures of Aβ1-42, T-tau (total tau) and P-tau181 (tau phosphorylated at threonine 181) from over 2000 CSF samples collected between 2005 and 2014. We present the results of statistical analyses of correlation, concordance, and variation in ADNI CSF assay data, and provide a comparison to prior studies of between-laboratory and within-laboratory variability. *Methods:* CSF samples were collected by lumbar puncture from ADNI participants on an annual basis. All samples were collected in the morning before breakfast and after an overnight fast, and were shipped overnight to the University of Pennsylvania AD Biomarker Fluid Bank Laboratory. Aβ1-42, T-tau and P-tau181 were measured using the multiplex xMAP Luminex platform with INNO-BIA AlzBio3 immunoassay kit-based reagents, as previously described (Shaw 2009). The CSF samples were assayed in 7 analytical runs between 2009 and 2014. Around 44% of samples tested for Aβ1-42 and T-tau had values from at least 2 analytical runs. This percentage is around 33% for P-tau181. Pearson correlation coefficients and concordance correlation coefficients (CCC) were calculated for each pair of analytical runs for Aβ1-42, T-tau and P-tau181. CCC is a measurement of the agreement in value between analytical runs (Lin, 1989, 2000; McBride 2005). Coefficient of variation (CV) was calculated as (standard deviation / mean) x 100% after combining all analytical runs for each biomarker. *Results:* Correlation coefficients for CSF Aβ1-42 ranged from 0.887 to 0.961 for the pairs of analytical run combinations, with 11 pairs out of total 13 (84.6%) having values 0.9 or higher. The CCC for Aβ1-42 ranged

from 0.886 to 0.960, with 9 pairs out of 13 (69.2%) having values 0.9 or higher. For CSF T-tau, correlation coefficients ranged from 0.829 to 0.994, and CCC ranged from 0.824 to 0.987. Both correlation coefficient and CCC for T-tau had 12 pairs out of 13 (92.3%) having values 0.9 or higher. Correlation coefficients for CSF P-tau181 ranged from 0.695 to 0.995, with only 4 pairs out of 9 (44.4%) having values 0.9 or higher while 3 pairs (33.3%) had values 0.8 or lower. The CCC for P-tau181 ranged from 0.611 to 0.983, with only 3 pairs (33.3%) having values 0.9 or higher while 3 pairs (33.3%) had values 0.8 or lower. The CV for Aβ1-42 ranged from 0.02% to 48.68% with a median of 5.72%. Approximately 95% of Aβ1-42 samples had CV less than 15%. The CV for T-tau ranged from 0.01% to 61.14% with a median of 7.38%. Approximately 90% of T-tau samples had CV less than 15%. The CV for P-tau181 ranged from 0.15% to 84.64% with a median of 11.14%. Approximately 65% of P-tau181 samples had CV less than 15%. *Conclusion:* In summary, reproducibility of Aβ1-42 and T-tau measurements was superior to P-tau181, with the measurements of Aβ1-42 demonstrating the best reproducibility among the three. Correlations and CCCs between pairs of analytical runs for CSF Aβ1-42 and T-tau were generally in the range of 0.9 or higher. Correlations and CCCs between pairs of P-tau181 analytical runs were lower, with some values in the range of 0.6. In a previous analysis of CSF xMAP assay variability by the Alzheimer's Association quality control program (Mattson 2013), mean CV was 28% (range 17%–38%) for Aβ1-42, 20% (range 13%–28%) for T-tau, and 21% (range 11%–30%) for P-tau181. This analysis also found that CVs between laboratories were two to three times higher than within-run CVs and longitudinal within-laboratory CVs. The relatively high within-lab precision observed in the ADNI dataset (particularly for Aβ1-42 and T-tau) further supports the analytical methods used in ADNI, and indicates that overall variability in CSF biomarker results in multicenter trials can be substantially reduced by use of an experienced central laboratory.

P2-25: CLINICAL DIAGNOSIS AND THE CONGRUENCE OF BIOMARKER CONSTELLATION IN AD. HERMANN-JOSEF GERTZ[1], DAVID WEISE[1,2], CAROLIN AWISSUS[1], SOLVEIG TIEPOLT[3], HENRYK BARTHEL[3], OSAMA SABRI[3], KARL-TITUS HOFFMANN[4], DONALD LOBSIEN[4], THORSTEN KAISER[5] *((1) Department of Psychiatry, University of Leipzig,Leipzig, Germany; (2) Department of Neurology, University of Leipzig, Leipzig, Germany; (3) Department of Nuclear Medicine, University of Leipzig,Leipzig, Germany; (4) Department of Neuroradiology, University of Leipzig,Leipzig, Germany; (5) Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, University of Leipzig, Leipzig, Germany)*

Background: The diagnosis of Alzheimer's disease (AD) can be made with reasonable accuracy using neuropsychological assessment and MRI. CSF and PET biomarkers have been incorporated in IWG-2 diagnostic criteria for AD (Dubois et al. 2014). In clinical practice the biomarker results are thought to confirm or exclude the diagnosis of AD. *Methods:* In a cross-sectional observational study 54 patients with mild cognitive impairment or dementia due to AD or not due to AD were investigated. Biomarkers of neuronal injury were medial temporal lobe atrophy (MTA) on magnetic resonance imaging (MRI) and tau concentration in the cerebrospinal fluid (CSF). CSF Aβ 1-42 and amyloid-targeting positron emission tomography (PET) were considered as biomarkers of amyloid pathology. *Results:* Fifty-four patients (mean age ± SD, 72.1 ± 7.8 y, range 52–90 y, 23 women) were included. The clinical diagnosis was MCI or dementia due to AD in 40 patients (74.1%) and MCI or dementia due to other diseases (e.g. vascular pathology or fronto-temporal degeneration) or unclear causes in 14 patients (25.9%). Clinical diagnosis of AD was conclusive by completely consistent pathological biomarkers in 13 cases (32.5%). In additional 18 subjects (45.0%) clinical diagnosis of AD was supported by biomarker results with at least one pathological degeneration and one pathological Aβ marker. Seven subjects (17.5%) had at least one pathological degeneration (n=3) or one pathological Aβ marker (n=4). In two patients (5%) clinical diagnosis of AD was switched to non-AD due to completely consistent non-pathological biomarker findings. No differences between groups were found regarding age ($\chi2(2) = 2.994$, $p = 0.393$) and MMSE ($\chi2(2) = 6.532$, $p = 0.080$). After dichotomous categorization of biomarker constellation (neuronal injury vs. amyloid dysfunction) in patients with clinical diagnosis of AD congruence of biomarkers for neuronal injury was 67.5 % (Table 3A). Kappa statistics revealed a fair agreement (k=0.249, CI -0.057 - 0.561). Biomarkers of amyloid dysfunction were also consistent in 67.5% . Again, kappa statistics revealed a fair agreement (k=0.212, CI -0.106 - 0.530). Pathological CSF tau values were found in three out of eight cases with pathological CSF Aβ1-42 but negative amyloid PET and in five out of five cases with positive amyloid PET but normal CSF Aβ1-42. In 30 AD cases (75%) pathological Aβ 1-42 together with pathological tau in CSF and/or increased tracer retention on amyloid PET appeared, fulfilling the IWG-2 criteria for AD. *Conclusions:* The design of this study does not allow to address the question of diagnostic accuracy since no gold standard in terms of neuropathological verification is available. Because of the impact of the biomarkers for the diagnosis, its congruence needs special attention. In our series the percentage of inconsistent findings was very high at 62.5%. Similar figures were found by Visser et al 2012 who reported that in a series of MCI subjects 60% had conflicting results for CSF Aβ 1-42, CSF tau and hippocampal atrophy. In another study comparing CSF Aβ and amyloid PET incongruence was less frequent (16%), but other CSF or MRI biomarkers were not considered.8 Comparing CSF Aß and amyloid targeted PET, Zwan et al 2014 found 35% incongruent cases. It remains still irritating to find cases where two degeneration and two amyloid markers were assessed but contradictory in terms. A non-pathological Aß marker naturally questions a pathological Aß marker irrespective of methodological–technical problems or pathogenetic variants. The same holds true for the neurodegeneration markers. The recent approach by Mattson et al 2014 to regard CSF Aß and Amyloid PET as independent informations is based exclusively on correlational statistic and is not helpful and probably not applicable in clinical practise on a single case level. *References:* Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, et al. Advancing re-search diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 2014;13: 614–29. Mattsson N, Insel PS, Donohue M, Landau S, Jagust WJ, Shaw LM, et al. Independent informa-tion from cerebrospinal fluid amyloid-β and florbetapir imaging in Alzheimer's disease. Brain : a journal of neurology 2014. Visser PJ, Wolf H, Frisoni G, Gertz H. Disclosure of Alzheimer's disease biomarker status in subjects with mild cognitive impairment. Biomark Med 2012;6: 365–8. Zwan M, van Harten A, Ossenkoppele R, Bouwman F, Teunissen C, Adriaanse S, et al. Concordance Between Cerebrospinal Fluid Biomarkers and [11C]PIB PET in a Memory Clinic Co-hort. J. Alzheimers Dis. 2014.

P2-26: A FRAGMENT OF BREVICAN AS A NOVEL BLOOD BIOMARKER OF ALZHEIMER'S DISEASE. DILEK INEKCI[1], DITTE JONESCO[1], OLE J VILHOLM[2], MORTEN KARSDAL[1], KIM HENRIKSEN[1] *((1) Biomarkers and Research, Nordic Bioscience, Herlev, Denmark; (2) Department of Neurology, Lillebaelt Hospital, Vejle, Denmark)*

Background: Alzheimer's disease (AD) is the most common cause of dementia. Biomarkers of AD to facilitate early diagnosis, but also to support the search for new treatments of AD are an urgent need. Serological biomarkers have emerged as a promising approach as these would provide a non-invasive and affordable

method of diagnosis. Brevican is an important component of specialized extracellular matrix structures involved in the stabilization of synapses, regulating outgrowth of neurites and maintaining neuroplasticity. Brevican has been detected in amyloid plaques and neurofibrillary tangles in postmortem AD brains and the protein has been suggested to increase the formation of Aβ. The objective of this study was to investigate whether a fragment of brevican (frag-brevican) could serve as serological biomarker of AD diagnosis. *Methods:* A highly sensitive ELISA specifically detecting frag-brevican was developed. The specificity and reactivity of the assay were characterized in human serum and the technical performance of the assay was evaluated. To assess that frag-brevican reflects a neurological process, a tissue profile of brevican was made using different rat tissue extracts. Well-characterized serum samples from patients with AD and mild cognitive impairment (MCI) (n=36), other dementias (n=42) and controls (n=51) were used to investigate the clinical potential of frag-brevican. *Results:* The ELISA assay specifically detected frag-brevican and was technically robust. The tissue profile showed that brevican was exclusively expressed in the brain with the strongest presence in the hippocampus and frontal cortex. This is an important finding, since hippocampus is involved in the early changes of AD. Brevican was present as large bands >150 kDa and as a band around 52 kDa. The latter correlates with an ADAMTS4 cleavage product of brevican, while the large bands reflect its glycosylated forms. The serum levels of frag-brevican were significantly elevated in AD/MCI patients when compared to other dementias (p=0.0003) and controls (p=0.043). *Conclusions:* Targeting brevican as a biomarker for AD is a novel approach. This study provides evidence for the pathological relevance of frag-brevican in AD and its potential as biomarker in serum for the diagnosis of AD as well as for differentiation of AD from other common dementias.

P2-27: ABETA LEVELS IN THE JAGULAR VEIN AND ABETA OLIGOMER LEVELS IN CSF CAN BE CHANGED AFTER THE TREATMENT OF IVIG FOR AD. TAKASHI KASAI[1], MASAKI KONDO[1], RYOTAROU ISHII[1], TOSHIKI MIZUNO[1], TAKAHIKO TOKUDA[2] *((1) Department of Neurology, Kyoto Prefectural University of Medicine, Kyoto, Japan; (2) Department of Molecular Pathobiology of Brain Diseases, Kyoto Prefectural University of Medicine, Kyoto, Japan)*

Intravenous immunoglobulin (IVIg) has been a promising candidate as a potential anti-amyloid passive immunotherapy for Alzheimer disease (AD) because it contains anti-amyloid β (Aβ) antibodies. Although several studies with IVIg in mild to moderate AD have been published, changing levels of 'peripheral sink' Aβ, or solubilization of aggregated Aβ species induced by immunotherapy, have not been properly investigated. Here, we carried out an open label study of add on therapy with IVIg in five relatively young patients with AD. We collected plasma samples from a peripheral vein (peripheral-plasma) and from the internal jugular vein (jugular-plasma) to estimate directly the levels of peripheral sink Aβ. We also measured high molecular weight (HMW) Aβ oligomers in CSF as a marker to detect disaggregated Aβ species. IVIg infusions were well tolerated in the majority of cases. However, one case had epileptic seizures after IVIg. Levels of HMW CSF Aβ oligomers in all participants were significantly increased after IVIg. Aβ40 and Aβ42 levels in jugular-plasma were continuously or temporarily elevated after treatment in three of five patients who also showed preserved cognitive function, whereas levels of these markers in peripheral-plasma did not correlate with reactivity to the treatment. Other conventional biomarkers including 11C-Pittsburgh compound B retention were not altered after the treatment. These findings imply that HMW Aβ oligomer levels could be a better biomarker to reflect the anti-amyloid effects of IVIg than conventional Aβ species; moreover, Aβ in jugular-plasma seems to be a more direct and precise biomarker to estimate clearance of Aβ from the brain in clinical trials rather than Aβ in peripheral-plasma.

P2-28: APOLIPOPROTEIN E GENOTYPE IN SUBJECTS WITH SUBJECTIVE MEMORY IMPAIRMENT ASSESSED FOR OBJECTIVE COGNITIVE IMPAIRMENT. GEORG ADLER, BINDER J, YVONNE LEMBACH *(Institut fuer Studien zur Psychischen Gesundheit (ISPG), Mannheim, Germany)*

Background: The apolipoprotein E (ApoE) epsilon4 allele is the largest known genetic risk factor for late-onset sporadic Alzheimer's dementia (AD). Populations for therapeutic or prevention studies usually are stratified by age, sex, cognitive performance and ApoE genotype. In order to provide an estimate of the ApoE genotype distribution for screening purposes, we studied subjects with subjective memory impairment (SMI) who underwent further cognitive assessment. *Methods:* In an ongoing screening project, we determined ApoE genotype in subjects with SMI. They had to have noticed a decline in memory during the last five years and had to be concerned about it. Cognitive performance was assessed by means of a standardized neuropsychological test battery including the ADAS-cog and the computer-assisted Memory and Attention Test (MAT). A two test-1.5 SD criterion was applied for a diagnosis of cognitive impairment. Activities of daily living were assessed by means of a structured interview and the DAD scale. In case of a diagnosis of dementia, further clinical, neuropsychological and neuroradiological examinations were inititated. *Results:* The assessments were carried out in 69 subjects with SMI at ages between 53 and 90 years (mean + SD: 70.4 + 9.1 years). In 36 (52 %) of them no cognitive impairment was found, in 18 (26 %) a mild cognitive impairment (MCI) and in 15 (22 %) a diagnosis of AD was ascertained. An ApoE epsilon4 allele was found in 18 of all subjects (26 %), in 3 (8 %) of the subjects with no cognitive impairment, in 9 (50 %) of the subjects with MCI and in 9 (60 %) of the subjects with AD. ApoE epsilon4 frequency was significantly higher in the subjects with MCI or AD compared to those with no cognitive impairment (Chi-square=17.37; p<0.001). *Conclusion:* The frequency of the ApoE epsilon4 allele in these unselected subjects with SMI, who came for cognitive assessment, is about twice as high as in the general population. In those subjects with SMI, in whom cognitive assessment and further diagnostics revealed MCI or AD, the ApoE epsilon4 allele was found seven times more often compared to the subjects without objective cognitive impairment. About half of the patients with subjective memory impairment, in whom further examination reveals MCI or AD, had an ApoE epsilon 4 allele.

P2-29: A FAST AND COST-EFFECTIVE METHOD FOR APOLIPOPROTEIN E ISOTYPING AS AN ALTERNATIVE TO APOE GENOTYPING FOR PATIENT STRATIFICATION IN CLINICAL TRIALS. MIGUEL CALERO[1], OLGA CALERO[3], ANDRÉS RODRÍGUEZ-MARTÍN[2], LUIS GIL-DE-GÓMEZ[2], SERGI GASSÓ[4], LUIS GARCÍA-ALBERT[5] *((1) Chronic Disease Programme, CIBERNED, and CIEN Foundation-Queen Sofia Foundation, Instituto de Salud Carlos III. Madrid, Spain; (2) Biocross, S.L., Valladolid, Spain; (3) CIBERNED and 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, Instituto de Salud Carlos III. Madrid, Spain)*

Background: Apolipoprotein E (ApoE) is a 34 kDa glycoprotein involved in lipid metabolism. The human APOE gene that encodes this protein is polymorphic and is located on chromosome 19. Three common codominant alleles (ε2, ε3 and ε4) encode three

ApoE protein isoforms (E2, E3 and E4), which differ at amino acid residues 112 and 158. E2 has cysteine residues at both sites, E4 has arginine residues at both sites, and E3, the most common isoform, has a cysteine at position 112 and an arginine at position 158. These differences have profound effects on the biological functions of ApoE. Isoform E4 is associated with an increased risk of developing Alzheimer's disease (AD). APOE genotyping is a source of much research interest can be used for patient stratification and to identify those at increased risk of AD. Several methods are used to distinguish APOE polymorphisms, including PCR-restriction fragment length analysis and TaqMan probes. However, PCR-based techniques require expensive reagents, involve multiple steps, including DNA isolation, and require informed consent for genetic analysis, limiting their use in routine clinical settings. Immunological techniques such as sandwich indirect ELISA are highly sensitive and not subject to the same constraints as genetic analysis. However, this type of ELISA requires three different antibodies, and is relatively expensive, technically demanding and time consuming. We have developed a fast, cost-effective method for ApoE isotyping using specific monoclonal anti-ApoE4 antibodies that can be easily translated to a clinical laboratory setting using immunoturbidimetry assays. This method can be easily implemented and performed using any random-access high-throughput clinical chemistry platform, which are present in most clinical laboratories. *Methods:* ApoE from plasma samples was captured on polystyrene surfaces. The presence/absence of ApoE4 was detected using a monoclonal antibody specific for the E4 isoform. To validate the method, we analysed 230 plasma samples from individuals previously genotyped by real-time PCR (e2/e3, n=16; e2/e4, n=4; e3/e3, n=141; e3/e4, n=59; e4/e4, n=10). *Results:* We determined the optimal conditions for plasma ApoE binding to polystyrene surfaces and specific detection of the ApoE4 isoform. In these conditions, plasma apolipoproteins, including ApoE, bind to polystyrene surfaces via highly resistant interactions. An alternative ELISA assay was developed for the specific detection of the ApoE4 isoform, precluding the need for a capture antibody, thus simplifying the assay and reducing reagent costs. Validation of the assay with 230 plasma samples (74 ApoE4 carriers, 153 non-ApoE4 carriers) revealed 100% concordance with APOE genotyping by real-time PCR. *Conclusions:* We have developed a simple, fast, cost-effective and reliable method for ApoE isotyping in plasma samples. Taken together, these results demonstrate that our ApoE4 agglutination test based on latex-enhanced immunoturbidimetric technology using polystyrene beads can be feasibly and reliably translated to a clinical laboratory setting

P2-30: TECHNICAL PERFORMANCE OF A NOVEL FULLY AUTOMATED ELECTROCHEMILUMINESCENCE IMMUNOASSAY FOR THE QUANTITATION OF AB1–42 IN HUMAN CEREBROSPINAL FLUID (CSF). TOBIAS BITTNER, CHRISTINA RABE, EKATERINA MANUILOVA, PETER HEISS *(Roche Diagnostics GmbH, Penzberg, Germany)*

Background: The Elecsys® β-Amyloid(1–42) assay (Roche Diagnostics) is a fully automated, quantitative immunoassay, based on electrochemiluminescence, for the quantitation of Aβ1–42 in human CSF. It is performed on the cobas e 601 analyzer module, which has an 18-minute turnaround time and throughput of 170 samples/hour. The assay has a measuring range of 200–1700 pg/mL. It is the first assay standardized to an International Federation of Clinical Chemistry-endorsed candidate reference measurement procedure and has excellent lot-to-lot comparability in terms of correlation and absolute value. The assay also demonstrates high precision, with repeatability coefficients of variation (CVs) of 1.0–1.6% and intermediate precision CVs of 1.9–4.0%, and showed the highest precision amongst Aβ1–42 assays included in the Alzheimer's Association Quality Control (AAQC) program (between-lab variability of 2.0–2.9%). We report here results from experiments including interference testing, cross-reactivity, high-dose hook effect and stability of assay reagents and calibrations. *Methods:* All experiments were performed according to applicable guidelines from the Clinical and Laboratory Standards Institute. Potential for interference of endogenous substances and drugs with the Elecsys® β-Amyloid(1–42) assay was tested using human CSF sample pools and artificial CSF (aCSF) spiked with calibrator peptide. Interference was assessed by measuring Aβ1–42 concentrations in CSF samples with and without each substance. Endogenous substances tested were Intralipid® (to test for the effect of lipemia), biotin, bilirubin, hemoglobin, rheumatoid factor, human serum albumin, human IgG, IgM and IgA, and human anti-mouse antibodies. Thirty-one drugs commonly administered in the target patient population were also tested. Cross-reactivity with amyloid peptides Aβ1–38 and Aβ1–40 was tested using CSF samples spiked with varying concentrations (0, 2.5, 5, 10 and 20 ng/mL) of Aβ1–38 and Aβ1–40 before measurement on the Elecsys® β-Amyloid(1–42) assay. Absence of cross-reactivity was established if the change in concentration relative to the spiked concentration was ≤10%. Any possible high-dose hook effect of the assay for Aβ1–42 was investigated using two aCSF dilution series spiked with calibrator peptide up to concentrations of 19,733 pg/mL and 15,424 pg/mL. The stability of reagent calibrations and the impact of storage conditions on the reagents were also investigated. On-board calibration frequency determined the time period that a calibration performed with a single reagent set remains valid, with the reagents left onboard the cobas e 601 module, before re-calibration of this individual reagent set has to be performed. Lot calibration frequency determined the time period that a calibration performed with a single reagent set remains valid for any other reagent set from the same reagent lot. Additional experiments included on-board reagent stability, to determine the time period that a single set of reagents is stable while left on-board the cobas e 601 module, duration of reagent stability at 2–8°C after first opening, and duration of reagent stability under transport conditions (≥25°C). *Results:* No interference was observed with CSF pools up to the highest concentrations of the endogenous substances tested. No interference of drugs was observed for all drugs at the lower drug concentrations tested. At the higher drug concentrations, no interference was noted, except with doxycycline (77.7–81.2% recovery at a drug concentration of 50 mg/L), phenylbutazone (76.7–81.9% recovery at a drug concentration of 400 mg/L) and metformin (77.6–84.3% recovery at a drug concentration of 12 g/L). No significant cross-reactivity was observed with either Aβ1–38 (cross-reactivity was –0.14 to –0.85% with the 500 pg/mL sample and –0.51 to 0.74% with the 1500 pg/mL sample) or Aβ1–40 (cross-reactivity was –0.23 to –0.89% with the 500 pg/mL sample and –0.53 to –1.55% with the 1500 pg/mL sample). No hook effect was observed up to 11,000 pg/mL and beyond, which exceeds the upper end of the measuring range (1700 pg/mL) by more than 6-fold. On-board calibration frequency exceeded 7 days and lot calibration frequency exceeded 4 weeks. On-board reagent stability was longer than 4 weeks, while reagent stability after first opening was more than 8 weeks at 2–8°C. Transport stability exceeded 1 week at 25°C. *Conclusions:* Here we describe technical performance aspects of a novel electrochemiluminescence immunoassay for the quantitation of Aβ1–42 in human CSF. No interference of the 10 endogenous substances investigated was observed, and of 31 drugs tested, only doxycycline, phenylbutazone and metformin exhibited any interference with the assay, and only at concentrations 4-, 6- and 80-fold higher than expected therapeutic CSF levels, respectively. Our results demonstrate that the Elecsys® β-Amyloid(1–42) assay has no cross-reactivity for Aβ1–38 or Aβ1–40, no high-dose hook effect, and assay calibrations and reagents that are stable over time under a wide variety of conditions. These results indicate that this novel assay provides all prerequisites for

the establishment of global cut-offs that are valid over time and demonstrates features supportive of potential routine clinical use.

P2-31: RETINAL ASSESSMENT WITH OPTICAL COHERENCE TOMOGRAPHY IN ALZHEIMER DISEASE AND MILD COGNITIVE IMPAIRMENT. D SÁNCHEZ-RUÍZ[1], M CASTILLA[1], O RODRIGUEZ-GOMEZ[1], J SERRA[1], A CIUDIN[12], O SIMÓ-SERVAT[2], C HERNÁNDEZ[2], A MAULEÓN[1], M ROSENDE-ROCA[1], L VARGAS[1], C ABDELNOUR[1], G ORTEGA[1], A ESPINOSA[1], I HERNÁNDEZ[1], M ALEGRET[1], R SIMÓ[2], A RUIZ[1], L TÁRRAGA[1], M BOADA[1] *((1) Alzheimer Research Center and Memory Clinic, Fundació ACE, Institut Català de Neurociències Aplicades, Barcelona, Spain; (2) Diabetes and Metabolism Department. Vall d´Hebron Research Institute, VHIR, Barcelona, Spain)*

Background: Visual symptoms in Alzheimer´s disease (AD) are frequent and well known. Classically these symptoms have been attributed to degenerative impairment of brain areas associated with visual processing. However, retinal ganglion cells loss and optic nerve degeneration have been described in pathological series of patients with AD. From an embryological point of view the retina is part of the central nervous system. Moreover, retinal abnormalities have been reported in several brain diseases. Optical coherence tomography (OCT) is a relatively novel technology based on low-coherence interferometry principle. OCT allows study in great detail the optic nerve and retinal layers providing an automated quantification of their thickness. OCT is quick and easy to implement, completely innocuous and inexpensive. Previous studies using OCT have found retinal thinning in patients with AD, mainly in the retinal nerve fiber layer (RNFL) but also in the ganglion cell layer. Studies that assessed retinal thickness in patients with mild cognitive impairment (MCI) found intermediate values between healthy controls and AD. Our objective was to ascertain whether RNFL thickness, as measured with OCT, is correlated with different degrees of cognitive impairment. *Methods:* All patients evaluated in our memory clinic between September 2014 and March 2015 were invited to participate in this ophthalmologic research study. Inclusion criterion was: clinical diagnosis of AD (NINCDS-ADRDA), MCI (Petersen criteria) or no cognitive impairment (NC). Exclusion criteria were: other diagnosis different from AD, MCI or NC; low quality OCT measures; ocular abnormalities potentially compromising retinal structures such as ocular trauma, retinal surgery or pathological amblyopia, retinal diseases as epiretinal membrane or macular edema and history of optic neuropathy, including glaucoma; inability to undergo OCT due to ophthalmologic or behavioral causes. The ophthalmologic evaluation included anamnesis, visual acuity and intraocular pressure measures. OCT was performed using 3D_H Disc protocol of the OCT 3D Topcon Maestro© machine. All patients underwent a neurological assessment including anamnesis, physical and neurological exploration. All patients underwent a comprehensive neuropsychological assessment with Fundació ACE Neuropsychological Battery (NBACE). Thickness of circunpapillary RNFL divisions (quadrants and dodecants) for each group was compared. T-test comparisons were executed for non-adjusted comparisons. Logistic regression was performed for adjusted analyses including age and gender as covariates. Right and left eyes were analyzed separately. All statistical analyses were performed using the Statistical Package for the Social Sciences (version 20.0; SPSS, Inc., Chicago, IL, USA). *Results:* 290 subjects were included in this analysis (119 CN, 112 MCI and 59 AD). The mean age was significantly different between groups (HC: 62.1 years, MCI: 70.2 years and AD:79.9 years. p<0.001). The biggest differences of RNFL thickness between groups were found in superior and inferior quadrants of both eyes. RNFL mean thickness of right superior quadrant: CN: 113.7μ, MCI: 112.1μ, AD: 101.6μ (p<0.0005). RNFL mean thickness of left superior quadrant: CN:108.7 μ , MCI:106.7 μ, AD: 97.5μ (p<0.0005). RNFL mean thickness of right inferior quadrant: CN: 120.1 μ , MCI:114.4μ , AD: 106.9μ (p<0.0005). RNFL mean thickness of left inferior quadrant: CN: 120.7 μ, MCI:113.6 μ, AD: 107.8μ (p<0.0005). However statistically significance disappeared for all quadrants after age adjustment and correction for multiple comparisons. *Conclusions:* Data suggest a tendency to RNFL thinning in AD patients. Nevertheless, age revealed to be the main factor related with RNFL thinning in our series, and might be masking genuine effects of cognitive phenotypes in retinal thickness. Age-matched studies can help to elucidate the potential of OCT techniques for AD and MCI assessment and its capability to discriminate between disease and normal age related retinal changes.

