

# 5<sup>th</sup> Conference Clinical Trials on Alzheimer's Disease

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Grimaldi Forum, Convention Center, Monte Carlo

**MONDAY, OCTOBER 29<sup>TH</sup>**

## SYMPOSIUM

### **S1 - HARMONIZING REGULATORY REQUIREMENTS TO BENEFIT FUTURE ALZHEIMER' DISEASE PATIENTS.**

D. PERRY<sup>1</sup>, D. STEPHENSON<sup>2</sup>, R. KATZ<sup>3</sup>, K. BROICH<sup>4</sup> (1. ACT-AD Coalition, Alliance for Aging Research, USA; 2. Coalition Against Major Diseases, Critical Path Institute, USA; 3. U.S. Food and Drug Administration; 4. Federal Institute for Drugs and Medical Devices (BfArM))

The coalition to Accelerate Cure/Treatments for Alzheimer's Disease (ACT-AD) is comprised of more than 50 not-for-profit organizations representing Alzheimer's patients, caregivers, older people, health care providers and researchers. ACT-AD began partnering with the U.S. Food and Drug Administration (FDA) in 2006 to identify national regulatory barriers, evaluate and recommend methods to improve the drug development process, and expedite regulatory reviews in the United States of potentially disease-modifying Alzheimer's therapies. The coalition has also facilitated collaboration among academic institutions and others involved in research leading to new treatments for dementia to bridge the gap between basic and clinical research. While there have been impressive advances made by the Alzheimer's research community in understanding the pathology of Alzheimer's disease, approaches to identifying the disease at its earliest stages, and strategies for more effectively intervening in the disease course prior to the manifestation of symptoms, there are no approved treatments to arrest, prevent or cure Alzheimer's disease. Much of the delay in better treating this disease can be attributed to previous gaps in scientific knowledge; however there are some who feel that regulatory authority standards in different parts of the world contribute significantly to the length and cost of research and development. We believe that policy-based impediments like these must be overcome to advance the successful development of meaningful Alzheimer's treatments in time to avert an international health crisis. Alzheimer's Disease International reports that as many as 65.7 million people will be living with dementia worldwide by 2030. That number will grow to 115.4 million people by 2050. Recognizing that Alzheimer's disease is not just a challenge to the United States but rather a global epidemic, ACT-AD proposes a symposium at the Clinical Trials in Alzheimer's Disease Conference (CTAD) to begin a dialogue that spurs global consensus on regulatory requirements for the approval of drugs to treat early Alzheimer's disease. *Discussion and Objectives:* While important standardization efforts for biochemical assays and neuroimaging protocols have been undertaken by the Alzheimer's Association, the Critical Path Institute, and others in the public and private sectors, few groups are addressing the differing regulatory authority requirements that are not substantive, but rather driven by principle or the structure of a particular regulatory body. There are three main objectives that we hope to achieve during this symposium: •Highlight the differences in current regulatory

requirements in the U.S. and Europe for demonstrating disease-modification in early Alzheimer's disease; • Identify whether these differences are scientifically based or influenced by the cultural factors within the regulatory bodies; and • Call for harmonization of current requirements that are not deemed scientifically based and propose a mechanism for collaboration among global regulatory bodies beyond the U.S. and Europe to harmonize the issuance of new guidelines or requirements for Alzheimer's disease. *Conclusion:* Alzheimer's disease is one of the most important health challenges in the world today. The World Health Organization in April 2012 called for nations to address dementia as a public health priority. Pursuing a global consensus on regulatory requirements for the approval of early Alzheimer's disease treatments is a timely topic and could have a significant impact on advancing drug development. CTAD has become a leading forum for international experts to engage in exchanges about opportunities and challenges for research and development across the spectrum of Alzheimer's disease. We believe that CTAD is the optimal venue to productively explore this important topic. Contact: Cynthia Bens, ACT-AD Coalition, cbens@agingresearch.org, 202-293-2856

## ORAL COMMUNICATIONS

### **OC1 - IS THE DEMENTIA OF ALZHEIMER'S DISEASE DUE TO THE TOXICITY OF B-AMYLOID OR TAU? THE IMPLICATIONS OF THIS QUESTION FOR DRUG DISCOVERY.** J.L. HOLTZMAN (University of Minnesota, Minneapolis, Minnesota, USA)

It is currently thought that the dementia of Alzheimer's disease is due to the neurotoxicity of the deposits or aggregates of  $\beta$ -amyloid in the extracellular space of the cerebral cortex. This model has been widely criticized because there is a poor correlation between deposits and dementia. Others have questioned whether  $\beta$ -amyloid is neurotoxic. Finally, seven clinical trials of drugs that were effective in transgenic mice failed to show any benefit in patients. Furthermore, since  $\beta$ -amyloid is produced in everyone, why are deposits only seen in the elderly? This issue must be resolved if we are to understand the etiology of the disease and develop test systems for diagnosis and drug discovery. Published studies from my laboratory demonstrate that in human CSF immunoreactive  $\beta$ -amyloid is only present as a complex with two chaperones, ERp57 and calreticulin and is N-glycosylated. These modifications keep it soluble. Yet, others have reported that in plaque it is only present as the naked peptide. Together these results suggest that both plaque and dementia are secondary to a decline in the capacity of the endoplasmic reticulum (ER) to catalyze the posttranslational processing of nascent proteins. Since many of the synaptic membrane proteins necessary for a functioning memory are also processed in the ER, this would suggest that the loss of cognition is due to a decline in the capacity of the neuron to produce and maintain functioning synapses. These observations have important implications for other phenomena associated with Alzheimer's disease. In particular, others have found that the ER is important in the

maintenance of mitochondrial function and integrity of plasma membranes. Together these observations suggest that declining ER function has a role in the late onset disease associated with polymorphisms in ApoE and TOMM40/TOM40 genes and the well recognized decrease in myelin seen with age.

**OC 2 - POTENTIAL OF HUMAN ANALOGUE OF MORRIS WATER MAZE IN TRANSLATIONAL MEDICINE AND THE ASSESSMENT OF THERAPEUTIC RESPONSE.** J. HARRISON<sup>2,4,5</sup>, J. LACZO<sup>1,2</sup>, M. WINDISCH<sup>2,3</sup>, J. HORT<sup>1,2</sup> (1. Memory Disorders Clinic, Department of Neurology, Charles University in Prague, 2nd Medical Faculty and University Hospital Motol, Prague, Czech Republic; 2. Polyhymnia Translational Research, London, UK; 3. JSW-Lifesciences GmbH, Grambach-Graz, Austria; 4. Metis Cognition Ltd., Kilmington, UK; 5. Dept. of Medicine, Imperial College, London, UK)

*Background:* Recent failures in the development of new therapies for Alzheimer disease (AD) have led to reconsideration of clinical trial design. Many therapies which proved efficacious in preclinical development using various animal models were tested using the Morris Water Maze (MWM) task. However, these compounds often failed in phase II or III in humans, suggesting low predictive validity. In these clinical trials traditional cognitive tests were used and primary outcome measures were not met. The reason for inefficiency may be related to ineffective compounds, clinical trial design with enrolment of subjects with too advanced disease, or the use of unsuitable measures of cognitive change. Furthermore, currently used tests appear not to translate preclinical findings to human studies. Previously we reported that spatial memory testing in real-space and computer-based versions of a human analogue MWM can reliably identify individuals at higher risk of AD within the heterogeneous population with mild cognitive impairment (MCI). Cross-sectional and forthcoming longitudinal data suggest that patients with multiple domain or hippocampal types of amnesic MCI or ApoE4 carriers have similar spatial navigation as those with AD. Identification of subjects with MCI at higher risk of AD could guide development of therapeutic interventions in MCI. Introduction of tasks analogous to those used in preclinical settings could improve predictive validity and diagnostic sensitivity/specificity, as well as preventing organisations from incurring the costs of expensive Phase 1 and Phase 2 clinical trials. In this study we examined the potential of the real version and computer-based tests of a human analogue of the MWM (hMWM) to assess the effect of therapy with cholinesterase inhibitors and anti-cholinergics in early AD and healthy volunteers. *Methods:* Two groups of newly diagnosed patients with early AD, treated by donepezil (n=11) and non-treated (n=12), were tested by the computer-based version of hMWM, which evaluates different spatial navigation strategies (egocentric, allocentric, allocentric-egocentric and delayed recall). Donepezil at 5 mg/day was started after initial testing and the dose was increased to 10 mg/day after 28 days. All patients were retested after 3 months. Another group of healthy volunteers received either placebo, Donepezil 5 mg and Scopolamine 0.6 mg or only Scopolamine 0.6mg, in single dose, three-way cross-over design. *Results:* Mild AD treatment groups did not differ in education, sex and baseline MMSE score ( $p$ 's>0.10) or spatial navigation performance ( $p$ 's≥0.20). The treated group showed stable or improved spatial navigation performance after 3 months, especially in the delayed recall subtask ( $p=0.075$ ). In other subtasks, the treated group improved or remained stable (average error distance in egocentric changed from 100 pixels to 51 pixels; in allocentric from 100 pixels to 87 pixels) compared to the non-treated group which was stable or impaired (average error distance in egocentric changed from 67 pixels to 59 pixels; in

allocentric from 67 pixels to 82 pixels); however, these findings were not significant ( $p$ 's≥0.279). Testing of volunteers group revealed that single dose of scopolamine had negative effects on spatial navigation. This effect was not observed in placebo group and was less evident in subjects who were administered both donepezil and scopolamine. *Conclusion:* The computer-based version of the hMWM has a potential to measure the effects of medication in early AD and in healthy volunteers. Our findings provide supportive evidence for the use of spatial navigation as an outcome measure in longer-term MCI clinical trials as well as in translating from preclinical animal data to human trials.

**OC3 - ASSUMPTIONS OF MORTALITY HAVE A GREAT IMPACT ON THE COST-EFFECTIVENESS OF DISEASE-MODIFYING DRUGS IN AD.** A. SKOLDUNGER<sup>1</sup>, K. JOHNELL<sup>1</sup>, B. WINBLAD<sup>2</sup>, A. WIMO<sup>2</sup>. (1. Aging Research Center, Karolinska Institutet and Stockholm University, Stockholm, Sweden; 2. KI-Alzheimer's Disease Research Center, Karolinska Institutet, Huddinge, Sweden)

*Background:* Cholinesterase inhibitors (CHEI) and memantine, the only drugs that are approved for the treatment of Alzheimer's Disease (AD), have been on the market now for many years. Their efficacy is statistically significant while the clinical relevance has been questioned. Furthermore, the cost effectiveness is under debate. The few empirical studies where data on resource utilization and costs are collected in RCTs have not confirmed cost effectiveness, mainly due to the fact that the studies not were powered for cost data. Based on the rather modest effects of the cholinesterase inhibitors and memantine, there is a great hope that disease modifying drugs/treatment (DMT) will be approved and enter the market. Since thus the underlying disease mechanism of AD is assumed to be altered, there are expectations for pure cost savings. *Methods:* Base case: We have constructed a 20 years Markov cohort model of DMT, based on Swedish care conditions. States and progression were defined according to MMSE (Mini Mental State Examination) Mild Cognitive Impairment and mild, moderate and severe dementia respectively. Based on epidemiological data and demographic statistics it was assumed that in 2010 there were 100,000 persons with MCI-AD in Sweden. *The Intervention:* Since there so far are no empirical data available regarding neither efficacy nor cost effectiveness of disease modifying treatment of AD, all used intervention scenarios are hypothetical. -In the base option, we hypothetically assume that for treated persons the annual risk for conversion to mild AD (and subsequent progression) is 5% instead of 10% (representing a responder rate of 50% vs the non treated arm in the model). A comprehensive sensitivity analysis was undertaken. *Results:* There are no cost savings when exploring costs for the whole cohort in the base model, on the contrary, costs increase. However, there is a strong outcome in terms of gained QALYS for the DMT treatment arm, and the ICER (incremental cost effectiveness ratio) is lower than a probable Willingness to pay level (WTP) level (around 600,000 SEK/QALY), and thus indicating cost-effectiveness. The reasons for the increased costs is, apart from the cost of the DMT, that a consequence of the model is that people are treated during many years in MCI and mild disease with low care costs even without DMT and that treated persons live longer than non-treated, resulting in more gained QALYS and higher costs. There was a great range in the different sensitivity analysis scenarios but none of the alternatives resulted in cost savings with DMT. *Conclusion:* DMT treatment will probably not save any costs but with an assumed WTP level of 600,000 SEK, treatment seems to be cost effective from a societal viewpoint.

**OC4 - THE NOVEL BACE INHIBITOR MK-8931 DRAMATICALLY LOWERS CSF A $\beta$  PEPTIDES IN HEALTHY SUBJECTS FOLLOWING SINGLE AND MULTIPLE DOSE ADMINISTRATION.** M.F. EGAN, M.S. FORMAN<sup>1</sup>, J. PALCZA<sup>1</sup>, J. TSENG<sup>1</sup>, J. LEEMPOELS<sup>2</sup>, S. RAMAEL<sup>2</sup>, D. HAN<sup>3,4</sup>, S. JHEE<sup>3</sup>, L. ERESHEFSKY<sup>3,5</sup>, M. TANEN<sup>1</sup>, O. LATERZA<sup>1</sup>, M. DOCKENDORF<sup>1</sup>, G. KRISHNA<sup>1</sup>, L. MA<sup>1</sup>, J.A. WAGNER<sup>1</sup>, M.D. TROYER<sup>1</sup> (1. Merck, Whitehouse Station, NJ, USA; 2. SGS Life Science Services, Antwerpen, Belgium; 3. Parexel International Early Phase, Glendale, CA, USA; 4. California Clinical Trials Medical Group, Glendale, CA; 5. University of Texas Health Science Center, San Antonio, TX, USA)

**Background:** Compelling evidence implicates abnormal accumulation of A $\beta$  peptides in the pathogenesis of Alzheimer's disease (AD). Inhibition of BACE to reduce the production of A $\beta$  is a promising approach to test the amyloid hypothesis. Here we report the pharmacodynamic effects of the novel BACE inhibitor MK-8931 on reduction of CSF A $\beta$  in the first studies in human. **Methods:** Randomized, double-blind, placebo-controlled rising single dose (RSD) and rising multiple dose (RMD) studies were conducted in healthy adults, 18-45 years of age. In the RSD, the pharmacodynamic effects of MK-8931 (20, 100, 550-mg) were assessed in 3 sequential cohorts (n=8/cohort, 6-active, 2-placebo). In the RMD, 5 sequential cohorts (n=8-12/cohort, active:placebo=3:1) were administered 10 to 250-mg MK-8931 daily for 14 days. CSF A $\beta$ 40, A $\beta$ 42 and sAPP $\beta$  concentrations were determined over 36 hrs postdose (Day 1 in RSD; Day 14 in RMD) using samples collected via lumbar catheterization. **Results:** Single and multiple doses of MK-8931 were generally well-tolerated; adverse events were generally mild to moderate in intensity. Following placebo administration, mean CSF A $\beta$ 40 concentrations increased relative to baseline. By contrast, MK-8931 resulted in a dose-dependent and sustained reduction in A $\beta$ 40. Following single dose administration, the mean (90% confidence interval) CSF A $\beta$ 40 percent of baseline time weighted average (TWA) from 0 to 36 hrs postdose was: 20-mg=75% (68%, 82%), 100-mg=52% (46%, 59%) and 550-mg=39% (31%, 46%) and the mean CSF A $\beta$ 40 percent of baseline at 36 hrs postdose was: 20-mg=79% (71%, 87%), 100-mg=25% (17%, 33%) and 550-mg=8% (0%, 17%). Following multiple dose administration, the mean CSF A $\beta$ 40 percent of baseline TWA0-36hr on Day 14 was 10-mg=68% (59%, 77%), 40-mg=20% (13%, 28%), 150-mg=9% (3%, 15%) and 250-mg=6% (1%, 12%). Similar reductions in CSF A $\beta$ 42 and sAPP $\beta$  were observed. **Conclusions:** Following single (20 to 550 mg) and multiple (10 to 250 mg daily for 14 days) dose administration, MK-8931 was well-tolerated and demonstrated a profound (up to 94%) reduction in CSF A $\beta$ . Thus, MK-8931 presents a unique opportunity to test the amyloid hypothesis of AD pathogenesis. Funded by Merck & Co., Inc.

## SYMPOSIUM

**S2 - BAPINEUZUMAB IV PHASE 3 RESULTS.** P. SCHELTENS<sup>1</sup>, R. SPERLING<sup>2</sup>, S. SALLOWAY<sup>3</sup>, N. FOX<sup>4</sup> (1. VU University Medical Center, Alzheimer Center, Amsterdam, the Netherlands; 2. Brigham & Women's Hospital, Boston, MA, USA; 3. Butler Hospital, Providence, RI, USA; 4. UCL, Institute of Neurology, London, United Kingdom)

**Introduction:** Alzheimer's disease (AD) is characterized by the presence of an elevated burden of amyloid plaques in the brain. The predominant component of these plaques is A $\beta$  protein, particularly a 42-amino acid isoform (A $\beta$ 1-42) that is derived from a larger amyloid precursor protein. The hypothesis underlying this program is that

administration of an antibody against A $\beta$  will reduce the formation or mediate the removal of plaque, in patients with AD and lead to a beneficial clinical effect. Bapineuzumab is a humanized anti-amyloid-beta monoclonal antibody in development for the treatment of AD. Bapineuzumab, given intravenously (IV), is being evaluated in a phase 3 clinical trial program designed to evaluate its efficacy as a potential disease modifier based on a combination of clinical and biomarker evidence. Separate trials have been designed for apolipoprotein E (APOE)  $\epsilon$ 4 allele carriers and non-carriers as phase 2 data suggested possible safety differences between these populations. **Objectives:** The objective of this session is to present results from two randomized, double-blind placebo controlled studies of bapineuzumab IV in AD patients who are APOE  $\epsilon$ 4 carriers and non-carriers. **Discussion:** These two studies randomized and dosed over 2,000 AD patients with mild to moderate dementia (MMSE 16-26). Following a 6 week screening period, patients received either bapineuzumab (0.5mg/kg) or placebo by IV infusion every 13 weeks and were followed until study endpoint at 78 weeks. The co-primary clinical endpoints are change in the Alzheimer's Disease Assessment Scale - Cognitive subscale (ADAS-Cog) and the Disability Assessment for Dementia (DAD) at week 78. Biomarker substudies assessing effects of bapineuzumab on PiB-PET brain amyloid burden, cerebrospinal fluid (CSF) phospho-tau, and brain volume were included. Statistical analyses will be performed to estimate treatment differences at study endpoint through mixed models for repeated measures and analysis of covariance. ADAS-Cog, DAD, and biomarker endpoints (PiB PET, CSF phospho-tau, volumetric MRI) as well as safety data will be presented. **Conclusion:** These clinical trials are designed to provide a robust evaluation of the efficacy and safety of bapineuzumab in AD patients with mild to moderate dementia who are APOE  $\epsilon$ 4 carriers and APOE  $\epsilon$ 4 non-carriers.

**S3 - EFFECTS OF APOLIPOPROTEIN E ISOFORMS ON PATIENT CHARACTERISTICS AND TRIALS OUTCOMES IN LIGHT OF RECENT PHASE 3 RESULTS: STRATIFIED MEDICINE FOR ALZHEIMER'S DISEASE DRUG DEVELOPMENT.** L.S. SCHNEIDER (University of Southern California, Los Angeles, CA, USA)

**Communications:** 1. *The Neurobiology and Impact of apoE4 and apoE2 Carriage on Clinical Trials*, T. Goldberg (Hofstra North Shore LIJ School of Medicine, Manhasset, New York, USA); 2. *Relation of apoE to Brain Structure and Function in Alzheimer's Disease and Aging*, M. Pievani (RCCS Fatebenefratelli Brescia, Brescia, Italy); 3. *Simulating apoE Stratified Medicine Trials in Alzheimer's Disease*, L.S. Schneider<sup>1</sup>, R. Kennedy<sup>2</sup>, G. Cutter<sup>2</sup> (1. Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA; 2. School of Public Health, University of Alabama, Birmingham, Alabama, USA)

**Introduction:** Post hoc analyses of AD trials based on apoE4 genotype carriage have provided interesting and sometimes contradictory results. Although some results might be due to play-of-chance in underpowered analyses, other outcomes may be due to actual interaction of the drug with the subgroup. As apoE4 is the strongest risk factor for AD, accounting for about 20% of the attributable risk for AD, is associated with A $\beta$  clearance, and with earlier age of late-onset of dementia, it has received particular attention for stratified medicine approaches. **Objectives:** This symposium provides an overview and argument for stratified medicine techniques in AD clinical trial design, using apoE genotypes as examples of biomarkers for targeted trials designs (c.f. Trusheim et al 2011). We will discuss the neurobiology of apoE, relationships

between apoE and MRI, A $\beta$ , and tau biomarkers, and a range of AD and MCI trials that include apoE genotype as a factor in sample selection or outcomes, focusing on the recent trials for which there is genotype data including tarenflurbil, rosiglitazone, and bapineuzemab. Dr. Goldberg will review basic apoE neurobiology, including its roles in lipid transport and amyloid clearance, and current work on isoform specific effects at the message, protein and biomarker levels. He will also review the treatment impact on E4 carriers in the context of clinical trials. Dr. Pievani will overview the relationships between apoE genotypes and MRI parameters, A $\beta$  and tau biomarkers, including the association of apoE4 with increased amyloid deposition and tau pathology, and reduced functional connectivity across brain regions. She will highlight that apoE4 might predispose to the development of AD by affecting amyloid processing; while in patients with AD it may mainly worsen tau pathology. Schneider and colleagues will review the few clinical trials that published outcomes based on apoE genotype, and then present trials simulations (i.e., Monte Carlo simulations) resampling an integrated ADCS and ADNI database that will empirically test the efficiencies for several clinical trials scenarios involving variations in apoE genotype carriage; specifically, what might be gained by several stratified medicine assumptions with respect to apoE4 carriage. For example, are trials that restrict entry to apoE4 carriers more efficient than other trials? Do they create patient samples of different clinical phenotypes? How does apoE2 carriage affect trials outcomes? *Discussion:* The effects of apoE4 and apoE2 carrier status on clinical trials outcomes is underappreciated when planning early AD trials. The clinical effects associated with different apoE alleles are important and may be greater than the potential statistical effects of drugs compared to placebo. ApoE genotype is an important consideration for targeted clinical trials, sample stratification, or for enrichment or as a covariate or factor for clinical outcomes and for biomarkers when they are used as potential surrogate or supporting outcomes. *Conclusion:* Proposed development programs and trials designs for prevention, prodromal, and early symptomatic AD must account for and model the possible effects of apoE genotypes on sample selection, treatment, and outcomes.

## ORAL COMMUNICATIONS

**OC5 - MEASURING COGNITIVE CHANGE FROM MILD COGNITIVE IMPAIRMENT TO PRODROMAL ALZHEIMER DISEASE.** T. MURA<sup>1,2,3,4</sup>, C. PROUST-LIMA<sup>5,6</sup>, H. JACQUIN-GADDA<sup>5,6</sup>, T.N. AKBARALY<sup>1,2,7</sup>, B. DUBOIS<sup>8</sup>, C. BERR<sup>1,2,9</sup> (1. INSERM, U1061, Neuropsychiatrie : Recherche Epidémiologique et Clinique, Montpellier, France; 2. Université Montpellier 1, Montpellier, France; 3. Département d'Information Médicale, Centre d'Investigation Clinique, CHU Montpellier, Montpellier, France; 4. INSERM, CIC 1001, Montpellier, France; 5. INSERM U897, Equipe de Biostatistique, Centre de Recherche en Epidémiologie et Biostatistique, Bordeaux, France; 6. Université Bordeaux Segalen, ISPED, Bordeaux, France; 7. Department of Epidemiology and Public Health, University College London, London, United Kingdom; 8. INSERM-UPMC UMRS 975, Institut de la Mémoire et de la Maladie d'Alzheimer, ICM, APHP, Salpêtrière Hospital, University Paris 6, Paris, France; 9. CMRR Languedoc Roussillon, service de Neurologie, CHU Montpellier, Montpellier, France)

*Background:* Because time before onset of dementia is not always the better outcome, investigating cognitive change over time in the prodromal stages of the disease has become one of the major outcomes in intervention trials designed to assess the effects of drugs on early

stage of AD. The used tests have to be able to detect changes in cognition in the specific range of cognitive levels observed in the target population, and should explore the cognitive domains affected by the disease at a given stage. This study aimed to investigate the sensitivity of a large set of neuropsychological tests to detect cognitive changes due to prodromal Alzheimer Disease (AD), and to compare the metrological properties of these tests in patients with Mild Cognitive Impairment (MCI); This comparison will aid in selecting a restricted number of psychometric tests for the clinical follow-up of MCI subjects. *Methods:* A total of 212 patients with MCI were tested at baseline by a standardized neuropsychological battery, which included: the Free and Cued Selective Recall Reminding Test (FCSRT), the Benton Visual Retention test, the DENO100, verbal fluency, a serial digit learning test, the double task of Baddeley, the WAIS similarities, the Trail Making Test, and the WAIS digit symbol test. The patients were followed at 6-month intervals for up to 3 years in order to identify those who converted to AD (retrospectively classified as prodromal-AD). Statistical analyses were performed using a nonlinear multivariate mixed model involving a latent process. This model assumes that the psychometric tests are nonlinear transformations of a common latent cognitive process (LCP). By modeling the relation between this LCP and the different neuropsychological test, we have been able to analyze and represent the varying sensibility to cognitive change of the 13 scores assessed in the study. We also used this model to analyze the sensibility of these scores to the specific cognitive change due to prodromal AD. *Results:* A total of 57 patients converted to AD. Probably because of a practice effect, MCI-non AD showed an improvement of their scores during the study ( $\beta$ :+0.25 IC95% 0.11; 0.39 units of LCP per year, p-value<0.001), whereas prodromal-AD declined during the follow-up ( $\beta$ :-0.35 SE: 0.14 IC95% -0.63; -0.07 units of LCP per year, p-value<0.012). The tests with the best sensitivities to detect cognitive changes due to prodromal-AD were the FCSRT, the semantic verbal-fluency, and the DENO100. The estimated transformations between each test and the common LCP highlighted a different sensitivity pattern for cognitive change over time. Some tests exhibited a better sensitivity to cognitive changes for subjects with high levels of cognition: the free-recall, free-delayed-recall scores (FCSRT) and the semantic verbal-fluency, whereas other showed a better sensitivity in low levels of cognition: the total-recall score (FCSRT). *Conclusions:* The tests that can be recommended for the follow-up of MCI subjects are those which show the best sensitivity to cognitive change due to prodromal phase of AD (the three scores FCSRT, the semantic verbal-fluency, and the DENO100) and which are able to detect changes in this specific range of cognitive levels. In the current study, the free-recall, the free-delayed-recall score (FCSRT) and the semantic verbal-fluency test cover a large cognitive range and seem adapted for the follow-up of subjects with an initial medium or high level of cognition. Conversely the total-recall score (FCSRT) suffered from a huge ceiling effect, but seemed to be the best score for following up subjects with an initial low cognitive level.

### OC6 - LONG-TERM LONGITUDINAL BIOMARKER TRIALS IN SUBJECTS AT GENETIC RISK OF DEVELOPING ALZHEIMER'S DISEASE: THE GEPARD-AD STUDIES.

J. ROSS<sup>1</sup>, P.M. THOMPSON<sup>2</sup>, R.S. DOODY<sup>3</sup>, P.N. TARIOT<sup>4</sup>, E.M. REIMAN<sup>4</sup>, J. LANGBAUM<sup>4</sup>, L.S. SCHNEIDER<sup>5</sup>, U. LUCCA<sup>6</sup>, E. FRIGERIO<sup>7</sup>, F. FIORENTINI<sup>7</sup>, L. GIARDINO<sup>8</sup>, L. CALZA<sup>8</sup>, D. NORRIS<sup>9</sup>, H. CICIRELLO<sup>9</sup>, D. CASULA<sup>9</sup>, B.P. IMBIMBO<sup>9</sup> (1. Memory Enhancement Center of America, 4 Industrial Way West, Eatontown, NJ 07724, USA; 2. Laboratory of Neuro Imaging, Dept. of Neurology, UCLA School of Medicine, Los Angeles, CA 90095-7332, USA; 3. Alzheimer's Disease and Memory Disorders Center, Baylor College of Medicine, Department of Neurology, 1977 Butler Blvd., Suite E 5.101, Houston, TX 77030, USA; 4. Banner Alzheimer's Institute, 901 E. Willetta St, Phoenix, 85006 AZ, USA; 5. University of Southern California Keck School of Medicine, 1510 San Pablo St, HCC 600, Los Angeles, CA 90033, USA; 6. Istituto di Ricerche Farmacologiche Mario Negri, Via Giuseppe La Masa 19, 20156 Milano, Italy; 7. Accelera Srl, Via Pasteur 10, 20014 Nerviano, Italy; 8. Health Sciences and Technologies - Interdepartmental Center for Industrial Research (HST-ICIR), University of Bologna, Via Tolara di Sopra 50, 40064 Ozzano Emilia, Bologna, Italy; 9. Research & Development, Chiesi Pharmaceuticals Inc., 9605 Medical Center Drive, Rockville, MD 20850, USA)

**Background:** There have been recent failures in clinical trials with supposed "disease-modifying" agents in patients with Alzheimer's disease (AD). These setbacks may be due to the fact that these drug candidates did not engage the proposed biological target or were pursuing the wrong pharmacological mechanism or were tested at the wrong clinical stage. Indeed, the AD pathophysiology process starts at least 10 years before clinical symptoms become apparent and this has raised awareness of the need to test new drug candidates in the earliest stages of the disease. Three epidemiological studies (Neurology 2008; 70: 17-24, BMC Geriatrics 2005; 5: 2, Neuroepidemiology 2004; 23: 135-43) have suggested that prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs) in middle age may protect against or delay AD onset in APOE4 carriers only. CHF5074 is a new NSAID-derivative, devoid of anti-cyclooxygenase activity, that lowers M1 inflammatory and increases M2 phagocytic responses to  $\beta$ -amyloid (A $\beta$ ) in mixed murine glial cells. In different transgenic mouse models of AD, CHF5074 reduces activated microglia, inhibits brain plaque deposition and attenuates or reverses memory deficit. In humans, CHF5074 has been shown to dose-dependently lower CSF biomarkers of neuroinflammation. In patients with mild cognitive impairment (MCI), the drug dose-dependently improved verbal memory, compared to baseline, after 26 weeks of treatment. **Methods:** Two 24-month, double-blind, randomized, placebo-controlled, multicenter clinical trials (GEPARD-AD or Genetically Enriched Population At Risk of Developing Alzheimer's Disease) will be carried out to assess the effects of CHF5074 on biomarkers of neurodegeneration and neuroinflammation in subjects at risk of developing AD. Study samples will be "enriched" based on two risk factors for AD: the presence of one or two APOE4 alleles and parental history of AD. One study will enroll 261 APOE4 carriers with amnesic MCI, with or without parental history of AD (GEPARD-AD1); the other study will involve 423 cognitively normal APOE4 carriers with parental history of AD (GEPARD-AD2). The presence of the APOE4 allele may increase the likelihood of a cognitive and neuroprotective response to CHF5074 treatment based on the suggested association between NSAIDs use and a lower risk of AD in APOE4 carriers. Participants will be 45 to 65 years-old since NSAIDs may reduce the risk of AD onset in this range of age. Two doses of CHF 5074 as well as placebo will be evaluated in the two studies. **Results:** The two trials were

recently approved by FDA, by the Data Safety Monitoring Board and by a centralized Institutional Review Board, and will be carried out in approximately 25 US sites. Outcomes will include MRI measures of brain volume (hippocampus, ventricles, whole brain, medial temporal cortex), cognitive performance (verbal memory, visual spatial memory), Clinical Dementia Rating-Sum of Boxes, PET measurement of cerebral glucose metabolism in AD-affected regions and CSF biomarkers (A $\beta$ 42, phospho-tau, sCD40L and TNF- $\alpha$ ). **Conclusion:** The GEPARD-AD clinical trials will establish whether a microglial modulator with neuroprotective activity is able to attenuate biomarker change and cognitive decline in MCI patients and in cognitively normal middle-aged persons at genetic risk of late onset of AD.

### OC7 - THE DOMINANTLY INHERITED ALZHEIMER'S NETWORK TRIALS. R. BATEMAN (Dominantly Inherited Alzheimer Network)

**Background:** Prevention studies are likely to be most successful for those with the highest risk of AD. Autosomal dominant AD accounts for less than 1% of all AD, but has 100% risk and usually occurs in the third to fifth decade of life. In 2008, the NIH funded the establishment of the Dominantly Inherited Alzheimer Network (DIAN, U01AG032438, JC Morris, PI; www.dian-info.org), an international network of leading research centers to investigate AD caused by mutations. The DIAN is the largest and most extensive worldwide network for mutation Alzheimer's research. In collaboration with other prevention initiatives, DIAN is preparing to launch the first prevention trials for autosomal dominant AD. **Methods:** Measurements to track disease progression using established clinical, cognitive, imaging and biomarker methods have been performed. The results from the study demonstrate the feasibility and promise of performing prevention studies in the DIAN population. In 2011, the DIAN Therapeutic Trials Unit (TTU) was established with funding from the Alzheimer's Association and a consortium of ten pharmaceutical companies (the DIAN Pharma Consortium). The DIAN TTU has developed an adaptive design to test multiple AD targets with the goal of prevention and intervention of cognitive decline in autosomal dominant AD. The DIAN Expanded Registry (www.DIANExpandedRegistry.org) is an international participant and researcher registry for DIAN trials. **Results:** A sequence of biomarker changes reveal a cascade of events beginning 10-20 years before the first symptoms of AD are manifest. The proposed design for the DIAN prevention trials is a two-stage study to delay, prevent, or restore cognitive loss in AD mutation carriers. The first stage will determine the biological engagement of the drug target and impact on biomarkers of neurodegeneration with imaging, cerebrospinal fluid, and other biomarkers. The second stage will determine if there is a cognitive benefit of treatment. Results of the DIAN trials design, participant engagement, drug selection process, practical aspects of implementation, statistical considerations, and trial implementation will be reviewed. **Conclusions:** Because the clinical and pathological phenotypes of dominantly inherited AD appear similar to those for the far more common late-onset "sporadic" AD, the nature and sequence of brain changes in early-onset AD are also likely relevant for late-onset AD. Clinical studies in AD caused by gene mutations are likely to pioneer the way to prevention trials for all forms of AD. The scientific knowledge gained from secondary prevention trials is likely to inform about the cause of AD, validate biomarkers to accelerate treatment development, and determine the effects of treating AD early.

## OC8 - DEFINITION OF HARMONIZED PROTOCOL FOR HIPPOCAMPAL SEGMENTATION.

M. BOCCARDI<sup>1</sup>, M. BOCCHETTA<sup>1,2</sup>, L. APOSTOLOVA<sup>3</sup>, J. BARNES<sup>4</sup>, G. BARTZOKIS<sup>5</sup>, G. CORBETTA<sup>1</sup>, C. DECARLI<sup>6</sup>, L. DETOLEDOMORRELL<sup>7</sup>, M. FIRBANK<sup>8</sup>, R. GANZOLA<sup>1</sup>, L. GERRITSEN<sup>9</sup>, W. HENNEMAN<sup>10</sup>, R.J. KILLIANY<sup>11</sup>, N.I. MALYKHIN<sup>12</sup>, P. PASQUALETTI<sup>2</sup>, J.C. PRUESSNER<sup>13</sup>, A. REDOLFI<sup>1</sup>, N. ROBITAILLE<sup>4</sup>, H. SOININEN<sup>15</sup>, D. TOLOMEO<sup>1</sup>, L. WANG<sup>16</sup>, C. WATSON<sup>17</sup>, H. WOLF<sup>18</sup>, S. DUCHESNE<sup>14</sup>, C.R. JACK JR<sup>19</sup>, G.B. FRISONI<sup>1</sup> (1. *LENITEM (Laboratory of Epidemiology, Neuroimaging and Telemedicine) IRCCS – S. Giovanni di Dio – Fatebenefratelli Brescia, Italy*; 2. *AFaR – Associazione Fatebenefratelli per la Ricerca, Rome, Italy*; 3. *Laboratory of NeuroImaging, David Geffen School of Medicine, University of California, Los Angeles, CA*; 4. *Dementia Research Centre, UCL Institute of Neurology, University College London, London, UK*; 5. *Department of Psychiatry, David Geffen School of Medicine at UCLA, Los Angeles, CA*; 6. *Department of Neurology, University of California, Davis, CA*; 7. *Department of Neurological Sciences, Rush University, Chicago, Illinois*; 8. *Institute for Ageing and Health, Newcastle University, Wolfson Research Centre, Newcastle, UK*; 9. *Karolinska Institute, Stockholm, Sweden*; 10. *Department of Radiology and Alzheimer Center, VU University Medical Center, Amsterdam, The Netherlands*; 11. *Department of Anatomy and Neurobiology, Boston University School of Medicine*; 12. *Department of Biomedical Engineering, Centre for Neuroscience, University of Alberta, Edmonton, Alberta, Canada*; 13. *McGill Centre for Studies in Aging, Department of Psychiatry, McGill University, Montreal, Quebec, Canada*; 14. *Department of Radiology, Université Laval and Centre de Recherche Université Laval – Robert Giffard, Quebec City, Canada*; 15. *Dept of Neurology, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland*; 16. *Northwestern University Feinberg School of Medicine, Department of Psychiatry and Behavioral Sciences, United States*; 17. *Wayne State University School of Medicine, D-University Health Center, St. Antoine, Detroit, MI*; 18. *Department of Psychiatry Research and Geriatric Psychiatry, Psychiatric University Hospitals, University of Zurich, Zurich, Switzerland*; 19. *Department of Diagnostic Radiology, Mayo Clinic and Foundation, Rochester, MN*)

**Backgrounds:** Heterogeneity of landmarks among protocols leads to different volume estimates, hampering comparison of studies and clinical use, for diagnosis and tracking of Alzheimer's disease (AD). There is an urgent need to define a harmonized protocol for manual hippocampal segmentation from magnetic resonance scans. Landmark differences among the 12 most common protocols were extracted, operationalized, and quantitatively investigated. The results were presented to the Delphi panel, consisting of sixteen researchers with substantial expertise in hippocampal segmentation, in order to reach an evidence-based consensus on segmentation landmarks. **Methods:** The Delphi panel participated in iterative anonymous voting sessions where feedback from previous rounds was utilized to progressively facilitate panelists' convergence on agreement. Panelists were presented with segmentation alternatives, each associated with quantitative data relating: (i) reliability, (ii) impact on whole hippocampal volume, and (iii) correlation with AD-related atrophy. Panelists were asked to choose among alternatives and provide justification, comments and level of agreement with the proposed solution. Anonymous votes and comments, and voting statistics of each round were fed into the following Delphi round. Exact probability on binomial tests of panelists' preferences was computed. **Results:** Sixteen panelists completed five Delphi rounds. Agreement was significant on (i) inclusion of alveus/fimbria ( $p=0.021$ ); inclusion

of the whole hippocampal tail ( $p=0.013$ ); (iii) segmentation of the medial border of the body following visible morphology as the first choice ( $p=0.006$ ) and following a horizontal line in the absence of morphological cues ( $p=0.021$ ); inclusion of the minimum hippocampus (comprising head and body) ( $p=0.001$ ); and inclusion of vestigial tissue in the segmentation of the tail ( $p=0.022$ ). Significant agreement was also achieved for exclusion of internal cerebrospinal fluid pools ( $p=0.004$ ). Based on previous quantitative investigation, the hippocampus so defined covers 100% of hippocampal tissue, captures 100% of AD-related atrophy, and has good intra-rater (0.99) and inter-rater (0.94) reliability. **Conclusion:** A Harmonized Protocol for Manual Segmentation has been agreed among an international panel of experts. The protocol will be validated with neuropathological data and its accuracy will be compared with protocols currently used in AD research. Updated information on this ongoing project is available at [www.hippocampal-protocol.net](http://www.hippocampal-protocol.net).

## OC9 - ROBUSTNESS OF AUTOMATED HIPPOCAMPAL VOLUMETRY ACROSS MR FIELD STRENGTHS AND SAME-DAY REPEAT SCANS.

R. WOLZ<sup>1,2</sup>, A.J. SCHWARZ<sup>3</sup>, P. YU<sup>3</sup>, P. COLE<sup>4</sup>, D. RUECKERT<sup>1,2</sup>, D. RAUNIG<sup>5</sup>, D. HILL<sup>1</sup> (1. *IXICO Ltd, London, UK*; 2. *Imperial College London, London, UK*; 3. *Elli Lilly and Company, Indianapolis IN, USA*; 4. *Cole Consulting, NJ, USA*; 5. *Icon Medical Imaging, Warrington PA, USA*)

**Background:** Low hippocampal volume has been shown to be a predictive measurement of MCI to AD conversion [1], and has been qualified by the EMA as a biomarker to enrich prodromal AD clinical trials [2]. It is important to characterize the performance of automatic algorithms that can be used to quantify this biomarker. This study proposes a methodology for assessing algorithm performance through measuring repeatability and reproducibility of hippocampal volumes obtained using, respectively, (a) intra-examination repeat scans and (b) repeat-scans acquired at different field strengths (1.5T and 3T) selected from the ADNI-1 datasets. This test-re-test methodology is applied to LEAP [3], an established algorithm for automatic hippocampal delineation. **Methods:** In ADNI-1 ([www.loni.ucla.edu/ADNI](http://www.loni.ucla.edu/ADNI)), T1 weighted MP-RAGE volumetric MR scans were acquired at 1.5T and 3T from a large cohort of healthy controls, subjects with MCI and patients with AD. For 153 of these subjects, two repeat scans at baseline and month 12 for both field strengths are available that have passed quality control. The 612 non-processed baseline MR scans from these 153 subjects were downloaded from the ADNI repository; only baseline scans are considered here. Each subject's 3T baseline scan was acquired  $27 \pm 18$  [3, 103] (mean $\pm$ SD [min,max]) days after the 1.5T baseline scan. For one subjects, the 3T scan was acquired 78 days before the 1.5T scan; for three subjects this information was not available. Each scan was individually skull-stripped [4] and bias corrected [5] before volumes for left and right hippocampus were individually extracted using LEAP. Signed differences were evaluated by subtracting the first scan from the second and used to evaluate intra-field strength reliability. Absolute (unsigned) differences were also used to evaluate the agreement between hippocampal volume measurements at the two field strengths. **Results:** Mean $\pm$ SD relative signed differences in hippocampal volume across intra-examination repeat scans were  $-0.02\% \pm 1.94\%$  (1.5T) and  $0.18\% \pm 2.04\%$  (3T). The mean $\pm$ SD signed difference (3T - 1.5T) in hippocampal volume across field strengths was  $1.06\% \pm 3.23\%$ , indicating only a small bias ( $0.32\sigma$ ). The mean $\pm$ SD unsigned difference between field strengths was  $2.77\% \pm 1.95\%$ . Intraclass correlation coefficients (ICCs) corresponding to the intra-examination repeat scans were 0.994 (1.5T) and 0.992 (3T); for the inter-field strength comparison the ICC was 0.979. The measured signed difference was not significantly different

between any of the clinical groups at the threshold of  $p=0.05$ . AD subjects ( $N=28$ ) show a lower hippocampal volume ( $1978\pm 343\text{mm}^3$ , averaged over all four measurements) than MCI subjects ( $N=74$ ,  $2178\pm 341\text{mm}^3$ ) and controls ( $N=51$ ,  $2457\pm 271\text{mm}^3$ ). The unsigned inter-field strength variation for AD subjects (difference:  $3.71\pm 2.20\%$ ) was significantly different to that in the MCI cohort (difference:  $2.62\pm 1.83\%$ ) and the control subjects (difference:  $2.48\pm 1.86\%$ ), indicating a relatively high intra-field strength difference for lower absolute volumes. The unsigned difference between MCI subjects and controls was not significantly different. No significant difference was observed in any measure when comparing different scanner vendors (GE Medical Systems, Philips Medical Systems, Siemens). **Conclusion:** This study used the ADNI-1 data to quantify the test-retest performance of hippocampal delineation using the LEAP algorithm. The results obtained here were obtained using intensity inhomogeneity correction with the N4 algorithm, but without any correction of gradient non-linearity or scaling error, as the ADNI database does not provide pre-processing for both of the back-to-back scans. The intra-examination test:retest provided extremely high repeatability ( $\text{ICC}>0.99$ ) at both 1.5T and 3T. The between field strength test:re-test also yielded very high reproducibility ( $\text{ICC}\sim 0.98$ ). Each of these comparisons is subject to different contributions to total variance between two MRI scans. The intra-examination test:re-test includes contributions of instrument noise, patient noise (eg: minor intrascan bulk and pulsatile motion) and automatic scanner adjustments (eg: centre frequency re-calibration), but not change in subject position, state (eg: hydration), or change in scanner. In contrast, the inter-field strength results include all these factors, as well as the effect of a change in the field strength and possibly scanner manufacturer. As a result, it might be expected that test:re-test experiments using data acquired on the same scanner in different scanning sessions or different scanners both at the same field strength would lie between the intra-examination and inter-field strength results obtained here. Further work is needed to confirm this. **References:** [1] C.R. Jack Jr, R.C. Petersen, Y.C. Xu, P.C. O'Brien, G.E. Smith, R.J. Ivnik, B.F. Boeve, S.C. Waring, E.G. Tangalos, E. Kokmen, Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology*. 22;52(7):1397-403, 1999; [2] [www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2011/10/WC500116264.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2011/10/WC500116264.pdf); [3] R. Wolz, P. Aljabar, J.V. Hajnal, A. Hammers, D. Rueckert, LEAP: Learning Embeddings for Atlas Propagation. *NeuroImage*, 49(2):1316-1325, 2010; [4] K. K. Leung, J. Barnes, M. Modat, G. R. Ridgway, J. W. Bartlett, N. C. Fox, S. Ourselin, Brain MAPS: An automated, accurate and robust brain extraction technique using a template library, *NeuroImage*, 55(3):1091-1108, 2011; [5] N.J. Tustison, B.B. Avants, P.A. Cook, Y. Zheng, A. Egan, P.A. Yushkevich, J.C. Gee, N4ITK: Improved N3 Bias Correction, *IEEE Trans Med Imag*, 29(6): 1310-1320, 2010

**OC10 - DISENTANGLING THE NORMAL AGING FROM THE PATHOLOGICAL ALZHEIMER'S DISEASE PROGRESSION ON STRUCTURAL MR IMAGES.** M. LORENZI<sup>1,2</sup>, N. AYACHE<sup>2</sup>, X. PENNEC<sup>2</sup>, G.B. FRISONI<sup>1</sup>, AND THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE (ADNI) (1. IRCCS San Giovanni di Dio Fatebenefratelli, Brescia, Italy; 2. Asclepios research project, INRIA Sophia antipolis, France)

**Background:** The morphology of the brain observed in patients affected by Alzheimer's disease (AD) is the contribution of different biological processes such as the normal aging and the AD-specific pathological matter loss. Being able to differentiate these complementary biological factors is fundamental in order to isolate and quantify the pathological AD-related structural changes, especially

at the earliest phase of the disease, at prodromal and preclinical stages. **Methods:** We chose the ADNI baseline structural MRIs for 37 healthy subjects positive to the CSF Ab42 (Ab+), 86 patients with mild cognitive impairment (MCI) which subsequently converted to AD, 110 stable MCI, and 134 AD patients. For each subject, a "virtual aging" component was defined as the closest point with respect to the longitudinal deformation modeled for the healthy aging of a group of 63 normal subjects negative to the CSF Ab42 [1]. Once removed the aging component, the remaining specific morphological changes were analyzed group-wise, in order to characterize the atrophy patterns at the different clinical stages, and to test their predictive power in encoding the pathological disease progression. **Results:** Even though the considered groups did not significantly differ for age, the estimated virtual ages increased as the clinical condition get worse, and were significantly higher for the MCI stable, converters, and AD groups when compared to the healthy  $\text{A}\beta^-$  ( $p<0.05$ , standard two sample t-test). After removing the healthy component, the morphological changes specific for the healthy  $\text{A}\beta^+$  were mild, while the changes specific for the MCI converters were more pronounced and mapped to frontal lobes, ventricles, temporal poles, entorhinal cortex and hippocampi. The same pattern, although slightly more pronounced, was appreciable for the AD patients. The stable MCIs showed a milder deformation pattern, mapping essentially to the ventricles and temporal poles. The predictive power of the specific component was 91% sensitivity and 84% specificity for the discrimination AD vs. healthy, and 67% sensitivity and 63% specificity for the discrimination MCI stable vs. MCI converters. **Conclusion:** We provided a rich description of the anatomical changes observed across the AD time span: normal aging, normal aging at risk, conversion to MCI and latest AD stages. More advanced AD stages were associated to both "virtually older" brains, and to increased specific morphological changes that were not related to the normal aging. Importantly, the specific changes provided a good identification of the pathological AD atrophy. These results provide new insights that can lead to new understandings of the AD dynamics, and to novel techniques for the modeling and the early detection of the disease.

## UPDATE ON CLINICAL TRIALS 1

**1- SAFETY AND EFFICACY OF SOLANEZUMAB IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE: RESULTS FROM PHASE 3.** R.S. DOODY (Baylor College of Medicine - Department of Neurology, Houston, Texas, USA)

**Background:** Solanezumab, a humanized monoclonal antibody developed for the treatment of Alzheimer's disease (AD), binds to the mid-domain of soluble amyloid beta ( $\text{A}\beta$ -peptide but not to deposited amyloid plaques. **Methods:** Patients with mild to moderate AD (i.e., met the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD and had a Mini-Mental State Exam scores of 16-26) were enrolled in two identical Phase 3 trials (EXPEDITION and EXPEDITION-2) between May 2009 and December 2010. Participants were randomized to 400 mg solanezumab IV or placebo once every 4 weeks for 80 weeks. Co-primary outcomes were the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog11) and the Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL) scale scores. All participants underwent magnetic resonance imaging at baseline and at Weeks 12, 28, 52 and 80. A subset of participants underwent florbetapir PET imaging or lumbar puncture at baseline and endpoint. Other efficacy, safety and quality of life measures were

included. **Results:** A total of 1012 and 1040 participants were randomized in EXPEDITION and EXPEDITION-2, respectively. The co-primary efficacy endpoint and safety findings from EXPEDITION-2 and other findings will be presented and discussed. **Conclusion:** These Phase 3 findings will provide important efficacy and safety data on solanezumab use in patients with mild to moderate AD, and will help to advance an understanding of the amyloid hypothesis, as well as AD therapeutics.

**2- THE EFFECTS OF ELND005 (SCYLLO-INOSITOL) ON AGITATION/AGGRESSION IN AD DEMENTIA: RESULTS FROM A 78 WEEK PHASE 2 STUDY IN MILD TO MODERATE AD.** S. ABUSHAKRA<sup>1</sup>, C. LYKETSOS<sup>2</sup>, G. CRANS<sup>1</sup>, P. NADKARNI<sup>1</sup>, C. HERNANDEZ<sup>1</sup>, B. VELLAS<sup>3</sup> (1. *Elan Pharmaceuticals, Inc., South San Francisco, CA, USA*; 2. *Johns Hopkins University, Baltimore, MD, USA*; 3. *University of Toulouse, Toulouse, France*)

**Introduction:** Neuropsychiatric symptoms (NPS) are common in AD and increase in prevalence with disease progression. Some NPS are thought to reflect regional monoaminergic dysfunction in prefrontal and anterior cingulate cortex. Agitation and aggression are among the most disruptive NPS frequently associated with increased morbidity, caregiver burden, and healthcare utilization. Agitation/aggression may be associated with dysfunction in orbitofrontal, temporal and mid/posterior cingulate cortex (D. Sultzer et al. AAIC 2011), and is associated with a more rapidly progressive disease course. Currently, there are no approved treatments for NPS in AD. There remains a large unmet need for safe and effective treatments of agitation and/or aggression. ELND005 in preclinical models has shown amyloid anti-aggregation effects (McLaurin et al. 2000), with a shift of amyloid from toxic oligomers to less toxic monomeric species (Zhao et al. 2011). In a phase 2 AD study (ELND005-AD201, Salloway et al. 2011) ELND005 decreased brain myo-inositol levels in the subset of patients who underwent MR spectroscopy (Tariot et al. AAIC, 2012). This effect was similar to the myo-inositol lowering effect of Lithium at mood stabilizing doses. Based on these 2 potential mechanisms of action, ELND005 may be a good candidate as a treatment of agitation and/or aggression. Since these NPS are usually more severe in Moderate than in Mild AD, Moderate AD would be an appropriate population for treatment trials. **Objectives:** To analyze the effects of ELND005, in Moderate AD patients, on: 1. reducing the new emergence of agitation and/or aggression over a 78 week period, and 2. reducing the severity of agitation and/or aggression symptoms, at both early and late time points. **Materials and Methods:** These post hoc analyses were performed using data from a Phase 2, 78-week, dose ranging, placebo-controlled study of ELND005 in 353 patients with Mild/Moderate AD (MMSE 16-26). The main efficacy and safety results have been reported (Salloway et al. 2011). Due to safety findings at the 2 highest doses, these 2 doses (1000mg bid, 2000mg bid) were discontinued and the efficacy analyses were based on the placebo and 250mg bid dose groups. The 12-item NPI, which includes 1 item for assessment of agitation and/or aggression, was a secondary outcome. Changes from baseline for agitation/aggression scores (CBL = baseline – endpoint score, positive CBL indicate improvement) were analyzed using a mixed effects repeated measures model. Analyses were performed on the modified Intent to Treat (mITT) and Per Protocol datasets (PPS). The PPS involved only study completers who were at least 80% compliant with study drug. In addition, emergence of individual NPI items was also analyzed. Emergence was defined as a score of 0 at baseline that became >0 at any subsequent visit. No adjustments were made for multiple testing. **Results:** The Moderate AD group (MMSE

16-21 inclusive, mean and median scores 17) included a total of 80 patients on placebo or 250mg (N=38, N= 42). At baseline, approximately 23% of patients in this group had agitation, 42% were prescribed antidepressants, and ~9% were prescribed anti-psychotic medications. The proportion of Moderate AD patients who developed newly emergent agitation/aggression at any time during the study was 34.3% on placebo and 30.8% on ELND005. Across all visits, the CBL in agitation/aggression scores showed a consistent positive trend favoring ELND005 over placebo, in both the m-ITT and PPS analyses (decrease in agitation/aggression scores). The results were consistent numerically across all visits (12, 24, 48, and 78 weeks, both m-ITT and PPS), and were significant at Week 12 (ELND005 CBL: 0.04, Placebo CBL: -0.7, m-ITT, p=0.021; PPS, p=0.086). In the Mild group, the treatment effects on CBL in agitation/aggression scores were not consistent across the visits. **Conclusion:** Post hoc analyses in the Moderate AD group showed that ELND005, at 250 mg BID, had a consistent beneficial trend on the severity of agitation/aggression at all study visits. At 12 weeks, when there were few study drop outs, this effect achieved significance versus placebo. These results, coupled with the acceptable safety profile of this dose over 78 weeks of treatment, support the evaluation of ELND005 as a potential treatment of clinically significant agitation and/or aggression at the more advanced stages of AD.

**3- ERP AS BIOMARKERS FOR PRECLINICAL-AD.** K. BENNYS<sup>1</sup>, A. GABELLE<sup>1</sup>, J. TOUCHON<sup>1,2</sup> (1. *Department of Neurology, Memory Research Resource Center for Alzheimer's Disease, University Hospital of Montpellier, France*; 2. *Inserm U1061, Montpellier, France*)

The development of "disease modifying drugs" highlights the need for more accurate biomarkers for AD and especially in the preclinical AD stage. Recently research on Preclinical AD proposed criteria based on the presence of symptoms and evidence of synaptic dysfunction. Elevated CSF phospho-tau is one such marker of synaptic dysfunction. Nowadays, neither EEG nor ERP markers have been included into these criteria. The Memory Research Resources Center for Montpellier has developed sensitive proteomic (eg., CSF A-beta amyloid-Phospho tau levels) and neurophysiological (e.g., QEEG, ERP) biomarkers of early AD detection. We particularly focused on the application of quantitative EEG and ERP technologies as markers of prodromal impairment and early disease progression. ERPs because particularly accessible to non invasive study and provide a sensitive measure of synaptic function which is early altered in AD. Also the high level of temporal resolution is greater than functional magnetic resonance imaging (fMRI) or Positron Emission Tomography (PET). There is a real need for improved electrophysiological markers to assess neuroplastic changes for the differentiation of Preclinical AD from normal aging. Another application of such a marker would be to monitor changes induced by pharmacological treatments as disease modifying drugs and may be cognitive ERP markers could be provided as potential biomarkers in future Clinical Trials on Prodromal AD. This symposium will review ERP studies that have shown sensitivity to preclinical stages of AD, particularly in those at increased genetic risk for AD. We will try to discuss the interest of ERPs to predict prognosis in MCI. The talk will also focused on the challenge for ERPs to may play a major role in AD clinical trials and drug development, with utilities in cohort selection, monitoring disease progression and cognitive improvement.



**4- THE SKT SHORT COGNITIVE PERFORMANCE TEST IN PRE-CLINICAL AND DEMENTIA STAGES OF NEUROCOGNITIVE DISORDERS.** M. STEMLER<sup>1</sup>, H. LEHFELD<sup>2</sup>, G. SÁNCHEZ BENAVIDES<sup>3</sup>, J. PEÑA-CASANOVA<sup>3</sup>, H. BICKEL<sup>4</sup> (1. University of Erlangen-Nuremberg, Germany; 2. Nuremberg Hospital, Germany; 3. Hospital del Mar Barcelona, Spain; 4. Technical University of Munich, Germany)

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 organic mental disorders. The range of severity for test application extends from mild cognitive impairment (MCI) to moderate dementia. As each subtest is confined to a maximum performance time of 60 seconds, total testing time barely exceeds 15 minutes. There are standardized scores for six age groups (17 - 44 years, 45 - 54 years, 55 - 64 years, 65 - 74 years, 75 - 84 years, and 85 years of age and above) and three levels of premorbid intelligence (IQ < 90, IQ 90 - 110, IQ > 110). Separate assessments of a patient's functioning in the areas of memory and attention are possible. For repeated test administration, even within short time periods, the SKT is available in five parallel forms: A to E. The main areas of application for the SKT are follow-up studies. However, the test is also widely used within routine clinical testing and basic research. Until 1990, the SKT was mainly used in German-speaking countries. Today, international SKT data have been published from Brazil, Chile, Greece, South Korea, Mexico, Norway, Russia, Spain, UK and the USA. H. Lehfeld will introduce the SKT to the audience and give an overview of its psychometric properties, i.e., different aspects of reliability (parallel test, test-retest, internal consistency) and validity (criterion, construct, factorial, international). The focus will be on the SKT's sensitivity to the degree of cognitive impairment and its sensitivity to change over time, e.g., within clinical trials or follow-up studies in populations at risk of cognitive decline. Furthermore, the diagnostic potential of the memory and attention subscores will be highlighted, e.g., for differentiation between Alzheimer's and vascular dementia and between MCI and depression. Finally, a brief overview of available international SKT data will be given. G. Sánchez Benavides and J. Peña-Casanova examined the usefulness of the SKT in diseases of multiple aetiologies, namely its ability to detect Alzheimer's disease (AD) and to determine the cognitive profile related to chronic heart failure (HF), a presumed risk factor for AD. They would like to present unpublished data from two sample populations studied at the Hospital del Mar in Barcelona (Spain). The first was composed of 882 subjects from dementia outpatient consultations (428 controls, 145 diagnosed with MCI and 309 diagnosed as having AD). With these data, they studied the ability of the SKT total score to discriminate between AD, MCI and controls, and they proposed optimal cut-off scores. In this study, the global ability of the test to discriminate no dementia from dementia (MCI+AD vs. control) was very good, with an Area Under the Curve (AUC), calculated from the Receiver Operating Characteristic curve, of 0.972. The AUC was even higher for the discrimination of AD from controls (0.989). After reviewing the data, they chose a total SKT score of 7 as a cut-off between AD and control subjects. This score was associated with both high sensitivity (0.94) and specificity (0.96) and very good positive and negative predictive values. Higher cut-offs

are accompanied by a marked loss of sensitivity in this sample. The second sample studied included patients with cardiovascular disease, which may be considered as a risk factor for AD. G. Sánchez Benavides and J. Peña-Casanova assessed 325 subjects diagnosed as having chronic HF. HF is a disease defined as an inability of the heart to supply enough blood to the body's tissues. As a consequence of the persistent hypoperfusion of the brain, cognitive function is compromised in many cases. It is noteworthy that cognitive dysfunction in these subjects has been related to the worst health outcomes and death. In this study, all HF patients and 50 control subjects underwent a brief neuropsychological assessment using the following battery: SKT, Mini-Mental State Examination (MMSE), Memory Impairment Screen (MIS), verbal fluency, the Clock-Drawing Test, backward span and backward series. The SKT outcomes were analyzed item by item, and attention and memory subscores were computed. In a direct comparison of z-normalized scores, the SKT was the most sensitive test for comparing HF patients with control subjects ( $z = -2.4$ ), and the MIS the least sensitive ( $z = -0.54$ ), with the MMSE lying in the middle ( $z = -1.89$ ). Mean SKT attention subscore was 4.7 and mean SKT memory subscore was 1.7. In the item by item analysis, the most sensitive items were Arranging Blocks and Reversal Naming. Altogether, the findings indicate a predominance of attentional and executive alterations in HF patients, accompanied by a relative preservation of memory function. These results suggest that the SKT possesses very good properties to detect cognitive impairment related to different diseases. H. Bickel will report a study evaluating the feasibility of the SKT as an instrument in the early detection of imminent dementia. Most forms of dementia develop gradually and have a prodromal stage during which they are heralded by a mild impairment in cognitive performance. The term "mild cognitive impairment" (MCI) has been coined for this pre-dementia stage. A prerequisite for the diagnosis of MCI is proof of reduced performance in a neuropsychological test. Until now, however, there has been no agreement as to which procedure should be used for this purpose. In a prospective longitudinal study, they investigated the suitability of the SKT for identifying the pre-dementia stages of cognitive decline. The study sample consisted of 562 persons, who were examined at baseline and three times afterwards at yearly intervals. The participants were initially between 65 and 85 years of age and were living in private households. In addition to the SKT, the MMSE, the Clock-Drawing Test and a test of verbal fluency were carried out during each examination wave. The severity of the cognitive disturbances was assessed on the basis of the Clinical Dementia Rating scale (CDR). Incident cases of dementia in the follow-up were diagnosed according to ICD-10 criteria with the aid of the "Structured Interview for the Diagnosis of Dementia" (SIDAM) test. The examinations were carried out by psychiatrically-trained doctors and psychologists at the participants' homes. In the present analysis, only those participants who had not been suffering from dementia at baseline ( $CDR \leq 0.5$ ;  $n=546$ ) were included. The mean age was 75.7 years ( $SD=5.5$ ); 40.3% of the participants were male. According to CDR, 67.4% were rated as cognitively unimpaired; 32.6% as mildly impaired ( $CDR=0.5$ ). During the observation period of three years, 84 new dementia cases arose. Among the participants with a total SKT score of 0 or 1 point at baseline, the conversion rate to dementia amounted to 0.4% per year, whereas for 2 to 4 points it rose to 3.6%, for 5 to 7 points to 16.3% and for over 7 points to 32.2% per year. After adjustment for age and sex, the hazard ratio (Cox proportional hazards regression) amounted to  $HR=9.7$  (95% CI: 2.2-42.3) for participants with 2-4 points at baseline, to  $HR=43.5$  (95% CI: 10.4-182.6) for participants with 5-7 points and to  $HR=108.1$  (95% CI: 25.9-451.6) for participants with over 7 points, in comparison with the reference group (0 or 1 points in the total score). The cumulative incidence over three years (Kaplan-Meier

estimator) increased with declining SKT performance from 1% (0-1 points), to 10% (2-4 points), 35% (5-7 points) and 70% (more than 7 points). Specificity was extremely high (98.8%). Of the participants initially scoring 0 or 1 point, only two converted to dementia – the first after more than two years and the second after more than three years. Retest reliability was high. The correlation of the total SKT scores between baseline and one year was  $r=0.81$ , after two years  $r=0.73$  and after three years  $r=0.70$ . In the present study, the SKT proved to be very practicable, time saving, reliable and prognostically valid. The instrument thus appears to be very suitable for estimating the risk of dementia among the elderly.

**5- APPLICABILITY OF NEW CRITERIA FOR CLINICAL TRIALS IN AD.** B. DUBOIS<sup>1</sup>, P. AISEN<sup>2</sup> (1. Dementia Research Center, Salpêtrière University Hospital, Paris, France; 2. Department of Neurosciences, UCSD, San Diego, USA)

*Introduction:* Recent criteria have introduced biological/neuroimaging markers in the diagnostic framework of Alzheimer's disease. A reevaluation of their added value is proposed in this symposium and their applicability in clinical trials will be discussed in view of the development of new research criteria for AD. *Objectives:* The strength of these proposed research criteria is the introduction of neurobiological measures on to the clinically based criteria. There are, however, many limitations and steps still needed. In their current formulation, these proposed diagnostic criteria still require decisions around how they are to be put into practice for clinical trials. For example, for the core criterion of significant episodic memory impairment, we have identified the memory test paradigms that can distinguish AD associated deficits from other memory difficulties, but we have not defined a magnitude of deficit or the comparative norms that should be used. In structural imaging, we have not presented a specific best test or method for MTL atrophy. There remains uncertainty as to the most effective method of assessment, qualitative or quantitative, and for the latter, the specific region within the MTL for measurement. There is no specification of the amount of atrophy that is optimally diagnostic of AD. Within molecular neuroimaging, there are similar open questions with regard to which regions are optimally diagnostic, whether a qualitative versus quantitative approach should be taken, and what degree of hypometabolism is diagnostic. Finally, we have not specified which cerebrospinal fluid marker or combination of markers should be used to support a positive diagnosis. Concentrations of cerebrospinal fluid markers vary substantially with different assays but also with the same assay done in different centers, raising important questions about measurements and sources of error. We would like to propose an update on these different markers that are useful for clinical trials.