P2-32: ACCURATE MEASUREMENT OF TAU IN SERUM AND PLASMA USING A NOVEL TECHNOLOGY WITH FG/ML SENSITIVITY. GALINA N NIKOLENKO, ROBERT UMEK, LAUKIK SARDESAI, ANU MATHEW, JOHN H KENTEN, ELI N. GLEZER, JACOB N WOHLSTADTER *(Meso Scale Discovery (MSD), Rockville, MD, USA)*

Background: Tau has emerged as a putative therapeutic target for many neurodegenerative disorders. This protein is a major component of paired helical filaments and other large intracellular aggregates in the brains of patients with Alzheimer's disease (AD) and other neurological disorders. Clinical diagnosis of AD most often occurs several years after neurodegeneration commences. The accumulation of Tau protein in the cerebrospinal fluid (CSF) of AD patients correlates with neurodegeneration, and may also be a useful biomarker for identifying patients with mild cognitive impairment (MCI). However, collection of CSF is invasive, painful, and inconvenient for use in routine screening for early detection of the disease. Use of peripheral samples such as blood and urine is greatly preferred, but levels of Tau in blood are largely undetectable with currently available technologies. Therefore, more sensitive detection methods are required to evaluate Tau as a biomarker for AD in blood. *Methods:* MSD® offers a human total Tau assay kit that has been validated for the detection of Tau protein in CSF. The MSD V-PLEX® Tau assay offers sensitivities competitive with other commercially available assays (LLOQ of 30 pg/mL). However, higher sensitivity is needed for the detection of Tau in serum or plasma. We developed a next-generation assay format, S-PLEX™ , using MSD's MULTI-ARRAY® electrochemiluminescence technology. The S-PLEX technology allows quantitation of previously unmeasurable levels of biomarkers with fg/mL sensitivity and a wide dynamic range. S-PLEX assays are compatible with existing MSD instrumentation. An S-PLEX assay was developed for Tau and used to measure Tau levels in serum/plasma samples from both normal and diseased individuals. Recombinant forms of known Tau isoforms were also tested. *Results:* The newly developed MSD S-PLEX Tau assay has a limit of detection (LOD) of 6 fg/mL, with lower and upper limits of quantitation of 21 fg/mL (LLOQ) and 160,000 fg/mL (ULOQ), respectively, covering a dynamic range of approximately 3 logs. The S-PLEX Tau assay detects all six isoforms of the protein tested. Spike recovery and dilutional linearity were between 80% and 120% for both serum and plasma samples. Levels of Tau in normal serum (n=16), normal plasma (n=16), and plasma from AD patients (n=13) were detectible in all samples, and median concentrations observed were 1.7 pg/mL (interquartile range [IQR] 1.1-2.5 pg/mL), 2.6 pg/mL (IQR 1.7-4.1 pg/mL), and 3.6 pg/mL (IQR 0.4-4.7 pg/mL), respectively. Elevated levels of Tau (n= 8, median concentration 13 pg/mL) were observed in plasma samples from patients with traumatic brain injury (TBI). Levels of Tau in all normal and diseased CSF samples were easily measureable using fifty-fold diluted samples. *Conclusion:* MSD has

developed a next-generation Tau assay that is up to 1,000x more sensitive than currently available Tau assays. This enables accurate determination of Tau concentrations in sample types, such as blood, where levels were previously unmeasurable. Only minimal amounts of CSF samples are required to measure levels of Tau, and the assay was able to recognize all isoforms of Tau tested. Importantly, Tau was measurable in all serum and plasma samples tested; from normal individuals, patients with AD, and individuals who suffered traumatic brain injuries. The MSD S-PLEX Tau assay makes it possible to reliably measure Tau protein at the low concentrations present in blood, and to evaluate its potential as a biomarker in AD and other neurological disorders.

P2-33: PREDICTORS OF AMYLOID POSITIVITY IN A STUDY SAMPLE WITH AMNESTIC MILD COGNITIVE IMPAIRMENT. YUKI MUKAI[1], YI MO[1], CYRILLE SUR[1], TIFFINI VOSS[1], YING ZHANG[1], JAMES KOST[1], GREGORY KLEIN[2], MEHUL SAMPAT[2], DAVIS STAEWON[2], DERK PURCELL[2,3,4], JEROME BARAKOS[2,3], JOYCE SUHY[2], DAVID MICHELSON[1], MICHAEL EGAN[1] *((1) Merck & Co., Inc., Kenilworth, NJ, USA; (2) BioClinica, Newark, CA, USA; (3) California Pacific Medical Center, San Francisco, CA, USA; (4) University of California San Francisco, San Francisco, CA, USA)*

Background: Subjects with amnestic mild cognitive impairment (aMCI) and increased brain beta amyloid have faster cognitive decline and higher risk of conversion to dementia compared to aMCI subjects without amyloid. Identifying amyloid positive individuals is important for prognosis and for trials of anti amyloid interventions in prodromal AD. The Phase III APECS trial in aMCI subjects is being conducted with MK8931, a potent inhibitor of beta secretase (BACE).We used screening data from this trial to evaluate clinical predictors of amyloid positivity. Identifying aMCI subjects with high likelihood of having brain amyloid using such variables may reduce the number of negative PET scans. *Methods:* A total of 549 individuals with aMCI underwent PET-imaging with a ligand to detect amyloid deposition; SUVRs were available for all subjects, while visual reads were available for 366 for these analyses. All subjects met inclusion criteria for aMCI, which included memory testing using Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Delayed Memory Index (DMI). Logistic regression was used to determine whether age, gender, education level, functional level, and cognitive measures predicted amyloid deposition by visual read. Alzheimer's Disease Cooperative Study –Activities of Daily Living (ADCS-ADL) was used to assess functional level. Cognitive measures included Alzheimer's Disease Assessment Scale-Cognitive subscale 13 item (ADAS-Cog13), Mini Mental Status Exam (MMSE), RBANS domains of Attention Index (AI), DMI, Immediate Memory Index (IMI), Language Index (LI), and Visuospatial/Constructional Index (VCI). In addition, 2x2 tables for the categorical variables of sex, geographic region, educational level (undergraduate degree) were examined. ApoE genotype was not available for these analyses. Finally, standardized uptake value ratio was generated using the pons as the reference region (SUVr pons) and was compared with analysis by visual read. *Results:* A total of 366 individuals with aMCI underwent PET-imaging and 258 (70.5%) were determined to be positive for amyloid deposition by PET visual read. Using univariate logistic regressions, five variables were significant in predicting PET positivity: RBANS DMI ($p<0.001$), RBANS IMI ($p<0.001$), ADAS-Cog13 ($p=0.028$), MMSE ($p=0.005$), and gender ($p=0.020$). In a multivariate model using logistic regression with these five variables, only RBANS DMI remained significant ($p<0.001$). The model had a 70.8% concordance between the predicted value and the observed value. 384 individuals out of 549 individuals with SUVr pons results met the threshold for amyloid positivity of > 0.62 (69.9%). There was 95.6% concordance between SUVr pons when compared to visual read. For individuals with positive visual read, the geometric mean SUVr pons was 0.80 while for individuals with negative visual read, the geometric mean SUVr pons was 0.52. *Conclusions:* Severity of episodic memory impairment, as assessed with the RBANS DMI, was the best predictor of amyloid positivity by PET using multivariate logistic regression model. When comparing SUVr pons to visual read, there was 95.6% concordance In a 5-variable logistic regression model using RBANS DMI, RBANS IMI, ADAS-Cog13, MMSE and gender, there was 70.8% concordance between the predicted value and the observed value. Although robust, the model may not be suitable for clinical use. Adding other variables, such as ApoE genotype, may improve model performance.

P2-34: USE OF STABLE ISOTOPE LABELING AMINO ACID IN-VIVO (SILAV) TO MONITOR CSF PROTEIN METABOLISM IN ALZHEIMER'S DISEASE PATIENTS. S LEHMANN[1], G GRAS COMBE[2], J VIALARET[1], L BAUCHET[2], ML TALL[3], O HANON[4], A GABELLE[1,5], C HIRTZ[1] *((1) CHRU de Montpellier and Université de Montpellier, IRMB, Laboratoire de Biochimie Protéomique Clinique, Montpellier, France; (2) Service de Neurochirurgie, CHRU de Montpellier, hôpital Gui de Chauliac, Montpellier, and Université de Montpellier ; Montpellier, France ; (3) Pharmacie, Groupement Hospitalier Edouard Herriot, Lyon, France; (4) AP-HP, Hôpital Broca, Service de Gériatrie, Paris, France. Université Paris Descartes, Sorbonne Paris Cité, Paris, France; (5) Centre Mémoire Ressources Recherche Languedoc-Roussillon, CHRU de Montpellier, hôpital Gui de Chauliac, Montpellier, and Université de Montpellier ; Montpellier, France)*

Background: It has been shown that disease states can be characterized by disturbances in protein production, accumulation, or clearance. In the CNS, alterations in the metabolism of proteins such as the amyloid precursor protein, alpha-synuclein, or tau are linked to the pathological events of neurodegenerative diseases such as Alzheimer's (AD) or Parkinson disease. Based on the seminal work of Bateman (Nat Med 12: 856-861), we set up a large scale proteomics exploration of human cerebrospinal fluid (CSF). Our SILAV approach is based on the administration of a stable isotope labeled amino acid (13C6-leucine) in patients, CSF kinetics sampling and tandem mass spectrometry analysis. It allows the quantification of the rates of synthesis and clearance of a large range of proteins. It has been implement with external ventricular CSF derivation, and with lumbar subarachnoid catheter in patients with neurological disorder and in particular AD. *Methods:* In vivo labeling was performed following the protocol of Bateman et al. by the IV perfusion of clinical grade solution of 13C6-leucine. CSF was collected kinetically every 1 to 3 hours for up to 38 h. After denaturation, trypsin digestion, fractionation of the peptides using Strong Cation eXchange chromatography (SCX) CSF samples were analysed by mass spectrometry using Nano-RSLC (Dionex) coupled to Q-TOF Impact II (Bruker Daltonics). Labeled leucine incorporation in the peptides was monitored using a skyline software homemade routine. *Results:* Our mass spectrometry workflow allowed us to identify in 40uL of CSF more than 4500 peptides containing leucine and corresponding to 1064 proteins. Monitor labeled leucine incorporation in these peptides allowed us to obtain the pattern of synthesis, degradation of more than 100 proteins in the CSF. Different groups of proteins with rapid or low synthesis/clearance rates could be identified and linked to metabolic pathways and/or neuropathological processes. Among the proteins of interest were monitored for example: APP, clusterin (ApoJ), YKL-40 (Chitinase-3-like protein 1), Pigment epithelium-derived factor (PEDF), ApoE, Chromogranin-A or Calsyntenin-1. *Conclusions:* The Stable Isotope Labeling Amino Acid in-Vivo (SILAV) approach coupled to a large scale proteomics analysis is a new method to progress toward the understanding of pathological

events in neurological disease and to exploit differences in synthesis/clearance rate as new biomarkers.

P2-35: HEADING FOR SUPERIOR ANALYTICAL PERFORMANCE: FROM INNOTEST TO THE FULLY AUTOMATED CHEMILUMINESCENT β-AMYLOID(1-42) AND TOTAL TAU ASSAYS ON THE LUMIPULSE® G INSTRUMENT SERIES. ANNELIES VANDERSTEEN, SANDRA PERESON, FILIP DEKEYSER, TINNE DUMONT, KATRIEN DE VUYST, WIM VANDEZANDE, KATHLEEN GORTEMAN, PAUL VANDEPONSEELE, PIETER VAN HECKE, MARTINE DAUWE, GEERT JANNES *(Fujirebio Europe N.V., Technologiepark 6, 9052 Gent, Belgium)*

Background: β-amyloid(1-42) peptide (Aβ1-42) and total tau protein in cerebrospinal fluid (CSF) are well-established biomarkers supporting Alzheimer's disease diagnosis. Today there is a growing need for in vitro diagnostic (IVD) assays quantifying both biomarkers in a reliable and highly precise manner. The novel Aβ1-42 and total tau assays in development for the LUMIPULSE G instrument series, a fully automated chemiluminescent enzyme immunoassay system, can fulfill these requirements. *Methods:* The LUMIPULSE G instrument series uses single, ready-to-use immunoreaction cartridges with a throughput of 60 tests/hour for the G 600 II instrument or 120 tests/hour for the G 1200 instrument. Sequential immunoreaction steps are carried out at pre-determined intervals while the cartridge is transported through the system. Each cartridge generates quantitative results for one biomarker within approximately 25 minutes and cartridges can be easily combined in the system enabling full characterization of a sample during one run. The Aβ1-42 and total tau assays were developed using established monoclonal antibodies. Analytical performance parameters e.g. limit of detection (LoD), limit of quantitation (LoQ), high-dose Hook effect, precision and a method comparison with INNOTEST β-AMYLOID(1-42) and INNOTEST hTAU Ag were performed on LUMIPULSE G 1200 according to established protocols. *Results:* Precision evaluation using CSF samples was shown to be less than 5% for both Aβ1-42 and total tau assays. LoD was determined to be <25 pg/mL for the Aβ1-42 assay and <30 pg/mL for the total tau assay, respectively. LoQ with a coefficient of variation of 10% was calculated to be <30 pg/mL and <50 pg/mL for the Aβ1-42 and total tau assays, respectively. No high-dose Hook effect was observed for Aβ1-42 and total tau assays as samples containing up to 200 000 pg/mL of Aβ1-42 calibrator and 100 000 pg/mL of total tau calibrator were determined as no lower than the highest calibrator. Both assays were found to correlate well (r>0.90) with the routinely used INNOTEST β-AMYLOID(1-42) and INNOTEST hTAU Ag assays. *Conclusions:* Automation and good reproducibility are key attributes making the LUMIPULSE G instrument series the ideal platform to fulfill today's needs for rapid quantification of Alzheimer's disease CSF biomarkers. The novel Aβ1-42 and total tau IVD assays under development on LUMIPULSE show good sensitivity and precision and correlate well with the established INNOTEST assays.

P2-36: METABOLIC BIOMARKERS OF COGNITIVE DECLINE IN HEALTHY POSTMENOPAUSAL WOMEN. ROBERTA DIAZ BRINTON[1], JAMAICA R RETTBERG[2], HOWARD N HODIS[3], VICTOR W HENDERSON[4], WENDY J MACK[5] *((1) Pharmacology & Pharmaceutical Sciences, University of Southern California, Los Angeles, CA, USA; (2) 23andMe, Mountain View, CA, USA; (3) Department of Medicine, University of Southern California, Los Angeles, CA, USA; (4) Department of Neurology, Stanford University, Palo Alto, CA, USA; (5) Department of Preventive Medicine, University of Southern California, Los Angeles, CA, USA)*

Background: Detecting at-risk populations is critical for preventing or delaying Alzheimer's disease. A systems biology integration of brain and body metabolism enables peripheral metabolic biomarkers to serve as reporters of brain bioenergetic status. *Methods:* Using clinical metabolic data derived from healthy postmenopausal women in the ELITE trial, we conducted a principal components analysis followed by k-means clustering analysis of nine biomarkers to define metabolic phenotypes. Metabolic clusters were correlated with cognitive performance and analyzed for change over five years. ApoE genotype and cluster membership was correlated with cognitive function. *Results:* Metabolic biomarkers at baseline generated three clusters, representing women with healthy, high blood pressure, and poor metabolic phenotypes. Compared to healthy women, poor metabolic women had lower verbal memory performance at baseline. Hormone therapy provided metabolic benefit to women in high blood pressure and poor metabolic phenotypes. Analysis of ApoE4 impact on cluster membership and cognitive function is ongoing. *Conclusion:* A panel of peripheral biomarkers represents an initial step towards developing an affordable, rapidly deployable, and clinically relevant strategy to detect an at-risk phenotype of sporadic Alzheimer's disease.

P2-37: CHARACTERIZATION OF ALBUMIN OXIDATION STATUS IN ALZHEIMER'S DISEASE PATIENTS. MONTSERRAT COSTA[1], RAQUEL HORRILLO[1], ANA MARIA ORTIZ[1], ALBA PÉREZ[1], POL HERRERO[12,3], NÚRIA CANELA[2,3], MERCÈ BOADA[4], AGUSTÍN RUIZ[4], ISABEL HERNÁNDEZ[4], NATALIA AFONSO[1], MIREIA TORRES[1], SALVADOR GRANCHA[1], JUAN IGNACIO JORQUERA[1] *((1) R&D and Clinical Operations, Bioscience Industrial Group, Grifols S.A., Barcelona, Spain; (2) Centre for Omic Sciences (COS), Universitat Rovira I Virgili (URV) Reus, Spain; (3) Centre Tecnològic en Nutrició I Salut (CTNS), Reus, Spain; (4) Fundació ACE (Barcelona Alzheimer Treatment & Reaseach Center), Barcelona, Spain)*

Background: Oxidative stress is considered a major player in Alzheimer's disease (AD). Oxidative stress has been associated with high levels of oxidative damage in brain and peripheral lymphocytes [1-3]. Albumin is the most abundant protein in human plasma and, interestingly, beyond its well-documented role as plasma expander, albumin is the main transporter and the main antioxidant in the plasma. This albumin antioxidant capacity mainly relies in its Cys34 residue, that has a thiol group (-SH) that can be transformed into more oxidized forms, preventing the oxidation of other entities. In AD, there is currently a new therapeutic approach under study (AMBAR Trial, NCT01561053) which design includes plasma exchange (removal of the patient's plasma that may carry known and unknown pathological factors such as the β-amyloid bound to albumin) and replacement with therapeutic albumin (Albutein®, Grifols). Albutein® has been previously verified to have undetectable levels of β-amyloid and β-amyloid binding capacity [4]. Basic research studies are in progress to describe the oxidation status of albumin from AD patients to hence understand the potential therapeutic role for albumin as antioxidant agent in AD, in addition to its capacity to bind β-amyloid. This study was aimed to characterize the oxidation status of albumin from AD patients in comparison to age-matched healthy donors. *Methods:* Plasma samples from 30 AD patients and 30 age-matched controls (including 10 subjects with normal cognitive status as confirmed by cognition tests [healthy cognitive controls; HCC]) were obtained to evaluate the oxidation status of albumin. Anionic exchange chromatography (Shodex-Asahipak ES-502N DEAE column) coupled to a fluorescent detector was used to separate three albumin fractions according to the oxidation status of the thiol group (-SH) at the Cys34 albumin residue: reduced, reversibly oxidized and irreversibly oxidized forms of albumin. Analysis of post-translational modifications (PTMs) of albumin in both groups of samples (10 AD vs

the 10 age-matched HCC) was performed by ultra-high performance liquid chromatography coupled to high resolution mass spectrometry (UHPLC-[ESI]HRMS) using a quadrupole-Time of Flight (qTOF) mass analyzer. *Results:* The analysis of albumin oxidation status from AD samples showed a higher content of reversibly oxidized form of albumin when compared with the albumin oxidation status of age-matched controls (42% ± 8% vs. 36% ± 4%, respectively; p<0.01; R2 0.216). This increase correlated with a lower content of reduced albumin, with the free thiol group at Cys 34. In the same direction, mass spectrometry results showed an increase in the cysteinylated form of albumin (HSA+Cys), the most predominant modification related to the reversibly oxidized albumin [5], when comparing AD samples versus age-matched HCC (21% ± 6% and 16% ± 2%, respectively; p< 0.05; R2 0.374). *Conclusion:* These results suggest that albumin in AD patients is slightly more oxidized than albumin of healthy subjects. This may open the path to further research on albumin's functionality to understand its potential role in AD as the major plasma antioxidant. 1. Sultana R et al. J Alzheimers Dis 2011;24:77-84. 2. Swomley AM et al. Biochim Biophys Acta. 2014;1842:1248-57. 3. Sultana R and Butterfield DA, J Alzheimers Dis. 2013;33 Suppl 1:S243-51. 4. Costa et al, J Alzheimers Dis 2012;29:159–70. 5. Colombo G et al. Antioxid Redox Signal 2012;17:1515-27.

P2-38: ALZHEIMER'S DISEASE CSF BIOMARKERS PREDICT COGNITIVE DECLINE IN DLB. CARLA ABDELNOUR[1], ELISABET LONDOS[2], MILICA KRAMBERGER[3], INGER VAN STEENOVEN[4], EVELIEN LEMSTRA[4], MERCÈ BOADA[1], DAG AARSLAND[5,6] ON BEHALF OF THE JPND DLB STUDY GROUP *((1) Fundació ACE Barcelona Alzheimer Treatment & Research Center, Barcelona, Spain; (2) Clinical Memory Research Unit, Department of Clinical Sciences, Lund University, Malmö, Sweden; (3) Department of Neurology, University Medical Centre, Ljubljana, Slovenia; (4) Alzheimer Centre, Department of Neurology, VU Medical Centre, Amsterdam, The Netherlands; (5) Department of Neurobiology, Care Sciences and Society, Division of Neurogeriatrics, Karolinska Institute, Stockholm, Sweden; (6) Center for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway)*

Background: Co-morbid Alzheimer's disease (AD) pathology is common in Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB). In PD, low CSF Aβ42 markers predict long-term cognitive decline, but its role in DLB is less known. The aim of this study is to determine if AD CSF biomarkers (Aβ42, t-tau and p-tau) predict cognitive decline in DLB patients. *Materials and methods:* From E-DLB, a large European multicenter study, we analyzed AD CSF biomarkers and serial MMSE (baseline, 1 and 2-year) in 74 DLB patients from four centers. Local assays and cut-off values were used to analyze and dichotomize CSF biomarkers as pathological or normal. We measured the association of repeated MMSE scores with a positive AD CSF profile (defined as pathological Aβ42 + pathological t-tau or p-tau) and with CSF biomarkers individually. In addition to Mann-Whitney and Student's T-test to compare longitudinal decline on MMSE by AD CSF profile, ANCOVA was performed adjusting for age, gender and MMSE at baseline. *Results:* DLB patients did not differ significantly in baseline demographic or clinical characteristics by AD CSF profile. A positive AD CSF profile and pathological values of CSF T-tau were significantly associated with more rapid decline from baseline to 2 year follow-up after adjusting for age, gender and baseline MMSE; whereas there was no statistically significant difference in MMSE at 2 year follow-up by CSF profile groups of Aβ42 and p-tau. *Conclusions:* AD CSF biomarker profile predicts cognitive decline at 2 year follow up in DLB. Of the three CSF markers, pathological CSF levels of T-tau were associated with 2 year MMSE. These results confirm previous findings where a percentage of patients with DLB exhibit amyloid pathology, and this overlap is associated with more rapid cognitive impairment. Future prospective studies should include larger samples, central CSF analyses and longer follow-up.

P2-39: ANALYSIS OF REST PROTEIN EXPRESSION IN ALZHEIMER'S DISEASE UTILIZING MONOCLONAL ANTIBODIES TO THIS BIOMARKER. RICHARD J KASCSAK[1], REGINA B KASCSAK[1], THOMAS WISNIEWSKI[2] *((1) New York State Institute for Basic Research in Developmental Disabilities, Staten Island, NY; (2) New York University School of Medicine, New York, NY)*

Background: The REST (Repressor Element 1 Silencing Transcription Factor) protein protects neurons from oxidative stress and amyloid beta/tau induced toxicity. This protein has been shown to play a role in the degenerative process in Alzheimer's disease (AD), frontal temporal dementia and dementia with Lewy bodies. REST is expressed during embryonic development, subsequently down regulated and re-expressed in the ageing brain. This protein appears to be a critical player in cognitive changes displayed by AD individuals. The IBR Monoclonal Antibody Facility (MAF) has developed a wide array of mAbs for the study, diagnosis and treatment of Alzheimer's disease. In this study, MAF has developed numerous new mAb clones to REST and utilized these antibodies as tools to study REST expression. *Methods:* Hydropathy protein plots were used to design immunogenic peptides to generate mAbs to the REST protein. Peptides synthesized were used to immunize Balb/cJ mice. Peptides were conjugated at the C-terminus with either KLH (immunogen) or ova (screnner). Monoclonal antibodies were developed as previously described (Spinner et al, J.Leukoctye Biol.,2007). Clones were screened for reactivity and specificity by ELISA, Western blot and immunohistochemistry (IHC) as previously described (Aucoutucier,Neurosci. Lett.,1999). Clones were characterized relative to their reactivity in these various assays. *Results:* Numerous hybridoma clones were generated based on ELISA reactivity. Nine clones, based on specificity and reactivity, were chosen for further characterization. Ascites was generated in Balb/cJ mice, purified and used to perform WB and IHC analysis using Alzheimer's and control brain tissue. Clones were sub-characterized according to their ability to perform in these assays. These studies show the diagnostic and possible therapeutic potential for the use of these mAbs. *Conclusions:* It has been suggested that there may be certain mechanisms that protect against beta amyloid/tau induced neuronal toxicity. REST has been proposed to control the balance between neuroprotection and neurodegeneration in Alzheimer's disease. Here we describe new mAbs to REST protein and their potential role in defining progression and possible therapeutic approaches for AD patients.

P2-40: MULTIPLEX CSF PHOSPHO-TAU SITE-SPECIFIC QUANTIFICATION BY MASS SPECTROMETRY TO ENABLE EARLIER DIAGNOSIS AND PHARMACODYNAMICS BIOMARKERS. IAN PIKE[1], CLAIRE RUSSELL[1], VIKRAM MITRA[1], HENRIK ZETTERBERG[2,3], MIKKO HILTUNEN[4], MALCOLM WARD[1] *((1) Proteome Sciences plc, Cobham, UK; (2) University of Gothenburg, Gothenburg, Sweden; (3) UCL, Queen Square, London, UK; (4) University of Eastern Finland, Kuopio, Finland)*

Background: Levels of phospho- and total-tau in cerebrospinal fluid (CSF) are routinely used as an aid in the diagnosis of Alzheimer's disease (AD). In this context a single phosphorylation site at pT181 is used as a surrogate for pathological tau although little is known about the timescale of its phosphorylation or role in pathology. Conversely, the pathological role of several other phosphorylation

sites on tau have been elucidated and C-terminal phosphorylation is proposed to be an early event and lead to fibrogenesis. We propose that comprehensive measurement of all circulating phospho-tau sites by quantitative mass spectrometry may therefore, provide earlier and more relevant diagnostic and pharmacodynamics measures than the phospho-T181/total-tau ratio. Mass spectrometry allows simultaneous measurement of multiple phosphorylation sites as well as total tau levels but suffers from poor sensitivity in complex samples such as CSF. To overcome this we have developed a novel mass spectrometry method using Tandem Mass Tags to mix a four point calibrant of AD brain lysate and six individual CSF samples in a single analysis. Levels of abundant proteins in the brain tissue drive MS ion selection whilst TMT reporter ions allow accurate quantification. We have analysed 3 CSF samples from biochemically diagnosed AD patients and 3 biochemically negative control individuals. *Methods:* A pooled digest of post-mortem human cortex from three individuals with severe tau pathology (Braak Stage V-VI) was labelled to form a standard reference peptide mix. Similarly, CSF samples (600 ul) from three patients with clinically and biomarker-defined AD, and three non-AD controls were digested and labelled with the remaining tags within the TMT 10-plex set. All labelled digests were pooled together to generate the TMTcalibrator analytical sample. The labelled brain tissue samples were mixed with the CSF at a concentration sufficient to ensure the vast majority of MS/MS acquisitions are made on tissue-derived peptides. The sample was fractionated by strong cation exchange chromatography and a small aliquot of each fraction retained for direct analysis. Phosphopeptides were subsequently enriched from the bulk fractions by TiO2 and IMAC. Both the phosphopeptide enriched and un-enriched fractions were analysed by LC-MS/MS (LTQ-Orbitrap Fusion - Thermo Scientific). *Results*: Over 85% coverage of full length (2N4R) tau was detected in the CSF in all 10 TMT reporter ion channels showing the peptides were present in both brain and CSF. In general the signal intensities in the reporter ions representing CSF samples were much lower than the brain digest channels confirming the need for enhanced triggering of MS. The coverage of phospho-tau sites was also high with 47 unique phosphopeptides covering 31 different phosphorylation sites. Quantitatively we observed differential regulation in AD CSF compared to non-AD controls. Of these, 11 phosphopepitdes representing four phosphorylation sites, including pT181 were up-regulated by at least 40%, along with an overall increase in tau levels in the CSF of AD patients relative to controls. There was a notable decrease in CSF levels of two phosphorylation sites in AD cases versus controls. *Conclusion:* We have developed a robust and comprehensive method for the enhanced detection and accurate quantification of phosphorylated tau peptides in CSF. At least six phosphorylation sites display a strong regulation in AD patients relative to controls and one of these is more than twice as elevated compared to the established CSF biomarker pT181 offering the prospect of an earlier diagnostic test. Phosphorylation at S262 was strongly increased in AD CSF and this site is known to promote release of tau from microtubules when phosphorylated. There was also a small but consistent decrease in phosphorylation of S214 which is also reported to block microtubule binding. Interestingly, tau containing pS214 and pS262 is reported to be blocked from aggregation and these may represent soluble, toxic tau species capable of propagating tau pathology within the brain at the earliest stages of disease. The generation of the first comprehensive map of CSF phospho-tau in AD will facilitate further studies on the pathological relevance of CSF markers and support assessment of the chronology of their appearance during the course of the disease. This in turn may enable development of earlier biomarkers. One of the advantages of the TMTcalibrator approach is that we can also look at the CSF levels of other disease-related proteins. We detected over 100 regulated proteins involved in abnormal synaptic function, dysregulation of calcium signalling, oxidative stress and protein aggregation pathways, amongst others. These represent excellent candidates for a pharmacodynamics biomarker panel that can be tailored to specific mechanisms of action.

P2-41: INFLAMMATORY MARKERS IN ALZHEIMER'S DISEASE WITH VARIOUS DEGREES OF DEMENTIA SEVERITY. TATYANA KLYUSHNIK, LYUBOV ANDROSOVA, NATALIA MIKHAYLOVA, SVETLANA ZOZULYA, ALEXANDER DUPIN, SVETLANA GAVRILOVA *(FSGI "The Mental Health Research Centre", Moscow, Russia)*

Background: There is much evidence, suggesting an important role for systemic inflammation in the pathogenesis of Alzheimer's disease and a close connection between systemic and central innate immune systems. The main objective of the study was to investigate the peripheral inflammatory immune responses in various degrees of dementia severity (mild, moderate, severe). *Material and methods:* The activity of human leukocyte elastase (LE), α1-proteinase inhibitor (α1-PI), the level of IL-6 and C-reactive protein (CRP) were determined in plasma of 75 AD patients and 39 healthy controls. Alzheimer's disease was diagnosed according to the ICD-10 and NINCDS-ADRDA criteria. The severity of dementia was determined by using the clinical method, applying Clinical Dementia Rating (CDR) and MMSE scores. The patients were examined at various stages of dementia (19 subjects with mild dementia, 30 subjects with moderate dementia, and 26 patients with p severe dementia). *Results:* The LE activity was significantly lower in the total group of AD patients ($p<0.0001$), but the activity of α1-PI, level of IL-6 and CRP were significantly higher as compared with the controls ($p<0.00001$, $p<0.01$, $p=0.05$, accordingly). Patients with mild AD were only characterized by a significant increase of α1-PI activity. The reduced LE activity and increased activity of α1-PI, level of IL-6 were revealed in moderate dementia. The reduced LE activity and increased activity of α1-PI, level of IL-6 and concentration of CRP, were revealed in severe dementia. LE activity positively correlated with the total score of evaluation of cognitive functions according to the MMSE ($r=0.28$, $p=0.017$). Direct correlation between the disease severity and IL-6 and CRP levels ($r=0.25$, $p=0.036$, $r=0.24$, $p=0.046$, correspondingly) was revealed. *Conclusion:* Thus inflammatory mechanisms are involved in the progression of the disease: α1-PI increased functional activity is only noticed in mild dementia, while in moderate and severe dementias LE reduced activity and increased activity/level of α1-PI, IL-6, and CRP are detected. *Key words*: Alzheimer's disease; dementia severity; inflammatory markers; leukocyte elastase

P2-42: THE ALZHEIMER'S METABOLOME: IDENTIFICATION OF NOVEL MARKERS AND TREATMENT TARGETS. JON B TOLEDO[1], J WILL THOMPSON,[2] LISA ST. JOHN-WILLIAMS[2], GUIDO DALLMANN[4], XIANLIN HAN[3], JESSICA D TENENBAUM[2], THERESE KOAL[4], SIAMAK MAHMOUDIANDEHKORDI[2], ALISON MOTSINGER[2], SUNGEUN KIM[5], VIJITHA SENANAYAKE[6], ANDREW J SAYKIN[5], REBECCA BAILLIE[3], LESLIE M SHAW[1], JOHN Q TROJANOWSKI[1], DAYAN B GOODENOWE[6], MITCHEL A KLING[1], ARTHUR MOSELEY, RIMA KADDURAH-DAOUK[2] FOR THE ALZHEIMER DISEASE NEUROIMAGING INITIATIVE AND THE ALZHEIMER'S DISEASE METABOLOMICS CONSORTIUM *((1) Department of Pathology & Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, USA; (2) Duke University Medical Center, Durham, NC, USA; (3) Sanford-Burnham Medical Research Institute, Orlando, FL, USA; (4) BIOCRATES Life Sciences AG, Innsbruck, Austria; (5) Indiana Alzheimer Disease Center, Indiana University School of Medicine, Indianapolis, IN, USA; (6) Phenomenome Discoveries Inc., Saskatoon, SK, Canada)*

Background: Metabolomics provides powerful tools to measure hundreds to thousands of metabolites to define the trajectory of biochemical changes, perturbations within and across biochemical pathways, and their relationship to clinical and pathologic progression in Alzheimer's disease (AD). Such information can lead to new insights about disease mechanism and development of diagnostic and prognostic biomarker signatures, and identify potential therapeutic targets. Metabotypes (metabolic traits of the patient represented by multiple analytes) can capture net interactions between the genome, environment and gut microbiome, providing information that can help bridge the gap between genotype and phenotype (e.g. disease subtypes, natural history, and response to treatments). *Methods:* We used flow injection analysis mass spectrometry (FIA-MS) to measure acylcarnitines, glycerophospholipids and sphingolipids, and ultra-high pressure liquid chromatography (UPLC) MS to measure amino acids and biogenic amines with the AbsoluteIDQ-p180 assay (Biocrates). 827 baseline serum samples from 807 AD Neuroimaging Initiative 1 (ADNI-1) subjects, including 20 blinded replicates, were analyzed for this study. Internal quality control pools and the ADNI-1 blinded samples were used to evaluate analytical performance of analytes and sample quality. The final dataset consisted of 145 analytes measured in 225 cognitively normal (CN), 390 mild cognitive impairment (MCI) and 189 AD participants. Multivariate, demographic and medication-adjusted analyses were performed to define between-group differences for MCI and AD clinical groups, APOE genotype and cerebrospinal fluid (CSF) AD-like biomarker signatures, including CSF Aβ1-42 levels. *Results:* Metabolites and their ratios revealed changes within the tryptophan metabolic pathway in MCI and AD subjects and several phospholipids were associated with clinical diagnosis, APOE genotype and pathologic CSF Aβ1-42 levels. *Conclusions:* Metabolomics/lipidomics data and its integration with AD CSF biomarkers point to major changes in the tryptophan metabolic pathway and membrane structure and function and facilitate a systems approach to the study of AD, ultimately helping to enable precision medicine for AD treatment and prevention. *Grant support:* NIA R01 grant: 1R01AG046171. PI: Rima Kaddurah-Daouk. Title: Metabolic Networks and Pathways in Alzheimer's Disease. *Supplement:* U01-AG024904-09. PI: Michael Weiner. Title: Alzheimer's Disease Neuroimaging Initiative.

P2-43: CORRELATION OF LOAD-RELATED APOE4 AND WTGSTO1 VARIANTS WITH MILD COGNITIVE IMPAIRMENT DEPENDS ON THE CLASSIFYING NEUROPSYCHOLOGICAL TEST. ELLEN UMLAUF[1], EDUARD RAPPOLD[1], BETTINA SCHILLER[1], PETRA FUCHS[2], MICHAEL RAINER[3], BRIGITTE WOLF[4], MARIA ZELLNER[1] *((1) Medical University of Vienna, Institute of Physiology, Vienna, 1090, Austria; (2) SMZ Otto Wagner Spital, 3rd Department of Psychiatry, Vienna, 1140, Austria; (3) SMZ Ost, Karl Landsteiner Institut für Gedächtnis- und Alzheimerforschung, Vienna, 1220, Austria; (4) Medical University of Vienna, Department of Surgery and Surgical Research, Vienna, 1090, Austria)*

Approximately 30 million people currently suffer from late-onset Alzheimer's disease (LOAD) worldwide. Twin studies have shown that 60 to 80% are genetically determined though 20% of this heritability still remains unassigned. In this study we genotyped 118 controls, 71 LOAD patients and 52 mild cognitive impairment (MCI) patients that suffered from the preceding stage of LOAD. Firstly, we corroborated our previous finding in an independent study set showing that the wild-type variant of the polymorphism rs4925 in GSTO1 was significantly associated (p=0.045) with an increased risk for LOAD. Secondly, we provided novel evidence that the prevalence of this genetic marker is also significantly increased in MCI (p=0.045). Thirdly, we demonstrated that the detailed test battery by the Consortium to Establish a Registry for Alzheimer's Disease was superior to the widely used short Mini Mental State examination (MMSE) in characterising the cognitive healthy reference group. Consequently, associations of the polymorphism variants rs4925 and APOE4 with MCI were broken when the group assignment was solely based on MMSE. In conclusion, this study highlighted rs4925 as genetic marker for cognitive impairment and emphasised the importance of well-defined study groups, not only for the case group but also for the reference set.

P2-44: PLASMA TAU IN ALZHEIMER'S DISEASE. NIKLAS MATTSSON[1], HENRIK ZETTERBERG[2], SHORENA JANELIDZE[1], ULF ANDREASSON[2], ERIK STOMRUD[1], SEBASTIAN PALMQVIST[1], DAVID BAKER[3], CRISTINA A TAN HEHIR[4], ANDREAS JEROMIN[5], DAVID HANLON[5], LESLIE M SHAW[6], JOHN Q TROJANOWSKI[6], MICHAEL W WEINER[7], OSKAR HANSSON[5], KAJ BLENNOW[2] *((1) Lund University; (2) University of Gothenburg; (3) Janssen R&D (J&J); (4) GE Global Research; (5) Quanterix; (6) University of Pennsylvania; (7) University of California San Francisco)*

Background: Cerebrospinal fluid (CSF) tau is increased in Alzheimer's disease, but the relevance of plasma tau in Alzheimer's disease is unclear. We tested if plasma tau was altered in Alzheimer's disease, and if it was related to cognition, CSF biomarkers of β-amyloid (Aβ) or tau pathology, brain atrophy measured by MRI and brain metabolism measured by FDG-PET. *Methods:* Plasma tau was evaluated in i) patients with Alzheimer's disease with dementia (AD, n=179), mild cognitive impairment (MCI, n=185) and cognitive normal subjects (CN, n=189) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and ii) patients with AD (n=61), MCI (n=214), subjective cognitive decline (n=174) and CN (n=274) from the BioFINDER study at the Clinical Memory Research Unit, Lund University, Sweden. Associations were tested between baseline plasma tau and diagnosis, CSF biomarkers, MRI measures, FDG-PET and cognition at baseline and follow-up. *Results:* Higher plasma tau was associated with higher CSF tau in both cohorts and with AD dementia and lower CSF Aβ42 in ADNI, but the correlations were weak. Longitudinal analysis in ADNI showed significant associations between baseline plasma tau and impaired cognition, atrophy and hypometabolism during follow-up (especially in AD). *Conclusions:* Plasma tau partly reflects AD pathology, but the overlap between healthy aging and AD is substantial, especially during pre-dementia stages. Although differences can be found at the group level, these results do not support plasma tau as a biomarker of AD pathology in individual subjects. Future studies may examine plasma tau as a longitudinal marker, which may be particiularly useful in clinical trials.

P2-45: ULTRA-SENSITIVE SINGLE MOLECULAR ARRAY (SIMOA) TECHNOLOGY FOR THE DETECTION OF TAU IN BLOOD: CNS APPLICATIONS. AMELIE CASTRO, LEI CHANG, DAVID HANLON, DAVID WILSON, ANDREAS JEROMIN *(Quanterix Corporation Lexington, MA, USA)*

Background: Methods for measuring the brain protein Tau in serum and plasma have until recently been unavailable and have commonly been measured in cerebrospinal fluid (CSF). However, the highly sensitive and specific measurement of peripheral total Tau is now available via Single Molecule Array (Simoa™) digital immunoassay. *Methods:* Simoa total tau assay reagents were developed for a paramagnetic bead-based ELISA for use in the Simoa HD-1 Analyzer. Anti-total tau capture beads were prepared by covalent coupling of antibody to carboxy paramagnetic microbeads and the detector antibody was biotinylated by standard methods, and an enzyme conjugate was prepared by covalent coupling of streptavidin and

beta–galactosidase. The HD-1 Analyzer first performs sandwich immunoassay using 42 μL of serum or plasma sample, then transfers washed and labeled capture beads to a Simoa disc where the beads are singulated in 50- femtoliter microwells, sealed in the presence of substrate, and interrogated for presence of enzyme label. A single labeled tau molecule provides sufficient fluorescence signal in 30 seconds to be counted by the HD-1 optical system. For the developed tau assay is the limit of quantification is 24 fg/ml. *Results:* In a number of different clinical studies of traumatic brain injury (TBI)/ concussion and neurodegeneration, total tau in either plasma or serum was measured. This includes the acute phase of sport-related concussion in ice hockey players and assessment of total tau in the chronic phase post-TBI in returning veterans. In sports-related concussion, tau in blood is acutely elevated and appears to correlate with return-to-play. Using Simoa technology, total tau in blood has also been shown to differentiate between cognitively normal, mild congnitive impairment and Alzheimer's disease subjects. *Conclusions:* This is the first time that a ultra-sensitive and specific assays for total tau in blood has been developed. The presented case studies highlight the clinical significance of measuring total tau in blood across neurodegenerative diseases and in traumatic brain injury. In addition to total tau other CNS-relevant and ultra-sensitive assays have been developed on Simoa. These assays can also be multiplexed and allow for an easy transfer of existing ELISAs to improve sensitivity.

P2-46: OLFACTORY DEFICITS PREDICT RESPONSE TO CHOLINESTERASE INHIBITORS IN MCI DUE TO ALZHEIMER DISEASE. DAVANGERE P DEVANAND[1], SEONJOO LEE[2], YAAKOV STERN[3], GREGORY H PELTON[1] *((1) Division of Geriatric Psychiatry, Columbia University Medical Center; (2) Biostatistics, Mailman School of Public Health, Columbia University; (3) Department of Neurology, Taub Institute, Columbia University Medical Center, New York City, NY, USA)*

Objective: To determine if odor identification deficits that indicate incipient Alzheimer's disease (AD) brain pathology predicts improvement with cholinesterase inhibitor (CheI) treatment in patients with mild cognitive impairment (MCI) who progress to Alzheimer's Disease. *Methods:* Patients with mild cognitive impairment were followed naturalistically in a longitudinal study of early markers of AD. During follow-up, 48 patients received CheI based on doctor's choice. The University of Pennsylvania Smell identification test (UPSIT) was administered at baseline and at 2-year and 4-year follow-up. The primary cognitive outcome was the 6-month change in Selective Reminding Test total immediate recall (SRT-tot) score during CheI treatment. *Results:* In multiple regression analyses on change in SRT total recall scores, the baseline UPSIT by diagnosis (progression or non-progression to AD) interaction was significant (β=-1.19, p=0.001). Lower baseline UPSIT was associated with greater improvement in SRT total recall with CheI treatment in patients who progressed to AD, and this association went in the opposite direction in the non-progression group ($p < .001$). Similar results were obtained with the last available UPSIT prior to CheI treatment. In patients with high UPSIT scores, there was no significant change in SRT total recall. *Conclusion:* Olfactory identification impairment, which is an established biomarker that predicts cognitive decline and the transition from MCI to AD, is associated with improvement with CheI treatment in those patients with MCI who progress to AD. This relatively simple, cost-effective, non-invasive test has the potential to identify which patients with MCI are likely to benefit from CheI treatment.

P2-47: HEALTH PLAN FOR ADULT SUBJECTS WITH DOWN SYNDROME AND DOWN ALZHEIMER BARCELONA NEUROIMAGING INITIATIVE (DABNI) PROJECT. SEBASTIAN VIDELA[1], MARÍA CARMONA-IRAGUI, LAURA VIDELA[1], SUSANA FERNÁNDEZ[1], BESSY BENEJAM[1], DANIEL ALCOLEA[2], VALLE CAMACHO[3], SANDRA GIMÉNEZ[4], SOFÍA GONZÁLEZ-ORTIZ[5], EDUARD VILAPLANA[1], JORDI CLARIMON[2], RAFAEL BLESA[2], ALBERTO LLEÓ[2], JUAN FORTEA[1,2] *((1) Fundació Catalana Síndrome de Down. Barcelona, Spain; (2) Memory Unit, Department of Neurology. Hospital de la Santa Creu i Sant Pau. Biomedical Research Institute Sant Pau. Barcelona, Spain; (3) Department of Nuclear Medicine. Hospital de la Santa Creu i Sant Pau. Biomedical Research Institute Sant Pau. Barcelona, Spain; (4) CIM Sant Pau. Biomedical Research Institute Sant Pau. Barcelona, Spain; (5) Radiology Department. Hospital del Mar. Barcelona, Spain)*

Objectives: Most subjects with Down syndrome (DS) develop presenile onset Alzheimer disease (AD), frequently associated with epilepsy, due to the presence of an extra copy of the amyloid precursor protein gene and increased life expectancy. However, AD diagnosis represents a diagnostic challenge due to the intellectual disability associated with DS and to a lack of appropriate instruments, and the natural history of AD and AD related biomarkers in DS remain under ascertained. In Catalonia, we have developed a health plan (HP) for adults with DS that includes periodical evaluations to assess AD and other medical and neurological disturbances, that is complemented with a research initiative to study AD biomarkers (Down Alzheimer Barcelona- DABNI- program). We present preliminary results. *Methods:* Setting: Down Medical Centre. Target population: All Catalan subjects with DS over the age of 18 (3500 estimated). Procedures of the health plan: A standardized medical, neurological and neuropsychological (which includes the CAMDEX-DS and the CAMCOG as well as other tests evaluating every cognitive domain), an electroencephalogram (EEG), and a blood test. Patients with neurological or other medical disturbances will be referred to a tertiary hospital that will centralize specialized care. Subjects are also offered to participate in DABNI research program. Those who accept are proposed to undergo a cerebrospinal fluid (CSF) study to determine AD biomarkers, a magnetic resonance imaging (MRI), a positron emission tomography (PET) with amyloid tracer, a F18-deoxiglucose (FDG) PET, and a polisomnogram. The starting point of this combined initiative was May 2014. *Results:* Between May 2014 and February 2015, 142 subjects have been evaluated. The mean age is 44.4 (range 18-69), 60.6% are male. Thirty-one patients have Alzheimer type dementia, 25 have cognitive impairment that does not meet dementia criteria, 16 have behavioural disorders that suggest a psychiatric aetiology, and 70 do not present a cognitive impairment. Thirteen have generalized epileptic seizures (7 are demented). Ninety-nine have undergone an EEG and 10 of them have epileptic activity (7 without a clinical correlate). Seventy-five patients accepted to participate in the DANBI program. So far, a CSF study was performed in 59 subjects with DS (median age: 47.5, 61.1% males), 29 without cognitive impairment. Forty underwent an MRI, 12 and 16 had also an amyloid and FDG PET respectively. A polisomnogram was performed in 28 subjects. Preliminary results show abnormal levels of CSF biomarkers in more than 72.7% of the subjects. They all correlate with age. The structural MRI analyses reflect an accelerated aging of DS brains with atrophy affecting the same areas as AD does. Florbetapir PET was positive for amyloid retention in 8/12 patients, FDG-PET was abnormal in 7/16 patients. Polisomnogram revealed several unnoticed sleep disturbances. *Conclusion:* AD represents the main medical problem in adults with DS. A longitudinal health plan is needed for the early detection, correct management and research purposes in AD in the DS population. The DABNI program will provide insights into the natural history of AD and AD related biomarkers in DS and will enable a better and earlier AD diagnosis in the DS population. Our first preliminary results are in agreement with the

recent conceptualization of DS as a form of preclinical AD.

P2-48: SERUM PLASMALOGENS, COGNITION, AND COGNITIVE DECLINE IN ALZHEIMER'S DISEASE. DAYAN B GOODENOWE[1], VIJITHA SENANAYAKE[1], MITCHEL A. KLING[2], JON B TOLEDO[3], TARA SMITH[1], ASUKA MOCHIZUKI[1], JESSICA TENENBAUM[4], EMILY BURKE[4], XIANLIN HAN[5], REBECCA BAILLIE[6], JOSEPH LUCAS[4], MURALI DORAISWAMY[7], JOHN Q TROJANOWSKI[3], LESLIE M SHAW[3], SUNGEUN KIM[8], ANDREW J SAYKIN[8], RIMA KADDURAH-DAOUK[7] AND THE ALZHEIMER DISEASE METABOLOMICS CONSORTIUM *((1) Phenomenome Discoveries Inc., Saskatoon, Saskatchewan, Canada; (2) Department of Psychiatry; (3) Department of Pathology & Laboratory Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; (4) Duke University Medical Center, Durham, NC; (5) Sanford-Burnham Medical Research Institute, Orlando, FL; (6) Rosa & Co. LLC, San Carlos, CA; (7) Duke Institute for Brain Sciences, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC; (8) Indiana Alzheimer Disease Center , Indiana University School of Medicine, Indianapolis, IN)*

Background: The Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-cog) and the Clinical Dementia Rating Sum of Boxes (CDR-SB) are the primary cognitive assessment scales used in randomized placebo-controlled clinical trials in Alzheimer's Disease (AD). A lower rate of cognitive decline in the treatment arm versus the placebo arm is used to determine therapeutic efficacy. Previous data indicate that plasmalogen deficiency may impact cognition. Therefore, the potential utility of baseline plasmalogen levels as a predictor of cognitive decline in AD was investigated. *Methods:* ADAS-cog and CDR-SB assessments were analyzed in 808 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI-1) at baseline and 12 months. Selected plasmalogen and phosphatidyl ethanolamine species were measured in baseline serum samples by stable isotope dilution, flow injection tandem mass spectrometry (FIA-MS-MS). Quality control samples at three concentrations and pooled sera were used to assess analytical reproducibility. A baseline, quantitative Plasmalogen Biosynthesis Value (PBV) was derived for each subject from the relative serum levels of three key plasmalogen species. Baseline models were adjusted for age education, sex, and Apolipoprotein E (APOE) genotype and 12-month models were additionally adjusted for baseline cognition. PBV associations are expressed per standard deviation (SD). *Results:* Higher PBV was associated with a lower baseline ADAS-cog (Coef= -0.647, p=4.4e-03) and a smaller increase in ADAS-cog at 12 months (Coef= -0.461, p=3.0e-03). The increase in ADAS-cog in representative AD participants (male, age 75, 16 years education, baseline ADAS-cog=19) with a baseline PBV in the 5th, 50th, and 95th PBV percentile was 1.2, 0.6, and -0.3 at 12-months. Similar results were observed using the CDR-SB scale. *Conclusion:* Higher baseline PBV is associated with higher levels of cognitive function at baseline and a lower rate of cognitive decline at 12 months. AD subjects with high baseline PBV did not exhibit cognitive decline during the first 12 months of a follow-up, which could be considered as a clinical benefit in a hypothetical AD clinical trial. Further statistical analyses are being carried out. Pharmaceutical interventions that increase PBV might have some utility as a treatment to prevent cognitive decline. Authors wish to acknowledge ADNI, including ADNI funding sources for the provision of samples and clinical data. Partly funded by the NIA R01 grant: 1R01AG046171.

P2-49: PERIPHERAL INFLAMMATORY STATUS IN AMYLOID POSITIVE PATIENTS: EFFECTS OF THE GUT MICROBIOTA. A CATTANEO[1,2], N CATTANE[1], D ALTOMARE[3], C FESTARI[3], M PIEVANI[3], P PASQUALETTI[4], C MUSCIO[5]5, M BOCCARDI[3], A PRELLE[6], D VILLANI[7], S GENTILE[8], D BELLANDI[9], M TURLA[10], G DALLA VOLTA[11], O ZANETTI[12], M DE FANTI CARLO[13], A PADOVANI[14], GB FRISONI[3] AND THE INDIA-FBF WORKING GROUP *((1) IRCCS Centro San Giovanni di Dio, Fatebenefratelli, Brescia, Italy; (2) Stress, Psychiatry and Immunology Laboratory, Department of Psychological Medicine, Institute of Psychiatry, King's College London, London, UK; (3) LENITEM-Laboratory of Epidemiology, Neuroimaging and Telemedicine, IRCCS Centro San Giovanni di Dio, Fatebenefratelli, Brescia, Italy; (4) SeSMIT, AFaR, Fatebenefratelli Hospital, Isola Tiberina, Rome; and Unit of Clinical and Molecular Epidemiology; (5) Fondazione Europea Ricerca Biomedica (FERB), Centro Eccellenza Alzheimer, Ospedale Briolini, Gazzaniga, Bergamo, Italy; (6) A.O. Ospedale Maggiore di Crema, Italy; (7) Casa di Cura Figlie di S. Camillo, Crema, Italy; (8) Casa di Cura Ancelle della Carità, Crema, Italy; (9) Fondazione Istituto Ospedaliero di Sospiro Onlus, Sospiro, Crema, Italy; (10) Ospedale di Vallecamonica Esine, Brescia, Italy; (11) Istituto Clinico Città di Brescia, Brescia, Italy; (12) ATM, IRCCS Centro San Giovanni di Dio, Fatebenefratelli, Brescia, Italy; (13) Centro Alzheimer di Gazzaniga, Bergamo, Italy; (14) Department of Medical and Experimental Sciences, Unit of Neurology, Brescia University, Brescia, Italy; (15) Memory Clinic and LANVIE - Laboratory of Neuroimaging of Aging, University Hospitals and University of Geneva Geneva, Switzerland)*

Background: The pathophysiological signalling from Aβ deposition to cognitive symptoms is not completely elucidated yet. Among candidate mechanisms, alterations in the inflammatory and immune system responses are widely observed in AD patients and may promote Aβ accumulation. However, it is not clear where this inflammation comes from. Recent data suggest that the gut microbiota (GMB) could play a key role in modulating peripheral and central inflammation, contributing to the neuropathological alterations observed in several brain disorders with an inflammatory component. Aim of this study was to evaluate the relationship between GMB and inflammation, and their role in Aβ accumulation. *Methods:* We analysed a group of 40 patients with cognitive deficits and characterized for brain amyloidosis (20 patients amyloid positive, Amy+; 20 patients amyloid negative, Amy-) through PET with Florbetapir. We measured the blood levels of the following inflammatory markers: pro-inflammatory cytokines IL-6, IL-1β, TNF-α CXCL2 and CXCL2; anti-inflammatory cytokines IL-10, IL-4 and IL-13; and a component of the inflammasome, NLR3P. Moreover, we evaluated in the stool samples of the same subjects the abundance of candidate bacteria strains having immunomodulatory properties: Escherichia/Shigella, Pseudomonas, Faecalibacterium Praunitzii, Eubacterium Rectale, Eubacterium Hallii. *Results:* We found that Amy+ patients had increased mRNA levels of IL-6 (+30%, p<0.05), CXCL2 (+28%, p<0.05) and NLR3P (+25%, p<0.05) as compared to Amy- patients, confirming an enhanced inflammatory status in association with brain amyloidosis. Moreover, amy+ patients had lower abundance of the Eubacterium rectale, known for its anti-inflammatory properties (p<0.001, Fold change, FC= -4.5), and a higher abundance of Escherichia/Shigella (p<0.05, FC=2.4), known to promote inflammation, as compared to Amy- patients. Correlation analyses between inflammatory status and bacteria strains abundance indicated a significant positive correlation between the three pro-inflammatory cytokines levels and the Escherichia/Shigella abundances (r2=0.654, p<0.05 for IL-6; r2=0.465, p<0.05 for CXCL2 and r2=0.585, p<0.05 for NLR3P). *Discussion:* Our data confirm the presence of an enhanced inflammation associated with brain amyloidosis. Moreover, they suggest for the first time that alterations in the GMB composition are observed in patients with cognitive deficits and with brain amyloidosis. This altered GMB composition,

together with a specific and GMB correlated pro-inflammatory pattern, supports a possible causative role of GMB in brain neurodegenerative alterations

P2-50: PHARMACOKINETIC PROFILE OF A NOVEL LOW DOSE EXTENDED RELEASE FORMULATION OF AGB101 (LEVETIRACETAM). SHARON ROSENZWEIG-LIPSON[1], STEVEN MULCAHY[1], KEN PAYIE[1], SARAH BULLOCK[2], ELSIE MELSOPP[3], JACK JAMES[3], MICHELA GALLAGHER[1] *((1) AgeneBio, Inc, Baltimore, MD, USA; (2) Worldwide Clinical Trials, Early Phase Services, San Antonio, TX, USA; (3) AAI Pharma, Wilmington, NC, USA)*

Background: A distinctive condition in the aMCI patient population is neural overactivity localized to the hippocampal formation by functional magnetic resonance imaging (fMRI) (Dickerson et al, 2005; Yassa et al., 2010). In clinical studies, the magnitude of such hippocampal overactivity longitudinally predicts subsequent cognitive decline/conversion to a dementia diagnosis (Miller et al., 2008; Putcha et al., 2011; Huijbers et al, 2015). In a Phase II study (Bakker et al., 2012, 2015), levetiracetam (125 – 500 mg total daily dose) was evaluated in patients with aMCI to determine its effects on hippocampal overactivity and on memory function in a behavioral pattern separation task performed during fMRI scans. Low doses of levetiracetam (125 – 250 mg daily), but not the high dose (500 mg daily) reduced hippocampal overactivity and significantly improved task related memory performance. Drug levels in aMCI patients were determined to be 2.9 ± 0.29 ug/mL (mean ± sem) for the 125 mg cohort and 4.4 ± 0.53 ug/mL for the 250 mg cohort. The ineffective dose of 500 mg provided a drug level of 7.91 ± 0.92 ug/mL. These levels of drug exposure are well below typical ranges for efficacy of levetiracetam as an antiepileptic agent, where doses of 1000-3000 mg/day are typical, achieving levels of 10-40 mg/mL. The efficacious exposures observed in aMCI patients were consistent with animal studies in age-impaired rats in which exposures of 1.9 – 3.9 mg/mL were efficacious and an exposure of 7.8 mg/mL was ineffective. We conducted a crossover food effect study of two novel low dose extended release formulations of AGB101 (low dose levetiracetam) at doses of 190 and 220 mg. The purposes of the study were to confirm the exposures associated with efficacy in the Phase II trial and in age-impaired rats were observed from the novel formulations and were maintained over the course of the daytime hours, to confirm the formulation PK profile was consistent with once daily dosing and to determine if there were any food effects on the PK profile. *Methods:* This was an open-label, randomized, two-group, single-dose, two-period crossover, food effect study in which 56 healthy adult subjects received a single dose of AGB101 extended-release tablet (either 190 or 220 mg) under fed conditions in one study period and a separate single dose of AGB101 extended-release tablet under fasted conditions in another study period. Fed treatment: Following an overnight fast of at least 10 hours, subjects consumed a Food and Drug Administration (FDA) standard high-calorie, high fat breakfast meal 30 minutes prior to administration of the study drug. Fasted treatment: Subjects were dosed after an overnight fast of at least 10 hours. Each drug administration was separated by a washout period of at least 7 days. Blood samples (1 × 6 mL) were collected in Vacutainer tubes containing K2 EDTA as a preservative, at 0 (predose) and at 1.0, 2.0, 3.0, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 8.0, 9.0, 10, 12, 18, 24, 32, and 48 hours post dosing. *Results:* Food-Effect: The 90% confidence intervals for the log transformed exposure parameters Cmax, AUClast, and AUCinf were within the 80% to 125% range for the 190 mg and 220 mg doses. The presence of food did not alter the pharmacokinetics of the 190 mg and 220 mg levetiracetam doses. Tmax was delayed by about 2 ½ hours under the fed condition relative to the fasted condition.