**TUESDAY, OCTOBER 30<sup>TH</sup>**

**ORAL COMMUNICATIONS**

**OC11 - BAYESIAN ADAPTIVE TRIAL DESIGN: A NEW APPROACH FOR PHASE 2 CLINICAL TRIALS IN ALZHEIMER'S DISEASE.** A. SATLIN<sup>1</sup>, V. LOGOVINSKY<sup>1</sup>, J. WANG<sup>1</sup>, C. SWANSON<sup>1</sup>, S. BERRY<sup>2</sup>, D. BERRY<sup>2</sup> (1. Eisai Inc., Neuroscience Product Creation Unit, 155 Tice Blvd, Woodcliff Lake, NJ, 07677; 2. Berry Consultants, LLC, 4301 Westbank Drive, Bldg B, Suite 140, Austin, TX 77846, USA)

*Background:* Traditionally, Phase 2 studies are designed to demonstrate proof-of-efficacy and for dose selection. Once these aims

have been achieved, trials move into Phase 3. However, the last 14 investigational agents that appeared to show promise in Phase 2 trials in Alzheimer's disease (AD) have failed in Phase 3. One reason for these failures may have been a reliance on biomarkers as surrogates of clinical effect in Phase 2. For disease-modifying therapies, biomarkers can demonstrate target engagement, but our incomplete understanding of the mechanism of disease progression in AD means that target engagement may not necessarily predict clinical outcomes. Therefore, Phase 2 trials of potential disease modifying agents such as amyloid-based therapies should be designed to demonstrate clinical efficacy in addition to a biomarker effect, which will typically require larger sample sizes. Another consideration for Phase 2 studies is that amyloid-based therapies are more likely to work earlier in the course of the disease. In addition, drugs that are expected to slow disease progression but not to have an acute symptomatic effect will only be able to separate from placebo with longer trial durations to ensure a sufficient degree of placebo decline. Innovative approaches to designing Phase 2 clinical trials in AD are therefore needed to mitigate the risks of embarking on larger and longer studies. The design of a Phase 2 study for a monoclonal antibody directed at amyloid protofibrils is presented as an example of several such innovations. *Methods:* Phase 2 trial objectives are to demonstrate efficacy and assess dose response and safety. In order to minimize sample sizes and ensure the fastest possible decision-making, a Bayesian adaptive design was chosen. This design incorporates interim analyses for success and futility, and allows response-adaptive randomization to allocate patients between placebo and the doses and dose-regimens for which emerging data would indicate the highest likelihood of target dose selection. The primary endpoint is the change from baseline to 52 weeks in a composite clinical score. First, we constructed a dose-response model for the mean change from baseline for each treatment arm. A Bayesian model was built to learn from the accruing information on the association between the early values and the final endpoint at 52 weeks, using information from subjects with incomplete information to the extent that the earlier values are correlated to the final 52-week value. This model was then used (using Bayesian imputation within Markov chain Monte Carlo) to update the dose-response model through simulations. Based on the posterior distributions of the parameters in the dose response model, we sampled 10,000 dose-response curves to estimate the probability that each dose is the maximum effective dose, and the probability that each dose is the lowest or least frequently administered dose that achieves 90% efficacy of the maximum effective dose. Utilizing an estimate for the clinically significant difference (CSD), the probability that each dose would be superior to placebo by at least the CSD was estimated. To characterize the performance of the trial design, we simulated the trial using 3 different longitudinal scenarios (based on assumptions of a clinical effect that would appear similar to symptomatic therapy, a linear progression effect, or a late onset effect) and 13 different dose response scenarios. Design parameters for determining futility or early success were adjusted in an iterative fashion based on these simulations. The sample size, trial duration, and probability of success for the final Bayesian adaptive trial design were calculated and compared with those for a traditional study. *Results:* Simulations of the Bayesian adaptive design indicate that the sample size required would be reduced by at least 20% compared with traditional design. In addition, a decision regarding success or futility could be reached at least 1 year earlier in an adaptive trial, and the probability of stopping early for success would be 66% based on reasonable dose response assumptions. The trial was also designed so that blinded treatment would continue for 18 months if the trial was not stopped early for futility, allowing positive effects that might require longer treatment duration to be seen, and to further characterize the longitudinal course

of clinical and biomarker effects and to determine whether these support the hypothesis of disease modification. *Conclusions:* Phase 2 clinical trials in AD need to be more efficient and also more predictive of success in Phase 3. Bayesian adaptive design is a novel approach that utilizes interim analyses to frequently update the randomization allocation and assess for drug futility or evidence for early success. Such a design can mitigate the risks associated with the need for larger and longer trials required to demonstrate clinical efficacy of amyloid-based, potentially disease-modifying therapies in early AD, and can lead to more efficient project termination, or else earlier advancement to a successful Phase 3 program.

**OC12 - A NEW TOOL FOR OPTIMIZING RESPONSIVENESS TO DECLINE IN EARLY AD.** S. HENDRIX<sup>1</sup>, V. LOGOVINSKY<sup>2</sup>, C. PERDOMO<sup>2</sup>, J. WANG<sup>2</sup>, A. SATLIN<sup>2</sup> (1. *Pentara Corporation, 2180 Claybourne Ave, Salt Lake City, UT, 84109, USA*; 2. *Eisai Inc., Neuroscience Product Creation Unit, 155 Tice Blvd, Woodcliff Lake, NJ, 07677, USA*)

*Background:* No standard endpoints exist that are sensitive to change in MCI populations in clinical trials. We developed a tool based on standard clinical items that would demonstrate maximum responsiveness to progression and to treatment in an MCI population, and that would also perform well in a mild AD population (collectively referred to as Early AD). *Methods:* The new clinical score was developed by investigating responsiveness to progression and treatment effects rather than sensitivity to baseline deficits or to discrimination between clinical stages of AD. A partial least squares (PLS) regression model used placebo data from 4 MCI studies over 12 months to select the combination of cognitive and functional items which was most sensitive to change over time, using items from a variety of well-established and validated scales. The PLS regression coefficients from the model were used to form a weighted composite score. Eight critical components of scale validity were assessed with the new composite score: 1) external responsiveness (ability to change with disease progression); and 2) internal responsiveness (ability to change with a treatment effect); 3) cross-validation to estimate bias; 4) internal consistency/reliability; 5) test/re-test reliability; 6) construct validity and item redundancy; 7) general item characteristics; 8) convergent or external validity. External responsiveness was assessed by comparing the Mean to Standard Deviation Ratio (MSDR) between the composite and standard scales in an MCI population. Responsiveness was also assessed in enriched MCI subgroups (CSF A $\beta$  positive and ApoE4 positive), in the presence of a treatment effect and in a mild AD patient population combining placebo data from 3 studies. Internal responsiveness was assessed by comparing treatment effect sizes of standard instruments to the new composite. Cross-validation was performed by taking 100 random training samples of half the data from the pooled MCI data set, and using PLS to calculate the optimal composite. The selected composite was evaluated using the rest of the data (test sample). Bias of the MSDR of the optimal composite score was assessed by comparing the mean MSDR between the training samples and test samples. The frequency of each item in the training samples was compared with the selected items. Cronbach's alpha at baseline and 12 months was used to assess the internal consistency/reliability. Test/re-test reliability could not be directly assessed, but was approximated using the month 12 assessment as a re-test of the baseline assessment. Construct validity was primarily assessed using principal components analysis, but was supported with assessment of item redundancy. Ceiling and floor effects were evaluated in order to better understand the included and excluded items. Convergent validity was assessed using correlations between the new composite and standard clinical tests. *Results:* The

new score consists of 4 items from ADAS-Cog, 2 items from MMSE and all 6 items from CDR. The score shows improved external responsiveness with an average of 157% improvement over the ADAS-cog, 89% improvement over the MMSE and 15% improvement over the CDR-SB (bias corrected). Further improvement in responsiveness was demonstrated with ApoE4 carriers (39-67%), and MCI due to AD (CSF A $\beta$ 1-42 level of <192 mg/mL) patients (90%) due to reduced heterogeneity and increased progression over time relative to MCI all-comers. Importantly, the MSDR for the MCI due to AD group are similar to those seen in the mild AD population indicating that the composite score is effective across a range of patient severities. Using data from subjects treated with donepezil, the composite score demonstrated improved internal responsiveness in MCI and comparable responsiveness in mild AD relative to that of standard instruments. The improved responsiveness of the composite score allows for substantial sample size reductions in non-enriched and enriched MCI populations for a 12-month study. The cross-validation analysis of the MSDR based on the new composite score resulted in an average bias of 5.8%. Items selected for the new combination were also the most frequently selected items in the training samples. The composite score was shown to be reliable. The composite score represents cognitive and functional domains as the principal components of the item space. Most excluded items had ceiling effects, indicating no change in this early stage of AD. Others were redundant with included items. The composite showed convergent validity in the change scores at 12 months with correlations of 0.422, -0.487 and 0.858 with the ADAS-cog, MMSE and CDR-SB, respectively. *Conclusions:* A new composite clinical score combining cognitive and functional items from standard clinical instruments demonstrates improved sensitivity to decline, as well as reduced heterogeneity, as compared with original scales and is responsive to currently available treatments. It shows validity as a clinical outcome and can be offered as a single clinical outcome in studies that target MCI, enriched MCI and mild AD populations. This tool will enable the use of substantially smaller sample sizes due to improved sensitivity to disease progression and treatment effects.

**OC13 - EFFECTS OF AGE AND APOE E4 ON THE COURSE OF CLINICAL AND STRUCTURAL DECLINE IN ALZHEIMER DISEASE.** D. HOLLAND<sup>1</sup>, L.K. MCEVOY<sup>2</sup>, R.S. DESIKAN<sup>2</sup>, A.M. DALE<sup>1,2</sup> (1. *Department of Neurosciences*; 2. *Department of Radiology, University of California, San Diego, CA, USA*)

*Background:* Age is the strongest risk factor for sporadic Alzheimer disease (AD), but the effect of age on clinical and atrophic rates of decline in AD has been largely unexplored. Since the elderly population is growing, and proportionally growing faster with increasing age, our purpose was to better understand whether and how age interacts with the disease process to affect rate of decline; to model age trajectories; and to assess implications for clinical trial sample sizes. Moreover, APOE  $\epsilon$ 4 is the strongest genetic risk factor for sporadic AD. It is important, therefore, also to assess additional contributions, if any, of APOE  $\epsilon$ 4 on age-related rates of decline. *Methods:* We examined longitudinal rates of change as a function of baseline age for measures of clinical decline and structural MRI-based regional brain atrophy, in cohorts of AD, mild cognitive impairment (MCI), and cognitively healthy (HC) older individuals (total n=723) from the Alzheimer's Disease Neuroimaging Initiative. The effects of age and APOE  $\epsilon$ 4 were modeled using mixed effects linear regression. We used the age-specific annual rates of change, relative to HCs, in power calculations to estimate sample sizes needed to adequately power a clinical trial when individuals of a given age comprise the

study sample. From baseline measures and rates of atrophy as a function of age, disease trajectories were modeled assuming the annual atrophy rate increases linearly with time. **Results:** There was pronounced deceleration with age in the rates of clinical and atrophic decline for AD and MCI individuals, while HCs showed evidence of an increase in rates of decline with age. This resulted in trends toward convergence in rates of change for HCs and patients near 90 years of age, regardless of  $\epsilon 4$  status and both for cohorts with and without  $\epsilon 4$ . Baseline cerebrospinal fluid densities of AD-relevant proteins, A $\beta$ 1-42, tau, and phospho-tau181p (ptau), showed a similar pattern of convergence across cohorts, particularly for ptau. In contrast, baseline clinical measures did not change with age, indicating uniformity of clinical severity at baseline. HCs and MCIs but not ADs exhibited significant additional atrophy rates — and clinical and cognitive rates in the case of MCI — arising from  $\epsilon 4$ . There were no significant age $\times\epsilon 4$  interactions. Sample sizes based on rates of change in clinical or morphometric measures, relative to HCs, showed dramatic increases with age of study sample. Calculated disease trajectories show the rapid decline from HC to MCI to AD in ~10 years. **Conclusion:** These results imply that the phenotypic expression of AD is relatively mild in individuals older than approximately 85 years. This may affect the ability to distinguish AD from normal aging in the very old. Our results also demonstrate that inclusion of older individuals in clinical trials can substantially reduce the power to detect beneficial effects of a disease-modifying treatment. APOE  $\epsilon 4$  contributes significantly to faster clinical and morphometric rates of decline only in the preclinical and prodromal stages. Age does not modulate this  $\epsilon 4$  effect. Finally, plausible disease trajectories can be modeled based on longitudinal morphometric data, indicating longer duration to clinical diagnosis the later the age of onset.

## SYMPOSIUM

### S4 - ENRICHMENT APPROACHES IN PREDEMENTIA AD CLINICAL TRIALS . J. CEDARBAUM<sup>1</sup>, A. BUDSON<sup>2</sup> (1. *Global Clinical Research, Neuroscience, Bristol Meyers Squibb, Princeton, NJ, USA*)

*Communications: 1. Optimizing Predementia AD Clinical Trial Enrichment Criteria.* J. Tiller (Global Clinical Research, Neuroscience, Bristol Meyers Squibb, Princeton, NJ, USA); 2. *Baseline Biomarker Data from CN156018 and Enrollment Experience.* R. Berman (Global Clinical Research, Neuroscience, Bristol-Myers Squibb, Wallingford, CT, USA); 3. *Predementia AD: Qualifying CSF and PET Biomarkers for Clinical Trial Use.* R. Cahn (Global Regulatory Sciences, Bristol-Myers Squibb, Rueil, France)

Treating Alzheimer's disease earlier - during the predementia stage is considered one of the key strategies towards improving drug development success in AD. A number of biomarkers have been identified which can improve the likelihood of selecting patients with underlying amyloid pathology and/or identify those patients most likely to progress to dementia of the AD type. There are many patient selection enrichment options in predementia AD ranging from use of ApoE genotype and cognition to use of multi-modal imaging strategies. For targets aimed at the modulation of underlying amyloid pathology, enrichment for patients with underlying amyloid pathology is critical. BMS is currently developing a gamma secretase inhibitor, avagacestat, for the treatment of Alzheimer's disease. A Phase II study in predementia AD patients is currently being conducted to test the safety and tolerability of the compound. Baseline cognitive status and CSF AB42 and Tau concentrations were utilized as eligibility criteria to target the right patients and to better understand the

challenges associated with use of biomarkers for patient selection. In addition, an amyloid PET substudy was conducted. The symposium summarizes the experiences with the use of more sensitive cognitive measures and challenges associated with the use of CSF and PET biomarkers, and some of the regulatory hurdles to adoption. In addition, the symposium will consider the future of other non-invasive methods for enrichment in clinical trials with the potential for real world use. 1) *Optimizing predementia AD clinical trial enrichment criteria:* During the planning stages for the avagacestat Phase II safety study in predementia AD, multiple datasets were reviewed to arrive at suitable memory test and CSF biomarker eligibility criteria to be used in the study. This section will discuss BMS efforts to understand memory test performance and results comparing the Free and Cued Selective Reminding Test and Wechsler logical memory tests based upon data analysis from the Einstein Aging Study. This section will also provide an overview of CSF A $\beta$ 42 and Tau results from ADNI and DESCRIPA studies. In addition, challenges faced with "research use only" assay tests will be reviewed as well as new advances in CSF ABeta and Tau assay development. Performance of CSF assays was also assessed in the context of how MCI was defined. This presentation will summarize the utility of CSF biomarkers and current hurdles that will need to be addressed for registration level studies. This talk will also focus on the future of early diagnosis in AD by discussing data on the utility of medial temporal lobe atrophy as an enrichment tool for predementia AD and the advances in the area of blood based biomarkers in Alzheimer's disease. 2) *Baseline biomarker data from CN156018 and enrollment experience:* CN156018 is an ongoing randomized, double blinded, placebo-controlled Phase II study designed to examine the safety and tolerability of avagacestat in patients with predementia AD (PDAD) over a 2 year treatment period. Key entry criteria for subjects included: subjective memory complaints, objective memory loss on the Wechsler Memory scale-Logical Memory II or the Free and Cued Selective Reminding Test (FCSRT), a CDR-global score of 0.5 with a memory box score of >0.5 and a MMSE score of 24-30. Entry criteria required that subjects not meet DSM-IV criteria for dementia and their MRI and laboratory findings showed no alternative cause for cognitive impairment. We further selected for patients hypothesized to have a high probability of amyloid pathology and more likely to progress to dementia of the AD type based upon low CSF AB42 (AB42 levels <200pg/ml using the AlzBio3 test) and high tau levels (Total tau/AB42 ratio of > 0.39). In this section we report the baseline demographics and biomarker characteristics of both the enrolled population and the biomarker negative observational cohort. In addition, the section will review enrollment statistics and challenges faced with use of eligibility criteria. 3) *Predementia AD: Qualifying CSF and PET biomarkers for clinical trial use:* Recently, the EMA released new regulatory guidelines to issue a qualification opinion on the "acceptability of the specific use of novel methodologies or biomarkers in a research and development context based upon the assessment of submitted data." In 2010, BMS submitted three briefing documents to review the suitability of low CSF AB42 and high Tau profiles and amyloid PET imaging as suitable biomarker tools for the enrichment of predementia and mild-moderate AD study populations. The briefing documents summarized supportive data for the use of both CSF and amyloid PET biomarkers as tools to identify those patients with underlying AD pathology as well as a use to identify cognitively impaired patients most likely to progress to dementia of the AD type. This section provides an overview of the BMS experience in qualifying A $\beta$ 42/Tau and amyloid PET biomarkers for use in predementia and mild-moderate AD clinical trials. The qualification process, critical milestones, and the clinical evidence supporting a positive opinion will be reviewed. Outstanding challenges and next steps will also be outlined.

## UPDATE ON CLINICAL TRIALS 2

**6- HARMONISATION OF REPORTING STANDARDS FOR STUDIES OF DIAGNOSTIC TEST ACCURACY IN DEMENTIA: THE STARDDEM (STANDARDS FOR THE REPORTING OF DIAGNOSTIC ACCURACY STUDIES-DEMENTIA) CRITERIA.** R. MCSHANE<sup>1</sup>, A. NOEL-STORR<sup>1</sup>, L. FLICKER<sup>2</sup>, C.W. RITCHIE<sup>3</sup>, G. WILCOCK<sup>4</sup> AND STARDDEM WORKING GROUP (1. *Cochrane Dementia and Cognitive Improvement Group, University of Oxford, United Kingdom*; 2. *Geriatric Medicine, University of Western Australia, Melbourne, Australia*; 3. *Old age psychiatry, Imperial College, London, United Kingdom*; 4. *Clinical Geratology, University of Oxford, United Kingdom*)

*Introduction:* Recent revisions to diagnostic criteria for Alzheimer's disease dementia, and licensing claims for diagnostic biomarkers, have highlighted the need for clear standards for reporting tests of diagnostic accuracy in dementia and cognitive impairment. A generic reporting guideline on STAndards of Reporting Diagnostic test accuracy (STARD, Bossuyt et al, Clinical Chemistry 2003) has been adopted by leading journals (e.g. JAMA). Using the STARD checklist in a systematic evaluation of biomarker studies, we established that there were significant deficiencies in reporting (Noel-Storr et al, *Alzheimers & Dementia* 2012; in press). The following features were particularly poorly reported: blinding of results of either the biomarker or reference standard, handling of missing or indeterminate data, sample selection methods and test reproducibility. *Objectives:* The STARDdem initiative aims to establish consensus on reporting standards in dementia by extending and operationalising the implementation of the generic standards of the STARD Statement to dementia. The scope is restricted to studies where 2x2 data (eg sensitivity and specificity) are reported. This symposium will stimulate further discussion and present the results of the STARDdem initiative to date. The STARDdem Working Group of 10 experts assessed reports of diagnostic studies against the STARD criteria. Dementia-specific rubrics for each STARD criterion were developed. Examples of good reporting were identified. After several iterations, a draft was sent out to an international group of stakeholders for transparent commentary via the STARDdem website. The draft was revised on the basis of these comments. An inter-rater reliability study of the new STARDdem items, as applied to a range of reports of diagnostic test accuracy, was then conducted. After this Consensus Symposium a final draft will be submitted for publication. Key areas that required a dementia-specific focus related to: reporting of time interval between tests; description of the targeted population, setting and locations where data were collected; recruitment and sampling methods, prospective vs. retrospective use of data; ensuring test-, centre-, rater-reliability/reproducibility; clear statements on whether blinding was performed or not, and ensuring all study participants are fully accounted for. These parallel the issues which are familiar in reporting of RCTs such as blinding, inclusion criteria, treatment of missing data and definition of analytical strategies. *Conclusion:* STARDdem is a comprehensive dementia-focused checklist for authors and editors to encourage high standards in reporting the methods and results of studies of diagnostic test accuracy. Consensus on the reporting of randomised clinical trials (e.g. CONSORT) has been instrumental in improving methodology and transparency. International adoption of STARDdem will have the same effect for studies of biomarkers and other diagnostic tests in dementia.

**7- IS THE BETA-AMYLOID CASCADE HYPOTHESIS DEAD? IF SO, CAN IT BE RESUSCITATED?** E. GIACOBINI (*University of Geneva, Medical School, Dept. Internal Medicine, Rehabilitation and Geriatrics, Geneva, Switzerland Email: ezio.giacobini@hcuge.ch*)

Following the beta-amyloid cascade hypothesis (Hardy et al.1992), three distinct clinical approaches have been attempted during the period 2004-2012 : a. to prevent aggregation of beta-amyloid ,b. to reduce its production by means of beta- or gamma-secretase inhibitors or modulators or by reducing APP synthesis, d. to prevent a-beta accumulation or facilitate its clearance from the brain by means of active or passive immunization. These attempts have so far failed to produce a cognitive improvement similar to the one produced by cholinesterase inhibitors in the same type of mild-moderate Alzheimer Disease (AD) patients. Two anti-A-beta monoclonal antibodies (bapineuzumab and solanezumab) are presently in phase III. The results of these clinical trials will tell us if monoclonal anti-A-beta may or not slow down the rate of deterioration of AD. The negative results of the previous attempts agree with the finding that an increase in cerebral A-beta burden seen with PIB-PET in mild-moderate AD patients, do not relate either with clinical status or with cognitive decline (Ewers et al. 2010, Villemagne et al. 2011, Lo et al. 2011) and a decrease following immunization (Rinne et al. 2010) do not result into a cognitive improvement. Drugs or vaccines targeting the alternative key molecule of the cascade hypothesis, i.e. tau protein and its aggregation, synthesis or phosphorylation are still missing. We need to rethink the cascade hypothesis and to incorporate in it recent findings pointing to a close relationship between a-beta oligomers and tau as a match and fuse inducing mechanism (Selkoe et.al 2012, Mucke et al.2012, Klein.2012) and the accumulation of misfolded tau protein mediated by progressive intercellular spreading of oligomeric tau seeds to different brain regions as a mechanism of diffusion and progression of the disease. A modified cascade hypothesis of AD including these mechanisms may generate new models of therapy directed to treat both early and advanced stages of the disease, thus avoiding difficult preventive interventions at preclinical stages.

## SYMPOSIUM

**S5 - SOLANEZUMAB PHASE 3 RESULTS: IMPLICATIONS FOR ALZHEIMER'S DISEASE MODIFICATION.** E. SIEMERS (*Eli Lilly and Company, Indianapolis, USA*)

*Background:* Solanezumab, a humanized monoclonal antibody developed for the treatment of Alzheimer's disease (AD), binds to the mid-domain of soluble amyloid beta (A $\beta$  peptide but not to deposited amyloid plaques. *Methods:* Patients were enrolled in two Phase 3 trials (EXPEDITION and EXPEDITION-2) between May 2009 and December 2010. Participants had mild to moderate AD, determined using National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria, and Mini-Mental State Exam scores of 16-26. Participants were randomized to 400 mg solanezumab IV or placebo once every 4 weeks for 80 weeks. Co-primary outcomes were the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog11) and the Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL) scale scores. All participants underwent magnetic resonance imaging at baseline and at Weeks 12, 28, 52 and 80. A subset of participants underwent florbetapir PET imaging or lumbar puncture at baseline and endpoint. *Results:* A total of 2052 participants were randomized. The co-primary efficacy endpoint findings, and safety and biomarker findings will be presented

and discussed. *Conclusion:* The Phase 3 results will provide important efficacy and safety data for solanezumab, as relates to its use in patients with mild to moderate AD, and will help to advance the understanding of the amyloid hypothesis.

## ORAL COMMUNICATIONS

**OC14 - ENRICHMENT, STRATIFICATION, AND OUTCOME MEASURES FOR PREDEMENTIA ALZHEIMER DISEASE CLINICAL TRIALS.** D. HOLLAND<sup>1</sup>, L.K. MCEVOY<sup>2</sup>, R.S. DESIKAN<sup>2</sup>, A.M. DALE<sup>1,2</sup> (1. Department of Neurosciences; 2. Department of Radiology, University of California, San Diego, CA, USA)

*Background:* There is increased interest in Alzheimer disease (AD) clinical trials focusing on the predementia stages, particularly the preclinical stage. This has been spurred, in part, by the prominence — though controversial — of the amyloid hypothesis and the failure of amyloid-clearing agents to produce cognitive improvement in trials involving participants with early clinical AD. Design of predementia clinical trials, however, are hampered by difficulty in identifying individuals who are in the earliest stages of the disorder, and by selection of appropriate outcome measures that will be sensitive to the subtle changes that occur in these earliest stages. Preventive trials in particular, involving cognitively intact participants, pose a considerable challenge, as the participants show very low rates of clinical and structural decline, raising a further question of how long the trial needs to last so that the success of a disease-modifying therapeutic agent could be demonstrated. To address these issues, here we examine enrichment strategies to select individuals most likely to experience decline over the course of predementia trials, and outcome measures most likely to be sensitive to disease-modifying therapeutic effects. *Methods:* Mild cognitive impairment (MCI) and cognitively healthy (HC) older individuals (total n=390) from the Alzheimer's Disease Neuroimaging Initiative were categorized into lower or higher risk groups with respect to threshold values of cerebrospinal fluid densities of AD-relevant proteins, A $\beta$ 1-42 (A $\beta$ ), tau, and phospho-tau181p (ptau). MCI participants were also categorized into risk groups based on baseline AD-like atrophy pattern. Longitudinal rates of change were modeled using mixed effects linear regression for measures of clinical decline (the Clinical Dementia Rating Scale, sum of boxes score, or CDR-SB) and structural MRI-based regional brain atrophy in participants who were assessed at 6- or 12-month intervals for up to three years. The control group consisted of HCs without CSF biomarker evidence of AD pathology (A $\beta$ - HCs), since these participants are unlikely to be in the preclinical phase of the disorder. We used the annual rates of change, relative to the control group, in power calculations to estimate sample sizes needed to adequately power clinical trials, given various enrichment strategies for both preclinical (HC with CSF biomarker evidence of AD pathology) and MCI cohorts. Trials were assumed to be of 24-months duration with 6-months assessment intervals, and to have 80% power and significance of 0.05. *Results:* For clinical trials aimed at the MCI phase, for each biomarker the high risk group showed substantially higher annual atrophy rates than the corresponding low risk group, and much higher still than the control group. As a result, enrichment for high risk based on any biomarker enabled substantial reductions in sample size. The HC participants most likely to be in a preclinical phase of the disorder (i.e. A $\beta$ +Ptau+ HCs) showed somewhat elevated rates of decline relative to the control group, but the differences in atrophy rates reached significance only for the amygdala and the parahippocampal gyrus, while the difference in annual rate of decline for CDR-SB approached significance (p=0.061). As a result of the small effect sizes, sample size estimates for morphometric and CDR-SB outcome

measures in preclinical preventive trials were prohibitively large. For example, using amygdala atrophy rate as the outcome variable, the required sample size per arm is n=773, with 95% confidence interval CI=[256 to 34673]; for the entorhinal cortex, n=2672, CI=[453 to >100000]; and for the hippocampus, n=1763, CI=[400 to >100000]. The clinical outcome measure showed a similarly large sample size estimate: CDR-SB n=1284, CI=[333 to >100000]. The extreme upper bounds in the CIs renders these rate-of-change measures ineffective as outcome measures in standard longitudinal trials. Extending the trial duration to 5-years (assuming the same rates of decline) did not substantially alter these estimates. *Conclusion:* For clinical trials aimed at individuals with MCI, the clinical and morphometric measures are adequately sensitivity to change over time, suggesting that detecting efficacy of candidate therapies in MCI participants is unlikely to be a limiting factor in AD therapeutics research. These outcome measures, however, are not sufficiently sensitive to change over time in the preclinical phase to be able to assess treatment efficacy. Thus, natural history trials of long duration — such that significantly higher rates of change begin to occur — will likely be required to establish estimates of baseline trajectories, so that improvements with respect to these can be assessed in future preventive trials of similar duration.

**OC15 - MISSING DATA IN ADCS CLINICAL TRIALS.** M. DONAHUE<sup>1,2</sup>, A. GAMST<sup>1,2</sup>, R. RAMAN<sup>1,2</sup>, R. THOMAS<sup>2</sup>, P. AISEN<sup>2</sup> (1. Division of Biostatistics & Bioinformatics, University of California, San Diego, USA; 2. Department of Neurosciences, University of California, San Diego, USA)

*Background:* Randomized clinical trials of Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) typically assess intervention efficacy with measures of cognitive or functional assessments repeated every six months for one to two years. Models that treat time as categorical are gaining popularity because they make no assumptions about the shape of the mean trajectory of the outcome over time. However, in some cases categorical time models may be over-parameterized and inefficient in detecting treatment effects relative to continuous time models of, say, the linear trend of the outcome over time. Linear mixed effects models can also be extended to model quadratic or cubic time effects, although it is questionable whether the duration and interval of observations in AD and MCI studies is sufficient to support such models. Furthermore, it is unknown which of these models are most robust to the missing data that plagues AD and MCI studies. *Methods:* We will conduct a meta-analysis characterizing patterns of observed missingness using data from 5 intervention studies conducted by the Alzheimer's Disease Cooperative Study (ADCS). The five studies include Donepezil and Vitamin E in MCI; and AD trials of Vitamin B, Prednisone, Simvastatin, and Docosahexaenoic (DHA). We will conduct retrospective analyses of these data to: (1) Summarize and categorize the visit process relative to other covariates and longitudinal outcomes, (2) Assess the goodness of fit, bias, and efficiency of the potential primary models of efficacy, (3) Conduct sensitivity analyses within each trial to assess the robustness of the candidate model to the effect of missing data. We will model the visit process as a time-to-event, where the recurrent event of interest is the study visit, typically scheduled at 6-month intervals. We conduct a sensitivity analysis to assess the effect of missing data and the visit process on primary efficacy inference and discern which models are most robust. *Conclusion:* Development and implementation of the most efficient and accurate data analysis methods is imperative. Our ongoing meta-analysis will help discern which models provide the estimates of treatment efficacy that are most robust to missing data typically encountered in ADCS clinical trials.

**OC16 - SOUVENAIID PRESERVES BRAIN FUNCTION IN PATIENTS WITH MILD ALZHEIMER'S DISEASE: RESULTS FROM A RANDOMISED CONTROLLED STUDY.** E.C.W. VAN STRAATEN<sup>1</sup>, H. DE WAAL<sup>2</sup>, M.M. LANSBERGEN<sup>3</sup>, P. SCHELTENS<sup>2</sup>, C.J. STAM<sup>1</sup> (1. Department of Clinical Neurophysiology, VU University Medical Centre, Amsterdam, The Netherlands; 2. Department of Neurology and Alzheimer Centre, VU University Medical Centre, Amsterdam, The Netherlands; 3. Nutricia Advanced Medical Nutrition, Danone Research, Centre for Specialised Nutrition, Wageningen, The Netherlands)

**Backgrounds:** Synaptic loss is a major hallmark of Alzheimer's disease (AD), which correlates strongly with loss of memory and cognition. Additionally, patients with AD are characterised by decreased connectivity within the brain that may be caused by synapse loss and be related to memory dysfunction. The medical food Souvenaid®, containing the nutrient combination Fortasyn™ Connect1, is designed to support synapse formation and function in AD by providing specific nutrients that enhance neuronal membrane formation. It is hypothesised that supporting synapse formation and function in AD will positively affect brain connectivity and thereby memory and cognition. Pre-clinical research has demonstrated that specific nutrients within Fortasyn Connect increase neurite outgrowth, dendritic spine density, both prerequisites for synapse formation, and synaptic proteins (Wurtman et al., 2009). Furthermore, two randomised controlled trials in patients with mild AD have shown that Souvenaid improved memory performance ('Souvenir I' study, Scheltens et al., 2010; 'Souvenir II' study, Scheltens et al., JAD 2012, in press; presented at CtAD 2011). To get more insight into the working mechanisms of Souvenaid and to provide evidence for the hypothesis that Souvenaid supports synapse formation and improves neuronal connectivity, electroencephalography (EEG) was included in the Souvenir II study as a secondary outcome parameter. EEG is a well-known, widely available measure to directly record neuronal activity in humans and, thus, indirectly synaptic activity. **Methods:** The Souvenir II study2 (NTR1975) was a randomised, controlled, double blind, parallel group, multi-country study, in which 259 drug-naïve patients with mild AD (MMSE  $\geq$  20) were randomised to receive either the active product Souvenaid (a 125 mL once-a-day drink containing Fortasyn Connect) or an isocaloric control product for a period of 24 weeks. Detailed methodology and results on the main study outcome parameters have been presented before (Scheltens et al., JAD 2012, in press, presented at CtAD 2011). The secondary EEG parameters to investigate the biological effect of Souvenaid were (a) peak frequency, defined as the dominant frequency in the EEG signal, (b) phase lag index (PLI) to investigate functional brain connectivity, and (c) two parameters that characterise the organisation of the brain network (normalised clustering coefficient C, signifying local connectivity, and normalised average shortest path length L, as a measure of global integration). It has been reported before that patients with AD have been characterised by slowing of the peak frequency, decreased functional brain connectivity and a less optimal brain network organisation compared to healthy control subjects (Stam et al., 2009). **Results:** EEG data were available for a subset of 179 patients (86 and 93 patients using Souvenaid and control product, respectively) as not all study sites were able to collect high quality EEG data. As expected in progressive AD, peak frequency slowed in the control group, which is indicative of cognitive deterioration. In contrast, peak frequency remained relatively stable in the active group, which was significantly different from the control group during the 24-week intervention period ( $p=0.019$ ). Functional connectivity (PLI) in the delta band also differed significantly over 24 weeks between study groups, in favour of the active group ( $p=0.011$ ). Networks of patients

receiving control product showed a decrease in normalised clustering coefficient C and in normalised average shortest path length L in the beta band. This suggests a shift from an optimal network organisation to a more random organisation, as expected in progressive AD. These network parameters remained stable for the patients receiving the active product, and differed from the control group ( $p=0.009$  for normalised clustering coefficient C and  $p=0.053$  for normalised average shortest path length L). Moreover, significant correlations were found between changes in the EEG parameters and changes in neuropsychological outcome parameters from baseline after the 24-week intervention. **Conclusion:** Souvenaid is designed to support synapse formation and function in AD, with the aim of changing connectivity within brain networks and improving cognition and memory. Pre-clinical results and positive memory outcomes in clinical studies support this hypothesis indirectly. The present Souvenir II study included EEG as biomarker of synaptic activity to validate this hypothesis in patients with mild AD. The control group showed changes in peak frequency, functional brain connectivity, and brain network organisation consistent with progressive AD, indicating a decline in brain function, possibly due to loss of synapses. In contrast, patients receiving Souvenaid showed preserved connectivity and optimal network organisation. Correlation analyses suggested that the biological effects may be related to the positive memory effects as found previously. In conclusion, the present biomarker findings extend the evidence for our hypothesis that Souvenaid supports synapse formation and function, thereby preserving functional brain connectivity and improving memory. Additional imaging studies are ongoing and planned to further investigate the mode of action of Souvenaid. 1. Souvenaid is a registered trademark of N.V. Nutricia. Fortasyn is a trademark of N.V. Nutricia. 2. Partly funded by NL Food & Nutrition Delta project, FND N°10003.

**OC17 - THE KINASE PKR: A DIAGNOSTIC AND THERAPEUTIC TARGET IN ALZHEIMER'S DISEASE.** J. HUGON, F. MOUTON-LIGER, J. DUMURGIER, C. PAQUETA (Memory Center Lariboisiere Hospital APHP, University Paris Diderot Paris France and Institut du Fer à Moulin, Inserm U 839 Paris France)

**Backgrounds:** Alzheimer Disease (AD) is clinically marked by memory disturbances followed by aphasia, apraxia and agnosia with behavioural symptoms. Neuropathological lesions include senile plaques formed by Amyloid peptide A $\beta$  1-42, neurofibrillary tangles made of hyperphosphorylated tau protein and synaptic and neuronal losses. The cause of AD is unknown but the oligomers of A $\beta$  1-42 could lead to neurodegeneration. The cerebrospinal fluid (CSF) levels of A $\beta$  1-42, Tau and phosphorylated tau (pTau) are modified in AD. PKR is a pro-apoptotic kinase that controls protein synthesis. PKR is activated by cytokines, calcium, viruses and A $\beta$  1-42. The activation of PKR induces inflammation, and modulates the levels of BACE 1 and A $\beta$  1-42 production as well as the phosphorylation of tau protein. The genetic knock down of PKR improves memory in normal experimental mice. The goal of the present study was to determine if the levels of PKR and activated PKR (pPKR) were increased in the CSF of AD patients compared to neurological controls. **Methods:** In a prospective cohort analysis, 45 AD patients, 11 patients with Mild Cognitive Impairment (MCI) and 35 neurological control individuals were included in this study. After diagnosis, all patients had a lumbar puncture to determine the CSF levels of A $\beta$  1-42, Tau and pTau using an ELISA assay (Innogenetics) and the concentrations of PKR and pPKR using western blot procedures. All patients or care giver gave their written informed consents. This study has been approved by the local ethics committee. **Results:** The mean CSF pPKR level was

increased by 300% in AD patients compared to neurological controls. The sensitivity was 91.1% and the specificity was 94.3%. pPKR concentrations were also increased in the majority of MCI patients. In AD patients PKR and pPKR levels correlate with pTau levels. Some AD patients with normal A $\beta$  1-42, Tau and pTau levels had abnormal pPKR concentrations. *Conclusions:* The evaluation of CSF PKR and pPKR concentrations could help to improve AD diagnosis and PKR is a new therapeutic target to decrease neurodegeneration and improve memory in AD patients.

**OC18 - TOWARDS STANDARDIZATION OF CSF BIOMARKERS: A MULTI-SITE STUDY USING VALIDATED ASSAYS FOR A $\beta$ 42 AND TAU.** R.M. UMEK, D.H. STEWART, J.M. DUNTY, N.L. PUSKAR, P. OBEROI, J.N. WOHLSTADTERA (Meso Scale Discovery, Gaithersburg, MD 20877 USA)

*Background:* The need for standardization in the measurement of biomarkers related to Alzheimer's disease is now widely appreciated. Working groups have been formed to advance the effort by the Alzheimer's Association, the French Society of Clinical Biology, and the Alzheimer's Disease Neuroimaging Initiative. Along with universal standardization, manufacturers must produce assays with minimal variability across manufacturing runs, users, and platforms in order to provide the research community with a means for accurate analysis of AD markers. Despite advances in the characterization of biomarkers from cerebral spinal fluid (CSF), commercially available assays for these biomarkers exhibit significant shortcomings which limit their utility. For example, all of the A $\beta$ 42 assays studied to date exhibit a matrix effect, an undefined activity in the sample matrix that results in under-recovery of the analyte. MSD® has developed validated assays for the amyloid beta 42 (A $\beta$ 42) peptide and total tau protein for use with CSF samples. The assays were developed using guidelines from "Fit-for-Purpose Method Development and Validation for Successful Biomarker Measurement" by J.W. Lee, et al. (2006Pharmaceutical Research, 23(2):312-328). Kits and control samples were distributed internationally to six laboratories with established expertise in the analysis of biomarkers using human CSF. *Methods:* The Human A $\beta$ 42 and Human Total Tau assays were validated using three independently-built kit lots. Testing for each kit involved a minimum of twelve runs conducted by three analysts across at least three days (N=54 runs across three kit lots). Each kit lot was built using different lots of raw materials that were characterized using multiple bioanalytical methods (gel electrophoresis, dynamic light scattering, and capillary isoelectric focusing). Limit of quantification samples, matrix-based validation samples, and controls were measured using multiple kit lots, plates, and analysts over multiple days to establish sensitivity, accuracy, precision, and assay calibration curves. Spike recovery and dilution linearity were evaluated using individual normal and AD patient samples. Assay specificity and tolerance to sample contamination with hemolyzed blood were evaluated. Assay robustness and stability were assessed through freeze-thaw testing and accelerated stability studies. *Results:* The validated Human A $\beta$ 42 Kit has a lower limit of quantification (LLOQ) of 3pg/ml and an upper limit of quantification (ULOQ) of 2,000 pg/ml. An 8-fold minimum required dilution (MRD) overcomes the matrix effect. Spike recovery was consistent (+20%) across three kit lots from 250-4,000 pg/ml of spiked A $\beta$ 42. The Human Total Tau Kit exhibits an LLOQ of 30pg/ml, a ULOQ of 8,000pg/ml, and an MRD of 1:2, although the assay is precise at 1:4 as well. Spike recovery was consistent (+20%) across three plate lots from 250-4,000 pg/ml of spiked tau. Kits were shipped to six international locations along with control CSF samples varying in A $\beta$ 42 and tau abundance and representative of the clinical range observed in normal individuals and Alzheimer's disease patients. Each

lab received technical training from a qualified operator. The results of the multi-site study will be presented. *Conclusion:* Validated assays for A $\beta$ 42 and tau using human CSF samples have been developed. The data from the validation package confirms that assay performance is consistent across three production lots as judged by the accurate characterization of control samples. The assays are available internationally and consistent results can be achieved when a qualified operator provides training for laboratory personnel.

**OC19 - ARE NEUROPSYCHOLOGICAL TESTS SUCH AS THOSE USED IN ADNI SUITABLE FOR LONG-TERM TRIALS OF COGNITION ENHANCERS FOR PRECLINICAL ALZHEIMER.** K. WESNES<sup>1,2</sup>, L. SCHNEIDER<sup>3</sup>, (1. Bracket Global, Goring, UK; 2. Swinburne University, Melbourne, Australia; 3. Keck School of Medicine of the University of Southern California, USA)

The search for substances to improve cognitive function and treat age-related cognitive decline is dependent upon having instruments which can reliably measure such effects. For example research criteria for 'preclinical' Alzheimer's disease (AD) acknowledge the requirement for sensitive measures of 'psychomotor function' to identify early clinical manifestations of AD (Sperling et al 2011). The Alzheimer's Disease Neuroimaging Initiative (ADNI) employed widely used neuropsychological tests to identify the transition from normal aging to the earliest stages of memory loss through MCI/AD. The purpose of the present analysis was to determine the utility of the ADNI tests for repeated administration in such research. *Methods:* Data from the control, amnesic MCI (MCI due to AD) and mild AD cohorts were downloaded from the ADNI website (29/Feb/2012) for the following tests: Digit Span, Trail Making, Digit Symbol, Clock Drawing, Category Fluency, Boston Naming, Logical Memory and Auditory Verbal Learning. A variety of methods were employed to characterise the performance of the tests, including clinical trial simulations. *Results:* Data for up to 5 years were available for 226 non-demented controls aged 60 to 90 years. While the tests had good test-retest reliability and were able to differentiate the control, MCI, and AD cohorts extremely well; for the controls, no consistent pattern of decline was detected on any task over the study period. On the contrary, significant improvements occurred with repeated testing on most tests, some lasting up to 5 years. The effect sizes of the improvements were notable in many cases. *Conclusion:* The various analyses and clinical trial simulations conducted indicate that the neuropsychological tests used in ADNI would not perform well in clinical trials of compounds designed to reduce age-related cognitive decline or treat preclinical AD. While test-retest reliability is a necessary property for cognitive tests in this field, it is clearly not sufficient.

**OC20 - PHASE II TRIAL OF METFORMIN IN AMNESTIC MCI.** J.A. LUCHSINGER<sup>1</sup>, J. MANLY<sup>2</sup>, J. STEFFENER<sup>2</sup>, E. BAGIELLA<sup>3</sup> (1. Department of Medicine, Columbia University Medical Center, New York, New York, USA; 2. Gertrude H. Sergievsky Center, Columbia University Medical Center, New York, New York, USA; 3. Biostatistics Center for Clinical Trials Management, Mt. Sinai School of Medicine, New York, NY, USA)

*Background:* Epidemiological studies have shown an association between type-2-diabetes and an increased risk of mild cognitive impairment and dementia. Hyperinsulinemia, which precedes and may accompany type-2-diabetes, may increase amyloid beta deposition in the brain, and is related to a higher risk of Alzheimer's disease in epidemiologic studies. Thus, interventions that prevent type-2-diabetes and decrease peripheral insulin levels could prevent Alzheimer's disease or its progression. A phase III clinical trial of rosiglitazone in



early Alzheimer's disease, an insulin sensitizer, was negative, and a trial of rosiglitazone in mild cognitive impairment has yet to be reported. Metformin, a medication of the biguanide class, is used for treatment of early type-2-diabetes, but has also demonstrated efficacy in prevention of type-2-diabetes and in decreasing insulin levels. Thus, we conducted a phase II clinical trial of metformin in amnesic mild cognitive impairment (MCI) to test safety, feasibility, and to obtain preliminary data on efficacy. We hypothesized that persons with metformin would have better cognitive outcomes after 12 months of treatment. *Methods:* The design of the study was a double blind placebo controlled trial of metformin vs. matching placebo. The duration of the trial was 12 months. Metformin was titrated to a maximum dose of 1000 mg twice a day from a starting dose of 500 mg once a day, as is common in clinical practice. The inclusion criteria included fulfilling criteria for amnesic MCI, being overweight or obese (body mass index > 25 kg/m<sup>2</sup>), and age 55 years and older. Exclusion criteria included a diagnosis of dementia, active psychiatric disease, treated diabetes, cancer within 5 years of recruitment, use of cholinesterase inhibitors, and contraindications to metformin. Participants were randomized to metformin or placebo in a 1:1 ratio with stratification by APOE- $\beta$  genotype. The primary clinical outcomes were differences in change in the ADAS-Cog and total recall of the Selective Reminding Test. The secondary outcome was change in uptake of fluorodeoxyglucose (FDG) in the posterior cingulate measured with brain positron emission tomography with co-registration using magnetic resonance imaging. The tertiary outcome was changes in plasma amyloid beta (A $\beta$ ) 40 and A $\beta$ 42. *Results:* Recruitment of 80 participants was finished in February of 2011. The last participant underwent the last visit in February of 2012; 54% of participants were women, 46% men, 60 % were aged 55 to 64 years, 30% between 65 and 74 years, and 10% were 75 years and older. At the time of submission of this abstract the study data was being prepared for analyses and the investigators remained blind to study arm allocation. We will analyze the effect of metformin on clinical outcomes in 80 participants, imaging outcomes in 33 participants, and plasma A $\beta$ 40 and A $\beta$ 42 in 77 participants. *Conclusion:* We will present preliminary data on the safety, feasibility, and efficacy of metformin in the prevention of cognitive decline in persons with amnesic MCI. The results presented will be used to decide whether a phase III trial of metformin in amnesic MCI should be carried out. Our data have gained increased importance because of recent reports raising the possibility that metformin increases brain A $\beta$  production and could increase the risk of Alzheimer's disease.

#### **OC21 - $\gamma$ -SECRETASE-LINKED CLINICAL TRIALS FAILURES: AN AMYLOID CASCADE HYPOTHESIS REBUTTAL OR JUST EXPERIMENTAL PITFALLS UNMASKED? F. CHECLER**

The amyloid cascade hypothesis predicts a key role of amyloid  $\beta$ -peptides in the etiology of Alzheimer's disease. In this context, all enzymatic machineries involved in Ab production, degradation or bio-transformation could be seen as putative targets aimed at interfering with the degenerative processes taking place in this pathology. The  $\alpha$ -secretase activity, that ultimately liberates the A $\beta$  peptides, has been at the center of a huge effort aimed at identifying the nature of this enzyme. A rather wide consensus agrees to present a presenilin-dependent  $\alpha$ -secretase complex as the guilty in this matter. This is supported by the observation that both pharmacological and genetic targeting of presenilins leads to full abolishment of A $\beta$  production in cells and animal models. However, recent clinical trials concerning presenilin-directed inhibitors failed. Thus, in two Phase III trials (involving 2600 patients with mild-to-moderate Alzheimer disease),

semagacestat, a  $\alpha$ -secretase inhibitor developed by Eli Lilly and Cie, did not slow down disease progression and was even shown to accentuate a subset of cognitive deficits. Even worse, semagacestat administration appears to increase the risk of skin cancers. Do these data invalidate the amyloid cascade hypothesis? Do these data indicate that, even if the hypothesis is good, targeting  $\alpha$ -secretase appears as a doubtful track to interfere with Alzheimer disease? Alternatively, can we take advantage of this data to set up an alternative strategy still targeting A $\beta$  but envisioning additional means? This will be discussed with respect to recent data delineating potential reasons for  $\alpha$ -secretase-directed semagacestat trial failure.

## **SYMPOSIUM**

### **S6 - MODELING THE COURSE OF AD: CONTRIBUTIONS TO BETTER CLINICAL TRIALS. R. SPIEGEL (*Memory Clinic, Department of Geriatrics, University Hospital, Basel, Switzerland*)**

*Introduction:* As a consequence of the increasing number of negative clinical trial results obtained with experimental drugs aimed at favorably affecting the course of AD, questions emerged as to the biological concepts of AD underlying the development of such compounds. Another set of questions concerned the clinical trials, usually late in development, that had produced negative results: are the testing strategies and procedures applied in these studies suitable for the assessment of disease-course altering drugs? More detailed questions were asked with regard to basically all aspects of recent clinical trials: patient selection criteria, methods of patient assessment, specific logistic aspects of large multinational-multicenter trials, the conventional organization of clinical development in phases 1, 2 and 3 and, eventually, the design and duration of phase 3 double-blind, placebo-controlled studies. *Objectives:* Several groups of investigators set out to more thoroughly follow and eventually model the long-term course of AD throughout different stages of the disease and at different levels of assessment. It is assumed that modeling the course of AD at different stages of its development, from the pre-symptomatic stages to severe dementia, will contribute to better planning and design of future clinical trials. Our symposium will present an overview and critical assessment of some of these modeling approaches.

*Communication 1: Predicting Progression of AD: Understanding the Variance, R.S. Doody<sup>1</sup>, C. Wen<sup>2</sup>, P. Valory<sup>1</sup>, P. Massman<sup>1,3</sup>, E. Darby<sup>1</sup>, S. Rountree<sup>1</sup> (1. Baylor College of Medicine - Department of Neurology, Houston, Texas, USA; 2. University of Texas Health Science Center, Houston, Texas, USA; 3. University of Houston, Texas, USA)*

In their pioneering work, Rachele Doody et al. assert that modeling of group disease progression is critical for estimating change in clinical trials of disease-modifying therapies. According to these authors multivariate models of disease progression can also foster the ability to stratify or predict progression in individual patients. Doody and her group have used mixed effects regression analysis to examine the role of demographic, biological, clinical, and psychometric characteristics in predicting progression of AD in a large patient cohort. This work suggests that premorbid IQ (probably a surrogate for cognitive reserve) and early, intrinsic progression rate are the most predictive variables, yet these are seldom captured as baseline characteristics and therefore seldom balanced or accounted for in the analysis of clinical trials. The persistence of anti-dementia drug use from the time of symptom onset is also a predictive variable, whereas most companies simply collect information on concurrent drug use at the time of randomization.

*Communication 2: Creating a New Composite Score for Optimizing Responsiveness to Decline in Early AD and Very Early AD*, S. Hendrix (Pentara Corporation, Salt Lake City, UT, USA)

Suzanne Hendrix has proposed composite outcome scores that optimize the power for measuring clinical disease progression for trials in an MCI population, or a pre-MCI population. The goal of this work is to improve the responsiveness of clinical outcomes to disease progression, particularly in early stages of AD, with the expectation that this will give treatments the best chance for showing a treatment effect. Several different approaches based on factor analysis, and different regression techniques are all used to maximize the mean to standard deviation ratio of the change over time. More responsive clinical outcome measures in early disease stages are possible using combinations of items that are currently collected as items within standard clinical outcomes. The models are competitive so that redundant items that do not improve responsiveness are removed from the composite score. In addition, items that are not relevant to decline in these early stages would not be included in the composite score. The weighting of the items reflects the relative importance of each item in the population under consideration. Composite scores can be constructed utilizing cognitive items only, global functional items only or a combination for optimal responsiveness. These responsive clinical outcomes will allow smaller and shorter clinical trials in early disease, and will help with validation of biomarkers in these early stages. Another important consideration in improving responsiveness is to know whether there are different subgroups of early AD patients that decline in different ways than the general population, primarily so that these different populations can be stratified, corrected for in an analysis or excluded from clinical trials, thus improving the sensitivity of a statistical outcome. The population selection must be considered in conjunction with the optimization for responsiveness in order to assure that the responsiveness is not decreased by the inclusion of individuals who may not have the same disease profile.

*Communication 3: The Placebo Group Simulation Approach (PGSA): An Alternative to Long-term Placebo-controlled Trials*, R. Spiegel<sup>1</sup>, M. Berres<sup>2</sup>, A.R. Miserez<sup>3</sup>, A.U. Monsch<sup>1</sup> (1. Memory Clinic, Department of Geriatrics, University Hospital, Basel, Switzerland; 2. University of Applied Sciences Koblenz, RheinAhr Campus, Remagen, Germany; 3. Diogene Laboratories Inc., Reinach, Switzerland)

The work of René Spiegel et al. addresses a scientific and an ethical issue inherent to long-term randomized placebo-controlled double-blind clinical trials (RPCTs), the conventional study design used in the late clinical development of disease-course altering drugs. These authors question whether AD patients (and their carers) who consent to take the risk of being treated for many months or even years with placebo are representative of the AD population at large. Generalization of findings from RPCTs to the majority of AD patients in early disease stages may thus be questioned. In the case of disease-course altering drugs undergoing confirmatory clinical testing in Phase 3 of development in prodromal patients, one may also question whether it is ethically acceptable to expose individuals who run a high risk of developing dementia to extended placebo treatment. In an attempt to provide a valid alternative to long-term RPCT designs, Spiegel et al. have developed mathematical models to forecast clinically relevant endpoints and disease trajectories of prodromal AD patient groups. These models comprise demographic, biological and neuropsychological measures that are routinely established at baseline of clinical studies. Model-based forecasted endpoints and trajectories constitute the quantified background - the "simulated placebo group" - against which potential drug effects will be contrasted. The models of

the Placebo-Group Simulation Approach (PGSA) were developed using data from MCI and normal control individuals available from the ADNI 1 (Alzheimer Disease Neuroimaging Initiative) database. The author will present new results from a validation study of one typical PGSA model, using data from aMCI patients kindly provided by the NACC (National Alzheimer's Coordination Center; Grant number U01 AG016976). The results obtained in this large database confirm that mathematically modelled disease trajectories show high concordance with the empirically observed outcomes in prodromal AD patients. The validity of the longitudinal PGSA model is supported by these findings. It is hoped that the PGSA will help to reduce long-term RPCTs in AD and possibly other medical conditions characterized (i) by a fatal outcome and (ii) by a quantifiable disease course. Discussion: Kristin Kahle-Wroblewski (Eli Lilly & Company, Indianapolis, IN, USA) will discuss the applicability of the models proposed by the session speakers to the drug development process and how balancing elements of these models may facilitate discussions with regulators and payers. Preliminary results of longitudinal biomarker data from a failed Phase 3 trial will be presented as additional parameters for consideration in the development of disease progression models. Conclusion: Current efforts in the modeling of disease progression have grown increasingly complex in an effort to account for the heterogeneity of patients with AD. Accurately predicting rate of progression is essential to the drug development process, as it is likely to facilitate detecting a signal in clinical trials and reduce uncertainty in extrapolating treatment effects beyond the trial time frame.

**S7 - MAPT (MULTIDOMAIN ALZHEIMER PREVENTIVE TRIAL) IMAGING (MRI, FDG-PET, AMYLOID-PET) DATA.** B. VELLAS<sup>1</sup>, J. TOUCHON<sup>2</sup>, M. WEINER<sup>3</sup> (1. *Gérontopôle, Département de Geriatries, CHU Toulouse, Purpan University Hospital, Toulouse, France*; 2. *Department of Neurology, Memory Research Resource Center for Alzheimer's Disease, University Hospital of Montpellier, Montpellier, INSERM U1061*; 3. *University of California, Center for Imaging of Neurodegenerative Disease, San Francisco, USA*)

*Communication 1: M.A.P.T Trial Design*, B. Vellas<sup>1,2,3,4</sup>, I. Carrie<sup>1</sup>, G. Abellan Van Kan<sup>1</sup>, S. Gillette-Guyonnet<sup>1,2,4</sup>, J.-F. Dartigues<sup>5</sup>, J. Touchon<sup>6</sup>, T. Dantoine<sup>7</sup>, O. Rouaud<sup>8</sup>, M. Bonnefoy<sup>9</sup>, P. Robert<sup>10</sup>, M.-N. Cuffi<sup>11</sup>, L. Bories<sup>12</sup>, S. Bordes<sup>13</sup>, Y. Gasnier<sup>13</sup>, F. Desclaux<sup>14</sup>, K. Sudres<sup>15</sup>, A. Pesce<sup>16</sup>, S. Andrieu<sup>1,2,3,4</sup> (1. *Gérontopôle, Département de Geriatries, CHU Toulouse, Purpan University Hospital, Toulouse, France*; 2. *Inserm Unit 1027, Toulouse, France*; 3. *Department of Epidemiology and Public Health, CHU Toulouse, Toulouse, France*; 4. *University of Toulouse III, Toulouse, France*; 5. *INSERM U897, Memory Research Resource Center for Alzheimer's Disease, University Hospital of Bordeaux, Bordeaux, France*; 6. *Department of Neurology, Memory Research Resource Center for Alzheimer's Disease, University Hospital of Montpellier, Montpellier*; 7. *Geriatrics Department, Memory Research Resource Center, University Hospital of Limoges, Limoges, France*; 8. *Memory Research Resource Center, Neurology department, University Hospital of Dijon, Dijon, France*; 9. *Geriatrics Department, Centre Hospitalier Lyon-Sud, Lyon, France*; 10. *Memory Research Resource Center, University Hospital of Nice, Nice, France*; 11. *Geriatrics Department, Hospital of Castres, Castres, France*; 12. *Geriatrics Department, Hospital of Foix, Foix, France*; 13. *Geriatrics Department, Hospital of Tarbes, Tarbes, France*; 14. *Geriatrics Department, Hospital of Lavaur, Lavaur, France*; 15. *Geriatrics Department, Hospital of Montauban, Montauban, France*; 16. *Geriatrics Department, Hospital of Princess Grace, Monaco*)

Prevention strategies for Alzheimer's disease (AD) are urgently needed due to its high and rising prevalence. Because of the multifactorial nature of AD, it now seems pertinent to propose a « multi-domain » intervention, combining interventions that target several physio-pathological pathways leading to the onset of the disease, in order to examine their potential synergistic action in reducing the risk. The Multidomain Alzheimer disease Preventive Trial (MAPT) is a three-year prospective study of frail older adults randomized to treatment (omega-3 and /or multi-domain intervention) or placebo. The proposed multidomain intervention consists of collective training sessions in the following three areas: nutrition, physical activity, cognitive training and preventive consultations (to control risk factors). The primary objective of the study is to determine the effect of treatment with omega-3 and/or multi-domain intervention on slopes of cognitive decline. The main outcome measure is the change in cognitive function at 3 years determined by the Grober and Buschke Test (a memory-recall test of 16 words). MAPT is a multicentre, randomized, placebo controlled study, using a 4-group design including 3 treatment groups (omega 3 alone, multi-domain intervention alone, omega 3 plus multi-domain intervention at n=420 each) and a placebo group (n=420). Visits are scheduled every 6 months to assess physical condition, diseases and corresponding treatments, adherence to and tolerance of omega 3 treatment, adherence to multi-domain intervention, and to deliver the supplement. Cognitive and functional assessments are conducted at baseline, six months, and annually at 1, 2 and 3 years by independent research staff blinded to intervention. All the assessments are performed by hospital practitioner memory experts. The protocol is registered on a public-access clinical trial database ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)). In addition, three neuroimaging ancillary studies were proposed to MAPT participants: (i) the MRI-MAPT study will explore the effects of interventions on cerebral atrophy (total brain and hippocampal volumes); (ii) the FDG-Pet study will explore the effects of multi-domain intervention on cerebral metabolism (only in Toulouse center) and (iii) the AV45-PET study will evaluate brain amyloid deposits. The recruitment goal for the MAPT trial was to enrol 1680 frail elderly people, aged 70 years and over, living independently in good functional and cognitive status. Definition of frailty is to date not consensual but we used three clinical components to identify frail persons based on epidemiological evidence: memory complaint, to their primary care physician, limitation in one instrumental activity of daily living (ability to use the telephone, shop, prepare meals, do housekeeping, do one's laundry, use transportation, follow a medication schedule and manage money) (IADL) and slow walking speed (speed lower than 0.8 m/s which means more than 5 seconds to walk 4 meters). Participants were excluded from the study when presenting dementia (DSMIV criteria), Mini Mental State Examination (MMSE) score lower than 24 over 30, subjects who had incapacities for basic activities of daily living (ADL score lower than 6 over 6), and those who were severely depressed (Geriatric Depression Scale (GDS) score over 15) and, other disorders that could interfere with the interpretation of the study (like visual or hearing impairments). The inclusion period lasted 33 months. Recruitment in neuroimaging ancillary studies MRI-MAPT ancillary study: The MRI-MAPT study was conducted in the 7 University Hospital centers (Toulouse, Bordeaux, Montpellier, Limoges, Dijon, Lyon and Nice) and 2 General Hospitals (Foix, Tarbes). The first inclusion was on January 8, 2010, and the targeted number of 500 participants was reached on August 31, 2011. Currently, 504 participants have undergone baseline MRI. A final MRI at the end of the study (3 years) will be performed. FDG-PET ancillary study: The first inclusion was on June 8, 2009, and the targeted number of 68 participants was reached on February 9, 2011. 40. All FDG-PET scans were performed at baseline

and at 6 months. A final FDG-PET scan at the end of the first year of the study will be performed. AV45-PET ancillary study: The first inclusion was on July 12, 2010, and the enrolment is still in progress. At this time, 220 PET-scans were performed during the two first years of the study. Acknowledgments: This study was supported by grants from the Gérontopôle of Toulouse, the French Ministry of Health (PHRC 2008, 2009), Pierre Fabre Research Institute (manufacturer of the omega-3 supplement), Exhonit Therapeutics SA, Avid Radiopharmaceuticals Inc. The promotion of this study was supported by the University Hospital Center of Toulouse.

*Communication 2: One year longitudinal study of FDG-PET in MAPT, T. Voisin, S. Peiffer, J. Delrieu, S. Andrieu, P. Payoux, B. Vellas (Gerontopole, Toulouse University Hospital, France, Inserm UMR1027 and UMR825)*

Numerous epidemiological studies to prevent cognitive decline or Alzheimer's disease have shown that nutrition, physical exercise, cognitive stimulation and social activities play a significant role in maintaining cognitive function. There are currently a number of epidemiological evidence for a protective role of each of these factors alone. In the United States and France, intervention studies called "multidomain" are being set up to evaluate long-term impact of such intervention in elderly patients to the onset of Alzheimer's disease. In addition, there are now data on the impact of a short multidomain intervention on brain metabolism measured by PET scan. This method could become an objective evaluation of such intervention. The study presented here is an ancillary study of the study MAPT (Multi-domain Alzheimer Disease Prevention Trail). The MAPT study is a Phase III study whose main objective is to evaluate the effectiveness of supplementation in omega-3 intervention or a "multidomain" intervention (nutrition, exercise, cognitive stimulation, social activities), or their association on the evolution of cognitive function in frail elderly people aged 70 and older. Main objective: The main objective of this ancillary study was to assess the impact of an intervention program that includes a multidomain cognitive stimulation, physical exercise, nutrition education and social activities on brain metabolism in FDG PET to assess the effectiveness of such intervention on neuroimaging. Study population: The study presented here focuses on 68 of the 1680 MAPT-study participants. Thirty-four subjects in the intervention group will carry out the program multidomain and 34 subjects not realize the program. Methodology and results: These 68 subjects will be evaluated as provided in the MAPT study that will support the clinical evaluation, biological monitoring (three years in the study MAPT clinical evaluation, neuropsychological, biological every 6 months). These 68 subjects performing for this ancillary study an FDG PET scan at baseline, 6 months and 1 year and a MRI at inclusion and 1 year comprising (T1-3D, T2-3D, Flair, DTI, T2\*). The criteria for inclusion are those of the study MAPT and exclusion criteria will resume with the study MAPT plus those related to the implementation of an MRI and a PET scan. The characteristics of this population are Age (mean, SD) 76.97 (4.25), MMSE (mean, SD) 28.17 (1.61), CDR 0: 65.7% (n=44) CDR 0.5 34.3% (n=23), Prefrail 41.8% (n=28) and frail 3% (n=2). We demonstrate changes in brain metabolism in patients undergoing the multidomain program at baseline vs 6 months (Z score : 6.41-7.48 ; FWE 0.01/100 in prefrontal region) and at baseline vs 12 months (Z score : 6.62-7.56 ; FWE 0.01/100 in prefrontal région). This could be an assessment of the effectiveness of such intervention on neuroimaging. Moreover, the data of the PET scans and other imaging like morphological brain imaging (MRI) could explain response or no response to stimulation program (presence of cerebral vascular lesions, brain atrophy, for example). The identification of early markers of

effectiveness of such intervention seems relevant to early target individuals who can best benefit from the impact of this type of prevention program of cognitive decline and Alzheimer's disease.