PK Profiles				
190 mg	Tmax (h)	Cmax (µg/mL)	AUCinf (h*µg/mL)	T1/2 (h)
Fasted	4.39	2.31	47.93	8.09
Fed	6.93	2.53	47.81	7.70
220 mg	Tmax (h)	Cmax (µg/mL)	AUCinf (h*µg/mL)	T1/2 (h)
Fasted	4.04	3.02	57.68	7.81
Fed	6.64	3.16	56.63	7.56

Conclusions: AGB101 (220 mg) met all preset criteria. Sustained plasma levels of levetiracetam consistent with Phase II efficacy were observed over a 14-hour period. The PK profile was consistent with an extended release formulation suitable for once daily dosing. There were no food effects on Cmax or AUC. This dose/formulation is suitable for use in our upcoming Phase III program in aMCI. *Funding:* AgeneBio gratefully acknowledges the support of ADDF in funding this study.

P2-51: NEW NEUROPROTECTIVE STRATEGY IN EARLY AD : ARGUMENTS FOR A TRITHERAPY. JACQUES HUGON, SARAH GOURMAUD, MARION TIBLE, ANNE SOPHIE CARRET, FRANCOIS MOUTON-LIGER, PASCAL MILLET, JULIEN DUMURGIER, CLAIRE PAQUET *(Memory Centre and Inserm UMRS 942 Lariboisière Hospital, APHP and University of Paris Diderot, Paris France)*

Background: Alzheimer's Disease (AD) is neuropathologically marked by synaptic and neuronal losses. The cause of neuronal death is unknown but could be linked to Aβ toxicity. Targeting neurodegeneration needs to decipher the early abnormal neuronal signalling induced by Aβ and occurring in humans. Biomarker studies have underlined the possibility that Aβ brain accumulation with reduced CSF levels could start 10 to 20 years before the onset of clinical signs. Aβ can activate in neurons the proapoptotic and pro-inflammatory kinases PKR and JNK3. *Methods and results:* We have shown previously that the CSF levels of the kinases are increased in AD and MCI patients suggesting that they undergo an early and detrimental activation over the course of the disease. In addition our recent results have demonstrated that 1-dual inhibition of PKR and JNK nearly abolished Aβ toxicity in primary neuronal cultures. 2- in two mice experimental models the genetic or pharmacological down regulations of PKR prevents Aβ synthesis and afford neuroprotection. 3- Aβ active vaccination produces enhanced neuronal loss in treated patients. All these results argue in favour of early pharmacological intervention trials in which neuroprotection is included for patients with mild cognitive impairment or subjective cognitive impairment and at risk for AD. *Conclusions:* Multi-target therapy could include BACE 1 inhibition or Aβ immunotherapy in association with two neuroprotective and anti-inflammatory kinase inhibitors able to carry out neuronal maintenance at a stage of the disease where the neuronal pool is moderately affected. This tritherapy is worth trying when drugs are available. *References:* Mouton-Liger et al Biol. Psy 2012, Dumurgier et al. Plos One 2013, Gourmaud et al. J Psy. Neurosci. 2014, Carret et al Nat. Sci. Rep. 2015, Paquet et al J. Pathol. 2015

P2-52: REPEATED EMOTIONAL STRESS EXACERBATES AMYLOID-β PEPTIDE INDUCED BRAIN PATHOLOGY IN ALZHEIMER'S DISEASE. POTENTIAL NEUROPROTECTIVE EFFECTS OF NANOWIRED DELIVERY OF CEREBROLYSIN. HARI S 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], ARUNA SHARMA[1]

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Background: Repeated emotional and combat stress is quite frequent in military. There are evidences that traumatic brain injury or post-traumatic stress disorders are linked as possible risk factors for Alzheimer's disease (AD) in military personnel. However, precipitation of AD in human civilian or military populations is still not well understood. Thus, explorations for preventive or therapeutic measures are not met with any great success. Our laboratory is engaged since last decades to find out the basic mechanisms or factors that could be involved in precipitation of AD like symptoms using experimental models. Since AD pathology is a complex thus use of single drug therapy could not be sufficient to ameliorate the AD pathology and improve patient care. Accordingly, we use multimodal drug e.g., Cerebrolsyin- a balanced composition of several neurotrophic factors and active peptide fragments to contain AD pathology in animal models. In addition, we also examine the modulatory effects of diabetes, brain injury, hypertension, hyperthermia, and/or nanoparticle intoxication in AD pathology. In this investigation we explored the possible role of repeated emotional stress on the development of AD pathology in our animal model and to see whether nanodelivery of cerebrolysin is able to induce neuroprotection in such situations. *Methods:* Experiments were carried out on Male Sprague Dawley rats (250-300 g, Age 30 to 35 weeks). Rats were subjected to emotional stress by partial immobilization in individual commercially available plastic tube that is well ventilated for proper respiration. Rats were placed in these tubes for 2 h daily for 4 weeks at room temperature (21±1° C). Control rats were placed in normal rat cages with free movements for comparison. In these control or immobilized rats AβP (1-40) was administered intraventricularly (i.c.v.) in the left lateral ventricle in a dose of 250 ng/10 μl once daily for 4 weeks. After 30 days of the 1st AβP 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. Another group of normal or immobilized rats received saline instead of AβP for comparison under identical conditions. *Results:* Our observations showed marked exacerbation of AβP deposits in the immobilized brain (ca. 2 to 4-fold higher than normal rats after identical AβP infusion within the cortex and in hippocampus. Also increased glial fibrillary acidic protein (GFAP) immunoreactivity, loss of myelin basic protein (MBP) immunoreactivity and increase in albumin immunoreaction were also exacerbated in stressed rats (2 to 3-fold higher) as compared to normal rats after AβP administration. Saline treated normal or stressed rats did not show any significant changes in these parameters. The cell loss as examined using Nissl or H&E stains was 4-to 6-times higher in stressed rats after AβP infusion as compared to normal rats. Whereas saline treated normal or stressed animals did not show neuronal loss or distortion. Breakdown of the BBB to Evans blue albumin or radioiodine and edema formation was 4-to 6-fold higher in stressed rats as compared to intact animals after identical 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 in stressed group. When TiO2 nanowired Cerebrolysin (25 μl, NWCBL) 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, the brain pathology was significantly reduced and the behavioral functions were markedly improved in normal rats. However, in stressed animals 50 μl NWCBL was needed to have the identical neuroprotection. Whereas, when the NWCBL (25 μl in normal and 50 μl in stressed group) was started 2 weeks after AβP infusion and continued until last infusion, the pathological changes and behavioral improvements were only mildly affected. However, enhancing the dose of NWCBL to 75 μg under identical conditions starting 2 weeks after AβP infusion markedly thwarted the brain pathology and deposition of AβP in the brain of normal or stressed rats, The behavioral function were also significantly improved in these animals after AβP infusion. Interestingly, NWCBL in 100 μg doses was able to induce pronounced neuroprotection and behavioral improvements if the drug was given only for 1 week daily starting from 3 weeks after AβP infusion. *Conclusions:* These observations are the first to suggest that emotional stress exacerbates AD pathology. Furthermore, NWCBL administration if given during a critical therapeutic time window is capable to attenuate exacerbation of AD pathology in stress. Higher doses of NWCBL allows us to start therapy even at a later stage of AβP infusion with effective neuroprotection This indicates that in situations of stress and AβP combinations late onset of therapy with higher doses of NWCBL is needed. Taken together, our observations for the first time show that stress could be a prominent risk factor in AD pathology and NWCBL may have potential therapeutic value in AD. Obviously reduction of stress levels may help in prevention of 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; 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.

P2-53: TRAUMATIC BRAIN INJURY EXACERBATES AMYLOID B–PEPTIDE INDUCED BRAIN PATHOLOGY IN ALZHEIMER'S DISEASE. SUPERIOR NEUROPROTECTIVE EFFECTS OF TIO2 NANOWIRED MESENCHYMAL STEM CELLS WITH POLY (D,L-LACTIDE-CO-GLYCOLIDE) NANOPARTICLES LOADED CEREBROLYSIN DELIVERY.

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Background: The pathophysiology of Alzheimer's Disease (AD) and its modulating factors are still not well known. Recent evidences suggest that our military personnel are at high risk for developing AD. This is because of the fact that traumatic brain injury (TBI) and post-traumatic stress disorders (PTSD) prevalent in military personnel are considered as potential risk factor in precipitating AD. Thus, further studies are needed in this area to unravel biological mechanisms of AD in order to explore suitable therapeutic strategies in clinics. Previous experiments from our laboratory showed that concussive head injury (CHI), hypertension, diabetes, hyperthermia, and/or nanoparticles exposure exacerbate amyloid beta peptide (AβP) infusion induced brain pathology in AD that was considerably reduced by nanodelivery of Cerebrolysin, a multimodal drug with suitable combinations of several neurotrophic factors and active peptide fragments. Recently, role of mesenchymal stem cells (MSCs) in reducing AD pathology has been suggested by a few researchers. Thus, it would be interesting to see whether nanodelivery of MSCs alone or together with cerebrolysin could have an additive/synergistic effects in inducing neuroprotection in AD. In this investigation, we examined influence of traumatic brain injury on AβP induced brain pathology in AD. Furthermore we evaluated co-administration of TiO2-nanowired MSCs and Poly (D,L-lactide-co-glycolide) nanoparticles (PLG-NPs) loaded cerebrolysin (PLGA-CBL) on AβP induced brain pathology in AD in our model experiments. *Methods:* TBI was inflicted in rats under Equithesin anesthesia by making a longitudinal incision over the right parietal cerebral cortex (2.5 mm deep and 5 mm long) after opening of the right parietal bone (4 mm o.d.). This experimental situation mimics stab injury in human cases. In these traumatized rats ABP (1-40) was administered intraventricularly (i.c.v.) in the left lateral ventricle in a dose of 250 ng/10 μl once daily for 4 weeks. After 30 days of the 1st ABP infusion in normal or TBI rats, ABP deposits, blood-brain barrier (BBB) disturbances, brain edema and neuronal damages were examined using standard procedures. In separate groups of normal and TBI rats TiO2-nanowired MSCs (106 cells) or PLGA-CBL (5 mg/kg) were administered either alone or in combination intravenously once daily for 1 week starting from 3rd week of 1st AβP infusion. All pathological parameters were measured 30 days after initial AβP infusion. *Results:* Our observations showed that 30 days after AβΠ infusion in TBI group resulted in 3- to 4-fold higher deposition of ABP in the hippocampus and in cerebral cortex as compared to normal animals. The inured side showed most pronounced deposit of AβP than the contralateral side. Breakdown of the BBB to Evans blue albumin (EBA) or radioiodine [131]-I was also exacerbated in TBI group by 3-to 4- fold after AβP infusion with 150 to 200 % greater extravasation in the injured half. Neuronal loss, gliosis and demyelination were also most severe in TBI group after AβP infusion as compared to normal rats. Interestingly, TiO2 nanowired delivery of MSCs or PLGA-CBL alone was able to reduce these AD pathologies in normal rats effectively. However, in TBI group co-administration of TiO2-MSCs and PLGA-CBL is needed to contain AD pathology after AβP infusion. This combination of MSCs and CBL is also effective when the therapy was initiated after 4th week of AβP infusion that lasted for only 2 days, a feature not seen by either agent given alone. *Conclusion:* Taken together, our observations are the first to point out that TBI exacerbates AD pathology probably though enhancing BBB disruption in widespread areas of the brain. Furthermore nanowired delivery of cerebrolysin in combination with MSCs has superior effects in reducing AD pathology in TBI as compared to MSCs or cerebrolysin alone, not reported earlier. These observations indicate that nanodelivery of MSCs and/or drugs e.g., Cerebrolsyin has promising future therapeutic potentials in clinical cases of AD in combination. *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.

P2-54:THE EFFECTS OF MUSIC BASED RELAXATION (MUSIC CARE© APP) ON AUTOBIOGRAPHICAL MEMORY AND ANXIETY IN ALZHEIMER'S DISEASE: RANDOMIZED CONTROLLED TRIAL. STÉPHANE GUÉTIN[1,3], JULIE DESTOUTZ[3], BÉRÉNICE CAGNAT[2], FLORENCE RICCIARDI[2], CLAIRE CADILHAC[1,2], JACQUES TOUCHON[1] *((1) Service de Neurologie (CMRR), CHRU Montpellier, INSERM U1061, Montpellier, France; (2) Département Universitaire d'Orthophonie, UFR Médecine, Université Montpellier, France; (3) MUSIC CARE, Research & Development, Paris, France)*

Introduction: Over the last few years, care in Alzheimer's Disease (AD) diversified to improve patients' quality of life and to alleviate some of the AD related symptoms. Support for AD patients is based on a global and multidisciplinary approach combining pharmacological and non-pharmacological treatments such as music therapy (1). *Objectives:* The objective of the study was to assess the effect of a music based relaxation on autobiographical memory and anxiety in patients with mild to moderate AD. *Methods:* A controlled, randomized, cross-over design was utilized, comparing the effects of music listening and the presentation of music-related pictures. 20 AD patients with a Mini Mental State Examination (MMSE) score between 16 and 26 participated in the study. Participants wither listened to personalized music for 20 minutes (U-sequence (2)) or were presented a picture, before answering the Kopelman Autobiographical Memory Interview (AMI). Anxiety was measured on a verbal rating scale before and after each intervention. *Results and Discussion:* Data analysis confirms the influence of relaxation music on autobiographical memory ($p<0{,}0001$), especially its semantic aspect, and anxiety ($p < 0{,}0001$). Results also show the existence of a time gradient for stages studied ($p = 0.0004$). One also notes a correlation between the autobiographical recall and MMSE. *Conclusion:* Significant improvements in autobiographical memory and anxiety were observed using the music therapy sequence and existence of a time gradient was confirmed. Receptive music therapy (MUSIC CARE© App) is a non-pharmacological method which can therefore be integrated in a multidisciplinary approach along with speech therapy for people with AD. *Keyword :* Music intervention, Alzheimer, Anxiety, randomized controlled trial, non-pharmacological. (1) Guetin, S., Charras, K. Touchon et al. (2013). An overview of the use of music therapy in the context of Alzheimer's disease: A report of a French Expert group. Dementia, 12 (5), 619–634. (2) Guetin S, Portet F, Picot MC, Touchon, et al. (2009). Effect of music therapy on anxiety and depression in patients with Alzheimer's type dementia: randomised, controlled study. Dementia and Geriatric Cognitive Disorders 28(1):36-46.

P2-55: ABSOLUTE BIOAVAILABILITY AND SAFETY OF A NOVEL RIVASTIGMINE INTRANASAL SPRAY IN

HEALTHY ELDERLY INDIVIDUALS. TIMOTHY MORGAN[1], BOB SOH[2] *((1) Lachesis Biosciences Pty Ltd, Warrnambool, VIC, AU; (2) Nucleus Network Ltd, Melbourne, VIC, AU)*

Backgrounds: An original aim for rivastigmine (RIV) reported by Cutler et al. (1998) was to provide "rapid, sustained, dose-dependent inhibition of central AChE, attended by a favorable tolerability profile...". Systemic intranasal delivery has the potential to provide this through adjustable, individual dosing of RIV during waking hours. This may reduce the problems of undesirable cholinergic burden (due to 24 h drug delivery), sleep disturbances and localised irritation which are associated with transdermal patch delivery. *Methods:* We conducted a sequential, crossover, absolute bioavailability and safety study with single dose RIV intranasal spray and intravenous solution in eight healthy elderly individuals (ACTRN12614001313628). A single intravenous dose of 1 mg RIV was administered on Day 1. Following a 2 day washout, a single intranasal spray dose of 3.126 mg RIV (one spray in each nostril) was administered on Day 4. Visual nasal mucosal examination occurred at screening, check-in, day 4 (pre-nasal-dose) and day 5 (24 h post-nasal-dose). A perceived nasal irritation questionnaire asked a series of relevant tolerability questions (stinging, itching, burning sensations in nose or throat, rhinalgia and lacrimation) at 20 and 75 mins post-nasal-dose. Plasma was collected for pharmacokinetic analysis of RIV and NAP226-90. *Results:* The individuals (4 females, 4 males) in the study had a mean (SD) age of 64.5 (6.4) yrs and weight of 74.9 (9.7) kg. The absolute bioavailability (F) of RIV intranasal spray was significant at 0.62 (0.15) using non-compartmental pharmacokinetic analysis ($p < 0.001$, $F > 0$, $n = 8$), which was superior to F values reported by other researchers for oral 0.36 (0.13) and transdermal patch 0.45 (0.10) delivery. The systemic dose of RIV absorbed was 2.0 (0.6) mg, Tmax was 1.1 (0.5) h and Cmax was 6.9 (2.0) ng/mL. The NAP226-90 to RIV AUC ratio was 0.78 (0.19); range 0.66 to 1.15, which confirmed systemic delivery of RIV across the nasal mucosa of each individual. The single dose safety for RIV intranasal spray was excellent with 2 of 5 adverse events reported plausibly related to RIV intranasal spray (one individual had mild nasal congestion and another had a mild, red, itchy stomach rash; both recovered within 12 hours without treatment). The remaining 3 adverse events where all mild (cough, drowsiness and rash) and were not related to study drug. Nasal (3/8) and throat (4/8) irritation were perceived as mild and transient, and both had resolved at 20 mins post-nasal-dose. An estimated dose of 2 to 3 sprays twice-daily with RIV intranasal spray would deliver comparable RIV exposure and efficacy as a 6 to 9.7 mg/d oral dose and a 10 cm2 transdermal patch, respectively. *Conclusion:* The RIV intranasal spray had superior absolute bioavailability, rapid onset of action, low NAP226-90 to RIV exposure ratio and a favourable safety and tolerability profile. The ability to achieve adjustable, individual, twice-daily dosing during waking hours has good potential to minimise undesirable cholinergic burden and sleep disturbances whilst delivering an effective RIV dose for the treatment of dementia associated with Alzheimer's and Parkinson's disease. Ref. Cutler NR, et al. Acta Neurol Scand 1998 97:244-50.

P2-56: NEW ANALOGUES OF 7-METHOXYTACRINE AND A POTENTIAL THERAPEUTIC USE IN ALZHEIMER DISEASE. JAN RICNY[1], ZDENA KRISTOFIKOVA[1], JANA SIROVA[1], JAN KORABECNY[2], KAMIL KUCA[2], KAMIL MUSILEK[3], DANIELA RIPOVA[1] *((1) NUDZ, Topolova 748, 250 67 Klecany, Czech Republic; (2) Faculty of Military Health Science, Hradec Kralove, Czech Republic; (3) Faculty of Science, University of Hradec Kralove, Hradec Kralove, Czech Republic)*

Backgrounds: Inhibitors of acetylcholinesterase (AChE), e.g. well known tacrine compounds, are used in the treatment of Alzheimer disease; however, they are toxic and can cause serious side-effects. We have prepared 8 new analogues of 7-methoxytacrine (7-MEOTA) that is less toxic compared to tacrine and evaluated them in experiments in vitro in order to find either compounds with minimal detrimental effects on cholinergic neurotransmitter system either more lipophilic drugs easily penetrating the blood-brain barrier. Choline transporters CHT1 involved in the high-affinity choline uptake (HACU) system play a key role in the synthesis of neurotransmitter acetylcholine. Evaluations of new drugs for the treatment of Alzheimer disease via measurements of their effects on transporters CHT1 can be therefore a very useful tool. Penetration of different drugs into membranes and subsequent changes in membrane anisotropy and can be evaluated by means of fluorescent probes. *Methods:* All experiments were performed on the brains of young adult male Wistar rats. AChE inhibition was were measured on brain extracts by modified Ellman method (1) as described (2). HACU was estimated by incorporation of (3H)choline chloride by hippocampal synaptosomes. In Aβ interaction experiments, synaptosomes were preincubated with particular Aβ isoforms (L-Aβ 1-40, D-Aβ 1-40 or L-Aβ 40-1 at 500 nM) and/or with drugs (at IC50 concentrations) for 30 min at 37ºC. Membrane anisotropy experiments were performed on cortical membranes with TMA-DPH or DPH probes (3). *Results:* In a comparison with 7-MEOTA, some of the new analogues showed an increased ability to inhibit AChE; however, all analogues were less efficient than tacrine and mostly evoked lesser detrimental effects on CHT1. All compounds were also weak inhibitors of the specific binding site of (3H)HC-3 (however, all were stronger inhibitors than tacrine and 7-MEOTA). Only tacrine was able to interact with Aβ via stereospecific mechanisms and the complexes eliminated the HACU inhibition. The other compounds either did not interact with Aβ or the complexes enhanced the detrimental effects on CHT1, probably via nonspecific interactions. On the other hand, only one analogue and tacrine were not able to change membrane fluidity, all remaining compounds increased fluidity (decreased anisotropy) especially in deeper parts of membrane. *Conclusion:* In summary, several synthesized analogues showed increased AChE inhibition activity, but based on our CHT1 experiments, no one of the new analogues of 7-MEOTA seem to be the better drugs for Alzheimer disease therapy than the parent compound. The research was supported by GACR P303/11/1907, GACR P304/12/G069, MH CZ–DRO (PCP,00023752) and ED2.100/03.0078 grants. *References:* (1) Ellman G.L. et al. (1961): A new and rapid colorimetric determination of acetylcholinesterase activity. Biochem. Pharmacol. 7, 88-95. (2) Korabecny J. et al. (2010): Synthesis and in vitro evaluation of N-alkyl-7-methoxytacrine hydrochlorides as potential cholinesterase inhibitors in Alzheimer disease. Bioorg. Med. Chem. Lett. 15, 6093-6095. (3) Kristofikova Z. et al. Sex-dependent actions of amyloid beta peptides on hippocampal choline carriers of postnatal rats. Neurochem Res 31, 351-60 (2006).

P2-57: APPLICATION OF TAI CHI 6 FORMS IN APPARATUS AND WII FOR BALANCE TRAING OF ELDERS WITH ALZHEIMER DISEASE. ALICE MK WONG[1,2], YIN-CHOU LIN[1], CHIA-WEI WANG[1], ALBERT CK CHEN[1], JEAN-LON CHEN[1], YU-CHENG PEI[1] *((1) Department of Physical & Rehabilitation medicine, Chang Chung Memorial Hospital, Taiwan, ROC; (2)Institute of Healthy Aging,Chang Gung University, Taiwan, ROC)*

Backgrounds : According to epidemiological studies in Taiwan, about 2-4% people over 65 years old suffer from dementia. Among them, Alzheimer's disease (AD) is the largest proportion , about 50 to 60% of all dementia. Many studies demonstrated that Tai Chi (TC) could improve the quality of life, balance and reduce the risk of falls for the elderly. However, for people with dementia, learning Tai Chi will be difficult in remember the different forms. Therefore,we

had developed TaiChi six forms of training equipment forthem with clinical document. Recently, we also develop the computer software Tai Chi 6 form in Wii (Kinet), so elders might be able to imitate the big pole 6 movements of Tai Chi exercise more easily.In this study,we try to compare the effect of these two different types of Tai Chi exercise. *Methods :* There were 48 elderly ith AD in mild (CDR 0.5-1 or MMSE 20-23) to moderate (CDR 2 or MMSE10-19) were invited to join this study. They were arranged by random into 3 different training groups. Group A :TC 6 apparatus traning, Group B: computer software Tai Chi Six form in Wii traing, Group C: sedentary occupational therapy (OT) for dementia patients as control. They should complete the training course of for 12 weeks, 2 times/ week, 45 minutes per each time.Balanc, fitness, and mental state were evaluated for 4 times at 0, 4, 8, 12 week during the training course.Equilibrium score was mearsured by Balance Master(Sensory Organization Test,SOT),fitness was checked by INBODY device set.Mental status were represented by MMSE (Mini-Mental State Examination) and CASI (Cognitive Abilities Screening Instrument). *Results:* Only 39 subjects could finished the full course of traing, 9 subjects were dropped out due to disease attack or unable to attend the class regularly during that 12 weeks. For the result of this study, Gr.A had 11 elders (age 76.7±11.0, M/F 5/6, CDR 0.82±0.64,), Gr.B had 16 elders (age 78.3±8.2, M/F 5/11,CDR 0.84±0.64),and Gr.C had 12 elders (age 76.5±5.9, M/F 5/11,CDR 0.84±0.40).They had no significant difference in education level. After 12 weeks of training,the change of equilibrium score in Gr.A is from 45.91±21.67 to 59.18±14.44, (p=0.001*), in gr.B is from 55.19±18.35 to 56.38±15.99 (p=0.670), while in control Gr.C is from 57.08±11.59 to 55.91±14.86(p=0.670). The improvement of was only found in Group A ,with TC 6 apparatus traning, but not in other 2 groups. The dynamic test of Rhythmic Weight Shifting (RWS in degee/second) of Gr.A in slow speech(S) was from 0.54±0.28 to 0.40±0.27(p=0.264), moderate speed(M) was 0.96±0.47 to 0.59±0.33(p=0.010*), fast speed(F) was 3.32±0.72 to 2.25±1.00 (p=0.000*), while there were no significant improvement in Gr.B(S: p= 0.122, M: p=0.670, F: p=0.398) or Gr.C (S: p= 0.701, M: p=0.849, F: p=0.655). The change of body weight in Gr.A was from 63.3±9.1 kg to 62.7±8.3 kg (with muscle mass from 62.5±5.0 % to 63.7±7.8 %, fat mass from 33.6±5.2 % to 33.6±5.1 %), and lung capacity increased from 1.9±0.5 liters to 2.1±0.8 liters (p=0.035*). There were no significant changes in Gr.B and Gr. C. For mental condition,the change of MMSE and CASI did not reach significance in these 3 groups by 12 weeks of training. *Conclusion:* This study suggested that elders with mild to moderate degree of Alzheimer disease might be benefit from Tai Chi 6 forms apparatus without depending on their memory for learning. The improvement of static balance in eqilibrium score and dynamic rhythmic weight shift showed significant improvement at medium and high speed of moving were significant in Gr.A. However,the effect of training by computer software Tai Chi 6 form in Wii did not reach significant might be due to no sensory feedack during training, or not easy to fulfill the forms of practice by themselves due to dementia.

P2-58: AMYPOSOMES®: A NEW NANOMEDICINE FOR THERAPY OF ALZHEIMER DISEASE, WAITING FOR CLINICAL TRIALS. MASSIMO MASSERINI, SIMONA MANCINI, FRANCESCA RE *(School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy)*

Background: Although the cause and progression of AD are still not well understood (with the exception of genetic forms), the amyloid hypothesis is dominant and widely accepted. Accordingly, accumulation of Aβ peptide (an hydrolytic fragment of Amyloid Precursor Protein) in the brain, eventually deposited as senile plaques (a main hallmark in AD), evokes inflammatory response, synaptic dysfunction, neuronal death and neurodegeneration. Formation of neurofibrillary tangles containing tau protein is proposed to result from an imbalance between Aβ production and clearance. Therefore, Aβ has served as a target in recent years for approaches in AD therapy. Although many Aβ-centric therapies have been attempted, they all failed and no efficacious therapy is available yet. *Methods:* Following an idea started with the FP7 NAD Project (Nanoparticles for therapy and diagnosis of Alzheimer Disease, 2008-2013), we have rationally designed and patented multi-functional liposomes (Amyposomes ®) composed of a matrix of sphingomyelin/cholesterol and functionalized with a dodeca-peptide synthesized by modification of the receptor-binding domain of apolipoprotein-E, for purposes of blood-brain barrier targeting, and with phosphatidic acid (PA) for the purpose of Aβ binding. Amyposomes® were administered for 3 weeks (I.P., 3 times a week; 2.6 mg total lipids/injection) to an AD mouse model (APP/PS1 Tg mice aged 10 months). At the end of the treatment, mice were submitted to the novel object recognition memory test (NORT). Then, mouse brains were collected and analyzed through histology and biochemistry for Aβ deposition (plaques visualized with anti Aβ antibodies and total Aβ assayed by ELISA). The same treatment was also administered to APP23 mice aged 15 months (a single transgenic AD model) and plaque deposition was followed by PET imaging with [11C]-PIB and by histology. Subsequently, different doses of Amyposomes® (0.4 mg to 2.6 mg total lipids/injection or 15 mg total lipids/injection; 3 injections/week for 3 weeks) were administered to APP/PS1 mice in order to fine tune an optimal dosage. *Results:* Proof-of-principle: Administration of Amyposomes® decreased total insoluble brain Aβ1-42, and the number and total plaque area. Also Aβ oligomers were reduced. Plaque reduction was confirmed in APP23 mice by PET imaging with [11C]-PIB and by histology. The reduction of brain Aβ was associated with its increase in liver and spleen. Notably, the treatment also restored mouse impaired memory to normal. Confocal microscopy experiments showed that Amyposomes® reach intact the brain tissue. *Conclusion:* These data suggest that Amyposomes®: i) target the brain , ii) promote disaggregation of brain Aβ assemblies, iii) reduce brain Aβ burden, iv) restore impaired memory, v) arrest pathology progression. Mechanism of Action: Amyposomes® reach intact the brain, destabilize brain Aβ aggregates and promote peptide removal from the brain and its peripheral clearance by sink effect. This all-in-one multitask therapeutic approach can be considered as a new candidate for AD treatment. University of Milano-Bicocca has established the Spin-off company AMYPOPHARMA for the exploitation of the IP connected to Amyposomes® with the aim to complete the preclinical development, to achieve the IND filing, and to carry out Clinical studies of Phase I and Phase II. The NewCo can develop a product that fulfills the increasing needs of Pharma, Biotech companies and individuals affected by AD. *References:* 1. Balducci C. et al. Multifunctional liposomes reduce brain β-amyloid burden and ameliorate memory impairment in Alzheimer's disease mouse models J Neurosci. 2014 34(42):14022-31

P2-59: SUVN-502 - SAFETY, TOLERABILITY AND PHARMACOKINETICS OF A POTENT AND SELECTIVE 5-HT6 RECEPTOR ANTAGONIST IN HEALTHY SUBJECTS. RAMAKRISHNA NIROGI, KOTESHWARA MUDIGONDA, KIRAN KUMAR PENTA, GOPINADH BHYRAPUNENI, DEVENDER REDDY AJJALA, NAGESWARARAO MUDDANA, VEERA RAGHAVA CHOWDARY PALACHARLA, VINOD KUMAR GOYAL, SANTOSH KUMAR PANDEY, RENNY ABRAHAM, PRADEEP JAYARAJAN, RAJESH KUMAR BADANGE, RAMASASTRY KAMBHAMPATI *(Discovery Research, Suven Life Sciences Ltd, Hyderabad, India)*

Background: SUVN-502 is a novel 5-HT6 receptor antagonist with high receptor affinity and high degree of selectivity. SUVN-

502 is orally bioavailable and has adequate brain penetration in preclinical species. In animal models of cognition, SUVN-502 acts on all three phases of cognition (acquisition, consolidation & retention) and it increases the acetylcholine levels. SUVN-502 also enhances spatial memory in aged rats. SUVN-502 has adequate margin of safety in long-term preclinical toxicity studies. SUVN-502 is being developed for the treatment of cognitive deficits associated with Alzheimer's disease (AD). *Methods:* SUVN-502 was studied in a single-center, multi-faceted, phase 1 clinical trial (US IND) to evaluate its safety, tolerability, and pharmacokinetics after multiple ascending doses in healthy elderly male subjects. Subjects were dosed with 50 or 100 mg orally for 14 days. The effect of gender and food on SUVN-502 pharmacokinetics following 100 mg single oral dose was also evaluated in healthy subjects. SUVN-502 and its active metabolite M1 of SUVN-502 were quantified in plasma using a validated LC-MS/MS method. *Results:* SUVN-502 was well tolerated up to the highest tested dose of 100 mg/day following single or multiple oral administration in healthy subjects. There were no clinically relevant or serious adverse events noted. There was no significant effect of gender and food on the pharmacokinetics of SUVN-502 and M1 of SUVN-502 after single oral administration of 100 mg SUVN-502. Following multiple administration of 50 or 100 mg of SUVN-502, steady state was reached within 2-4 days for SUVN 502 and 4-6 days for metabolite M1 of SUVN-502. The exposure of SUVN-502 was comparable between Day 14 and Day 1, while metabolite M1 of SUVN-502 exposure was approximately 2.0 fold higher on Day 14 compared to Day 1. *Conclusion:* SUVN-502 has shown a favorable safety and pharmacokinetic profile after single and repeated dose administration. Gender and food did not have any clinically meaningful effect on pharmacokinetic parameters of SUVN-502. SUVN-502 and M1 of SUVN-502 achieved the projected efficacy concentrations and attained steady state within seven days upon multiple administrations in elderly subjects. SUVN-502 is well tolerated in humans with adequate plasma exposure for efficacy and favorable pharmacokinetics suitable for once a day oral administration. A Phase 2A multicenter, randomized, double-blind, parallel group, 26 week, placebo-controlled study of SUVN-502 at two dose levels and placebo in subjects with moderate Alzheimer's disease currently treated with donepezil hydrochloride and memantine hydrochloride is initiated in USA. A total of approximately 530 subjects will be enrolled and randomized into one of three treatment groups. The study population will include male or female subjects, 50 to 85 years of age, with moderate Alzheimer's disease.

P2-60: EFFECT OF COMBINATION THERAPY OF CAFFEINATED COFFEE AND SELECTIVE 5-HT4 AGONIST, PRUCALOPRIDE, IN AN ALZHEIMER'S DISEASE MOUSE MODEL: POSSIBLE IMPLICATIONS ON AMYLOID BETA FORMATION. NOURAN AH AL SHEHABY[1], KHALED ABOU AISHA[3,4], MONA RADY[3], LAILA MAHRAN[1], NESRINE S EL SAYED[1,2] *((1) Pharmacology & Toxicology Department, Faculty of Pharmacy & Biotechnology, German University in Cairo, CAI, EG; (2) Pharmacology & Toxicology Department, Faculty of Pharmacy, Cairo University, CAI, EG; (3) Pharmaceutical Biology Department, Faculty of Pharmacy & Biotechnology, German University in Cairo, CAI, EG; (4) Pharmaceutical Biology Department, Faculty of Pharmacy, Cairo University, CAI, EG)*

Background: Lately, Alzheimer's Disease (AD) has become an interest for research in an attempt to improve the quality of life for the elderly as well as investigating possible approaches to halt the progression of the disease. Among the many proposed hypotheses for the progression of AD, Amyloid Beta (Aβ) production has proven to be the most contributing to the aggression of the disease. Many researches over the years approached to halt the production of Aβ through targeting either the blockade of amyloidogenic β-secretase pathway or enhancing the non-amyloidogenic α-secretase pathway. This research is conducted to investigate the possible synergistic effect of Prucalopride, a selective 5-HT4 receptor agonist with an effect on enhancing non-amyloidogenic α-secretase pathway, and coffee which possesses the ability to antagonize adenosine A2A receptors associated with suppression of amyloidogenic β-secretase pathway. *Methods:* AD was induced in mice using single intracerebroventricular Streptozotocin (STZ) at a dose of 3mg/kg. Prucalopride was subcutaneously injected at a dose of 10mg/kg and coffee was administered in two methods to mimic short term coffee administration where a single dose of 200μl concentrated coffee was intraperetoneally injected and long term coffee administration where 100μl concentrated coffee was orally administered twice weekly for 3 months. Cognitive functions changes between groups were evaluated using Morris Water Maze (MWM) testing and Ymi testing. APP cleaving enzymes (α and β sectretases) expression levels were evaluated using Real time qPCR analysis, while their activity was evaluated using Fluorometric Assay kits. Aβ levels in the brain was quantified using ELISA technique. *Results:* Results showed that combining Prucalopride and coffee (short term or long term) demonstrated a much higher effect on enhancing spatial working memory and non-spatial working memory in MWM and Ymi testing. Also, using the combinatory treatment resulted in halting the rate of Aβ production compared to using either Prucalopried or coffee alone as a treatment through increasing the expression and activity of α-secretase enzyme and decreasing expression and activity of β-secretase enzyme. *Conclusion:* Among the many approaches to slow the progression, drugs targeting certain pathways of AD pathogenesis have been extensively studied and produced promising results which lead to them reaching clinical trials for use in humans. The current study demonstrated an efficient method in managing AD, aiming to widen the scope of research to combining drugs with non-overlapping pathways to further achieve higher effect on halting the progression of AD and give rise to hope for the development of new therapeutic drugs that promises a good quality of living for AD patients.

P2-61: IN SILICO EVALUATION AND SYNTHESIS OF NEW MOLECULES AS THERAPEUTIC ALTERNATIVES IN THE ALZHEIMER DISEASE. GARCÍA MARÍN IOHANAN DANIEL[3] HERNÁNDEZ RODRÍGUEZ MARICARMEN[2], ROSALES-HERNÁNDEZ MARTHA CECILIA[2], CORREA-BASURTO JOSÉ[1], MANUEL JONATHAN FRAGOSO VÁZQUEZ[3] *((1) Laboratorio de Modelado Molecular y Bioinformatica, Escuela Superior de Medicina, Instituto Politécnico Nacional Plan de San Luis y Díaz Mirón s/n, 11340 México City, D.F., México; (2) Laboratorio de Biofísica y Biocatalisis, Escuela Superior de Medicina, Instituto Politécnico Nacional, Plan de San Luis y Díaz Mirón s/n, 11340 México City, D.F., México; (3) Laboratorio de Investigacion Bioquımica. Laboratorio de Investigacion Bioquımica, Seccion de Estudios de Posgrado e Investigacion Plan de San Luis y Dıaz Miron s/n, 11340 Mexico City, D.F., Mexico)*

Background: Actually there are several treatments for Alzheimer's Disease (AD) but many of them are aimed to controlling the symptoms only. Then it is important new therapies to avoid the disease process. The physiopathology of AD has been related mainly to increased production and aggregation of a peptide called β-amyloid of 42 residues (Aβ1-42). Once the Aβ1-42 is released from the membrane undergoes a conformational change from α-helix to β-sheet forming an electrostatic interaction between Asp23 and Lys28 allowing the formation of highly neurotoxic oligomers and fibrils. Studies done by our workgroup have allowed find the required pharmacophores to avoid this conformational change, such as the presence of a tertiary amine in the chemical structure of the molecules capable to ionize

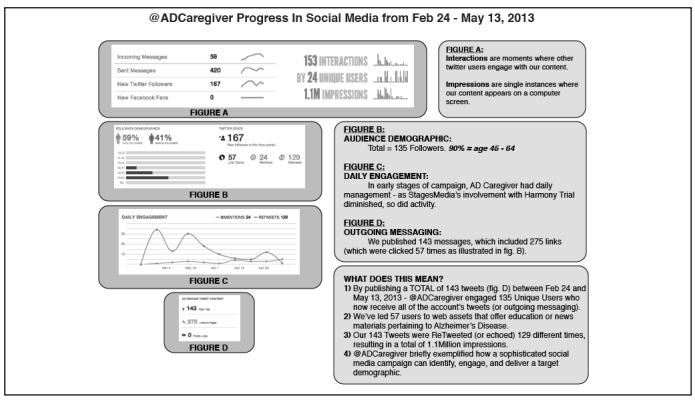
at physiological pH and interact with the Asp23 and Glu22 residues of Aβ1-42 and aromatic rings with aliphatic substituent's to form hydrophobic interactions with Phe19 and Phe20 to stabilize the α-helix conformation, thus avoiding the oligomers and fibrils formation. Therefore, we design new molecules with these pharmacophores to be evaluated as a possible alternative therapeutic in the EA thus preventing its progress. *Methods:* 28 compounds were designed having within their structure a tertiary amine and an aromatic ring with different chemical substituents. The 3D structure of the were designed with ChemBioDraw Ultra 13.0. The molecular docking studies were performed with Aβ1-42 in α-helix, β-folded conformations (PDB ID 1Z0Q and 2BEG respectively) and an structure in random coil which was obtained through studies Molecular Dynamics simulations. The docking studies were carried out using Autodock 3.4. to evaluate the binding affinity and the principally chemical interactions. After three of the compound with less ΔG values on Aβ1-42 in α-helix were choice. One of them was synthesized and its characterization was done using Infrared (IR) spectroscopy and mass spectrometry (MS). *Results:* According to the results it was observed that the F2S4, F3S4 and F4S4 compounds showed less ΔG values on Aβ1-42 in α-helix being 8.06, 8.32 and 7.56 respectively, with a difference of two orders of magnitude compared to Aβ1-42 in β-sheet. Once the compound was synthesized its characterization was done using IR being note for the expected signals aliphatic C-O and the absence of the C-Cl band. In MS the molecular ion has a m/z of 268.9974 which could correspond to the expected molecular mass of the compound (267.1703). *Conclusions:* Based on the docking results the F3S4, F2S4 and F4S4 compounds have the highest affinity (less ΔG values) for Aβ1-42 in α-helix and random coil having less affinity for Aβ1-42 in β-sheet conformation. Then, the pharmacophore proposed could be important to avoid the conformational change from α-helix to β-sheet. The synthesis of these compounds is feasible.

Saturday, November 7th

P3-1: MINIMIZING TRIAL COSTS BY ACCELERATING/ IMPROVING ENROLLMENT/RETENTION IN AD TRIALS IN GLOBAL CLINICAL TRIALS FOR ALZHEIMER'S DISEASE.

DEBBIE N COTÉ (*Clinical R&D Consultant, San Francisco, California US)*

Background: The Reality of Patient Enrollment and Retention according to an industry-wide research and development 2011 New York Times report, has shown spending has increased to more than $45 billion annually, more than doubling since 2000 (32). Among these and other figures seen in the pharmaceutical and healthcare industry - i.e. annual national health expenditures to expand to $4.6 trillion in 2020, according to the US health department of Health and Human Services (32) - seldom considered is the value of these dollars against the trial participants. Experienced recruitment providers have long acknowledged that scientific and artistic skill-sets are needed to develop successful recruitment campaigns. The science is locating the right study sites and intangible components that require an artistic flare to help develop the messaging and the appropriate material. Mapping across regions, countries, and study sites may give a false sense of confidence that the evidenced –based recruitment initiative will identify the right audience. Yet, despite this degree of specificity, without the right message a recruitment campaign may not be successful. Branding the trial to appreciate the needs, interests and motivations of the target audience is the most effective route: The message needs to be understandable, interesting, eye catching, ear catching with an emotional appeal that creates a call to action. *Methods:* To optimize accrual, clinical operational planning should take into account a more focused approach in setting recruitment goals and timelines. As efficacy is measured, recruitment strategy becomes more scientific and evidence-based activity that now relies on informatic tools; disease incidence databases, insurance claims databases, prescribing databases, and investigator databases to pinpoint the right sites and investigators. (31) Along with media campaigns multiple strategies using several tactics will most likely achieve the best outcome. As trials progress, the efforts of the recruitment campaign are measured on a continual basis permitting development and fine-tuning to the metrics leading to on-time completion of enrollment. Patient enrollment is an extremely labor intensive aspect of the clinical trial process, and it is the leading cause of trial delays (behind contract and budget delays) which can take up to 30% of the clinical timeline. As social media campaigns are designed to raise awareness, they strive to become influencers within the virtual Alzheimer community by developing content to be shared throughout all the social spheres. As the campaign builds momentum, and followers take note, the audience is expanded – thus driving interested followers to priority web assets. The content on the website is educational, disease focused, and an intake pre screener questionnaire directs visitors to a site locator to identify the closest study site without exposing study-specific information. The use of centralized call centers foster rapid processing of large volume of data across multiple sites, protocols, and various social marketing campaigns. So often people are interested in finding out more about clinical research and may prefer the option of speaking to a person outside the study site to understand more about clinical research trial prior to being 'transferred' to the trial site. One of the many benefits of having a dedicated call center is a live and trained professional responding to potential study participants: they ask a series of questions to determine if candidates are eligible based on sub sets of questions. If the caller meets certain criteria they are asked if they would like to 'opt in' and be transferred to the closest study site. The call center has a direct line to the study site and transfers the caller directly to a site staff member; if the caller passes the pre-screener questions and meets basic study entry requirements, an appointment is made to meet with the Investigator to determine eligibility. This is a great alternative to sites that don't have resources to respond to callers until after hours. *Results:* Social media presents an incredible opportunity to connect with trial participants on a level never seen before, 'Patients engage' regularly with each other in online health communities. In a recent pilot test, a PR firm - with a specialized social media focus - sought to facilitate a patient recruitment campaign alongside a large-scale Alzheimer's study. In the three months that the group was actively engaging with the community – 1M digital impressions proved widespread exposure to the group's effort: they had generated traffic to a Alzheimer-specific web asset, contributed to the dialogue surrounding the disease in the social sphere; and consequently harnessed a group of around 300 unique users (including large Alzheimer support groups) who interacted with the account on a daily basis. In a matter of 90 days, the PR firm had gotten a foothold on the digital AD discussion and had showed how the social media campaign can play a highly effective



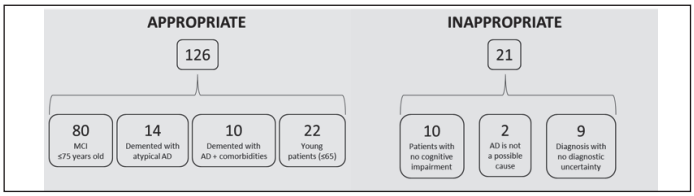
patient recruitment effort. Figure 1 represents the metrics from a large Alzheimer trial, which consisted of: 240 sites, 6000 participants signed consent, 2,650 randomized/dosed, and 1715 subjects completed the trial. Enrollment forecasting was 18 months; it took 3 years to complete; This was due in part to having to cast a much wider net then originally predicted - due to a 41% screen failure rate and a drop out rate of 30%. Monitoring the flow of patients through the pipeline – and focusing on the 'leaks' - may diminish the response to specific interventions. While sponsors, sites, and recruitment specialists work to refine their metrics tracking and reporting systems - the process of subject participation may significantly improve the rate of return for recruitment and retention in future trials. *Conclusions:* Improving patient recruitment rates offers Biopharma companies one of the biggest opportunities to accelerate the pace of clinical trials – making it possible to reduce time to market. As the # of AD patients needed for trials rises – as safety and regulatory issues trend toward larger and longer trials – the demand for patient recruitment services has grown exponentially. Having a line item in the budget for recruitment services encourages planning and execution of the program during start-up planning. Successful factors resulting in enhanced recruitment are directly impacted when study teams and sites focus on 'how to' locate and communicate with patients and families of AD patients. As efficacy is measured, recruitment strategy becomes more scientific and evidence-based activity relying on informatic tools; disease incidence databases, insurance databases, prescribing databases, and investigator databases to pinpoint the right sites & investigators. (31) Along with media campaigns, multiple strategies using several tactics will most likely achieve the best outcome. As trials progress, the efforts of the recruitment campaign are measured on a continual basis permitting development and fine-tuning to the metrics leading to on-time completion of enrollment.

P3-2: APPRAISAL OF THE UTILITY OF THE AMYLOID IMAGING TASKFORCE RECOMMENDATIONS FOR AMYLOID-PET PRESCRIPTION. BOCCARDI MARINA[1], ALTOMARE DANIELE[1], GUERRA UGO PAOLO[2], PIEVANI MICHELA[1], ALBANESE EMILIANO[3], FESTARI CRISTINA[1], ANTELMI LUIGI[1], PASQUALETTI PATRIZIO[4], MUSCIO CRISTINA[1,5], NOBILI FLAVIO[6], PADOVANI ALESSANDRO[7], FRISONI GIOVANNI BATTISTA[1,8] & THE INDIA-FBP WORKING GROUP *((1) Laboratory of Alzheimer's Neuroimaging and Epidemiology, IRCCS Fatebenefratelli, Brescia, Italy; (2) Department of Nuclear Medicine, Poliambulanza Foundation, Brescia, Italy; (3) Department of Mental Health and Psychiatry, University Hospital of Geneva, Geneva, Switzerland; (4) Fatebenefratelli Hospital of Isola Tiberina, Roma, Italy; (5) European Foundation Biomedical Research (FERB), Center of Excellence Alzheimer, Ospedale Briolini of Gazzaniga, Bergamo, Italy; (6) Clinical Neurology, Department of Neuroscience (DINOGMI), University of Genoa, Genoa, Italy; (7) Centre for Neurodegenerative Disorders, Neurology Unit, University of Brescia, Brescia, Italy; (8) Memory Clinic and LANVIE - Laboratory of Neuroimaging of Aging, University Hospitals and University of Geneva, Geneva, Switzerland) *Full list of INDIA-FBP participants: http://www.centroalzheimer.org/sito/contenuti/ip_lilly_publications/INDIA-FBP_WORKING_GROUP.pdf, Project link: http://www.centroalzheimer.org/sito/ip_lilly.php)*

Backgrounds: Recommendations for the prescription of amyloid-PET, although not yet evidence-based, have been published (Amyloid Imaging Taskforce – AIT, Johnson et al. 2013). Here we test the hypothesis that Appropriate prescription based on the AIT criteria is associated to greater clinical utility than Inappropriate prescription. *Methods:* From a previous study on the added diagnostic value of amyloid-PET, we extracted 126 patients with Appropriate and 21 with Inappropriate prescription; Figure). We evaluated clinical utility measuring consistent diagnostic changes (i.e., diagnosis of Alzheimer's Disease (AD) revised into non-AD after negative amyloid-PET scan, or vice-versa for patients <65yr) and consistent therapeutic change (i.e., AD-specific medications reduced after negative, or increased after positive amyloid-PET) with Fisher's Exact Test. *Results:* Consistent diagnostic changes occurred for 25% of patients with Appropriate prescription and in 29% of those with Inappropriate prescription (p=0.79). Consistent therapeutic changes occurred in 33% of the Appropriate and in 29% of the Inappropriate group (p=0.81) (Table). *Conclusion:* Contrary to our a priori hypothesis, Appropriate prescription does not correspond to greater clinical utility. Future investigation needs to unveil whether this is due to partial comprehension and use of the recommendations by clinicians, or whether the recommendations need to be improved, based on the evidence that current studies on amyloid-PET are collecting.

Figure

Patients with Appropriate and Inappropriate amyloid-PET prescription



Table

Consistent diagnostic and therapeutic changes in patients with Appropriate and Inappropriate amyloid-PET prescription

	N	Consistent diagnostic change	Consistent therapeutic change
Appropriate	126	24.6%	32.5%
Inappropriate	21	28.6%	28.6%

P3-3: ASSESSING THE FINANCIAL BURDEN ASSOCIATED WITH MILD COGNITIVE IMPAIRMENT. THANH GN TON[1], THOMAS DELEIRE[2], SUEPATTRA G MAY[1], NINGQI HOU[1], JENNIFER BENNER[1], ER CHEN[3], JOSHUA CHODOSH[4] *((1) Precision Health Economics, Los Angeles, CA, USA; (2) McCourt School of Public Policy, Georgetown University, Washington, DC, USA; (3) Genentech, Inc., San Francisco, CA, USA; (4) Department of Medicine, University of California Los Angeles, Los Angeles, CA, USA)*

Background: Those diagnosed with mild cognitive impairment (MCI) are at an elevated risk of developing Alzheimer's Disease (AD), [1] which represents the most common cause of age-related dementia, affecting >36 million people worldwide. [2] While much is known about the economic burden associated with AD, little is known about the direct and indirect costs associated with MCI. Using data from the Health and Retirement Study (HRS) and the Aging, Demographics, and Memory Study (ADAMS), a nationally representative population-based study of dementia using in-home clinical assessments, we conducted a cross-sectional analysis of cognitive status and financial costs, adjusted for inflation to 2015 US dollars, in order to assess the formal and informal health costs associated with level of cognitive impairment. *Methods:* Our primary cognitive status is defined as normal, amnestic MCI (aMCI), and AD dementia using data from the 2002 wave of the ADAMS (n=856). Cognitive status and its etiology were assigned by a consensus panel. We defined aMCI (n=121) as those with cognitive impairment but without vascular, psychiatric, mental/developmental, drug-induced, and other medical etiologies. For

AD, we included those assigned as probable and possible AD by the consensus panel (n=174). We further characterized AD severity using the Clinical Dementia Rating (1=mild, 2=moderate, and ≥3=severe). A total of 316 participants were classified as cognitively normal. We assessed annual direct medical spending (hospital, nursing home, doctor visits, dental visits, outpatient surgeries, prescription drugs, home health care, special facilities), total annual household income (for both respondent and spouse: earnings, pensions, annuities, social security disability, veteran benefits, security retirement), and spouse's income. We used linear regression models to assess the association between cognitive status (normal, MCI, AD: mild, moderate, severe) and financial burden, adjusting for demographic characteristics. We used sampling weights to obtain representative estimates for the US elderly population. *Results:* The weighted prevalence rate was 79.6% for normal, 11.7% for aMCI, and 8.7% for AD. Among those with AD, 42.4% were mild, 18.9% were moderate, and 38.7% were severe. Worse cognitive status was associated with increasing age (p<0.001), female sex (p=0.02), lower education (p<0.001), single marital status (p=0.008), and non-White race (p<0.001). Adjusting for demographic characteristics, people with normal cognition had $6,233 (95% CI: -$13,732, $26,000) lower annual direct medical spending than those with aMCI. People with aMCI had $45,673, (95% CI: -$128,626, $37,279), $38,918 (95% CI: -$93,696, $15,859), and $130,207 (95% CI: -$193,330, -$67,083) lower annual direct medical spending when compared to people with mild, moderate, and severe AD (linear trend: p<0.001). A statistically significant decreasing linear trend was also observed for annual household income (p=0.019) with an average decrease of $5,067 (95% CI: -$9,293, -$841) across the five cognitive status categories. A decreasing non-significant linear trend in annual income for the spouse was observed (-$420; 95% CI: -$1,269, $429) across the five cognitive status categories. The same yet attenuated trends were observed when comorbidities were adjusted for in the model. *Conclusion:* In this study, aMCI was associated with a statistically significant linear increasing trend in annual direct medical spending and decreasing trend in annual household income relative to those with normal cognition. Amnestic MCI was also associated with significantly less medical spending and greater household income compared to those with AD dementia. Findings from this study provide valuable data for healthcare professionals, payers, policymakers, patients and their families to understand the potential value of effective early interventions that may delay AD disease progression. *Sponsorship:* Support for this research was provided by Genentech. 1. Lin, P.-J. and P.J. Neumann, The economics of mild cognitive impairment. Alzheimer's & Dementia, 2013. 9(1): p. 58-62. 2. Lundkvist, J., et al., The battle of Alzheimer's Disease – the beginning of the future Unleashing the potential of academic discoveries. Frontiers in Pharmacology, 2014. 5: p. 102.