*Communication 3: High Prevalence of Amyloid Positive PET in Frailty Subjects. A Multicenter Study*, D. Adel, J. Delrieu, M. Alonso, A. S. Brun, A. Hitzel, M. Tafani, D. De Verbizier, M. Razzouk, F. Lamarre, T. Voisin, S. Gillette, B. Vellas, P. Payoux

**Objectives:** Florbetapir is a F18-labeled amyloid-binding ligand that has recently been introduced as a PET agent for amyloid imaging in the brain of patients presenting Alzheimer Disease (AD). Furthermore a relationship has been established between the existence of frailty and AD occurrence has been demonstrated (Buchman and al. 2008), but in vivo amyloid neuroimaging by Florbetapir-PET in frailty patients has not been documented yet. This prospective study was conducted, to evaluate the presence and  $\beta$ -amyloid density in elderly frail volunteers who don't meet the criteria of dementia or AD (DSM IV criteria). **Methods:** The Florbetapir ancillary study is based on the Multidomain Alzheimer Preventive Trial (MAPT) survey. The MAPT Study is a 3-year, randomized, controlled trial enrolling frail elderly volunteers, who don't meet the criteria of dementia or AD, on the basis of at least one of the following criteria: subjective memory complaint spontaneously expressed to a general practitioner, limitation in one instrumental activity of daily living, and slow walking speed (speed  $\leq$  0.8 m/s). The main objective of the MAPT study is to assess the efficacy of isolated supplementation with omega-3 fatty acid, an isolated multi-domain intervention (nutrition, physical exercise, cognitive stimulation, social activities), or their combination on the change of cognitive functions in frail elderly subjects aged of 70 years and older over 3 years. Ten to fifteen minutes list mode acquisitions were performed 50 minutes after IV administration of 3.7 MBq/kg of  $^{18}\text{F}$  Florbetapir in four different centers. Datas were visually assessed by 3 observers using a semi-quantitative score ranging from 0 (no amyloid) to 4, (high levels of cortical amyloid) as described by Clark (Clark and al. 2011), the median rating of the readers served as a primary outcome variable. Then, a semi-automated quantitative analysis was applied and the ratio of cortical to cerebellar signal (SUVr) was calculated in 18 cortical regions of interest (ROI : hippocampus, centrum semiovale, Post cingulate, ant cingulate, mid cingulate, cerebellum, frontal, frontal, orbital, occipital, parietal, precuneus, left putamen, right putamen ,temporal, pallidum, right caudate, left caudate). Then the SUVrs was calculated with the mean of 6 cortical ROI (frontal, temporal, parietal, anterior cingulate, post cingulate, and precuneus). The anatomical ROI mask was created using the Wake Forest University Pick Atlas. The cerebellum was has been reported to be a region free of amyloid plaques in AD. **Data acquisition:** PET scans were performed on whole body hybrid PET/CT including two Biograph 6 TruePoint HiRez (Siemens medical Solutions), Discovery RX VCT & PET/CT 690 (GE HealthCare), in Montpellier, Bordeaux, Nice and Toulouse. All of those PET/CT operated in 3D detection mode. The images were reconstructed using 3D ordered subset expectation maximization (OSEM) algorithm with corrections for random, scatter, and attenuation provided by the manufacturer and no partial volume correction was performed. **Image analysis:** Pet images were spatially normalized (Ashburner and Friston, 1999) into the International consortium for Brain Mapping space with ICBM-AV-45 template provided by Avid®, the normalization was achieved using Statistical Parametric Mapping (Version 8, Wellcome trust center for neuroimaging, <http://www.fil.ion.ucl.ac.uk/spm/>). SPM8 is implemented in MatLab R2011b (Mathworks, MA, USA). Each images was post-smoothed with an isotropic Gaussian filter with a full width at half maximum

(FWHM) of 8 mm for increase the signal to noise ratio and to minimize the difference of resolution between the scanners. **Results:** From July 2010 to April 2012, 138 volunteers (79 F, 59 M,  $79.3 \pm 4.4$  yrs) were recruited from hospice, long-term care, and community health care. On visual analysis, data were considered as pathological in near than 50 % of the cases. The mean quantitative estimates of cortical uptake were positive (SUVr $>$ 1.4) for 47.8% of the subject. Anterior cingulate was the area the most concerned by amyloid deposits and we highlight that in this region the amyloid positive subjects were younger than amyloid negative ( $77.2$  yrs  $\pm$  4.43 and  $75.6$  yrs  $\pm$  4.19 respectively,  $p=0.02$ ). Also that precuneus and temporal SUVr ( $1.35 \pm 0.22$  and  $1.30 \pm 0.14$  respectively) presents more florbetapir uptake than the other cortical regions of interest but without statistical significance. **Conclusions:** Prevalence of amyloid positive PET is high in frailty no demented population. Furthermore amyloid deposits are high in ant cingulate in youngest. These data provide evidence that a molecular imaging procedure can identify amyloid pathology in the brains of individuals during life. Additional studies are required to understand the appropriate use of Florbetapir-PET imaging in frailty.

*Communication 4: Are frailty indicators related to brain and hippocampal volumes? The MAPT-MRI study*, C. Dufouil<sup>1,2</sup>, M. Chupin<sup>3</sup>, A. Bouyahia<sup>3</sup>, C. Cognard<sup>4</sup>, F. Chollet<sup>5</sup>, J.-F. Dartigues<sup>6</sup>, M. Allard<sup>7</sup>, J. Touchon<sup>8</sup>, A. Bonafe<sup>9</sup>, T. Dantoine<sup>10</sup>, M.P. Boncoeur-Martel<sup>11</sup>, O. Rouaud<sup>12</sup>, F. Riccolfi<sup>13</sup>, M. Bonnefoy<sup>14</sup>, F. Cotton<sup>15</sup>, P. Robert<sup>16</sup>, S. Chanalet<sup>17</sup>, L. Bories<sup>18</sup>, J.J. Delbousquet<sup>19</sup>, Y. Gasnier<sup>20</sup>, F. Hugon<sup>21</sup>, S. Gillette<sup>22</sup>, B. Vellas<sup>22</sup>, J.F. Mangin<sup>23</sup>, S. Lehericy<sup>24</sup> (1. CIC-EC7, INSERM, Bordeaux Segalen University, Bordeaux, France; 2. INSERM U708, Bordeaux Segalen University, Bordeaux, France; 3. CRICM, UMR 7225 / UMR-S 975, UPMC/CNRS/INSERM, Paris, France; 4. Neuroradiology Department, University Hospital of Toulouse, France; 5. INSERM U825, IFR 96, Toulouse, France; 6. Memory Research Resource Center for Alzheimer's Disease, University Hospital of Bordeaux, Bordeaux, France; 7. Nuclear medicine department, University Hospital of Bordeaux, Bordeaux, France; 8. Department of Neurology, Memory Research Resource Center for Alzheimer's Disease, University Hospital of Montpellier, Montpellier; 9. Department of Neuroradiology, University Hospital of Montpellier; 10. Geriatrics Department, Memory Research Resource Center, University Hospital of Limoges, Limoges, France; 11. Radiology and medical imaging department. University Hospital of Limoges, Limoges, France; 12. Memory Research Resource Center, Neurology department, University Hospital of Dijon, Dijon, France; 13. Neuroradiology department, University Hospital of Dijon, Dijon, France; 14. Geriatrics Department, Centre Hospitalier Lyon-Sud, Lyon, France; 15. Radiology Department, Centre Hospitalier Lyon-Sud, Lyon, France; 16. Memory Research Resource Center, University Hospital of Nice, Nice, France; 17. Radiology department, Pasteur Hospital of Nice, Nice, France; 18. Geriatrics Department, Hospital of Foix, Foix, France; 19. Radiology Department, Hospital of Foix, Foix, France; 20. Geriatrics Department, Hospital of Tarbes, Tarbes, France; 21. Radiology Department, Hospital of Tarbes, Tarbes, France; 22. Gérontopôle, Departement of Geriatrics, CHU Toulouse, Purpan University Hospital, Toulouse; 23. I(2)BM, CEA, Gif-sur-Yvette; 24. Neuroimaging research center, Pitié-Salpêtrière Hospital, UPMC, Paris6, Paris, France)

**Main objective:** Several studies suggest that physical frailty, a frequent condition in the elderly, could be related to future cognitive decline and dementia risk. Similarly, brain atrophy is a common neuroimaging finding in healthy elderly individuals as well as in patients with movement-related disorders. The relationship between

brain atrophy and frailty indicators has not been frequently reported. This study investigates these relationships within the MAPT-MRI study. *Methods:* The MAPT-MRI study is an ancillary study of the MAPT trial which primary objective is to assess the impact of the interventions on the evolution of cerebral atrophy. Secondary objectives will be to assess the impact of the intervention on other neuroimaging markers changes such as hippocampal or amygdala volumes, white matter lesions volumes, silent brain infarcts and microbleeds incidences. Subjects will have MRI at trial entry (within 6 months following randomization) as well as end of the trial (within 6 months following treatment termination). At both examinations, MRI will be performed using a standardized protocol. High-resolution MRI data will be acquired at each center using either a 1.5-T or 3.0 T. A 3-dimensional volumetric spoiled gradient recalled acquisition sequence will be obtained for the whole brain. Locally, images will be checked for quality (absence of head motion or artefacts). Images will then be transferred to the "Centre d'Acquisition et de Traitement de l'Image". Images will be checked centrally quality and artefacts, consistency of images parameters and head coils, brain positioning. Centers will be contacted for failed acquisitions and participants will be rescanned whenever possible. Frailty indicators measurements will include cognitive complaints to the general practitioner, number of limitations at instrumental activities of daily living scale and walking speed. The results presented will rely on the data collected at baseline of the MAPT trial and will be based on cross-sectional analyses. The statistical analyses will consist in random effects models, adjusting for potential confounders and taking into account intra-centre correlations. *Results and perspectives:* In total, 9 centers have agreed to take part in the MAPT-MRI ancillary study. Between January 2010 and September 2011, 633 MAPT participants, out of the 691 included in the trial in these 9 centers, have agreed to have a cerebral MRI (acceptance rate =91.6%). But in total 503 MRI have been performed, 130 MRI could not be performed within the delay imposed by the protocol. Among the 503 MRI performed, 54 had a quality that will require additional checking for validation. Participants who had MRI did not differ from the other participants in MAPT for gender distribution ( $p=0.60$ ), multidomain intervention distribution ( $p=0.40$ ) but the MAPT-MRI participants were on average younger (75.3 vs. 76.0,  $p<0.001$ ). The results of the association between brain volumes (Grey matter volume + white matter volume), hippocampal and amygdala volumes will be presented and discussed in comparison with the existing literature.

## ORAL COMMUNICATIONS

### OC22 - STATISTICAL POWER OF A PREVENTIVE TRIAL IN ALZHEIMER'S DISEASE, ABOUT THE GUIDAGE STUDY.

B. SCHERRER<sup>1</sup>, P. GARNIER<sup>2</sup>, H. MATHIEX-FORTUNET<sup>2</sup>, S. ANDRIEU<sup>3</sup>, B. VELLAS<sup>4</sup> (1. Conseil, St Arnoult, France; 2. Ipsen, Boulogne, France; 3. Inserm UMR 1027, Toulouse, France; 4. Gérontopole, Toulouse, France)

*Background:* The efficiency of time to event statistical tests depends upon the time course of the hazard ratio (HR). If the HR is constant over time then the logrank test is very powerful, if the HR is decreasing over time then the Gehan-Wilcoxon test is powerful, if the HR is increasing then the Fleming Harrington test (FHT) ( $p = 0.5$  and  $q = 2$ ) is appropriate and if the HR function increases and then decreases, the FHT ( $p = 0.5$  and  $q = 0.5$ ) becomes efficient. *Methods:* GUIDAGE study, a 5-year EGb761 treatment vs placebo for AD prevention study, showed that the choice of the primary test makes the difference between a positive and a non conclusive study ( $p = 0.310$  for the logrank and  $p = 0.005$  for the FHT with  $p = 0$  and  $q = 3$  due to a late observed difference between groups). GUIDAGE data was used to

estimate through simulations the power of the FHT according to the following parameterization:  $p = 0$  and  $q = 0$  (logrank),  $p = 0.5$  and  $q = 2$ ,  $p = 0$  and  $q = 1$ , and  $p = 0$  and  $q = 3$  respectively efficient for a constant HR, an increasing HR, a delayed effect and a late difference. Various reasonable time profiles for the HR function were used:  $RR = 1, 1, 1.3, 1.6$  and  $2$  for a 5-year trial and around this profile as well as  $RR = 1, 1, 1.25, 1.5, 1.75, 1.75$  for a 6-year trial. *Results:* These simulations showed that in an enriched population ( $\geq 75$  years, MMSE recall score at 0 or 1) more than 1600 patients per group followed during 5 years are necessary to reach a power at the limit of 80% for  $p = 0$  and  $q = 1$ . A six year follow-up makes the power less dependent upon the parameterization of the FHT with 1500 patients per group ( $1 - \beta = 0.89, 0.86, 0.79$  for  $p = 0, 0.5$  and  $0$  and  $q = 1, 2$  and  $3$  respectively). *Conclusion:* In simulations based on the GuidAge study, the number of patients is large whatever the test and the follow-up needs to be long. The usual logrank test never provided sufficient power with the expected retained effect over time and sample sizes and Fleming Harrington test was the more efficient test with  $p = 0$  and  $q = 1$  or  $p = 0.5$  and  $q = 2$ .

### OC23 - DETECTING AND INTERVENING IN MILD COGNITIVE IMPAIRMENT: IS IT COST EFFECTIVE?

J. BARNETT<sup>1,2</sup>, L. LEWIS<sup>3</sup>, A. BLACKWELL<sup>1,2</sup>, M. TAYLOR<sup>3</sup> (1. Cambridge Cognition; 2. University of Cambridge Department of Psychiatry; 3. York Health Economics Consortium, University of York)

*Background:* Improved public awareness of dementia is pushing older adults who experience memory problems to seek help at an increasingly early stage. Many of these individuals meet criteria for mild cognitive impairment (MCI) but not dementia. At present there are no licensed treatments for MCI but it is plausible that low-cost lifestyle interventions delivered in primary care could stave off cognitive decline and protect against dementia. The study aimed to establish whether detecting and intervening in MCI would be cost effective in the UK National Health Service. *Methods:* Using the known natural history of MMSE decline for nine years prior to AD diagnosis (Amieva et al. 2005), we assessed the cost effectiveness of detection and intervention at stages prior to the onset of dementia. We modelled the effects of an early detection arm comprising a primary care triage, a secondary care assessment based on current UK guidelines, and a lifestyle intervention which produced a one-point improvement in MMSE score. Because it is not clear whether such interventions would produce lasting improvements, we assessed the health economics impact of various scenarios for delay and convergence to the 'natural' decline seen in MCI. Following Getsios et al. (2012), quality of life and health care costs were taken to be a function of MMSE score, with additional decrements for patients who required institutionalisation. Quality of life scores were combined with survival rates to produce outcomes for quality-adjusted life years (QALYs), reflecting the overall impact of the intervention on the patient's health. *Results:* Without early detection, patients were expected to experience a total of 5.13 QALYs. In a modestly 'disease-modifying' scenario, the one-point improvement in MMSE was maintained for 12 months, then converged with the natural rate after 24 months. This led to a gain of 0.052 QALYs and savings of £2,393 to the healthcare system for every patient who was diagnosed one year earlier due to early detection. Diagnosing four years earlier was estimated to result in a gain of 0.02 QALYs and savings of £1,014. A second scenario assumed no delay in deterioration following the initial effectiveness of the intervention, and assumed that the patient's MMSE converged to its natural rate of decline after 12 months. In this scenario, intervening one year earlier resulted in a gain of 0.007 QALYs and saved £351 in costs. Intervening four years earlier than the base case led to a gain of 0.006 QALYs and saved £334 in costs.

*Discussion:* Cost-effective early detection and intervention is realistic for patients with MCI, even in the absence of a pharmaceutical therapy. Cost-effectiveness is maximal when early detection coincides with the point at which the MMSE curve begins to show a substantial steepening, allowing interventions to have a potentially greater impact in delaying progression. This effect is more pronounced when the effectiveness of interventions is likely to be maintained over a longer period of time. Public policy should consider the ‘optimal MMSE’ for cost-effective intervention, which is likely to be several years prior to current standard practice.

## WEDNESDAY, OCTOBER 31<sup>TH</sup>

### UPDATE ON CLINICAL TRIALS 3

#### 8- CHALLENGES AND PERSPECTIVES IN DESIGNING AND CONDUCTING STUDIES IN ALZHEIMER’S DISEASE (AD).

C. YAVORSKY (CROnos CCS, Hamilton, NJ, USA)

*Introduction:* Key scientific advances in genetics, cell and molecular biology, biomarkers, and neuroscience over the last 35 years have altered the way we think about AD and have presented further knowledge of the pathogenesis of the disease. Yet translating this research into the development of informative biomarkers, reliable methods of early diagnosis, inexpensive or safe therapies, and the design and implementation of new clinical trials still needs work. *Objectives:* At the 2012 CTAD meeting, a diverse group of scientists will discuss current challenges in the AD field and present recommendations in the areas of clinical trials (design, development, surveillance, measurement tools, and regulator issues). The authors hope the discussion and recommendations will enhance clinical trials progress in AD and increase the probability of developing effective therapies in future trials. *Discussion:* Over the past 2 decades there have been a number of disappointing outcomes in AD treatment trials based on epidemiological data. This emphasizes the separation between results from epidemiological samples and randomized clinical trials in individuals with AD. For instance, epidemiological data indicates that anti-inflammatory medications (e.g., nonsteroidal anti-inflammatory drugs; NSAIDs) decrease the risk for AD, clinical trials assessing NSAIDs in AD have not shown efficacy. Additionally, studies in the community characterize the entire continuum of AD, including individuals whose clinical symptoms are mild, who have limited access to medical care, and/or whose cognitive impairment or dementia has not been yet been identified as AD, whereas clinical trials do not capture these individuals. Additionally, genetic association studies have recognized significant risk factors for AD. Yet, with the number of genetic variants being tested, it is likely that many of the positive findings reported in the literature to date may prove to be false positive findings explained simply by random fluctuation in data and type I error. Considering these difficulties in clinical trials, the following will be discussed.

#### 9- IMPROVING DETECTION OF TREATMENT EFFECT THROUGH BETTER METHODOLOGY. W.R. SHANKLE<sup>1,2</sup>

(1. Shankle Clinic, Newport Beach, CA USA; 2. Memory and Cognitive Disorders Program, Hoag Neurosciences Institute; Medical Care Corporation; Dept of Cognitive Sciences, University of California at Irvine, CA, USA)

*Introduction:* Increasingly, clinical drug trials will target earlier and earlier stages of Alzheimer’s disease (AD). Such studies require more sensitive and accurate measures of cognition to improve the ability to:

1) efficiently recruit early stage AD patients; 2) detect treatment effects in AD stages where cognition declines at a slower rate over a longer time; 3) relate cognitive changes to biomarker changes. Three ways to improve cognitive measurement in clinical trials are to: 1) Invent new tools; 2) Improve the scoring of existing ones; and 3) Improve the methods of measuring change over time. Inventing new tools requires long periods of time to validate and accept them for use in clinical trials. Improving the scoring of existing cognitive tools that are already used in clinical trials is becoming recognized as an important first step. Improving the methods of measuring change over time is also becoming recognized as a useful way to improve evaluation of treatment effects in clinical trials. *Optimal Scaling of Cognitive Performance:* With regard to the current methods of scoring in the neuropsychological assessment domains, test items that subjects respond to incorrectly are typically assigned scores of “0”, and those that subjects respond to correctly are typically assigned scores of “1”. These item response scores are then added, analyzed or otherwise algebraically manipulated to generate a summary score. Yet the assignment of “0” and “1” is arbitrary. It is not based on methods of optimal scaling using modern measurement theory. This scoring underlies a deeply ingrained notion that “0” and “1” are the correct numeric values of responses given by humans performing cognitive tasks. This notion has been repeatedly shown to be incorrect over decades of social science research. Algebraic operations, such as summing the item responses, should not be applied until the item responses have been properly numerically scaled. Similarly, statistical analyses that assume the underlying data have numeric properties should not be applied until the underlying data have been properly numerically scaled. We have previously shown in the Phase 3 clinical trial of Flurizan vs. placebo in AD patients that optimal scaling of ADAS-Cog Wordlist Memory task item responses detected a significant treatment effect that was missed using standard “0” “1” item response scoring. The issue of proper numeric scaling is therefore substantive for clinical trials. *Improving Longitudinal Analysis of Treatment Effect in Clinical Trial:* With regard to improving the methods of measuring change over time, recent advances in the methods of longitudinal comparison may further improve detection of treatment effects. Current clinical trials often utilize analysis of a single number per subject that indexes change. In this approach, the problem of analyzing longitudinal data is approached by summarizing the relevant aspect of longitudinal change for each subject with a single numeric value that can then be further analyzed with any of the traditional between-subject methods. The most common summary score utilized in analysis of longitudinal clinical trials is the “change score” that is obtained by calculating the difference between the first and last observation for any given subject. However, a difference in two time points is generally a poor method of longitudinal analysis unless a) they are the only time points available for each subject; and b) the time difference between them is fairly uniform across subjects, not thought to matter, or is adjusted with a time interval covariate. If subjects have more than two time points of data available, using only the two boundary points not only wastes hard-earned data and squanders potential information, but also is blind to the trajectory between these two boundary points, including any nonlinearity that might be of interest. Using ordinary least squares (OLS) regression, the subject-specific slopes of the dependent variable against the time variable has recently attracted interest as a better index of summary change that may also reflect potential disease-modification effects. However, a weakness of OLS slope analysis is that it gives slope coefficients for subjects with only a few time points the same weight, importance or reliability, as subjects with many more time points. Also, the strong dependency between subject measures that are close in time makes them less informative, and they should not be used to infer changes within or between subjects over longer time periods. An

example of a more informative summary measure of longitudinal change in clinical trials involves computing the areas under the curves (AUC) of placebo and drug treatment groups, comparing their areas for significant differences. Another more informative method to assess potential disease-modifying treatment effects and trajectories is to analyze the totality of data using mixed effects models (MEM) with linear and non-linear terms. Both these methods (AUC and MEM) incorporate the full event history trajectory, not simple cross sections and change scores, and are not limited by linear change of time in making inferences and interpreting results. Finally, estimating and modeling missing data can be incorporated into the MEM approach to more accurately assess treatment-related effects, to better understand how the missing data were produced, and how they impacted the clinical trial results. *Vertical Integration of Drug Development and Validation*: A substantial improvement in clinical trials methodology can be obtained by vertically integrating drug assessment—from target identification to Phase IV studies. Currently, drug discovery teams involved in target selection and validation are dispersed well before Phase Ib-II studies are conducted, which weakens the translation of knowledge from preclinical to clinical trials levels. With vertical integration of the drug discovery process, a model-based approach continually revisits and refines the underlying disease and therapeutic concepts. This is accomplished by constructing a hierarchical model that relates spatial and temporal scales at different levels of biological complexity (e.g., molecules, cells, tissues, organs, subjects and populations), and uses data from preclinical, literature and patient-derived sources. In AD drug development, vertical integration has substantial advantages because knowledge needs to be transferred from the level of in-vitro characterization—such as molecular analysis of compounds—to effects on cellular physiological pathways, to effects on AD animal models, and finally to effects on humans. An improvement in knowledge transfer across these levels of complexity, which span many orders of magnitude, could significantly reduce the probability that an identified drug will fail as it ascends the scaffold of biological complexity—from test tubes to humans. One should consider the potential value of retesting working hypotheses to ensure they are not rejected as the level of biological complexity increases. Such consideration could lead to retrospective experiments in which multi-scale models could be built and tested to predict “lack of efficacy” using multi-level data from previous drugs that resulted in failed phase II-III studies. Such retrospective experiments could inform us about multi-scale network behavior—from molecules and genes to cellular pathways to animal models to humans. For example, such retrospective experiments could examine prior drug development data to predict toxicity in target tissues, thus avoiding more costly development of compounds doomed to fail, and possibly resulting in refined compounds that could succeed. *Objectives*: The present communication will present two topics reflecting the second and third ways to improve cognitive measurement in clinical trials, plus present how vertical integration of phases I to IV clinical trials could substantially improve discovery of meaningful treatment effect information. 1. A method for optimally scoring each patient’s test item responses and overall test performance, for determining the number of dimensions underlying the test’s performance, and for adjusting for sample bias effects. 2. Methods of measuring changes over time that account for the totality of time points using two different approaches: calculation of AUCs and assessing clinical trajectories using MEM that model linear and non-linear effects and missing data. 3. To show how vertical integration can improve knowledge transfer and drug development.

**10- USE OF BIOMARKERS FOR AD CLINICAL TRIALS: HOW ADNI HELPS.** M.W. WEINER (*Professor of Radiology, Medicine, Psychiatry and Neurology, University of California San Francisco, USA*)

The recent failures of two major monoclonal antibody trials appropriately raise a number of questions. Some believe that these recent failures support the weaknesses of the amyloid hypothesis. Alternatively, it should be kept in mind that the Phase 2 data which was obtained to support these Phase 3 trials was weak. The important questions are: Where do we go from here?, and How can we perform better Phase 2 and Phase 3 studies? The experience of the Alzheimer’s Disease Neuroimaging Experience (ADNI) should be helpful. It should be firmly kept in mind that the entire creation of ADNI was based on the perceived need for improved standardization and validation of biological measurements including those from MRI, PET, and biofluids. About 1/3 of ADNI funding comes from the private sector, and participating companies make up the Private Partners Scientific Board, organized by the Foundation for NIH. ADNI was initially funded in 2004, ADNI received a 2nd round of funding from the US Government “stimulus funds”, and in 2010 ADNI was refunded for another 5 years. Due to slow enrollment (which concludes in 2013) ADNI will continue through 2017. ADNI is thoroughly described at ADNI-info.org, and all ADNI data is available without embargo at UCLA/LONI/ADNI. An initial emphasis of ADNI was to identify which biomarkers measured rate of change with highest sensitivity. The rationale for this question was that clinical and neuropsychological measurements would detect symptomatic effects (which are produced for example by acetylcholine esterase inhibitors or memantine) as well as disease modifying effects (slowing of neurodegeneration). Thus the effects of treatments on clinical and neuropsychological measurements could not be attributed solely to disease modifying effects. In contrast, measurements of brain atrophy (using structural MRI) or CSF amyloid/tau would reveal effects of treatments on the brain which could be considered to be disease modifying. In any event, numerous publications from ADNI have already demonstrated that measuring the rate of brain atrophy by use of longitudinal structural MRI (T-1 weighted) MRI has much more statistical power (ie lower sample size to detect a treatment effect) than do any available clinical or neuropsychological measurement. During the forthcoming year, it will be extremely interesting to learn about the structural MRI studies performed during the two recent monoclonal antibody studies. It is possible that statistically significant slowing of the rate of change, suggesting slowing of neurodegeneration, will be detected, suggesting that the treatments were having a beneficial disease modifying effect, but that the clinical and cognitive measures that were used as primary endpoints were underpowered in the current trial design. When ADNI was initially planned, there was low expectation that lumbar puncture to obtain CSF would be widely accepted, and we planned only 20% LP acceptance by the subjects. Surprisingly we obtained 60% LP enrollment, and in the current ADNI we are requiring LP at baseline in all subjects. Major accomplishments of ADNI have been the demonstration of LP acceptance in clinical trials, and the standardization of CSF amyloid and tau measurements by the ADNI Biomarker Core. But despite heroic efforts at standardization, problems in this field continue because the “lots” of antibodies have different potency, and no general standard for CSF amyloid or tau have emerged. It has already been shown, by ADNI and by other clinical trials, that satisfactory data may be obtained within one large trial, but how a standardized CSF measurement of amyloid and tau would reach the clinical marketplace is very unclear. This fact makes it difficult to use CSF amyloid/tau as an inclusion criteria in a clinical trial to identify subjects with brain amyloid loads.

The development of PIB by Mathis and Klunk emerged as ADNI was initially funded. After one year Chet Mathis proposed a PIB add-on to ADNI, which became the first multisite amyloid-imaging study. The results demonstrated the feasibility of this approach, and co analysis with CSF amyloid suggested a good correlation between increased brain amyloid (by PIB) and decreased CSF amyloid. More recently, ADNI has performed more than a thousand Amyvid scans, and one surprising result is that only about 80% of patients diagnosed with clinical AD are amyloid positive. The results are most consistent with inaccurate diagnosis of AD, raising the question of how many subjects enrolled in AD trials do not have brain amyloid. At the same time, the amyloid imaging data of ADNI, and other studies, now shows that about 60% of MCI subjects have brain amyloid, and that these subjects convert to AD dementia at quite a high rate (20-30%/yr) while MCI subjects without brain amyloid hardly convert to AD. Furthermore, about 30% of normal healthy controls age 70 are amyloid positive, and their rate of conversion to MCI is high higher than amyloid negative controls. All of these results point to the critical importance of measures that detect brain amyloid, especially as clinical trials on MCI, and even normal asymptomatic subjects are planned and executed. Perhaps the most important lesson of the recently failed trials is: phase 3 trials should only be launched if there is satisfactory phase 2 data. There is now very great interest in performing phase 2 and phase 3 trials on subjects with MCI, subjects with mild memory complaints or normal healthy subjects "at risk" (ie prevention trials). Because these subjects have a lower rate of amyloid positivity than those with AD dementia, use of biomarkers that detect brain amyloid will be virtually mandatory, and there will be a search for less expensive and less invasive surrogate measures which "predict the presence of high brain amyloid". In any event, the rich ADNI data set becomes even more important as we attempt to plan cost efficient, yet biomarker-data intensive studies on MCI and preclinical AD.

## ORAL COMMUNICATIONS

**OC24 - CLINICAL TRIALS AND ETHICAL ISSUES: NEW CHALLENGES, NEW PERSPECTIVES . F. PALERMITI<sup>1</sup>, C. PASTOR<sup>2</sup>** (1. Lawyer, Project manager, AMPA (Monegasque Association for research on Alzheimer's disease), Monte Carlo; 2. President, AMPA (Monegasque Association for research on Alzheimer's disease), Monte Carlo)

Over the last years there has been an unprecedented mobilization from the international scientific community for the research on Alzheimer's disease. Significant progress has been made concerning the knowledge of the disease. These advances suggest real hope for new therapeutic solutions. These new treatments are currently being tested in several international clinical trials. However, due to the disease, the patients involved in these trials are particularly vulnerable. Thus, ethical and legal perspectives must be a major concern. In the future, development of new tools for investigation will confront researchers to deontological issues with new theoretical contours that deserve a deeper analysis. Through an international scientific literature review, this communication will (1) discuss the main issues highlighted by the scientific community regarding clinical trials on Alzheimer's disease, (2) question the ethical challenges encountered and (3) suggest some preliminary recommendations for future research. In a context of scientific uncertainty, anticipating these issues on an international scale is a challenge regarding the rights of people with Alzheimer's disease and the respect of their integrity and dignity.

## **OC25 - A MULTI-CENTER CLINICAL TRIAL TO VALIDATE EVENT-RELATED POTENTIALS AS USEFUL BIOMARKERS FOR EARLY DETECTION OF ALZHEIMER'S DISEASE.**

K.C. FADEM<sup>1</sup>, M. CECCHI<sup>1</sup>, S. BERG<sup>1</sup>, C. SMITH<sup>2</sup>, G. JICHA<sup>3</sup>, P. SOLOMON<sup>3</sup>, C. SADOWSKY<sup>4</sup>, P.M. DORAISWAMY<sup>5</sup>, S. ARNOLD<sup>6</sup> (1. *Neuronetrix, KY, USA*; 2. *Neurology Department, University of Kentucky, KY, USA*; 3. *The Memory Clinic, VT, USA*; 4. *Premiere Research Institute, FL, USA*; 5. *Psychiatry Department, Duke University, NC, USA*; 6. *Psychiatry Department, University of Pennsylvania, PA, USA*)

*Backgrounds:* Recent advances in Alzheimer's disease (AD) biomarkers have generated significant interest in biochemical, structural, and metabolic markers. Nonetheless, cognitive symptoms evaluated with psychometric tests form the core criteria of AD diagnosis and seem to outperform other markers in predicting progression to AD. Given the time-consuming nature of psychometric testing and the limited expertise in outpatient settings, event-related potentials (ERPs) have emerged as a potentially useful biomarker of cognitive performance. ERPs are the part of a measured EEG response that is generated by sensory and cognitive processing of external stimuli. As such, ERPs provide a real-time physiological measure of fundamental cognitive processes. ERPs generate a waveform that consists of a series of peaks and troughs that reflects the sum of underlying components. Some of the ERP components have demonstrated sensitivity to AD and their analysis could help discriminate patients with mild or moderate AD from age-matched cognitively normal individuals. A second kind of the analysis of ERPs generated waveforms that has shown promising results when applied to early diagnosis of AD is based on the use of an ensemble of classifiers. In this case, ERPs are decomposed into different frequency bands, and the resulting data are used to train an ensemble of classifiers to discriminate individuals affected by AD from normal controls. Recent studies have shown that wavelet decomposition of ERPs and subsequent training of artificial neural networks can yield high classification accuracy between individuals with early AD and age-matched controls. Even though the diagnostic potential of the ERP method has been known for several years, the promise of this technique has not reached widespread clinical application. Primary reasons have been the lack of standardization of ERPs acquisition and data analysis techniques across clinical sites, and the impracticality of running ERP tests in clinical environments on real patients. Application of advanced electronics and sophisticated analysis algorithms for ERPs has made it possible to administer such tests in a physician's office in a standardized, user-friendly manner. The goal of this ongoing study is to determine whether ERPs collected with standardized methods and in an outpatient setting can be a useful biomarker for early detection of AD. *Methods:* 100 subjects between 60 and 90 years old with probable mild-to-moderate AD and 100 age-matched controls are being recruited across six clinical sites. All subjects go through an initial psychometric evaluation. In addition, subjects with probable AD undergo extended psychometric testing, blood testing, MRI volumetric analysis, and optional CSF analysis to support the diagnosis. ERP testing on the study subjects is conducted using a two-deviant auditory oddball paradigm that targets specific cognitive impairments implicated in AD. During this ERP protocol an unexpected (distractor) tone is played occasionally during a stimulus sequence of frequent (standard) and infrequent (target) tones. The overall shape of the waveform and the ERP components generated during the test are compared between subjects with AD and controls to investigate possible differences. In addition, wavelet decomposition of the ERP waveform is being used to train artificial neural networks to automatically classify subjects with AD from cognitively normal



controls. **Results:** Comparison of grand-average waveforms for target and distractor tones showed a different overall shape for controls vs. AD subjects. Controls have a more pronounced positivity between 300 and 500ms for the target tone, and between 250 and 450ms for the distractor tone at all the electrodes analyzed. Preliminary analysis of the ERP components generated during testing revealed a significant decrease in amplitude and increase in latency of the P300 component for AD subjects at electrodes placed in correspondence of the midline. The P300 component generated during target tones (P3b) has been linked to task-relevant processes such as context updating and working memory. The P300 component generated during distractor tones (p3a) has been associated with brain activity related to the engagement of attention and the processing of novelty. Overall, the observed changes in P300 reflect a decline in memory and cognitive performance in individuals affected by AD that could help discriminate them from individuals that are cognitively normal. Analysis of other ERP components that have been associated with AD pathology such as N100 and P200 are underway. Comparison of tests conducted at different clinical sites show little inter-site variability, suggesting that the use of a fully-integrated hardware/system for ERP testing and analysis helps overcome the lack of standardization of ERPs acquisition and data analysis techniques that have restricted the clinical applicability of ERPs in the past. Finally, training of the neural network to establish baseline performance in terms of overall accuracy, sensitivity, and specificity is underway. **Conclusion:** Auditory ERPs are abnormal in individuals with mild-to-moderate AD. The observed changes in the overall shape of the ERP generated waveform, and in the ERP components generated during testing support the clinical utility of ERPs as useful biomarkers for early AD.

**OC26 - POSITIVE EFFECTS ON COGNITION AND CLINICAL FUNCTION IN MILD TO MODERATE ALZHEIMER'S DISEASE PATIENTS WITH A SELECTIVE ALPHA-7 NICOTINIC PARTIAL AGONISTS: INTERPRETATION OF EFFECTS BASED ON A PK/PD MODEL.** D.C. HILT<sup>1</sup>, M. GAWRYL<sup>1</sup>, G. KOENIG<sup>1</sup>, N. DGETLUCK<sup>1</sup>, J. HARRISON<sup>2</sup>, H.J. MOEBIUS<sup>1</sup>, G. LOEWEN<sup>1</sup> AND THE EVP-6124-010 STUDY GROUP (1. *EnVivo Pharmaceuticals, Watertown, MA 02472 USA*; 2. *Metis Cognition Ltd*)

Alzheimer's disease (AD) symptomatic therapy is presently limited to AChEIs and Memantine. Additional symptomatic therapies are desirable, even if disease modifying treatments are eventually developed. Alpha-7 nicotinic agonists may provide such a therapy. EVP-6124 is a selective, potent, partial,  $\alpha$ -7 nicotinic agonist that has procognitive effects in normal volunteers and in patients with schizophrenia or AD. A Phase 2b study in AD patients was conducted to investigate the potential cognitive and clinical effects of EVP-6124. 409 mild to moderate AD patients, either on stable AChEI therapy (donepezil or rivastigmine at approved doses) or on no AChEI therapy were enrolled in a 6-month, double blind, placebo-controlled study to placebo (n=104), 0.3 mg/d (n=104), 1 mg/d (n=101), or 2 mg/d (n=100). ADAS-Cog-13 and the CDR-SB were the two prespecified primary efficacy endpoints with additional pre-specified endpoints including ADAS-Cog-11, COWAT, CFT, NPI, ADCS-ADL (23), and composite measures for cognition, memory, and executive function. The 2 mg group (ITT population) when compared to the placebo group at 23 weeks (last efficacy measurement time point) had a significant effect on the ADAS-Cog-13 (cohen's  $d=0.39$ ,  $p=0.0189$ , multiplicity adjusted) and CDR-SB ( $d=0.31$ ,  $p=0.0253$ ). This group also showed significance compared to placebo for the ADAS-Cog 11 ( $d=0.34$ ,  $p=0.0151$ ), COWAT ( $d=0.35$ ,  $p=0.0135$ ), cognition composite ( $p=0.0037$ ), memory composite ( $p=0.0088$ ) and executive function

composite ( $p=0.0427$ ). Favoring the 2 mg group vs placebo were the MMSE ( $d=0.21$ ,  $p=0.0955$ ), and ADCS-ADL-23 ( $d=0.20$ ,  $p=0.092$ ). A responder analysis ('Responder' being defined as an ADAS-Cog-13 improvement of  $>3$  pts) showed a significant ( $p=$ ) response rate for the 2 mg group (45%) compared to the other treatment groups: placebo (26%), 0.3 mg (25%), and 1 mg (28%). A significant ( $p=0.003$ ) relationship between mean trough plasma EVP-6124 concentrations and the probability of experiencing an ADAS-Cog-13 improvement  $>3$  pts was demonstrated using logistic regression analysis. EVP-6124 was generally safe and well tolerated. Some mild to moderate gastrointestinal side effects were reported in a minority of patients in both the 1 and 2 mg dose groups. These results demonstrate that EVP-6124 has statistical and clinically significant effects in mild to moderate AD patients either on AChEI therapy or on no specific therapy and that these effects are related to plasma EVP-6124 levels. EVP-6124 may provide useful benefit for such patients.

**OC27 - STABILITY OF SYMMETRIC ATROPHY MEASUREMENT ALGORITHMS: IMPACTS ON INTERIM AND FINAL ANALYSES.** D.M. CASH<sup>1,2</sup>, J. BARTLETT<sup>1,3</sup>, S. FINNEGAN<sup>1</sup>, K.K. LEUNG<sup>1</sup>, G.R. RIDGWAY<sup>4</sup>, M.J. CARDOSO<sup>1,2</sup>, J.M. SCHOTT<sup>1</sup>, S. OURSELIN<sup>1,2</sup>, N.C. FOX<sup>1</sup> FOR THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE GROUP (1. *Dementia Research Centre, UCL Institute of Neurology, University College London*; 2. *Centre for Medical Image Computing, Department of Computer Science, University College London*; 3. *Department of Medical Statistics, London School of Hygiene and Tropical Medicine*; 4. *Wellcome Trust Centre for Neuroimaging, UCL Institute of Neurology*)

**Background:** Imaging biomarkers of neurodegeneration using structural MRI are valuable secondary and exploratory endpoints for clinical trials in Alzheimer's disease. Historical approaches to atrophy measurement involved simple volumetric measurements performed independently as each image arrived. Several modern techniques use registration-based approaches that align the two or more images together, directly measuring the change between them. This approach improves the precision and sensitivity of the measurements and thus the statistical power, but increases the risk of introducing methodological bias. In most registration-based approaches, the follow-up images are aligned to match the baseline image. Thus, the follow-up images undergo additional processing compared to the baseline, and this asymmetry in processing has been shown to introduce bias in the resulting measurements, which can lead to underestimation of the sample size required to effectively power studies<sup>1-5</sup>. One proposed solution to avoid this bias is to use "symmetric" or "consistent" algorithms that register all time-points to each other<sup>6</sup> or to a within-subject average<sup>7</sup> (analogous to "group-wise" approaches used for between-subject alignment). Such algorithms ideally require all time-points to be acquired before analyzing each subject. It is possible to perform interim analysis on subsets of time-points, but estimates of atrophy between early time points can then change when later time-points are acquired. For example, the atrophy rate from baseline to six-months calculated by a symmetric algorithm could have a different value if re-calculated to incorporate the one-year follow-up scan, and potentially different again with the two-year follow-up, etc. Waiting for all the data to be available presents challenges when incorporating symmetric techniques into clinical trials, which often perform interim analyses, additional follow-up studies, or retrospective analysis of time-points not originally included. This study assesses the severity of this potential problem by quantifying the variation in atrophy measurements when using all of the data compared to using the partial subsets. The goal of the study is to determine whether this variation is

so large that it is necessary to wait until all the data has been collected before beginning analysis or if interim analyses with incomplete data sets would produce results that would be sufficiently similar so as not to be of concern. *Methods:* We included 170 healthy controls (HC), 229 patients with mild cognitive impairment (MCI), and 102 patients with AD from the Alzheimer's Disease Neuroimaging Initiative (ADNI); this represents all subjects where baseline, month 6, month 12, and month 24 scans were available. Atrophy measurements were calculated using the consistent boundary shift integral (BSI) approach<sup>6</sup>. For each subject, the BSI between the first two time-points (baseline and month 6) was computed in three ways: (1) using only the first two time-points, (2) using the first three time-points (baseline, month 6 and month 12) and (3) using all four time-points. The resulting data were fitted with random intercept models, separately in each diagnostic group. From each model, estimates were obtained for the mean, the between-subject standard deviation (SD), and the within-subject SD, for the baseline to month 6 BSI measurements. The within-subject SD represents the variation in the baseline to month 6 BSI measurement as the later time-points are added. *Results:* The mean (between-/ within-subject SD) estimates are: • HC: 3.0ml (5.9ml / 0.45ml); • MCI: 5.3ml (7.6ml / 0.42ml); • AD: 7.9ml (7.1ml / 0.43ml). The low within-subject variability, coupled with the relatively high between-subject variability indicates that this measurement has high reliability, reflected by high intra-class correlations (0.994 for HC, 0.997 for MCI, and 0.996 for AD). From this model, we can also estimate the SD of differences between any two equivalent BSI measurements (of atrophy for the same period), which was 0.63ml (HC), 0.59ml (MCI), and 0.61ml (AD). These values mean we would expect 95% of differences between two BSI measurements of the same atrophy to be  $\pm(1.96 \times 0.63\text{ml}) = 1.2\text{ ml}$ . *Conclusions:* In all three groups, the within-subject variability in the (0-6m) BSI measurement was less than 10% of the between-subject variability. Therefore, the BSI measurement using the first two time-points will be quite similar to the corresponding measurement using the complete data set. If the group level statistics noticeably change between analyses, then it would be far more likely that inclusion of new subjects would be the cause rather than the inclusion of additional time-points. Quality control of images is still important, as one poor quality scan would introduce error on all measurements for a subject. Given these caveats, the small changes between the BSI measurements using incomplete and complete data are unlikely to be of concern, justifying the use of consistent group-wise BSI for both interim and final analysis, given the other already-documented advantages of such symmetric methods. *References:* 1. Yushkevich P a, Avants BB, Das SR, Pluta J, Altinay M, Craige C. Bias in estimation of hippocampal atrophy using deformation-based morphometry arises from asymmetric global normalization: an illustration in ADNI 3 T MRI data. *NeuroImage*. Elsevier Inc.; 2010 Apr 1;50(2):434–45. 2. Hua X, Lee S, Hibar DP, et al. Mapping Alzheimer's disease progression in 1309 MRI scans: power estimates for different inter-scan intervals. *NeuroImage*. Elsevier Inc.; 2010 May 15;51(1):63–75. 3. Thompson WK, Holland D. Bias in tensor based morphometry Stat-ROI measures may result in unrealistic power estimates. *NeuroImage*. Elsevier Inc.; 2011 Jul 1;57(1):1–4. 4. Fox NC, Ridgway GR, Schott JM. Algorithms, atrophy and Alzheimer's disease: cautionary tales for clinical trials. *NeuroImage*. Elsevier Inc.; 2011 Jul 1;57(1):15–8. 5. Hua X, Gutman B, Boyle CP, et al. Accurate measurement of brain changes in longitudinal MRI scans using tensor-based morphometry. *NeuroImage*. Elsevier Inc.; 2011 Jul 1;57(1):5–14. 6. Leung KK, Ridgway GR, Ourselin S, Fox NC. Consistent multi-time-point brain atrophy estimation from the boundary shift integral. *NeuroImage*. Elsevier Inc.; 2011 Oct 28;59(4):3995–4005. 7. Reuter M, Fischl B. Avoiding asymmetry-induced bias in longitudinal image processing. *NeuroImage*. Elsevier Inc.; 2011 Jul 1;57(1):19–21.

**OC28 - pS422 TAU-IMMUNOTHERAPY IN THY-TAU22 TRANSGENIC MICE.** L. BUEE, L. TROQUIER, P. LASSALLE, D. BLUM (*Inserm U837 - Alzheimer & Tauopathies, Faculty of Medicine, Research Department, Lille, France*)

Vaccination of mice in experimental models of Tauopathies has previously been reported to delay the pathology. Despite any adverse effect reported in these studies, passive immunotherapy may be preferred. Indeed, vaccination usually involves delivery of a strong adjuvant to boost antibody production and may induce an undesirable immune response as in the AN-1792 clinical trial. Passive immunotherapy uses antibodies that are specific and then, safer than vaccination. As for vaccination, the choice of the Tau epitope to target is very important. Indeed, targeting non-phosphorylated Tau has been shown to be deleterious. Both passive and active immunotherapies were performed in the well-characterized Tau transgenic mouse model: THY-Tau22. We have shown that vaccination with a Tau fragment phosphorylated at Ser422, a pathological epitope, was effective at reducing Tau pathology and cognitive impairment. In addition, we have shown that administration of a monoclonal Tau antibody directed against phospho-Ser422 (2H9) had a therapeutic effect on Tau pathology and associated cognitive performance. Both immunotherapies may facilitate Tau clearance through blood transfer with a mechanism described as the peripheral sink hypothesis. Tau immunotherapy is a promising approach in Alzheimer's disease and related disorders.

**OC29 - OUTPATIENTS WITH SEVERE ALZHEIMER'S DISEASE PARTICIPATING IN AN OBSERVATIONAL STUDY: BASELINE RESULTS OF THE GERAS STUDY.** C. REED<sup>1</sup>, J.M. ARGIMON<sup>2</sup>, M. BELGER<sup>1</sup>, G. BRUNO<sup>3</sup>, R. DODEL<sup>4</sup>, M. HAPPICH<sup>5</sup>, J.M. HARO<sup>6</sup>, R.W. JONES<sup>7</sup>, B. VELLAS<sup>8</sup>, A. WIMO<sup>6</sup> (*1. Eli Lilly and Company Limited, Windlesham, UK; 2. Servei Català de la Salut, Barcelona, Spain; 3. University of Rome "Sapienza", Rome, Italy; 4. Philipps-University, Marburg, Germany; 5. Lilly Deutschland GmbH, Bad Homburg, Germany; 6. Parc Santari Sant Joan de Déu, CIBERSAM, Universitat de Barcelona, Barcelona, Spain; 7. The RICE Centre, Royal United Hospital, Bath, UK; 8. Toulouse University Hospital, Toulouse, France; 9. Karolinska Institute, Stockholm, Sweden*)

*Background:* Observational studies are important in understanding the impact of Alzheimer's disease (AD) treatments as they provide naturalistic estimates of 'real-life' outcomes, such as resource use, to complement data from clinical trials. The majority of current trials in AD do not include severe AD as treatments are indicated for mild and moderate disease severity only. Extrapolation of study outcomes in severe AD (e.g. disease progression, cost) can use a variety of sources and techniques. The GERAS study was designed to assess the country costs associated with AD for patients and caregivers over 18 months, stratified by severity of patients' AD at baseline. The objective of this analysis is to describe patients with severe AD compared to mild and moderate AD living in the community participating in an observational study. *Method:* The GERAS study is a prospective, multi-centre, naturalistic, non-interventional, cohort study in the UK, France and Germany. Patients presenting within the normal course of care who were >55 years, diagnosed with probable AD (NINCDS-ADRDA), not institutionalised, and with an informal caregiver were categorised according to Mini Mental State Examination (MMSE) score as mild (26-21), moderate (20-15) or severe (14 or less) AD. Enrolment took place October 2010-October 2011. The study aimed to enrol a similar number of patients in each MMSE category in each respective country. Data collected included demographic characteristics, medical conditions, current medications and resource use on both patient and

caregiver (RUD), clinical measures of cognition (ADAS-cog - except if MMSE<15), function (ADCS-ADL) and behaviour (NPI) of the patient, as well as the burden (Zarit Burden Interview) and health-related quality of life (EQ-5D – caregiver and proxy version) from the caregiver. Following the baseline assessment, 6-monthly visits up to 18 months in the UK and up to 3 years in France and Germany will be completed. Patient and caregiver characteristics and clinical outcomes are reported by MMSE category. Cochran–Mantel–Haenszel (CMH) tests are used for severity group comparisons of categorical data, stratified by country. For continuous data ANOVA with independent factors for MMSE severity and country are used. **Results:** The study cohort included 1497 AD patients (38% mild, 32% moderate and 31% severe AD) and their caregivers (n=419 France, n=552 Germany and n=526 UK) with a mean (SD) patient age of 77.6 (7.7) years (77.3 mild; 77.8 moderate; 77.6 severe), 55% female (48% mild; 57% moderate; 61% severe; p<0.001) and an average of 2.2 (SD 2.2) years since AD diagnosis (1.7 mild; 2.1 moderate; 3.1 severe; p<0.001). A similar proportion of AD patients across all severity groups were married/cohabitating (75% mild, 68% moderate and 73% severe AD) whereas much fewer patients with severe AD were living alone in their own home (11% of severe AD compared to 23% moderate and 19% mild AD patients; p<0.001). The number of severe patients with comorbidities was similar to those in the mild and moderate groups; 72% of severe AD patients reported at least one co-morbid condition compared with 75% mild and 73% moderate AD. Caregivers had a mean (SD) age of 67.3 (12.0) years (68.1 mild; 66.7 moderate; 67.0 severe), 64% female (69% mild, 64% moderate, 58% severe, p=0.004) and 66% were the spouse of the AD patient (71% mild, 63% moderate, 63% severe, p=0.021). Mean (SD) total ADCS-ADL scores (range of possible scores 0-78) were mild 58.5 (14.2), moderate 48.3 (15.4) and severe 30.0 (17.3) which were significantly different between groups (p<0.001). Mean (SD) total NPI scores (range 0-144) were mild 10.2 (10.8), moderate 14.3 (12.6) and severe 22.0 (19.4) which were significantly different between groups (p<0.001). Caregiver burden as assessed by the ZBI (range 0-88) was significantly higher when caring for severe AD patients [mean (SD) score for mild 24.7 (14.2), moderate 29.4 (14.8) and severe 34.1 (14.8); p<0.001]. **Conclusions:** The GERAS study provides comprehensive information on a large AD cohort including a large sample of severe AD patients living in the community. The severe AD group are of a similar age to those in the mild and moderate groups and have a similar rate of at least one comorbid condition such that the severe AD group are younger and with less co-morbidity than anticipated. As expected, the clinical findings demonstrate that functional and behavioural measures deteriorate with increasing AD severity. Both patient characteristics and outcome measures of the severe AD GERAS cohort, particularly the longitudinal results, will be important for outcome modelling in AD. This study is sponsored and funded by Eli Lilly and Company Limited.

**OC30 - LEVEL OF EDUCATION, RISK OF ALZHEIMER'S DISEASE, AND COGNITIVE DECLINE IN THE GUIDAGE PREVENTION TRIAL.** N. COLEY<sup>1,2</sup>, G. GUERNEC<sup>1</sup>, B. VELLAS<sup>1,2,3</sup>, S. ANDRIEU<sup>1,2,3,4</sup> AND THE GUIDAGE STUDY GROUP (1. INSERM, U1027, F-31073 Toulouse, France; 2. Université de Toulouse III, F-31073, Toulouse, France; 3. Gérontopôle, Centre Hospitalier Universitaire de Toulouse, Toulouse, France; 4. Département d'Epidémiologie et Santé Publique, Centre Hospitalier Universitaire de Toulouse, Toulouse, France)

**Background:** In observational studies, education has been frequently found to be associated with the risk of dementia, with individuals with higher levels of education thought to be at lower risk. Furthermore, individuals with a higher level of education may undergo

different trajectories of cognitive decline prior to Alzheimer's disease (AD) diagnosis, with a sharper decline in cognitive function in the years immediately prior to diagnosis. These observations are concurrent with the cognitive reserve hypothesis. AD prevention trials are frequently confronted with the problem of lower than expected rates of AD incidence or cognitive decline. This could be due to recruitment bias, since individuals with higher levels of education are often over-represented in such trials. The objective of this analysis was to study the effect of education level on the risk of Alzheimer's dementia and the rate of cognitive decline in the GuidAge prevention trial. **Methods:** GuidAge was a 5-year double-blind randomized placebo-controlled multicenter trial assessing the efficacy of standardised Ginkgo biloba extract (EGb 761®, 240mg/d) for the prevention of Alzheimer's dementia. 2854 subjects aged 70 or older who spontaneously reported subjective memory complaints to their primary care physician (PCP) were included between 2002-2004 throughout France and followed-up for up to 5 years. All subjects underwent a full cognitive evaluation at baseline and annually thereafter in an expert memory centre. The following tests were performed: MMSE, Free and Cued Selective Reminding Test, Trail Making Tests, Verbal Fluency, CDR, IADL. DSM-IV and NINCDS-ADRDA criteria for dementia/AD were also assessed. Level of education was recorded at baseline, and was measured in terms of the highest diploma obtained. We dichotomised the education variable into "low" (≤Primary school certificate) versus "high" (≥Secondary (high school) education), and compared the baseline characteristics of subjects by education level. Cox proportional hazards models were used to evaluate the risk of AD in subjects with a high level of education compared to those with a low level of education. All subjects from the placebo group in the GuidAge ITT population were included in these analyses, except for those that developed non-AD forms of dementia during follow-up. Further analyses will be conducted using longitudinal mixed effects models to evaluate the effect of education on the rate of cognitive decline in subjects who developed AD and those who remained dementia-free. **Results:** The mean age of the 1387 subjects included in the analysis was 76.3 years and 68% were female. Primary school certificate was the highest diploma obtained by 65% of subjects, and 19% obtained a high school diploma (Baccalaureate) or higher. The level of education in GuidAge participants was higher than in the general French population (in 1999, only 12% of French over 65's had obtained a high school diploma or higher; National Institute of Statistics and Economic Studies). At baseline, compared to subjects with a low level of education (n=895; 65%), those with a higher level of education (n=492; 35%) had significantly better performances on all cognitive tests (all p-values <0.001), better functional status (94.9% versus 88.8% without IADL limitations, p<0.001), longer mean duration of memory complaints (55.9 versus 49.0 months, p=0.001), and lower BMI (25.4 versus 26.4; p<0.001). They also included a significantly higher proportion of alcohol consumers (50.0% versus 43.2%, p=0.015), and smokers/ex-smokers (p=0.001), and a lower proportion of individuals with hypercholesterolemia (25.4% versus 32%, p=0.011). There were borderline significant differences between subjects with high and low levels of education in baseline age (76.1 versus 76.3, p=0.051), anxiety (p=0.052) and depression scores (p=0.0854), and the proportion of subjects with diabetes (p=0.065), and no significant difference in the proportion of males (p=0.147), subjects with hypertension (p=0.710) or ApoE epsilon 4 carriers (p=0.997). In this population of subjects who spontaneously reported a memory complaint to their PCP and who were included in a 5-year AD prevention trial, there was a borderline significant decreased risk of AD in subjects with higher level of education compared to those with a lower level of education in an unadjusted analysis (HR 0.60; 95% CI: 0.36-1.01; p=0.056). After

adjustment for baseline cognitive and functional status, duration of memory complaints, age, sex and cardiovascular risk factors, the effect of education was not significant (HR 0.78; 95%CI: 0.44-1.39; p=0.396). The trajectories of cognitive decline in AD and non-AD subjects with high and low levels of education will be presented. *Conclusion:* The GuidAge study population was more highly educated than the general French population. There were numerous differences in baseline characteristics between subjects with low and high levels of education, but education level was not associated with AD risk. This result is somewhat surprising, but may be explained by the relatively short period of follow-up, lack of statistical power (AD incidence was lower than expected), and the reduced variability in education levels in this population. Further analyses will enable us to determine if education affected trajectories of cognitive decline.

**OC31 - REPURPOSING CARDIOVASCULAR DRUGS AS ALZHEIMER'S DISEASE MODIFYING AGENTS.** G.M. PASINETTI<sup>1</sup>, P. ROSENBERG<sup>2</sup> (1. Department of Neurology, Mount Sinai School of Medicine, New York, USA; 2. Department of Psychiatry, Johns Hopkins School of Medicine, Baltimore, USA)

*Background:* Current FDA-approved Alzheimer's disease (AD) treatments have modest symptomatic effects at best, and do not significantly modify disease course. In a population-based sample of incident AD, we observed that the use of  $\beta$ -adrenergic antagonists was associated with slower functional decline. Our data combined with other epidemiologic data point to the potential therapeutic effect of  $\beta$ -adrenergic antagonists in patients with AD. One agent that passed the screen was carvedilol, a  $\beta$ -adrenergic antagonist FDA-approved for several cardiac indications. In two different transgenic mouse models of AD, chronic oral administration of carvedilol decreased brain monomeric and oligomeric  $\beta$ -amyloid (A $\beta$ ) content, attenuated cognitive deterioration, and improved basal neuronal transmission in the brain. Thus, a treatment that lowers brain A $\beta$  oligomer levels may be particularly beneficial in early AD. Additionally, carvedilol may have a beneficial effect on vascular risk factors for AD by stabilizing blood pressure and improving brain perfusion since it is an approved treatment for hypertension and congestive heart failure and has been shown to be neuroprotective in brain ischemia models. Should carvedilol have a beneficial effect in AD, it offers the advantages of being relatively safe and inexpensive. *Methods:* We are clinically exploring a target dose of 25 mg daily of carvedilol to 50 AD patients in a 6 month randomized, placebo-controlled, double-blind, single-site trial, with change in episodic recall as the primary outcome and biomarker change and safety/tolerability as secondary measures. *Results:* The results of this proof-of-concept trial underlie a "Go-No-Go" decision. If we observe a significant improvement in clinical outcomes, we will propose a definitive trial of carvedilol in AD. If we observe a change only in biomarker outcomes, this will inform further studies of similar treatment mechanisms (whether carvedilol or alternative agents). *Conclusions:* Should carvedilol prove to be effective in AD, it has several advantages over novel agents in human trials since it has a well-characterized, generally well-tolerated safety profile and is available as a generic drug. Supported by NIH AG037504 to Giulio Maria Pasinetti.

**OC32 - COMPARISON OF INTERIM RESULT AFTER ONE AND TWO YEARS OF TREATMENT OF ASCOMALVA TRIAL ON THE ASSOCIATION BETWEEN THE CHOLINESTERASE INHIBITOR DONEPEZIL AND THE CHOLINERGIC PRECURSOR CHOLINE ALPHOSCERATE IN ALZHEIMER'S DISEASE.** F. AMENTA<sup>1</sup>, A. CAROTENUTO<sup>1</sup>, R. REA<sup>1</sup>, E. TRAINI<sup>1</sup>, A.M. FASANARO<sup>2</sup> (1. Centro Ricerche Cliniche, Telemedicina e Telefarmacia, Università di Camerino, 62032 Camerino; 2. Unità Valutativa Alzheimer e Malattie Involutive Cerebrali, Azienda Ospedaliera Rilievo Nazionale A. Cardarelli, 80131 Napoli, Italy)

*Background:* The double-blind multicentre trial "Effect of association between a cholinesterase inhibitor and choline alfoscerate on cognitive deficits in Alzheimer's disease associated with cerebrovascular impairment" (ASCOMALVA) investigates the effects of association between the cholinesterase inhibitor donepezil (10 mg/day) and choline alfoscerate (1,200 mg/day) on Alzheimer's disease with cerebrovascular impairment over a 24 months period. *Methods.* Patients were included in the protocol with a MMSE score between 15 and 24. Patients with AD, diagnosed according to Nincds ADRDA criteria, also suffered from ischemic brain damage documented by neuroimaging (MRI and CT scan), with a score  $\geq 2$  in at least one subfield of the New Rating Scale for Age-Related White Matter Changes (ARWMC). Patients were randomly allotted to an active treatment group (donepezil + choline alfoscerate) or to a reference treatment group (donepezil + placebo) and were examined at the recruitment and after 3, 6, 9, 12, 18 and 24 months of treatment. The trial investigates on cognitive decline by Mental State Evaluation (MMSE) and Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-cog), on functional activities by Basic Activities of Daily Living (BADL) and Instrumental Activities of Daily Living (IADL), on behavioural disorders by Neuropsychiatric Inventory frequency x severity (NPI-F) and distress of the caregiver (NPI-D). *Results.* At this point a quarter of planned number have reached the 24 months endpoint and a half the 12 months. The interim results after a year of treatment shows, in the reference group, a global time-dependent worsening of all the considered parameters respect to the treatment group. The worsening is more evident after two years, while in the treatment group the cognitive decline is slowed and the behavioral disorders and caregiver's distress are improved. The response ratio in all the considered parameters is greater in the treatment group and comparing the first and second year of treatment the difference is wider after 24 months. *Conclusion.* These results suggest that association of choline alfoscerate to the standard treatment with a ChE-I may represent an option to prolong beneficial effects of cholinergic therapies in Alzheimer's disease with concomitant ischemic cerebrovascular injury.

**OC33 - TRANSLATING COGNITIVE PERFORMANCE TO FUNCTIONAL ABILITY IN ALZHEIMER'S, LEWY BODY, CEREBROVASCULAR, AND FRONTAL LOBE DISEASES.** W.R. SHANKLE<sup>1,3,5</sup>, J. HARA<sup>1,2</sup>, B. REISBERG<sup>4</sup>, M. LEE<sup>5</sup>, J. POOLEY<sup>5</sup> (1. Shankle Clinic, Newport Beach, CA, USA; 2. Medical Care Corporation, Newport Beach, CA, USA; 3. Hoag Neurosciences Institute, Newport Beach, CA, USA; 4. Aging & Dementia Research Center, New York University, New York, USA; 5. Dept. of Cognitive Sciences, University of California at Irvine, Irvine, CA, USA)

*Background:* Translating a cognitive performance measure into its functional equivalent is important in both clinical practice and clinical trials because it can be difficult to interpret the meaning or relevance of a change of a few points on a cognitive test score. For example, the

significance of a treatment's effect in an FDA clinical trial could be more readily understood if a primary cognitive outcome measure were translated into its cognitively related functional equivalent. This is also true in clinical practice, where a change in a cognitive test score may be difficult to communicate to patients and their families, but a change in its cognitively related functional ability is more easily understood. Previously, we have shown - using hierarchical Bayesian cognitive processing models (HBCP) - that a cognitive process underlying delayed recognition memory task performance can be reliably translated into a continuous-valued measure of functional activities of daily living. These findings were demonstrated in a sample of 2,558 repeated measures from 344 patients who had either normal cognition, mild cognitive impairment or dementia due to Alzheimer's disease (AD), cerebrovascular disease (VD), Frontal-temporal lobe disease (FTLD), Lewy Body Disease (LBD) or a mixed etiology (Mixed ADRD). This previous finding was demonstrated for the entire sample. However, it was not examined for each etiology separately. The present study examines this cognitive-functional relationship for each etiology. *Methods:* The sample consisted of 304 patients (N), who had 2,086 repeated assessments (R) for up to 9 years, using the MCI Screen (MCIS) and the Functional Assessment Staging Test procedure (FAST). 40 patients from the previous study were excluded because their ADRD etiology was not well established. Sample sizes were as follows: Normal (N=19, R=85), AD (N=163, R=1274), VD (N=131, R=800), LBD (N=23, R=174), FTLD (N=18, R=101), and Mixed ADRD (N=88, R=652). The HBCP model consisted of recognition memory performance parameters of discriminability and response bias (response strategy), evaluated at each FAST stage, patient and assessment within a graphical hierarchical Bayesian framework. Discriminability is a measure of the strength and persistence of memory storage. Response bias is a measure of executive function. For each diagnostic group, and for all groups combined, a transfer function was developed to relate discriminability to the continuum of values underlying the discrete FAST stages. Bayesian analysis was used to implement the model, and infer the parameters of the transfer function. *Results:* The transfer functions of the AD, LBD, VD and Mixed ADRD groups were well behaved and had narrow credible intervals, but those of the normal and FTLD groups did not accurately translate cognition to function. In VD, discriminability declined twice as slowly compared to other groups. *Conclusions:* HBCP models accurately translated memory storage strength and persistence (discriminability) into a continuous-valued measure of functional severity in AD, VD, LBD and Mixed ADRD. It is notable that the slower rate of functional decline in the VD group compared to the AD group is consistent with the generally slower rate of progression in VD. These findings suggest that the FAST procedure—originally developed for AD—is also useful for monitoring other ADRD etiologies. The poor translation of discriminability to its functional equivalent in normal and FTLD needs further evaluation. The differences between FAST stages, such as mild cognitive impairment (FAST 3) and mild dementia (FAST 4) are more easily interpretable than changes on a cognitive test score. Therefore, it can be helpful in clinical trials and clinical practice to translate a primary cognitive outcome measure onto a continuous-valued measure of its cognitively related functional equivalent (i.e., FAST staging or other similar scale) so that a treatment's effects can be more easily understood and interpreted.