P3-4: MULTICULTURAL DIFFERENCES TOWARD ALZHEIMER'S EDUCATION AND CLINICAL TRIAL PARTICIPATION ON ALZHEIMER'S UNIVERSE (WWW.ALZU.ORG). VANESSA COOPER[1], CANDACE L HADDOX[2], JACLYN L CHEN[3], MAX PENSACK[3], CIARA GAGLIO[3], ALON SEIFAN[3], RICHARD S ISAACSON[3] *((1) New York Medical College, New York, NY, USA; (2) Mayo Clinic, Rochester, MN, USA; (3) Weill Cornell Medical College, New York, NY, USA)*

Background: Social stigma and misunderstanding about Alzheimer's disease (AD) represent significant barriers to diagnosis, treatment, advocacy, and clinical trial engagement. This is especially true for minority communities, particularly Latinos and African Americans in the United States. Online educational interventions serve as low-cost and potentially powerful tools to broadly address these barriers, and represent an underutilized means of efficiently reaching the public. Alzheimer's Universe (www.AlzU.org) was created to address unmet educational needs of individuals at risk for AD and/or caring for people with AD. AlzU.org currently provides an evidence-based online course including 6 interactive lessons (~10 minutes each), 12 activities (e.g. computer-based cognitive assessments; referral to other online AD initiatives such as endalznow.org and brainhealthregistry.org; clinical trial referrals including A4; US Against Alzheimer's referral; and user discussion forums), and a technological platform to study the effectiveness of course completion on pre- vs post-knowledge, measures of behavioral intent, and willingness to participate in AD clinical trials. A token economy system was employed to promote lesson completion, which included periodic awards for the completion of core milestones, as well as "brain-health" points awarded for each task finished. AlzU.org has been shown to significantly improve medical knowledge about AD and improve willingness to participate in AD clinical trials. However, baseline differences among multicultural populations remains unexplored. *Methods:* From January 1 – March 31, 2015, we targeted potential users through social media (Facebook.com). Visits were generated via a series of page posts with promotional advertisements that specifically targeted individuals in the United States who had previously expressed interest in "Alzheimer's disease," "liked" the Alzheimer's Association page, or followed www.facebook.com/AlzheimersDisease. Advertising used different promotional taglines using "Cost Per Click" and the "Optimized for Engagement" settings in Facebook Advertising Manager. Additional visits were generated through media outreach (e.g., NBC Today Show, Yahoo Health) and collaboration with partner sites (e.g., endalznow.org). Prior to completing any of the activities on AlzU.org, a pre-survey collected basic demographic information, health and lifestyle patterns (e.g., height, weight, exercise and dietary patterns), baseline AD knowledge and willingness to participate in AD research studies. After course completion, a post-survey collected identical comparative data. Results: Of 2331 subjects surveyed, 84% were female and the most common age group was 50-60 years old. The sample was comprised of 1994 Caucasians (89.4%), 116 Hispanics (5.2%), and 54 African Americans (2.4%). About 45% of Caucasians "know where to go" for high-quality information about AD, versus 37% of African Americans and 35% of Hispanics. Prior to course completion, 62% of Caucasians, 61% of Hispanics, and 60% of African Americans were interested in participating in an AD research study. 73% of African Americans, 63% of Caucasians, and 57% of Hispanics were very likely to "participate in AD research studies that require answering questions on a computer and taking memory tests." 22% of Hispanics, 21% of African Americans and 17% of Caucasians were very interested in "participating in a clinical trial that involved taking medication." 50% of African Americans, 38% of Hispanics, and 35% of Caucasians were very likely to "participate in AD research studies focusing on the effects of lifestyle (e.g., nutrition and/or exercise)". *Conclusions:* While sample sizes of Hispanics and African Americans were somewhat small (7.6% of users), preliminary data suggests some baseline differences between subgroups in subjective reporting of knowing where to find high quality AD information, and willingness to participate in a variety of different types of AD research studies. Interestingly, in this cohort of subjects, African Americans demonstrated the strongest desire to participate in online research, as well as in studies involving lifestyle approaches toward AD management. Future efforts will focus on boosting minority recruitment to AlzU.org and aim to determine the effectiveness of online education on willingness to participate in AD clinical trials and online AD trial registries in diverse subgroups.

P3-5: USING SOCIAL MEDIA TO EDUCATE ABOUT CLINICAL TRIALS ON ALZHEIMER'S PREVENTION & TREATMENT VIA ALZHEIMER'S UNIVERSE (WWW.ALZU.ORG). CANDACE L HADDOX[1], CIARA GAGLIO[2], JACLYN L CHEN[2], MAX PENSACK[2], ALON SEIFAN[2], RICHARD S

ISAACSON[2] *((1) Mayo Clinic, Rochester, MN, USA; (2) Weill Cornell Medical College, New York, NY, USA)*

Background: The use of social media may be a valuable tool for dissemination of patient education interventions. However, in Alzheimer's disease (AD), little data exists about effectiveness, associated costs, or conditions for maximizing user recruitment to the online learning content. *Methods:* Alzheimer's Universe (www.AlzU.org) was developed to address unmet educational needs for AD patients and their family members at risk. AlzU.org provides an evidence-based online course including short interactive lessons and activities such as cognitive assessments, referral to AD clinical trials and registries, and discussion forums. The site is integrated with a customized learning management system, which tracks various parameters of interest, including changes in pre- vs. post-course AD knowledge scores, behavioral attitudes, willingness to participate in AD trials, and activity click-through rates. In order to evaluate the effectiveness of using social media to disseminate online AD patient education via AlzU.org, multiple ad campaigns were launched on Facebook.com. We tested a variety of different promotional taglines and images, using the "Cost Per Click" and the "Optimized for Engagement" settings in the Facebook Advertising Manager. Using A/B testing, a variety of landing pages were shown to similar users and join rates were directly compared. We tracked overall conversion rates (the number of unique visitors who joined AlzU.org after viewing an ad), and the differential effectiveness and costs of a variety of different advertising strategies. We then analyzed course completion rates and satisfaction of users who completed the introductory course (5 lessons). *Results:* From April 1 – May 30, 2015, an advertising budget of $5,000 USD resulted in 12,829 visits for an average cost per click (CPC) of $.39 (range $.25 - .72). The most successful ads targeted individuals in the United States, Canada, the United Kingdom, and Australia, who previously expressed interest in "Alzheimer's disease," those who had "liked" the Alzheimer's Association page, and followers of www.facebook.com/AlzheimersDisease. The promotional tag line that worked best was among the most simplistic, highlighting the free nature of the course, and asking users to share to enhance virility. Depending on the landing page, conversion rates ranged from 9.8% to 24.86%. The landing page which generated the highest conversion rate was also the simplest and also incorporated an image of a family, a clear call to action, and the comparatively fewest hyperlinked buttons (to either join or learn more about the course). A total of 2254 visitors joined AlzU.org (average 17.5% join rate), 1837 engaged with at least one lesson/activity (81.4%), and 821 completed the pre-specified goal of the first 5 lessons on AlzU.org (36.4%) with an average time on site of 72 minutes. Users were primarily women (81%) and the most common age group was 50-60 years old (41%, range 18-92). The majority joined to learn more about AD prevention or treatment (68.5% and 64.2%, respectively). Users who completed the introductory course reported a 99% satisfaction rate (Likert scale 4.63). *Conclusion:* Subjects were easily and fairly cost-effectively recruited, and were highly satisfied with the AD education research platform, AlzU.org. Advertising cost-effectiveness improved through multiple rounds of A/B testing, as well as tag line and image use refinement trials. Based on these data, average cost per introductory course completion was $6.09. Overall, Facebook.com was an effective means of disseminating AD education online.

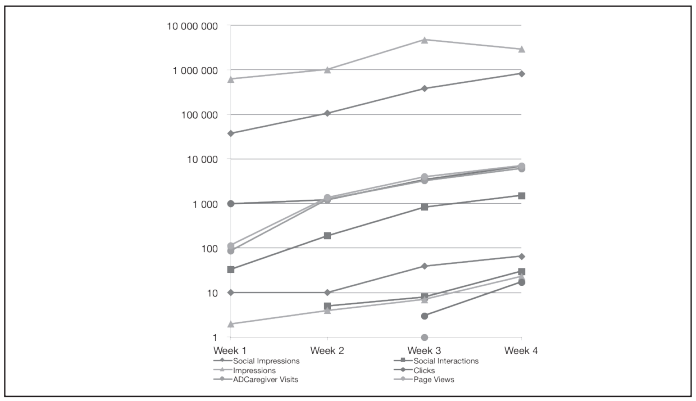
P3-6: MINIMIZING TRIAL COSTS BY ACCELERATING/IMPROVING ENROLLMENT/RETENTION IN AD TRIALS.
DEBBIE N COTÉ

GLOBAL CLINICAL TRIALS FOR ALZHEIMER'S DISEASE: DESIGN, IMPLEMENTATION, AND STANDARDIZATION.
MENGHIS BAIRU, MICHAEL WEINER

Background: • The Reality of Patient Enrollment and Retention according to an industry-wide research and development 2011 New York Times report, has shown spending has increased to more than $45 billion annually, more than doubling since 2000 (32). • According to the U.S. Health Department of Health and Human Services (32), annual national health expenditures will expand to $4.6 trillion in 2020, which is seldom considered in the value of these dollars against the trial participants. • Patient enrollment is an extremely labor intensive aspect of the clinical trial process, and it is the leading cause of trial delays (behind contract and budget delays) which can take up to 30% of the clinical timeline. • Experienced recruitment providers have long acknowledged that scientific and creative skill-sets are needed to develop successful recruitment campaigns. *Methods:* • Identification: o Utilizing big data to pinpoint the right sites and investigators – informatics tools, disease incidence databases, insurance claims databases, prescribing databases; o Media campaigns to reach desired target audience – digital marketing, print, radio and television advertising; o Social media campaigns desired to raise awareness throughout social spheres – banner ads, online communities, study specific websites (educational, disease focused information with an intake pre-screener questionnaire that directs visitors to a site locator to identify the closest study site without exposing study-specific information); o Carefully define the study subject profile via demographics, and other elements from the protocol; o Identify the relevant locales where one would find the subject profile that is being sought after. • Acquisition & Action: o Deploy search engine campaigns via Google, Bing, & Yahoo to set up large funnel to draw prospective subjects/family/friends seeking help in; o Target prospective subjects by geo-location, and other demographics relevant to study subject profile; o Draw prospective subjects into landing sites (any web page that a visitor can arrive at or 'land' via searching) with disease specific relevant original content – CONTENT IS KING – graphical memes, video, articles, blogs, and deep links to other relevant content to build organic ranking in addition to the paid ranking; o Define Value Proposition – what would lend assistance to the prospective subject/family/friend searching for help, provide it to them and in return, propel them to 'Act' , i.e., call an 800 number, live chat/text with AD healthcare representative, complete short screening form. • Processing: o Centralized call center services utilized to support all inquiries. • Call center benefits. • Provides an ACTIONABLE connection for prospective subjects. • Centralizes all incoming traffic (prospective subjects) into funnel. • Reduces staff burden. • Increases referral to screen ratio. • Ensures quality of referrals vs. quantity of referrals. • Use of trained healthcare professionals increases credibility by sites. • Database management. • All incoming interactions by prospective subjects are captured into SQL database to establish metrics: o Screening form data captured; o Prospective subject geo-location, IP address, gender, landing site interactions, i.e., clicks, click throughs, bounces are captured. • Metrics: o Deploy tools (search & social media) to monitor search engine and social media campaigns, interactions with influencers (e.g. sproutsocial.com, searchmetrics.com), meme performance, content performance and other campaign parameters; o Deploy real-time metrics to be able to react to off-performing campaigns and to make real-time adjustments to all parameters (search, social, landing sites). *Case study:* • Study Specifics: o Agitation in Alzheimer's Disease; o 240 sites; o 6,000 patients to sign consent to yield 2,650 randomized/dosed patients. • Challenges: o 41% screen fail rate; o 30% drop out rate. • Program Goal: o Reach enough potential participants to offset aforementioned challenges. • Outcomes: o Digital campaign came online in May 2013; o Study completion target with prior rate of enrollment December 2025; o Revised completion target with implementation of digital program August 2015; o In three

months, more than 1M digital impressions were received to the study specific website, which resulted in a group of around 300 unique users (including large Alzheimer support groups). *Conclusion:* • As the number of AD patients needed for trials rises – as safety and regulatory issues trend toward larger and longer trials – the demand for patient recruitment services has grown exponentially. • Successful factors resulting in enhanced recruitment are directly impacted when study teams and sites focus on 'how to' locate and communicate with patients and families of AD patients. • Having a line item in the budget for recruitment services encourages planning and execution of the program during start-up planning. • Improving patient recruitment rates offers Biopharma companies one of the biggest opportunities to accelerate the pace of clinical trials – making it possible to reduce time to market.

Logarithmic Graph Denoting Multiple-Axis of Performance for a campaign trial (2 weeks) deployed to test real-time marketing campaign parameters.



P3-7: MODIFIABLE RISK FACTORS FOR DEMENTIA: A STRATEGY TO COUNTERACT THE POOR PROSPECTS?
JESPER SKOV NEERGAARD, KATRINE DRAGSBÆK, HENRIK BO HANSEN, KIM HENRIKSEN, CLAUS CHRISTIANSEN, MORTEN ASSER KARSDAL *(Nordic Bioscience A/S, Herlev, Denmark)*

Backgrounds: Recent research suggests a decline or at least stagnation in dementia prevalence. One reason for the change in prevalence is thought to be the cardiovascular disease prevention strategies during the recent decades. Around one third of Alzheimer's disease cases worldwide are believed to be caused by modifiable risk factors. Modifiable risk factors including diabetes, midlife hypertension, midlife obesity, physical inactivity, depression, smoking and low educational attainment has all been linked to dementia. This suggests that prevention strategies with focus on modifiable risk factors are ways to counteract the otherwise poor prospects for dementia in the ageing population. Despite an extensive research effort it is not clear whether the results of the previous studies are of sufficient strength to warrant specific recommendations for disease prevention. In the absence of randomized control trials, large prospective cohort studies with long follow up is the best way to extend the evidence on these risk factors in order to identify the best strategy for prevention. In the present study, we used the second largest individual cohort study of elderly women, to identify and validate modifiable risk factors. *Methods:* Risk Factors for incident dementia were assessed in the Prospective Epidemiologic Risk Factor (PERF) cohort, a large observational, prospective follow-up study of Danish women, conducted between 1999 and 2001 (n=5,855). The Follow-up information was retrieved from the national Danish registries. A Cox proportional hazards regression model using age as time scale was applied to calculate mutually adjusted hazard ratios (HR) for potential risk factors. *Results:* Of 5,840 eligible subjects aged 70.8 years (48-89 years), 636 developed dementia after 15 years of follow up. The independent risk factors associated with increased risk of dementia were depression (HR = 2.04[95% CI 1.50-2.77]) and impaired fasting glucose levels. A dose-response relation was observed with fasting plasma glucose with HRs of 1.28[1.06-1.54] and 1.44[0.97-2.12] for impaired and hyperglycemic glucose levels, respectively. The risk factors associated with a decreased risk for development of dementia were overweight (as compared to normal weight women) (HR = 0.70[0.57-0.85]) and physical activity (HR = 0.78[0.65-0.94]). Obesity (BMI ≥ 30) was not associated with development of dementia. Current Smoking (as compared to current non-smoking) and hypertension were not associated with increased risk of dementia (HR = 1.10[0.88-1.38] and (HR = 1.04[0.88-1.22], respectively). Further educational attainment was not associated with risk of dementia when comparing primary school (reference) to high school and university degree (HR = 0.91[0.72-1.14] and (HR = 0.87[0.62-1.24], respectively). *Conclusion:* This is the second largest individual study of elderly women with the aim of accessing risk factors for dementia. We assessed some of the most frequently reported risk factors in relation to dementia in late-life. We found that the risk factors associated with an increased risk of dementia were physical inactivity, depression and impaired fasting glucose. A protective relation was found for overweight (BMI 25-29.9), which could likely be a marker of good general health rather than an actual risk factor. These risk factors are all considered modifiable and therefore provide further evidence that prevention strategies could be a way to counteract the otherwise poor future prospects for dementias in the ageing population.

P3-8: GENETIC EPIDEMIOLOGY OF ALZHEIMER'S DISEASE: GWAS SIGNIFICANT RISK FACTORS IN CHROMOSOME 19 AND THE APOE LOCUS CURSE.
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Backgrounds: Genetic research is uncovering panoply of loci associated to late onset Alzheimer's Disease (LOAD). This information might serve to stimulate the generation of novel therapeutic hypotheses. Additionally, genetic information -once refined and increased- will provide a paradigm to identify subjects at risk of LOAD. This future paradigm would permit the development pre-clinical trials in advance of amyloidosis. Multiple loci located at human chromosome 19 have been associated to LOAD. The APOE locus, discovered 28 years ago, is the single most significant genetic risk factor identified for LOAD. Interestingly, other signals

have appeared around its chromosomal location at 19q13.32. These signals are TOMM40 (19q13.32), EXOC3L2 (19q13.32), CD33 (19q13.41) and PLD3 (19q13.2). Additionally, the ABCA7 gene maps in the short arm of chromosome 19 (19p13.3) and is completely unlinked to APOE. Most closed signal to APOE locus (TOMM40 and EXOC3L2) never resisted APOE conditional association. Other signals in the long arm of chromosome 19 like PLD3 and CD33 loci are providing conflicting results in several independent studies. In fact, we and others have failed to replicate PLD3 involvement in AD risk (Heilmann et al. Nature. 2015 Apr 2;520(7545):E3-5). On the other hand, ABCA7 association has been replicated in most populations. *Methods:* The role of ABCA7 rs4147929 and CD33 rs3865444 loci as genetic risk factors of AD in the Spanish population was explored using a case-control design. One thousand seven hundred ninety six unrelated late onset sporadic AD patients and 2642 healthy controls were used to carry out case-control genetic association studies (n=4438 unrelated subjects). All patients fulfilled the Diagnostic and Statistical Manual for Mental Disorders criteria of the American Psychiatric Association (DSM-IV) criteria for dementia and were diagnosed according to the criteria of the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for possible and probable AD. As control group, we recruited healthy unrelated individuals from the general population. To avoid population stratification problems, all individuals enrolled in this study were white Mediterranean with registered Spanish ancestors (2 generations) as recorded by clinical researchers. The referral centers' ethics committees have approved this research protocol. Written informed consents were obtained from all individuals included in this study. Crude, adjusted and APOE stratified association studies were carried out using plink software. Effect size estimates are reported with 95% confidence intervals. *Results:* In the present replication effort, a nominally significant signal (P<0.05) was detected for ABCA7 rs4147929 SNP (crude p-value=0.008202, OR=1.147, C.I.95%[1.036-1.27]). The observed effect size resisted co-variation and APOE stratification. Observed effect size and direction for rs4147929 was strictly concordant with International Genomics of Alzheimer project (IGAP) results. In contrast, we failed to replicate CD33 rs3865444 protective effect previously reported (crude p-value=0.6659, OR= 0.9795, C.I.95%[0.8915-1.076]). *Conclusion:* Observed associations are in accordance with IGAP results. The ABCA7 locus or a near gene contains an undisputable candidate function that merits for further molecular research and drug development in Alzheimer's disease. In contrast, CD33 locus seems to be affected by the "APOE curse" which consists in the impossibility to find out any firm, clear and independent replication around APOE genetic region. The large contribution of APOE allele to AD risk, the existence of long range linkage disequilibrium regions in different populations, the existence of hidden familial cases and population inbreeding could be distorting and masking genetic results of multiple loci around APOE and might help to explain observed divergences between studies. *Funding:* Instituto de Salud Carlos III (ISCIII). Ministerio de Economía y Competitividad, in Spain (grant: PI13/02434). Ms. Trinitat Port Carbó legacy.

P3-9: APOE GENOTYPE MODIFIES THE RELATIONSHIP BETWEEN VASCULAR RISK FACTORS AND COGNITIVE DECLINE. T Juarez-Cedillo[1], O Rosas-Carrasco[2], LA Gutiérrez-Gutiérrez[3] *((1) Instituto Mexicano del Seguro Social, Centro Médico Nacional Siglo XXI. México D.F; (2) Instituto Nacional de Geriatría, SSA, México; (3) Instituto Nacional de la Nutrición Salvador Subirán. SSA. México)*

Background: Vascular risk factors have been associated with cognitive decline; however, it remains unclear whether apolipoprotein E (APOE) genotype modifies this relationship. We aim was to elucidate this relationship between the cognitive assessment and APOE. *Methods:* The participants from the prospective Study on Aging and Dementia in Mexico (SADEM) underwent health examination from 2009 to 2010, followed by a baseline neuropsychological assessment and a repeat neuropsychological assessment approximately 2 years later (2012-2013). Multivariate linear regression analyses were performed to examine the relationship vascular risk factors, presence of the APOE ε4 allele, and cognitive change. *Results:* APOE genotype significantly modified the associations between both midlife hypertension and cardiovascular disease and decline in verbal memory, attention, and visuospatial abilities. Associations between increased midlife vascular risk burden and greater cognitive decline were observed among APOE ε4 carriers but not noncarriers. *Conclusions:* The present findings revealed a subgroup at increased risk for cognitive decline (APOE ε4 carriers with midlife exposure to vascular risk factors) and suggest that treatment of vascular risk factors may reduce the risk of cognitive impairment, particularly among APOE ε4 carriers.

P3-10: CLINICAL-PATHOLOGIC CORRELATION IN A DEMENTIA UNIT IN BARCELONA. ISABEL HERNÁNDEZ[1], ANA MAULEON[1], MAITEÉ ROSENDE[1], LILIANA VARGAS[1], MONTSE ALEGRET[1], ANA ESPINOSA[1], GEMMA GARCIA[1], PILAR CAÑABATE[1], MARIOLA MORENO[2], ELLEN GELPÍ[2], Mª JESÚS REY[2], LLUIS TARRAGA[1], MERCE BOADA[1] *((1) Fundació ACE. (ICNA). Barcelona; (2) IDIBAPS. Banc de Teixits Neurológics de Catalunya)*

Background: One of the objectives of dementia units in Catalonia is to contribute to research on the causes of neurodegenerative processes. Neurological tissue banks are one source of samples needed for basic researchers to continue to study these pathologies, clinical-pathologic correlation being an essential tool to achieve reliable results. *Methods:* 123 cases followed in the Diagnostic Unit of Fundació ACE from 1996 to the present who were donors at Banc de Teixits de Catalunya (IDIBAPS). The observed frequency and demography of neurodegenerative diseases, their clinical-pathologic correlation, starting symptoms and survival time from diagnosis, is described. *Results:* The most common proteotype found was amyloidopathy (N=85), with 90% of correlation in those patients with a clinical diagnosis of Alzheimer disease (AD), in its different phenotypes and combined presentations. The next most frequent proteotype was Frontotemporal Lobar Degeneration (FTLD) with its different phenotypes (n = 25) with a correlation of 86%. Finally, for the synucleopathy proteotypes (N = 10) a correlation of 70% was observed. *Conclusions:* Neurological tissue samples with good clinical correlation provide to basic researchers information for the development of new molecules, and potential clinical trials. Clinical diagnosis accuracy observed in pathological series from Fundació ACE is equivalent to the precision observed in other neuropathological cohorts (Schneider 2009). *Reference:* Schneider JA1, Aggarwal NT, Barnes L, Boyle P, Bennett DA. The neuropathology of older persons with and without dementia from community versus clinic cohorts. J Alzheimers Dis. 2009;18(3):691-701. http://doi.org/10.3233/JAD-2009-1227. Manuscript, A., & Dementia, W. (2010). NIH Public Access, 18(3), 691–701

P3-11: RESTING-STATE CARDIAC WORKLOAD IS RELATED TO BOTH INCREASED NEOCORTICAL AGGREGATION OF B-AMYLOID PROTEIN AND RELATIVE IMPAIRMENTS IN SPATIAL WORKING MEMORY IN PRE-CLINICAL ALZHEIMER'S DISEASE. CLAUDIA Y SANTOS[1], YEN YING LIM[2,3], WEN-CHIH WU[4], SHAHENA POLYNICE[5], PAUL MARUFF[3,6], PETER J SNYDER[1,2] *((1) Interdisciplinary Neuroscience Program, University of Rhode Island, Kingston,*

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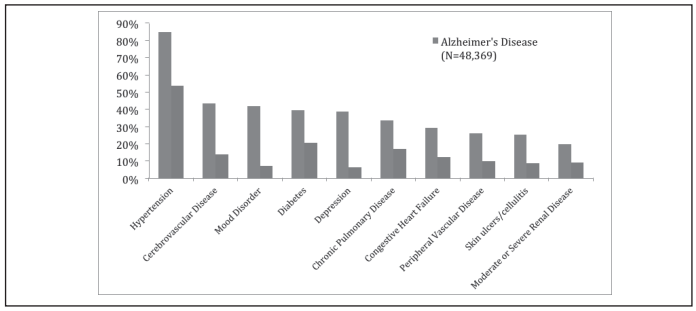
Background: Cardiovascular disease is common in older adults, and risk factors such as chronic hypertension, atherosclerosis and arteriosclerosis are also known risk factors for mild cognitive impairment (MCI) and Alzheimer's disease (AD). Cardiovascular diseases can lead to cognitive impairment as a result of sustained cerebral hypoperfusion, the proliferation of cerebral microemboli, cerebral infarction, and other insults that result in oxidative stress and neuroinflammatory responses (Napoli & Shah, 2011; Muqtadar, Testai & Gorelick, 2012). Moreover, the neuropathologic process of AD itself leads to deleterious changes to the integrity of the cerebrovascular system, resulting in impaired vascular function (Smith & Greenberg, 2009). This high co-morbidity between Alzheimer's disease and cardiovascular disease is thus both well-known and results from a very complex bidirectional mechanistic relationship that leads to important considerations for establishing subject inclusion and exclusion criteria for clinical trials. Hence, it is important to better understand relationships between cardiovascular health and AD processes. We sought to determine whether there is any association between a cardiac workload marker, rate-pressure-product (RPP), working memory and cortical beta-amyloid (Aβ) burden in 63 cognitively normal older adults with and without preclinical AD. *Methods:* Cognitively normal midlife adults (N=63, Mage= 62.7), with first-degree family histories of AD and with complaints of significant subjective memory impairment (SMI), underwent 18F-florbetapir PET imaging to measure neocortical β-amyloid aggregation. PET standardized uptake value (SUV) data were summed and normalized to the whole cerebellum SUV, resulting in a region-to-cerebellum ratio termed SUV ratio (SUVr). Blood pressure and heart rate data were collected, during an initial baseline visit, while subjects were at rest, with all assessments occurring between 0800 and 0900. Subsequent to the collection of these measures, all subjects completed the Groton Maze Learning Test (GMLT; www.cogstate.com). The GMLT has been described in numerous previous publications as a computer (iPad) administered hidden maze test that differentially measures both spatial working memory and reasoning/problem solving cognitive functions. *Results:* The results show a moderate relationship between increasing cardiac workload (at rest) and increasing impairments on the GMLT, but only for the 15 subjects with evidence of substantial neocortical amyloid aggregation (Florbetapir PET imaging) ($R2 = 0.30$; $p = .034$). By comparison, no such relationship was observed for the 48 subjects without any evidence of cortical Aβ plaque burden ($R2 = .02$, ns). With all 63 subjects considered together, there is a small-to-moderate relationship between neocortical Aβ burden and RPP ($r = 0.261$, $p = .039$), with increasing cardiac workload at rest associated with greater neocortical amyloidosis. This relationship remained significant, after statistical control for body mass index ($r = 0.262$, $p = .040$) and age ($r = .258$, $p = .043$). *Conclusion:* This study may be the first to demonstrate that increased cardiac workload, as a surrogate of myocardial oxygen use, at rest, is related to neocortical amyloidosis in midlife adults with preclinical AD. This relationship is modest, and RPP does not have the potential to serve as a biomarker of cortical Aβ burden in preclinical AD. Rather, we were impressed by finding a significant relationship at all, given that our study subjects are all relatively young, healthy, living independently and free of any diagnosable cardiological or neurological diseases. These results suggest that there is a small to moderate correlation between increased RPP levels and neocortical Aβ burden in individuals with first-degree family history of AD as well as persistent subjective memory impairment, consistent with suspected pre-clinical AD (Doherty et al., 2015; Koppara et al., 2015; Schultz et al., 2015). We have shown previously that, in older adults, elevated resting state RPP is associated with relatively poorer cognitive performance on a modified version of the GMLT, but this prior cohort was not specifically screened for possible occult disease (Mathewson et al, 2011). These current results corroborate that initial report, as we observed a strong linear correlation between RPP and performance on the GMLT, with increasing cardiac workload at rest associated with greater impairment on the spatial working memory measure of this test, but only for those subjects with PET amyloid imaging evidence of likely preclinical AD. Taken together, these results support a direct relationship between at least one major neuropathologic pathway for the disease (the aggregation of beta-amyloid protein plaques in the neocortex), increasing cognitive impairment and more inefficient myocardial oxygen use in the absence of significant metabolic demands, although the mechanistic nature of this relationship remains unclear. We are currently re-evaluating the subject cohort described in this report, to determine whether indices of phasic vagal cardiac control such as their resting sinus arrhythmia (RSA) and heart rate variability (HRV) measures are also related to cortical amyloidosis in preclinical AD, since both cardiac phenomena are directly modulated by muscarinic cholinergic and nicotinic autonomic neurotransmission.

P3-12: BURDEN OF ALZHEIMER'S DISEASE: CLINICAL COMORBIDITIES AND CO-MEDICATIONS. NAWAL BENT-ENNAKHIL[1], LIN XIE[2], MYRLENE SANON[3], FLORENCE COSTE[1], YUEXI WANG[2], M FURAHA KARIBURYO[2], PETER NEUMANN[4], HOWARD FILLIT[5,6] *((1) Global Epidemiology, Lundbeck SAS, Issy-Les-Moulineaux, France; (2) StatinMed Research, Ann Arbor, MI, USA; (3) Health Economics and Outcomes Research, Otsuka America Pharmaceuticals, Princeton, NJ, USA; (4) Tufts-New England Medical Center, Boston, Massachusetts, USA; (5) Mount Sinai Medical Center, New York City, USA; (6) Alzheimer's Drug Discovery Foundation, New York, NY, USA)*

Background: Previous studies have reported a significant medical burden among persons with Alzheimer's disease (AD). However, most findings have several limitations including: study cohorts with only Medicare Advantage enrollees (employer-sponsored coverage) thus limiting generalizability; heterogeneity of the methodology; or outdated research. Updated data on the management of common comorbidities in AD patients is warranted to support resource allocations for providers of care to patients with AD. Therefore, a retrospective longitudinal population-based study was conducted to examine the association of AD with comorbidity burden, use of co-medications, and mortality, using medical and pharmacy claims data, in a large US nationally representative Medicare sample. *Methods:* Patients diagnosed with AD (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9 CM] code 331.0 and ≥1 anti-AD prescription [donepezil, rivastigmine, galantamine, memantine] or a second AD diagnosis) were selected (01JAN2010-31DEC2012) from the Medicare claims dataset 5% sample. The first AD diagnosis date occurring during the inclusion period was designated as the index date. Control patients without an AD diagnosis, AD-related dementia diagnosis or anti-AD prescriptions were matched 1:1 to AD case patients based on gender, race, U.S. region and study year. The same index date for case patients was assigned to matched control patients. Patients were required to be aged 65-100 years, with continuous medical and pharmacy benefits for 24 months pre- index date (baseline period) and at least 6 months post-index date. Patient data recorded until the earliest of death, health plan disenrollment or end of the study period (follow-up period)

were extracted. Propensity score matching, adjusting for baseline demographics and individual comorbidities, was used to compare the use of co-medications and mortality rates between AD cases and controls. *Results:* 48,369 AD patients were identified in the Medicare population during the study period and matched to 48,369 non-AD controls. Baseline demographics were consistent across cohorts after the match; mean age 83 years and greatest proportion of patients between the ages 75 and 94 years. Eighty-one percent of the sample was White, followed by Black (11%), Hispanic (4%), and Asian (2%). During the baseline period, the most common comorbidities observed for AD patients were hypertension (84.9% vs. 53.7% for controls), followed by cerebrovascular disease (43.5% vs. 13.7% for controls), mood disorders (42.0% vs. 7.1% for controls) and diabetes (39.5% vs. 20.7% for controls) (Figure 1). AD patients also had higher Charlson Comorbidity Index (CCI) scores than non-AD controls (4.88 vs. 2.31). The mean follow-up length was 1.73 years (Standard Deviation, SD: 0.79). The frequency of use of co-medications was higher in AD patients compared with the non-AD individuals during the follow-up period; the difference was particularly pronounced for psychotropic medications. After adjusting for comorbidity differences, the picture reversed. In particular dyslipidemia drugs, antihypertensives and NSAIDs were more used in non-AD compared to AD individuals. Only psychotropic drugs remained more frequently used in AD compared to non-AD individuals. The mortality rates (per 100 person years) are significantly higher for AD individuals (16.4) than for non-AD individuals (4.3), even after adjusting for comorbidity differences (15.5 vs. 4.4).

Figure 1
24-month Baseline Top Ten Comorbidities

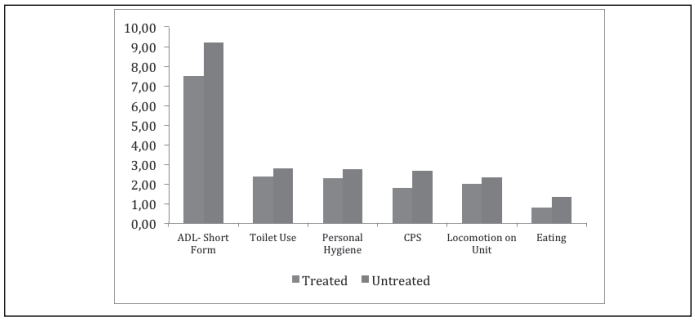


Conclusion: During the baseline period, AD patients experienced greater medical comorbidities than matched controls, as shown by the CCI scores and rates of individual comorbidities- including hypertension and mental disorders. After adjusting for comorbidity differences, the use of most of co-medications, in particular antihypertensives and dyslipidemia drugs, during the follow-up period was significantly lower in the AD cohort compared to the control group, suggesting a poor management of comorbidities in persons with AD.

P3-13: AN UPDATE ON ALZHEIMER'S DISEASE PATIENT & TREATMENT CHARACTERISTICS IN THE UNITED STATES (US). MYRLENE SANON[1], LIN XIE[2], NAWAL BENT-ENNAKHIL[3], FLORENCE COSTE[3], YUEXI WANG[2], M FURAHA KARIBURYO[2], PETER NEUMANN[4], HOWARD FILLIT[5,6] *((1) Health Economics and Outcomes Research, Otsuka America Pharmaceuticals, Princeton, NJ, USA; (2) StatinMed Research, Ann Arbor, MI, USA; (3) Global Epidemiology, Lundbeck SAS, Issy-Les-Moulineaux, France; (4) Tufts New England Medical Center, Boston, Massachusetts, USA; (5) Mount Sinai Medical Center, New York City, USA; (6) Alzheimer's Drug Discovery, New York, NY, USA)*

Background: Anti-dementia treatments can aid in the management of symptoms of Alzheimer's Disease (AD). However, few studies have recently evaluated treatment exposure and characteristics of treated versus untreated patients newly diagnosed with AD. *Methods:* A retrospective database analysis using Medicare fee-for-service claims data was conducted to examine patient and disease characteristics, AD treatment, and healthcare resource utilization among Medicare beneficiaries enrolled in Medicare Part D between January 2008 and December 2012. The study sample included beneficiaries with: 1) at least 1 claim with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 331.0 for AD; 2) at least 1 pharmacy claim for donepezil, galantamine, rivastigmine, or memantine or a second confirmatory ICD-9 claim for AD diagnosis; 3) age 65-100 years; and 4) continuous enrollment with medical and pharmacy benefits 12 months during the baseline and at least 6 months after index date. The first AD diagnosis date occurring during the inclusion period was designated as the index date. Additionally, the Minimum Data Set (MDS) linked with Medicare data was also retrieved and included for eligible study patients. Cohort assignment (treated vs. untreated) were based on treatment received and descriptive analyses were undertaken. Healthcare resource utilization between cohorts was evaluated during the 12 month baseline.

Figure 1
Alzheimer-related severity indexes, mean scores between treated and untreated patients



CPS: Cognitive Performance Scale, ADL: Activities of Daily Living

Results: A total of 9,812 incident AD patients were included in the study; 41% were between 75-84 years old, 39% between 85-94 years old, 75% were female, and 79% were Caucasian. Twenty-four percent of study patients had MDS linked Medicare data. Of the total identified patients, 56% percent (n=5,567) received an anti-dementia therapy during follow-up. Significant differences were observed between the treated and untreated cohorts at baseline in mean years of age (82 vs. 85), proportion of female gender (74 vs. 77%), mean Charlson comorbidity index score (3.29 vs. 3.56). AD-severity indexes (i.e., cognitive performance scale, activities of daily living) were also greater in the untreated cohort (Figure 1). During the baseline period untreated patients incurred greater healthcare resource utilization compared with treated patients, notably the per patient per month mean number of pharmacy visits was 2.08 vs. 1.75 and hospice visits 0.02 vs. 0.00, respectively. *Conclusion:* Significant baseline differences were observed between patients treated with an anti-dementia treatment versus those who are untreated. Forty-four percent of newly diagnosed patients are not treated with anti-dementia treatment over the course of a two-year observation period after diagnosis. Untreated patients are older, have greater disease comorbidity, worsened AD-related disease severity scores, and greater healthcare utilization. Study findings provide an updated review of treatment characteristics and baseline healthcare resource utilization among patients with AD.

P3-14: IDENTIFICATION OF A FAST PROGRESSION DEMENTIA PHENOTYPE: A COMPARATIVE EVALUATION OF TWO SHORT COGNITIVE SCREENING INSTRUMENTS.
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Background: There is a need for earlier diagnosis, to delay disease progression. Cognitive impairment is often considered a very early stage of dementia, i.e. a stage of disease where disease modification is most likely to be possible. The causes of cognitive impairment are not yet completely understood. It is well known that mild cognitive impairment (MCI) increases the risk of later developing dementia; however some people with MCI never progress or even return to normal levels. MCI is believed to be a very heterogeneous condition and therefore there is a need for population based studies to identify subgroups of individuals who are most likely to progress to dementia. Different cognitive screening instruments may identify different drivers of diseases, and could consequently be used to identify different subpopulations of progression. In the current study, we compared the Short Blessed Test (SBT) to the Verbal Fluency Test (VFT), for assessing cognitive function in 5601 elderly women from the PERF I study. The aim was to identity test specific risk factors with the purpose of identifying fast progression indicators. *Methods:* The SBT is a six-item test, assessing; orientation, concentration, and memory. Scores range from 0 to 28, with lower scores indicating better performance. The VFT measures verbal production, semantic memory, and language. In this test subjects name as many animals as possible in 60 seconds. Higher scores indicate better performance. The study population was grouped based on their cognitive performance. The cut-off score used for the SBT was 6/7 and 14/15 for the VFT. Spearman's correlation was used to measure the association between scores of the two tests. A logistic regression was used to assess the cross-sectional relation between various risk factors and cognitive impairment in each of the tests. In order to validate the prognostic potential of each test, dementia diagnoses were retrieved from national Danish registries. 596 developed dementia from baseline until retrieval of register data on Dec 31th 2014. Women diagnosed with dementia prior to baseline were excluded (n=15). Spearman's correlation was used to measure the association between time to diagnosis and each test. *Results:* Of the 5590 eligible subjects, 8.0% (447/5590) scored above the cut-off of 6/7 in the SBT, and 10.8% (605/5586) scored above the cut-off of 14/15 in the VFT. One hundred and thirty two (2.4%) scored above the cut-off on both cognitive tests. There was a small albeit significant negative correlation between scores in the SBT and the VFT (rho = -0.204 [-0.230 to -0.178], p <0.0001). Both tests showed significant correlation with time to dementia diagnose: SBT (rho = -0.179 [-0.258 to -0.098], p <0.0001) and VFT (rho = 0.260 [0.181 to 0.336], p <0.0001). Age, education level, alcohol consumption and depression were cross sectionally associated with cognitive impairment in both tests (data not shown). In the SBT self-reported diabetes and high serum cholesterol levels was also associated with cognitive impairment. In contrast, high white blood cell count and physical inactivity was associated with cognitive impairment in the VFT. The prognostic performances of the SBT and VFT individually and in combination were assessed by calculating the sensitivity, specificity, positive predictive value (PPV) and negative predictive (NPV) for each cut-off score and their combination. SBT: (Sensitivity(%)=14.7; Specificity(%)=92.8; PPV(%)=19.7; NPV(%)=90.1), VFT: (Sensitivity(%)=20.0; Specificity(%)=90.3; PPV(%)=19.7; NPV(%)=90.4) and combination: (Sensitivity(%)=7.2; Specificity(%)=98.2; PPV(%)=32.6; NPV(%)=89.9). Subjects above the cut-off had a significantly decreased average time to diagnosis. The average time to diagnosis for subjects above the cut-off score in the SBT was 6.6±4.0 years (P<0.001, impaired vs. normal). The VFT showed similar results with an average time to diagnosis of 6.8±3.9 (P<0.001) years for subjects scoring below the cut-off. The average time to diagnosis for subjects considered impaired in both tests had an average time to diagnosis of 5.2±3.8 years (P<0.001). *Conclusion:* We identified a fast progression phenotype by combining to cognitive tests. These simple tests had both similar and different drivers of disease, explaining their additive value. Despite the significant correlation between the two tests, the magnitude of the correlation coefficient indicates that the two tests measure different types of cognitive impairment. While the individual test intends only to assess a limited aspect of cognition, the combination may reflect a widespread impairment. The performance of the combined tests for the identification of subjects with cognitive impairment whom progressed to dementia was superior to either test alone. This combination is able to identify a fast-progression phenotype that is more likely to develop dementia within a shorter timeframe, and even suggest that some cognitive tests are more suited for some interventions than others depending on the risk factors present.

P3-15: GENETIC VALIDATION OF DRUG TARGETS FOR SECONDARY PREVENTION OF ALZHEIMER'S DISEASE.
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Backgrounds: Alzheimer's Disease (AD) is a complicated multifactorial disease, with environmental and genetic factors acting together to develop the disease. Comprehensive genome-wide association studies (GWAS) and exome sequencing has revealed various low-penetrance variants. More recently, the International Genomics of Alzheimer Project (IGAP) duplicated the number of loci related to AD. The clinical execution and rating of exposed AD risk markers in Mild Cognitive Impairment (MCI) to AD conversion prediction is almost undiscovered. The information on loci acting in prodromal stages of AD, i.e. MCI, will be of relevance for drug target selection for secondary prevention trials. *Methods:* In order to gain insight into the role of well-established AD risk genetic markers in MCI progression, we conducted a new study by genotyping 40 single nucleotide polymorphism (SNPs), formerly associated to AD investigating its role in MCI pheno-conversion to AD. Single marker and combined polygenic scores effects were measured using Cox proportional hazards models and subsequent meta-analyses in four independent datasets with available follow-up data from Germany, Spain, and The Netherlands. (n=3226 MCI subjects). *Results:* This work distinguishes Clusterin (CLU) locus as an independent genetic factor associated with MCI progression to AD (CLU rs933188: HR=1·187[0·054-1·32]; p=0·0035). We also constructed a polygenic score (PGS1), comprising nine well-established genome-wide AD risk loci, with a small effect on risk of MCI progression to AD in APOE ε4 carriers (HR=1·746[1·029-2·965]; p=0·038). In contrast, our findings do not endorse a major contribution of newly identified AD loci by IGAP on MCI pheno-conversion to AD. *Conclusion:* CLU-related molecular pathways are potential drug targets for secondary prevention of AD. CLU SNPs are potential markers for MCI to AD progression. SNP-based polygenic risk scores constituting currently available AD genetic markers are not sufficient to forecast MCI to AD pheno-conversion. *Funding:* Instituto de Salud Carlos III (ISCIII). Ministerio de Economía y Competitividad, in Spain (grants: PI13/02434, PI10/00954), Agència d'Avaluació de Tecnologia i Recerca Mèdiques, Departament de Salut de la Generalitat de Catalunya (grant 390/06/2009). The German Federal Ministry of Education and Research (grants KND: 01GI0102, 01GI0420, 01GI0422, 01GI0423, 01GI0429, 01GI0431, 01GI0433, 01GI0434; grants KNDD: 01GI0710, 01GI0711, 01GI0712, 01GI0713, 01GI0714, 01GI0715, 01GI0716, 01ET1006B). Stichting Alzheimer Nederland, Stichting VUmc fonds and Stichting Dioraphte. E. Louwersheimer was supported by a research fellowship from Alzheimer Nederland (WE 15-2014-04).

P3-16: REPRESENTATIVENESS OF CLINICAL TRIAL POPULATIONS IN MILD AD DEMENTIA – A COMPARISON OF 18 MONTH OUTCOMES WITH REAL WORLD DATA FROM THE GERAS OBSERVATIONAL STUDY. ANNABEL BARRETT[1], MARK BELGER[1], GRAZIA DELL'AGNELLO[2], KRISTIN K WROBLESKI[3], SETHURAMAN GOPALAN[3], DAVID HENLEY[3], JOEL RASKIN[3], CATHERINE REED[1] *((1) Eli Lilly and Company Limited, Windlesham, UK; (2) Eli Lilly Italia, Sesto Fiorentino, Italy; (3) Eli Lilly and Company, Indianapolis, US)*

Background: Randomised controlled trials (RCTs) are generally considered to be a gold standard approach for assessing the efficacy of treatments. Lack of external validity or generalisability is often a criticism of RCTs with key areas of concern being representativeness of patients, differences between trial protocols and clinical practice, clinical trial setting and measurements of effect. Differences between RCTs and the real-world may or may not impact treatment effects; nevertheless it is important to identify both differences and similarities between RCT patients and real-world patients and practice. The aim of this study is to describe the mild dementia due to Alzheimer's disease (AD) baseline patient populations of two RCTs in AD [the EXPEDITION trial programme] and a real-world cohort of patients with AD (the GERAS observational study).18 month disease and health outcomes of patients in the placebo arms of the EXPEDITION trials will be compared with outcomes of patients in the GERAS cohort. *Methods:* The EXPEDITION trials were two 18-month, international, randomized, double-blind, placebo-controlled trials of solanezumab in mild and moderate AD dementia patients. GERAS is a prospective, non-interventional study of AD patients of all severities in France, Germany and the UK who presented within the normal course of care. All patients were aged >55 years, diagnosed with probable AD (NINCDS-ADRDA), not institutionalised and with an informal caregiver and the majority were receiving standard of care treatment(s). Data collected in all studies included demographics, medical history, cholinesterase inhibitor (AChEI)/memantine use and measures of cognition (MMSE and ADAS-Cog), function (ADCS-ADL), behaviour (NPI) and health-related quality of life [HRQoL (EQ-5D)]. For this analysis the subgroups of placebo patients with mild dementia due to AD (MMSE 26-20) from the two RCTs were pooled and patients with mild AD from GERAS (MMSE 26-21) were used. Demographics and baseline characteristics were summarized using descriptive statistics based on non-missing observations. Disease and health outcomes at 18 months of the control arms of the RCTs and the GERAS cohort were independently adjusted using Generalised linear models for key baseline factors including age, baseline AChEI/memantine use and baseline outcome score. *Results:* Patients in the pooled RCT placebo populations (n=663) were slightly younger (mean 73 (sd=7.9) versus 77 (6.9) years) than patients in the observational study (n=566) with more females in the RCT (55% versus 48%). Time since diagnosis was similar in both populations (2.0 (1.85) EXPEDITION versus 1.7 (2.00) years GERAS). Patients had similar use of at least one AChEI and/or memantine (89% RCT versus 85%); however combination AD treatment use (AChEI + memantine) was higher in the RCT population (24% versus 5%). Performance was similar on cognitive scales at baseline, although patients in the observational study had slightly greater functional and behavioural impairment and lower HRQoL. After 18 months, data was available for n=521 (79%) EXPEDITION patients and n=417 (74%) in GERAS. LS mean (standard error) change in MMSE score from baseline was similar in the RCT group [–2.8 (0.22) compared to GERAS -2.7 (0.21)]. In ADAS-Cog14 the change from baseline was 6.2 (0.49) and 4.4 (0.65) for RCT and observational patients respectively. Functional ability on instrumental activities, measured with ADCS-ADL over the 18 months was -6.8 (0.46) and -6.6 (0.65) for RCT and observational patients respectively. NPI change from baseline was 1.1 (0.57) (EXPEDITION) and 4.1 (0.58) for GERAS patients. Adjusted proxy-rated EQ-5D health state scores both showed minimal change from baseline after 18 months: -0.04 (0.01) (EXPEDITION) and -0.06 (0.02) (GERAS). *Conclusion:* Patient demographics and baseline disease characteristics of these two mild AD dementia populations demonstrate some differences; however, they are not as pronounced as potentially expected given more restrictive inclusion and exclusion criteria for clinical trials compared to real world patients. Differences in baseline AD treatment use may be due to regional variations dependent on where the studies were run. Disease progression based on adjusted estimates of change in outcomes at 18 month was largely similar in the two populations. These results provide supporting evidence that RCT and observational studies can provide complementary data to assess longitudinal patient outcomes on disease progression in mild AD dementia patients. Sponsored and funded by Eli Lilly and Company.

P3-17: THE DEMENTIA OF ALZHEIMER'S DISEASE

MAY BE DUE TO A DECLINE IN THE MONOSACCHRIDE TRANSFERASE, ALG7, THAT IS INVOLVED IN THE N-GLYCOSYLATION PATHWAY. JORDAN L HOLTZMAN *(University of Minnesota, Minneapolis, Minnesota, USA)*

Background: It is widely held that the dementia seen in both early and late onset Alzheimer's disease (AD) is due to the neurotoxicity of the deposits and aggregates of β-amyloid (Aβ). Based on this paradigm many investigators have created transgenic mice with mutant genes associated with the familial forms of the early onset disease. This seemed reasonable since the two forms of AD share many of the same histopathological and clinical features. Hence, it has been thought that the treatments that were effective in the familial forms should also be effective in the late onset disease. Yet, in a recent review of the database, www.ClinicalTrials.gov, Cummings et al. reported that 244 drugs that were effective in these models and entered phase I-III clinical trials have all failed to show any benefit in AD patients. These findings suggest that there is a need to seek new paradigms for the etiology of AD. We began our search for an alternative paradigm with the question that since Aβ is produced in everyone why deposits are only seen in the brains of the elderly? Our studies suggest that both the deposition of Aβ and the dementia are due to a decline in the capacity of the endoplasmic reticulum (ER) to catalyze the posttranslational folding of nascent proteins. We believe that this decline may be primarily due to a decrease in the activity of the ER N-glycosylation pathway. *Methods:* CSF was obtained from normal volunteers. Western blots were run on fresh or fresh frozen samples without any pretreatment. After running on SDS-PAGE the samples were transferred to PVDF membranes and the bands were determined by immunophospatase and chemiluminescence reactions. Blots were run with multiple antibodies against Aβ and six ER chaperones. *Results:* All the immunoreactive Aβ appeared as a single band at 62 kDa. One chaperone, ERp57, had a doublet at 57 and 62 kDa. The ERp57 upper band and the Aβ band colocalized on immunopurification. The Aβ-ERp57 complex was stable after treatment with formic or trifluroacetic acid, but base treatment liberated free Aβ. The complex bound to a polybornate column indicating that it contains carbohydrate. *Conclusions:* Our studies indicate that Aβ is normally N-glycosylated and covalently bound to the ER chaperone, ERp57. These modifications keep the Aβ in solution. The complex is formed in the ER during the posttranslational processing of the amyloid precursor protein (APP). When there is a decline in the capacity of the ER to catalyze the formation of this complex, the naked Aβ peptide is dumped into the extracellular space and aggregates to form plaque. These data suggest that plaque is only a biomarker for a decline in this ER pathway. The ER posttranslational protein processing is a highly conserved pathway found in all eukaryotes. It catalyzes the folding of approximately 40% of the cellular proteins, including the synaptic, membrane proteins that are necessary for a functioning memory. Hence, the cognitive decline seen in AD may be due to a decreased capacity to process these synaptic proteins. N-glycosylation is a critical step in protein folding in the ER. In this reaction a complex carbohydrate is attached to the nascent protein chain. This carbohydrate complex is initially synthesized attached to a lipid cofactor, dolicol. After the addition of 15 sugars, the complex is transferred from the dolicol to the ε-animo group of an asparagine. The addition of each sugar to the dolicol is catalyzed by a set of unique monosaccharide transferases (MST). An unusual aspect of dolicol metabolism is that a number of laboratories have reported that the tissue levels of this lipid increases 5-10 fold with age without any increase in synthesis. This suggests that there is a metabolic block in its utilization, most likely secondary to a decline in the activity of the MST, ALG7, that catalyzes the initial synthesis of the carbohydrate complex on the dolicol. This would lead to decreased N-glycosylation of the nascent proteins and an increase in the fraction of the proteins that fail to fold properly. Those that fail to fold activate the unfolded protein response (UPR) of the ER quality surveillance system. Activation of the UPR turns off the transcription of all proteins that are not critical for cell survival. With further increased levels of unfolded proteins, the UPR activates apoptosis. These considerations suggest cellular models for rapid drug screening in which a gene for a fluorescent protein is imbedded in the gene for ALG7 in immortalized neuronal cells. The effect of potential therapeutic agents on ALG7 levels can then be monitored in a plate reader by changes in fluorescence.

P3-18: BUTYRYLCHOLISNTERASE K-VARIANT - A GENETIC MARKER OF POOR RESPONSE TO DONEPEZIL IN MILD COGNITIVE IMPAIRMENT. SOPHIE SOKOLOW[1,2], X LI[3,4], L CHEN[1], KD TAYLOR[3,4], JI ROTTER[3,4], RA RISSMAN[5,6], PS AISEN[7], LG APOSTOLOVA[8] *((1) School of Nursing, University of California at Los Angeles, Los Angeles, CA, USA; (2) Brain Research Institute, University of California at Los Angeles, Los Angeles, CA, USA; (3) Institute for Translational Genomics and Population Sciences, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA; (4) Division of Genomic Outcomes and Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, CA, USA; (5) Alzheimer's disease cooperative study, University of California San Diego, San Diego, CA, USA; (6) Department of Neuroscience,School of Medicine at UCSD, University of California San Diego, San Diego, CA, USA; (7) Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, CA, USA (8) Indiana University School of Medicine, Indiana Alzheimer's Disease Center, Indianapolis, IN, USA)*

Background: Donepezil is an acetylcholinesterase inhibitor (AChEI) widely prescribed for the symptomatic treatment of mild cognitive impairment (MCI) and Alzheimer's disease (AD). The K-variant of butyrylcholinesterase (BChE) is associated with lower BChE expression and acetylcholine-hydrolyzing activity. It also displays synergistic effects with APOε4 on the incidence of late-onset AD and on the risk of progression from MCI to AD. Results still conflict regarding the influence of BChE K-variant genotype on AChEI response in AD patients. As of yet, studies examining the influence of BChE genotype on donepezil efficacy in MCI have not been reported. The purpose of our study was to evaluate the interaction between BChE polymorphism (rs1803274) and the efficacy of donepezil in the treatment of cognitive and executive dysfunction in MCI. *Methods:* We took advantage of the genotyping performed with the Illumina Human610-Quad Bead-Chip and neurological outcomes data collected during the vitamin E/donepezil trial to examine the effect of BCHE polymorphism rs1803274 (K-variant) on donepezil response. We used linear regression models adjusting for age, gender and APOE4 to test the influence of BChE polymorphism rs1803274 - on changes in Mini-Mental State Examination (MMSE) and Clinical Dementia Rating sum of boxes (CDR-SB) scores at the end of the 3-year trial. We estimated the beta regression coefficient for rs1803274 in each group as implemented in Plink software v1.07. To determine whether the association was a response to treatment, or due to a main effect of genotype on the history of disease progression, we also tested the interaction term of rs1803274 and donepezil treatment (treated vs. non-treated (i.e. vit. E and placebo arms) subjects) on MMSE and CDR-SB by the linear regression model adjusting for covariates stated above. *Results:* The variant of BChE (rs1803274) is significantly associated with non-response to donepezil when examining changes in MMSE and CDR-SB after 36 months of treatment; the K-variant is associated with a greater worsening in MMSE [-7.2 ± 3.4 (K homozygous),-2.2 ± 0.5 (K heterozygous) and-0.9 ± 0.4 (non-K)] and CDR-SB [(4.1 ± 1.9 (K homozygous), 1.3 ± 0.4 (K heterozygous) and1.082 ± 0.3 (non-

K)] compared to the common allele (P = 0.0004 and P = 0.040, respectively). Interestingly, in the control group, no association was found between the BChE K-variant and MMSE or CDR-SB worsening at m-36. The main effect of BCHE-K genotype on changes of MMSE or CDR-SB scores was not significant either at the end of the trial. But the interaction between BChE genotype and donepezil treatment is highly significant (p = 0.006) when comparing MMSE decline in treated and non-treated groups at m-36. Our findings also suggest that MMSE and CDR-SB scores tend to get worse faster in subjects carrying the BChE K-variant when treated with donepezil compared to placebo, while in non-carriers a benefit is observed after 3-years of donepezil therapy. *Conclusion:* We found a significant association between the BChE K-variant and donepezil non-response as assessed by a steeper deterioration in MMSE and CDR-SB after 3-year of donepezil treatment in MCI. This study represents a first effort at examining the influence of genetic predictors in the response of donepezil in MCI subjects and points out the importance of genetics in assessing drug response in complex diseases such as MCI and AD. This study also reinforces the importance of elucidating BChE biological pathways in MCI and in donepezil pharmacology as it can not only lead to personalized medicine but also the development of novel pharmacological compounds for the treatment of MCI and AD.