**OC34 - HYPERPHOSPHORYLATION OF NEURONAL CYTOSKELETAL PROTEINS IS INHIBITED BY PEPTIDES DERIVED FROM ITS ACTIVATOR P35; A NOVEL APPROACH TO RESCUE THE PATHOLOGY INDUCED BY DEREGULATION OF KINASES.** H.C. PANT (NINDS / NIH, Bethesda, MD 20892 USA)

The Biology of Neurodegeneration program evolved from my laboratory studying the basic biology of neuronal cytoskeletal protein phosphorylation during development and normal function in the adult. To understand the molecular basis of neurodegeneration our major focus has been to study the regulation of compartment-specific patterns of cytoskeletal protein phosphorylation in neuronal perikarya and axons. We have demonstrated that phosphorylation of the numerous acceptor sites on such proteins as Tau and neurofilaments was tightly regulated topographically and generally confined to the axonal compartment. It was recognized that in neurodegenerative disorders such as Alzheimer's disease (AD) and Amyotrophic lateral sclerosis (ALS), the pathology was characterized by an accumulation of aberrantly phosphorylated cytoskeletal proteins in cell bodies, suggesting that topographic regulation had been compromised. This led us to discover a neuron specific cyclin dependent like kinase kinase, Cdk5, a multifunctional kinase involved in nervous system development and survival. Its activity is tightly regulated in the nervous system. The diverse roles of Cdk5 are based, in part, on evidence that it is a key player in signal transduction networks and kinase cross talk underlying neuronal cell survival, growth and differentiation. We have found that Cdk5 not only phosphorylates the non-enzymatic molecules but also phosphorylates the kinases and phosphatases. For example, it phosphorylates and down regulates MAPKs and JNKs and upregulates PI3Ks. In addition phosphorylated PP1 and regulates synaptic activity. Cdk5 is involved with survival and apoptotic pathways. Its regulated activity is essential for nervous system development and survival. It appears to act to modulate the intensity of the response to specific signals. Neuronal stress-induced cleavage of the activator p35 to p25 and a p10 N-terminal domain induces deregulated Cdk5 hyperactivity, perikaryal aggregations of hyperphosphorylated tau and neurofilaments (NFs), pathogenic hallmarks in neurodegenerative diseases such as AD and ALS, respectively. Unlike many other laboratories and drug companies to use ATP analogs as a therapeutic agents to rescue the pathology we have developed peptides derived from, p35, a neuron specific activator of cdk5, for deregulated Cdk5 activity which rescue cells in vitro and in situ from this stress induced pathology. Our study of site specific interactions between Cdk5 and truncated forms of its p35 regulator have revealed a central p35 fragment, 125 and 24 amino acids residues (CIP, P5) that has high affinity for and inhibit the in vitro and in situ activity of the Cdk5/p25 complex. We have shown that CIP specifically inhibits Cdk5/p25 activity in transfected cells and also reduces phosphorylation of ransfected tau. It is important to note that CIP does not affect the activity of Cdc2 and other mitotic kinases. Now we have shown that CIP inhibits cdk5/p25 activity in primary neurons. Recently, we have found a much smaller truncated peptide of 24 amino acids derived from p35 can also specifically inhibits the cdk5-deregulated activity. This may provide a possible new therapeutic route for intervention to prevent or reduce the neurodegenerative diseases induced by Cdk5 deregulation.

**OC35 - DISEASE-MODIFYING POWER ESTIMATION FOR TAURX GLOBAL PHASE 3 TRIAL PROGRAM IN AD WITH TAU-AGGREGATION INHIBITOR LMTX.** C.M. WISCHIK, D.J. WISCHIK (*TauRx Therapeutics*)

**Background.** Following the failure of a number of major amyloid-based Phase 3 trials, there is interest in alternative approaches to meet the urgent unmet medical need for disease-modifying treatments in AD. Inhibition of aggregation of tau protein offers a potential alternative. TauRx has US regulatory approval to proceed with its Phase 3 program in AD and bvFTD using LMTX, and will initiate its program in fourth quarter of 2012. LMTX is a stabilized reduced form of methylthionine (MT), which delivers MT with improved tolerability, safety and availability relative to MTC (the chloride salt of the oxidized MT+ form, commonly known as methylene blue). In a Phase 2 trial in 321 patients, MT showed potential benefit in slowing the rate of clinical decline in AD at a dose of 138 mg/MT per day over 24 months. HMPAO-SPECT scans, measured in approximately half the subjects, showed that patients receiving MT at this dose had less deterioration in the frontal, temporal, parietal, and occipital lobes than patients receiving placebo. **Methodology.** For a trial of a putative disease-modifying treatment, it is necessary to take account of both expected rate of placebo decline and anticipated effect size on the ADAS-cog scale. A failure on placebo decline assumptions makes it impossible to detect a disease-modifying effect. We have undertaken a meta-analysis of all publically available placebo decline data to estimate within-trial and between-trial variance. A modified intent to treat analysis repeated measures linear mixed model without imputation appears to be the most acceptable from a regulatory point of view for studies longer than 6 months. We have therefore applied this method to our Phase 2 data to derive an estimate of the expected effect size and its standard error. We have combined these two analyses, taking account of confidence intervals for placebo decline and for effect size, to derive a measure of trial power that is more suitable for the planned program than approaches based on point estimates. **Results.** The meta-analysis shows that for AD of mild/moderate severity, the mean placebo decline over 12 months is 5.55 ADAS-cog units, but the 99%, 95%, 90% or 80% lower confidence bounds are 1.43, 2.68, 2.35 and 4.16 respectively. For AD of mild severity, the mean decline over 18 months is 7.50, but the 99%, 95%, 90% or 80% lower bounds are 2.72, 4.12, 4.87 and 5.78 respectively. Between-trial variability makes a 3-fold greater contribution to the standard error of placebo decline than within-trial variability. Measurement of absolute effect size from the Phase 2 data varies by severity, duration and placebo decline, but effect size expressed as a percentage of placebo decline ("effect-fraction") remains relatively constant, as would be expected for a disease-modifying treatment, and so does its standard error. Using a repeated measures linear mixed model without imputation, the decline in the control arm in mild/moderate AD over 12 months was 4.26 (se 0.94), the effect size 3.63 (se 1.29) and the effect-fraction was 85.1% (se 30.3%), with p-value 0.0053 for 138 mg/MT per day. The decline estimated in the control arm in mild AD over 18 months (projected from 12 month data) was 6.46 (se 1.68), the decline observed in the arm treated with 138 mg/MT per day for 18 months was 0.44 (se 1.45), the implied effect size was 6.02 (se 2.47) and the effect-fraction was 92.3% (se 38.2%), with estimated p-value 0.015. For a disease-modifying treatment, a power calculation based on percentage reduction in decline depends critically on the placebo decline estimate. Given that the mean and standard error of effect-fraction were found not to depend on placebo decline, the absolute effect size in ADAS-cog units is the product of two independent random variables, one for placebo decline and the other for effect fraction, and we can find its

mean and standard error by simple integration. This enables us to compute the distribution of overall power. **Conclusion.** From this, we calculate that a 12-month study in mild/moderate AD (MMSE 14 – 26) conducted over 12 months in 833 subjects comparing LMTX doses delivering 150 and 250 mg MT/day with placebo is adequate to demonstrate a significant effect on the ADAS-cog scale in at least one arm with greater than 90% probability, assuming a withdrawal rate of 40%. This requires an absolute effect size irrespective of placebo decline of at least 1.38 in either arm for significance assuming the standard deviation is 6.21. Similarly, an 18-month study in mild AD (MMSE 22 – 26) in 500 subjects comparing a dose of LMTX delivering 200 mg MT/day with placebo is adequate to demonstrate a significant effect on the ADAS-cog scale with greater than 90% probability, assuming a withdrawal rate of 40%. This requires an absolute effect size of at least 1.59 for significance assuming standard deviation 8.11. The approved trials were planned accordingly.

## POSTERS

### CLINICAL TRIALS : METHODOLOGICAL ASPECTS

**P1 - META-ANALYSIS FOR BEHAVIORAL AND NEUROPSYCHIATRIC SYMPTOMS IN ALZHEIMER'S DISEASE (AD) CLINICAL TRIALS.** K. ITO, S. AHADIEH, P. LOCKWOOD, T. TENSFELDT, B. CORRIGAN (*Pfizer Inc, Primary Care Business Unit, Groton, CT, USA*)

**Background:** In addition to cognitive deterioration, behavioral abnormalities and neuropsychiatric symptoms are important manifestations of Alzheimer's disease, and clinical measurements of those symptoms, such as ADCS-ADL (Alzheimer's Disease Cooperative Study-Activities of Daily Living), DAD (Disability Assessment for Dementia), NPI (Neuropsychiatric Inventory), are included in AD clinical trials as co-primary or secondary outcomes. Relative to ADAS-cog (Alzheimer's Disease Assessment Scale-Cognitive Subscale), limited summary reviews for these endpoints have been reported. Therefore, the purpose of this meta-analysis is to summarize the clinical outcomes for behavioral and neuropsychiatric scores from all publically available data sources. **Methods:** A systematic search of public data sources (Medline, Embase, Cochrane, NICE and Summary for Basis of Approvals at FDA) from 1990 to 2011 was conducted. Key search terms included drug names (donepezil, galantamine, rivastigmine, memantine), clinical outcome endpoints of interest (ADCS-ADL, DAD, NPI, SIB etc.) and clinical trial design descriptions (double-blind, randomized, etc.). The observed data was summarized in forest plots with the estimated mean effect for each drug and the above mentioned endpoints using metaphor package ([www.r-project.org](http://www.r-project.org)) in fitting the random effect model. **Results:** Among 149 extracted papers that met the search criteria, 42 publications were reporting ADCS-ADL, 19 publications for DAD, 18 publications for SIB. Some publications reported scores over time (longitudinal data), where others reported the results at the last time point of the study likely due to the fact that these endpoints were co-primary or secondary endpoint in the clinical trials. Improvements in treatment groups compared with placebo in behavioral and neuropsychiatric scores were observed; the mean changes from baseline considering the variability between the studies [95% CI] for ADCS-ADL at 24 to 28 weeks were -1.78 [-2.31, -1.25], -1.92 [-3.16, -0.68], -2.76 [-3.82, -1.71] for donepezil, memantine, and placebo group respectively. DAD changes from baseline at 24 weeks were -1.07 [-2.92, 0.78], -2.45 [-3.77, -1.13], -7.79 [-10.2, -5.43] for

donepezil, galantamine, and placebo group respectively. NPI changes from baseline at 20 to 30 weeks were -4.3 [-7.26, -1.6], -2.04[-2.84, -1.25], -2.67[-6.04, 0.71], -0.47 [-2.1, 1.06] for donepezil, rivastigmine, memantine, and placebo group respectively. The SIB (Severe Impairment Battery) is a neuro-psychological test in moderate to severe AD patient clinical trials, was also summarized in this analysis. Most papers were for donepezil studies and its effect size (improvement from placebo) was 5.4 [6.72, 4.09]. **Conclusions:** It is important to understand the overall magnitude of clinical benefit in behavioral and neuropsychiatric symptom and the uncertainty surrounding these values in order to leverage these measures in design of new clinical trials and facilitate comparison with historical data to differentiate various pharmacotherapies. This meta-analysis provides overall summaries of clinical benefits for anti-dementia agents which demonstrate beneficial behavioral and neuropsychiatric outcomes from randomized clinical trials published from 1990 to 2011, where Cochrane reviews in 2009 [1] summarized 5 publications for ADL, and 2 publications for DAD. Most clinical studies were designed to test the primary endpoint (ADAS-cog) and these endpoints (ADCS-ADL, DAD, NPI, SIB etc.) are usually relegated to supporting the efficacy claims in the labels. [1] <http://summaries.cochrane.org/CD005593/cholinesterase-inhibitors-cheis-donepezil-galantamine-and-rivastigmine-are-efficacious-for-mild-to-moderate-alzheimers-disease>

## **P2 - CHARACTERISTICS OF ALZHEIMER'S PATIENTS PARTICIPATING IN RESEARCH WITHIN THE FRENCH NATIONAL ALZHEIMER BANK NETWORK.**

K. TIFRATENE<sup>1,2</sup>, F. LEDUFF<sup>1</sup>, C. PRADIER<sup>1</sup>, M. LAYE<sup>2</sup>, R. CHEVRIER<sup>1</sup>, P. ROBERT<sup>2</sup> (1. Public Health Department, Nice University Hospital, France; 2. CMRR, EA CobTeK, Nice University)

**Backgrounds:** Research in Alzheimer Disease faces the double challenge to recruit representative patients of the real world disease and to enroll patients able to give their consent and to potentially respond or tolerate the research effects. The French National Alzheimer Bank (BNA) is part of the French Alzheimer plan and aims to improve the epidemiologic knowledge of the disease and related disorders. It records activity data of memory centers across the country since 2010 and is theoretically able to identify patients participating to any kind of research. This study was set up to describe patient's characteristics participating to research. **Methods:** We analyzed a cross section of the BNA based on data recorded during 2010 and 2011. We selected only patients with a diagnosis of AD and consulting a memory center (CM) or a research and resources memory center (CMRR). Univariate analyses were performed for 3 types of data : medical characteristics of the patient, social and environmental determinants and center type. **Results:** Among the 208 842 patients consulting the CM and CMRR and recorded in BNA in 2010 and 2011, 57 739 (28.1%) had a diagnosis of AD. Women represented 70.7%, mean age was 80.9 years old (+/- 7.7) and mean MMSE score was 17.1 (+/-6.1). AD patients mainly consulted in CM (73.6%) rather than CMRR (26.4%). Patients recorded as Participant to Research (PR) account for 3.8% (2 221) of AD patients. Medical characteristics of the patients: male patient were more represented among PR patients than among non PR patients 36.4% vs 29% (p<10-5), PR patients were younger (mean age 75.6 years old vs 81.1; p<10-5) and with better MMSE scores (mean MMSE 18.1 vs 17; p<10-5). Drugs associated with participation to research were: cholinesterase inhibitors (OD: 1.88[1.71-2.08]), NMDA receptor antagonist (OD: 1.38[1.27-1.51]) and antidepressant (OD: 1.36 [1.34-1.48]). Antipsychotic drugs were negatively associated with PR (OD: 0.72 [0.60-0.85]) and hypnotics and anxiolytics were used in the same proportions in each group. As a cause or a consequence imaging (MRI, SPECT, PET but not scanners)

and determination of CSF biomarkers were more frequent in PR group with respective ODs: 2.22 [2.01-2.45], 4.98 [4.16-5.96], 15.41 [11.42-20.79], 0.513 [0.45-0.59] and 9.43 [8.15-10.9]. Social and environmental determinants: PR patients lived more at home than non PR (91.1% vs 82.5%), were less living alone (25.5% vs 32.4%) and had less social support measures (19.8% vs 29.4%) (All differences were statistically significant). University level was more frequent in PR group (15.3% vs 7.1%; p<10-5). CMRR included 10.9% of their AD patients in a research protocol versus only 1.3% for the CM (p<10-5). **Conclusion:** The rate of AD patients participating to a research was low in the BNA (3.8%) and certainly underestimates the true number of AD patients included in research in France as BNA is still not an exhaustive collection and that population data collection is also done by different networks. However Using BNA data it is possible to have general demographics characteristic of the patients. In this way BNA data confirms that research selects younger and less cognitively or socially injured patients. Taking into account the prognosis of AD and the poor therapeutic weapons we have a more representative AD research population is desirable respective to ethical aspects.

## **P3 - CLINICAL BACKGROUND OF PARTICIPANTS OF CLINICAL TRIALS ON ALZHEIMER'S DISEASE IS DIFFERENT FROM THAT OF ACTUAL PATIENTS.**

M. YUTANI<sup>1</sup>, M. TAKAHASHI<sup>2</sup>, S. OISHI<sup>2</sup>, K. SHICHIJOU<sup>3</sup>, H. MIYAOKA<sup>2</sup> (1. Kitasato University Graduate School of Medical Sciences; 2. Department of Psychiatry, Kitasato University School of Medicine; 3. Clinical trial center, Kitasato University East Hospital)

**Backgrounds:** Clinical trials are designed to prove the effectiveness and safety of new drugs. The participants are selected on the basis of inclusion criteria. Therefore, participants may have different backgrounds from actual patients. Clinical trials on Alzheimer's disease (AD) require magnetic resonance imaging (MRI) examination and the patients with severe cerebrovascular changes are usually excluded. However, about one-half to two-thirds of AD patients have moderate or severe cerebrovascular changes. Cerebrovascular changes are commonly associated with comorbidities, such as hypertension, diabetes mellitus, hyperlipidemia, heart disease, or chronic renal disease. Therefore, we are interested in the differences in the profile of physical complications between clinical trial participants and actual patients. Such differences may affect the effectiveness or safety of new drugs; therefore, we should take such differences into account when evaluating the results of clinical trials. To clarify whether the clinical background of participants, particularly physical complications, is different from that of actual patients, we performed this comparison study. **Methods:** The subjects were 28 participants of two clinical trials on AD (CTAD group) and 105 AD patients (AD group) using the dementia discriminating course from 2004 to 2010. Written informed consent to use clinical data to the study was obtained. For the diagnosis of AD, the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria were used. Age, gender, mini-mental state examination (MMSE) score, and physical complications were compared between the two groups. Regarding physical complications, the presence or absence of lifestyle-related diseases (hypertension, diabetes mellitus, or hyperlipidemia), heart disease, and renal disease was investigated, and the total number of complications was counted in each patients. The t-test and chi square test were performed to determine the significance of differences between the two groups. P values of <0.05 were considered to indicate statistically significant differences. **Results:** The mean age of the

CTAD group was lower than that of the AD group, 69.1y and 76.1y, respectively ( $p < 0.0001$ ). The percentage of females and mean MMSE score were similar between the two groups. The mean number of complications of the CTAD group was smaller than that of the AD group, 0.6 and 1.0, respectively ( $p = 0.019$ ). In particular, heart disease and diabetes mellitus occurred less frequently in the CTAD group than in the AD group, 23.8% and 3.6% ( $p = 0.015$ ), and 17.1% and 3.6% ( $p = 0.076$ ), respectively. Hypertension occurred at a slightly lower frequency in the CATD groups. The frequencies of hyperlipidemia and renal disease were similar between the two groups. In summary, the age was lower in the CTAD group, and the frequencies of heart disease and diabetes mellitus were lower in the CTAD group. These findings suggest that we should pay attention to age and lifestyle-related diseases when using new drugs. These factors may be associated with more severe adverse effects or unexpected adverse effects. Moreover, patients having physical complications usually take drugs to control such complications. Therefore, we have to be aware of possible interactions between drugs for physical complications and a new AD drug. Regarding clinical trials on AD, we would like to propose that the criteria for selection of phase III trial participants should be changed such that they represent actual patients who will be taking the new drug. Regarding the limitations of this study, we did not check the medications taken by the patients in this study, and the number of participants group was small. **Conclusions:** The clinical background was different between the CATD group and the AD group. Therefore, new drugs should be administered to actual patients carefully because actual patients may have more complications and take more medications. Moreover, we propose to change the inclusion criteria of phase III studies such that the selected participants represent actual patients in terms of clinical background.

#### **P4 - PREDICTORS OF PROGRESSION FROM MILD COGNITIVE IMPAIRMENT TO ALZHEIMER'S DISEASE IN THE PLACEBO ARM OF A CLINICAL TRIAL POPULATION.**

N.D. PRINS<sup>1</sup>, W.M. VAN DER FLIER<sup>1</sup>, H.R. BRASHEAR<sup>2</sup>, F. BARKHOF<sup>1,3</sup>, P. SCHELTENS<sup>1</sup> (1. Alzheimer Center and department of Neurology, VU University Medical Centre, Amsterdam, the Netherlands; 2. Janssen Alzheimer Immunotherapy Research and Development, South San Francisco, CA, USA; 3. Alzheimer Centre, Department of Radiology, and Image Analysis Centre, VU University Medical Centre, Amsterdam, The Netherlands)

**Background:** biological markers and memory tests may be used to enrich trials of MCI to secure statistical power. Our objective was to prospectively study the predictive value of cognitive performance, vascular risk factors, apolipoprotein E (APOE) genotype, and structural brain changes on MRI, on progression to Alzheimer's disease (AD) in a large clinical trial population of patients with mild cognitive impairment (MCI). **Methods:** we studied the 426 placebo patients with MCI who participated in a large multi-centre study (Gal-Int-11). At baseline, we performed cognitive testing using the ADAS-cog/MCI test, the New York University Paragraph Recall Test, and the Digit Symbol Coding Test. We assessed vascular risk factors and APOE genotype. Medial temporal lobe atrophy (MTA), white matter hyperintensities (WMH) and lacunes were assessed on MRI. We used Cox proportional-hazards regression analysis to examine the associations of age, sex, ADAS-cog/MCI score, Delayed recall score, Digit symbol score, vascular risk factors, and structural brain changes on MRI, with the risk of progression to AD during follow-up. **Results:** over two years of follow-up, 81 patients (19%) progressed to AD. Worse performance on the ADAS-cog/MCI, Delayed recall, and Digit symbol test, presence of an APOE  $\epsilon 4$  allele, and more MTA on MRI increased the risk of progression to AD in age- and sex-adjusted

analyses. Vascular risk factors, and WMH and lacunes on MRI, were not associated with progression to AD. Baseline performance on the ADAS-cog/MCI test (HR 1.08 per point increase; 95% CI 1.06-1.10) and on the Delayed recall test (HR 0.76 per point increase; 95% CI 0.68-0.85), as well as MTA on MRI (HR 1.33; 95% CI 1.00-1.76) were independent predictors of conversion to AD in a step-wise Cox proportional-hazards regression model with age and sex forced into the model. **Conclusion:** global cognitive function and episodic memory performance, as well as atrophy of the medial temporal lobe on MRI, are independent predictors of progression to AD in patients with MCI.

#### **P5 - THE SKT SHORT COGNITIVE PERFORMANCE TEST IN PATIENTS WITH DEMENTIA: CROSS-SECTIONAL AND LONGITUDINAL CORRELATIONS WITH ACTIVITIES OF DAILY LIVING IN TWO INDEPENDENT CLINICAL TRIALS.**

R. HOERR<sup>1</sup>, H. LEHFELD<sup>2</sup>, S. SCHLAEFKE<sup>1</sup> (1. Clinical Research Department, Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany; 2. Department of Psychiatry and Psychotherapy, Nuremberg Hospital, Nuremberg, Germany)

**Backgrounds:** The ability of patients with dementia to execute activities of daily living does not only depend on their remaining cognitive abilities, but also on concomitant physical diseases and mental disorders as well as their social environment. Treatment-related improvements in cognition do not necessarily translate into better capability to cope with the demands of everyday living. The goal of this additional analysis of data from two independent clinical trials was to assess to what extent cognitive performance as measured by the Syndrome Short Test (SKT), a brief cognitive performance test, correlates with activities of daily living as measured by the Activities-of-Daily-Living International Scale (ADL-IS). **Methods:** Two randomized, placebo-controlled, double-blind, multicentric clinical trials, both following identical protocols, were conducted independently from each other in different European countries. Patients with mild to moderate Alzheimer's disease (AD) with or without cerebrovascular disease (CVD) or vascular dementia (diagnosed in accordance with NINCDS/ADRDA and/or NINDS/AIREN diagnostic criteria, as appropriate), who scored between 9 and 23 points on the SKT and at least 6 points on the Neuropsychiatric Inventory (NPI), were enrolled and treated with Ginkgo biloba extract EGb 761® (240 mg per day) or placebo for a period of 24 weeks. The SKT total score and the NPI composite score were primary outcome variables, the ADL-IS total score was one of the secondary outcome variables. Linear regression analyses were performed on baseline scores (cross-sectional perspective) and changes from baseline to week 24 (longitudinal perspective) for the SKT total score, the SKT memory subscore and the SKT attention subscore as independent variables and the ADL-IS total score as the dependent variable, using pooled data from both trials. **Results:** The GOTADAY Study enrolled 404 patients, the GOT-IT! Study 402 patients; in each study about two thirds of patients were female and the average age was 65 years. Mean baseline scores were 17 for the SKT and 2 for the ADL-IS in the GOTADAY Study and 15 and 2, respectively, in the GOT-IT! Study. Statistically significant correlations were found in cross-sectional (SKT total / ADL-IS,  $\rho = 0.52$ ,  $p < 0.0001$ ; SKT memory,  $\rho = 0.36$ ,  $p < 0.0001$ ; SKT attention / ADL-IS,  $\rho = 0.44$ ,  $p < 0.0001$ ) and longitudinal analyses (SKT total / ADL-IS,  $\rho = 0.48$ ,  $p < 0.0001$ ; SKT memory / ADL-IS,  $\rho = 0.40$ ,  $p < 0.0001$ ; SKT attention / ADL-IS,  $\rho = 0.41$ ,  $p < 0.0001$ ). Supplementary analyses of data from each trial did not reveal major differences between the two trials. **Conclusion:** The moderate, yet highly significant relationships between SKT and ADL-IS scores found in cross-sectional as well as in longitudinal analyses are well in



line with correlations between performance tests and ADL instruments reported in literature. They suggest that the cognitive abilities measured by the SKT are, in fact, relevant to the patients' daily living. From a longitudinal perspective, it can be concluded that improvements in SKT scores are likely to result in improvements in the patients' abilities to cope with the demands of everyday life. The SKT cognitive battery can therefore be regarded as an instrument with ecological validity.

**P6 - INNOVATIVE DIGITAL PATIENT RECRUITMENT STRATEGIES IN PRODROMAL AD TRIALS.** L. HUGHES, A. KALALI, C. VANBELLE, E. CASCADE (*Quintiles, Inc*)

*Background:* As potential disease modification products move towards the final analysis stage of their development, in the mild-moderate patient population, there has been an increased focus of attention on utilising such products in the earlier stages of AD – at the prodromal AD (pAD) stage. This is driven by the potential effect that disease modifying products will have in decreasing (or preventing) the amyloid burden and thus slowing down the progression of AD. Towards this, the current challenge for clinical research is to be able to identify the earlier stage subjects who are suitable for trial participation, and to minimise the burden on the site by the high screen failure rate observed in such trials – which currently stands at some 80%. *Methods:* To utilize our Patient Communities and the broader digital patient universe to support protocol feasibility, patient recruitment. With respect to Alzheimer's disease, Mild Cognitive Impairment, and Prodromal Alzheimer's disease, we have conducted 15 programs over the past three years using digital outreach to screen potential subjects on-line regarding their self-reported cognitive symptoms. *Results:* pAD/MCI symptoms are prevalent in the community, but patients do not self-identify with these conditions. In the surveys conducted to date, no patients have ever self-reported a perception of having pAD and only 5% have reported a diagnosis of MCI. Only 30% of patients experiencing at least one symptom have visited a physician, suggesting a large available pool of community-based patients for a pAD/MCI study. Similar to AD patients, the potential for lumbar puncture and other procedures as well as the study time commitment are primary concerns in pAD/MCI patients. Across the pAD/MCI surveys conducted to date, about 40% of patients would not participate in a study requiring a lumbar puncture. This would have a significant effect on recruitment. Study time commitments, reimbursement for time and travel, and careful screening tools to accurately assess the subjects cognitive functioning are critical. *Conclusion:* Recruitment in AD trials has been challenging. With the more recent interest in pAD, innovation recruitment methods are needed. Digital outreach has been shown to be very useful for identifying potential subjects for pAD trials. 1. Quintiles, Inc.

**P7 - COGNITIVE IMPAIRMENT, DEMENTIA AND "GOOD PERFORMERS": PREVALENCE IN THE POPULATION STUDY "INVECE.AB".** A. GUAITA<sup>1</sup>, S. ABBONDANZA<sup>1</sup>, M. COLOMBO<sup>2</sup>, A. DAVIN<sup>1</sup>, G. FORLONI<sup>3</sup>, L. POLITO<sup>1</sup>, R. VACCARO<sup>1</sup>, E. VALLE<sup>1</sup>, S. VITALI<sup>2</sup>, V.V. FERRETTI<sup>4</sup>, S. VILLANI<sup>4</sup> (1. *GolgiCenci Foundation, Abbiategrasso (Milan), Italy*; 2. *Geriatric Institute "C. Golgi", Abbiategrasso (Milan), Italy*; 3. *Department of Neuroscience, Mario Negri Institute for Pharmacological Research, Milan, Italy*; 4. *Department of Health Sciences, Section of Medical Statistics and Epidemiology, University of Pavia, Pavia, Italy*)

*Background:* The prevalence of dementia in the elderly has been estimated by several Italian studies and ranging between 5.9-7.1% in

the over sixties (Ravaglia G et al, *Dement Geriatr Cogn Disord.* , 2002; 14:90-100; Spada RS et al, *J Neurol Sci.* 2009, 283:62-65). The choice of the different diagnostic tools as well as small samples size with few individuals by age categories biased the prevalence estimates and comparability among the studies. So it is important to investigate an homogeneous elder population to produce robust estimates of dementia. It is interesting to study people between 70 and 75 years old, because this is a crucial age of transition influencing the successful aging. To estimate the prevalence, incidence and progression of dementia and cognitive impairment and to investigate their determinants a two-phase InveCe.Ab study (Invecchiamento Cerebrale in Abbiategrasso = aging of the brain in Abbiategrasso), was planned. *Methods:* The InveCe.Ab study began with the phase I on November 2009 and involved all people (1644) living in Abbiategrasso and born between 1935 and 1939. Multidimensional assessment (medical, social and cognitive aspects) was made and a blood sample was collected from each participant. Precisely, the cognitive functions were assessed with an extended neuropsychological battery (MMSE, Clock Drawing Test, Trail Making Test A and B, Attentional Matrices, Tale of Babcock, Tests of 15 Rey's words, phonemic Verbal Fluency Test, Verbal Fluency Test for Categories, Test of Rey-Osterrieth Complex Figure, Test of Raven's Coloured Progressive Matrices, Geriatric Depression Scale 15 items). The presence of dementia was defined using the Italian version of the Diagnostic and Statistical Manual of mental disorders IV (DSM IV- TR) criteria, NINCS-ADRDA criteria for diagnosis of Alzheimer's disease, NINDS-AIREN criteria for the diagnosis of vascular dementia, Petersen's criteria for the diagnosis of mild cognitive impairment (MCI) and the "Third Canadian Consensus Conference" criteria for Cognitive Impairment No Dementia (CIND). It was also introduced the definition of "good performers" for subjects who have a score on MMSE corrected for age and education  $\geq 28.3$ , corresponding to the 75 th percentile of 1256 people with full test. The social aspects have been investigated by administering a questionnaire regarding the subject's everyday lifestyle. The blood samples were stored at  $-80^{\circ}\text{C}$ , for DNA isolation, plasma separation and lymphocytes extraction. ApoE genotype were determined for the whole population. On February 2012, the phase II of the study (follow-up) started and the same assessment was repeated. The InveCe.Ab was registered at the National Institutes of Health, USA (<http://clinicaltrials.gov/>, number: NCT01345110). *Results:* 1321 people attended the study (phase I): the mean age was 72.7 yrs ( $\pm 1.3$  yrs) and 54% women. The 93.9% of subjects was self-sufficient in all basic activities of daily living, and 90.8% was independent in handling money, using the telephone and managing medications. The prevalence of overall dementia was 3%, while that of Alzheimer's Disease was 1.1%, vascular dementia 1.5% and other types of dementia 0.4% (Parkinson - dementia, post traumatic dementia, alcoholic dementia). The prevalence of cognitive impairment was 7.8%, of which 5% are affected from "mild cognitive impairment" (MCI) and 2.8% from "cognitive impairment no dementia" (CIND). The prevalence of dementia in men overlapped that in women (3% versus 2.8%,  $p = 0.855$ ). The Alzheimer disease prevalence was higher in females than in males, however not significantly (1.6% versus 0.7%,  $p = 0.132$ ). The prevalence of vascular dementia and MCI + CIND was greater in men than in women (1.8% versus 1%,  $p = 0.192$  and 11.1% versus 5%,  $p < 0.001$ , respectively), although only in last case the difference was statistically relevant. Further on the subgroup without any kind of dementia or cognitive impairment (1007 people), 268 subjects were defined "good performers" (26.6%) with a significant differences between genders (29.2% in females versus 23.4% in males,  $p = 0.039$ ). ApoE 4+ were significantly more present in the persons with dementia. *Conclusion:* Our findings show a low prevalence of dementia and loss of autonomy in the people ranging 70-

75 yrs, but a high prevalence of MCI. Male gender shows more presence of vascular dementia and cognitive impairment, while female has more “good performers”. The results about dementia largely confirm the evidences of previous studies conducted in Europe and in Italy.

#### **P8 - THE PLACEBO GROUP SIMULATION APPROACH (PGSA): ITS VALIDITY WHEN APPLIED TO DATA FROM ALZHEIMER PATIENTS IN THE ADNI 1 DATABASE.**

R. SPIEGEL<sup>1</sup>, M. BERRES<sup>2</sup>, A.U. MONSCH<sup>1</sup> (1. University Hospital, Department of Geriatrics, Memory Clinic, Basel Switzerland; 2. University of Applied Sciences Koblenz, RheinAhr Campus, Remagen Germany)

As an alternative to conventional Phase 3 long-term randomized placebo-controlled double-blind clinical trials (RPCTs) our group has proposed a novel clinical study design, termed Placebo Group Simulation Approach (PGSA; Spiegel et al, *Alzheimers Res & Ther* 2011, Mar 21; 3 (2): 9). The PGSA uses mathematical modelling to forecast the outcomes of patients with prodromal AD from their own baseline data recorded at the outset of a clinical trial. These model-based forecasted outcomes are compared with the outcomes observed when patients are on a treatment being tested, and thus substitute for a real concomitant placebo group. Our claim is that PGSA trials are easier to perform, ethically more acceptable and more externally valid (more representative) than RPCTs. The original PGSA models were developed and tested using data from subjects with a diagnosis of MCI available in the ADNI 1 database. A crucial point to be addressed in the development of the PGSA concerns the possibility of generalizing its algorithms to other AD patient samples, as a prerequisite for their application in long-term clinical trials with experimental drugs intended for use in prodromal or symptomatic AD. *Objectives:* This analysis investigates whether the published PGSA algorithms, that were developed using data from the MCI population of the Alzheimer Disease Neuroimaging Initiative (ADNI 1), are supported by findings from a distinct, clinically more advanced subject sample also available from ADNI 1. The analysis focuses on an integrated measure of cognitive performance that is clinically relevant and has higher reliability and better metric properties than, e.g., “time to conversion” or “time to progression” to dementia. *Materials and methods:* Z values for the 9 subtest scores of the neuropsychological battery (NP-Batt) as used in ADNI 1 were calculated from the respective ADNI 1 normal aged subjects’ data. Results from visits at 6, 12 and 24 months were considered (there are no 18 month data in the ADNI 1 AD dataset). The longitudinal PGSA model (a linear mixed-effects model) for the averaged z-scores of the NP-Batt, as described in Spiegel et al (loc. cit.), was used. It was challenged by applying it to the data of the ADNI 1 AD patient sample (n=197) and by subsequent comparison between the model-based forecasted values and the observed values as recorded in the ADNI 1 database. *Results:* Comparison between the observed longitudinal and model-based forecasted data showed very high concordance with regard to mean values, medians, standard deviation and interquartile ranges at all time points. The respective values for z scores of the NP-Batt are: Observed vs. simulated means -2.05 vs. -2.08 (SD 0.87 vs. 0.89); observed vs. simulated medians -1.95 vs. -2.00 (1st quartile -2.66 vs. -2.65; 3rd quartile -1.40 vs. -1.45). More detailed results and graphs will be presented on the poster. *Discussion:* The AD dataset of ADNI 1 is smaller than the MCI dataset, and the patients are more advanced in the disease process. They show more cognitive decline, more deficits in daily activities and use more symptomatic anti-dementia medication. Despite these differences, there was a very high degree of concordance between the observed and the forecasted z scores on the NP-Batt, an integrated

measure of cognitive performance. This is an indication that the mathematical model established from the ADNI 1 MCI data is also valid for datasets from patients with dementia; that is, over a wide range of prodromal and symptomatic AD patients. In addition to the current analysis, we have applied some of the PGSA algorithms to a larger sample of aMCI subjects available from the NACC (National Alzheimer’s Coordinating Center) database in order to check whether our models are also valid outside of the (highly selected) ADNI datasets. A report on these analyses has been submitted for publication. *Conclusion:* The PGSA algorithms are used to produce a simulated, model-based concomitant placebo group from baseline data of the experimental group in a clinical trial, allowing subsequent comparison of observed treatment outcomes with forecasted outcomes in the simulated placebo group. PGSA models originally derived from ADNI 1 MCI data can predict both, cognitive endpoints and trajectories that correspond well with real observed values. The present analysis using data from patients with a diagnosis of AD support the validity of the published PGSA algorithms. It is proposed to use the PGSA mainly in advanced stages of clinical development of new drugs, i.e., at a point when extensive safety/tolerability data and first evidence of efficacy are available from Phase 1 and 2 RPCTs of usually shorter duration. What is needed now is the proof of the PGSA concept in a prospective study, i.e., a trial with prospective use of the PGSA models and the possibility of comparing forecasted with subsequently observed data.

#### **P9 - INTRA-INDIVIDUAL VARIABILITY (IIV) VS. TOTAL SCORES AS THE TARGET OUTCOME IN CLINICAL TRIALS.**

R.E. TRACTENBERG<sup>1,2</sup>, F. YUMOTO<sup>2,3</sup>, P.S. AISEN<sup>4</sup> (1. Departments of Neurology, Biostatistics, Bioinformatics & Biomathematics, and Psychiatry, Georgetown University Medical Center, Washington, D.C., USA; 2. Collaborative for Research on Outcomes and –Metrics, USA; 3. University of Maryland University College, College Park, MD, USA; 4. Department of Neurology, University of California, San Diego, La Jolla, CA, USA)

*Background:* Intra-individual variability (IIV) has been identified as complementing more global performance summaries (e.g., total scores on common assessments) and may improve prediction of global decline, functional decline, and incident dementia. It has been suggested that estimates of IIV provide a quantitative measure of neurobiological integrity in cognitive aging and neurodegenerative disease, as greater mean IIV levels have been reported in samples with mild cognitive impairment and mild dementia. We analyzed the data from two negative clinical trials for interventions in mild to moderate AD (MMSE between 14 and 26, inclusive) to explore whether IIV was associated with clinical changes in severity as identified by change in CDR global staging or CGIC. *Methods:* Data: Two 18 month-long multi-center randomized, double-blind, placebo-controlled trials were conducted on individuals with mild to moderate AD. Homocysteine (HC): 409 participants were randomly assigned (60% treated with high-dose supplements [5 mg/d of folate, 25 mg/d of vitamin B(6), 1 mg/d of vitamin B(12)] and 40% treated with placebo). ADAS and CDR Global rating were primary endpoints. Simvastatin (LL): 406 individuals were randomized: 204 to simvastatin (20 mg/day, for 6 weeks then 40 mg per day) and 202 to identical placebo. ADAS and CGIC were primary endpoints. *Outcomes:* We computed IIV for MMSE based on the individual’s standard deviation (ISD) of z-transformed MMSE subdomains that have been reported elsewhere and the ISD of all MMSE items; for the ADAS we used the ISD of both z-transformed and the untransformed values for subtests 1-7 and 9-12. We also analyzed the totals based on these subtests (abbreviated MMSE, ADAS) and the 30-point MMSE. *Analyses:* Areas under

Receiver Operant Characteristic (ROC) curves (AUC) and their 95% confidence intervals were estimated using SPSS v. 19.0 first for the treatment arms (to confirm that the treatment groups could be collapsed, as each clinical trial was negative). Only complete cases (i.e., having final visit scores) were analyzed. **Results:** HC: There were no significant differences in the predictive power for treatment of any outcomes at bl, m18 or changes in the HC study (all  $p > 0.26$ ). Overall, 163 completers had greater CDR severity after 18 months, 161 had unchanged CDR (10 improvers were excluded). The MMSE variability estimates were consistently weaker at predicting CDR change than the MMSE totals; in most cases they were not predictive of CDR change when MMSE totals were. Higher ADAS scores at baseline were associated with CDR change at 18 mos ( $p < 0.05$ ). Level of variability at baseline was NOT (both  $p \geq .19$ ). Higher ADAS scores and higher variability at 18 mos were both associated with CDR change at 18 mos, but the ADAS total had greater predictive power for CDR global change. Lower levels of 18 month change in both the total ADAS and ADAS variability were associated with CDR worsening (all  $p < 0.05$ ). LL: The MMSE variability estimates were consistently weaker at predicting worsening on CGIC than the MMSE totals; in most cases they were not predictive of CGIC worsening when MMSE totals were. Baseline ADAS values were compared for those with worsening CGIC (N=243) at 18 months and those with unchanged CGIC (N=50) (improvers, N=9, were excluded). Higher baseline total ADAS was associated with CGIC worsening,  $p < 0.05$  and this effect was more dramatic in the placebo than the treated group); variability at baseline was not ( $p > 0.70$ ). Higher M18 total ADAS and variability (both  $p < 0.001$ ) predicted CGIC worsening at 18 mos. Greater change in ADAS total and variability between baseline and M18 predicted no change in CGIC at 18 mos. **Conclusions:** IIV-based on ADAS, but not MMSE, was significantly associated with clinical worsening in two clinical cohorts, although the total score summaries for the ADAS and MMSE were more strongly predictive in both of these well-characterized clinical samples. These results are consistent with previous reports that estimating IIV using all items on MMSE and ADAS was not superior to using the total scores. This work shows that IIV is associated with clinically meaningful change for clinical trialists seeking to avoid a “points lost” outcome.

**P10 - REVIEW AND ANALYSIS OF RATER ERRORS ON THE NEUROPSYCHOLOGICAL TEST BATTERY (NTB) IN AN INTERNATIONAL ALZHEIMER'S DISEASE CLINICAL TRIAL.** L. KINGERY<sup>1</sup>, J. CROMER<sup>1,2</sup>, B. MERRY<sup>1</sup>, A. MINER<sup>1,2</sup>, J. JAEGER<sup>1</sup>, A. VEROFF<sup>1</sup>, P. MARUFF<sup>3</sup> (1. Cogstate, New Haven, CT, USA; 2. Hospital for Special Care, New Britain, CT, USA; 3. CogState, Melbourne, Victoria, Australia)

**Background:** Quality control of cognitive outcome data is necessary in Alzheimer's disease (AD) clinical trials as raters make errors that could put trial outcomes at risk. Trial data have shown that rating errors occur throughout the neuropsychological assessment process including failure to follow test administration procedures, inaccurate recording of responses, inaccurate rating or scoring responses, inaccurate calculation of sums of scores, and transcription errors in the transmission of data. Understanding the nature and impact of these errors is essential in planning training and rater monitoring and feedback programs during clinical trials. These issues become even more challenging when trials are conducted in multiple countries, as some tests of the Neuropsychological Test Battery (NTB) require language-specific skills to review the neuropsychological test results in an expert manner. The purpose of this research was to retrospectively review, assess, and summarize the nature and scope of rater errors on

the NTB in an international AD clinical trial. **Methods:** As part of a comprehensive rater training and central monitoring program, CogState reviewed a sample of NTB source documents in a 21-site AD clinical trial conducted in 4 countries (Canada, Peru, South Africa, and Poland). The standard NTB was used in this study, with subtests including the Wechsler Memory Scale-Revised Visual Paired Associates Test (VisPA; Immediate and Delayed Recall), Wechsler Memory Scale-Revised Verbal Paired Associates Test (VerPA; Immediate and Delayed Recall), Wechsler Memory Scale-Revised Digit Span, Rey Auditory Verbal Learning Test (RAVLT), Controlled Oral Word Association Test (COWAT), and Category Fluency Test (CFT). All test data were reviewed by an experienced psychometrist or clinical neuropsychologist; French, Spanish, Polish and Afrikaans reviews of the COWAT and CFT were conducted in conjunction with a translator. During the study, approximately 10% of the visits were selected pseudo-randomly, yielding 75 visits for review: 21 Screening visits, 18 Baseline visits, 12 Week 4 visits, 12 Week 8 visits, and 12 Week 12 visits. Rater errors were classified errors in administration, scoring, or recording. In addition, errors in data management were also evaluated (e.g., the correct number of responses written on the response form did not match the values entered into an electronic data capture system). **Results:** Results indicate that the prevalence and type of errors differ across NTB subtests, but that rater errors appear to be common. Of the 75 visits reviewed, there were 19 test administration errors, 35 recording errors, 47 scoring or calculation errors, and 24 transcription errors; 17% of the visits had at least 1 administration error, 34% had at least 1 recording error, and 45% had at least 1 scoring error. COWAT and Digit Span were the subtests with the most frequent errors for both scoring and recording. VisPA, VerPA, RAVLT, and CFT had fewer errors in each category. **Conclusion:** Our review and analyses indicate that rater errors are evident on the NTB and careful review of study subject data by experienced neuropsychologists and psychometricians can help capture and intervene when rater errors are discovered. Many of the errors may have had limited impact on the study data (e.g., a score difference of 1 point on COWAT). However, other errors detected can have a more substantial impact on subject selection and on the outcome data. For example, failure to discontinue the VisPA or VerPA during immediate recall after the criterion was met for discontinuation exposes the subject to additional learning trials invalidating delayed recall. Based on these data it appears the NTB subtests are not equally prone to error by raters such that errors are more common in the COWAT and Digit Span subtests than other NTB subtests. Implications for rater training and monitoring programs are discussed.

**P11 - INROADS: INTERNATIONAL REGISTRY OF ALZHEIMER'S DISEASE PATIENTS.** R.A. STERN<sup>1</sup>, P.N. TARIOT<sup>2</sup>, H.M. ARRIGHI<sup>3</sup>, L.A. LACEY<sup>4</sup>, G.A. RIPON<sup>5</sup>, V. MENON<sup>6</sup>, M.T. ROPACKI<sup>6</sup> (1. Boston University, Boston, MA; 2. Banner Alzheimer's Institute, Phoenix, AZ; 3. Janssen Alzheimer Immunotherapy Research & Development, LLC, South San Francisco, CA, USA; 4. Janssen Alzheimer Immunotherapy, Dublin, Ireland; 5. Pfizer Inc, Collegetown, PA; 6. Outcome Sciences, Cambridge, MA)

**Background:** Registries of AD patients, including Consortium to Establish a Registry for AD (CEAD), AD Neuroimaging Initiative (ADNI, ADNI-2), and Australian Imaging Biomarkers and Lifestyle study (AIBL), are aimed to standardize instruments used in diagnosis, elucidate disease pathogenesis, and develop diagnostic and prognostic biomarkers. However, these existing registries are limited in terms of: restrictive inclusion/exclusion criteria similar to clinical trials; small samples; short duration; and/or were completed over a decade ago

(i.e., CERAD 1988-1997). An unmet need remains to fully understand prognostic factors, disease course, disease burden, and patterns of care in 'real world' current day practice. The goal of the planned International Registry Of Alzheimer's Disease patientS (INROADS) is to address knowledge gaps in AD, including natural history of disease, rates and characteristics of co-morbidities, time to therapy initiation, factors influencing choice of treatments, and impact of therapy. **Methods:** As designed, INROADS is planned to enroll up to 6,000 patients with clinically diagnosed mild to moderate AD across approximately 500 sites initially in the US, Canada, and Europe. Patients will be followed every 6 months for at least four years. Pilot phase patient recruitment is ongoing in 2012 and the study is currently planned to end in approximately 2018. INROADS utilizes standardized and validated measurements capturing data on AD patient progression, cognition, mood, behavior, dependence, functional impairment, caregiver burden and resource utilization. The specific measures include the MMSE (Mini-Mental State Examination), RBANS (Repeatable Battery Assessment of Neuropsychological Status), GDS (Geriatric Depression Scale), NPI-Q (NeuroPsychiatric Inventory Questionnaire), DS (Dependence Scale), DAD (Disability Assessment in Dementia), ZBI (Zarit Burden Interview) and the RUD-Lite (Resource Utilization in Dementia- Lite version 2.4). **Results:** Patient population, inclusion/exclusion criteria, demographics, Alzheimer's disease history, standardized measures, comorbidities and adverse events data collection procedures will be described and presented, as will baseline data-to-date. **Conclusion:** INROADS is planned to be a large, comprehensive, real world, prospective, international, multicenter, observational AD registry, capturing data on AD patient progression, cognition, mood, behavior, dependence, functional impairment, comorbidities and resource utilization, including AD medications and caregiver burden. Patient recruitment is ongoing. Study methodology and preliminary baseline demographics will be presented.

**P12 - NEUROPSYCHIATRIC SYNDROMES IN MILD VERSUS MODERATE AD: FACTOR ANALYSIS FROM A CLINICAL TRIAL POPULATION.** C. LYKETSOS<sup>1</sup>, S. ABUSHAKRA<sup>2</sup>, G. CRANS<sup>2</sup>, C. HERNANDEZ<sup>2</sup>, S. ANDRIEU<sup>3</sup>, B. VELLAS<sup>3</sup> (1. Johns Hopkins University, Baltimore, MD, USA; 2. Elan Pharmaceuticals, Inc., South San Francisco, CA, USA; 3. University of Toulouse, Toulouse, France)

**Introduction:** Neuropsychiatric symptoms (NPS) are highly prevalent in AD dementia and are frequently associated with patient distress and increased morbidity. Of these NPS, agitation and/or aggression are a leading cause of institutionalization in patients with dementia. Effective and safe treatments for NPS, including agitation/aggression, remain elusive, and are thus important targets for drug development. The prevalence and profile of NPS evolve with increasing disease severity. NPS occur in specific clusters suggesting syndromes that may have distinct underlying pathobiology. A better characterization of neuropsychiatric syndromes at various stages of AD is necessary for optimal design of treatment trials. Consistent NPS clusters have been reported across various AD populations and clinical settings. However, few studies have compared NPS clusters in Mild versus Moderate AD populations. **Objective:** To describe and compare the clusters of NPS in patients with Mild versus Moderate AD enrolled in an interventional clinical trial that included stratification by ApoE4 carrier status and use of symptomatic AD drugs. **Methods:** Baseline data from a placebo-controlled Phase 2 study of ELND005 (Scyllo-inositol) in 353 patients with Mild/Moderate AD (S. Salloway et al. 2011) were used for analysis. The MMSE range was 16-26, with Mild defined as 22-26 and Moderate as 16-21 inclusive. Randomization was

stratified by ApoE4 carrier status (carrier or non-carrier) and use of symptomatic AD medications. The 12-item NPI, which includes one sub-item for agitation and aggression, was a secondary outcome. Baseline NPI ratings were available from 348 patients (Mild N= 178, Moderate N= 170). The Mild and Moderate groups were comparable in demographics (Salloway et al., 2011), proportion of ApoE4 carriers (Mild ~68%, Moderate ~59%), proportion using AD medications (~90%), and proportion on baseline psychotropic medications (Mild ~47%, Moderate ~39%). The baseline NPI total and NPI-agitation scores were also similar between the Mild (NPI-t = 8.99, NPI-agit = 0.71) and Moderate (NPI-t =10.64, NPI-agit =0.81) groups. A factor analysis was performed using Varimax rotation. Two methods were used for sensitivity analyses. **Results:** In the overall population, the factor analysis yielded 3 main factors that were distinct in the Mild and Moderate groups. In the overall population, the 3 factors consisted of the following: Factor 1. Agitation/aggression, depression, anxiety, apathy, as well as nighttime behavior and appetite changes; Factor 2. hallucinations and delusions; and Factor 3. disinhibition and elation. In the Mild group, the factors consisted of the following: Factor 1: Agitation/aggression, irritability, delusions as well as nighttime behavior and appetite changes; Factor 2: Depression and apathy; and Factor 3: Elation and aberrant motor behavior. In the Moderate group, the factors consisted of: Factor 1: Agitation/aggression, depression, anxiety, apathy; Factor 2: Delusions, hallucinations and elation; and Factor 3: Disinhibition. The above results were consistent using 2 other factor analysis rotation methods (Quartimax and Parsimax). **Conclusion:** These results, in agreement with prior studies (J. Garre-Olmo et al., 2010, P. Aalten et al. 2008), support the existence of 3 main clusters that have features of three syndromes: Affective, psychotic, and behavioral or hyperactivity. In Mild AD, depression and apathy comprised the core affective cluster; while agitation/aggression was associated with delusions and irritability in the psychotic cluster. In Moderate AD, the affective cluster included agitation/aggression and anxiety in addition to the core of depression and apathy; while the psychotic cluster included delusions, hallucinations, and elation. The association of agitation/aggression with distinct syndromes in Mild versus Moderate disease suggests that the underlying pathology may be affecting potentially distinct neuronal networks. These results also suggest that as the disease advances from Mild to Moderate stage, the affective cluster worsens and includes agitation/aggression. Moderate AD may be the optimal population for conducting clinical trials targeting the treatment of agitation/aggression, as part of an affective syndrome. In designing these trials, consideration should be given to the occurrence of agitation/aggression on a background of depression, and the frequent use of concomitant antidepressants medications.

## CLINICAL TRIALS ASSESSMENT TOOLS

**P13 - PATIENT AND CARER VIEWS ON CLINICAL TRIALS USING IMMUNOTHERAPY FOR PRODRIMAL ALZHEIMER'S DISEASE.** V. LAWRENCE<sup>1</sup>, J. PICKETT<sup>2</sup>, J. MURRAY<sup>1</sup> (1. Institute of Psychiatry, King's College London, UK; 2. Alzheimer's Society, London, UK)

**Backgrounds:** There is great interest in conducting clinical trials of disease-modifying therapies in the prodromal stages of Alzheimer's Disease. For potential participants, deciding whether to take part is a complex process in which risks must be balanced against uncertain benefits and there is scant research on the views of this population to the desirability of such trials. We conducted a series of focus groups with people with Mild Cognitive Impairment (MCI) and their carers to

discuss their views in participating in clinical trial of an immunotherapy treatment, for which the risk to benefit profile is complex. *Methods:* Data was collected through three focus groups in east London, UK (13 patients with mild memory problems, 6 carers) conducted during December 2011. Recruitment was conducted through an Alzheimer's Society run peer support for people with mild memory complaints, referred via a local NHS memory service. Discussions were modelled around a hypothetical trial of an immunotherapy for people with mild memory problems, based on published and unpublished trial protocols. Focus groups were transcribed and analysed thematically using qualitative methods. Ethical approval for this study was obtained. *Results:* There was a great deal of uncertainty shared by people with memory problems concerning the underlying cause of their condition. Participants expressed a wish for a clear diagnosis and the 'screening' stage was identified as one of the primary benefits of participating in the trial. Few participants expressed concern about being labelled with "dementia". Participants varied according to the emphasis that they placed on the negative impact of their memory problems; many expressed fear of further cognitive decline and displayed a strong interest in participating in a clinical trial. Conversely, others were often suffering from co-existing physical complaints and feared that participating in a clinical trial might "upset the balance" in managing their medication, physical health, and cognitive impairment. Considering the risks of participating in a trial, few appeared worried about the side effects that had been reported in previous studies. A common view was that all medications have associated side effects. Certain tests and procedures involved in the trial, particularly the lumbar puncture and MRI scan, provoked anxiety across the groups. However, whether the study demands were construed as off-putting or tolerable seemed in part to reflect how concerned participants were about their cognitive or their physical condition. In comparison, receiving a placebo was considered to be a highly undesirable outcome and a risk to participation for all. There appeared to be a widespread assumption that receiving the study drug would be beneficial. The majority accepted that the intervention did not promise to improve their cognitive stage; there was a consensus that limiting further cognitive deterioration would be benefit enough. Potential benefits to society were recognised, but this was not in itself considered an adequate reason to take part in a clinical trial. Individuals were clear that the decision to participate had to be the right one for them. Participants described a step-wise approach to the decision making process: first, participants sought more information on issues that caused them anxiety; this as often around practicalities of the clinical trial, role of the study partner, and the randomisation process. Next, they would undertake the 'screening' to gain a better indication of the underlying cause of memory problems; then, they would evaluate whether they wish to be involved in a trial. This was seen as a joint decision that would often be made within the family, acknowledging the perceived burden and "inconvenience" to family members that participating in a clinical trial may cause. *Conclusions:* Despite the complexities involved, people with mild memory problems have a clear idea about whether they would like to participate in a clinical trial of this sort. We conclude that people with recognised memory problems are generally highly motivated to find out more about the underlying cause of their memory problem, regardless of their desire to participate in a clinical trial. The patients' perception of risks from participating in a clinical trial of immunotherapy may be different to that of clinician and regulators. Patients and carers expressed minimal concern regarding the risk of adverse events associated with immunotherapy, whereas there was greater anxiety on practical demands of participating in a trial, some of the tests and procedures proposed in the trial protocol and the randomisation process. These

findings have implications for the preparation of information for potential participants in clinical trials. Overall, this study highlights that the views and preferences of people with memory problems and their relatives can be used positively to inform the ethical debate around the disclosure of biomarker status to individuals with memory complaints as in the design of clinical trials and the content of trial information for this population. Funding: This research was funded by Roche Products Ltd by a grant to Alzheimer's Society. Alzheimer's Society made a grant to King's College London. Roche Products Ltd initiated this research, and provided unpublished information regarding risks and trial protocols, but took no further part in the delivery or analysis of data.

**P14 - CAN SCREEN TO BASELINE MMSE VARIABILITY IN AD CLINICAL TRIALS AFFECT PRIMARY OUTCOME MEASUREMENT?** D.S. MILLER<sup>1</sup>, Y. XU<sup>1</sup>, P. SAMUELSON<sup>1</sup>, D. HENLEY<sup>2</sup>, G. SETHURAMAN<sup>2</sup>, K. SUNDELL<sup>2</sup> (1. Bracket, Wayne, PA, USA; 2. Eli Lilly & Co., Indianapolis, IN, USA)

*Backgrounds:* In Alzheimer's disease (AD) clinical trials, where other potential causes of a subject's cognitive impairment must be ruled out, it is paramount that only subjects who meet the defined inclusion/exclusion and specified severity criteria be enrolled. Frequently, the Mini-Mental State Exam (MMSE), a brief cognitive assessment with a total score of 30 points, is used to determine the severity level, and may even be used to further stratify subjects within a trial. The MMSE entry criteria are often established only at the screening visit. Prior research has shown that 7% of subjects in 4 separate, but methodologically similar, multi-national AD clinical trials had MMSE score changes from Screen to Baseline visits that would have excluded them from the trial, should they have been required to meet MMSE criteria at Baseline as well. In those studies, raters whose experience with the scales fell below a predetermined level received additional Enriched training. This curriculum has previously been shown to enable these raters to both certify to participate, and perform comparably to their more experienced colleagues regarding the need for remediation in-study. Additionally, an endpoint reliability program was implemented to ensure that raters were adhering to scale administration and study conventions at select visits. When errors were detected by calibrated Clinicians, the raters in question were remediated and the scoring was corrected. Such a program has been shown to significantly decrease the error rate on subsequent assessments. Objectives: 1) To see if the degree of MMSE changes from Screen to Baseline influenced the ability to separate response to drug versus placebo. 2) To see how raters who received Enriched training performed compared to their more experienced colleagues with regard to separating drug from placebo. Methods: Data from 582 subjects in 2 of the AD trials was available for analysis. MMSE scores at both Screen (when inclusion criteria were established) and Baseline visits were assessed for the degree of change, and whether the degree of change influenced separation between study drug (at both doses) and placebo at week 52. This program employed an endpoint reliability program to assess the quality of the ongoing ratings. The 52 week time point was selected in an attempt to increase quality of scale administration prior to endpoint. One component of this program was to assess raters' adherence to MMSE administration and scoring conventions at the Screening (but not Baseline) visit. An additional component involved assessing the quality of the ADAS-Cog (a co-primary outcome measure) administrations at Baseline and 52 weeks. Results: 468 (80.4%) subjects changed <2 points on the MMSE from Screen to Baseline (including 180 (31.25%) whose score did not change), while 114 (19.6%) changed 3 or more points. The distribution of score changes

that showed improvement on the MMSE from Screen to Baseline was similar to that that showed worsening. This is consistent with what we previously demonstrated in the combined analysis of the 2 separate, but methodologically similar, multi-national AD programs. The degree of MMSE score change from Screen to Baseline significantly correlated with a rater's ability to detect a difference on the ADAS-Cog (a co-primary) between patients on drug compared to those on placebo. When we compared patients who changed <3 points on the MMSE from Screen to Baseline visits with those who changed > 3, only those who changed <3 points separated from placebo at 52 weeks ( $p=0.019$  for ADAS-Cog11,  $p=0.043$  for ADAS-Cog14, compared by LS Mean from mixed model). We further compared raters who went thru the additional Enriched training curriculum with those who did not regarding their performance in-study. At 52 weeks, the ADAS-Cog ratings from both of the groups of raters were comparable. While neither group separated drug from placebo at that point, there was a trend toward subjects doing worse on the ADAS-Cog when on drug versus placebo. **Conclusion:** This analysis raises the possibility of needing to limit the degree of permissible score swings on the MMSE between the Screen and Baseline visits. 19.6% of study subjects had a score swing of 3 or more points on the MMSE in less than the month between Screen and Baseline visits. Previous published estimates of annual change on the MMSE range between -2.4 and -3.8 points, respectively. In this analysis, it is unlikely that the practice effect alone could have accounted for the score swings, as subjects were as likely to show an improvement of 3 or more points as they were to show worsening. Other possible explanations include a change in the subject's medical status and/or medications. Both of these needs to be addressed by the investigator when they become aware of such a significant score swing over a relatively short interval. Additionally, the combined use of an Enriched training program and endpoint reliability program should be considered in an effort to enhance data quality.

**P15 - ADAS-COG IS AN EFFECTIVE TOOL FOR COGNITIVE RESEARCH IN SOUTHEAST ASIA.** N. KANDIAH, I. CHEW, S. HUANG, A. NG (*Department of Neurology, National Neuroscience Institute, Singapore*)

**Background:** Cognitive research requires cognitive evaluation both at the cross sectional phase and longitudinal follow-up. While there are numerous cognitive evaluation tools available, the choice of an appropriate tool assumes greater importance when the research involves populations with multiple races, languages and cultural backgrounds. **Objectives:** 1) To study the effectiveness of the ADAS-Cog in distinguishing patients with mild cognitive impairment and mild Alzheimer's disease from normal controls in a multiracial Southeast population. 2) To study the effectiveness of the ADAS-Cog in tracking longitudinal change in cognitive status. **Methods:** For objective 1, data on subjects from 2 ongoing research studies at the National Neuroscience Institute, Singapore, who have been administered the ADAS-Cog were recruited. Mild cognitive impairment (MCI) was diagnosed based on the Peterson's criteria and Alzheimer's disease (AD) was diagnosed based on the NINCDS-ADRDA criteria. Only AD patients with a CDR of 1 were included in this study. For objective 2, data from an ongoing longitudinal study among patients with Parkinson's disease was analyzed. MCI in PD (PD-MCI) and dementia in PD (PDD) was diagnosed using the Movement Disorder Society (MDS) Consensus criteria. In addition to ADAS-Cog, all research subjects were administered the Montreal Cognitive Evaluation tool and underwent neuropsychological evaluation. 2 raters blinded to the clinical information administered the ADAS-Cog for all the subjects in the above studies. **Results:** In the

cross sectional study, data on 207 subjects were analyzed. The mean age was 64.1 years. There were Chinese, Malay and Indian subjects reflective of a Southeast Asian population. Age, education and ADAS-Cog scores were significantly different across the 3 clinical groups. The mean ADAS-Cog in the healthy control (HC) group, MCI and mild AD were 4.24 (SD 2.64), 7.50 (SD 4.40) and 20.7 (8.38) respectively. Linear regression revealed that age ( $p<0.001$ ) and education ( $p<0.001$ ) were independently associated with ADAS-Cog scores. ROC analyses indicated that there was a clear break point in years of education that was associated with ADAS-Cog scores, but no such clear break point was available for age. A score correction for an education cut-off of 11 years provided the best sensitivity and specificity. Repeat ROC analyses after correction for education demonstrated that a ADAS-Cog cut-off score of >11 when education is below 11 years and a ADAS-Cog cut-off score of > 13 when education was 11 or more years provided a sensitivity of 94% for the diagnosis of mild AD. For the diagnosis of MCI, an ADAS-Cog score of >8 provided a sensitivity of 93% irrespective of education status. In the longitudinal study, 100 PD patients with a mean Hoehn & Yahr score of 1.9 and mean age of 65.1 years were studied. 28 patients satisfied the MDS criteria for MCI. The mean ADAS-Cog score for the PD-MCI group was 9.79 (SD 3.51) and the PD patients with normal cognition (PD-NCI) had an ADAS-Cog score of 6.6 (SD 4.2). Over a period of 1 year follow-up, the mean change in ADAS-Cog score among patients who retained the diagnosis of PD-NCI at both visits was +0.4 (SD 0.3). PD-NCI patients who progressed to PD-MCI had a change score of +4.17 (SD 2.2) and PD-MCI patients who progressed to PDD had an ADAS-Cog change score of +5.5 (SD 2.1). Data on subsequent follow-up visits will be further analyzed. **Conclusions:** In a multiracial Southeast Asian population, the ADAS-Cog is a sensitive tool in cross-sectional studies for the diagnosis of MCI and mild AD, and in longitudinal studies, it demonstrates adequate sensitivity in tracking cognitive decline.