P3-19: A NEW CLINICAL DIAGNOSTIC FRAMEWORK FOR ASSESSING PRECLINICAL ALZHEIMER'S DISEASE IN HEALTHY AT-RISK ADULTS: A WORK IN PROGRESS.
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Background: Preclinical Alzheimer's Disease (AD) is a condition marked by biomarker positivity for abnormal brain amyloidosis, neuronal injury, or both, without significant cognitive impairment. While research-based criteria for diagnosing prodromal AD are published, no clinical diagnostic criteria exist to aid clinicians in identifying prodromal stages of neurodegenerative diseases (ND). A clinical framework for preclinical diagnosis that can be applied in the practice of AD prevention is necessary, especially for patients presenting with minor, yet detectable cognitive impairment (DCI), below the threshold of mild cognitive impairment (MCI). Many patients are also experiencing prodromal, often non-cognitive symptoms that may be suggestive of AD or other ND. The Alzheimer's Prevention Clinic at Weill Cornell Medical College/ NewYork-Presbyterian Hospital has provided direct clinical care to family members of AD (and other AD) patients since 2013. Patients seeking to lower their AD risk undergo a comprehensive assessment, receive a personalized plan based on rapidly evolving scientific evidence, and are followed longitudinally over time. We sought to establish initial feasibility of clinical criteria using only data elicited using standardized, widely available clinical tools. The clinical criteria were designed to identify AD prevention patients with DCI whose cognitive deficits could be reliably predicted to be due to underlying, prodromal ND ("DCI -ND"). Ultimately, if the criteria are indeed feasible and practical, they could be used by clinicians and researchers in the clinical practice of AD prevention. *Methods:* We modeled our preliminary diagnostic framework after the published diagnostic criteria for diagnosing MCI due to AD. We also incorporated evidence from extensive review of the literature on prodromal ND, combined with two years of clinical experience in the APC, and input from several experts in the field of AD prevention. Our diagnostic framework relies on a detailed clinical history (with focus on family history, ND risk factors, cognitive / non-cognitive symptoms using NIH PROMIS measures, and a comprehensive questionnaire), neurologic examination, anthropometrics, as well as computer-based cognitive testing in the clinic (NIH toolbox) and at home (Cognitive Function Test) via our web-based cognitive testing portal (www.AlzU.org/APC). The criteria are applied in weekly, multi-disciplinary patient case consensus conferences with a team of (at least) two neurologists and two neuropsychologists, as well as a host of other healthcare providers (preventative cardiologists, nutritionists, neurogeneticists, research personnel, and periodic visiting international experts). Conferences are webcast Wednesdays (11:00 am EST) and open to interactive participation for colleagues world-wide who are interested in joining. *Results:* Our current criteria highlights variations on patient classifications who would otherwise be classified as "normal". We classify patients who have no significant cognitive symptoms/findings as Normal with Low, Moderate or High Risk, using commonly available risk indices for cerebrovascular disease and AD. Specifically, Normal-High Risk patients are those who we predict to already be biomarker positive (i.e., Stage 1/Stage 2 Preclinical AD). After Normal, the next diagnostic category is termed detectable cognitive impairment (DCI), which identifies patients with objective cognitive deficits below the threshold for MCI. They may or may not have associated risk factors or subjective cognitive complaints. We then attempt to classify DCI patients as either DCI-ND or DCI not otherwise specified (DCI-NOS), based solely on the presence or absence of non-cognitive symptoms which have been robustly identified in the literature to be associated with any ND. Once classified as DCI-ND, we further attempt to predict the underlying pathology. We stratify DCI-ND as DCI due to typical AD (DCI-AD), DCI due to synucleinopathy (DCI-SN) and DCI due to Atypical ND (DCI-AND). This latter category includes patients with expected prodromal Posterior Cortical Atrophy, Primary Progressive Aphasia, Frontotemporal Lobar Degeneration, or other tauopathies). To distinguish among different predicted pathologies, we integrate the evidence regarding cognitive, mood, motor, sleep and family history features that are specific to different ND. For example, distinguishing features in DCI-AD include presence of amnestic-type memory changes, sleep inefficiency, late-life mood changes (i.e., irritability, depression), and slowed walking (without Parkinsonism). Distinguishing features in DCI-SN (such as from Parkinson's disease or Dementia with Lewy Bodies) are primarily non-amnestic cognitive deficits (e.g., bradyphrenia, poor learning, logopenia), REM behavior, features of autonomic disturbance (e.g., constipation, orthostatic hypotension) and early-life anxiety disorders. DCI-AND features include non-amnestic cognitive changes, history of atypical development (dyslexia, dyscalculia, dysgraphia, stuttering, etc.) and/ or other atypical factors (muscle atrophy, myoclonus, dystonia, gaze paralysis). *Conclusion:* While preliminary, these draft criteria allow practicing dementia prevention clinicians to classify patients at various levels of risk for ND based purely on clinical history, examination and freely available, standardized measures. Further research is warranted to identify the sensitivity and specificity of these consensus diagnoses with respect to verified AD and other ND biomarkers. Ultimately, a practical system for detecting prodromal dementias among asymptomatic or minimally symptomatic, at-risk patients, will aid in earlier diagnosis, more rapid initiation of prevention therapies (including more timely recruitment into prevention trials), and may delay disease onset.

P3-20: INTRANASAL DELIVERY OF STEM CELL FACTORS DECREASE ABETA AMYLOIDOSIS IN ANIMAL MODELS.
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Background: Recently we demonstrated that a repeated intravenous delivery of human mesenchymal stem cells (hMSC) can significantly decrease cerebral Abeta amyloidosis in an transgenic model of Alzheimer's disease (AD) (Bolmont T, Lukashev A, Lasser T. Peripheral delivery of human adult allogeneic stem cells reduces Abeta amyloid pathology in a mouse model of AD. Clinical Trials on Alzheimer's Disease. CTAD 2014). To further understand the mechanism(s) of action of stem cells delivered peripherally - whether it is a direct one due to penetration of the cells into the brain or an indirect due to releasing a number of cytokines and growth factors which in turn as smaller molecules penetrate through brain blood barrier in greater efficiency, - we investigated the impact of repeated intranasal delivery of stem cells factors (SCF) released during culturing of hMSC on cerebral Abeta amyloidosis in a mouse model of AD. *Methods:* For the preparation of soluble SCF, hMSC were expanded in oxygen deprived atmosphere. After reaching 80–100% confluence, cellular monolayers were washed to remove bovine serum. Serum-free cell-conditioned medium was harvested later. The medium was concentrated, mixed with sucrose, and preserved by vacuum foam drying technique. It was validated that stem cell conditioned media preserved by this method maintain its biological activity after more than 24 months storage at room temperature. Analysis and concentrations of solubilized proteins was measured by Raybiotech Q2000 human cytokine array that detects 120 human inflammatory factors, growth factors, and chemokines. The final formulation was prepared by adding 2 ml of distilled water into a sterile bottle containing dried sucrose-protein foam. 5 μl of the final formulation SCF was delivered in each mouse nostril for a total 10 μl intranasally per session. Young (3 month-old) Alzheimer APPPS21 mice received the repeated application of either SCF (n=6) or LRS as control (n= 4). The animals were infused daily for a total experiment duration of 3 weeks. The animals were sacrificed 2 days after the last SCF application. The brains were collected and immmunostained with a mouse monoclonal anti-Abeta antibody (6E10). *Results:* Quantification of amyloid load on 6E10-stained sections revealed that cerebral Abeta amyloidosis was reduced by 25% following SCF treatment. We believe that this effect was achieved by combined action of different growth factors, cytokines and chemokines. Analysis of selected factors secreted by hMSC revealed that several of them bear the potential to impact amyloid pathology, and in particular vascular endothelial growth factor-A (VEGF-A), TIMP-1 and insulin-like growth factor-binding proteins (IGFBP). VEGF-A was reported to induce angiogenesis and improve vascular survival (Religa et al., 2013) but also to lower Abeta levels, Abeta amyloid burden (Bürger et al., 2009; Spuch et al., 2010) and ameliorate memory impairments (Wang et al., 2011). TIMP-1 inhibits activity of MMP collagenases, enhances astrocyte proliferation (Hernandez-Guillamon et al., 2004), and was shown to be expressed in Alzheimer but not in control vessels (Thirumangalakudi et al., 2006). IGFBP-3 levels were reported to be increased in patients with AD in serum but not cerebrospinal fluid as compared to non-demented controls. *Conclusion:* The positive impact of soluble factors secreted by hMSC on cerebral Abeta amyloidosis argue that this represents a valuable complementary therapeutic approach to intravenous hMSC delivery. Due to a long- term shelf life in a preserved form, an easy way of reconstitution and delivery SCF can also be used independently as a candidate for moderate managing of Abeta amyloidosis as well as maintenance therapy between intravenous treatments by hMSC. Studies are initiated to determine whether SCF can delay or maintain cognitive impairments induced by cerebral amyloidosis as observed in Alzheimer mouse models. A clinical trial with SCF for AD is planned for 2016.

P3-21: BI 409306, A NOVEL PHOSPHODIESTERASE 9A INHIBITOR, INCREASES CGMP IN CSF: RESULTS FROM NON-CLINICAL AND CLINICAL TRANSLATIONAL PROOF-OF-MECHANISM STUDIES. HOLGER ROSENBROCK[1], KATJA BOLAND[2], VIKTORIA MOSCHETTI[1], HOLGER FUCHS[1], FRANK RUNGE[1], MICHAEL SAND[3], CHANTARATSAMON DANSIRIKUL[2], SOLEN PICHEREAU[2], LIEN GHEYLE[4], GLEN WUNDERLICH[5] *((1) Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany; (2) Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany; (3) Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA; (4) SGS Life Science Services – Clinical Research, Antwerpen, Belgium; (5) Boehringer Ingelheim (Canada) Ltd, Burlington, ON, Canada)*

Background: Phosphodiesterase 9A (PDE9A) inhibitors have been hypothesised to improve cognitive function through strengthening synaptic plasticity in the brain by enhancing N-methyl-D-aspartate receptor-related cyclic guanosine monophosphate (cGMP) signalling. Memory enhancement that may ensue from elevated cGMP levels is of potential interest in the symptomatic treatment of Alzheimer's disease (AD). Thus, this study characterises the effects of the novel PDE9A inhibitor BI 409306 on cGMP increase in rat prefrontal cortex and cerebrospinal fluid (CSF) in order to show central target engagement, i.e. PDE9A inhibition in brain. In order to translate this non-clinical proof-of-mechanism study to humans, BI 409306 was further evaluated in healthy volunteers for increase of cGMP levels in CSF after single oral administration in a placebo-controlled clinical trial. *Methods:* Non-clinical: Effects on cGMP levels in rat prefrontal cortex were determined with a microdialysis technique following a single intraperitoneal administration of BI 409306. Concentrations of cGMP in microdialysis probes were measured using a cGMP-specific radio-immunoassay. Rat CSF was collected from the cisterna magna at 30 minutes (since this is approximately equal to the time, tmax, to reach maximum concentration [Cmax] of BI 409306 in plasma) after a single oral administration of BI 409306; cGMP levels were determined by HPLC-MS/MS technique. Clinical: The effect of BI 409306 on cGMP levels in CSF was assessed in healthy male volunteers. In this randomised, parallel-group, double-blind, double-dummy, placebo-controlled trial, subjects were allocated in equal numbers to receive a single oral dose of 25, 50, 100 and 200 mg BI 409306, or placebo. The following were evaluated: Cmax and tmax of cGMP in CSF; Cmax and tmax of BI 409306 in plasma and CSF; and safety and tolerability profile of BI 409306. *Results:* BI 409306 induced a dose-dependent increase of cGMP in rat prefrontal cortex and CSF at the highest dose tested. As shown by microdialysis, peak levels of cGMP in prefrontal cortex were achieved at 20 minutes after intraperitoneal administration of BI 409306. The dose-dependent increase in rat CSF cGMP levels correlated well with CSF cGMP levels among humans in our clinical study. In the 20 healthy volunteers who completed the phase I trial, CSF cGMP concentrations increased in a dose-dependent manner. The CSF cGMP profile over time closely followed BI 409306 concentrations in plasma and CSF. The tmax of CSF cGMP was 2-5 hours and the median tmax of BI 409306 in plasma and CSF was 0.75-1.25 hours and 1.5-2.0 hours, respectively. After maximum level, CSF cGMP declined to baseline levels 10-14 hours after oral administration of BI 409306. The dose-adjusted gMean (90% CI) CSF to plasma ratio of the BI 409306 Cmax was 28.31% (25.42% to 31.53%). Overall, the study drug was safe and well tolerated. Most adverse events (AEs) were mild in severity and no dose-dependent increase in the number or intensity of reported AEs or clustering of specific AEs was observed. There were no deaths or serious AEs reported. *Conclusion:* Systemic administration of BI 409306 led to an increase in cGMP levels in rat prefrontal cortex and CSF demonstrating functional target engagement, i.e. PDE9A inhibition in the brain. This shows that cGMP levels in CSF can be used to assess PDE9A inhibition centrally. This outcome was translated into a clinical study aiming at demonstrating functional target engagement in human brain. A single oral dose of BI 409306 (25-200 mg) prompted a dose- and concentration-dependent

increase in CSF cGMP in healthy volunteers. These results provide evidence for BI 409306-induced PDE9A inhibition in the target tissue and therefore a potential therapeutic role for cognitive improvement in AD.

P3-22: MICRORNA-574 IS INVOLVED IN COGNITIVE IMPAIRMENT IN 5-MONTH-OLD APP/PS1 MICE THROUGH REGULATION OF NEURITIN. FEI LI[1], GANG WEI[2], YE BAI[1], YUNJUN LI[1], FENGYUAN HUANG[1], JIAN LIN[1], QIUKE HOU[1], RUDONG DENG[1], JIAN HONG ZHOU[1], SAI XIA ZHANG[1], DONG FENG CHEN[1] *((1) Department of Anatomy, Guangzhou University of Traditional Chinese Medicine, Guangzhou, China; (2) Research & Development of New Drugs, Guangzhou University of Traditional Chinese Medicine, Guangzhou, China)*

Backgrounds: Alzheimer's disease (AD) is the most common form of dementia in the elderly. The recent evidence in AD research suggests that alterations in the microRNA (miRNA) could contribute to risk for the disease. However, little is understood about the roles of miRNAs in cognitive impairment in early Alzheimer's disease (AD). *Methods:* Here, we used 5-month-old APP/PS1 mice, which mimic many of the salient features of the early stage of AD pathological process, to further investigate the roles of miRNAs in synaptic loss involved in learning and memory. We used miRNA expression microarrays on RNA extracted from the hippocampus of 5-month-old APP/PS1 mice and wild type mice. Real-time reverse transcription PCR was conducted to verify the candidate miRNAs discovered by microarray analysis. *Results:* The data showed that miR-574 was increased significantly in the hippocampus of 5-month-old APP/PS1 mice, which were concomitant with that APP/PS1 mice at the same age displayed a significant synaptic loss and cognitive deficits. Bioinformatic analysis predicted that neuritin (Nrn1) mRNA is targeted by miR-574. Overexpression of miR-574 lowers the levels of neuritin and synaptic proteins expression in HT22 cells damage induced by Aβ25-35. In contrast, suppression of miR-574 by miR-574 inhibitor significantly results in higher levels of neuritin and synaptic proteins expression. *Conclusion:* Taken together, miR-574 is involved in cognitive impairment in 5-month-old APP/PS1 mice through regulation of neuritin. *Keywords:* miR-574, neuritin, cognitive impairment, synapse, 5-month-old APP/PS1mice

P3-23: MODULATION OF THE IMPAIRMENT OF NEUROENDOCRINE-IMMUNE SYSTEM IN 3XTG-AD: EFFECTS OF POSTNATAL HANDLING AND NMDA-INDUCED STRESS. LYDIA GIMÉNEZ-LLORT[1], RAQUEL BAETA-CORRAL[1], MÓNICA DE LA FUENTE[2] *((1) Institute of Neuroscience & Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Spain; (2) Department of Physiology (Animals Phisiology II) Complutense University of Madrid, Spain)*

Background: The neuroimmunomodulation hypothesis for Alzheimer's disease postulates that alterations in the innate immune system triggered by several kind of damage signals result in adverse effects in neuronal functions. Our precedent work has demonstrated the impairment of the neuroimmunoendocrine system in 3xTg-AD mice, since early stages of the disease, and in a gender-dependent manner. Interestingly, the effects at the peripheral level could be also recorded by means of both total and relative weights of immunoendocrine tissues, which were shown to provide an indirect measure of their functionality. Thus, the 'organometrics' of thymus, spleen and adrenal glands correlated with the sex-dependent impairment of the neuroimmunoendocrine network described at several stages of the AD neuropathology. Objectives: In the present work, we have studied the long-term effects of postnatal handling (PH) in the neuroimmunoendocrine system of 6-month-old male and female 3xTg-AD and non-transgenic (NTg) mice. PH is a treatment of ambiental stimulation consisting in tactile sensorial stimulation which is administered to animals all through their ontogenic development. Thereafter, in the same animals, we assessed the effects of NMDA (low dose, 25mg/kg, i.p.) known to induce a biphasic depressant/hyperactivity motor response as a result of adenosine/dopamine-dependent (respectively) mechanisms in front of such a potentially excitotoxic stimulus. *Methods:* Postnatal handling (PH) was administered from birth (postnatal day 1) to weaning (postnatal day 21). At 6 months of age animals of both genders and genotypes were behaviorally assessed in the corner, open-field and dark-light box tests in order to study their anxious-like profile and the effects of the treatment. Thereafter, the neuroprotective effects of PH on the NMDA-induced excitotoxic/stressful stimulus were addressed at the behavioral level. Motor activity response was assessed by means of infrared photocells activity meter cages. Finally, body weight and organometrics of the peripheral tissues of the neuro-immune-endocrine network (spleen, thymus and adrenals) were recorded. The plasma was also obtained to analyze the corticosterone content. *Results:* In agreement with previous work, sexual dimorphism and overweight reported for 3xTg-AD mice were observed. Impairment of the peripheral immune-endocrine network was clearly observed in the spleen, while gender-dependent differences were found in the relative weight of all these peripheral organs. The long-lasting effects of PH were selectively shown in 3xTg-AD mice at the endocrine level with the restoration of the adrenals size. Besides, we the measures of immunoendocrine system correlated with anxiety-like behaviors in NTg and 3xTg-AD mice. The immediate NMDA-induced motor activity response was sensitive to gender in the 3xTg-AD genotype, with females showing an immediate reduced activity that was reverted by PH. During the phase of NMDA-induced depression of motor activity, a higher depressant effect was shown by NTg females and was potentiated by handling. Finally, higher levels of NMDA-induced corticosterone response were found in NTg females and 3xTg-AD mice. *Conclusions:* The present results show that early neuropsychiatric (BPSD-like) symptoms such as anxiety exhibited by 3xTg-AD mice at this early stages of the disease correlate with changes in the organometrics of pheripheral immune tissues, such as thymus and spleen, indirect indicators of the immunological status. The NMDA-induced motor activity and endocrine responses were sensitive to gender. PH exerted genotype-dependent effects on NMDA-induced motor activity and endocrine response. Support: FIS PI10/00283, PI15/01787, and (RETICEF, RD12/0043/0018) from the ISCIII-FEDER of the European Union. RBC receives a predoctoral grant from AGAUR. *Keywords:* Alzheimer´s Disease, 3xTg-AD mice, early stages, BPSD-like behaviours, biomarkers, immune function, NMDA, plasma glucocorticoids, spleen, thymus, gender.

P3-24: ENRICHED ENVIRONMENT (EE): IMMEDIATE AND LONG TERM EFFECTS ON SPATIAL MEMORY. EDVALDO SOARES *(Sao Paulo State University, Laboratory of Cognitive Neuroscience-LaNeC, Marilia, São Paulo, Brazil)*

Environmental factors seem to play an important role in terms of mental and functional/behavioral plasticity, either in humans or other animals. The application of different methods in terms of environmental enrichment generates long-term physiological and behavioral effects. This research verified the immediate and long-term effects of environmental conditions through the application of environmental enrichment (EE) protocol on the spatial memory of mice. At the 70th day of their lives, animals were tested on Morris' Labyrinth (ML) and it was observed that the group subjected to EE had a better performance locating the submerged platform at the ML than the group not subjected to EE. After completing 120 days of life,

without being submitted to EE, both groups were retested at ML and, was featured that, although the average time of the group not subjected to EE had been twice than in the group subjected to EE, this difference was not statistically significant. The data indicates that EE improves the performance in terms of spatial memory, an effect that, despite decreasing when the subject is no longer submitted to EE, lasts for long terms. *Keywords:* environmental enrichment, plasticity, memory, aging

P3-25: SUVN-502, A NOVEL 5-HT6 RECEPTOR ANTAGONIST: PRECLINICAL EVIDENCE FOR THE DESIGN OF PHASE II STUDIES FOR ALZHEIMER'S DISEASE. RAMAKRISHNA NIROGI, PRADEEP JAYARAJAN, RENNY ABRAHAM, GOPINADH BHYRAPUNENI, VIJAY BENADE, RAJESH BABU MEDAPATTI, NAGESWARARAO MUDDANA, SAIVISHAL DARIPELLI, RAMASASTRY KAMBHAMPATI *(Discovery Research, Suven Life Sciences Ltd, Hyderabad, India)*

Background: Alzheimer's disease (AD) is the most common type of dementia that accounts for an estimated 60%–80% of dementia cases. Existing therapies are associated with modest efficacy, offset by dose-limiting side effects. The need for improved AD therapies is unmet. Current greatest interest is to exploit the therapeutic potential of serotonin 6 receptor (5-HT6) receptor compounds for treating the deficits associated with learning and memory processes. 5-HT6 receptors are abundant in the brain regions such as hippocampus, nucleus accumbens and striatum, supporting their role in learning and memory. *Methods:* SUVN-502, a potent and selective 5-HT6 receptor antagonist, was evaluated for its pharmacokinetic properties using in vitro and in vivo techniques. The efficacy of this molecule was evaluated using object recognition task, fear conditioning task, Morris water maze task and radial arm maze task in rats. Modulation of acetylcholine levels by SUVN-502 was evaluated using brain microdialysis technique in freely moving rats. The pharmacological effects of combined treatment of SUVN-502 with donepezil or donepezil and memantine were studied using object recognition task, microdialysis and electroencephalography (EEG). *Results:* SUVN-502 has desirable preclinical ADME-PK profile and adequate brain penetration. SUVN-502 reversed the time induced episodic memory deficits in object recognition task. It also reversed the scopolamine induced emotional and working memory deficits in fear conditioning task and radial arm maze task, respectively. In aged rats, SUVN-502 improved the cognitive abilities when assessed using the Morris water maze task. Oral administration of SUVN-502 significantly increased the brain acetylcholine levels indicating the involvement of cholinergic neurotransmission in pro-cognitive effects. When combined with donepezil or donepezil and memantine combination, SUVN-502 enhanced the procognitive or neurochemical effects in object recognition task and microdialysis, respectively. In EEG, SUVN-502 potentiated the effects of current standard of care on stimulated theta activity indicating increase in the brain activity upon combined administration. *Conclusion:* SUVN-502 is a potent, selective, orally bioavailable and efficacious 5-HT6 receptor antagonist. Preclinical efficacy studies indicate that SUVN-502 has a potential for the treatment of cognitive deficits associated with Alzheimer's disease.

P3-26: MODULATION OF THE IMPAIRMENT OF NEUROENDOCRINE-IMMUNE SYSTEM IN 3XTG-AD: EFFECTS OF POSTNATAL HANDLING AND NMDA-INDUCED STRESS. LYDIA GIMÉNEZ-LLORT[1], RAQUEL BAETA-CORRAL[1], MÓNICA DE LA FUENTE[2] *((1) Institute of Neuroscience & Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Spain; (2) Department of Physiology (Animals Phisiology II) Complutense University of Madrid, Spain)*

Background: The neuroimmunomodulation hypothesis for Alzheimer's disease postulates that alterations in the innate immune system triggered by several kind of damage signals result in adverse effects in neuronal functions. Our precedent work has demonstrated the impairment of the neuroimmunoendocrine system in 3xTg-AD mice, since early stages of the disease, and in a gender-dependent manner. Interestingly, the effects at the peripheral level could be also recorded by means of both total and relative weights of immunoendocrine tissues, which were shown to provide an indirect measure of their functionality. Thus, the 'organometrics' of thymus, spleen and adrenal glands correlated with the sex-dependent impairment of the neuroimmunoendocrine network described at several stages of the AD neuropathology. Objectives: In the present work, we have studied the long-term effects of postnatal handling (PH) in the neuroimmunoendocrine system of 6-month-old male and female 3xTg-AD and non-transgenic (NTg) mice. PH is a treatment of ambiental stimulation consisting in tactile sensorial stimulation which is administered to animals all through their ontogenic development. Thereafter, in the same animals, we assessed the effects of NMDA (low dose, 25mg/kg, i.p.) known to induce a biphasic depressant/hyperactivity motor response as a result of adenosine/dopamine-dependent (respectively) mechanisms in front of such a potentially excitotoxic stimulus. *Methods:* Postnatal handling (PH) was administered from birth (postnatal day 1) to weaning (postnatal day 21). At 6 months of age animals of both genders and genotypes were behaviorally assessed in the corner, open-field and dark-light box tests in order to study their anxious-like profile and the effects of the treatment. Thereafter, the neuroprotective effects of PH on the NMDA-induced excitotoxic/stressful stimulus were addressed at the behavioral level. Motor activity response was assessed by means of infrared photocells activity meter cages. Finally, body weight and organometrics of the peripheral tissues of the neuro-immune-endocrine network (spleen, thymus and adrenals) were recorded. The plasma was also obtained to analyze the corticosterone content. *Results:* In agreement with previous work, sexual dimorphism and overweight reported for 3xTg-AD mice were observed. Impairment of the peripheral immune-endocrine network was clearly observed in the spleen, while gender-dependent differences were found in the relative weight of all these peripheral organs. The long-lasting effects of PH were selectively shown in 3xTg-AD mice at the endocrine level with the restoration of the adrenals size. Besides, we the measures of immunoendocrine system correlated with anxiety-like behaviors in NTg and 3xTg-AD mice. The immediate NMDA-induced motor activity response was sensitive to gender in the 3xTg-AD genotype, with females showing an immediate reduced activity that was reverted by PH. During the phase of NMDA-induced depression of motor activity, a higher depressant effect was shown by NTg females and was potentiated by handling. Finally, higher levels of NMDA-induced corticosterone response were found in NTg females and 3xTg-AD mice. *Conclusions:* The present results show that early neuropsychiatric (BPSD-like) symptoms such as anxiety exhibited by 3xTg-AD mice at this early stages of the disease correlate with changes in the organometrics of pheripheral immune tissues, such as thymus and spleen, indirect indicators of the immunological status. The NMDA-induced motor activity and endocrine responses were sensitive to gender. PH exerted genotype-dependent effects on NMDA-induced motor activity and endocrine response. Support: FIS PI10/00283, PI15/01787, and (RETICEF, RD12/0043/0018) from the ISCIII-FEDER of the European Union. RBC receives a predoctoral grant from AGAUR. Keywords: Alzheimer´s Disease, 3xTg-AD mice, early stages, BPSD-like behaviours, biomarkers, immune function, NMDA, plasma glucocorticoids, spleen, thymus, gender.