**P16 - NATIONAL INSTITUTIONAL REVIEW BOARD FOR NEURODEGENERATIVE DISEASES (NIRB-ND) FOR THE UNITED STATES.** A.S. KHACHATURIAN<sup>1</sup>, P.J. SNYDER<sup>2</sup>, M. CARRILLO<sup>3</sup>, D.S. KNOPMAN<sup>4</sup> (1. *The Campaign to Prevent Alzheimer's Disease by 2020 (PAD2020), Rockville, Maryland, USA;* 2. *Lifespan Hospitals & Alpert Medical School of Brown University, Providence, Rhode Island, USA;* 3. *The Alzheimer's Association, Chicago Illinois, USA;* 4. *The Mayo Clinic & Alzheimer's Disease Cooperative Study, Rochester, Minnesota, USA*)

**Introduction:** Since the mid-twentieth century, international governments have instituted robust systems to provide the safety of human participants in clinical research. One important regulatory approach to assure protection has been the development of the institutional review board (IRB). In the United States (US), although local community representation has been a key feature of IRB reviews for clinical research, new and more complex study designs, often involving multiple research sites and extending over large geographical distances are complicating the review process. The problems associated with multisite IRB reviews are particularly relevant for neurodegenerative disease research. A key consensus recommendation recently released by the NIH Alzheimer's Disease Summit to overcome this hurdle in the United States is the launch of a National Institutional Review Board for Neurodegenerative Diseases (NIRB-ND). The purpose of this new ethical oversight panel would be to enhance patient/volunteer safety, to increase the efficiency in the conduct of large-scale multi-site trials and to serve as an international model for global prevention studies. This abstract describes the ongoing development of the NIRB-ND. The enterprise will provide centralized IRB services to support of all phases of clinical drug,

device, and biologics development for multi-center studies. The NIRB-ND will initially accept protocols for studies of Alzheimer's disease, dementia, and related disorders effecting memory, movement and mood as early as late 2012. *Method:* The NIRB-ND will build upon on the experiences of the National Cancer Institute and the NeuroNEXT central IRBs for prevention trials of neurodegenerative diseases. The NIRB-ND will provide support to study sponsors, participating research institutions, principal investigators, and co-investigators and project staff. Initially, the enterprise will provide advisory reviews of research protocols and studies as related to human subjects' protection. By year four, the NIRB-ND will provide fully independent reviews and will serve as the IRB-of-record. The delivery of the service will be through the administration of a contract to be established during the start-up phase of the business development. The contract development will focus on using the resources of Rhode Island Hospital an 800-bed medical center that serves as the principal teaching affiliate institution of the Alpert Medical School of Brown University. Rhode Island Hospital (RIH) is already home to two separate IRBs that each has full accreditation from the Association for the Accreditation of Human Research Protections Programs (AAHRPP) – the most widely regarded accrediting body for IRBs in the United States. *Results:* As of December 1, 2011, using data from clinicaltrials.gov, there were nearly 2,750 open studies, Phase I-IV, on disease indications affecting memory, movement and mood in the US. This includes 330 studies on Alzheimer's disease and dementia, 173 on cognition (exclusive of dementia and Alzheimer's disease), and 204 on memory (exclusive of dementia, Alzheimer's disease and cognition). In total, there are approximately 1,151 ongoing studies investigating indications associated with major neurodegenerative diseases. Since 2006, approximately 9,200 patient volunteers across 896 study locations have been planned for possible enrollment for phase III, industry-based, clinical trials indicated for the treatment of Alzheimer's disease and dementia. There are no major national or centralized IRBs providing services for this research area. *Conclusion:* The NIRB-ND will initially accept protocols for studies of Alzheimer's disease, dementia, and related disorders effecting memory and cognition. The phase of development will focus on disorder affecting movement such as Parkinson's disease, ALS, and Huntington's disease. The last phase of development will be on disorders affecting mood and other neuropsychiatric and neurological disorders. The project team will also evaluate the possibility of using the facilitated review model in an international context with partnerships starting with Canadian ADCS member sites. With the exception of the NCI the Veterans' Administration, no commercial or non-profit IRBs have envisioned consolidating their services through a centralized approach in the neuroscience domain. NINDS has launched a centralized IRB to be run under contract by Massachusetts General Hospital, but with the limited scope supporting the cooperative group called Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT). The design of the NIRB-ND relies substantially on the experiences of the US National Cancer Institute, and the creation and management of their central IRB over the past decade. After a 12-month start-up phase, the NIRB will be fully operational. Protocols for studies of Alzheimer's disease, dementia, Parkinson's disease, ALS, and Huntington's disease will be considered. Future development will focus on disorders affecting mood and other neuropsychiatric and neurological disorders. Within three years, the NIRB-ND will submit an initial application for accreditation by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). The project will also evaluate the possibility of using the facilitated review model in an international context with partnerships starting with Canadian ADCS member sites and other international sites.

**P17 - ASSESSMENT OF CONSENT ABILITY IN ALZHEIMER'S DISEASE DURING RESEARCH: A PILOT STUDY OF A FRENCH QUESTIONNAIRE.** N. PHILIPPI<sup>1</sup>, C. CHAULET-DALARD<sup>2</sup>, I. MIGEON-DUBALLET<sup>3</sup>, B. JUNG<sup>1</sup>, O. USPENSKAYA<sup>4</sup>, H. MOLLION<sup>5</sup>, K. BENNYNS<sup>2</sup>, L. TOUATI<sup>2</sup>, A. GABELLE-DELOUSTAL<sup>2</sup>, J. TOUCHON<sup>2,7</sup>, B. CRETIN<sup>1</sup>, M. PACCALIN<sup>3</sup>, C. MARTIN-HUNYADI<sup>1</sup>, F. BLANC<sup>1</sup>, J.-C. WEBER<sup>1</sup> (1. Strasbourg University Hospital, France; 2. Montpellier University Hospital, France; 3. Poitiers University Hospital, France; 4. IM2A, Pitié-Salpêtrière University Hospital, Paris, France; 5. Lyon University Hospital, France; 6. IRIST – EA 3424, Strasbourg University, France; 7. INSERM U1061, Montpellier, France)

*Background:* Although clinical research is needed in Alzheimer's disease (AD), it raises specific ethical issues around the patients' capacity to consent due to their cognitive impairment. To give informed consent, patients are required to understand the information provided during enrollment into a trial, to decide for themselves and to express their consent. To date, no tool exists to help the clinician evaluating the patients' ability to give consent in France. The present work is a pilot study which aimed at evaluating a questionnaire designed to assess the ability to give consent in patients with AD and to analyze the determiners of the patients' decision-making. *Methods:* This is a French multi-centric study, for which we developed a questionnaire with three parts: one dedicated to the patient, one to one of their relatives, and one to the investigator. It consisted of closed questions, most of them assessing the ability of the patients to understand the critical points of the trial, as compared to healthy controls, i.e. their relatives, while controlling the information given by the investigator. We also evaluated their feeling about their decision-making ability and the aspects which we expected to be crucial for consent, such as anosognosia, the attitude of the three groups of participants toward the validity of the consent for the future, and the judgment of the investigator about the patient's capacity to consent for themselves. Twelve different investigators took part into the study and included 39 AD patients with prodromal, mild or moderate stages of the disease, as well as 24 of their relatives (healthy controls), during both therapeutic and non-therapeutic trials. To compare the patients' responses to that of the controls', we studied associations between some responses of interest within and between the different groups of participants. We also tested correlations between the age, the educational level and the score on the MMSE. Finally, we built ROC curves of the scores obtained with our questionnaire and those obtained with the MMSE as compared to the investigator's judgment on the patient's capacity to consent. *Results:* We showed (i) that the feeling of the patients in their own decision-making around accepting to be enrolled in a trial was not concordant with neither with the judgment of the investigator nor with their relative's opinion ('surrogate consent'). (ii) Most of the participants considered that a consent given at the time of enrollment could be considered as valid for the future. (iii) Controls' understanding of the information was better than the patients' understanding only during therapeutic trials. (iv) The patients understanding score was correlated to the educational level ( $p=.05$ ) but not to the score on the MMSE ( $p=.49$ ). (v) Contrary to the score on the MMSE, our questionnaire appears to be both sensitive and specific to evaluate the consent capacity as compared to the judgment of the investigators involved in the study. *Conclusion:* This preliminary study (i and ii) would favor 'anticipated directives' rather than a 'surrogate consent'. (iii) The information delivered during therapeutic trials appears to be more complex for the patients to understand in comparison to both their relatives' understanding and to the information delivered during non therapeutic trials, unless their

relative disclose a better understanding because they are more careful during a therapeutic trial, regarding the stakes of testing a new drug. (iv) The educational level, rather than the MMSE score, is crucial for understanding the information, which should encourage the adaptation of the information given during trials to, in particular, the patients' educational level. (v) Even though this questionnaire should be further evaluated with a larger sample, it could be a useful evaluative tool in the enrolment of AD patients into clinical research.

**P18 - THE MEMORY AND ATTENTION TEST (MAT): A COMPUTER-BASED TEST FOR STUDIES IN DEMENTIA.** G. ADLER<sup>1</sup>, M. BEKTASN<sup>1</sup>, N. BAUMGART<sup>2</sup>, Y. LEMBACH<sup>1</sup> (1. Institut fuer Studien zur Psychischen Gesundheit (ISPG), Mannheim, Germany; 2. Dynamikos GmbH, Mannheim, Germany)

The Memory and Attention Test (MAT), a computer-based performance test, was evaluated in a group of patients with mild-to-moderate Alzheimer's dementia (AD) and an age-, sex- and education-matched control group at ages between 60 and 85 years. By means of the MAT, selective attention as well as working and short-term memory for verbal, figural and episodic material are assessed. For evaluation purposes, the findings in MAT subtests were compared to the findings in well established reference methods for the different domains, as the Auditory Verbal Learning Test (AVLT), immediate and delayed reproduction of the Taylor figure and the subtests "working memory" and "logical memory" of the Wechsler Memory Scale (WMS). Acceptance for the MAT was assessed by means of questionnaire. Computerized testing was accepted surprisingly well by the subjects. There were highly significant positive correlations between performance in the MAT subtests and performance in the respective reference assessments. Discrimination of patient and control groups was very good, particularly for the episodic short-term memory subtest. Thus, the MAT may be useful diagnostic tool for the assessment of dementia patients. It may be applied for early diagnosis, assessment of progression of disease and demonstration of treatment effects, particularly for disease-modifying treatments in AD. The test is standardized for age, sex and education. The development of versions in various languages is under way.

**P19 - ESTABLISHING THRESHOLD SCORES AND PROFILES OF COGNITIVE IMPAIRMENT FOR THE ALZHEIMER'S DISEASE ASSESSMENT SCALE (ADAS-COG) FOR PATIENTS WITH PROBABLE MILD COGNITIVE IMPAIRMENT (MCI).** C. YAVORSKY<sup>1,2</sup>, G. DICLEMENTE<sup>1</sup>, M. OPLER<sup>2</sup>, A. KHAN<sup>2,3</sup>, S. JOVIC<sup>2</sup>, B. ROTHMAN<sup>2</sup> (1. CROnos CCS, Hamilton, NJ; 2. ProPhase LLC, New York, NY USA; 3. Nathan S. Kline Institute for Psychiatric Research)

**Background:** Despite its utility, the Mini-Mental State Examination (MMSE) has proven to be relatively insensitive to conditions associated with frontal-executive and subcortical dysfunction, and to milder forms of cognitive impairment. The Alzheimer's Disease Assessment Scale (ADAS-Cog) is both convenient for screening of probable AD and as a measure of cognitive functioning during drug intervention. **Goal:** The aim of the present study was to assess the ADAS-Cog's ability as a cognitive screening tool through examination of standard threshold scores, for patients with higher dementia (MMSE < 12; n = 92), AD (MMSE 13 to 25; n = 2263) or probable MCI (MMSE ≥ 26; n = 422), and to assess cognitive symptom profiles among groups. **Methods:** AD data was obtained from the Critical Path Institute Online Data Repository (CODR). The diagnostic accuracy of the ADAS-Cog for clinical screening of Higher Dementia, AD and probable MCI, was assessed

through receiver operating characteristics (ROC) curve analysis. For the predictive value of the ADAS-Cog, for each cut-off point, sensitivity and specificity were computed. An exploratory factor analysis using promax rotation was also carried out on the ADAS-Cog, to assess factor structures. **Results:** The discriminant potential of the ADAS-Cog for AD was excellent, with an AUC of 0.906 [95% confidence interval (CI), 0.801-0.918], and that for Higher Dementia was high, with an AUC of 0.884 (95% CI, 0.745-0.907). The discriminant potential for MCI was moderate with 0.756 (75%CI, 0.705-0.843) possibly indicating different classification accuracies of the ADAS-Cog for milder cognitive impairment. The optimal cut-off point for maximum accuracy and the respective values of sensitivity, specificity, PPV, NPV, and classification accuracy was < 87 for Higher Dementia, < 79 for AD and < 51 for probable MCI. The three groups displayed different factor loadings that could also help discriminate severity alongside total score. **Conclusion:** The ADAS-Cog is valuable for early detection of the illness and staging. ADAS-Cog plays an important role in the diagnostic makeup of AD. The cognitive profile in Higher Dementia and probable MCI groups differs significantly from that in AD. Performance on tests of Language performance and praxis attitudes are best in differentiating the groups.

**P21 - ADAS-EXEC: A COGNITIVE COMPOSITE DERIVED FROM THE ADAS-COG AND NTBA.** J. HARRISON<sup>1,2</sup>, J. ALTMAN<sup>3</sup>, G. KEMPLER<sup>4</sup>, D. ANGUS<sup>4</sup>, C. HERD<sup>4</sup>, S. TARGUM<sup>5</sup>, J. CUMMINGS<sup>6</sup>, C. RITCHIE<sup>2</sup> (1. Metis Cognition Ltd., Kilmington Common, UK; 2. Imperial College, London, UK; 3. Freelance Statistician, Redhill, UK; 4. Prana Biotechnology Ltd., Melbourne, Australia; 5. Clintara Inc, Boston, US; 6. Cleveland Clinic's Lou Ruvo Center for Brain Health, Las Vegas, Nevada)

**Background:** A number of deficiencies with the traditional measures of cognitive efficacy employed in clinical drug trials have been identified. The ADAS-cog, the most commonly employed test, is prone to ceiling effects in the majority of mild patients on nine of the twelve most commonly used subtests. Further, there are a number of cognitive domains known to be impaired in early Alzheimer's disease, but which are not measured by the ADAS-cog. These include areas such as working memory and aspects of executive function (EF), functions indexed by aspects of the NTB, especially the tests of Digit Span and verbal fluency. Agencies such as the FDA have encouraged the use of innovative metrics, though some reluctance on the part of sponsors has been evident. Consequently, in spite of its deficiencies the ADAS-cog is routinely selected as the primary cognitive efficacy measure. Given these circumstances we sought to evaluate the potential value of a new composite cognitive based on the ADAS-cog and the NTB. **Methods:** Compound PBT2 has in previous analyses been shown to improve aspects of executive function with more modest effects on tests of memory. The most recently published study of this compound's use in patients with mild AD employed both the ADAS-cog and a version of the NTB (augmented with the Trail Making Test - TMT). An averaged, change from baseline z-score has been a popular method of deriving cognitive domain (e.g. EF and memory) and global composite scores. We extended the use of this approach to ADAS-cog subtest scores. For example, measures such as 'Object/Finger Naming' and 'Word Recall', which range naturally between 0-17 and 0-30 respectively, were analysed in their raw score format rather than being scaled to 0-5 and 0-10 as would normally occur when scoring these subtests. In order to derive this new composite we included the original 11 ADAS-cog subtests to which we added data for the traditional NTB EF measures and TMT Part B performance. **Results:** A single, composite score for all 15 test



measures was calculated using the previously reported PBT2 EURO study data. A baseline mean and standard deviation score were calculated for the entire study cohort and using these parameters individual z-scores were obtained for each of the 15 test measures. In order to derive the composite ADAS-EXEC score these z-scores were averaged for each study participant at screening and week 12. The change from screening in the composite score was determined and compared over the three study arms (placebo, 50mg & 250mg) using an analysis of variance model with terms for centre and treatment. A treatment effect close to significance ( $P=0.067$ ) was observed with means of 0.041 for placebo, 0.061 for 50mg and 0.137 for 250 mg. *Conclusions:* This new approach to the analysis of data drawn from traditional methods provides an alternative method of testing clinical trial data for cognitive efficacy. Amongst the benefits of this approach are broad coverage of cognitive domains known to be at risk in patients with mild AD, preservation of the traditional content of the ADAS-cog, and inclusion of brief EF measures that have been shown to be sensitive to pharmaceutical intervention. The most obvious limitation of this preliminary study is that we have employed only EF NTB data and deliberately not included memory scores. It seems likely that NTB memory data interacts with ADAS-cog test performance and so some caution must be attached to the generalizability of our observations. We are aware of on-going studies that feature test combinations similar to those we have analysed here. In due course these studies may further inform our understanding of the dynamics and utility of ADAS-EXEC-type analyses.

**P22 - BENEFITS OF AN ITEM RESPONSE THEORY BASED ANALYSIS OF ADAS-COG ASSESSMENTS.** S. UECKERT<sup>1</sup>, E.L. PLAN<sup>2</sup>, K. ITO<sup>3</sup>, M.O. KARLSSON<sup>1</sup>, B. CORRIGAN<sup>3</sup>, A.C. HOOKER<sup>1</sup> (1. Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden; 2. Metrum Research Group, Tariffville, CT, USA; 3. Pfizer Inc, Primary Care Business Unit, Groton, CT, USA)

*Background:* Despite an increasing interest in biomarkers, cognition remains the primary regulatory accepted clinical endpoint in Alzheimer's Disease (AD). The most frequently used test, ADAS-cog, consists of a broad spectrum of tasks evaluating cognition. The total ADAS-cog score is obtained by summing up the subscores resulting from rating a subject's performance in each of the subtests. Despite its frequent application, the total ADAS-cog score has a number of practically relevant weaknesses. A major problem is the low sensitivity of the assessment in mild cognitive impairment (MCI) patients and severe AD patients and the consequential necessity to adapt the assessment. This adaptation is often not only heuristic in nature but also reduces the ability to compare results across trials. Additionally, a potential bias arises if a subject refuses to perform one or more tests and a subscore has to be imputed. In this work we present an alternative method to analyse ADAS-cog assessments. Based on the statistical framework of item response theory (IRT), this method interprets each test as a surrogate measure for the hypothetical unobserved variable "cognitive disability". Each test outcome is linked to the hidden variable through mathematical models, thus allowing a determination of a subject's most likely cognitive disability for a given response pattern and providing an implicit mechanism to handle missing test scores. *Methods:* Data: Baseline ADAS-cog assessments with item level data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Coalition Against Major Diseases (CAMD) databases were used to estimate model parameters in the developed IRT model. In total the data consisted of 2651 subjects from 7 studies with a total of 152313 baseline observations. *Data Analysis:* For each subtest of the cognitive assessment, depending on the nature of the

arising data, a binary, count or ordered categorical model was developed, describing the probability of a failed test outcome as a function of the latent cognitive disability. All parameters characterizing the individual subtest were expressed as fixed effects, whereas the cognitive disability was modeled as a subject specific random effect. The model performance was evaluated through comparison of observed and simulated data for each subtest. *Optimal Test Design:* Based on the developed IRT model, the Fisher information for estimating a patient's cognitive disability was calculated for each item in the ADAS-cog test. The test items were ranked by information content within a mild cognitively impaired (MCI) and a mild AD (mAD) patient population. Furthermore, the additional amount of information added to an ADAS-cog assessment through incorporation of additional components ("delayed word recall" and "number cancellation") were evaluated in both populations. *Results:* ADAS-cog IRT Model: The final ADAS-cog IRT model consisted of 39 binary, 5 binomial, 1 generalized Poisson and 5 ordered categorical submodels with a total of 166 parameters. Simulations from each of the models were in excellent agreement with the observed data. All but one estimated characteristic curves for the test items were well defined with a low failure probability for healthy subjects and high failure probability for severely impaired patients. Only the characteristic curve for the task "state your name" was essentially flat. *Optimal Test Design:* The information content ranking of the subcomponents in a classical ADAS-cog assessment differed between the two patient populations. For the MCI population the word recall component was most informative, while for the mAD population the orientation component carried most information. Similarly, there was an apparent difference in the relative amount of information added by including the "delayed word recall" and "number cancellation" components. With the additional components, the information content of the complete ADAS-cog assessment increased by 78% in the MCI population compared to only 35% for the mAD population. *Conclusion:* By treating each item of the ADAS-cog assessment as a measurement for "cognitive disability", the approach presented in this work takes into account each single item response instead of only one summary score. As a consequence, the assessment data from different ADAS-cog variants can easily be combined in a common analysis and results from one variant can be translated to another. Missing subscore data due to refusal of a subject or omission by a physician does not bias the outcome but are reflected in an increased uncertainty of the analysis. Furthermore, the availability of individual response functions for each test item allows for explicit quantification of the information content of the individual components as well as the ability to adapt a cognitive assessment test to a specific patient population's degree of disability. A population specific test would not only be more sensitive to changes due to disease progression or drug effect, but also reduce the assessment time and thus burden for the patient.

**P23 - PHARMACOMETRIC MODELING OF CLINICAL ADAS-COG ASSESSMENT DATA USING ITEM RESPONSE THEORY.** S. UECKERT<sup>1</sup>, E.L. PLAN<sup>2</sup>, K. ITO<sup>3</sup>, M.O. KARLSSON<sup>1</sup>, B. CORRIGAN<sup>3</sup>, A.C. HOOKER<sup>1</sup> (1. Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden; 2. Metrum Research Group, Tariffville, CT, USA; 3. Pfizer Inc, Primary Care Business Unit, Groton, CT, USA)

*Background:* Several publications have demonstrated the potential value of modeling and simulation for drug development and the resulting increased application of pharmacometric methods throughout the development process. In the therapeutic area of Alzheimer's Disease (AD), the ADAS-cog score is an endpoint of particular importance and models are developed in order to describe the

longitudinal change of this response. Generally, these models treat the ADAS-cog score as a continuous variable, therefore ignoring the underlying discrete nature of the score. In a separate communication, we present the benefits of an item response theory (IRT) based analysis of ADAS-cog assessments by linking the subscores of the ADAS-cog subtests to the non-observable variable “cognitive disability”. Here, we demonstrate how this approach can be extended to longitudinal Alzheimer’s Disease trial data. Our aim is to investigate the potential benefits of this approach in terms of description of the score distribution, drug effect detection power and flexibility of clinical trial simulations. *Methods:* Data: The modeling analysis was based on data from the placebo arm of a phase III study with mild to moderate AD patients. The data utilized consisted of item level ADAS-cog assessment data from 322 patients with 6 scheduled assessments over a time range of 18 month. A total of 84,907 data entries were available for the analysis. Model: The basis for this work was an ADAS-cog IRT model (presented separately) describing the responses of individual test items from an ADAS-cog assessment as a function of the hidden variable cognitive disability. All test specific parameters in the baseline model were fixed and the longitudinal change of cognitive disability was characterized through a linear function with subject specific slope and intercept (model structure as published by Ito et al.). Model adequacy was assessed through visual predictive checks (VPCs) both on the ADAS-cog score level and on the item level. Clinical Trial Simulations: The power to detect a drug effect using either the ADAS-cog IRT or the summary score model was compared through clinical trial simulations (CTSs) for various study sizes. First, 500 clinical trials were simulated from the longitudinal IRT model assuming a placebo controlled trial (mild-moderate AD patients, 18 months duration) for a disease modifying agent (20 % reduction in disease progression rate, introduced on the hidden variable). Subsequently, the resulting datasets were separately analyzed with the IRT and the summary score models. Drug effect detection power with each approach was calculated as the fraction of trials for which the drug effect was statistically significantly different from zero (assessed through log-likelihood ratio test). Additionally, the possibility to perform CTSs for different patient populations and different ADAS-cog variants was demonstrated by repeating the outlined procedure with baseline parameter values for a mild cognitively impaired and a mild AD patient population as well as for an ADAS-cog assessment with and without the delayed word recall test. *Results:* All parameters were estimated with satisfactory precision from the available data (relative standard error between 4.2% and 10.1%). The typical baseline ADAS-cog value was found to be 22.2 points and the typical yearly increase, 3.5 points. VPCs indicated satisfactory data description on the summary score level and for most items (subscores). Some items of the “naming objects and fingers” and the “remembering test instructions” components presented discrepancies between model simulations and observations, but were judged marginal for the overall model performance. Analysis with the ADAS-cog IRT model resulted in a considerably higher power to detect a drug effect in the CTSs. In order to reach 80% power the summary score analysis needed more than 600 individuals, whereas the IRT-based analysis achieved the same power with about 400 individuals, corresponding to a reduction of 33% in sample size. CTSs in different patient populations revealed a slightly higher power to detect a drug effect in the mild cognitively impaired population than in the mild AD population. Removing the “delayed word recall” component decreased the power in both populations. *Conclusion:* By using an IRT ADAS-cog model, we combined ADAS-cog data from a longitudinal clinical trial with information characterizing the relationships between the individual items of a cognitive assessment as obtained from clinical trial databases. The resulting longitudinal

ADAS-cog accurately describes the underlying distribution of the summary score by considering the inherent discrete and bounded nature of the data. In the CTSs, the IRT model showed considerably higher power to detect drug effects than the continuous summary score model. An additional feature of this approach is the separation of test, patient population and drug specific parameters, increasing the flexibility of CTS and thus providing additional tools for planning future trials.

## THERAPEUTIC TRIALS IN AD

### P24 - LONG-TERM ADMINISTRATION OF ACTIVE IMMUNOTHERAPY CAD106 IN PHASE IIA OPEN-LABEL EXTENSION STUDIES IN ALZHEIMER PATIENTS.

A. GRAF, M.E. RIVIERE<sup>1</sup>, M. FARLOW<sup>2</sup>, N. ANDREASEN<sup>3</sup>, P. QUARG<sup>1</sup>, A. CAPUTO<sup>1</sup>, I. VOSTIAR<sup>1</sup>, B. WINBLAD<sup>3</sup>, J.M. ORGOGOZO<sup>4</sup> (1. Novartis Pharma AG, Basel, Switzerland; 2. Indiana University, Indianapolis, USA; 3. Karolinska Universitetssjukhuset, Huddinge, Sweden; 4. Université de Bordeaux, France)

*Background:* CAD106 is an active immunotherapy being developed for Alzheimer’s disease (AD). First-in-man studies have shown that three injections of CAD106 induce an A $\beta$ -antibody response, with local or systemic injection-related reactions as main safety/tolerability findings. The antibody response lasted about six months, indicating that further immunizations are required to ensure long-term exposure to antibodies. *Aims:* To investigate the effects of CAD106 during long-term repeated administration. *Methods:* Safety, tolerability, A $\beta$ -antibody response and effects on plasma A $\beta$  of additional 4 injections of CAD106 were assessed in patients with mild AD who completed one of two Phase II core studies and continued in open-label extensions. CAD106 150 $\mu$ g was administered at quarterly intervals at weeks 56/68/80/92 either subcutaneously or intramuscularly. Patients were followed for 28 months (core plus extension). *Results:* A total of 45 patients continued receiving CAD106 treatment in the extensions: 32 completed, 4 discontinued for adverse events unrelated to study medication, 6 for other reasons; 3 patients are ongoing. A total of seven SAE (including 1 death) were reported but none were related to study medication. Two patients had new cerebral micro-hemorrhages. Brief self-limited injection-related reactions were observed in a majority of patients as in the core studies<sup>2</sup>. The antibody response over the 4 additional injections confirms the preliminary profiles reported earlier<sup>1</sup>, showing sustained A $\beta$ -antibody titers above the responder threshold between 2 consecutive injections during the extension phase. A prolonged time for the titers to decline was observed in the extensions compared to the core studies. Total plasma A $\beta$ 1-40 levels doubled following the third injection in the core studies, while a three-fold increase was consistently observed in the extensions, versus pre-treatment levels. A similar profile was also seen for A $\beta$ 1-42. *Conclusions:* Long-term administration of CAD106 was associated with a similar safety and tolerability profile as with the initial injections. The additional four injections induced a similar antibody titer as the initial three injections, however, with a higher increase in plasma A $\beta$  which may be explained by affinity maturation of the A $\beta$ -specific antibodies upon repeated injections. These findings, along with a good safety and tolerability profile, confirm that CAD106 is suitable for chronic treatment in AD.

**P25 - EVALUATING THE COGNITIVE EFFECTS OF DONEPEZIL 23 MG/D IN MODERATE AND SEVERE ALZHEIMER'S DISEASE: A PATIENT SUBGROUP ANALYSIS.** M. SABBAGH<sup>1</sup>, J. CUMMINGS<sup>2</sup>, D. CHRISTENSEN<sup>3</sup>, R. DOODY<sup>4</sup>, M. FARLOW<sup>5</sup>, J. MACKELL<sup>6</sup>, R. FAIN<sup>7</sup> (1. Banner Sun Health Research Institute, Sun City, AZ, USA; 2. Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA; 3. University of Utah, Salt Lake City, UT, USA; 4. Baylor College of Medicine, Houston, TX, USA; 5. Indiana University School of Medicine, Indianapolis, IN, USA; 6. Pfizer Inc, New York, NY, USA; 7. Eisai Inc., Woodcliff Lake, NJ, USA)

**Background:** Patients with Alzheimer's disease (AD) show variable responses to acetylcholinesterase inhibitor treatment. Identification of patient characteristics that might be associated with a positive response to acetylcholinesterase inhibitor therapy would be useful for treating physicians when considering the optimum management strategy for their patients with AD. In 2010, the US Food and Drug Administration approved a higher 23 mg daily dose of the acetylcholinesterase inhibitor Donepezil for the treatment of moderate to severe AD based on the results of a large clinical trial comparing the 23 mg/d dose with the standard 10 mg/d donepezil dose (NCT 00478205). In these analyses, we investigated the relationships between baseline patient characteristics or demographics and cognitive response in patients receiving either donepezil 23 mg/d or donepezil 10 mg/d. **Methods:** A post hoc analysis was conducted using data from a 24-week randomized, double-blind trial comparing donepezil 23 mg/d with donepezil 10 mg/d in more than 1400 patients with moderate or severe AD (baseline Mini-Mental State Examination [MMSE], 0-20). Least squares (LS) mean changes in Severe Impairment Battery (SIB) scores at Week 24 were analyzed for subgroups of patients based on key patient and demographic characteristics at study baseline, including; age, gender, weight, concomitant memantine use, geographic region, prestudy donepezil 10 mg/d treatment duration, baseline cognitive severity (MMSE score), and baseline functional severity (Alzheimer's Disease Cooperative Study-Activities of Daily Living-severe version [ADCS-ADL-sev] score). Univariate/multivariate analyses were also performed in order to identify any significant interactions. **Results:** Donepezil 23 mg/d provided statistically significant incremental cognitive benefits over donepezil 10 mg/d, as measured by the SIB, regardless of age ( $P < 0.05$ ), gender ( $P < 0.05$ ), weight ( $P < 0.05$ ), concomitant memantine use ( $P < 0.01$ ), geographic region ( $P < 0.05$ ), or prestudy donepezil 10 mg/d treatment duration ( $P < 0.05$ ). For the analyses based on gender (male vs female), weight (above vs below median kg), and prestudy donepezil 10 mg/d treatment duration (above vs below median weeks), the pattern of response was similar between the respective subgroups, with SIB scores increased from baseline with donepezil 23 mg/d and stabilized/marginally increased with donepezil 10 mg/d. For the analyses based on age (above vs below median years), concomitant memantine use (yes vs no), and geographic region (US vs non-US), the pattern of response differed between subgroups, although statistically significant incremental benefits of donepezil 23 mg/d over 10 mg/d were maintained. When patients were categorized based on functional severity (above vs below median ADCS-ADL-sev score at baseline), donepezil 23 mg/d again provided statistically significant incremental cognitive benefits over donepezil 10 mg/d in both subgroups ( $P < 0.05$ ). SIB scores increased from baseline in patients receiving donepezil 23 mg/d in both ADCS-ADL-sev subgroups, and in patients receiving donepezil 10 mg/d with ADCS-ADL-sev scores above the median value; however, SIB scores decreased in patients receiving donepezil 10 mg/d with ADCS-ADL-sev scores below the median. When patients were categorized by baseline cognitive

severity, significant benefits of donepezil 23 mg/d over 10 mg/d were seen when the subgroups were based on MMSE scores of 0-9 versus 10-20 ( $P = 0.011$  and  $P = 0.0038$ , respectively), but only in the more severe subgroup when based on MMSE scores of 0-16 versus 17-20 ( $P < 0.0001$  and  $P = 0.9385$ , respectively). In the 2 subgroups based on more severe baseline cognition (ie, MMSE, 0-9 or MMSE, 0-16), SIB scores were either stabilized (MMSE, 0-9 subgroup) or increased (MMSE, 0-16 subgroup) from baseline among patients receiving donepezil 23 mg/d, but declined from baseline among patients receiving donepezil 10 mg/d. In the multivariate analysis, the only significant interaction was between treatment and baseline MMSE score. **Conclusion:** Results from this post hoc analysis suggest that patients with moderate or severe AD who are receiving stable donepezil 10 mg/d may gain cognitive benefits from switching to donepezil 23 mg/d regardless of their age, gender, weight, concomitant memantine use, geographic location, prior time taking donepezil 10 mg/d, and functional severity. Moreover, the findings suggest that the cognitive benefits of donepezil 23 mg/d over 10 mg/d may be most apparent in those patients at a more advanced stage of disease and/or who progressively deteriorate while receiving donepezil 10 mg/d. These data may be useful in helping practicing physicians make informed treatment decisions for their patients with advanced AD.

**P26 - DONEPEZIL 23 MG/D FOR MODERATE TO SEVERE ALZHEIMER'S DISEASE: ASSESSING SUBDOMAINS OF THE SEVERE IMPAIRMENT BATTERY.** S. FERRIS<sup>1</sup>, J. CUMMINGS<sup>2</sup>, D. CHRISTENSEN<sup>3</sup>, R. DOODY<sup>4</sup>, M. FARLOW<sup>5</sup>, M. SABBAGH<sup>6</sup>, J. MACKELL<sup>7</sup>, R. FAIN<sup>8</sup> (1. Alzheimer Disease Center, New York University Langone Medical Center, New York, NY, USA; 2. Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA; 3. University of Utah, Salt Lake City, UT, USA; 4. Baylor College of Medicine, Houston, TX, USA; 5. Indiana University School of Medicine, Indianapolis, IN, USA; 6. Banner Sun Health Research Institute, Sun City, AZ, USA; 7. Pfizer Inc, New York, NY, USA; 8. Eisai Inc., Woodcliff Lake, NJ, USA)

**Background:** The US Food and Drug Administration has approved a 23 mg daily dose of donepezil for the treatment of moderate to severe Alzheimer's disease (AD) based on outcomes from a large clinical trial comparing the 23 mg/d dose with the standard 10 mg/d donepezil dose (NCT 00478205). Results from this trial indicated that after 24 weeks of treatment, donepezil 23 mg/d provided statistically significant incremental cognitive benefits over donepezil 10 mg/d as measured using the Severe Impairment Battery (SIB). The SIB, a 100-point scale, was designed to assess cognitive function across 9 domains: social interaction (6 points), memory (14 points), orientation (6 points), language (46 points), attention (6 points), praxis (8 points), visuospatial ability (8 points), construction (4 points), and orienting to name (2 points). Subsequent analyses of data from the clinical trial of donepezil 23 mg/d versus 10 mg/d, utilizing SIB-derived language subscales, indicated that the overall cognitive benefits of donepezil 23 mg/d were driven disproportionately by language benefits. In the analyses reported herein, we further characterize the range of cognitive domains impacted by treatment with donepezil 23 mg/d. **Methods:** A post hoc analysis was conducted using data from a 24-week randomized, double-blind trial comparing donepezil 23 mg/d with donepezil 10 mg/d in 1467 patients with moderate or severe AD (baseline Mini-Mental State Examination [MMSE], 0-20). Least squares (LS) mean changes from baseline to Week 24 in the 9 individual SIB domain scores were analyzed for each donepezil treatment group. Analyses were conducted in the overall intent to treat (ITT) population (MMSE, 0-20 at baseline), the cohort of patients with more advanced AD (MMSE, 0-16 at baseline), and in additional

severity strata based on baseline MMSE scores (0-5, 6-10, 11-15, 16-20). **Results:** In the ITT population, changes in 6 of the 9 SIB domains (memory, language, attention, praxis, visuospatial ability, and construction) favored donepezil 23 mg/d over donepezil 10 mg/d. LS mean treatment differences were statistically significant for the language, visuospatial ability, and construction domains ( $P < 0.001$ ,  $P < 0.05$ , and  $P < 0.01$ , respectively). No between-treatment differences were seen for the social interaction, orientation, and orienting to name domains. In the more advanced cohort of patients (MMSE scores 0-16 at baseline), LS mean treatment differences were statistically significant in favor of donepezil 23 mg/d in 5 of the 9 domains: memory ( $P < 0.05$ ), language ( $P < 0.001$ ), attention ( $P < 0.05$ ), visuospatial ability ( $P < 0.05$ ), and construction ( $P < 0.01$ ); again, between-treatment differences were not observed for the social interaction, orientation, and orienting to name domains. Descriptive analysis of LS mean changes in SIB domain scores in the 4 baseline severity strata showed variable patterns of response. Patients in both of the 2 severe strata (MMSE, 0-5 and 6-10) tended to exhibit the greatest treatment differences in favor of donepezil 23 mg/d for the domains of social interaction, memory, language, praxis, visuospatial ability, and construction. Patients in the 2 more moderate strata (MMSE, 11-15 and 16-20) tended to show smaller between-treatment differences and in some domains (visuospatial ability, construction, and orienting to name) no between-treatment differences were seen in these strata. Overall, the descriptive analysis across the 4 severity strata indicated that the cognitive benefits of donepezil 23 mg/d, compared with donepezil 10 mg/d, were greatest in patients with MMSE scores of 0 to 15. **Conclusion:** Results from this post hoc analysis suggest that donepezil 23 mg/d provides benefits over 10 mg/d across a range of cognitive domains. The magnitude of these benefits and the specific domains impacted varied depending on the stage of AD; the analyses indicated that the greatest incremental benefits with the higher donepezil dose were apparent across multiple cognitive domains and predominantly in patients at more advanced stages of the disease.

**P27 - SIMVASTATIN VERSUS ATORVASTATIN: WHICH IS THE OPTIMAL CHOICE TO PREVENT ALZHEIMER'S DISEASE?** S. SIERRA, J.S. BURGOS (*BioPharma Division, Neuron Bio, Parque Tecnológico de Ciencias de la Salud, Granada, Spain*)

**Backgrounds:** Over the last decade, a large number of experimental observations have suggested a relationship between alterations in cholesterol homeostasis and Alzheimer's disease (AD). Long-term prospective population-based studies have indicated that elevated cholesterol levels in midlife are associated with an increase in the risk to suffer AD in later life. Polymorphisms in apolipoprotein E (apoE) and other proteins involved in cholesterol metabolism are considered as risk factors for AD. In addition, epidemiological studies have pointed an association between statin treatment and a decrease in the risk of having AD. For these reasons, a large number of clinical trials (CTs) have been carried out to determine whether the statins can prevent the progression of AD. However, these studies have not provided evidence yet for the therapeutic efficacy in AD although several considerations could be taken into account to improve clinical design and increase the possibility of success. **Methods:** We performed an unbiased search of the PubMed database for relevant studies in the English language, without regard to publication date. Additional studies were identified by citations in the resultant studies and also by the recommendation of the coauthors or consultants. We included articles which provided well-controlled studies and clearly interpretable conclusions about this topic. Search terms were: Alzheimer's disease, clinical trials, simvastatin, atorvastatin, neuroprotection, biomarkers and risk factors. **Results:** The majority of epidemiological studies and the CTs have been performed using two

statins: simvastatin and atorvastatin. Both statins present a very different molecular structure, origin, physico-chemical properties, brain penetration, efficacy as neuroprotectants and pharmacokinetic and pharmacodynamics profiles. Besides the parameters mentioned, other findings in the use of both statins as neuroprotectants have been evaluated in this work: (i) efficacy in epidemiological studies, (ii) analysis of completed or ongoing CTs, (iii) modulation of the classical AD signs ( $\beta$ -amyloid deposition, tau hyperphosphorylation, neuronal death, etc), and (iv) changes in critical biomarkers for AD. The comparison of these results suggests that simvastatin presents a better profile for preventing neurodegenerative conditions than atorvastatin. In addition, the analysis of the whole data suggests that changes in the design of the CTs could increase the probability of success for AD. CTs must be designed to prevent very early rather than dementia stage of AD, selecting participants with proved hypercholesterolemia, and using additional biomarkers of the effects on plasma and brain cholesterol or neuroinflammation. In spite of the possible success of simvastatin in the prevention of AD with this new approach, it appears necessary to identify novel statins with optimized brain penetration and/or stronger intrinsic neuroprotective activity. **Conclusions:** We objectively analyze the pros and cons of the use of simvastatin or atorvastatin in the AD prevention. This analysis suggests that simvastatin is a better candidate to prevent AD than atorvastatin. The final aim of this study is to propose a solid rationale for the correct choice of statins as neuroprotectants in the future therapies for AD.

**P28 - A NICOTINIC-ALPHA-7 PARTIAL AGONIST AS ADJUNCTIVE THERAPY TO STABLE DONEPEZIL.** D. MASTERMAN<sup>1</sup>, T. AWIPI<sup>1</sup>, E. ASHFORD<sup>1</sup>, S. NAVE<sup>1</sup>, K. YOO<sup>1</sup>, B. VELLAS<sup>2</sup>, L. SANTARELLI<sup>1</sup> (*1. CNS DTA, F. Hoffmann-La Roche, Ltd., Basel, Switzerland; 2. Clinic of Internal Medicine and Gerontology, University Hospital Center, Toulouse, France*)

**Background:** RG3487 (also known as RO5313534 or MEM3454), a potent and selective alpha-7-nicotinic acetylcholine receptor (NicA7) partial agonist, has demonstrated improved learning and memory function in healthy and aged animals and showed cognitive enhancement on memory in healthy volunteers and in an earlier study in patients with mild to moderate Alzheimer's disease (AD) treated for 8 weeks (monotherapy). In this study we examined the efficacy and safety of 24 weeks treatment of fixed doses of RG3487 compared to placebo added to stable doses of background donepezil (5 or 10 mg/day) on cognition in patients with mild-to-moderate AD. (Trial Registration: clinicaltrials.gov Identifier: NCT00884507). **Methods:** We conducted a 3 dose (1, 5, 15 mg po qd), PhIIb, randomized, double-blind placebo-controlled trial of RG3487 as an add-on therapy in patients with mild to moderate symptoms of Alzheimer's disease ( $n = 389$ , Mini-Mental State Examination scores between 13 and 22, inclusive). Primary measure of cognition was the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog). Secondary measures included assessment with the Cambridge Neuropsychological Test Automated Battery (Cantab). The study was conducted between May 2009 and January 2011, across 63 sites in 13 countries. **Results:** Baseline patient characteristics were well balanced among treatment groups and typical for patients in mild-moderate AD clinical trials (mean age 75, 58% female, baseline MMSE 18.5, baseline ADAS-cog 24.6 and 58% ApoE4 carriers). Of the 389 patients enrolled in the study 327 (84%) completed the trial. Primary endpoint: No difference was detected in the change in the ADAS-Cog total score from baseline to week 24 between RG3487 + donepezil and placebo + donepezil for any dose group (effect size 0.06 in the ITT population for the best dose). The change in the ADAS-cog (for the best dose of 5mg at 24 weeks was 0.89 placebo compared to -0.05 for RG3487 ( $p=0.35$ ). Secondary endpoint: A transient improvement was

seen in the Cantab delayed matched to sample test (percent correct, all delays) at week 12 in the 5mg group, but this effect was not sustained through week 24. A similar effect was seen in the Cantab paired associate learning test (total errors adjusted). Other secondary measures did not show effects consistently better than placebo. Safety: RG3487 was safe and well tolerated in combination with donepezil and at doses ranging from 1 to 15 mg/day with the most common adverse effect being constipation (5% placebo compared to 15% in the high dose). *Conclusion:* The selective nicotinic alpha-7 partial agonist, RG3487 did not show any clinically relevant effects on cognition as measured by the ADAS-cog or Cantab in patients with mild-moderate AD on stable background donepezil treatment.

**P29 - EFFECTS OF ELND005 (SCYLLO-INOSITOL) ON NEUROPSYCHIATRIC SYMPTOMS (NPS) IN MILD / MODERATE AD: CORRELATIONS OF ELND005 EXPOSURES TO NEUROPSYCHIATRIC OUTCOMES IN A 78-WEEK PHASE 2 STUDY.** E. LIANG<sup>1</sup>, J. WAGG<sup>2</sup>, M. KURTH<sup>1</sup>, S. ABUSHAKRA<sup>1</sup> (1. *Elan Pharmaceuticals, Inc., South San Francisco, CA, USA*; 2. *Pharsight/Cartara Corporation, St. Louis, MO, USA*)

*Introduction:* Neuropsychiatric symptoms (NPS) are commonly associated with increased morbidity and are thus an important target for drug development. Some NPS may reflect regional monoaminergic dysfunction in prefrontal areas. NPS occurs in specific clusters that suggest clinical syndromes with distinct underlying neuropathologic correlates. In AD patients with NPS, myo-inositol elevations in anterior cingulate cortex correlated with NPS severity (Shinno et al., 2007). ELND005, a myo-inositol stereoisomer, has amyloid anti-aggregation effects and has shown pathological and cognitive benefits in preclinical models. In a Phase 2 study (Study AD201, Salloway et al. 2011), ELND005 treatment led to dose-dependent increases in brain scyllo-inositol, reductions in brain myo-inositol, and reduced emergence of NPS (Tariot et al. Neurology 2012). *Objective:* To analyze the correlations between ELND005 exposures and corresponding effects on both emergence and severity of NPS in AD study patients. *Methods:* These PK/PD analyses were performed using data from a Phase 2, 78-week, dose ranging, Phase 2, placebo-controlled study of ELND005 in 353 patients with Mild/Moderate AD. The 3 ELND005 doses were 250mg, 1000mg, and 2000mg (all given BID). Mild and Moderate AD were defined as MMSE scores of 22-26 and 16-21, respectively. NPS were assessed at baseline, and Weeks 12, 24, 48, and 78 using the 12-item NPI; changes from baseline (CBL) were the protocol specified analyses. NPS emergence (a post hoc analysis) was defined as a score of 0 at baseline that became >0 at up to a subsequent visit. Steady-state ELND005 exposure metrics in plasma, CSF and brain were estimated based on a prior established population PK model (Liang et al, 2011, AAIC). Probability of NPI sub-item emergence (p) within a given group was calculated. Severity of NPS of each NPI sub-item was calculated based on CBL defined as:  $CBL = NPI(BL) - NPI(t)$ . Logistic regressions of emergence probability for each NPS versus the various exposure metrics were performed in 163 patients in placebo or 250 mg dose groups. A regression coefficient was considered statistically significant if the p-values were either <0.1 (near significant) or <0.05 (significant); a negative correlation coefficient suggested clinical improvement. Pair-wise Pearson correlation analysis between NPI sub-item CBL (in severity) and exposure metrics in patients from the placebo or 250 mg BID dose groups were also performed; a positive correlation coefficient suggested clinical improvement. *Results:* Of the 12 NPI sub-items, V-shaped patterns were observed in several sub-items with lowest probability of emergence mostly at the 2nd quartile

of drug exposures, which corresponded to the 250 mg dose (given BID). Further efforts on exposure/response correlation hence focused on patients in the 250 mg and placebo groups. In the overall Mild/Moderate patients in the 250 mg and placebo groups, logistic regression analyses (N=61-155) revealed near significant or significant trends between increased estimated exposure metrics and decreased emergence probabilities of agitation/aggression (Week 12, p<0.05; Week 24, p<0.1), depression (Week 48, p<0.1; Week 78, p<0.05), anxiety (Week 78, p<0.1), disinhibition (Week 78, p<0.1), and nighttime behaviors (Week 78, p<0.05). Further analyses suggested that effects on agitation/aggression at earlier time points were mainly seen in Moderate AD; effects on depression at later time points were mainly seen in Mild AD; effects on disinhibition and nighttime behaviors at later time points were mainly seen in Moderate AD patients. Further pair-wise Pearson correlation analyses for CBL in NPS severity and the exposure metrics between 250 mg and placebo groups (N=106-163) confirmed the above observations in Mild/Moderate AD, i.e. near significant or significant effect on agitation/aggression at early time point (Week 12) mainly seen in Moderate AD patients, and on depression at later time point (Week 78) mainly seen in Mild AD patients. *Conclusion:* In Moderate AD patients, increased exposure to ELND005 was associated with both decreased emergence probability of agitation/aggression, and decreased worsening in its severity, both observed at 12 weeks. In Mild AD patients, increased exposure to ELND005 was associated with decreased emergence probability of depression, and decrease worsening in its severity, both observed at 78 weeks. The effects of ELND005 on agitation/aggression were most pronounced at early time points, while effects on depression were more pronounced later in the study. These effects on both agitation/aggression and depression support the potential of ELND005 as a treatment of agitation and/or aggression in Moderate AD, since agitation occurs in the context of a depressive syndrome in these patients.

**P30 - THE STUDY OF PHARMACOLOGICAL EFFICACY OF DRY MULBERRY BURIRUM-60 IN ALZHEIMER'S DISEASE.** B. SRICHAIKU (*Waraporn Sutthisa Hospital, Thailand*)

Alzheimer's Disease is a condition in which occurs in the area concerning the deterioration of brain function. This condition of disease is not completely curative treatment by medicines and always happens in the elderly with ages over 55 years old. However it can delay and maintain the condition of the stages of deterioration of brain function. In this experiment. We used *Morus alba* Linn. Burirum 60 leaves collected from Mahasarakham University Research Plantation Field, the Division of Research Innovation and were prepared as a powder in capsule form to control the incidence and maintain brain function condition in Mild stage of Alzheimer's disease patients. *Morus alba* Linn. contains many minerals and vitamin A, vitamin B, vitamin B3, vitamin B12, vitamin C, essential amino acids, Zinc, Magnesium, Sodium, deoxyojirimycin, GABA, Phytosterol, Calcium, Potassium, folic acid etc. The samples of this research were collected from silk weaving women, ages of 55-70 years old in Silk Innovation Weaving Village, supported by Mahasarakham University. The samples were divided into 4 groups as follows: group no.1 of feeding silkworms weaving women and intake *Morus alba* Burirum 60 capsule, group no.2 of feeding silkworms weaving women and intake placebo, group no.3 of non feeding silkworm weaving women and intake *Morus alba* Burirum 60 capsule, group no.4 of non feeding silkworms weaving women and intake the placebo. All samples were tested with Cognitive Testing Scale and the selected samples were Mild cognitive memory function group. The dosage of *Morus alba* capsule would have 2 capsules after meals, once daily for 3 months and all the

samples were tested for cognitive memory function using the scales of Sage1, Mini-Mental state Examination (MMSE), Functional Assessment Stage tool (Fast) for evaluation and confirmation of the efficacy of Mulberry (*Morus alba* Burirum 60) effecting the brain function. The data were tested with Wilcoxon Signed Rank Test and Kruskal Wallis statistical analysis. The result revealed that each 4 groups of Group no.1, no.2, no.3, and no.4 were 3.00, 1.50, 3.00 and 2.00 respectively. It showed that in each group had indicated mean scores with statistical significant difference at p-value 0.05. It showed the development of changing scores tested by SAGE1 scale within the group. Then we compared the mean scores difference among or in between groups by using the Kruskal Wallis statistical method. The result found that the mean rank score among 4 groups before the experiment were 14.10, 12.70, 7.30 and 7.90 respectively and the mean rank score among 4 groups after the experiment were 17.70, 8.70, 11.00 and 4.60 respectively. The higher rank of each groups indicated the higher development in obtaining the scores of SAGE1 tested by Kruskal Wallis after the experiment by oral intake of *Morus alba* Linn. Burirum-60 capsules with the dosage of 200 mg daily for 3 months. It showed the development of cognitive memory function by increasing the ranking scores of group no.1, group no.3 and group no.2 respectively. The suggestion of this study for the future research is to increase the size of samples and clinical confirmed with CT-SCAN or NMR in order to measure the comparison of improvement in the density and brain image before and after the experiment and also the duration of administering or intake *Morus alba* Linn. Burirum-60 should be recommended to extend longer period of time and may be increase in the daily dosage. Keywords: mild cognitive memory impairment, MMSE, SAGE1, FAST, Alzheimer Disease.

### **P31 - CEREBROLYSIN, A NOVEL DRUG FOR THE TREATMENT OF ALZHEIMER'S DISEASE. AN EXPERIMENTAL STUDY USING NANOWIRED DELIVERY.**

H.S. SHARMA<sup>1</sup>, R.J. CASTELLANI<sup>2</sup>, M.A. SMITH<sup>3</sup>, Z.R. TIAN<sup>4</sup>, D.F. MURESANU<sup>5</sup>, H. MOSSLER<sup>6</sup>, A. SHARMA<sup>1</sup> (1. *Cerebrovascular Research Laboratory, Department of Surgical Sciences, Anesthesiology & Intensive Care Medicine, University Hospital, Uppsala University, Sweden*; 2. *Department of Pathology, University of Maryland, Baltimore, MD, USA*; 3. *Department of Pathology, Case Western Reserve University, Cleveland, Ohio USA*; 4. *Department of Chemistry & Biochemistry, University of Arkansas Fayetteville, Fayetteville, AR, USA*; 5. *Department of Neurosciences, University of Medicine & Pharmacy, University Hospital, Cluj-Napoca, Romania*; 6. *Ever Neuro Pharma, Oberburgau, Austria*)

Cerebrolysin (Ever NeuroPharma, Austria) is a mixture of several neurotrophic factors and active peptide fragments and has multimodal action on brain cells inducing neuroprotection, neuroregeneration and angiogenesis. Due to these potential beneficial effects of cerebrolysin clinical trial of the drug was carried out in AD. The results clearly show some benefit to AD patient giving hope for this drug as a potential future drug for treating cognitive, sensory and intellectual dysfunction commonly seen in AD. Furthermore, Cerebrolysin improved cognition and reduced synaptic and behavioral deficits in transgenic (tg) mice overexpressing the amyloid precursor protein (APP). The memory deficits and brain pathology were reduced by cerebrolysin up to 3 months after discontinuation of the treatment. However, these beneficial effects were no longer seen following 6 months after withdrawal of cerebrolysin. Interestingly, Cerebrolysin reduced the neocortical and hippocampal amyloid plaque load immediately after treatment but could not block these effects after 3 months of discontinuation. This suggests that Cerebrolysin may have

beneficial effects independent of amyloid- $\beta$  deposition and further indicate that the prolonged effects up to 3 months may be due to its neurotrophic factor-like activity. With advancement in nanotechnology for diagnostic or drug delivery purposes, use of nanotechnology to treat AD is becoming more relevant today. Recent research in AD therapy suggests that nanodrug delivery of compounds or specific iron chelators attenuate AD pathology by targeting amyloid beta deposition in the brain. These treatments could also reduce oxidative stress in AD models. Thus, this is quite likely that therapeutic agents if delivered through nanotechnologies will induce long-term neuroprotection and improves cognitive and sensory function in AD. The AD lesions in brain contain abnormal metal accumulation. Thus, metal chelation therapy could reduce neuronal deterioration. These chelating agents bind to and remove excess transition metals to reduce the oxidative damages caused by these metals in the brain. Since BBB protects transport of these chelating agents to enter into the brain, nanoparticles comprising natural organic polymers could transport metal chelating agents across the BBB regardless of their size and hydrophilicity. Thus, nanoparticle delivery systems for AD therapy could be exciting prospects for AD treatment in future. Another way to use nanotechnology in AD is to use of engineered nanoparticles having high specificity for brain capillary endothelial cells. These specifically designed nanoparticles could be used for advanced diagnosis of AD as well as for the treatment. In addition, nanoparticles with high affinity for the circulating amyloid- $\beta$  ( $A\beta$ ) will induce a "sink effect" causing improvement in AD. Ultrasensitive nanoparticles-based bio-barcodes, immunosensors, and scanning tunneling microscopy are capable of detecting  $A\beta$  (1-40) and  $A\beta$  (1-42) precisely. However, possible nanoparticles-mediated adverse events in the brain or nanoneurotoxicological aspects in AD are not very well known. Thus, further studies on the use of nanoparticles in AD for diagnosis or therapy are needed. New observations in our laboratory showed that nanodrug delivery of cerebrolysin using TiO<sub>2</sub> nanowires in a transgenic mouse model of AD resulted in enhanced neuroprotection and degradation of ABP in cortical and hippocampal areas up to 6 weeks after treatment. However, normal cerebrolysin delivered in the transgenic AD mouse models, the neuroprotection could not be seen after 3 weeks of treatment. These observations clearly suggest that nanotechnologies is the need of hour to treat AD in future. However, to use nanowired or nanodrug delivery of novel therapeutic agents in AD require further investigation related to the possible toxic effects of the nanomaterials used for diagnostic or drug delivery process in AD.

### **P32 - IMPLICATION OF INTEGRATIVE TREATMENT FOR REAL-LIFE GERIATRIC PATIENTS WITH DEPRESSION, DEMENTIA AND MULTIPLE CHRONIC DISEASES: A 60-MONTH FOLLOW-UP OF A NATURALISTIC STUDY.**

G. ALIEV<sup>1,2</sup>, V. BRAGIN<sup>3</sup>, R. CACABELOS<sup>4</sup> (1. *Department of Health Science and Healthcare Administration, University of Atlanta, Atlanta, GA USA*; 2. *GALLY™ International Biomedical Research Consulting LLC, San Antonio, TX, USA*; 3. *Stress Relief and Memory Training Center, Brooklyn, New York, NY USA*; 4. *EuroEspes Biomedical Research Center, Institute for CNS Disorders and Genomic Medicine & Camilo José Cela University, La Coruña, Spain*)

*Background:* Neurodegeneration [Stroke and Alzheimer disease (AD)] is fastly becoming one of the leading causes of age-associated disability, dementia, and death. In addition, the Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics recently reported that AD has surpassed diabetes as a leading cause of death and is now considered the sixth-leading cause of death in the United States. Unfortunately, currently no effective treatments are available against this devastating disease. In the past we have

shown the preservation and improvement of cognitive tasks in depressed and demented patients after 24 and 36 months of combined pharmacological and non-pharmacological treatment. Here we present the results of our ongoing, naturalistic study, in the same outpatient setting, at the 60 month follow up. **Materials and Methods:** The study group consisted of 156 medically ill, physically-disabled patients with mild to moderate dementia and depression. Patients were treated with antidepressants, cholinesterase inhibitors, and NMDA antagonists, along with their regular medication regimen. Non-pharmacological intervention was centered on a home-based program of physical and cognitive exercises as well as with vitamins and supplements (multivitamins, vitamin E, L-methylfolate, alpha-lipoic acid, acetyl-L-carnitine, omega-3, and coenzyme Q-10) and diet modification. Cognitive assessments were performed yearly. **Results:** After 60 months of treatment, performance of all tasks remained at or above baseline. The MMSE, Cognistat-Attention, Cognistat-Judgment, and RFFT - Total Unique Designs demonstrated significant improvement. **Conclusion:** Our results, for the first time, demonstrate arrest in cognitive decline in demented/depressed patients with multiple medical co-morbidities for 60 months. Future investigations addressing the application of a combined, integrative treatment models in clinical practices are warranted.

**P33 - A PHARMACOGENETICS-SUPPORTED CLINICAL TRIAL TO DELAY ONSET OF MILD COGNITIVE IMPAIRMENT (MCI) DUE TO ALZHEIMER'S DISEASE (AD).** A.D. ROSES<sup>1,2</sup>, K.A. WELSH-BOHMER<sup>3</sup>, D.K. BURNS<sup>1</sup>, C. CHIANG<sup>1</sup>, D.G. CRENSHAW<sup>1,2</sup>, M.W. LUTZ<sup>1,2</sup>, C.A. METZ<sup>1</sup>, A.M. SAUNDERS<sup>1,2</sup>, S. BRANNAN<sup>3</sup>, M. MALHOTRA<sup>3</sup> (1. Zinfandel Pharmaceuticals, Inc., Durham, NC, USA; 2. Duke Bryan ADRC, Durham, NC, USA; 3. Takeda Global Research & Development Center, Inc., Deerfield, IL, USA)

**Background:** The increasing number of individuals at risk for development of late onset AD (LOAD) has refocused attention on preventing or delaying the onset of LOAD symptoms. Length variation of a poly T tract (rs10524523) in the TOMM40 gene has been associated with age of onset of LOAD. TOMM40 is adjacent to, and in linkage disequilibrium with, the APOE gene. An algorithm, based on data from prospectively followed cohorts, has been developed to identify individuals at high or low risk for developing MCI due to AD in the next 5 years. The algorithm incorporates an individual's current age along with TOMM40 and APOE genotypes. Several lines of evidence have suggested that thiazolidinediones (TZDs) may have utility in improving or sparing cognition. **Methods:** We will initiate and conduct a phase 3 double-blind, randomized, placebo-controlled, clinical trial to simultaneously (1) qualify a biomarker algorithm for assigning near-term risk for developing MCI due to AD, and (2) evaluate the efficacy of low-dose pioglitazone, a TZD, as a treatment to delay the onset of MCI due to AD in normal individuals. **Results:** The study design incorporates the biomarker risk algorithm to assign cognitively normal subjects to high- and low-risk strata for treatment evaluation, including a low-risk placebo cohort to qualify the algorithm and prospectively test its positive and negative predictive values. Subjects in the high-risk stratum will be randomized to receive either once-daily pioglitazone or placebo. The study will enroll approximately 5000 participants between ages 68 and 83 and will operationalize the recently published clinical criteria (Albert et al. 2011) for identifying participants with MCI due to AD as the endpoint. The study duration is anticipated to be approximately 5 years, ending when a target number of primary endpoint diagnoses have been reached. Along with the Clinical Dementia Rating scale, the key assessments that enable this primary endpoint diagnosis are the tests of the neuropsychological battery. It is composed of 11 measures from 8

widely utilized instruments that inform 5 key domains (episodic memory, executive function, expressive language, attention, and visuospatial function) for assessing early cognitive decline. As this is one of the first interventional global studies in early cognitive decline, a separate validation strategy has been created to ensure the test battery performs consistently across cultures and languages. Test performance measures for cognitive decline have been established and will be used to trigger a full clinical workup by the study investigator to assess cause, including imaging for stroke or presence of tumor. Assignment of an MCI due to AD diagnosis will be guided by predetermined criteria and cutpoints for neuropsychological tests, but will be clinically adjudicated by an independent expert committee with access to all study subject information. The protocol also includes exploratory imaging substudies to provide data on brain changes during the course of the study. In addition to regular surveillance by the investigator and the sponsor, the safety of subjects will be evaluated by an independent Data Safety and Monitoring Board (DSMB). It is anticipated that the clinical study will supply the necessary data to support the qualification of the biomarker for clinical use. **Conclusions:** The study is anticipated to begin enrolling participants in 4 Q 2012. Discussion with regulatory authorities in the US and EU is ongoing. This study represents a unique opportunity to explore therapeutic intervention in the earliest phase of the AD continuum.

**P34 - COGNITIVE STIMULATION AND APOE GENOTYPE IN NON-DEMENTED ELDERLY SUBJECTS: A RANDOMIZED CONTROLLED STUDY (RCT).** G. FORLONI<sup>1</sup>, L. POLITO<sup>2</sup>, A. DAVIN<sup>2</sup>, S. ABBONDANZA<sup>2</sup>, R. VACCARO<sup>2</sup>, E. VALLE<sup>2</sup>, A. GUAITA<sup>2</sup>, M. COLOMBO<sup>3</sup>, S. VITALI<sup>3</sup>, V.V. FERRETTI<sup>4</sup>, S. VILLANI<sup>4</sup> (1. Department of Neuroscience, Mario Negri Institute for Pharmacological Research, Milan, Italy; 2. GolgiCenci Foundation, Abbiategrasso (Milan), Italy; 3. Geriatric Institute "C. Golgi", Abbiategrasso (Milan), Italy; 4. Dep. of Health Sciences, Biostatistics and Clinical Epidemiology unit, Pavia University, Pavia, Italy)

**Background:** Cognitive stimulation (CS) is a non-pharmacological intervention able to prevent or delay cognitive decline in elderly subjects. Recently, a meta-analysis of 15 randomized controlled trials provided consistent evidence that CS benefit cognition in people with mild to moderate dementia (Woods, 2012; Cochrane Database of Systematic Reviews, Issue 2). More research is needed to find out whether contributing factors could exist to predict change in the outcome of CS. For example, little is known about the genetic characteristics of people who are more likely to benefit from CS. The aim of this presentation is to investigate with a randomized controlled trial whether 1) CS improve cognitive performance measured by MONTreal Cognitive Assessment (MOCA) in non-demented elderly subjects at risk to develop dementia, 2) there could be any difference in the response to CS between subjects with and without cognitive decline, 3) the main genetic risk factor for dementia, APOE Epsilon 4 allele, may impact on the efficacy of CS intervention. **Methods:** This work was a part of ALLENA-MENTE randomized open label controlled trial conducted to evaluate the long-term efficacy (4 years) of cognitive stimulation (CS, intervention group) with respect to sanitary education treatment (SE, "active" control group) on cognitive level measured by MMSE. Both groups were compound by two subsamples: mild cognitive impairment (MCI) and non-MCI with familiarity for dementia (NDFAM). Participants were recruited from the "InveCe.Ab" study, a longitudinal assessment of cognitive function in people born between 1935-39 and resident in Abbiategrasso. 16 MCI subjects in each arm were enough to detect a difference of 2 points in

MMSE between CS and SE group with a statistical power of 80% and two-sided alpha of 0.05. 20 patients were enrolled in each study group to compensate a drop-out rate of 20% in the follow-up period. Similarly, 36 NDFAM people needed to detect a difference of 1 point in MMSE among CS and SE with an increasing of 10% to take into account the drop-out. A randomization stratified by birth year and schooling (1:1) between groups was made. CS consisted in a 10-session of cognitive stimulation made by trained operators (2-hours over 5 weeks): language stimulation, abstract reasoning, executive functioning, memory. SE was made of two sanitary education lessons. MOCA test administered pre and post-treatment was used to measure cognitive performance. A blood sample was collected from each participant for genomic DNA extraction and ApoE genotyping (Real Time PCR Assay). Variation in MOCA test between baseline and the end of treatment were analyzed using paired t test, while the efficacy of CS stimulation with respect to ES was investigated by unpaired t test. A multivariate linear regression analysis was applied to adjust the efficacy of CS on final MOCA score for confounders (sex, schooling, APOE genotype). Baseline MOCA score and a variable identifying 2 subsamples were among covariates. The interaction between APOE and treatment was also tested. Statistical analyses were carried out with SPSS11. The study was approved by the Ethics Committee of the University of Pavia (Italy). **Results:** 121 people participated to the trial: 44 MCI and 77 NDFAM. The subjects enrolled in the CS group were 61 (23 MCI and 38 NDFAM) and 60 (21 MCI and 39 NDFAM) in the ES one. A significant improvement in cognitive performance within CS (baseline: 21.8 end: 23.7;  $t=-6.5$ ;  $p<0.0001$ ) and ES interventions (baseline: 21.8 end: 22.9;  $t=-3.6$ ;  $p=0.0007$ ) was found. Anyway, the gain in MOCA score was significantly higher in the CS group than in the SE group (CS:  $1.89 \pm 2.26$ , SE:  $1.05 \pm 2.27$ ;  $t=2.0$ ,  $p=0.045$ ). The efficacy of CS intervention was still statistically significant after adjustment for confounders ( $p=0.045$ ). At baseline, MCI subsample showed a lower MOCA score than NDFAM ( $19.30 \pm 3.12$  vs  $23.22 \pm 3.54$ ;  $t=-6.4$ ;  $p=0.001$ ). MOCA score significantly improved in CS with respect to SE only in the NDFAM subsample (NDFAM-CS:  $2.39 \pm 2.34$ , SE:  $0.9 \pm 2.57$ ;  $t=2.67$ ;  $p=0.009$ ; MCI-CS:  $1.04 \pm 1.87$ , SE:  $1.33 \pm 1.59$ ;  $t=-0.55$ ;  $p=0.585$ ). APOE genotype was significantly associated to the final MOCA score ( $p=0.013$ ), but the interaction term was not relevant ( $p=0.19$ ). **Conclusions:** The findings indicate that cognitive stimulation benefits cognition in elderly non-demented subjects. Moreover, few sessions of CS are potentially more beneficial for subjects without cognitive deficits (NDFAM) rather than in MCI at short term. Follow-up evaluations are necessary to assess the long-term effect of this kind of intervention and potentially to highlight a benefit also for MCI subjects in terms of a slower cognitive decline over time. APOE genotype does not modify the efficacy of CS compared to SE, even if it impacts on the gain in MOCA score.

### **P35 - LIMITATIONS OF MTC (METHYLENE BLUE) AND REPLACEMENT BY LMTXTM IN TAURX PHASE 3 PROGRAM. C.M. WISCHIK<sup>1,2</sup> (1. University of Aberdeen, UK; 2. TauRx Therapeutics)**

**Background:** Alzheimer's disease (AD) is characterized by accumulation of a toxic aggregated form of the protein Tau which is able to spread transneuronally and is correlated with clinical dementia. A drug such as methylthionine (MT) which dissolves pathological Tau polymers and oligomers isolated from AD brain (Wischnik et al., 1996) has potential utility as a disease-modifying treatment for AD. MT was given as the chloride salt of the oxidized form (MT+, MTC, methylene blue) at a dose of 138 mg MT/day (180 mg MTC/day, delivered as a 60mg MTC capsule t.i.d.) in a Phase 2 trial in 321 patients. MT was

found to slow the rate of decline on the ADAS-cog scale by  $85\% \pm 31\%$  (mean  $\pm$  sem) over 1 year in both mild and moderate patients ( $p=0.0053$ ). Evidence of clinical efficacy was supported by neuroimaging in a substudy in 138 subjects. MT at a dose of 138 mg MT/day was found to eliminate entirely the decline seen in controls over 24 weeks in medial temporal lobe and temporo-parietal blood flow (rCBF) using HMPAO-SPECT ( $p=0.002$ ). However, on both clinical and imaging measures, MT at a dose of 228 mg MT/day (300mg MTC/day, delivered as 100mg MTC capsules t.i.d.) was found to have reduced or entirely absent efficacy. We have sought to define the factors responsible for apparently reduced efficacy at higher dose. **Methodology:** The 60mg and 100mg capsules used in the Phase 2 study were found to have markedly different dissolution profiles in vitro due to the extent of cross-linking of the gelatin capsules due to contact of MT+ (the oxidized form of MT which comprises MTC). Since MTC has a measurable effect on haemoglobin in vivo, we undertook a comparative analysis of dose-response comparing haematological change and cognitive efficacy. A dissociation between the two was found at the highest dose which could be explained theoretically by a two-species absorption model depending on the redox state of MT. We created a novel stabilized crystalline form of the reduced form of MT (leuco-MT, LMTXTM) which can be formulated as a tablet. The properties of LMTXTM were studied in cell uptake systems, in a cell-based Tau aggregation model, in two Tau-transgenic mouse lines and in two Phase 1 studies comparing absorption of MTC and LMTXTM with and without food in elderly volunteers. **Results:** A 2-species model of MT absorption explained both haematological effects and cognitive efficacy with a high correlation coefficient ( $r=0.996$ ). Cognitive efficacy appears to be driven by absorption of the reduced form (leuco-MT) which requires reduction of MT+ at the low pH of the stomach. Presented as the LMTXTM salt, MT was found to be absorbed more completely and more rapidly than MTC in a number of cell systems. Brain levels of MT were higher after oral administration as LMTXTM versus MTC in a transgenic mouse model of Tau pathology, with higher corresponding levels of MT and a better affect on Tau pathology and behaviour for the same MT dose. In the first Phase 1 study, MTC was given at single doses corresponding to the 60mg or 100mg doses used in the Phase 2 study. Co-administration with food was found to significantly inhibit absorption of the 100mg MTC dose, but not the 60mg dose. In the second study using LMTX, there was no evidence of food interference with absorption of MT at high dose. LMTXTM was found to be well tolerated up to a single dose of 800 mg of MT. **Conclusion:** MTC (methylene blue) has limited clinical utility as it is poorly tolerated in the fasted state and is poorly absorbed as the clinically active species in the presence of food, which is required to minimize nausea and vomiting. We have developed a novel form of MT which delivers the active moiety with better tolerability and absorption. It also achieves higher brain levels and higher efficacy in Tau-transgenic mouse models. Since the same MT moiety is present in blood, the Phase 2 results with MTC have been accepted as providing a regulatory basis for proceeding with the TauRx Phase 3 program using LMTXTM.



## FUNDAMENTAL RESEARCH FOR AD CLINICAL TRIALS

### **P36 - DOPAMINE D2-AGONIST ROTIGOTINE EFFECTS ON CORTICAL EXCITABILITY AND CENTRAL CHOLINERGIC TRANSMISSION IN ALZHEIMER'S DISEASE PATIENTS.**

A. MARTORANA<sup>1</sup>, G. KOCH<sup>2</sup> (1. *Clinica Neurologica- Dipartimento di Neuroscienze, Centro di Riferimento per la Malattia di Alzheimer- Università di Roma, Italy*; 2. *Fondazione Santa Lucia IRCCS, Rome, Italy*)

*Background:* dopamine is a neurotransmitter involved in several brain functions ranging from emotions control, movement organization, memory formation. It is also involved in the regulation of mechanisms of synaptic plasticity. However, its role in Alzheimer's disease (AD) pathogenesis is still puzzling. Several recent line of research instead indicate a clear role for dopamine in both amyloid  $\beta$  formation as well as in cognitive decline progression. In particular it has been shown that dopamine D2-like receptors (namely D3 and D2) could be mostly responsible for dopamine dysfunction in AD. *Methods:* here we aimed to study the effects of the dopamine agonist on cortical excitability and on central cholinergic transmission in cases of AD. Rotigotine is a dopamine agonist with a pharmacological profile with high affinity for D3 and D2 receptors. This profile made the drug particularly indicated for our purposes. We used paired pulse protocols assessing short intracortical inhibition (SICI) and intracortical facilitation (ICF) to assess cortical excitability over the primary motor cortex and Short Latency Afferent Inhibition (SLAI) protocols, to verify the effects of the drug on central cholinergic transmission in a group of AD patients compared to age-matched controls. *Results:* we observed that Rotigotine induces unexpected changes in both cortical excitability, that resulted increased and central cholinergic transmission, that appeared as restored in AD patients. *Conclusions:* The unexpected effects of Rotigotine might be due to dopamine D2-like receptors dysfunction described in AD brains and may constitute the basis for future strategies to ameliorate AD cognitive decline.

### **P37 - CELLULAR AND ANIMAL MODELS FOR HIGH THROUGH-PUT SCREENING OF THERAPEUTIC AGENTS FOR THE TREATMENT OF DISEASES OF AGING IN GENERAL AND ALZHEIMER'S DISEASE IN PARTICULAR.**

J.L. HOLTZMAN (Departments of Pharmacology and Medicine and Division of Environmental Health Sciences, University of Minnesota, Minneapolis, USA)

It is currently thought that the dementia of Alzheimer's disease is due to the neurotoxicity of the deposits or aggregates of  $\beta$ -amyloid in the extracellular space of the cerebral cortex. This model has been widely criticized because there is a poor correlation between deposits and dementia. Others have questioned whether  $\beta$ -amyloid is neurotoxic. Finally, seven clinical trials of drugs that were effective in transgenic mice failed to show any benefit in patients. Furthermore, since  $\beta$ -amyloid is produced in everyone, why are deposits only seen in the elderly? This issue must be resolved if we are to understand the etiology of the disease and develop test systems for diagnosis and drug discovery. Published studies from my laboratory demonstrate that in human CSF immunoreactive  $\beta$ -amyloid is only present as a complex with two chaperones, ERp57 and calreticulin and is N-glycosylated. These modifications keep it solution. Yet, others have reported that in plaque it is only present as the naked peptide. Together these results suggest that both plaque and dementia are secondary to a decline in the

capacity of the endoplasmic reticulum (ER) to catalyze the posttranslational processing of nascent proteins. Since many of the synaptic membrane proteins necessary for a functioning memory are also processed in the ER, this would suggest that the loss of cognition is due to a decline in the capacity of the neuron to produce and maintain functioning synapses. These observations have important implications for other phenomena associated with Alzheimer's disease. In particular, others have found that the ER is important in the maintenance of mitochondrial function and integrity of plasma membranes. Together these observations suggest that declining ER function has a role in the late onset disease associated with polymorphisms in ApoE and TOMM40/TOM40 genes and the well recognized decrease in myelin seen with age.

### **P38 - POTENTIAL OF HUMAN ANALOGUE OF MORRIS WATER MAZE IN TRANSLATIONAL MEDICINE AND THE ASSESSMENT OF THERAPEUTIC RESPONSE.**

J. HARRISON<sup>2,4,5</sup>, J. LACZO<sup>1,2</sup>, M. WINDISCH<sup>2,3</sup>, J. HORT<sup>1,2</sup> (1. *Memory Disorders Clinic, Department of Neurology, Charles University in Prague, 2nd Medical Faculty and University Hospital Motol, Prague, Czech Republic*; 2. *Polyhymnia Translational Research, London, UK*; 3. *JSW-Lifesciences GmbH, Grambach-Graz, Austria*; 4. *Metis Cognition Ltd., Kilmington, UK*; 5. *Dept. of Medicine, Imperial College, London, UK*)

*Background:* Recent failures in the development of new therapies for Alzheimer disease (AD) have led to reconsideration of clinical trial design. Many therapies which proved efficacious in preclinical development using various animal models were tested using the Morris Water Maze (MWM) task. However, these compounds often failed in phase II or III in humans, suggesting low predictive validity. In these clinical trials traditional cognitive tests were used and primary outcome measures were not met. The reason for inefficiency may be related to ineffective compounds, clinical trial design with enrolment of subjects with too advanced disease, or the use of unsuitable measures of cognitive change. Furthermore, currently used tests appear not to translate preclinical findings to human studies. Previously we reported that spatial memory testing in real-space and computer-based versions of a human analogue MWM can reliably identify individuals at higher risk of AD within the heterogeneous population with mild cognitive impairment (MCI). Cross-sectional and forthcoming longitudinal data suggest that patients with multiple domain or hippocampal types of amnesic MCI or ApoE4 carriers have similar spatial navigation as those with AD. Identification of subjects with MCI at higher risk of AD could guide development of therapeutic interventions in MCI. Introduction of tasks analogous to those used in preclinical settings could improve predictive validity and diagnostic sensitivity/specificity, as well as preventing organisations from incurring the costs of expensive Phase 1 and Phase 2 clinical trials. In this study we examined the potential of the real version and computer-based tests of a human analogue of the MWM (hMWM) to assess the effect of therapy with cholinesterase inhibitors and anti-cholinergics in early AD and healthy volunteers. *Methods:* Two groups of newly diagnosed patients with early AD, treated by donepezil (n=11) and non-treated (n=12), were tested by the computer-based version of hMWM, which evaluates different spatial navigation strategies (egocentric, allocentric, allocentric-egocentric and delayed recall). Donepezil at 5 mg/day was started after initial testing and the dose was increased to 10 mg/day after 28 days. All patients were retested after 3 months. Another group of healthy volunteers received either placebo, Donepezil 5 mg and Scopolamine 0.6 mg or only Scopolamine 0.6mg, in single dose, three-way cross-over design. *Results:* Mild AD treatment groups did not differ in education, sex and baseline MMSE

score ( $p$ 's>0.10) or spatial navigation performance ( $p$ 's≥0.20). The treated group showed stable or improved spatial navigation performance after 3 months, especially in the delayed recall subtask ( $p=0.075$ ). In other subtasks, the treated group improved or remained stable (average error distance in egocentric changed from 100 pixels to 51 pixels; in allocentric from 100 pixels to 87 pixels) compared to the non-treated group which was stable or impaired (average error distance in egocentric changed from 67 pixels to 59 pixels; in allocentric from 67 pixels to 82 pixels); however, these findings were not significant ( $p$ 's≥0.279). Testing of volunteers group revealed that single dose of scopolamine had negative effects on spatial navigation. This effect was not observed in placebo group and was less evident in subjects who were administered both donepezil and scopolamine. **Conclusion:** The computer-based version of the hMWM has a potential to measure the effects of medication in early AD and in healthy volunteers. Our findings provide supportive evidence for the use of spatial navigation as an outcome measure in longer-term MCI clinical trials as well as in translating from preclinical animal data to human trials.

**P39 - VOLUNTARY EXERCISE SUPPRESSES ENHANCED TAU PATHOLOGY BY HIGH CALORIE DIET IN A TAUOPATHY MOUSE MODEL.** Y. YOSHIYAMA (*Department of Neurology and Clinical Research Center, Chiba East National Hospital, Chiba 260-8712, Japan*)

**Background:** A life-style characterized by high calorie diet (HCD) and physical inactivity may induce so-called metabolic syndrome, which refers to a condition including obesity, diabetes mellitus, dyslipidemia, hypertension and a proinflammatory state. This condition has been recognized as known risk factors for a wide variety of diseases including coronary heart disease, cerebrovascular disease and Alzheimer's disease (AD). However, the precise mechanism relating AD and this condition is unclear. To elucidate the effects of HCD on the pathomechanism of AD, we fed HCD (Fat=15.3%; 4.3 Cal/g) to tauopathy model transgenic mice (PS19), and then we neuropathologically and biochemically analyzed HCD-fed PS19 mice compared with standard diet (Fat=4.5%; 3.3 Cal/g) (SD)-fed PS19 mice. Interestingly, HCD enhanced tau pathology but voluntary exercise counteracted that enhancement. **Methods:** PS19 mice, which express human tau with a P301S mutation and start to show neurofibrillary tangles (NFTs) at 6 months of age, were divided into HCD-fed ( $n = 35$ ) and SD-fed ( $n = 30$ ) groups. Moreover, to assess the effect of exercise on HCD intake, the HCD group was subdivided into no-exercise (HCD,  $n = 25$ ) and exercise (HCD+EX,  $n = 10$ ) groups. HCD+EX group mice were housed in cages equipped with a running wheel for voluntary exercise from the age of 2 months, and SD and HCD group mice were housed in ordinary box-type cages. All mice were sacrificed at the age of 10 months. **Results:** Body weight (BW) was significantly elevated in HCD and HCD+EX groups, but there was no difference between HCD and HCD+EX groups at any time points. The levels of fasted blood-sugar (FBS), serum insulin, cholesterol, triglyceride (TG) and serum-leptin (s-Lep) were higher in HCD than those in SD, but only TG and s-Lep showed significant differences between these two groups. Although the levels of serum insulin and FBS in HCD did not show a significant difference, the glucose tolerance test (GTT) revealed a significant elevation of blood sugar at 15, 60 and 120 min in the HCD group, and the insulin tolerance test (ITT) also showed elevated blood sugar at 15 and 30 min in the HCD group, suggesting insulin resistance in HCD. EX significantly recovered those metabolic abnormalities, and intriguingly s-Lep elevation completely recovered without BW reduction in the HCD+EX group. Histopathology of the brains in HCD PS19 mice

showed enhanced tau pathology and synaptic degeneration, but HCD+EX PS19 brains exhibited milder pathologies. Insolubility and phosphorylation of tau were increased in HCD. Tau kinase activities of p38 and CDK5 were activated in HCD, and EX suppressed JNK activity in addition to restoring elevated p38 and CDK5 activities. Looking at the glial reaction, enhanced microglial and astroglial activations were seen in HCD PS19 brains. Since EX obviously improved the Lep resistance, we examined the expression of Lep receptors (LepRs) in brains by immunohistochemistry. Interestingly, a short isoform of LepRs, LepRa, was preferentially expressed on astrocytes but not on neurons, while a long isoform LepRb, was mainly expressed by basomedial hypothalamic neurons but weakly expressed by neurons in other areas and by glial cells. The LepRa-positive astrocytes distributed in the hippocampus, amygdala, and entorhinal cortices where tau pathology was overt. Meanwhile LepRb-positive astrocytes distributed throughout the whole brain. STAT3 expression, which was activated by Lep through LepRb, was suppressed in HCD, indicating Lep resistance in neurons. **Conclusions:** We have demonstrated that HCD can enhance tau pathology, synaptic degeneration and glial reactivity. Meanwhile, voluntary exercise restores those neuropathological deteriorations independent of body weight reduction. This indicates that the beneficial effect of exercise is not dependent on the reduction of BW. Although some insulin resistance could be observed, obvious Lep resistance occurred in HCD and those resistances were completely recovered by EX. Interestingly, although LepRb expression was not changed with HCD, astrocytic but not neuronal LepRa expression was enhanced. HCD might enhance signal transductions downstream of LepRa in astrocytes but not in neurons. The function of LepRa is unclear, but some papers indicate that some proinflammatory cytokines are induced by LepRa. Because it is well-known that inflammation plays an important role in tau pathology formation and neurodegeneration, and we previously reported that an immunosuppressant reduced tau pathology in PS19 mice, LepRa activation induced by HCD might enhance tau pathology though inflammation and EX might suppress LepRa activation by restoring Lep resistance.

**P40 - MONOCLONAL ANTIBODY GENERATION BASED ON THE HUMANIZED YEAST MODEL SYSTEM: IMPROVING TAU DIAGNOSTICS.** J. VAN DEN BRANDE<sup>1,2</sup>, J. ROSSEELS<sup>1</sup>, P. BORGHAEF<sup>3</sup>, D. JACOBS<sup>2</sup>, M. MICHELS<sup>1</sup>, L. BUEE<sup>4</sup>, F. VAN LEUVEN<sup>3</sup>, E. VANMECHELEN<sup>2</sup>, J. WINDERICKX<sup>1</sup> (*1. Functional Biology, KU Leuven, Heverlee, Belgium; 2. ADx Neurosciences, Ghent, Belgium; 3. LEGTEGG, KU Leuven, Belgium; 4. Inserm, U837, Alzheimer & Tauopathies, Lille, France; Université Lille Nord de France, JP Aubert Research Centre, IMPRT, Lille, France; UDSL, Faculté de Médecine-Pole Recherche, Lille, France; CHU-Lille, Lille, France*)

**Background:** Tau-based tangles as well as A $\beta$ -based plaque pathology have become the focus of immunotherapy in Alzheimer's disease and other tauopathies. Efficacy of immunotherapy, in particular passive immunotherapy, is highly dependent on the blood brain barrier integrity in both early stages, if used prior to the clinical dementia, and late stages of Alzheimer's disease. Since tau and its tangles are predominantly present intracellularly, the cellular/neuronal membrane is an additional barrier to overcome in tau-based immunotherapy. Yeast has proven to be an excellent model system to target new potential intracellular mechanisms of new drug development (Khurana & Lindquist, Nat Rev Neurosci 2010;11:436-449), not only restricted to immunotherapy but also for the development of new small drug entities (Lagoja et al, Eur J Pharm Sci 2012;43:386-392; Griffioen et al, BBA 2006;1762:312-318). **Methods:**

A unique *Saccharomyces cerevisiae* model has recently been developed allowing to study the repercussions of specific post-translational modifications and mutations of heterologously expressed protein tau on its oligomerisation and cytotoxicity (Vandebroek et al, *Biochemistry* 2005; 44:11466-11475; Vanhelmont T et al, *FEMS Yeast Res* 2010; 10:992-1005; De Vos et al, *Int J Alzheimers Dis* 2011; Apr 6:428970). We have further optimized this model system for easy purification of specific polymorphic forms of tau by introducing an N-terminal His-tag on the longest tau isoform (tau441 or tau2N4R), thereby obtaining improved purity and higher yields. Purified tau was subsequently used for in vitro seeding trails using the isolated most phosphorylated isoform as initial seed. Furthermore, new monoclonal antibodies (mAbs) have been generated using this highly purified yeast tau form, which were subsequently characterized using the yeast model, transgenic mice and brain biopsy samples of control and AD-patients. Finally, the diagnostic potential of the new mAbs was assessed for their ability to discriminate between healthy persons and AD-patients based on a CSF samples in a multiparametric assay. **Results:** Examination of purified tau confirmed (hyper) phosphorylation at key AD epitopes, like AD2 (pSer396/pSer404), AT270 (pThr181) and PG5 (Pser404), its ability to adopt the presumed disease-associated conformation, as detected by the conformation-specific antibody MC1/Alz50, and and to form oligomers and aggregates. We demonstrated that hyperphosphorylated tau, in contrast to dephosphorylated tau, induces oligomerisation and aggregation of other tau molecules in vitro, supporting the viewpoint that conformationally altered hyperphosphorylated tau can act as a seed in the oligomerisation process. Protein tau purified from yeast was used to generate novel monoclonal antibodies. Three types of mAbs were obtained. First, a high affinity tau-tau mAb, YT1.15, which recognized monomeric and oligomeric tau isoforms in the yeast model, transgenic mice as well as in CSF samples and brain biopsy samples of AD-patients. This high affinity mAb was also capable of discriminating AD patients from healthy persons based on quantification of the tau/Ptau ratios in CSF samples. Two other mAb's, i.e. YT1.10 and YT1.11, displayed specific immunoreactivity to oligomeric species formed by hyperphosphorylated tau, thereby corroborating the link between hyperphosphorylation and oligomerisation. Finally, a phospho-specific mAb (YT3.04) was obtained that specifically recognizes the phospho-threonine 181 epitope. **Conclusion:** Combined, these novel tau mAbs, together with the humanized yeast model system, will help us to further dissect relevant mechanisms involved in the pathobiology of AD. They provide a first stepping stone in the development of novel diagnostic tools and immune-based therapies and allow for a better understanding and documentation of tau immunotherapy as a potential valid therapy for AD and tauopathies.

**P41 - EXAMINING START UP FOR A MULTICENTER CLINICAL TRIAL OF NEUROSURGICAL ADMINISTRATION OF NERVE GROWTH FACTOR GENE TRANSFER.** S. WALTER<sup>1</sup>, E. SHAFFER-BACAREZA<sup>1</sup>, R. CHAVEZ<sup>1</sup>, K. WOODS<sup>1</sup>, G. MATTHEWS<sup>1</sup>, P. AISEN<sup>1</sup>, J. GRILL<sup>2</sup> (1. *Alzheimer's Disease Cooperative Study, University of California San Diego, La Jolla, CA, USA*; 2. *Mary S. Easton Center for Alzheimer's Disease Research, Department of Neurology, David Geffen School of Medicine, University of California, Los Angeles, CA, USA*)

**Introduction:** To date, few multicenter Alzheimer's disease (AD) trials have investigated neurosurgical interventions and no multicenter AD trial has examined gene therapy. The Alzheimer's Disease Cooperative Study (ADCS) Nerve Growth Factor (NGF) Study is a Phase 2 multi-centered randomized placebo-controlled clinical trial

funded by the NIH and conducted in collaboration with Ceregene, Inc. It will enroll 50 participants across 11 US centers. While enrollment challenges have been studied and reviewed, less attention has been given to understanding the impact of regulatory and other requirements before a multi-centered clinical trial can be initiated. **Background:** CERE-110 is a genetically engineered, serotype 2 adeno-associated virus (AAV2) modified to transfer human nerve growth factor (NGF) DNA. CERE-110 is delivered via bilateral stereotactic injections to the nucleus basalis of Meynert (NBM). Sham surgery control participants receive bilateral scalp incisions and partial burr holes under general anesthesia. **Methods:** We explored barriers to start-up in the following categories. 1. Institutional Review Board (IRB) approval. Mean site time to final IRB approval were calculated. 2. Other regulatory and institutional requirements. Participating institutions also required review/approval by the local Institutional Biosafety Committee (IBC) - including staff viral vector and biosafety training, Radioactive Drug Research Committee (RDRC) and other bodies (e.g. Internal Scientific Peer Review committee). 3. Other certifications and requirements. Sites were required to complete these additional requirements in order to obtain approval to enroll: MRI certification, PET certification, and Neurosurgeon Training. Once final IRB approval was obtained, each site underwent an Initiation Visit conducted by the ADCS and Ceregene. Site time to achieve these milestones was examined. 4. Participant Enrollment. The length of time from committee approval to the first patient screened was examined. **Results:** The Protocol was sent to sites November 2008. An Investigator Meeting was held in January 2009. Enrollment began in November 2009 and is ongoing at the time of submission. All eleven sites achieved IRB approval for the protocol. The mean time to approval was 10.34 months (Range: 3.47 - 15.33 months). The single site which also participated in the Phase 1 trial of the same therapy also had the shortest time to full IRB approval (3.47 months). Other certifications and requirements did contribute to further delays in site start-up. The mean time to site final approval was 14.87 months (Range: 9.77 - 26.8 months). At the time of submission, 70 participants had been screened for the study. Of these, 44 participants had been randomized (undergone surgery). Enrollment is ongoing. The mean overall rate of randomization for the study at the time of submission was 1.47 participants per month. The highest number of participants enrolled across sites in any single month was 4. Ten of the eleven sites successfully randomized participants (Range: 1-8 participants per site). The mean number of participants randomized per site per month was 0.13. The screening rate across sites was 2.19 participants per month. 31% of participants who signed consent and passed capacity assessment were subsequently screen failed. **Conclusion:** The ADCS NGF trial is a unique Phase II study in AD. Start up to this study faced additional regulatory burdens and recruitment has been relatively slow. Identification of challenges and potential solutions to the encountered barriers for this trial will guide future similar trials.

**P42 - MOLECULAR DYNAMICS SIMULATIONS APPLYING FOR DESIGNING COMPOUNDS THAT CAN BE USED FOR TREATMENT OF ALZHEIMER'S DISEASE.** M. HERNANDEZ<sup>1</sup>, M. ROSALES<sup>2</sup>, J. CORREA BASURTO<sup>1</sup> (1. *Laboratory of Molecular Modeling and Bioinformatics. Escuela Superior de Medicina. IPN*; 2. *Laboratory of Biophysics and Biocatalysis. Escuela Superior de Medicina. IPN*)

**Backgrounds:** There are several etiologies associated to the pathophysiology of Alzheimer's disease (AD), where the formation of insoluble amyloid beta peptide (A $\beta$ ) fibrils are the principal event. The A $\beta$  is release from enzymatic degradation of amyloid precursor protein

(APP) by sequential action of  $\beta$  and  $\gamma$  and secretases. Once released, Ab undergoes a secondary conformational change to switch from  $\alpha$ -helix conformation to  $\beta$ -sheet folded, where the rate limiting step is the formation of electrostatic interaction between D23 and K28 aminoacid residues. Then Ab in  $\beta$ -sheet conformation can interact with other monomers in the oligomerization process with the formation of fibrils, which are particularly toxic since it has been shown to have the capability to produce H<sub>2</sub>O<sub>2</sub>, which react with the metals such as iron or copper, presents in high concentrations to produce hydroxyl radical (OH $\cdot$ ) radical via Fenton reaction, establishing a permanent state of oxidative stress and due to the wide distribution of senile plaques in areas which are rich in cholinergic neurotransmission associate to memory and other important brain functions. Due the limited therapeutic alternatives for AD patients is necessary to design molecules that can act at key points in the pathophysiology of the disease by inhibiting  $\beta$ -secretase, AChE (Acetylcholinesterase) and Ab oligomerization and has antioxidant activity. **Methods:** We designed a family of compounds derived from 5-amino salicylic acid (5-ASA) based on its antioxidant activity. To 5-ASA was adding two pharmacophore groups to offer then AChE,  $\beta$ -secretase inhibitor properties, thus was based on reports the mention as pharmacophore, a hydrophobic and amine tertiary that can protonate allowing inhibit the Ab oligomerisation. The physicochemical characteristics of compounds based on Lipinski's rule by the server OSIRIS Property Explorer were evaluated. Molecular Dynamics (MD) simulations were performed using NAMD 2.6 program, 50 ns on AChE (pdb 1ACJ),  $\beta$ -secretase (pdb 2QP8) and Ab (pdb 1IYT) to obtain many conformers of every 5ns. Docking studies were focused toward the catalytic site of AChE,  $\beta$ -secretase, D23 and E22 of Ab for each compound. The geometry optimization of the ligands was carried out using Gaussian 03. Auto Dock 4.2 program was selected for docking studies. All simulations were performed using the Lamarckian genetic algorithm. The results for each ligand were subjected to analysis of energies and geometry of binding. Docking studies of Galantamine and Semagacestat, AChE and  $\beta$ -secretase inhibitors, respectively, were performed in order to validate this study. **Results:** Five molecules were designed based on the desired characteristics, which showed high affinity for the catalytic sites of AChE and  $\beta$ -secretase and E22 and D23 in Ab, and also satisfy physicochemical parameters based on Lipinski's rule (less than 5 Hydrogen bonds donors, molecular weight less than 500, octanol-water partition coefficient log P not greater than 5 and not more than 10 hydrogen bond acceptors). In the MD simulation of AChE is observed that convergence was reached at 15 ns, becoming stable throughout the simulation. The structural analyses do not show local significant variations in catalytic site, but for the simulation of the  $\beta$ -secretase was observed a great variability of the catalytic site, also not reached the convergence. However, these changes had no effect importantly on the recognition of the compounds as were obtained  $\Delta G$  similar to each conformer. We chose the compound having greater affinity for the target protein, selecting the referred compound 1. It is noted that the compound interacts with the catalytic site of AChE with S200 and W86 importantly, obtaining a  $\Delta G = -9.41$  and a  $K_d = 0.06 \mu M$ . The same compound interacts importantly with D228 and S35 of  $\beta$ -secretase, aminoacid residues important in inhibitors recognition, having a  $\Delta G = -9.04$  and a  $K_d = 0.11 \mu M$ , so it is observed that the tertiary amine present in compound 1 interacts via electrostatic interactions with E22 and D23. **Conclusion:** The results obtained showed that compound 1 have the best score, therefore it is considered for synthesis in order to evaluate in vitro, confirming that keep the proposed activity and could be considered potential drug for AD models.

## BIOMARKERS/IMAGING IN AD CLINICAL TRIALS

**P43 - CHANGES OF BIOLOGICAL MARKERS AND BRAIN PET IMAGING AND CLINICAL EFFECTS OF MEMANTINE FOR PATIENTS WITH MODERATE TO SEVERE ALZHEIMER'S DISEASE: A 24 WEEK DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY.** S. XIAO<sup>1,2</sup>, T. WANG<sup>1,2</sup>, Q. HUANG<sup>3</sup>, K. CHEN<sup>3,4</sup>, E. REIMAN<sup>4</sup> (1. Geriatric Psychiatry Department, Shanghai Mental Health Center, Shanghai JiaoTong University School of Medicine, Shanghai, China; 2. Alzheimer's Disease and Related Disorder Center, Shanghai JiaoTong University, Shanghai, China; 3. Med-X Institute, Shanghai Jiaotong University, Shanghai, China; 4. Banner Alzheimer's Institute and Banner Good Samaritan Medical Center, PET Center, Phoenix, AZ, USA)

**Objectives:** To investigate the effects of memantine on cognition, biological markers and cerebral glucose metabolism measured by Fluorodeoxyglucose (FDG)-positron emission tomography (PET) for patients with moderate to severe Alzheimer's disease (AD) after 24 week treatment period in contrast to that of placebo. **Methods:** This is a double-blind, randomized, placebo-controlled study. 22 AD patients were randomly assigned to either the treatment or the placebo group. Plasma and cerebrospinal fluid (CSF) interleukin-10 (IL-10), amyloid  $\beta$ -40 (A $\beta$ -40), total tau protein, measures of cognitive function tests such as the AD Assessment Scale-Cognitive Subscale (ADAS-cog), the Mini-Mental State Exam (MMSE) and the Severe Impairment Battery (SIB) as well as FDG-PET were acquired at the baseline and after the 24 week treatment period. The memantine dose was 20mg/day from initially 5mg/day in the treatment group. For the image analysis, the follow-up PET was realigned to the baseline scan for each subject and both were normalized to the standard brain template using SPM8. Voxel-wise general linear model based 2-sample t-test was performed to examine the difference of the longitudinal changes in glucose metabolism between the treatment and placebo groups. **Results:** The two groups did not differ in their age (placebo group 64.7 $\pm$ 11.5 vs. treatment group 65.7 $\pm$ 12.5), gender (female/male 7/4 vs. 7/4) and education (placebo group 7.2 $\pm$ 2.4 vs. treatment group 6.9 $\pm$ 2.1). MMSE score ( $p=0.02$ ), ADAS-Cog ( $p=0.03$ ) and total SIB ( $p=0.05$ ) were statistically different between the two groups at week 24 though they were not at baseline ( $p=0.08$ , 0.1 and 0.2 respectively). The change of SIB score was statistically different between the two groups ( $p=0.037$ ). The Plasma and CSF IL-10, A $\beta$ -40, total tau Protein were not statistically different between the two groups both at baseline and at week 24 and change of them from baseline to week 24. The placebo group had significant FDG uptake decline in precuneus, posterior cingulate, temporal, and occipital regions ( $p=0.005$  uncorrected). In comparison to the placebo group, the memantine treatment group either had a reduced decline in posterior cingulate and temporal or showed increase in FDG uptake at week 24 in precuneus and temporal ( $p=0.005$  uncorrected). **Conclusion:** Our findings demonstrate that N-methyl-D-aspartic acid (NMDA) receptor non-competitive agent memantine in 24 weeks show the potential effect of slowing down the progression of AD.

**P44 - ORGANOTYPIC HIPPOCAMPAL SLICES COUPLED WITH MULTI-ELECTRODE ARRAY: AN INNOVATIVE METHOD TO INVESTIGATE NEUROACTIVE COMPOUNDS IN NEURODEGENERATIVE DISORDERS.** V. DUVEAU<sup>1</sup>, C. BOUYSSIERES<sup>1</sup>, M. LANGLOIS<sup>1</sup>, C. ROUCARD<sup>1</sup> (1. SynapCell SAS, Biopolis, La Tronche, France)

Neurodegenerative disorders (e.g. Parkinson's, Alzheimer's, Huntington's diseases) are a class of progressive disorders

characterized by a neuronal loss. Mechanisms underlying this neurodegeneration are diverse and depend on the specificity of the disease (genetic mutation, protein misfolding or accumulation, excitotoxicity etc...). The occurrence of neurodegenerative disorders is increasing with population ageing and new neuroprotective drugs are mandatory. Some neurodegenerative disorders are as well characterized by learning and memory impairments, which are associated with an alteration of long term potentiation (LTP). One important approach to reducing attrition rates in clinical development is to improve the validity of the preclinical models used to support new drug candidates. Organotypic hippocampal slices represent a relevant *ex vivo* model of a neuronal network. Indeed the anatomy of the hippocampus and the intrahippocampal connections are well preserved. Moreover, the glial cells-neurons interaction is maintained, which is critical for the intrinsic neuronal activity in the hippocampus. The technology of Multi-Electrode Array (MEA) allows to record the electrophysiological activity of neuronal networks in organotypic and/or in acute hippocampal slices. Synaptic plasticity, such as paired-pulse facilitation, LTP (long term potentiation) or long term depression (LTD), can easily be tested and are particularly of interest in neurodegenerative disorders. SynapCell has developed preclinical solutions to: (i) Assess the functional neuroprotective effect of new compounds against neurotoxic molecules by recording evoked and spontaneous electrophysiological activity of the hippocampal network using MEA. (ii) Evaluate cognitive impairments in mutant murine models and/or beneficial or deleterious effects of compounds on cognition, by LTP assessment. Using this innovative method, SynapCell proposes a broad range of preclinical services to test neuroactive compounds targeting neurodegenerative disorders.

**P45 - DEVELOPMENT AND APPLICATION OF A MATHEMATICAL MODEL OF MODULATION OF CSF A $\beta$ 40 IN CEREBROSPINAL FLUID AFTER TREATMENT WITH  $\gamma$  AND B-SECRETASE INHIBITORS.** H.J. KLEIJN, L. MA, M. DOCKENDORF, R. DE GREEF, J. PALCZA, J. KOST, M. FORMAN, M.F. EGAN, J. STONE (*Merck Research Laboratories, Whitehouse Station, NJ*)

**Background:** A mathematical model representation of key amyloid pathway physiology to describe A $\beta$ 40 modulation in CSF was developed to: (1) quantify clinical drug potency of  $\gamma$ -secretase (GS) and  $\beta$ -secretase (BACE1) inhibitors; (2) enable benchmarking across compounds; (3) facilitate dose selection for efficacy trials **Methods:** Lumbar CSF A $\beta$ 40 concentration data in healthy adults treated with placebo; GS inhibitors MK-0752 or semagacestat (from literature); or BACE inhibitor MK-8931 were available. Model-predicted drug brain concentrations were used as driver for CSF A $\beta$ 40 modulation. An Emax relationship described inhibition of A $\beta$ 40 production and a distribution delay between brain and lumbar CSF A $\beta$ 40 was incorporated. An additive baseline drift model informed by study-specific placebo data allowed for drift correction. Data were fit using non-linear mixed effects modelling and model performance was qualified. This model was combined with population PK models to predicted dose – response profiles for brain and CSF A $\beta$ 40 inhibition. Trial performance predictions were made taking into account AD population demographics and knowledge on non-compliance. **Results:** An Emax inhibition model combined with delay compartments best described the CSF A $\beta$ 40 response upon inhibition of GS or BACE. Maximum inhibition (Emax) estimates were 0.87, 0.86, 0.96 and for plasma concentration at 50% of maximum (EC50) were 933 ng.mL<sup>-1</sup>, 6250 ng.mL<sup>-1</sup>, 10.2 ng.mL<sup>-1</sup> for semagacestat, MK-0752, and MK-8931, respectively. Dose – response profiles demonstrated greater

potency and achievable CSF A $\beta$ 40 suppression with MK-8931 compared to other compounds at clinically feasible doses. CSF A $\beta$ 40 reductions between 50-75%, and between 75-100% from baseline were predicted to be achieved in 90% of the patients at doses of 12 and 40 mg MK-8931, respectively. **Conclusions:** CSF A $\beta$ 40 response following placebo and GS or BACE inhibition were characterized by a common model framework. Comparative analysis among compounds suggests that semagacestat produces only limited (<11% ) inhibition of A $\beta$  production. MK-8931 showed superior potency in the expected therapeutic dose range resulting in almost full suppression of CSF A $\beta$ 40. Simulations indicate that 12 and 40 mg MK-8931 inhibit A $\beta$  production by >50% and >75%, respectively, suggesting that clinical trials in AD with MK-8931 may provide a more robust test of the amyloid hypothesis, compared to semagacestat

**P46 - DEFINITION OF HARMONIZED PROTOCOL FOR HIPPOCAMPAL SEGMENTATION.** M. BOCCARDI<sup>1</sup>, M. BOCCHETTA<sup>1,2</sup>, L. APOSTOLOVA<sup>3</sup>, J. BARNES<sup>4</sup>, G. BARTZOKIS<sup>5</sup>, G. CORBETTA<sup>1</sup>, C. DECARLI<sup>6</sup>, L. DETOLEDO-MORRELL<sup>7</sup>, M. FIRBANK<sup>8</sup>, R. GANZOLA<sup>1</sup>, L. GERRITSEN<sup>9</sup>, W. HENNEMAN<sup>10</sup>, R.J. KILLIANY<sup>11</sup>, N. MALYKHIN<sup>12</sup>, P. PASQUALETTI<sup>2</sup>, J.C. PRUESSNER<sup>13</sup>, A. REDOLFI<sup>1</sup>, N. ROBITAILLE<sup>14</sup>, H. SOININEN<sup>15</sup>, D. TOLOMEO<sup>1</sup>, L. WANG<sup>16</sup>, C. WATSON<sup>17</sup>, H. WOLF<sup>18</sup>, S. DUCHESNE<sup>14</sup>, C.R. JACK JR<sup>19</sup>, G.B. FRISONI<sup>1</sup> (*1. LENITEM (Laboratory of Epidemiology, Neuroimaging and Telemedicine) IRCCS – S. Giovanni di Dio – Fatebenefratelli Brescia, Italy; 2. AFaR – Associazione Fatebenefratelli per la Ricerca, Rome, Italy; 3. Laboratory of NeuroImaging, David Geffen School of Medicine, University of California, Los Angeles, CA; 4. Dementia Research Centre, UCL Institute of Neurology, University College London, London, UK; 5. Department of Psychiatry, David Geffen School of Medicine at UCLA, Los Angeles, CA; 6. Department of Neurology, University of California, Davis, CA; 7. Department of Neurological Sciences, Rush University, Chicago, Illinois; 8. Institute for Ageing and Health, Newcastle University, Wolfson Research Centre, Newcastle, UK; 9. Karolinska Institute, Stockholm, Sweden; 10. Department of Radiology and Alzheimer Center, VU University Medical Center, Amsterdam, The Netherlands; 11. Department of Anatomy and Neurobiology, Boston University School of Medicine; 12. Department of Biomedical Engineering, Centre for Neuroscience, University of Alberta, Edmonton, Alberta, Canada; 13. McGill Centre for Studies in Aging, Department of Psychiatry, McGill University, Montreal, Quebec, Canada; 14. Department of Radiology, Université Laval and Centre de Recherche Université Laval – Robert Giffard, Quebec City, Canada; 15. Dept of Neurology, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland; 16. Northwestern University Feinberg School of Medicine, Department of Psychiatry and Behavioral Sciences, United States; 17. Wayne State University School of Medicine, D-University Health Center, St. Antoine, Detroit, MI; 18. Department of Psychiatry Research and Geriatric Psychiatry, Psychiatric University Hospitals, University of Zurich, Zurich, Switzerland; 19. Department of Diagnostic Radiology, Mayo Clinic and Foundation, Rochester, MN)*

**Backgrounds:** Heterogeneity of landmarks among protocols leads to different volume estimates, hampering comparison of studies and clinical use, for diagnosis and tracking of Alzheimer's disease (AD). There is an urgent need to define a harmonized protocol for manual hippocampal segmentation from magnetic resonance scans. Landmark differences among the 12 most common protocols were extracted, operationalized, and quantitatively investigated. The results were

presented to the Delphi panel, consisting of sixteen researchers with substantial expertise in hippocampal segmentation, in order to reach an evidence-based consensus on segmentation landmarks. *Methods:* The Delphi panel participated in iterative anonymous voting sessions where feedback from previous rounds was utilized to progressively facilitate panelists' convergence on agreement. Panelists were presented with segmentation alternatives, each associated with quantitative data relating: (i) reliability, (ii) impact on whole hippocampal volume, and (iii) correlation with AD-related atrophy. Panelists were asked to choose among alternatives and provide justification, comments and level of agreement with the proposed solution. Anonymous votes and comments, and voting statistics of each round were fed into the following Delphi round. Exact probability on binomial tests of panelists' preferences was computed. *Results:* Sixteen panelists completed five Delphi rounds. Agreement was significant on (i) inclusion of alveus/fimbria ( $p=0.021$ ); inclusion of the whole hippocampal tail ( $p=0.013$ ); (iii) segmentation of the medial border of the body following visible morphology as the first choice ( $p=0.006$ ) and following a horizontal line in the absence of morphological cues ( $p=0.021$ ); inclusion of the minimum hippocampus (comprising head and body) ( $p=0.001$ ); and inclusion of vestigial tissue in the segmentation of the tail ( $p=0.022$ ). Significant agreement was also achieved for exclusion of internal cerebrospinal fluid pools ( $p=0.004$ ). Based on previous quantitative investigation, the hippocampus so defined covers 100% of hippocampal tissue, captures 100% of AD-related atrophy, and has good intra-rater (0.99) and inter-rater (0.94) reliability. *Conclusion:* A Harmonized Protocol for Manual Segmentation has been agreed among an international panel of experts. The protocol will be validated with neuropathological data and its accuracy will be compared with protocols currently used in AD research. Updated information on this ongoing project is available at [www.hippocampal-protocol.net](http://www.hippocampal-protocol.net).

**P47 - ROBUSTNESS OF AUTOMATED HIPPOCAMPAL VOLUMETRY ACROSS MR FIELD STRENGTHS AND SAME-DAY REPEAT SCANS.** R. WOLZ<sup>1,2</sup>, A.J. SCHWARZ<sup>3</sup>, P. YU<sup>3</sup>, P. COLE<sup>4</sup>, D. RUECKERT<sup>1,2</sup>, D. RAUNIG<sup>5</sup>, D. HILL<sup>1</sup> (1. IXICO Ltd, London, UK; 2. Imperial College London, London, UK; 3. Elli Lilly and Company, Indianapolis IN, USA; 4. Cole Consulting, NJ, USA; 5. Icon Medical Imaging, Warrington PA, USA)

*Background:* Low hippocampal volume has been shown to be a predictive measurement of MCI to AD conversion [1], and has been qualified by the EMA as a biomarker to enrich prodromal AD clinical trials [2]. It is important to characterize the performance of automatic algorithms that can be used to quantify this biomarker. This study proposes a methodology for assessing algorithm performance through measuring repeatability and reproducibility of hippocampal volumes obtained using, respectively, (a) intra-examination repeat scans and (b) repeat-scans acquired at different field strengths (1.5T and 3T) selected from the ADNI-1 datasets. This test:re-test methodology is applied to LEAP [3], an established algorithm for automatic hippocampal delineation. *Methods:* In ADNI-1 ([www.loni.ucla.edu/ADNI](http://www.loni.ucla.edu/ADNI)), T1 weighted MP-RAGE volumetric MR scans were acquired at 1.5T and 3T from a large cohort of healthy controls, subjects with MCI and patients with AD. For 153 of these subjects, two repeat scans at baseline and month 12 for both field strengths are available that have passed quality control. The 612 non-processed baseline MR scans from these 153 subjects were downloaded from the ADNI repository; only baseline scans are considered here. Each subject's 3T baseline scan was acquired  $27\pm 18$  [3, 103] (mean $\pm$ SD [min,max]) days after the 1.5T baseline scan. For one subjects, the 3T scan was acquired 78 days before the 1.5T scan; for three subjects this information was not available. Each scan was

individually skull-stripped [4] and bias corrected [5] before volumes for left and right hippocampus were individually extracted using LEAP. Signed differences were evaluated by subtracting the first scan from the second and used to evaluate intra-field strength reliability. Absolute (unsigned) differences were also used to evaluate the agreement between hippocampal volume measurements at the two field strengths. *Results:* Mean $\pm$ SD relative signed differences in hippocampal volume across intra-examination repeat scans were  $-0.02\%\pm 1.94\%$  (1.5T) and  $0.18\%\pm 2.04\%$  (3T). The mean $\pm$ SD signed difference (3T - 1.5T) in hippocampal volume across field strengths was  $1.06\%\pm 3.23\%$ , indicating only a small bias ( $0.32\sigma$ ). The mean $\pm$ SD unsigned difference between field strengths was  $2.77\%\pm 1.95\%$ . Intraclass correlation coefficients (ICCs) corresponding to the intra-examination repeat scans were 0.994 (1.5T) and 0.992 (3T); for the inter-field strength comparison the ICC was 0.979. The measured signed difference was not significantly different between any of the clinical groups at the threshold of  $p=0.05$ . AD subjects ( $N=28$ ) show a lower hippocampal volume ( $1978\pm 343\text{mm}^3$ , averaged over all four measurements) than MCI subjects ( $N=74$ ,  $2178\pm 341\text{mm}^3$ ) and controls ( $N=51$ ,  $2457\pm 271\text{mm}^3$ ). The unsigned inter-field strength variation for AD subjects (difference:  $3.71\pm 2.20\%$ ) was significantly different to that in the MCI cohort (difference:  $2.62\pm 1.83\%$ ) and the control subjects (difference:  $2.48\pm 1.86\%$ ), indicating a relatively high intra-field strength difference for lower absolute volumes. The unsigned difference between MCI subjects and controls was not significantly different. No significant difference was observed in any measure when comparing different scanner vendors (GE Medical Systems, Philips Medical Systems, Siemens). *Conclusion:* This study used the ADNI-1 data to quantify the test:re-test performance of hippocampal delineation using the LEAP algorithm. The results obtained here were obtained using intensity inhomogeneity correction with the N4 algorithm, but without any correction of gradient non-linearity or scaling error, as the ADNI database does not provide pre-processing for both of the back-to-back scans. The intra-examination test:retest provided extremely high repeatability (ICC $>0.99$ ) at both 1.5T and 3T. The between field strength test:re-test also yielded very high reproducibility (ICC $\sim 0.98$ ). Each of these comparisons is subject to different contributions to total variance between two MRI scans. The intra-examination test:re-test includes contributions of instrument noise, patient noise (eg: minor intrascan bulk and pulsatile motion) and automatic scanner adjustments (eg: centre frequency re-calibration), but not change in subject position, state (eg: hydration), or change in scanner. In contrast, the inter-field strength results include all these factors, as well as the effect of a change in the field strength and possibly scanner manufacturer. As a result, it might be expected that test:re-test experiments using data acquired on the same scanner in different scanning sessions or different scanners both at the same field strength would lie between the intra-examination and inter-field strength results obtained here. Further work is needed to confirm this. *References:* [1] C.R. Jack Jr, R.C. Petersen, Y.C. Xu, P.C. O'Brien, G.E. Smith, R.J. Ivnik, B.F. Boeve, S.C. Waring, E.G. Tangalos, E.Kokmen, Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology*. 22;52(7):1397-403, 1999; [2] [www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2011/10/WC500116264.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2011/10/WC500116264.pdf); [3] R. Wolz, P. Aljabar, J.V. Hajnal, A. Hammers, D. Rueckert, LEAP: Learning Embeddings for Atlas Propagation. *NeuroImage*, 49(2):1316-1325, 2010; [4] K. K. Leung, J. Barnes, M. Modat, G. R. Ridgway, J. W. Bartlett, N. C. Fox, S. Ourselin, Brain MAPS: An automated, accurate and robust brain extraction technique using a template library, *NeuroImage*, 55(3):1091-1108, 2011; [5] N.J. Tustison, B.B. Avants, P.A. Cook, Y. Zheng, A. Egan, P.A. Yushkevich, J.C. Gee, N4ITK: Improved N3 Bias Correction, *IEEE Trans Med Imag*, 29(6): 1310-1320, 2010

**P48 - DISENTANGLING THE NORMAL AGING FROM THE PATHOLOGICAL ALZHEIMER'S DISEASE PROGRESSION ON STRUCTURAL MR IMAGES.** M. LORENZI<sup>1,2</sup>, N. AYACHE<sup>2</sup>, X. PENNEC<sup>2</sup>, G.B. FRISONI<sup>1</sup> AND THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE (ADNI) (1. IRCCS San Giovanni di Dio Fatebenefratelli, Brescia, Italy; 2. Asclepios research project, INRIA Sophia antipolis, France)

**Background:** The morphology of the brain observed in patients affected by Alzheimer's disease (AD) is the contribution of different biological processes such as the normal aging and the AD-specific pathological matter loss. Being able to differentiate these complementary biological factors is fundamental in order to isolate and quantify the pathological AD-related structural changes, especially at the earliest phase of the disease, at prodromal and preclinical stages. **Methods:** We chose the ADNI baseline structural MRIs for 37 healthy subjects positive to the CSF Ab42 (Ab+), 86 patients with mild cognitive impairment (MCI) which subsequently converted to AD, 110 stable MCI, and 134 AD patients. For each subject, a "virtual aging" component was defined as the closest point with respect to the longitudinal deformation modeled for the healthy aging of a group of 63 normal subjects negative to the CSF Ab42 [1]. Once removed the aging component, the remaining specific morphological changes were analyzed group-wise, in order to characterize the atrophy patterns at the different clinical stages, and to test their predictive power in encoding the pathological disease progression. **Results:** Even though the considered groups did not significantly differ for age, the estimated virtual ages increased as the clinical condition get worse, and were significantly higher for the MCI stable, converters, and AD groups when compared to the healthy A $\beta$ - ( $p < 0.05$ , standard two sample t-test). After removing the healthy component, the morphological changes specific for the healthy A $\beta$ + were mild, while the changes specific for the MCI converters were more pronounced and mapped to frontal lobes, ventricles, temporal poles, entorhinal cortex and hippocampi. The same pattern, although slightly more pronounced, was appreciable for the AD patients. The stable MCIs showed a milder deformation pattern, mapping essentially to the ventricles and temporal poles. The predictive power of the specific component was 91% sensitivity and 84% specificity for the discrimination AD vs. healthy, and 67% sensitivity and 63% specificity for the discrimination MCI stable vs. MCI converters. **Conclusion:** We provided a rich description of the anatomical changes observed across the AD time span: normal aging, normal aging at risk, conversion to MCI and latest AD stages. More advanced AD stages were associated to both "virtually older" brains, and to increased specific morphological changes that were not related to the normal aging. Importantly, the specific changes provided a good identification of the pathological AD atrophy. These results provide new insights that can lead to new understandings of the AD dynamics, and to novel techniques for the modeling and the early detection of the disease.

**P49 - INTEGRATING BIOMARKERS IN 12 AD PROGRAMS.** A. KALALI, C. VANBELLE, R. HAYDUK, L. HUGHES (1. Quintiles Inc.)

**Background:** An increasing number of AD trials are integrating biomarkers, in particular imaging and lumbar punctures. The imaging modalities requested are, in general, volumetric MRI and amyloid PET imaging utilising either Avids Flortbetapir or GE's Flutemetamol. The geographical distribution of the labelling centres dictates the ultimate site and country distribution for each imaging modality. The compliance with the LPs and MRIs will also have a major influence on the final dataset available for biomarker analysis. **Methods:** We report

on 12 AD programs which have utilised potential disease modifying drugs and all of which had a significant biomarker component. These trials have spanned 31 countries and in excess of 500 investigative sites globally. We have been tracking the biomarker compliance across all of these trials including the location of the MRI scanner, the Tesla strength of the MRI scanner, the PET ligand utilised and the overall compliance with the LP procedure – in addition, the method(s) used to inform subjects and caregivers regarding this procedure and the country-specific compliance rates. These data and the geographical distribution will be presented. **Results:** If the biomarker assessments are within an integrated protocol then the compliance with the requested procedures is higher than if each biomarker assessment is presented as a separate addendum with a separate consent form. In particular, at sites in Japan, compliance went from 0% to 100% when the LPs were mandated in the protocol. Access to an MRI up to a 3T is not an issue globally for the investigative sites, however compliance with the procedure is enhanced if the scanner is on site rather than subjects having to go off site for this procedure. PET compliance is up to 72% of sites having had experience with Flortbetapir and 29% of sites with Flutemetamol (although this percentage is increasing), due to the location of the labelling distribution centers. Lumbar punctures still represent the biggest challenge for subjects and for caregivers. The percentage of compliance with this procedure has improved over time from 8% to 50% due to support given to investigative sites including local language DVDs of the procedure, watching the procedures, using sedation, using x-ray guided techniques, utilizing the services of anesthesiologists to perform this procedure, workshops with PIs, utilizing a "champion" site to motivate other sites and shared "lessons learned". **Conclusions:** Compliance with biomarker assessments can be enhanced by a number of factors including mandating the procedure in the protocol rather than providing as a separate set of addenda, utilising sites with on-site imaging facilities and working closely from a tool box of techniques to improve LP compliance. Our LP compliance rate has risen from 8% in 2005 to more than 50% currently.

**P50 - CONTRIBUTION OF THE N400 EVENT RELATED POTENTIAL IN THE STUDY OF THE PRIMARY PROGRESSIVE APHASIA.** K. BENNY<sup>1</sup>, E. BENATTAR<sup>1</sup>, G. RONDOUIN<sup>2</sup>, S. MORITZ-GASSER<sup>1</sup>, G. TAIEB<sup>3</sup>, J. TOUCHON<sup>1,4</sup> A. GABELLE-DELOUSTAL<sup>1</sup> (1. Department of Neurology, Memory Research Ressource Center for Alzheimer's Disease, University Hospital of Montpellier, France; 2. Neurophysiology Unit, Department of Neurology, University Hospital of Montpellier, France; 3. Department of Neurology, University Hospital of Nîmes, France; 4. INSERM U1061, Montpellier, France)

**Backgrounds:** Cognitive ERPs provide a powerful, non-invasive tool for studying the brain functioning. The N400 is a scalp negativity wave that appears in the EEG waveform 400 milliseconds after reading an inappropriate word that occurs unexpectedly at the end of a sentence with a maximum pick at central parietal area. The N400 has possible functional relation to the lexical-semantic process. N400 amplitude is sensitive to the semantic congruity of the eliciting stimulus with the context, being larger in an incongruous context, than congruous one. The effect of semantic congruity on N400 amplitude is called "N400 effect". Investigations of the N400 congruity effect have generally found abnormalities in neurodegenerative disease. Primary progressive aphasia (PPA) is a rare and insidious language impairment, begins with anomia and characterized by a progressive decline. Most of the time patients with PPA progresses to Fronto Temporal dementia or Alzheimer's disease. The aim of our study was to evaluate the semantic processing in non fluent PPA patients

compared to elderly subjects control group without cognitive impairment and to young healthy subjects group. **Methods:** 3 groups had been studied within the Memory Center of Montpellier: 30 healthy younger subjects (Group Y), 20 healthy older subjects (Group O) and 7 PPA patients (Group PPA). The group O and PPA groups had a language and neuropsychological evaluation. Language evaluation, using the Pyramid and Palm Tree Test, the 80 Pictures Denomination test, comprehension, repetition and writing subtests of the Montreal-Toulouse 86 protocol, new and fixed metaphor of the Montreal Communication's Evaluation protocol (MEC). Electrophysiological recording: 4 electrodes were placed on the median axis of the scalp in frontal (Fz), central (Cz), parietal (Pz) and occipital (Oz). Experimental paradigm: all groups have been evaluated with 3 paradigms. (1) Presentation of 40 priming words randomly paired with a target word that is concordant or discordant; (2) presentation of 40 sentences randomly paired with target word that is concordant or discordant; (3) presentation of 40 usual expressions randomly paired with target word that is correct or incorrect. The 1st and 2nd paradigms solicit the lexical and post-lexical treatment, whereas the 3rd is specific of the semantic treatment. The participant had to indicate if there was congruence or incongruence. **Results:** We showed a significant increase of the N400 wave latency in the group O ( $p < 0.0001$ ) and PPA ( $p < 0.001$ ) groups compared to the Y group. We observed a significant "N400 effect" under central parietal derivations for the group Y ( $p < 0.01$ ) and the group O ( $p < 0.05$ ) whereas it disappears for the PPA group whatever the paradigm used. We also observed that the "N400 effect" was better for the words and the sentences paradigms in the group Y than in the expressions paradigm. Otherwise, we showed in the group O a larger "N400 effect" for the sentences and expressions paradigms. In the PPA group, "N400 effect" was not significant for the expressions paradigm and disappeared for the words and sentences paradigms. **Conclusion:** The conservation of the "N400 effect" in the group O confirmed that the semantic and lexical treatment, even slowed, was kept in this population. Moreover, the absence of significant N400 effect in the PPA group may be reflected alteration of the lexical-semantic process occurred very early in this population. The non significant "N400 effect" in the expressions paradigm observed in PPA group despite the small number of patients could be probably linked to a semantic memory, which activate during this cognitive task. The N400 appears to be a good tool for the assessment of the impaired semantic processing in PPA.

**P51- SUPPORTING EVIDENCE OF THE AD BIOMARKER DYNAMIC MODEL IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT.** S. GALLUZZI<sup>1</sup>, C. GEROLDI<sup>2</sup>, G. AMICUCCI<sup>3</sup>, L. BOCCHIO-CHIAVETTO<sup>4</sup>, M. BONETTI<sup>5</sup>, C. BONVICINI<sup>6</sup>, M. COTELLI<sup>7</sup>, R. GHIDONI<sup>8</sup>, B. PAGHERA<sup>9</sup>, O. ZANETTI<sup>2</sup>, G.B. FRISONI<sup>1</sup> TRANSLATIONAL OUTPATIENT MEMORY CLINIC WORKING GROUP (1. *Laboratory of Epidemiology, Neuroimaging and Telemedicine*; 2. *Alzheimer's Unit*; 4. *Neuropsychopharmacology Unit*; 6. *Genetics Unit*; 7. *Laboratory of the Neuropsychology Cognitive Neuroscience Unit*; 8. *Proteomics Unit, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy*; 3. *Service of Anesthesiology, Azienda Ospedaliera Mellino Mellini di Chiari, Brescia, Italy*; 5. *Neuroradiology Service, Istituto Clinico Citta' di Brescia, Brescia, Italy*; 9. *Nuclear Medicine Service, Spedali Civili di Brescia, Brescia, Italy*)

**Background:** A pathophysiologic model of Alzheimer's disease (AD) has been recently proposed in which beta amyloid accumulation occurs earlier (indexed by abnormal CSF Abeta42), followed by tau-mediated neuronal injury and dysfunction (abnormal CSF tau or FDG-

PET) and lastly atrophic changes (abnormal hippocampal volume, HV). The aim of this study is to validate this model by comparing clinical features and conversion to AD and other dementias among groups of patients with mild cognitive impairment (MCI) with different abnormal biomarker profiles. **Methods:** The patients of this study were 58 with MCI coming to observation to the Translational Outpatient Memory Clinic (TOMC) of the Italian National Centre for AD in Brescia, Italy, in whom all the above AD biomarkers were collected. Patients were divided into 3 groups of no abnormal biomarker, AD biomarker pattern (including 3 subgroups of early=only abnormal Abeta42, intermediate=abnormal Abeta42 and FDG-PET or tau, and late=abnormal Abeta42, FDG-PET or tau, and HV), and any other biomarker combination. Clinical characteristics were compared across groups and subgroups and clinical cases representative of the three groups were described. Abnormality of biomarkers was defined as Abeta42 and tau below/above published cutoffs, temporoparietal hypometabolism on 18F-FDG PET above Herholz's t-sum cutoff, and HV below the 5th percentile of the distribution in healthy elders. **Results:** MCI patients with AD biomarker pattern had lower behavioural disturbances by the NeuroPsychiatry Inventory than patients with any other biomarker combination ( $p < .0005$  on post-hoc comparison) and lower performance on verbal and non verbal memory than the other two groups ( $p = .07$  and  $p = .004$ , respectively, on ANOVA test among groups). Within the subgroups with early, intermediate, and late AD biomarker pattern there was a significant trend to higher rate of conversion to dementia ( $p$  for trend = .006). Moreover, the type of incident dementia was AD in 100% of patients with an AD biomarker pattern, but 0% and 27% in converters with no abnormal biomarker and any other biomarker combination, respectively ( $p = .002$ ). **Conclusions:** The results of this study provide evidence in favour of the dynamic biomarker model and support the use of biomarkers for the diagnosis of MCI due to AD according to the new recently published research criteria.

**P52 - MASS SPECTROMETRY QUANTITATION OF MULTI-COMPONENT PROTEIN BIOMARKER PANELS OF ALZHEIMER'S DISEASE.** E.L. SCHOFIELD<sup>1</sup>, I. PIKE<sup>1</sup>, S. JUNG<sup>2</sup>, H.D. ZUCHT<sup>2</sup>, S. SELZER<sup>2</sup>, C. LOBNE<sup>2</sup>, M.A. WARD<sup>1</sup>, (1. *Proteome Sciences plc, UK*; 2. *Proteome Sciences R&D GmbH & Co. KG, Frankfurt/Main, Germany*)

**Background:** The use of Tandem Mass Tag (TMT) isobaric and isotopic reagents has enabled the development of routine methods for screening of plasma specimens from clinical cohorts. Mass spectrometry experiments are performed using either untargeted or target methods to quantify panels of candidate biomarkers of Alzheimer's disease (AD) in undepleted plasma. Clusterin, complement C3, complement C3a, serum amyloid P component (SAP), alpha-2-macroglobulin (A2M), gelsolin, fibrinogen gamma-chain (FGG) and complement factor H (CFH) have emerged as candidate AD biomarkers from discovery exercises using two-dimensional gel electrophoresis and TMT labeling technologies (Hyeet al., 2006; Lee et al., 2007; Verwey et al., 2008; Thambisetty et al., 2010; Güntert et al., 2010). Furthermore, possession of the apolipoprotein E (Apo E) E4 allele is the only unequivocal genetic risk factor known to-date for late-onset AD and the protein expression of this genetic association may translate as an AD biomarker (Coon et al., 2007). The expression levels and absolute quantitative amounts of these proteins across large patient populations have yet to be described. **Methods:** Results from the analysis of an extensive, well characterised cohort of AD, MCI and Control patients will be reviewed to demonstrate the performance characteristics of the



analytical methods as well as the trends associated with the biomarkers themselves. EDTA plasma was collected from 430 Alzheimer's disease subjects, 395 cognitively normal and 173 mild cognitively impairment subjects were recruited from 2 large multi-centre cohorts. LC/MS/MS screening experiments were performed on a subset of samples using an OrbitrapVelos LC/MS/MS instrument (Thermo Fisher) and a TSQ Vantage triple quadrupole system, programmed to operate in Selected Reaction monitoring (SRM) mode. **Results:** Comprehensive statistical analysis, involving both univariate and MV techniques reveals several correlates within the quantitative proteomics information obtained and these findings will be described in detail. **Conclusions:** The results presented hold promise for the development of a compound biomarker panel for AD to support current clinical practices. Further studies are required to investigate these biomarker signatures to determine their association with other forms of dementia and individual patient response to therapy.

**P53 - INVESTIGATING TAU AND PHOSPHO-TAU MOIETIES PRESENT WITHIN CSF TO FURTHER BIOMARKER DEVELOPMENT.** E.L. SCHOFIELD<sup>1</sup>, C.L. RUSSELL<sup>1</sup>, C. LOBNER<sup>2</sup>, T. PRINZ<sup>2</sup>, M.A. WARD<sup>1</sup>, I. PIKE<sup>1</sup> (1. Proteome Sciences plc, UK; 2. Proteome Sciences R&D GmbH & Co. KG, Frankfurt/Main, Germany)

**Background:** Cerebral spinal fluid (CSF) measurements of A $\beta$ 1-42, T-Tau and P-Tau181 have been demonstrated to have biomarker utility in the context of Alzheimer's disease (AD). However, to our knowledge, a complete characterisation of Tau and its phosphorylation status in CSF from control and AD patients has yet to be undertaken. PHF-Tau from post mortem AD brain is known exist in multiple, hyper-phosphorylated forms. Previous LC-MS/MS studies of post-mortem brain revealed 12 novel phosphorylation sites (Hanger et al, 2007) as well as phosphorylation of Tyr394 (Derkinderen et al, 2005). We have recently demonstrated the preclinical application of multiplexed quantitative mass spectrometry (MS) assays (Phospho-Tau SRM) for Tau phosphorylation screening (Loffler et al., 2012) and we now endeavour to extend these measurements into CSF. Advancing the Phospho-Tau SRM approach towards the analysis of such clinical materials is attractive because additional phosphorylated epitopes of CSF Tau may provide further informative biomarker utility. **Methods:** Pooled hospital remnant CSF (Seralab Laboratories International Ltd.), depleted of abundant proteins (MARS-6 depletion column, Agilent), was prepared for 2-DE as described by Hanisch et al., 2010, with minor modifications. Tau and P-Tau specific antibodies (DAKO Tau, BT2, HT7, pT181, pS202, pT231 and pS396) were used to detect spots containing different epitopes. For MS, hospital remnant CSF (1mL) was precipitated with 2.5% perchloric acid prior to immunoprecipitation (IP) with Tau and P-Tau antibodies as described by Portelius et al., 2008, with minor modifications. Immunoprecipitated proteins were analysed via GeLC-MS/MS using a Top20 collision induced dissociation (CID) method (OrbitrapVelos, ThermoFisher Scientific) and the Phospho-Tau SRM assay (Proteome Sciences plc). **Results:** Here we describe the characterisation of numerous Tau and P-Tau moieties present within CSF. Two-dimensional gel electrophoresis and Western blotting highlights multiple features with distinct iso-electric points and molecular weights. Interestingly, low molecular weight species are detected at ~14kDa and at least one of these moieties is found to originate from the central region of the Tau sequence. A C-terminal fragment of Tau encompassing the full DAKO epitope is also observed. Mass spectrometry characterization of the individual 2DE spots is on-going at the time of abstract submission and we anticipate further annotation of individual Tau moieties will be presented. Preliminary LC-MS/MS

analysis of Tau species enriched from hospital remnant CSF (500uL) via IP (BT2) identified the Tau peptide TPSLTPPTR. Analysis via LC-SRM (1mL) identified SGYSSPGSPGTPGSR, STPTAEDVTAPL VDEGAPGK, IGSTENLK, SPVVSVDTSR and STPTAEAEAGIG DTPSLEDEAAGHVTQAR (1N Tau isoforms). Experiments with additional IP antibodies and phosphopeptide enrichment techniques will provide further insights into the nature of CSF Tau from control and AD patients. **Conclusions:** Complete characterisation of Tau and its phosphorylation status in control, MCI and AD CSF is the next crucial step if CSF measurements of Tau and PhosphoTau are to be fully utilised as a biomarker of AD diagnosis, prognosis and drug discovery. Phospho-Tau SRM assays provide the most comprehensive phospho-site specific array for Tau. With appropriate sample preparation to enrich Tau molecules from CSF, the Phospho-Tau SRM methodology can be extended from preclinical models of AD into clinical materials (CSF). The application of Phospho-Tau SRM assays to support clinical trials will add significant value to AD drug development activities providing further diagnostic utility.

**P54 - QUANTIFICATION OF CEREBRAL GLUCOSE METABOLISM DURING NORMAL AGING: A COMPARISON OF CEREBRAL METABOLIC RATE AND SPM ANALYSIS.** S. NUGENT<sup>1,2</sup>, S. TREMBLAY<sup>1,3,4</sup>, A. CASTELLANO<sup>1,2</sup>, M. FORTIER<sup>1</sup>, E. TURCOTTE<sup>3,4</sup>, T. FULOP<sup>1,5</sup>, M. ALLARD<sup>6</sup>, S. CUNNANE<sup>1,2,5</sup> (1. Research Center on Aging, Sherbrooke, QC, Canada; 2. Department of Physiology and Biophysics, Université de Sherbrooke, QC, Canada; 3. Department of Radiobiology and Nuclear Medicine, Université de Sherbrooke, QC, Canada; 4. Centre for Molecular Imaging, Sherbrooke, QC, Canada; 5. Department of Medicine, Université de Sherbrooke, QC, Canada; 6. Nuclear Medicine Service, Hôpital Pellegrin, UMR-CNRS-5227, EPHE, Bordeaux, France)

**Background:** It is still unclear as to whether lower brain glucose uptake is present in the elderly. The partial volume effect (PVE) is particularly marked when cortical atrophy is present and must be applied as a correction. PVE correction was performed in three relatively recent brain PET studies in which cerebral glucose metabolism was determined in normal aging, and in each case, no aging-related difference remained after PVE correction. However, in a fourth study glucose hypometabolism was observed in the frontal cortex (Kalpouzos et al 2009). Hence, these studies agree that there are few if any regions affected by hypometabolism during normal aging after incorporation of PVE correction. All of these studies used statistical parametric mapping (SPM) to assess the effect of aging and expressed glucose metabolism as a relative measure. There are a few older studies which have both expressed brain glucose metabolism as an absolute value (cerebral metabolic rate of glucose; CMRg,  $\text{Omol}/100 \text{ g}/\text{min}$ ) and have concurrently corrected for PVE. Our aim in the present study was to evaluate whether CMRg or SPM with PVE correction would be better able to detect significant regional differences in brain glucose metabolism during normal aging. **Methods:** Twelve young adults ( $29.6 \pm 3.6 \text{ y}$ ) and fifteen healthy elderly ( $75.8 \pm 4.1 \text{ y}$ ) participants were included in this study. Mini-Mental State Examinations (MMSE), medical histories and blood chemistries were compiled for all participants. MRI acquisition was performed on a Siemens 1.5T scanner. PET scans were acquired using a Philips Gemini TF. Freesurfer and PMOD® 3.3 software were used to calculate regional brain volumes and quantify 18F-FDG uptake. PVE correction was performed in the regions of interest analysis before either calculating CMRg or undertaking SPM. Data were compared using independent Student t-tests. A 0.01 FDR

correction was applied in order to correct for multiple comparisons. **Results:** The elderly had very similar blood chemistry and MMSE scores when compared with the young participants (MMSE:  $29.6 \pm 0.7$  vs.  $29.1 \pm 1.0$ , respectively). Overall, grey matter volume was 16% lower ( $p \leq 0.001$ ) and cerebral spinal fluid was 15% higher in elderly group ( $p \leq 0.05$ ). There was no difference between groups in white matter volume or intracranial space ( $p > 0.05$ ). Grey matter volumes were decreased in all major regions (frontal, temporal, parietal, occipital, cingulate, and subcortical) of the brain in the elderly participants, unpaired t-test). In the elderly, CMRg after PVE correction was 22% lower (24 vs 19  $\mu\text{mol}/100 \text{ g}/\text{min}$ ) and 19% lower (26 vs 21  $\mu\text{mol}/100 \text{ g}/\text{min}$ ) in the left and right olfactory lobes, respectively, 15% lower (42 vs 35  $\mu\text{mol}/100 \text{ g}/\text{min}$ ) and 16% lower (42 vs 35  $\mu\text{mol}/100 \text{ g}/\text{min}$ ) in the left and right superior frontal regions, respectively, and 15% lower (39 vs 33  $\mu\text{mol}/100 \text{ g}/\text{min}$ ) and 19% lower (41 vs 33  $\mu\text{mol}/100 \text{ g}/\text{min}$ ) in the left and right thalamus, respectively (all 0.01 FDR correction). In the elderly, CMRg was also 17% lower (38 vs 32  $\mu\text{mol}/100 \text{ g}/\text{min}$ ) in the right caudate and 11% lower (32 vs 29  $\mu\text{mol}/100 \text{ g}/\text{min}$ ) in the left temporal lobe, (all 0.01 FDR corrected). The voxel-wise SPM approach revealed four clusters of age-related glucose hypometabolism: the left frontal superior medial region, bilaterally in the frontal medial orbital region, the anterior cingulate, and the caudate (0.01 FWE correction). Using SPM, there were also significant clusters of glucose hypermetabolism with age in the left pallidum, bilaterally in the thalamus, as well as in several cerebellar regions (0.01 FWE correction). **Conclusion:** There was general agreement between the two methods employed to assess brain glucose metabolism in the elderly in this study. Glucose hypometabolism with age was widely present in various frontal regions as well as in the caudate, and detected by both methods. However, CMRg has the advantage of permitting calculation of a percent difference between the groups, which is not possible with SPM. Significant brain glucose hypermetabolism in the pallidum, thalamus and cerebellum seen with SPM was not observed in any region when the data were expressed as CMRg. Relative glucose hypermetabolism in these regions may arise because of global mean normalization and its artificial inflation of all regions in which the activity is less decreased than the global mean itself. Larger sample size may be needed in order to validate these results. Technical support by Éric Lavallée, Conrad Filteau, Laurent Hubert and Jennifer Tremblay-Mercier. Financial support from CRC, CIHR, CFI, CFQCU, FRQS and the Université de Sherbrooke.

**P55 - MR IMAGING FEATURES OF ARIA (AMYLOID-RELATED IMAGING ABNORMALITIES) IN PATIENTS TREATED IN PHASE 2 CLINICAL STUDIES OF BAPINEUZUMAB.** J. BARAKOS, R. SPERLING, S. SALLOWAY, C. JACK, A. GASS, J. FIEBACH, D. TAMPIERI, D. MELANCON, Y. MIAUX, G. RIPPON, R. BLACK, Y. LU, H.R. BRASHEAR, H.M. ARRIGHI, K. MORRIS, M. GRUNDMAN.

**Background:** Magnetic resonance (MR) imaging abnormalities have been reported in clinical studies of Alzheimer's disease (AD) with several agents that target cerebral  $\beta$ -amyloid (A). These abnormalities have collectively been referred to as ARIA (Amyloid-Related Imaging Abnormalities). ARIA includes ARIA-E, consisting of parenchymal or sulcal hyperintensities on FLAIR indicative of parenchymal edema or sulcal effusions; and ARIA-H, consisting of hypointense regions on GRE/T2\* indicative of hemosiderin deposition, classified as small ( $< 10\text{mm}$ ) and large ( $\geq 10\text{mm}$ ). A spectrum of ARIA findings identified during studies of bapineuzumab, a humanized monoclonal antibody against  $A\beta$ , are described. **Methods:** Two neuroradiologists, with knowledge of imaging changes reflective

of ARIA, reviewed MRI scans from 210 bapineuzumab-treated patients from three phase 2 studies. ARIA-E and -H were identified and a spectrum of findings was selected for presentation. **Results:** Thirty-six patients were identified with incident ARIA-E, exhibiting a spectrum of MR presentations. Twenty-four patients were identified with incident small ARIA-H. The most commonly encountered MR feature of ARIA-E at detection consisted of a region of sulcal hyperintensity, occurring in 78% (28/36) cases; of these, 13 also had some degree of parenchymal hyperintensity on FLAIR. Parenchymal hyperintensity without a sulcal focus on FLAIR was observed in 8 patients. Of the ARIA-E patients, 35 had acceptable GRE/T2\* images for ARIA-H assessment and of these, 49% (17/35) had incident small ARIA-H. Seven patients developed incident small ARIA-H without ARIA-E. Two other patients with ARIA-E also developed large ARIA-H during follow-up. A variety of ARIA findings will be presented. **Conclusions:** In this report we describe the radiologic features of ARIA, as well as findings which allow ARIA to be differentiated from other pathological conditions. Familiarity with ARIA should permit radiologists and clinicians to recognize and communicate ARIA findings more reliably for optimal patient management.

**P56 - MEASUREMENT INVARIANCE IN MRI-DERIVED VOLUMETRICS, BUT NOT MEMORY TESTS: IMPLICATIONS FOR LONGITUDINAL RESEARCH OF NEURODEGENERATIVE DISEASE.** R.E. TRACTENBERG<sup>1,2</sup>, F. YUMOTO<sup>2,3</sup> (1. Departments of Neurology, Biostatistics, Bioinformatics & Biomathematics, and Psychiatry, Georgetown University Medical Center, Washington, D.C., USA; 2. Collaborative for Research on Outcomes and -Metrics, USA; 3. University of Maryland University College, College Park, MD, USA; 4. Department of Neurology, University of California, San Diego, La Jolla, CA, USA)

**Background:** Large scale studies are collecting biomarker data in unprecedented sample sizes around the world in order to better understand Alzheimer's disease (AD), mild cognitive impairment (MCI), and normal brain aging. Validated biomarkers may be useful for detecting the earliest signals of the neuropathology that is eventually manifested as MCI and/or AD. An additional, and unexplored feature of biomarkers is their potential to be modeled as systems of related variables. Neuropsychological tests can also be modeled as systems, but typically, clinical evaluation of normal and pathological brain aging requires many, varied, assessments. These can be challenging to model as coherent and consistent systems. One analytic method for estimating the coherence and consistency of a system of variables is to test for measurement invariance. **Methods:** Overview: This study explored the measurement invariance of latent variable models based on MRI-derived volumes and cortical thicknesses, and based on memory tests, taken at the baseline and 12 month visits in the data of the Alzheimer's Disease Neuroimaging Initiative (ADNI). Data analyzed had been archived for 650 participants as of November 2009. Because measurement invariance implies consistency of the construct (volumetrics and memory in this case) irrespective of the cognitive status of the individual, we modeled the data from normal controls, and persons with diagnoses of MCI and AD together. Volumetrics: Seven MRI-derived volumetric biomarkers were modeled: right & left hippocampal volumes, which were divided by a factor of 1000 to be compatible in the modeling with the four cortical thickness variables: cortical thicknesses from right and left entorhinal cortex and right and left medial temporal lobes; whole brain volume was included after being divided by a factor of 100,000 for compatibility with the other volumetric variables. Memory: Within the

ADNI data set are five specific memory tests: digits forward, digit reverse, immediate logical memory, delayed logical memory, and three subtests of the ADAS-Cog (immediate recall, delayed recall, and recognition). Analyses: Confirmatory factor analyses were completed using EQS testing the fit of three models of each type of outcome (volumes, memory) at both the baseline and 12 month visits. These models were: 1A. One factor ("F1") is the single cause of the variability and covariability among the variables (7 volumetric, five memory). 1B. Two correlated factors (F1, F2) each contribute to the observed variability & covariability in the indicators (volumes). 1C. Two factors (F1, F2) each contributes independently to the observed variability/covariability in the indicators. The relationship between F1 and F2 is explicitly modeled as being zero. Hypothesis testing: Model fit statistics were compiled to identify the best fit at two visits 12 months apart. The "best" fit was defined as that model fitting well and best in both of the visits. Fit statistics were model chi square, Akaike's Information Criterion, AIC, comparative fit index, CFI, root mean squared error of approximation, RMSEA and standardized root mean square residual, SRMR. Model fit was only interpreted if robust and standard fit statistics led to the same conclusion. We tested the hypotheses that one of these three models would fit. *Results:* Model 1B fit the volumetric data both well (i.e., all five fit statistics within specified ranges) and best at both visits; thus, model form invariance over time was observed for the MRI-derived values when they were modeled as a two-correlated factor latent variable model. Stricter forms of invariance (e.g., equality of path weights over time) were not observed for the volumetrics. No level of invariance was observed for the memory tests; none of these three models fit the memory data well (including the one-factor model, 1A) – and one model did not fit well and best at both baseline and 1 year later. *Conclusions:* Longitudinal modeling with latent variables is an extremely powerful and flexible approach that is gaining attention across scientific domains. Latent growth curve modeling can be applied to single observed scores modeled over time or, with greater power and the potential to estimate precision of trajectories, to systems of observed variables ("multiple indicators"). However, multiple indicator latent growth curve modeling requires that the system of indicators that is being modeled over time is consistent, i.e., that the measurement model is invariant, over time. Latent growth curve modeling of memory in neurodegenerative diseases could be based on only one memory test score over time (not addressed in this study), but such models cannot take advantage of the known complexity of memory, nor of the statistical power that multiple-indicator models possess. Multiple-indicator latent growth curve models could be built and fit for systems of MRI-derived volumes, but not for these memory tests.

**P57 - THE DISTRIBUTION OF AB42 AMONG THE DIFFERENT BLOOD FRACTIONS MIGHT HELP IN THE EARLY DIAGNOSIS OF ALZHEIMER'S DISEASE.** P. PESINI<sup>1,2</sup>, V. PEREZ-GRIJALBA<sup>1</sup>, M. BOADA<sup>3</sup>, L. TARRAGA<sup>3</sup>, P. MARTINEZ-LAGE<sup>3</sup>, I. SAN-JOSE<sup>2</sup>, M. SARASA<sup>1,2</sup> (1. Araclon Biotech Ltd., Proteomic Laboratory, CIBIR Logroño, Spain; 2. Araclon Biotech Ltd., I + D Laboratory, Zaragoza, Spain; 3. Alzheimer Research Center and Memory Clinic. Fundació ACE. Institut Català de Neurociències Aplicades. Barcelona, Spain)

*Background:* There is a growing interest in the development of blood based biomarkers that could be used as enrollment criteria or surrogate output for efficacy in clinical trials and eventually, for screening people at risk of developing Alzheimer's disease (AD) in community settings. We have approached the assessment of the A $\beta$  blood levels in a comprehensive way quantifying levels of A $\beta$ 40 and A $\beta$ 42 free in plasma (FP), bound to plasma proteins (PB) and bound to

blood cells (CB). A pilot study showed that several of those A $\beta$  blood markers could help to distinguish between mild cognitive impairment patients (MCI) and cognitively healthy controls (HC). *Methods:* Here we explore if the relative distribution of both A $\beta$ 40 and A $\beta$ 42 peptide levels in plasma and blood (quantified by ELISA assay), varies among a population sample including HC (n = 18), MCI (n = 30) and AD (n = 17) patients. The MCI patients were subdivided in (i) MCI prodromal AD (MCI-PAD; n = 15) those with a hippocampal memory syndrome, and positive MRI and/or FDG-PET; and (ii) MCI- non prodromal AD (MCI-nPAD; n = 15) those with a memory syndrome and negative MRI or FDG-PET. *Results:* Regarding A $\beta$ 40, the ratio FP/PB, in percentage, was significantly lower in the AD group [median (range interquartil): 105.49 (103.91)] than in the HC, MCI-nPAD and MCI-PAD groups [175.93 (79.28), 191.49 (139.42), 147.09 (159.40); respectively]. The ratio FP/CB40 behaved in a similar way among these groups. In contrast, regarding A $\beta$ 42 the ratio FP/PB was significantly lower in MCI-nPAD, MCI-PAD and AD groups [23.26 (12.15), 31.23 (34.95) and 26.47 (20.74); respectively] than in the HC groups [52.29 (36.50)]. The ratio FP/CB42 behaved in a similar way among these groups. *Conclusion:* The diagnostic value of A $\beta$  in blood might not reside just in a simple plasma A $\beta$  level quantification. It is key to quantify the levels of A $\beta$  peptides free in plasma, bound to plasma proteins and bound to blood cells. Further, the distribution of the A $\beta$  peptide levels among these three blood fractions could also be useful for diagnostic purpose.

**P58 - VALIDATION OF A MULTI-ATLAS SEGMENTATION TECHNIQUE FOR THE QUANTIFICATION OF HIPPOCAMPAL VOLUME - APPLICATION AS A SELECTION CRITERION IN CLINICAL TRIALS IN ALZHEIMER'S DISEASE.** H.J. YU<sup>1</sup>, L. BRACOU<sup>1</sup>, J. SCHAEERER<sup>1</sup>, D. XU<sup>1</sup>, F. ROCHE<sup>1</sup>, B. BELAROUSSI<sup>1</sup>, C. PACHAT<sup>1</sup>, C. DECARLI<sup>2</sup> AND THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE (1. BioClinica Inc., Lyon, France and Newtown, PA, USA; 2. University of California at Davis, CA, USA)

*Backgrounds:* Hippocampal volume (HCV) has been proposed as a key inclusion biomarker in Alzheimer's Disease (AD) studies, to improve diagnostic homogeneity and to select subjects who are likely to undergo measurable clinical change during the course of a clinical trial. An enrichment strategy based on a HCV cutpoint was previously described [1]. However, the optimal HCV cutpoint could differ depending on the HCV quantification methodology used to derive such threshold. This work explored the operating characteristics of low HCV measured by a BioClinica multi-atlas hippocampal segmentation technique (BIOCMA) in predicting disease progression as compared to other published techniques. This work also examined differences in the HCV cutpoints under the same assumptions for subject selection as well as the corresponding sensitivity & specificity results. *Methods:* Subjects: The Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort (data downloaded on March 29th, 2012) of subjects with amnesic mild cognitive impairment (aMCI) was used as a reference dataset to simulate a typical clinical trial population. aMCI subjects were included if they had an MRI with interpretable HCV at baseline and clinical status known or inferred at three years (n = 265). Normal Control (NC, n = 201) subjects with interpretable HCV and with stable clinical status throughout follow-up of up to 36 months were used as a normative dataset to establish regression models allowing an adjustment for age and ICV. Image processing: HCVs were computed with the previously described BioClinica Multi-Atlas method (BIOCMA) combining segmentation propagation, refinement and decision fusion [2]. For comparison, HCVs resulting from the

following methods were obtained from the ADNI website: • Neuroquant, as generated by UCSD on the ADNI website (UCSDNQ); • FreeSurfer Longitudinal v4.4, as generated by UCSF on the ADNI website (UCSFFSL); • FreeSurfer Cross-sectional v4.3, as generated by UCSF on the ADNI website (UCSFFSX). Method for adjustment of hippocampal volume: HCV values, taken as the mean of left and right hippocampi, were adjusted for age and intracranial volume (ICV) as generated by UCSD on the ADNI website based on multiple linear regression models derived from the ADNI NC dataset for each quantification technique. For all subjects in the aMCI dataset, HCV was adjusted according to the following equation:  $HCV\_Adjusted = HCV\_NC\_Mean + Regression\ Residuals$ , Where  $Regression\ Residuals = HCV\_Measured - HCV\_Predicted$  and  $HCV\_Predicted = A + B \times Age + C \times ICV$ , with A, B & C being the regression coefficients computed based on NC dataset of each method and HCV\_NC\_Mean being the mean HCV value of NC dataset for a given method. Analyses A receiver operating characteristic (ROC) curve for HCV was generated, where the outcome of interest was conversion to dementia, predicted by lower HCVs. The area under the curve (AUC) was calculated. Sensitivity, specificity and the cumulative proportion of subjects that would be included in the trial, based on the HCV point were compared amongst all HCV quantification methods. **Results:** The AUC values for adjusted HCVs based on BIOCMA, UCSDNQ, UCSFFSL, and UCSFFSX were 0.691, 0.698, 0.716 and 0.717 respectively. With 67% cumulative subjects (i.e., no more than 1/3 subjects would be excluded using an enrichment strategy based on any of these hippocampus segmentation techniques), the adjusted HCV cutpoints (in mm<sup>3</sup>) based on each method were 3488, 3344, 3022 and 3266 respectively. The corresponding sensitivity and specificity values for such HCV cutpoints were 81.6% and 49.2% for BIOCMA, 78.7% and 46.7% for UCSDNQ, 82.3% and 50.8% for UCSFFSL and 81.6% and 50.8% for UCSFFSX. **Conclusion:** The proposed multi-atlas hippocampus segmentation method successfully compared with published ADNI methods for the assessment of HCV and prediction of conversion from MCI to AD. The performance of discrimination, as demonstrated by the ROC curve based on this new method was similar to those obtained from these other methods. Besides, the optimal HCV cutpoint established based on the multi-atlas method was comparable to other methods. This work also demonstrated the robustness of HCV enrichment strategy for AD clinical trials. **References:** [1]: G. Novak et al., Choice of Threshold Hippocampal Volume as a Selection Criterion in Prodromal Alzheimer's Disease, AAIC 2012, Vancouver, Canada; [2]: B. Belaroussi et al., Multi-atlas segmentation of the hippocampus refined with intensity-based tissue classification, AAIC 2012, Vancouver, Canada

**P58BIS- VALIDATION OF A MULTI-ATLAS SEGMENTATION TECHNIQUE FOR THE QUANTIFICATION OF HIPPOCAMPAL VOLUME – APPLICATION TO ADNI I.** J. SCHAEERER<sup>1</sup>, L. BRACOU<sup>1</sup>, F. ROCHE<sup>1</sup>, HJ. YU<sup>1</sup>, B. BELAROUSHI<sup>1</sup>, D. XU<sup>1</sup>, C. PACHAI<sup>1</sup>, C. DECARLI<sup>2</sup> AND THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE (1. BioClinica Inc., Lyon, France and Newtown, PA, USA; 2. University of California at Davis, CA, USA)

**Backgrounds:** Hippocampal volume (HCV) has been proposed as a key MRI biomarker in Alzheimer's Disease (AD) studies, both for improved subject selection and for monitoring treatment efficacy. HCV measurements must be as automated, accurate and reproducible as possible. A novel automated hippocampus segmentation technique combining multi-atlas propagation and intensity-based tissue classification was previously proposed and demonstrated a good

accuracy of the resulting contours. In this work, this new method was compared to other published HCV quantification techniques using the baseline scans of all ADNI I subjects. Inter-techniques correlations as well as the ability of each one to dissociate subject groups were explored. **Methods:** Data A total of 735 subjects from the ADNI I database were studied. These were broken down as follows: 189 normal control (NC) subjects, 395 subjects with Mild Cognitive Impairment (MCI), and 151 AD subjects. The mean age (standard deviation) of these groups were 76.3 (5.2), 74.9 (7.4) and 75.6 (7.9) years, respectively. Age differences were statistically significant between MCI and NC ( $p < 0.05$ ). **Image processing:** HCVs were computed with the previously described Multi-Atlas method (BIOCMA) combining segmentation propagation, refinement and decision fusion [1]. This method is based on the following steps: • Fully automatic extraction of the intracranial volume (ICV) using a multi-atlas method [2]; • Classification of the voxels inside the ICV into CSF, gray matter and white matter classes using an unsupervised 3D segmentation algorithm using Bayesian classification and Markov Random Field (MRF); • Automatic selection of the best 15 hippocampal atlases from a library of 88 cases using mutual information; • Propagation of the selected atlases using the diffeomorphic demons registration algorithm; • Combination of these segmentations using majority voting; • Refinement of the resulting mask based on the results of the tissue classification; • Decision fusion between the mask after the majority voting step and the refined mask to correct for possible minor mistakes introduced by the refinement step; • No manual correction was performed either on ICV or HCV masks. Mean of the right and left HCVs resulting from the above BioClinica Multi-Atlas method (BIOCMA) were compared to mean HCVs resulting from the following other methods, all of which were based on files downloaded from the ADNI website (<https://ida.loni.ucla.edu>) on March 29th, 2012: • Neuroquant, as generated by UCSD on the ADNI website (UCSDVOL); • FreeSurfer Longitudinal v4.4, as generated by UCSF on the ADNI website (UCSFFSL); • FreeSurfer Cross-sectional v4.3, as generated by UCSF on the ADNI website (UCSFFSX). In addition, ICV as generated by UCSD on the ADNI website was used to control for variations in head size. **Statistics:** Pearson correlations were used to examine associations between all methods amongst all 735 subjects. The HCV values were then z-transformed to eliminate systematic differences between the different methods. Agreement between methods was then tested using the intra-class correlations coefficient (ICC), with Cronbach's alpha used to measure consistency among subjects, for the entire cohort and for each group separately. Finally, an analysis of covariance (ANCOVA) was performed on raw values, using Age and ICV as covariates, in order to assess the ability of each method to discriminate Normal, MCI and AD groups. **Results:** HCVs from all methods were found to be highly and significantly correlated ( $p < 0.001$ ) with each other. Pearson correlations coefficients between the proposed method (BIOCMA) and UCSDNQ, UCSFFSL, UCSFFSX were 0.940, 0.936 and 0.943 respectively. Comparison of methods demonstrated a Cronbach's alpha of 0.990, confirming excellent inter-method consistency. When looking at each population separately, value remained similar (0.984, 0.989 and 0.989 for the NC, MCI and AD groups respectively). When taking either method out, Cronbach's alpha remained  $\geq 0.973$ . Subject groups differed significantly for each method ( $F > 115$ ,  $p < 0.001$ ). Pairwise comparison showed that groups also differed significantly from each other for each method. For the BIOCMA method, estimated marginal means were 3760 mm<sup>3</sup> (standard error = 32.7), 3313 mm<sup>3</sup> (23.4) and 3003 mm<sup>3</sup> (40.1), for the NC, MCI and AD groups respectively. **Conclusion:** The proposed new method successfully compares with NeuroQuant, FreeSurfer Longitudinal and Cross-sectional for the assessment of HCV. Results

strongly correlate to those obtained from these other methods and all methods provided consistent results. Besides, group dissociation between NC, MCI and AD is similar. The comparison results suggest that the proposed automated algorithm is a suitable method for quantifying HCV. *References:* [1]: B. Belaroussi et al., Multi-atlas segmentation of the hippocampus refined with intensity-based tissue classification, AAIC 2012, Poster session (in-press); [2]: J. Schaerer et al., Accurate Intracranial cavity volume estimation in Mild Cognitively Impaired population using multi-atlas segmentation, AAIC 2012, Poster session (in-press).

**P59 - CHANGES OF BIOLOGICAL MARKERS AND BRAIN PET IMAGING AND CLINICAL EFFECTS OF MEMANTINE FOR PATIENTS WITH MODERATE TO SEVERE ALZHEIMER'S DISEASE: A 24 WEEK DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY.**

S. XIAO<sup>1,2</sup>, T. WANG<sup>1,2</sup>, Q. HUANG<sup>3</sup>, K. CHEN<sup>3,4</sup>, E. REIMAN<sup>1,2,4</sup>  
(1. Geriatric Psychiatry Department, Shanghai Mental Health Center, Shanghai JiaoTong University School of Medicine, Shanghai, China; 2. Alzheimer's Disease and Related Disorder Center, Shanghai JiaoTong University, Shanghai, China; 3. Med-X Institute, Shanghai Jiaotong University, Shanghai, China; 4. Banner Alzheimer's Institute and Banner Good Samaritan Medical Center, PET Center, Phoenix, AZ, USA.)

*Objectives:* To investigate the effects of memantine on cognition, biological markers and cerebral glucose metabolism measured by Fluodeoxyglucose (FDG)-positron emission tomography (PET) for patients with moderate to severe Alzheimer's disease (AD) after 24 week treatment period in contrast to that of placebo. *Methods:* This is a double-blind, randomized, placebo-controlled study. 22 AD patients were randomly assigned to either the treatment or the placebo group. Plasma and cerebrospinal fluid (CSF) interleukin-10 (IL-10), amyloid  $\beta$ -40 (A $\beta$ -40), total tau protein, measures of cognitive function tests such as the AD Assessment Scale-Cognitive Subscale (ADAS-cog), the Mini-Mental State Exam (MMSE) and the Severe Impairment Battery (SIB) as well as FDG-PET were acquired at the baseline and after the 24 week treatment period. The memantine dose was 20mg/day from initially 5mg/day in the treatment group. For the image analysis, the follow-up PET was realigned to the baseline scan for each subject and both were normalized to the standard brain template using SPM8. Voxel-wise general linear model based 2-sample t-test was performed to examine the difference of the longitudinal changes in glucose metabolism between the treatment and placebo groups. *Results:* The two groups did not differ in their age (placebo group 64.7 $\pm$ 11.5 vs treatment group 65.7 $\pm$ 12.5), gender (female/male 7/4 vs 7/4) and education (placebo group 7.2 $\pm$ 2.4 vs treatment group 6.9 $\pm$ 2.1). MMSE score (p=0.02), ADAS-Cog (p=0.03) and total SIB (p=0.05) were statistically different between the two groups at week 24 though they were not at baseline (p=0.08, 0.1 and 0.2 respectively). The change of SIB score was statistically different between the two groups (p=0.037). The Plasma and CSF IL-10, A $\beta$ -40, total tau Protein were not statistically different between the two groups both at baseline and at week 24 and change of them from baseline to week 24. The placebo group had significant FDG uptake decline in precuneus, posterior cingulate, temporal, and occipital regions (p=0.005 uncorrected). In comparison to the placebo group, the memantine treatment group either had a reduced decline in posterior cingulate and temporal or showed increase in FDG uptake at week 24 in precuneus and temporal (p=0.005 uncorrected). *Conclusion:* Our findings demonstrate that N-methyl-D-aspartic acid (NMDA) receptor noncompetitive agent memantine in 24 weeks show the potential effect of slowing down the progression of AD.

**P60 - A NEW MAGNETIC RESONANCE-BASED APPROACH TO ASSESSMENT OF PATHOLOGY IN EARLY ALZHEIMER'S DISEASE.** T. JAMES<sup>1</sup>, K. JAMES<sup>1</sup>, L. FARR<sup>1</sup>, G. THOMAS<sup>1</sup>, J. RAFFERTY<sup>1</sup>, M. BRADY<sup>2</sup>, D. CHASE<sup>1</sup> (1. *Acuitas Medical Ltd., Swansea, Wales, UK;* 2. *Dept. of Engineering Science, University of Oxford, UK*)

*Background:* We have developed a new technique that enables in vivo monitoring with near cellular scale resolution of the cortical lesions and neuronal organisation disruption attendant with Alzheimer's disease. Understanding the cause of AD, quantifying risk, and monitoring progression is currently the greatest unmet need in clinical neurology. Though deposition of plaques in the brain is clearly associated with AD, these can occur many years in advance of symptom onset and there is, as yet, no quantifiable measure of their role in pathology development. Nuclear medicine techniques have advanced plaque imaging, but the attendant radiation exposure makes PET an invasive modality. MR is the only available non-invasive tool for assessing pathology-related changes in the brain, allowing longitudinal studies of disease progression and early assessment prior to onset of dementia for gathering population statistics. However quantitative measure of plaques and other fine lesions, as well as of the columnar organisation of cortical neurons, observed in post mortem histology to be a sensitive indicator of AD progression, are on the size scale well outside the capability of current MR imaging. A new magnetic resonance-based technique capable of this resolution has been used to resolve texture within the human cortex and to monitor changes in this tissue due to ageing and pathology. This technique has also been used in a preclinical study comparing the quantitative structural data obtained from a postmortem porcine brain to histology from the same organ, thereby providing verification of the textural measurement. The technique achieves this resolution by targeting structural variation along a single dimension, measuring texture—the repeat spacing of structures in specific tissue—rather than forming an image. This allows rapid data acquisition (scans are between 4 and 6 minutes) so as to minimize patient motion and thereby enable high precision (sub-millimetre) positioning. In the clinical pilot study, a specially-designed, memory foam-lined head cradle allowed precise positioning of the acquisition volume within the middle layers of the cortex. *Method:* Clinical study: 15 subjects ranging in age from 22 to 76 years old were assessed, including three patients diagnosed with moderate AD. Finely sampled, one-dimensional, spatially-encoded echoes were acquired along the long axis of an inner prismatic volume positioned within the cortex, via the application of an in-house-developed pulse sequence. Tailored analysis of regions of interest within the resulting signal intensity profile yield a spectrum of textural wavelengths (structural spacing and regularity) present within the selected tissue volume. Multiple echo recording allows determination of the statistical significance of the peaks present in the textural mid-cortex, running parallel to the top of a cortical fold. Use of a small RF surface coil positioned directly atop the cortical fold under study provides high signal, further boosting S/N. Preclinical study: a porcine brain was obtained from a local abattoir and immersed in saline solution for scanning in a 7T clinical scanner, positioning the sampled volume mid-cortex, parallel to the top of a fold. The brain was subsequently soaked in fixative solution for three weeks and histology sections sliced and mounted for imaging. *Results:* In this pilot study we have: 1) demonstrated the ability of a new technique to resolve texture below 50 microns, even at the top of the brain stem, a notoriously difficult region to image due to cardiac-induced motion. This resolution is sufficient to detect textural changes from various types of finely dispersed lesions associated with AD. 2) differentiated structural elements (vasculature and the myelinated axon bundles) in

the cortex by varying MR contrast. 3) demonstrated that the technique is capable of monitoring age and pathology related changes in neuronal organisation within the cortex. 4) demonstrated the efficacy of an immobilizing head cradle used to provide precise positioning. 5) developed an under-20 minute scanning protocol allowing acquisition of both T1 and T2\* weighted data sets on compromised subjects. 6) demonstrated the correlation between structures seen in histology with those recorded using the new technique in a porcine brain. **Conclusions:** A new, non-invasive technique can measure texture in the brain in vivo with resolution near the cellular level. By use of tailored sequence parameters it is possible to differentiate the sources of texture, whether vasculature, myelinated axon bundles, or cell bundles, their degree of order, and their size. Using this method it should be possible to track pathology associated disruption. The non-invasive nature of the technique, the ease of patient positioning, and the speed of data taking make this new technique uniquely compatible with large scale clinical studies of dementia progression and therapy response. By using standard head coil arrays, the technique can be applied to lesions deeper in the brain, such as in the hippocampus. 1. Chance et al. *Cerebral Cortex*, August 2011.

**P61 - EVALUATION OF BRAIN FUEL METABOLISM DURING NORMAL AGING AND IN MILD ALZHEIMER'S DISEASE (AD): COMPARISON OF 18F-FLUORODEOXYGLUCOSE WITH A NOVEL PET KETONE TRACE - CARBON -11 - ACETOACETATE.** C.-A. CASTELLANO<sup>1,2</sup>, S.T. NUGENT<sup>1,2</sup>, S. TREMBLAY<sup>1,3</sup>, M. FORTIER<sup>1</sup>, N. PAQUET<sup>3</sup>, C. BOCTI<sup>4</sup>, G. LACOMBE<sup>4</sup>, É. TURCOTTE<sup>3</sup>, T. FULOP<sup>1,4</sup>, S.C. CUNNANE<sup>1,2,4</sup> (1. *Research Center on Aging, CSSS-IUGS, Sherbrooke, QC, Canada*; 2. *Department of Physiology and Biophysics, Université de Sherbrooke, QC, Canada*; 3. *Department of Radiobiology and Nuclear Medicine, Université de Sherbrooke, QC, Canada*; 4. *Department of Medicine, Université de Sherbrooke, QC, Canada*)

**Background:** Several studies suggest that lower regional cerebral metabolic rate of glucose (CMRg) is present during normal aging and could be a potential marker of risk of future cognitive decline. Glucose hypometabolism in specific brain regions may play a causal role in the development and/or progression of AD, but it is unclear whether altered cerebral glucose uptake in AD represents a global problem of brain energy metabolism or is specific to glucose. The ketones – acetoacetate (AcAc) and beta-hydroxybutyrate are the brain's main alternative energy substrates to glucose and supply up to 70% of brain energy requirements during prolonged fasting or in other forms of significant glucose deficit. To address these issues, we compared brain fuel metabolism in three groups: young healthy adults, healthy elderly and mild AD. The specific objectives were to: (i) quantify brain regional volumes by magnetic resonance imaging (MRI); (ii) quantify cerebral glucose and ketone uptake by positron emission tomography (PET) with [18F]-fluorodeoxyglucose (18F-FDG) and [11C]-AcAc, respectively, and (iii) compare regional brain volumes, CMRg and CMRk between the healthy young adults and elderly, and between the healthy elderly and mild AD. **Methods:** Twelve young adults (29.6 ± 3.6 y), fifteen healthy elderly (75.8 ± 4.1 y) and eight mild AD (76.6 ± 3.5 y;) were evaluated. Medical histories and blood chemistries were compiled for all participants. Diagnostic of mild AD was established according to the NINCDS-ADRDA AD criteria. Volumetric MRIs were acquired on a Siemens 1.5T scanner. PET images were acquired on a Philips Gemini TF scanner. Freesurfer and PMOD® 3.3 software were used to calculate regional brain volumes and quantify 11C-AcAc and 18F-FDG uptake (mmol/100 g/min). Partial volume correction was performed in the region of interest analysis. Data were compared using a t-test (healthy young vs. elderly and healthy elderly vs. mild

AD). A 0.01 FDR correction was applied to correct for multiple comparisons. **Results:** The young adults had very similar blood chemistry when compared with the healthy elderly and mild AD groups. Mini-Mental State Examination [MMSE] scores (/30) were 29.6 ± 0.7, 29.1 ± 1.0 and 26.5 ± 2.6, respectively. Compared to the young adults, healthy elderly showed a significant decreases in total gray matter (-16%; p<0.001), thalamus (-16%; p <0.001), and hippocampal (-12%; p <0.004) volumes and a significant increase in ventricular volume (+133%; p <0.001). Mild AD was associated with 18% lower intracranial volume, 12% lower white matter volume, and 68% bigger ventricles compared to the healthy elderly. Hippocampal volume was also significantly lower in mild AD (-22%; p <0.003). Brain metabolic profiles in young and elderly groups showed that, globally, brain 18F-FDG uptake was 7 ± 7% lower in the elderly (p<0.006), a difference present in 8/64 brain regions studied, mostly in the frontal cortex, thalamus and caudate. Brain 11C-AcAc uptake was also 17 ± 6% lower in the elderly (p<0.007), a deficit present in 9/64 brain regions mostly in the frontal cortex and cingulate. Globally, brain 18F-FDG uptake was 21 ± 3% lower in AD compared to the healthy elderly (p<0.006), a deficit present in 6/64 brain regions mostly in the cingulate, parietal cortex, precuneus and thalamus. Brain 11C-AcAc uptake was globally 46 ± 5% lower in AD compared to the healthy elderly (p<0.003), a deficit present specifically in the amygdala and caudate. **Conclusion:** The present results show that after rigorous correction for volume differences and multiple comparisons, global brain fuel uptake (mmol/100 g/min) is lower in the healthy elderly and in mild AD, and affects both brain glucose and ketone metabolism. Specific regions with lower brain fuel uptake were different in the elderly from those in mild AD, suggesting different causes. In both the elderly and in mild AD, the brain regions in which glucose uptake was lower were also different from those with lower ketone uptake, and were mostly also different from regions in which the volumes differed. In contrast to brain glucose uptake, brain ketone uptake is controlled principally by plasma [ketone], so we are now evaluating brain fuel uptake in these three groups during mild, experimental ketonemia. Excellent technical support by Éric Lavallée, Conrad Filteau and Jennifer Tremblay-Mercier. Financial support from CRC, CIHR, CFI, FRQS and the Université de Sherbrooke.

**P62 - A DUAL TRACER PET AND MRI APPROACH TO STUDY DETERIORATING BRAIN FUEL METABOLISM DURING AGING.** S.C. CUNNANE<sup>1,2,3</sup>, A. COURCHESNE-LOYER<sup>1,2</sup>, M. ROY<sup>1,2</sup>, S. NUGENT<sup>1,2</sup>, C.A. CASTELLANO<sup>1,2</sup>, S. TREMBLAY<sup>1,4</sup>, É. TURCOTTE<sup>4</sup>, T. FULOP<sup>1,3</sup> (1. *Research Center on Aging, Sherbrooke, QC, Canada*; 2. *Department Physiology and Biophysics, Université de Sherbrooke, QC, Canada*; 3. *Department of Medicine, Université de Sherbrooke, QC, Canada*; 4. *Department of Radiobiology and Nuclear Medicine, Université de Sherbrooke, QC, Canada*)

**Background:** Lower brain glucose uptake is now well-established in Alzheimer's disease (AD) and is generally interpreted as being a consequence of neuronal failure/loss as AD progresses; logically, with neuronal loss, the brain would need less glucose. Nevertheless, lower brain glucose uptake is present in three distinct conditions in which cognition is still normal, but in each of which the risk of AD is increased: (i) carriers of apolipoprotein E epsilon 4, (ii) individuals with a maternal family history AD but still pre-symptomatic, and (iii) elderly pre-diabetics. In each of these three examples, lower and/alter pattern of brain glucose uptake is present before the onset of cognitive deterioration. Whether lower brain glucose uptake is present during aging - a fourth and important risk factor for AD - is still unclear (Cunnane et al, *Nutrition* 27, 3-20, 2011). If chronically lower brain fuel uptake does increase the risk of neuronal death and

cognitive decline in AD, three predictions follow: (i) Lower brain glucose uptake should be present in the healthy elderly before evidence of cognitive decline. (ii) The ketones – acetoacetate (AcAc) and beta-hydroxybutyrate – are the brain's main alternative energy substrates to glucose and supply up to 70% of brain energy requirements during prolonged fasting or in other forms of significant glucose deficit. Brain ketone uptake is regulated by different transporters than for glucose and is modulated by plasma [ketone]. Hence, brain PET using a ketone tracer should indicate whether deteriorating brain fuel uptake is a non-specific global problem in AD, i.e. because the neurons are dying, or is specific to glucose. (iii) At least in the early stages of AD including mild cognitive impairment (MCI), cognitive improvement should be possible if the brain is provided with a ketogenic supplement to bypass deteriorating glucose uptake. We developed a new PET tracer – [11C]-acetoacetate ([11C]-AcAc) – to study brain ketone metabolism in both humans and animal models and test the first two predictions. The third prediction is supported by several published reports of beneficial effects of ketogenic supplements on cognition in mild AD and MCI, suggesting that improved brain fuel supply permits at least partial recovery of neuronal function in MCI and mild AD. *Methods:* Our healthy elderly (65-85 y old) and young adults (18-30 y old) are intensively screened to exclude potentially confounding medical and metabolic conditions, and undergo a battery of cognitive tests. At present, our AD cases are all on an anti-cholinesterase for 3 months prior to brain PET-MRI imaging. We employ a dual tracer PET protocol in which [11C]-AcAc is injected first, followed by a wash-out period and then [18F-FDG] injection. Cerebral metabolic rates ( $\mu\text{mol}/100\text{ g}/\text{min}$ ) of AcAc (CMRAcAc) and glucose (CMRg) are calculated using image-derived input functions corrected against radioactivity in blood samples. Volumetric magnetic resonance images (MRI) are obtained to co-register and quantify the PET data, and correct for brain atrophy with age. Statistical treatment includes FWE adjustment for multiple comparisons. Essentially the same PET-MRI protocol is also used in aged rats  $\pm$  ketogenic diet in order to identify correlates of brain transporter and/or receptor expression that may help explain the PET data. *Results:* Compared to young adults ( $n=15/\text{group}$ ), CMRg in our healthy elderly ( $n=15/\text{group}$ ) was reduced by 15-20% in a few specific brain regions, notably the caudate, thalamus and part of the frontal cortex (both  $p<0.01$ ). These results were similar regardless of the way in which the [18F-FDG] data were expressed (CMR, statistical parametric mapping, principle component analysis). In the healthy elderly, CMRAcAc was lower in the superior frontal cortex and cingulate but not in the thalamus or caudate (both  $p<0.01$ ). Again, different brain regions had lower CMRg and lower CMRAcAc in mild AD than in the elderly. In aged rats on a ketogenic diet, not only was CMRAcAc increased by 28% as anticipated, but CMRg also increased 44% (both  $p<0.01$ ). There was little or no direct link between CMRg or CMRAcAc and glucose or ketone transporter expression in the brain. *Conclusion:* These data support prediction 1 (lower CMRg in the cognitively-healthy elderly) and partially support prediction 2 (both brain fuels affected but different pattern of CMRAcAc than CMRg in both the healthy elderly and in mild AD). Hence, aging-related brain glucose hypometabolism should be distinguished from brain ketone hypometabolism and may contribute to as well as be a consequence of AD. We are developing protocols with ketogenic pharmaceuticals and nutraceuticals in order to sustainably induce mild, experimental ketonemia in both human participants and animal models. The aim will be to determine whether mild ketonemia can correct or bypass deteriorating brain glucose uptake in the elderly, thereby possibly reducing the risk of brain exhaustion and cognitive decline leading to AD. Excellent technical support by Éric Lavallée, Conrad Filteau and Jennifer Tremblay-Mercier. Financial support from CRC, CIHR, CFI, FRQS, CFQCU and the Université de Sherbrooke.

**P63 - AN EVENT- RELATED POTENTIAL INDEX AS A TOOL FOR THE EARLY DIAGNOSIS AND DRUG DEVELOPMENT FOR ALZHEIMER'S DISEASE.** V. PAPALIAGKAS<sup>1,2</sup>, M. TSOLAKI<sup>2</sup>, V. KIMISKIDIS<sup>2</sup> (1. Department of Neurology, Royal London Hospital, London, UK; 2. Third Neurological Clinic, Aristotle University of Thessaloniki, Greece)

*Background:* Cognitive event-related potentials (ERP's) are being used more and more often during the last years in the search for an early diagnostic marker of Alzheimer's Disease (AD). ERP's reflect a sum of several cortical processes that operate simultaneously. While individual ERP components may reveal the underlying mechanisms of particular brain functions, the combination of more components is obviously a more advantageous approach that may improve diagnosis of MCI and AD and aid in new drug development. The aim of the current study was to measure time changes in the N200 and P300 components of auditory event-related potentials (AERP) in Mild Cognitive Impairment (MCI) patients. *Methods:* The study group consists of 22 MCI patients (mean  $\pm$  SD age =  $67.4 \pm 7.8$ ), and a control group of 30 age-matched controls. MCI was diagnosed according to the widely used criteria of Petersen et al. (2001). AERPs were performed at baseline for both groups and in particular for MCI patients at two follow-ups, the first after an average period of  $14 \pm 5.2$  months and the second after  $23 \pm 3$  months after the baseline exam, using the "oddball paradigm". During this time period, 3 patients developed AD diagnosed according to the DSM-IV-TR criteria. N200, P300 and Slow Wave and the N200-P300 peak-to-peak amplitudes and latencies were determined, and correlations between them and neuropsychological tests including MMSE, CDR for cognitive function, GDS for depression and IADL for the activities of daily living were performed. *Results:* Significant differences at baseline between MCI patients and controls were observed for N200 latencies ( $p=0.042$ ) and amplitudes ( $p=0.002$ ), and for SW latencies ( $p=0.024$ ). Over time, P300 latency and N200 amplitude showed statistically significant increase ( $p=0.001$ ) and decrease respectively ( $p=0.001$ ) between examinations. The only correlation observed between psychometric tests and ERP parameters, was between N200 latency and baseline MMSE scores in the group of MCI patients ( $r_s=-0.488$ ,  $p=0.021$ ). In order to better describe the gradual progress of MCI and its transition to AD, we used a new N2-P3 inter-peak index (IPI), defined as the ratio of the N2-P3 interpeak amplitude to latency. In this study, IPI decreased from  $186.2 \pm 69.2\ \mu\text{V}/\text{s}$  at baseline to  $144 \pm 60.8\ \mu\text{V}/\text{s}$  at the 14-month follow-up and to  $122.6 \pm 51.0\ \mu\text{V}/\text{s}$  at the 23-month follow-up ( $p < 0.001$ ). Changes over time of IPI were significantly lower in the MCI-stable than in the AD-converted subgroup. *Conclusions:* Based on the observation that the N200 latency and the P300 amplitude remained unchanged over time, we used a new N2-P3 inter-peak index (IPI) that incorporates changes in N200 and P300 latencies and amplitudes into one single parameter in order to better describe the gradual progress of MCI and its transition to AD. This index appears to be more sensitive than any single ERP parameter in identifying longitudinal changes of the overall cognitive function and discriminating between AD converting and MCI-stable patients. Therefore it may prove a useful tool in the early diagnosis and new drug development for AD.

## NUTRITION AND ALZHEIMER'S DISEASE

**P64 - SUPPORTING SYNAPSE FORMATION AND FUNCTION IN ALZHEIMER'S DISEASE: MODE OF ACTION OF THE SPECIFIC NUTRIENT COMBINATION FORTASYN™ CONNECT.** J.W. SIJZEN, M.C. DE WILDE, M. GROENENDIJK, R.J. HAGEMAN, P.J. KAMPHUIS, L.M. BROERSEN (*Nutricia Advanced Medical Nutrition, Danone Research, Centre for Specialised Nutrition, Wageningen, The Netherlands*)

**Backgrounds:** Alzheimer's disease (AD) patients exhibit significant reductions in synaptic membranes and in numbers of synapses. It is recognized that synaptic loss is the best correlate to the cognitive deficits of AD patients. Synapses and neurites consist of neuronal membranes largely composed of phospholipids. Synthesis of phospholipids depends on the presence of the dietary precursors DHA, UMP and choline. Professor Wurtman and co-workers (MIT) have shown that combined administration of these nutrients increases membrane and dendritic spine formation and improves learning and memory in animal models. **Methods:** B-vitamins and phospholipids act as dietary co-factors in the synthesis pathway of neuronal membranes by increasing precursor availability. Rodent studies have shown that nutrients synergistically enhance membrane integrity, thereby influencing membrane-dependent processes such as M1 receptor function and APP processing, as shown by reduced Abeta production and plaque burden, as well as Abeta toxicity. Epidemiological studies suggest that low intake of n-3 fatty acids, B-vitamins, and antioxidants increases the risk of AD. Other studies suggest that patients with AD have lower plasma levels of these nutrients compared to age-matched controls. **Results:** Based on these insights the multi-nutrient mixture Fortasyn™ Connect was developed. The effect of Souvenaid®, a 125 ml drink containing Fortasyn™ Connect, on memory and cognitive performance was assessed in 2 randomized controlled, double-blind studies, Souvenir I and Souvenir II, with drug-naïve mild AD patients (MMSE 20-26). The studies showed that Souvenaid given for 12 or 24 weeks improves memory in drug-naïve mild AD patients (Scheltens, 2010 and Scheltens, 2012). **Conclusion:** Souvenaid has been shown to improve memory in drug-naïve mild AD patients. To confirm and extend these findings, additional clinical studies on the long term effects and on biomarkers are ongoing. 1. Souvenaid and Fortasyn are registered trademarks of N.V. Nutricia.

**P65 - NUTRITIONAL INTERVENTION WITH FORTASYN™ CONNECT: BENEFICIAL EFFECTS IN EXPERIMENTAL MODELS OF ALZHEIMER'S PATHOLOGY AND FUNCTIONAL DECLINE.** N. VAN WIJK<sup>1</sup>, M.C. DE WILDE<sup>1</sup>, A.A.M. KUIPERS<sup>1</sup>, M. BALVERS<sup>1</sup>, M. GROENENDIJK<sup>1</sup>, J.W. SIJZEN<sup>1</sup>, P.J. KAMPHUIS<sup>1,2</sup>, H. KOIVISTO<sup>3,4</sup>, H. TANILA<sup>3,4</sup>, D. JANSEN<sup>5,6</sup>, V. ZERBI<sup>5,6</sup>, A.J. KILIAAN<sup>5,6</sup>, L.M. BROERSEN<sup>1</sup> (*1. Nutricia Advanced Medical Nutrition, Danone Research, Centre for Specialised Nutrition, Wageningen, The Netherlands; 2. Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands; 3. A. I. Virtanen Institute, University of Eastern Finland, Kuopio, Finland; 4. Neurology, Kuopio University Hospital, Kuopio, Finland; 5. Dept. Anatomy, Donders Centre for Neuroscience, RUNMC, Nijmegen, The Netherlands; 6. Dept. Cognitive Neuroscience, Donders Centre for Neuroscience, RUNMC, Nijmegen, The Netherlands*)

**Backgrounds:** The neurotoxic cascade of beta-amyloid (Abeta) may be initiated at neuronal cell membranes, and soluble Abeta oligomers are thought to disturb membrane properties by binding to membrane

components. As such, the precise composition of neuronal membranes may influence the membrane disrupting properties of Abeta and therefore its toxicity. Moreover, membrane composition has been shown to exert a direct impact on APP processing and the generation of Abeta. The hypothesis that nutritional interventions that positively affect membrane formation and composition will reduce Abeta production, Abeta toxicity and Abeta-induced pathology was tested in a series of experiments using rodent models of Alzheimer's disease (AD). **Methods:** Fortasyn™ Connect (FC) is a nutritional composition that contains both precursors and cofactors for neuronal membrane synthesis, viz. DHA, EPA, UMP, choline, folate, vit.B12, vit.B6, phospholipids, vit.C, vit.E, and selenium. We assessed the potential protective effects of dietary enrichment with FC in the intracerebroventricular Abeta infusion model, and the APP/PS1 transgenic mouse model of AD. **Results:** In the Abeta infusion model, dietary enrichment with FC protected cholinergic neurons from Abeta-induced toxicity, as evidenced by preserved immunoreactivity for the membrane-bound enzymes ChAT and VAcT. FC also prevented the Abeta-induced reduction in exploratory activity. In young APP/PS1 transgenic mice, FC enriched diet decreased brain Abeta levels, amyloid plaque burden in the hippocampus, and neurodegeneration in the neocortex. In aged mice, FC normalized hippocampal levels of the neuronal marker N-acetylaspartate, which were reduced in the APP/PS1 mice. Additionally, FC was effective in alleviating poor spatial learning in aged APP/PS1 mice. **Conclusion:** In line with our hypothesis, FC intervention had a positive influence on the outcome of membrane-bound processes in different rodent models of AD. The effects of this nutritional intervention on AD-like pathology and behavioral changes in AD models warrant further evaluation in AD patients. Fortasyn is a trademark of N.V. Nutricia. Funded by EU FP7-Food project LipiDiDiet (Grant\_211696).

**P66 - THE SOUVENAIID CLINICAL STUDY PROGRAM FOR ALZHEIMER'S DISEASE.** P. SCHELTENS<sup>1</sup>, R.C. SHAH<sup>2</sup>, D.A. BENNETT<sup>2</sup>, R.L. WIEGERS<sup>3</sup>, T. HARTMANN<sup>4,5</sup>, H. SOININEN<sup>6</sup>, P.J.G.H. KAMPHUIS<sup>3</sup> (*1. Department of Neurology, Alzheimer Center, VU University Medical Center, Amsterdam, The Netherlands; 2. Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, Illinois, United States; 3. Nutricia Advanced Medical Nutrition, Danone Research, Centre for Specialised Nutrition, Wageningen, The Netherlands; 4. Deutsches Institut für Demenz Prävention (DIDP), Neurodegeneration and Neurobiology; 5. Experimental Neurology, Homburg, Germany; 6. Department of Neurology, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland*)

**Backgrounds:** Souvenaid®, containing the specific nutrient combination Fortasyn™ Connect1, is designed to improve synapse formation and function in patients with Alzheimer's disease (AD). The nutrients in Fortasyn Connect are precursors and cofactors for the formation of neuronal membranes. Increasing their dietary intake can promote the synthesis of new brain synapses. The proof-of-concept Souvenir I study demonstrated that 12-week use of Souvenaid improves memory performance in drug-naïve patients with mild AD (MMSE 20-26) (Scheltens et al., 2010) and secondary analysis suggested a possible beneficial effect on cognition in patients with worse baseline cognitive performance (ADAS-cog) (Kamphuis et al., 2011). **Methods:** To confirm and extend these results, additional randomised controlled double-blind studies with Souvenaid were designed within the Souvenaid Clinical Study Program: 1) S-Connect study: 24-week study investigating the effects on cognitive performance (ADAS-cog) in mild-to-moderate AD patients (MMSE 14-24) using AD medication; 2) Souvenir II study; 3) 24-week study



investigating the effects on memory performance (memory domain of a Neuropsychological Test Battery (NTB)) in drug-naïve patients with mild AD (MMSE $\geq$ 20); 3) Souvenir II open-label-extension study: 24-week study with the objective to collect long-term safety and compliance data in patients who completed the Souvenir II study; 4) LipiDiDiet study4: 24-36 month study investigating the effects on cognitive performance (NTB) in 300 subjects with prodromal AD (Dubois et al., 20072); 5) Studies to investigate the mode of action of Souvenaid: a) secondary electroencephalography (EEG) and magnetoencephalography (MEG) outcomes in the Souvenir II (sub)study; b) biomarkers in the LipiDiDiet study (MRI atrophy rates and CSF measures); c) magnetic resonance spectroscopy (MRS) study and d) 18F-fluorodeoxyglucose-positron emission tomography in a future study. **Results:** The Souvenir II study demonstrated that Souvenaid significantly improved memory performance (NTB memory domain) during 24 weeks in drug-naïve mild AD patients (Scheltens et al., 20122), thereby confirming and extending the Souvenir I study results. S-Connect did not show an effect on cognition in mild-to-moderate AD patients on AD medication. Compliance was high (>94%), and Souvenaid was well-tolerated in both the Souvenir II and S-Connect study. The hypothesis that Souvenaid acts via improving synapse formation and function was supported by significant effects on EEG measures of functional connectivity in the Souvenir II study. The Souvenir II open-label extension study showed that the use of Souvenaid for 48 weeks was safe and well-tolerated in patients with mild AD. In addition, this study suggested that Souvenaid improves memory performance for up to 48 weeks. Clinical studies to investigate the long-term clinical effects of Souvenaid (LipiDiDiet study) and studies to further support the mode of action of Souvenaid in early AD (MRS study, MEG substudy, biomarkers in the LipiDiDiet study) are ongoing. **Conclusion:** Souvenaid is well tolerated and improves memory performance in drug-naïve mild AD. The clinical efficacy of Souvenaid and mechanisms of action during different stages of AD continue to be evaluated in the Souvenaid Clinical Trial program. 1. Souvenaid is a registered trademark of N.V. Nutricia. Fortasyn is a trademark of N.V. Nutricia. 2. Scheltens et al. *Alzheimers Dement.* 2010; 6(1), 1-10; Kamhuis et al. *J Nutr Health Aging* 2011; 15(8):720-24; Dubois et al. *Lancet Neurol* 2007;6(8):734-46; Scheltens et al. *JAD* 2012, in press (presented at CtAD 2011). 3. Partly funded by NL Food & Nutrition Delta project, FND N°10003. 4. Funded by the EUFP7 project LipiDiDiet, Grant agreement N°211696.

**P67 - UPDATE OF THE LIPIDIET STUDY: A STUDY ON THE EFFECTS OF THE MEDICAL FOOD SOUENAID IN SUBJECTS WITH PRODROMAL AD.** Y. FREUND-LEVI<sup>1</sup>, P.J. VISSER<sup>2,3</sup>, M. KIVIPELTO<sup>4</sup>, P.J.G.H. KAMPHUIS<sup>5</sup>, R.L. WIEGERS<sup>5</sup>, T. HARTMANN<sup>6,7</sup>, H. SOININEN<sup>8</sup> (1. Department of NVS, Section of Clinical Geriatrics, Karolinska Institutet, Karolinska University Hospital, Huddinge, Sweden; 2. Department of Psychiatry and Neuropsychology, Alzheimer Center Limburg, University of Maastricht, The Netherlands; 3. Department of Neurology, Alzheimer Center, VU University Medical Center, Amsterdam, The Netherlands; 4. Aging Research Center, Karolinska Institutet and Stockholm Gerontology Research Center, Stockholm, Sweden; 5. Nutricia Advanced Medical Nutrition, Danone Research, Centre for Specialised Nutrition, Wageningen, The Netherlands; 6. Deutsches Institut für DemenzPrävention (DIDP), Neurodegeneration and Neurobiology; 7. Experimental Neurology, Homburg, Germany; 8. Department of Neurology, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland)

**Backgrounds:** Souvenaid®, containing the specific nutrient combination Fortasyn™ Connect1, is designed to support synapse

formation and function in patients with Alzheimer's disease (AD). The nutrients in Fortasyn Connect are precursors and cofactors for the formation of neuronal membranes and increasing their intake can promote synaptogenesis. Two earlier randomised controlled clinical trials have shown that Souvenaid improves memory performance in drug-naïve patients with mild AD (MMSE 20-26; Scheltens et al., 2010; MMSE  $\geq$  20; Scheltens et al., 20122), indicating that Souvenaid may be most efficacious in the early phases of AD. The 'LipiDiDiet' study3 was designed to investigate the effect of Souvenaid on cognitive performance in the prodromal phase of AD. **Methods:** The LipiDiDiet study is a 24-month, randomised, controlled, double-blind, multi-centre study, investigating the effects of Souvenaid in 300 subjects with prodromal AD (criteria Dubois et al., 20072), having a MMSE score  $\geq$ 24. In a subset of study centres, patients are invited to continue in an optional 12-month double-blind controlled extension period. Primary outcome measure is memory functioning as assessed by a Neuropsychological Test Battery. Secondary outcome measures include progression to AD, cognitive performance (MMSE, ADAS-cog), functional abilities (ADCS-ADL), depression (MADRS), MRI atrophy rate, dementia biomarkers (plasma and CSF), safety, tolerance and nutritional parameters. The main study parameters are assessed at baseline, and after 6, 12 and 24 months of the intervention. **Results:** The LipiDiDiet study started in 2009. Enrolment is expected to be completed in 2012, and first results will be available in 2014. Baseline characteristics of the study population will be presented. **Conclusion:** The LipiDiDiet study investigates the long-term effects of Souvenaid on memory and cognitive performance in subjects with prodromal AD. 1. Souvenaid is a registered trademark of N.V. Nutricia. Fortasyn is a trademark of N.V. Nutricia. 2. Scheltens et al. *Alzheimers Dement.* 2010; 6(1), 1-10; Scheltens et al. *JAD* 2012, in press (presented at CtAD 2011); Dubois et al. *Lancet Neurol* 2007;6(8):734-46. 3. Funded by the EU FP7 project LipiDiDiet, Grant Agreement N°211696.

**P68 - COMBINED NUTRIENT ENRICHMENT INDUCES CHANGES IN SYNAPTIC PROTEIN EXPRESSION IN VITRO.**

P.J. SAVELKOUL<sup>1</sup>, A.A. KUIPERS<sup>1</sup>, A. GOUDRIAAN<sup>2</sup>, R.J. HAGEMAN<sup>1</sup>, J.W. SIJZEN<sup>1</sup>, G.A.B. SMIT<sup>2</sup>, M.H.G. VERHEIJEN<sup>2</sup>, P.J. KAMPHUIS<sup>1,3</sup>, L.M. BROERSEN<sup>1</sup> (1. Nutricia Advanced Medical Nutrition, Danone Research, Centre for Specialised Nutrition, Wageningen, The Netherlands; 2. Dept. Molecular and Cellular Neurobiology, CNCR, VU University, Amsterdam, The Netherlands; 3. Utrecht Institute for Pharmaceutical Sciences (UIPS), University Utrecht, The Netherlands)

**Backgrounds:** Alzheimer's disease (AD) is a progressive neurodegenerative disease and although its etiology is not yet completely understood, it is clear that loss of dendritic spines and synaptic connections are one of the hallmarks of AD. Preclinical work indicates that nutrients such as DHA, EPA, UMP, choline, B-vitamins, folate, phospholipids, vitamin C and E, and selenium (combined in Fortasyn™ Connect, FC) are precursors or cofactors in the synthesis pathway of new neuronal membranes and act synergistically to support synapse formation. To explore the molecular mechanisms by which these nutrient combinations stimulate synaptogenesis, we tested their effects on synaptic protein expression in vitro. **Methods:** PC12 cells were differentiated with NGF to induce neuronal differentiation (characterized by neurite outgrowth and neuronal protein expression) and supplemented with or without combinations of DHA and EPA, UMP, choline, B-vitamins, phospholipids and vitamin C and E and selenium. Subsequently, the effects of multi-nutrient supplementation on gene expression of several proteins involved in synapse formation were determined using Real-Time PCR. In addition, changes in neurite length and in pre- and postsynaptic protein expression were

investigated in control versus FC supplemented primary hippocampal mouse neurons, using high content analysis (Cellomics). *Results:* Analysis of the data showed an increase in mRNA and protein expression of synaptic proteins related to neurite outgrowth and synapse formation upon nutrient supplementation. *Conclusion:* In general, the specific nutrient combination in Fortasyn™ Connect increased synaptic gene expression more than the other nutrient combinations tested. Fortasyn™ Connect is a registered trademark of N.V. Nutricia

#### **P69 - ALZHEIMER'S DIET MODIFICATION: A WEB-BASED NUTRITION TRACKING SYSTEM FOR PATIENT MANAGEMENT AND OUTCOMES RESEARCH.**

R.S. ISAACSON, R.D. KHAN, C.N. OCHNER (1. Department of Neurology, University of Miami Miller School of Medicine, Miami USA; 2. Evolvix, NYC, USA; 3. Department of Psychology, Columbia University College of Physicians and Surgeons, NYC, USA)

*Background:* Recent research shows that Alzheimer's Disease (AD) may be effectively managed through diet and nutrition. The last several years have brought about a rapid expansion in our understanding of the role of dietary intake in both the pathogenesis and treatment of AD. While the rise in AD cases is likely due to a variety of factors (e.g., advancing age of our population, improved ability to make an accurate diagnosis), epidemiological data suggests changes in diet and nutrition patterns may also be causative. The "Western diet" has been extensively studied and epidemiological data supports an association with a higher risk of developing AD. A variety of mechanisms have been proposed to relate high dietary carbohydrate intake, insulin dysregulation, and insulin resistance, to the pathogenesis of cognitive aging and AD. Highly prevalent conditions such as diabetes mellitus (type 2), where insulin resistance may lead to cerebral dysfunction and brain pathology, are associated with age-related cognitive decline and AD. Recent studies have demonstrated the potential for significant memory benefits from specific dietary approaches. In randomized trials, mild cognitive impairment (MCI) patients who adhered to a very low carbohydrate diet, and AD patients who adhered to a low carbohydrate, low saturated fat diet, demonstrated significant improvement in memory performance. Additionally, several vitamins have been shown in randomized trials to both significantly improve memory function in MCI patients, and improve efficacy of cholinesterase-inhibitor drugs in patients with AD. While further studies are warranted, recent randomized, double-blind, placebo controlled trials support the use of the Omega-3 fatty acid docosahexaenoic acid (DHA) and the medium-chain triglyceride caprylidene in the management of AD. Pharmacogenomic data suggests that these interventions may preferentially work in APOε-4 AD patients. The non-pharmacologic dietary approaches that balance safety with scientific evidence are an essential consideration for clinicians in the comprehensive management of MCI and AD. *Methods:* In an effort to allow clinicians a platform to more optimally study the effects of dietary patterns, we developed a comprehensive, web-based AD nutrition tracking system (AD-NTS). The platform was created by using open source php scripting language in conjunction with MySQL database to store, track and monitor daily dietary patterns of patients. We developed a secure interface, which allows users to create their own username and password, and subsequently login to their customized administrative AD-NTS portal. Patients can track pre-specified daily dietary intake parameters (e.g. macronutrients, servings of fish, other lean proteins, and antioxidants), as well as medications, vitamins and supplements prescribed. Users can also track daily exercise patterns, and body markers (e.g., body weight, waist circumference). Customized reporting features include

summary emails (containing text, or an attached Microsoft Word or Adobe pdf document) sent to the user by aggregating pre-specified data points from the AD-NTS database. We are using an open source API from Google Charts to produce reports as graphical representations of the user data on the site as well. All data and overall interaction with our web-based application uses SSL technology to provide data security. All communication on the site is encrypted using 256-bit SSL encryption. Overall server and application infrastructure is built using LAMP stack and open source php framework and technology. *Results:* The AD-NTS has been successfully developed and is currently being utilized in beta testing by users via a web-based platform. Interim data suggests users are highly satisfied with the current functionality and Likert scale ratings are also uniformly positive. Several user suggestions for additional functionality are in process of being developed and will be demonstrated. *Conclusion:* Additional tools to assist with the scientific study and patient management of dietary interventions for AD are necessary. Further multi-institutional study is warranted to determine the usability and user perceptions of this innovative pilot software.

#### **P70 - EVIDENCE ON DIET MODIFICATION FOR ALZHEIMER'S DISEASE AND MILD COGNITIVE IMPAIRMENT.**

C.N. OCHNER<sup>1</sup>, D. BARRIOS<sup>2</sup>, C. LEE<sup>2</sup>, C.E. GREER<sup>3</sup>, R.S. ISAACSON<sup>3</sup> (1. Columbia University, College of Physicians & Surgeons, NYC, USA; 2. Columbia University, Institute of Human Nutrition, NYC, USA; 3. University of Miami Miller School of Medicine, Miami, USA)

*Background:* Recent research has tested the effect of dietary interventions for Alzheimer's disease (AD) and mild cognitive impairment (MCI). It is essential for clinicians to be aware of this research in order to best educate and inform patients. *Methods:* Pubmed was used to identify clinical trials and additional studies addressing the relation between dietary practices and memory function. Evidence, with deference to clinical trials, surrounding the use of dietary interventions for the prevention and treatment of AD and MCI is rated as: Strong, Moderate, Weak or Insufficient. *Results:* Mediterranean Diet: A Mediterranean-style diet is proposed to increase vascular health and have possible neuroprotective effects against oxidative damage and inflammation. Although clinical trials are lacking, a preponderance of prospective evidence (Scarmeas [et al.]; 2006; 2007; 2009; Gu, 2010; Tangney, 2011) suggests that adherence to a Mediterranean-style diet reduces risk for the development of AD. Combined with additional associated health benefits and low risk of adverse effects, there is Moderate evidence supporting the use of a Mediterranean-style diet for AD and MCI. Low Carbohydrate/Glycemic Diet. Decreasing carbohydrate intake is proposed to minimize impairment of neuronal functioning and oxidative damage. It may also generate ketone bodies, which may be utilized by the brain as an alternate fuel source. There are several supportive trials (Craft 2011; Krikorian 2010; Cao 2007; Van der Auwera 2005) and studies (Pasinetti and Eberstein 2008; Henderson 2004; Barberger-Gateau 2007; Seneff 2011) in MCI and AD. Other studies have not supported these findings (Luchsinger 2007). However, due to the low-risk nature of this diet (in non-diabetics) and current evidence, there is Moderate support for carbohydrate reduction for AD and MCI. Low Saturated Fat Diet. A low saturated fat diet is proposed to reduce amyloid deposition, inflammation of blood-brain-barrier vessels and nerve cell death. The most relevant clinical trial (Bayer-Carter 2011) demonstrated that, in combination with low glycemic index, low saturated fat diets suppressed biomarkers associated with AD and CNS free radical injury. Several other studies (Craft 2011, Scarmeas 2006; Morris 2006; Morris, 2003) were also

supportive. Overall, a low saturated fat diet carries minimal risk of adverse effects and has Moderate supportive evidence for AD and MCI. Antioxidants. Primarily for prevention, antioxidants are proposed to neutralize free radicals and counteract mitochondrial & cytosolic oxidative stress. The only clinical trial (Galasko 2012) found that neither a combination of Vitamin E, C, and alpha-lipoic acid (pill form) or CoQ-10 had any effect on AD. However, other studies (Milgram 2005; Pop 2010; Fahnstock 2012; Devore 2012) have shown a positive relationship between antioxidant intake (e.g., berries rich in flavonoids) and memory function. Overall, antioxidant supplementation and antioxidant rich diets carry low risk of adverse effects and has Weak to Moderate supportive evidence for MCI and AD. Omega-3 Fatty Acids. Omega-3 fatty acids are proposed to augment the production of LR11, a protein that may reduce beta amyloid plaques and help reduce brain inflammation. Several trials (Kotani 2006; Chiu 2008; Yurko-Mauro 2010) demonstrated enhanced cognitive performance in MCI patients treated with omega-3 supplements. However, others showed no effect in MCI (Van de Rest 2008), with mixed results in AD (Boston 2004; Freund-Levi 2006). The most recent (Quinn 2010) found pharmacogenomic considerations (possible effectiveness in subset of APOE4 negative patients). Overall, omega-3 supplementation (DHA and/or EPA) carries low risk of adverse effects and has Moderate supportive evidence. Coconut Oil. Coconut oil (high in medium chain triglycerides) is thought to increase the production of ketone bodies. To date, no trial or study has been conducted to assess the relation between coconut oil intake and the incidence, progression or treatment of MCI or AD. In clinical practice, hydrogenated forms can raise cholesterol and should be avoided, as should those containing trans-fats. Thus, there is insufficient evidence to recommend use of coconut oil for AD or MCI. *Conclusion:* There is evidence in support of certain specific nutritional interventions for AD and MCI. Moderate evidence supports the Mediterranean diet for reducing risk of developing MCI and converting from MCI to AD. There is Moderate support for the use of low carbohydrate and low saturated fat diets. The synergistic effects of these dietary combinations is reported. These diets appear relatively safe and have been associated with additional health benefits in overweight and obese individuals. Evidence of neuroprotective effects of dietary antioxidants and Omega-3 fatty acids is growing. Due to the lack of empirical evidence and potential for adverse effects (atherosclerosis and hypercholesterolemia), there is Insufficient evidence to support coconut oil for MCI or AD. Ultimately, there remains a clear need for further scientific evaluation of the use of dietary interventions for the treatment and prevention of AD. There is a particular need for clinical trials to determine whether the dietary interventions discussed here have a definitive causal role in protecting and/or regaining memory function.

## MISCELLANEOUS IN CLINICAL TRIALS

### **P72 - FACE-NAME ASSOCIATIONS MEMORY TRAINING DURING NON-INVASIVE BRAIN STIMULATION IMPROVES MEMORY IN ALZHEIMER'S PATIENTS.**

M. COTELLI<sup>1</sup>, R. MANENTI<sup>1</sup>, M. PETESI<sup>1</sup>, M. BRAMBILLA<sup>1</sup>, S. ROSINI<sup>1</sup>, O. ZANETTI<sup>1</sup>, C. MINIUSSI<sup>1,3</sup> (1. IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy; 2. Centre for Brain Aging and Neurodegenerative Disorders, Neurology Unit, University of Brescia, Italy; 3. Department of Clinical and Experimental Sciences, National Neuroscience Institute, School of Medicine, University of Brescia Italy)

*Background:* Given the limited effectiveness of pharmacological treatments, non-pharmacological interventions in Alzheimer disease (AD) has gained attention in recent years. Currently, there are many

different approaches under study that range from multi-strategy approaches to cognitive training (Cotelli et al. 2006a). Recent studies have reported enhanced performance on specific cognitive tasks in patients with several types of neurological diseases after receiving non-invasive brain stimulation (NIBS), i.e., repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) to specific cortical areas (Miniussi et al., 2008). Specifically, NIBS reduces vocal reaction times for picture naming in normal subjects (Cappa et al., 2002; Cotelli et al. 2010) and improves the number of correct responses in AD patients affected with mild to moderate (Cotelli et al., 2006b) and moderate to severe (Cotelli et al., 2008) dementia. In addition, persistent beneficial effects of off-line rTMS on sentence comprehension in AD patients have been described recently (Cotelli et al., 2011). Using tDCS, it has also been recently shown that a single tDCS session can ameliorate visuospatial attention deficits in stroke patients (Sparing et al., 2009) naming abilities in vascular aphasia (Baker et al., 2010; Monti et al., 2008) and memory in AD (Boggio et al., 2009; Ferrucci et al., 2008) and many others pathologies (Nitsche et al., 2008). In particular, anodal tDCS seems to be a good candidate to increase neuronal excitability and, consequently, performance in patients. It has been hypothesized that tDCS modifies cortical plasticity and has effects that may outlast the stimulation period itself. Despite the impact that these clinical applications could have on the society to relieve the burden of disease in pathologies that are prevalent among elderly population, studies in this field have been scarce. The aim of the present study is to investigate the beneficial effects of anodal tDCS and specific memory training on face-name associations memory in a AD patients sample. The protocol will allow us to investigate the additional effects of the combined treatment. *Methods:* During the project period, we evaluated the specific effect on the performance of face-name associations memory and motor tasks from anodal tDCS combined with memory training for face-name associations vs. placebo tDCS combined with memory training for face-name associations and vs. anodal tDCS combined with motor training. 30 AD patients were randomly assigned to one of three study groups: Group 1 (11 AD patients), anodal tDCS during memory training; Group 2 (12 AD patients), placebo tDCS during memory training; Control Group 3 (7 AD patients), anodal tDCS motor training. The treatment session consisted of the application of anodal or placebo tDCS over the dorsolateral prefrontal cortex for 25 minutes during the specific training. *Results:* We run a 2 (timing: baseline, 2 weeks) X 3 (group: Group 1, Group 2, Group 3) repeated measures ANOVA over the performance in the face-name associations memory task. A significant interaction between group and timing was observed ( $p < 0.03$ ). Post-Hoc (LSD Fisher) analyses revealed that a significant improvement in memory was observed in Group 1 and Group 2, whereas no changes were recorded in Group 3. No effects were observed in motor abilities. *Conclusion:* Our findings suggest a potential role of tDCS treatment in combination with Face-Name training in AD. Longer follow-up will evaluate the beneficial effect in these patients over time.

### **P73 - PHYSICAL EXERCISE TRAINING IN OLDER ADULTS DIAGNOSED WITH MILD TO MODERATE DEMENTIA.**

A. ZAMFIRESCU<sup>1</sup>, A. CAPISIZU<sup>1</sup>, M. SLAVILA<sup>2</sup>, A.A. CAPISIZU<sup>3</sup>, A. ROMILA<sup>1</sup> (1. University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania "Sf. Luca" Hospital, Clinic of Geriatrics, Bucharest, Romania; 2. National Academy of Physical Education and Sports, Bucharest, Romania; 3. Alexandru Obregia Hospital, Clinic of Neurology, Bucharest, Romania)

*Backgrounds:* In Europe 5 million people suffering from dementia are estimated, Alzheimer's disease being the most common type of

dementia. Unless new treatments are developed the number of individuals suffering from dementia are expected to increase, as the population ageing progress is powered by long-term low fertility and gains in longevity. Population ageing has started later in Romania but its speed is now among the fastest in Europe. Since dementia proves to be a multifactorial disease, multidomain interventions, both pharmacological and non-pharmacological, could prove to be a solution. Physical exercise is known to influence many of the dementia risk factors such as cholesterol, inflammation, and atherosclerosis. It increases cerebral perfusion and oxygenation, decreasing amyloid deposition and possibly tauopathy, positively influencing cognition and thus being neuroprotective. Our objective was to prove the effectiveness of physical exercise training in older adults diagnosed with dementia. *Methods:* We investigated two groups of 10 patients, diagnosed with mild to moderate dementia, on specific dementia medication, first group with physical training intervention, and the second group without. The intervention consisted in 30 to 40 minutes of aerobic exercise training, 5 days per week, 3 months. Patients were recruited from Sf. Luca Hospital, Clinic of Geriatrics, in Bucharest-Romania, being enrolled in a clinical trial regarding treatment opportunities in dementia, from the branch of specific dementia treatment (acetylcholinesterase inhibitors (AChEI) and/or NMDA receptor blockers) accordingly to their diagnose and current national guidelines. All patients and / or caregivers had received instruction on the importance of cognitive and physical exercise training, nutrition, socialization. The intervention group included 10 patients diagnosed with dementia (4 with degenerative AD type dementia, 2 with vascular type dementia and 2 with mixed dementia). The control group of 10 patients, with same diagnostic type and dementia degree (based on MMSE), had similar median age (71.5 in the first group versus 71) and educational level. We used baseline neuropsychological tests: MMSE, Clock Drawing Test, GDS (Global Deterioration Test, Reisberg), R-ACER (Romanian version of Adenbrooke's Cognitive Evaluation Revised), Geriatric Depression Scale, ADL/IADL (Activities of Daily Living / instrumental ADL) and "physical" measurement testes such us: BMI, hand grip, inferior limb circumference, spirometry and the short physical performance battery consisting in balance tests, gait seed test and chair stand test. Follow up consisted in re-evaluations in both groups at 3 weeks, 6 weeks, 9 weeks and 3 months. The intervention aimed individualized physical exercise training program adapted to age, gender and comorbidities. One of main concerns of the intervention was patients' compliance. First general than specific warm up exercises were performed, for the main muscle groups. General warm up started from head to neck, trunk, upper limbs, pelvis, lower limbs, and specific postural exercises. We targeted walking, balance and breathing exercises, with a general recommendation of 2 breath in/ 4 breath out, recovery pauses after dosed 2 to 3 series of 5 to 10 repetitions, adjusted to each patient's physical abilities, with a slow yet constant tendency to increase the effort. Cool down exercises and relaxation ended each session. *Results:* At 3 weeks there were no significant changes in cognitive or physical tests, the latter could be explained by a longer period of time needed for adaptation to physical effort in the elderly. There was an evident amelioration on Geriatric Depression Scale in the intervention group, which could be due to the exposure to socialization and other environmental changes as annex benefits; this positive effect on depression was maintained through the entire study. Improvement of short physical performance battery in the intervention group was observed starting at week 3 and 9, and an exponential tendency of increasing between week 9 and the 3 months control, with statistical power for the intervention versus nonintervention group at 3 months. As regarding cognitive tests, better MMSE and R-ACER scores were obtained in the intervention group at all dementia types, after 6 weeks, up to the 3 months visit as compared

to the control group. No significant changes in Global Deterioration Scale could be found. Participants will be followed for an additional 3 to 6 months after the 3 months physical exercise training, in order to determine post intervention benefits. *Conclusions:* The benefits of physical exercise in older adults diagnosed with mild to moderate dementia prove to be effective on cognitive, physical performance, and mood disorders. Further studies on a larger number of patients are necessary in order to create a protocol of physical exercise rehabilitation in dementia. Physical exercise is a cost efficient therapy targeting a lot of neurophysiological pass ways. Multimodal intervention in dementia, considering both pharmacological treatments and non-pharmacological treatment's development seem to be the hope for a better management of patients diagnosed with dementia.

#### **P74 - COGNITIVE IMPAIRMENT PREVALENCE AND CORRELATIONS WITH SUBJECTIVE MEMORY IMPAIRMENT: FINDINGS FROM BRASOV, ROMANIA.**

M. GURGU<sup>1</sup>, A. ZAMFIRESCU<sup>1,3</sup>, A.M. STROIE<sup>1,4</sup>, R. AUREL<sup>1</sup> (1. University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania; 2. Department of Geriatrics, Emergency Hospital- Brasov, Romania; 3. Clinic of Geriatrics, "Sf. Luca" Hospital, Bucharest, Romania; 4. Department of Geriatrics, Hospitalier Bretagne, Vannes, France )

*Background:* Brasov, as well as Romania, and most of the European countries, face demographic ageing, with a high prevalence of chronic diseases which often co-exist in the elderly. Dementia has one of the fastest growing prevalence, being also one of the most disabling chronic diseases. Early evaluation of cognitive functioning is essential to establish adequate preventive and intervention strategies. Our aim was to investigate the association between subjective memory impairment (SMI) and objective cognitive impairment (CI), and to assess correlations with age, sex, education, depressive symptoms, thyroid function, cardio and cerebrovascular risk factors, and other comorbidities in a group of people screening for memory and physical health from Brasov, Romania. The study was part of the campaign of Romanian Alzheimer's Disease Society - Brasov department; the primary endpoint of the campaign was to promote recognition of early symptoms of AD, and to inform patients and caregivers on existing treatment and care possibilities. *Methodology:* The study enrolled 248 people who were willing to test their memory and physical health (from Oct. 2011 till May 2012). We excluded AD or any other type of dementia or mental illness diagnosed patients. History taking included data on educational level, marital status, smoking, alcohol intake, physical exercise and nutritional habits, cranial traumatism, thyroid dysfunction, depression, hypertension, diabetes and dyslipidemia history, cerebrovascular disease, Parkinson disease; infectious disease, arthritis. Body mass index and blood pressure were determined. A short physical and neurological examination was performed. SMI was noted and neuropsychological evaluations of cognitive function performed (MMSE, Clock Drawing Test). Fervency of visits to the general practitioner and number of hospitalization was also pointed. *Results:* All patients were from the urban area. The mean age was 68.9; 75% of the patients were female; 73% had medium educational level, 23% had superior educational level; 3.3 % had no education. Prevalence of SMI was very high, 87% of the patients. Most of the patients- 84% were between the normal limits of MMSE, 15% had mild cognitive impairment (MMSE  $\geq$  21), less than 1% had moderate cognitive impairment; no severe cognitive impairment was detected. This distribution is due to the fact that dementia was an exclusion criteria from the study. Severe stages of cognitive decline accompanied by behavioral changes in demented people are easily recognized and patients frequently get to health professionals at this

late stage. So the challenge is to detect early stage cognitive impairment. In the logistic regression, cognitive impairment was associated with older age, female gender and depression. Marital status and the level of education influenced cognitive impairment (weak correlation). There was a good correlation between depression, hypothyroidism and cognitive decline. The prevalence of depression was significantly higher in women at adult age; depression in adult life could be a positive predictor of cognitive impairment in older age. In the group with mild cognitive impairment the prevalence of cardiovascular (CV) risk factors was higher than in the group with normal MMSE. There was only 1 very-old person, in whom we observed the presence of only 2 cardio-vascular risk factors out of 9 that we pointed. This is probably due to the fact that only healthy, strong individuals survive to their old-old period of life. Visiting frequency to the GP is increasing with age, and has a negative correlation to hospitalization. *Conclusions:* Subjective memory impairment has a high prevalence, 87% of the evaluated patients had SMI. It has to be correlated with neuropsychological tests in order to determine a cognitive impairment. Cardiovascular risk factors, depression, hypothyroidism, and certain chronic disease such as hypertension and diabetes are frequent in subjective memory impairment, could be used as prognostic factors for cognitive impairment. Interdisciplinary approach in cognitive impairment, collaboration between specialists in neurology, cardiology, psychiatry, geriatrics and primary health care professionals is very important for a better control of risk factors, and an efficient primary and secondary prevention of dementia syndromes. Campaigns for information on cognitive decline through the local Alzheimer's Disease Society are good opportunities for early detection and intervention strategies development.

**P75 - COMPUTERISED COGNITIVE TESTING CAN IDENTIFY YEAR BY YEAR DECLINES IN NON-DEMENTED ELDERLY AGED 70 TO 90 YEARS.** K.A. WESNES<sup>1,2</sup>, B.K. SAXBY<sup>3</sup> (1. Bracket Global, Goring-on-Thames, UK; 2. Centre for Human Psychopharmacology, Swinburne University, Melbourne, Australia; 3. Newcastle University, Newcastle upon Tyne, UK)

*Background:* The deficits to cognitive function which occur in normal ageing can potentially be treated with pharmaceutical and other products. Further, as criteria have now been proposed for pre-clinical dementia, trials are now being planned with compounds designed to prevent or reduce cognitive decline in groups of 'healthy volunteers' identified to be at risk of developing Alzheimer's disease. However, in order to conduct such trials, cognitive tests need to be employed which can reliably assess such change. *Methods:* The CDR System is a computerised set of 9 tests of attention, working and episodic memory which has been widely used in trials of potential cognition enhancers in healthy volunteers, age-related cognitive decline, MCI and the dementias. 256 normotensive volunteers (113 females), mean age 76 years (range 70 to 90), mean MMSE 28.8 (range 23 to 30), were trained on the CDR System before a baseline was established, and then retested yearly for up to 5 years. *Results:* Composite factor scores were derived from the various test measures. Performance was found to decline significantly over the study period on four of the five scores: power of attention, quality of episodic recognition memory, quality of working memory and speed of retrieval of information held in memory. Power of attention showed significant deficits from year one onwards, two other measures showed deficits by year one, and all showed significant deficits from year three onwards. *Conclusions:* This study has demonstrated that the use of validated and sensitive tests of cognitive function can detect decline over a 5-year period in healthy elderly volunteers. Such testing is therefore fit for purpose for the evaluation of treatments aimed at preventing or even reversing age-

related declines in cognitive function, as well as treatments which may delay the onset of Alzheimer's disease in high risk but otherwise healthy populations. *Disclosures:* No funding was received for the conduct of this research. The main author reports potential conflicts which are described in the program. Sperling RA, Aisen PS, Beckett LA et al.(2011) Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia* 7:280-292.

**P76 - THE TRANSITION OF COGNITIVE DECLINE FROM NORMAL AGEING TO MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE.** K. WESNES<sup>1,2</sup>, W. LENDERKING<sup>3</sup> (1. Bracket Global, Goring, UK; 2. Swinburne University, Melbourne, Australia; 3. United BioSource, Boston, USA)

*Background:* The deficits to cognitive function which occur in normal ageing can potentially be treated with pharmaceutical and other products. Further, as criteria have now been proposed for pre-clinical dementia, trials are now being planned with compounds designed to prevent or reduce cognitive decline in groups of 'healthy volunteers' identified to be at risk of developing Alzheimer's disease. However, in order to conduct such trials, cognitive tests need to be employed which can reliably assess such change. *Methods:* The CDR System is a computerised set of 9 tests of attention, working and episodic memory which has been widely used in trials of potential cognition enhancers in healthy volunteers, age-related cognitive decline, MCI and the dementias. 256 normotensive volunteers (113 females), mean age 76 years (range 70 to 90), mean MMSE 28.8 (range 23 to 30), were trained on the CDR System before a baseline was established, and then retested yearly for up to 5 years. *Results:* Composite factor scores were derived from the various test measures. Performance was found to decline significantly over the study period on four of the five scores: power of attention, quality of episodic recognition memory, quality of working memory and speed of retrieval of information held in memory. Power of attention showed significant deficits from year one onwards, two other measures showed deficits by year one, and all showed significant deficits from year three onwards. *Conclusions:* This study has demonstrated that the use of validated and sensitive tests of cognitive function can detect decline over a 5-year period in healthy elderly volunteers. Such testing is therefore fit for purpose for the evaluation of treatments aimed at preventing or even reversing age-related declines in cognitive function, as well as treatments which may delay the onset of Alzheimer's disease in high risk but otherwise healthy populations. *Disclosures:* No funding was received for the conduct of this research. The main author reports potential conflicts which are described in the program. Sperling RA, Aisen PS, Beckett LA et al.(2011) Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia* 7:280-292.

**P77 - A COGNITIVE TASK SENSITIVE TO DENTATE GYRUS ACTIVITY WHICH HAS IMPLICATIONS FOR ASSESSING NEUROGENESIS STATUS IN NORMAL AND PATHOLOGICAL AGEING.** K.A. WESNES<sup>1</sup> (1. Bracket Global, Goring on Thames, United Kingdom; 2. Swinburne University, Melbourne, Australia)

*Background:* The seminal discovery in 1998 that the human dentate gyrus (DG) retains its ability to generate neurons throughout life, has raised the possibility that therapies could be developed to protect or promote this neurogenesis as it deteriorates due to ageing, insult and

disease. The DG plays a crucial role in associative memory, and the degenerative changes which compromise neurogenesis in the DG are believed to contribute to memory disturbances in normal ageing and the early stages of AD. Pattern separation has been demonstrated to be under the control of the DG, and fMRI studies have identified the DG to be highly and selectively active when volunteers perform visual object pattern separation tasks. The CDR System picture recognition task assesses visual object pattern separation, and in a cohort of over 3000 volunteers aged 18 to 87 years, a selective, marked and highly significant age-related decline was identified in the ability to discriminate originally presented pictures from different but very similar pictures. This task thus offers the opportunity to assess DG activity in clinical trials. The aims of the present investigation were (1) to extend these findings by determining whether the time to make these discriminations was also selectively impaired by ageing, (2) to investigate the pattern of changes in children & adolescents from 5 to 17 years, (3) and to investigate whether this discrimination was poorer in clinical populations including Parkinson's disease and late-life depression. *Methods:* Data from 47,731 individuals aged 5 to 100 who performed the CDR System picture recognition task on-line were analysed. Data from clinical populations including late life depression and oncology were also evaluated. *Results:* This study confirmed the original pattern with regard to the decreased ability with adult ageing to discriminate the originally presented pictures from the very similar ones; and extended our knowledge by revealing that younger children were also compromised in this ability. Further, the declining ability to discriminate the pictures with ageing was also associated with selectively longer reaction times, extending our understanding of the phenomenon of declining pattern separation accuracy by showing that it is accompanied by declining speed. Further, other analyses revealed that patients with Parkinson's disease and late-life depression were also found to be selectively impaired on this task, as were oncology patients. *Conclusions:* This task provides an opportunity to assess DG activity in various clinical populations, and could be a useful tool in evaluating compounds aimed at promoting, maintaining or restoring neurogenesis. It can serve as both a proof of principle and an outcome measure. The opportunity to study large populations via the internet has applications to the various long-term patient registries being set up to study preclinical dementia.

**P78 - USE OF THE DOLL WITH DEMENTIA-AFFECTED PATIENTS WITH BEHAVIOR DISTURBANCES IN A NURSING HOME FOR ALZHEIMER PATIENTS.** I. CILESI (*Pedagogist Educational Psychologist Italy (Responsible Service of Cognitive Rehabilitation and non Pharmacological Therapies in Alzheimer Centre in the Foundation S. Maria Ausiliatrice (Bergamo), Consultant Alzheimer Centre of Excellence Hospital Briolini in Gazzaniga (Bergamo), Consultant in Alzheimer Centers in Goteborg (Sweden), Consultant at the Alzheimer Center of Pio Albergo Trivulzio in Milan*)

*Background:* International guidelines indicated for the treatment of behavior disturbances in demented patients the importance of non pharmacological therapies. We focused our attention on doll therapy. *Methods:* Reduction of medication needed to control behavior in demented patients. *Methods:* 6 patients were evaluated (5 Females, 1 Male), median age 81.33 years old, CDR 3, MMSE lower than 10, MPI media, and followed for 6 months (the study is still ongoing). Staff were trained also with use of videos, care givers were informed and their consent obtained, patients were filmed and their videos were shown to their care givers as well, MMSE checked at the beginning and at the end of the period, as well as MPI and the doses of antipsychotic and benzodiazepines medications used on a regular and

as required basis as reported on staff diary. Dolls were administered in established times and for established periods of time as detailed in the individual schedules prepared according to the behavioral disturbance. Handing over, observing and taking back the doll were recorded each time in the individual schedule. *Results:* It was observed a reduction in the doses of antipsychotic and benzodiazepine medications administered regularly and on a as required basis, while the care giver, formal and informal, showed an ameliorated perspective of the situation. *Conclusions:* Use of empathy dolls in our experience diminished the use of pharmacological intervention in Dementia-affected patients with behavior disturbances. The study is ongoing.

**P79 - THERAPEUTIC VIRTUAL TRAIN WITH DEMENTIA-AFFECTED PATIENTS WITH BEHAVIOUR DISTURBANCES IN A NURSING HOME FOR ALZHEIMER PATIENTS.** I. CILESI (*Pedagogist Educational Psychologist Italy (Responsible Service of Cognitive Rehabilitation and non Pharmacological Therapies in Alzheimer Centre in the Foundation S. Maria Ausiliatrice (Bergamo), Consultant Alzheimer Centre of Excellence Hospital Briolini in Gazzaniga (Bergamo), Consultant in Alzheimer Centers in Goteborg (Sweden), Consultant at the Alzheimer Center of Pio Albergo Trivulzio in Milan*)

*Backgrounds:* It is important to analyze the idea of the trip, as moment of life, of escape and care. The program is organized inside the program of the computer. The run is organized to the interested people by the departure (stamping tickets) and they sit in the places inside the space compartment train. The sounds and the sensory stimulations are chosen to be activate during the trip. In first place we decide a theme modulated on an individual or on a homogeneous group. A separation of the patient from the reality in partnership often to difficulty of acceptance of the closed space, and at the same time strengthened by the desire of escape. This situation is often connected to the onset of evident behavioural troubles. It is interesting to observe that the people included showed pauses aided by the active dynamics of the journey which in this case, in my opinion, helped to relax the patients. An interesting reflection concerns the active dynamics of the journey and the perception of the patient. The virtual journey becomes a real journey and in this light, the patient's perception of the real movement of the train aids the perception of the closed space which, in this case, becomes a moment of passage towards the outside. The journey is towards a destination that is often undefined and is perceived by the patient in the here and now (the journey is undoubtedly therapeutic), where the rituality of the actions that accompany the journey assumes fundamental importance. *Methods:* 37 patients have been included and of these 31 patients have accepted the therapeutic train space positively. Patients suffering from wandering have initially accepted the restrictive space of the train and immediately began to have pauses of considerable significance in their disorder. Of the patients included in the project suffering from wandering (12), 9 were treated positively showing pauses in their purposeless movement. Other disorders treated efficaciously have definitely been states of agitation (8 out of 9 patients were treated positively), states of anxiety, irritability, apathy and sleep disorders. All the people included in the project were assessed using the MMSE to ascertain their residual cognitive capacity. They were all given a score of between 6 and not assessable. Insertion proposed to established schedules in relationship to the times of onset of the troubles. Insertion proposed to the need in the acute phase of the trouble. *Results:* Decreasing of the states of nervousness, aggressiveness and wandering. Stimulate the attention, emotional processes, dialogue and ability report. Decreasing of the troubles is in the acute phase of the trouble. Reduction pharmacological therapies to

the need and therapies administered by therapeutic protocol. It is important and interesting are the data regarding the acceptance of the train compartment environment, a very positive result which encourages us to continue with the course of clinical experimentation and begin new therapeutic journey scenarios. Another interesting fact concerns the start of dialogical dynamics, of rituality connected with memories of the past, reminiscences, stimuli connected with the preservation of attentive capacities, moments of relaxation which the patients showed during the first tests of the experimentation. **Conclusion:** The results of experiments reinforce that the train is an important opportunity for therapeutic treatment of people with Alzheimer's disease at different times of day. In the next few months we will undoubtedly have far more data concerning the quantitative aspect (the number of patients included in the experimentation), details that will help us to demonstrate with greater emphasis the already positive trend of the experimentation and the therapeutic train as an opportunity to be used for daily treatment.

**P80 - ASSESSMENT OF AN AUTOMATED TELEVIGILANCE SYSTEM ON SERIOUS FALLS PREVENTION IN A DEMENTIA SPECIALIZED CARE UNIT: THE URCC.** I. SAULNIER<sup>1</sup>, F. LACHAL<sup>1</sup>, A. TCHALLA<sup>1</sup>, J. TRIMOUILLAS<sup>1</sup>, F. GOURDEAU-NAUCHE<sup>2</sup>, L. BERNARD-BOURZEIX<sup>1</sup>, S. PEYRICHOU<sup>1</sup>, S. FORTUNE<sup>2</sup>, T. DANTOINE<sup>1</sup> (1. Geriatric Department, Limoges University Hospital, France; 2. Geriatric Department, Brive Hospital, France)

**Background:** Aging is often related to autonomy loss problems. Falls are a major issue that leads to autonomy loss. Falls incidence is particularly high in dementia (increased risk by 2 or 3 times compared to the general elderly population). Falls are also responsible for high morbi-mortality rates themselves responsible for high socio-economical costs. Seriousness of falls is related to traumas and high length of stay on the floor. Since many falls in geriatric units do not have any witness, it is important to detect them as soon as possible in order to decrease aggregative factors. In France, special Alzheimer's units called URCC were recently (2008: French political plan to fight Alzheimer) created for functional and cognitive decompensated patients. Automated televigilance system could be both a solution to falls early detection and a preventive tool for the caring staff. Since high length of stay on the floor will be avoided with the televigilance system and that physicians and nurses would be able to identify causes of the falls, this system could decrease serious falls rates for elderly people hospitalized in URCC. It could also be able to decrease falls rates as well as fall risk of cognitively impaired patients and dementia related behavioral disorders. **Methods:** GET-BETTER is an opened prospective, randomized into 2 parallel groups study ran from april 2012 to april 2013. 2 units in the Limousin region (France) are equipped with the automated televigilance system. One group will have cameras installed and the other will not and will act as a comparison group. 350 subjects are expected to enter the study. Patients will be assessed twice during the study, at admission in (inclusion visit) and at outcome from the URCC (end of study visit). Each assessment implies a standard geriatric assessment, and a fall questionnaire. Every fall will be considered as adverse events and will therefore be listed along the study and characterized in types and number. The primary outcome is to compare the impact of the automated televigilance system on the incidence rate of falls with serious outcomes between the two groups during their hospitalization in URCC. Rooms of the patient of the "intervention group" will be equipped with cameras. These cameras can either work in visible or infrared range. They are physically linked to a server that will store encrypted video and analyze images data in real-time. The server

works 24h/24 and 7d/7 and will send an alert to the care staff via their computers and personal pagers if it detects a fall. Physician can also watch images in order to determine the cause of the incident and then act preventively and induce treatment / care strategies. Patient in the "non-equipped" group will have usual care. Statistical analysis that will be performed includes paired t tests comparison or de Mann-Whitney test for quantitative variables, Chi2 tests or Fisher test for qualitative variables with significant alpha risk 0.05. **Expected results:** – A decrease in serious falls in the intervention group; – A slower functional decline; – Fewer behavioral disorders; – A decrease in deases; – A fast identification of individual falls risks factors. **Conclusion:** Real time falls detection will allow physicians to introduce individual secondary prevention program of functional decline. It could also help to manage adverse events in dementia specific units.

**P81 - ROBOT ASSISTED COGNITIVE TRAINING CAN CHANGE THE BRAIN IN THE ELDERLY: A SINGLE BLIND, RANDOMIZED CONTROLLED TRIAL OF CLINICAL EFFICACY.** G.H. KIM<sup>1</sup>, S. JEON<sup>3</sup>, B.H. LEE<sup>1</sup>, H.S. KIM<sup>3</sup>, J.H. CHIN<sup>1</sup>, G.Y. KIM<sup>1</sup>, H. JEONG<sup>1</sup>, J.M. LEE<sup>3</sup>, S.W. SEO<sup>1</sup>, J.S. SHIN<sup>1</sup>, H. CHO<sup>1</sup>, Y. NOH<sup>1</sup>, S.E. PARK<sup>4</sup>, H.J. KIM<sup>4</sup>, C.W. YOON<sup>1</sup>, H.J. KIM<sup>1</sup>, S.T. KIM<sup>2</sup>, M.-T. CHOI<sup>5</sup>, M.S. KIM<sup>5</sup>, J.H. LEE<sup>6</sup>, D.L. NA<sup>1</sup> (1. Department of Neurology and Radiology; 2. Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Republic of Korea; 3. Department of Biomedical Engineering, Hanyang University, Seoul, Republic of Korea; 4. Samsung Advanced Institute for Health Sciences and Technology, Sungkyunkwan University, Republic of Korea; 5. Korea Center for Intelligent Robotics at Korea Institute Science and Technology, Seoul, Republic of Korea; 6. Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea)

**Backgrounds:** Previous studies about cognitive intervention targeting older adults revealed that cognitive training had effects on the improvement of cognitive function. However, there have been few studies that investigat direct changes of brain structures after cognitive training. The advanced scientific technique allowed us to develop service robots designed to assist human work, which can be important with an increase in the aging population and high costs of elderly care. In this regard, we considered robots for elderly's cognitive training and developed 17 cognitive programs in collaboration with Center for Intelligent Robotics at Korea Institute of Science and Technology. The purpose of this study was to demonstrate the effects of our newly developed robotic cognitive training programs on the brain structures in older adults without dementia. **Methods:** This study was a randomized, controlled single blind trial. Eighty-five volunteers aged 60 years or older were recruited from a single community center in Seoul, Korea. All of them were screened using Mini-Menal State Examination (MMSE) and those with scores lower than 26 were excluded. Persons were also excluded from participation if they had known dementia or significant cognitive impairment accompanied by dysfunction of daily living activities. Participants were given baseline assessments and randomly assigned to 3 groups; 24 with robot assisted cognitive training (Robot group), 24 with experienced behavioral therapist (Conventional group), and 37 without cognitive training (Control group).The cognitive training consisted of 60 sessions which organized daily 90 minutes,5 days per week for 12 weeks. Pre- and post-intervention assessment included brain MRI, neuropsychological tests, and questionnaires about life style. The primary outcome of this study was the change in cortical thickness between the baseline and the post-intervention assessment. **Results:** There were no statistical differences between 3 groups in terms of age, sex, years of education

and the baseline scores of MMSE. The risk factors for dementia including frequency of ApoE 4 allele, diabetes, hypertension and hyperlipidemia between 3 groups were not different either. One participant in the robot intervention group and 2 persons in the control group dropped out from the study because they withdrew the consent during the study. The primary reason for withdrawing was time commitment to training and assessment. All 47 participants in the intervention groups attended 51 and more ( $\geq 85\%$ ) out of 60 sessions. The robot group showed a tendency that the mean cortical thickness increased by 0.012 mm during 12 weeks while decreased in the conventional and control group during the same period. But there was no statistical significant time-by group interaction ( $p=0.163$ ). The topographical analysis showed that compared to control group, the conventional group showed significant lesser cortical thinning in the left medial prefrontal and several areas on the right middle temporal gyrus. Compared to controls, the robot group also demonstrated lesser cortical thinning in the bilateral medial frontal, dorsolateral prefrontal, orbitofrontal cortex and right parahippocampal, primary motor and sensory cortices. When conventional and robot groups were directly compared, the robot group revealed attenuated cortical thinning, particularly on bilateral dorsal anterior cingulate cortices (ACC). **Conclusion:** Lesser cortical thinning found in two intervention groups compared to control group can suggest that cognitive training is helpful to mitigate against decreasing cortical thickness. Especially in the present study, the robot assisted cognitive training program would bring about a favorable effect over the conventional behavioral therapy on bilateral prefrontal areas including ACC that are well known for executive attention, error detection and conflict monitoring. **Financial disclosure/Conflict of Interest:** This study was funded by Gaha Corporation through research grant to Samsung Medical Center, a grant of the Korea Healthcare Technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea (A102065), a grant from Samsung Medical Center Clinical Research Development Program grant (CRL-108011 & CRS 110-14-1), and the Korea Science and Engineering Foundation (KOSEF) NLRL program grant funded by the Korean Government (MEST) (2011-0028333).

**P82 - SEPSIS AND COGNITIVE FUNCTION.** C. WIDMANN<sup>1</sup>, A. SEMMLER<sup>1,7</sup>, T. OKULLA<sup>1</sup>, H. URBACH<sup>3</sup>, M. KAISER<sup>2,6</sup>, G. WIDMAN<sup>4</sup>, F. MORMANN<sup>4</sup>, J. WEIDE<sup>2</sup>, K. FLIESSBACH<sup>4</sup>, T. KLOCKGETHER<sup>1</sup>, A. HOEFT<sup>2</sup>, F. JESSEN<sup>5</sup>, C. PUTENSEN<sup>2</sup>, M.T. HENEKA<sup>2</sup> (1. University of Bonn, Department of Neurology; 2. University of Bonn, Department of Anaesthesiology and Intensive Care Medicine; 3. University of Bonn, Department of Radiology/Neuroradiology; 4. University of Bonn, Department of Epileptology; 5. University of Bonn, Department of Psychiatry; 6. Department of Anesthesiology, Medical College of Wisconsin, USA, current affiliation; 7. University of Zurich, Department of Neurology, Switzerland)

**Background:** Although it is well recognized that acute sepsis can result in a slowing of cognitive processing, impaired attention, memory dysfunction, delirium and coma in the short term, it has often been assumed to be transient in nature. However, animal studies indicate that structural changes in the brain may indeed lead to permanent cognitive impairments (Siami et al, 2008, Young et al., 1990, Weberpals et al., 2009). Recently, the American Health and Retirement Study (Iwashyna et al, 2010) demonstrated permanent global cognitive deficits in 17% of an elderly cohort of sepsis survivors a minimum of 8 years following acute illness. Inferences about individual cognitive domains have been made on the basis of subjective self-report in a very small sample of 8 showing sensory processing, emotional functioning, concentration, and memory deficits

1-4 years post-sepsis (Lazosky et al, 2009). Hence, an in-depth examination of long-term cognitive change in sepsis patients is warranted. This study presents findings of a preliminary study to link cognitive change, structural brain changes and changes in brain activity (EEG) to the sepsis experience. **Participants:** Sepsis Survivors ( $n = 25$ , 12 female, 13 male) included patients diagnosed with either sepsis ( $n = 8$ ) or severe sepsis ( $n = 17$ ). ICU Survivors ( $n = 26$ , 9 female, 17 male) were selected who were at the ICU after polytrauma, cardiac arrhythmia, myocardial infarction and cardiac surgery with aortocoronary bypass grafting without a diagnosis of sepsis. Measures used included structural MRI, resting state EEG, a neuropsychological battery NeuroCogFX plus TMT A & B, Auditory Verbal Learning Test, Rey Complex Figure, a health-related quality of life questionnaire Short Form-36, and a psychological well-being Symptom Checklist-90-R. Statistical methods included t-tests, multivariate analysis of covariance and Pearson correlations. **Design:** Two-center follow-up study 6-24 months after hospital release using published norms and existing databases of healthy controls for comparison. Resting state EEG, neuropsychological examination, health questionnaires were administered on one day. MRI-scans were conducted within two months of examination. **Conclusion:** Long-term cognitive deficits were found in both patient groups for several domains, as well as brain dysfunction in EEG. Brain volume analysis revealed left-sided hippocampal shrinkage in sepsis patients compared to healthy. Lowered quality of life and higher psychiatric burden were also found. It remains unclear to what extent these changes are attributable specific illness or other factors during ICU stay (disease severity, dosage of vasopressors, sedatives and analgesics or episodes of hemodynamic instability) or thereafter (psychotherapy, cognitive rehabilitation, psychotherapy, support with reintegration into work and family). Hence, future studies should carefully control for these factors, use a larger sample, and take into account possible age effects. In addition, the timing of cognitive change should be carefully tracked, as many studies indicate that cognition post-icu reverts back to normal levels. Future therapeutic strategies to prevent or lessen cognitive deficits associated with sepsis and improve psychological health after ICU stay should be developed and tested in future studies.

**P83 - ADCS EDC.** G.A JIMENEZ-MAGGIORA<sup>1</sup>, R.G THOMAS<sup>1</sup>, P. HONG<sup>1</sup>, P.S AISEN<sup>1</sup> (1. Department of Neurosciences, UCSD, USA)

**Background:** The Alzheimer's Disease Cooperative Study was founded in 1991 in response to a NIA RFA. The primary aim of the ADCS is to 'advance research in the development of interventions that might be useful for treating, delaying, or preventing AD'. Toward that goal the ADCS has designed, managed, and analyzed 15 phase II and III clinical trials, and 5 large cohort investigations. The psychometric, clinical, and biological data from these trials have been collected using a locally-developed, web-based electronic data capture (EDC) system. This system serves as a central hub used to coordinate the data management, quality assurance, and monitoring activities of thousands of staff across several continents. **Methods:** In 2000, the ADCS Steering Committee asked the Data Core to evaluate the feasibility of using web-based technologies to facilitate data management activities for multi-site clinical trials. Being academically based, the Data Core eschewed existing commercial solutions and developed a novel EDC system which leveraged its extensive clinical trials experience and quantitative orientation. A key design choice was the exclusive use of open source software packages to support each of the systems core functions. Special emphasis was placed on streamlining study startup and shutdown activities such that new trials could be brought online in a matter of hours and study databases could be locked immediately following the last participant's visit. Analysis reports, previously run



offline several months after study milestones were achieved, could be run online on an ongoing basis over the course of a study. **Results:** This poster has the following aims: 1. Provide a description of the EDC systems key components and functionality. 2. List the EDC's guiding design principles and goals. 3. Discuss the how the EDC was used to accelerate study startup and shutdown activities. 4. Provide a description of the EDC's data quality model. 5. Discuss the impact of real-time data quality assurance on study shutdown and analysis. **Conclusion:** The ADCS EDC system was developed as a collaboration among biostatisticians, informaticians, and clinical staff and has supported the successful completion of more than 20 large, multi-site AD clinical trials. It is also used to support several extra-ADCS projects, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Dominantly Inherited Alzheimer's Network (DIAN), that are deemed to be significant contributions to the advancement of Neuro/AD research.

#### **P84 - HIGH LEVELS OF CSF A-SYNUCLEIN OLIGOMERS IN PARKINSON'S DISEASE WITH DEMENTIA AND DEMENTIA WITH LEWY BODIES BUT NOT IN ALZHEIMER'S DISEASES.**

O.M.A. EL-AGNAF<sup>1</sup>, O. HANSSON<sup>2,3,4</sup>, S. HALL<sup>2,3</sup>, A. ÖHRFELT<sup>3</sup>, S. VARGHESE<sup>1</sup>, M.M. QURESHI<sup>1</sup>, A. AL-HAYANI<sup>6</sup> (1. Department of Biochemistry, Faculty of Medicine and Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates; 2. Department of Clinical Sciences, Lund University, Sweden; 3. Neurology clinic, Skåne University Hospital, Sweden; 4. Memory clinic, Skåne University Hospital, Sweden; 5. Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, The Sahlgrenska Academy at University of Gothenburg, Sweden; 6. Department of Anatomy, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia)

**Background:** To study whether  $\alpha$ -synuclein oligomers are altered in the cerebrospinal fluid (CSF) of patients with dementia including Parkinson's disease with dementia (PDD), dementia with Lewy bodies (DLB) and Alzheimer's disease (AD) compared to age-matched controls. **Methods:** Total of 185 CSF samples were assessed in this study including 71 patients with DLB, 32 with PDD, 48 with AD and 34 healthy age-matched controls were analyzed for both total and oligomeric  $\alpha$ -synuclein levels using well established immunoassays. **Results:** The levels of  $\alpha$ -synuclein oligomers in CSF were significantly increased in patients with PDD ( $P<0.05$ ) and DLB ( $P<0.05$ ) when compared with AD patients. Importantly, the levels of CSF  $\alpha$ -synuclein oligomers and the ratio of oligomeric/total- $\alpha$ -synuclein could distinguish DLB or PDD patients from AD patients with AUC of 0.63 and 0.74, respectively. Interestingly, AD patients with high levels of CSF  $\alpha$ -synuclein oligomers correlated positively with worse performance on MMSE ( $R_s=-0.31$ ;  $P<0.05$ ). **Conclusion:** The levels of  $\alpha$ -synuclein oligomers are increased in CSF from  $\alpha$ -synucleinopathies patients with dementia compared to AD cases and healthy controls. Quantification of the oligomeric  $\alpha$ -synuclein in CSF could be useful marker for selecting patients to clinical trials testing new drug candidates targeting  $\alpha$ -synuclein aggregation in the brains.

#### **P85 - REVIEW OF SAFETY OF SPINAL CATHETER PLACEMENT FOR INTERMITTENT CEREBROSPINAL FLUID SAMPLING IN CLINICAL TRIALS ON HEALTHY VOLUNTEERS**

S. RAMAEL<sup>1</sup>, L. CAVENS<sup>2</sup>, A. DHAR<sup>1</sup>, E. WOLTERS<sup>1</sup> (1. SGS Life Science Services, Clinical Pharmacology Unit, Antwerp, Belgium; 2. Department of Neurosurgery, ZNA Middelheim, Antwerp, Belgium)

**Background:** CSF sampling is often used in early phase clinical trials for assessing pharmacokinetics and pharmacodynamics of new

chemical entities acting on the CNS. We reviewed the safety data of 285 healthy volunteers undergoing spinal catheterization for CSF sampling between 2009 and 2011. Data were analysed to assess possible effects of CSF sampling duration and total CSF sampling volumes on occurrence and severity of adverse events (AE). Special attention goes to the occurrence of postdural puncture headache (PDPH) as this review only includes healthy volunteers without any comorbidities at time of procedure (i.e. unlike reports arising from patient populations needing local anesthesia). In this abstract we review the AEs that have been attributed to the procedure of spinal catheterization by the Investigator, based on time of onset, time between onset and procedure and expectedness based the Investigator's Brochure (IB). **Methods:** Pooled analysis of AEs of 9 different phase I trials using spinal catheterization for CSF sampling performed by 2 Investigators between 2009 and 2011. All AEs have been recorded according to SGS' standard operating procedures using a three-staged approach for grading and causality. AEs were subsequently coded using MedDRA version 12.0. A headache was classified as PDPH only if the clinical presentation was consistent with that diagnosis. A first causality of the adverse events in relation to the technical procedure has been assessed by the Investigators during the trials and a second blinded assessment has been performed on the complete list of AEs taking into account time between onset and spinal procedure and expectedness according to the respective IBs. Analysis was done a first time on length of CSF sampling (12h, 24h or 36h) and once using total withdrawn volume of CSF over the sampling period (168-222 mL, 96-120 mL and 20-65 mL). Descriptive statistics were applied for description of the observations. **Results:** In total 285 subjects of which 204 males and 81 females were randomized for spinal catheterization. Mean age was 45y (min/max: 18/73). Procedure related AEs (PrAE) have been reported in 210 (73.7%) subjects, 75 (26.3%) subjects did not report a PrAE and 24 (8.4%) subjects did not report any AE at all. A total of 1181 AEs have been recorded, of which 426 were classified as PrAE. Duration of sampling was 36 hours (n=195), 24 hours (n=82) and 12 hours (n=8). PrAEs occurred in 138 (70.8%), 66 (80.5%) and 6 (75.0%) respectively. When looked at it starting from sampling volumes, we had 104 subjects in the high volume (HVol: 168-222 mL CSF) group, 127 subjects in the intermediate volume (MVol: 96-120 mL CSF) group and 54 subjects in the low volume (LVol: 20-65 mL) group. PrAEs occurred in 65 (62.5%), 102 (80.3%) and 43 (79.6%) of trial subjects respectively. PDPH was reported overall in 79 subjects (27.7%). The 36 hour group reported 51 (26.1%) cases of PDPH, the 24h group 25 (30.5%) and none in the 12h group. When classified per total volume CSF withdrawn is taken into account, PDPH was reported in 23 (22.1%) of the HVol subjects, 37 (29.1%) of the MVol group and in 16 (29.6%) of the LVol subjects. Of all PDPH cases, 30 (38%) have been treated using an epidural bloodpatch (EBP), the rest was treated conservatively (per os fluids and caffeine, paracetamol and/or NSAIDs as needed). The need for EBP was evenly distributed over the different analysis groups. Onset time for PDPH since removal of spinal catheter was on average 28h (min/max 0h/214h SD 33) and duration was on average 100h (min/max 3h/393h SD 80) Overall occurrence of moderate/severe PrAEs in the 36h - 24h - 12h groups was 17.7%/5.8% - 16.9%/4.0% and 0%/0% respectively. Of note is that the 12h only has 8 subjects. When observed per volume, respective incidences of moderate/severe PrAEs for HVol - MVol - LVol are 12.3%/9.8% - 18.2%/3.3% - 21.1%/3.3%. (In total 23 severe PrAEs have been recorded of which 16 were severe PDPH, 4 vasovagal syncope, 1 painful paresthesia L5 and 2 skin infections at the catheter site). **Conclusion:** Spinal catheterization for CSF sampling in phase I trials is generally well-tolerated by healthy volunteers between 18 and 75 years. The occurrence of PrAEs doesn't seem to be related to sampling duration or total sampled volume of CSF, although the

incidence of severe PrAEs rises significantly in the HVol sample group. The incidence of PDPH is only 27.7%, which is a bit lower than what could be expected from review of other literature sources. Incidence is not related to sampling duration, nor sampled volume. We consider this technique as safe and well-tolerated when performed by experienced Investigators. Special caution needs to be taken to prevent infections of the puncture site and to minimize the impact of procedure-related AEs on the daily life of participating volunteers.

**P86 - A NEW 26-WEEK, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, STUDY OF AC-1204 (CAPRYLIC TRIGLYCERIDE) IN MILD TO MODERATE ALZHEIMER'S DISEASE: PRESENTATION OF STUDY DESIGN.** R. DOODY<sup>1</sup>, J. GALVIN<sup>2</sup>, M. FARLOW<sup>3</sup>, R. SHAH<sup>4</sup>, P.M. DORAISWAMY<sup>5</sup>, S. FERRIS<sup>2</sup>, J. ZETLAOUI<sup>6</sup>, S. HENDERSON<sup>7</sup>, R.S. ISAACSON<sup>8</sup> (1. Alzheimer's Disease and Memory Disorders Center, Department of Neurology, Baylor College of Medicine, Houston, TX; 2. Alzheimer's Disease Center, NYU Langone Medical Center, NYC, NY; 3. Alzheimer's Disease Center, Indiana School of Medicine, Indianapolis, IN; 4. Rush University, Chicago, IL; 5. Department of Psychiatry, Duke University, Durham, NC; 6. Nestle Health Science, Lutry, Switzerland; 7. Accera Inc, Broomfield, CO; 8. Department of Neurology, University of Miami Miller School of Medicine, Miami, FL)

*Background:* Alzheimer's disease (AD) is characterized by reductions in regional cerebral glucose metabolism. In addition to glucose, the brain can efficiently metabolize ketone bodies (beta-hydroxybutyrate, acetoacetate and acetone) generated from fat stores during periods of glucose deprivation. Ketone bodies may provide an alternative energy substrate to supplement brain energy needs in AD. Induction of ketosis by caprylic triglyceride in a Phase 2 trial was well tolerated with benefit in the ADAS-cog in mild-to-moderate AD in a sub group analysis of APOE4 non-carriers (p=0.015), supporting the initiation of a Phase 3 study. *Methods:* AC-1204, a new proprietary formulation of caprylic triglyceride, induces mild ketosis with predictable levels of beta-hydroxybutyrate. Clinical efficacy will be assessed in a randomized, double-blind, placebo-controlled, parallel-group, multi-center trial in mild-to-moderate AD. Eligible AD patients (NINCDS-ADRDA) with MMSE 14-26 will be randomized to receive either AC-1204 or placebo for 26 weeks. Four hundred and eighty participants at approximately 60 sites throughout the United States will be stratified into two groups: 360 APOE4(-) and 120 APOE4(+). Completers will be eligible for an optional 26 week open-label extension. The primary outcome measure will be changes in ADAS-Cog compared to placebo among APOE4(-) participants at 26 weeks. Secondary outcome measures will include ADCS-CGIC, ADCS-ADL, AD-QoL and selected components of RUD-lite. Additional pre-specified analyses will include: comparisons between APOE4(+) and APOE4(-) groups, comparisons of mild versus moderate groups defined by MMSE score, and selected cognitive sub-domains such as visuospatial function and constructional praxis. For the first two weeks of the trial, participants will be instructed to follow a Graduated Dosing Plan: starting with 10 grams AC-1204 or placebo daily for 4 days and increasing by 10 grams every 4 days (on days 5, 9, and 13). Beginning on Day 13, participants will take 40 grams AC-1204 or placebo for the remaining 24 weeks. Participants will be instructed to shake/blend each serving with 4-8 oz water or other liquid as preferred, and sip slowly after breakfast or lunch (whichever meal is bigger). During the optional 26 week open-label extension, the Graduated Dosing Plan will be repeated for two weeks, followed by 40 grams daily of AC-1204 for the remaining 24 weeks. *Results:* The study is expected to begin in first quarter 2013 and to enroll over a one

year period, with expected completion in 32 months. *Conclusion:* Previous studies suggest that daily administration of caprylic triglyceride in mild-moderate AD may improve performance on ADAS-Cog compared to placebo. As this effect was more apparent in APOE4(-) participants, this trial will specifically assess clinical efficacy and safety in APOE4 stratified subgroups. If positive, this study will provide further evidence of the clinical efficacy for ketosis as a therapeutic intervention in mild-to-moderate AD.

**P87 - PREVENTION TRIALS FOR ALZHEIMER'S DISEASE IN NON-DEMENTED SUBJECTS. A REVIEW OF STUDIES THAT USE BIOMARKERS FOR INCLUSION OR AS OUTCOME.** D. BERTENS<sup>1</sup>, P.J. VISSER<sup>1,2</sup>, P. SCHELTENS<sup>1</sup>. (1. Alzheimer Centre, Department of Neurology, VU University Medical Centre, Amsterdam, The Netherlands; 2. Alzheimer Centre, School for Mental Health and Neuroscience (MHeNS), University Medical Centre, Maastricht, The Netherlands)

*Background:* Treatment of Alzheimer's disease is probably most effective when given early in the course of the disease. The design of prevention trials is challenging and may be facilitated by the use of AD biomarkers. Biomarkers can select non-demented subjects with underlying AD pathology more accurately than clinical measures. Furthermore, biomarkers are useful to measure respond to therapy and disease progression. The aim of our study was to give an overview of prevention trials that have used biomarkers for inclusion of subjects or as endpoint. *Methods:* We searched for trials on [www.pubmed.com](http://www.pubmed.com), [www.clinicaltrials.gov](http://www.clinicaltrials.gov), [www.who.int](http://www.who.int), [www.controlled-trials.com](http://www.controlled-trials.com) and [www.alzforum.org](http://www.alzforum.org). Search terms used were 'prevention Alzheimer's disease', 'therapy prodromal AD', 'therapy MCI', 'MCI' and 'mild cognitive impairment'. We included studies that had been performed in cognitively normal subjects, subjects with MCI or subjects with mild AD. Furthermore, AD biomarkers had to be a part of the inclusion criteria or outcome measure. *Results:* In total 36 trials met our criteria. Seven trials were performed in cognitively normal subjects, four trials in cognitively normal subjects or subjects with MCI, 21 trials selected subjects with MCI and four trials included subjects with MCI or mild AD. Biomarkers were used for selection of MCI subjects in five trials but not in any trials with cognitively normal subjects. All trials used biomarkers as endpoint of which 8 trials used biomarkers as co-primary outcome and 12 studies that used biomarkers as the only primary outcome. In three trials, biomarkers were used as outcome measure in a subset of subjects only. The remaining studies used biomarkers as secondary outcome measure. Biomarkers used for inclusion and/or endpoint, were abeta 1-42 or tau in cerebrospinal fluid (CSF), amyloid binding on PET scanning, brain atrophy (whole brain or medial temporal lobe atrophy) on MRI or FDG-PET binding. Cognition and biomarkers were co-primary outcome measures in 8 trials. So far, nine studies have been completed and published. *Conclusion:* In AD prevention trials, with non-demented subjects, biomarkers have so far been mainly used as endpoint. Design of future prevention trials in non-demented subjects may benefit from the increased availability of AD biomarkers. This may help to select subjects most likely to respond to intervention and may reduce the sample size and study duration to find treatment effects.

**P88 - VERBAL COMMUNICATION BETWEEN ALZHEIMER'S PATIENTS AND CAREGIVERS: IMPROVING AND ENHANCING COMMUNICATION.** R.P. ALEGRIA<sup>1,2</sup>, C.C. SANTANA<sup>2</sup>, C.P. GALLO<sup>2</sup>, M.G. BOLSO<sup>2</sup>, C.M.C. BOTTINO<sup>2</sup>; M.I. NOGUEIRA<sup>1</sup> (1. Neuroscience and Behavior, Institute of Psychology, University of Sao Paulo; 2. PROTER- Old Age Research Group, Institute of Psychiatry, Hospital das Clinicas, School of Medicine, University of São Paulo)

*Background:* Research of verbal communication between Alzheimer's disease patients and caregivers shows to enhance and improve verbal interaction using some linguistic and social strategies. Enhancing and improving verbal communication, it is recommended to have activity-based approaches, linguistic and memory aids during the interaction between patients and caregivers. To have an effective verbal interaction it is important to research and verify which lexical items are preserved in those patients. And the objective of this study is to show that using some verbal strategies, communication with Alzheimer's disease patients can be improved. *Methods:* We analyzed, compared and did interventions with the discourse performance of twenty three Alzheimer's disease patients and twenty three healthy controls. The patients were 10 men and thirteen women

aged 72 and older, and the controls were eight male and fifteen female, aged 65 and older. All patients were from PROTER- Old Age Research Program - ambulatory care of the Institute of Psychiatry of the School of Medicine of the University of Sao Paulo. The patients and controls had 4 to 26 years of schooling; their Mini Mental State Exam (MMSE) scores 13 to 30. Moreover, the controls were also assessed with SRQ-20- Self reporting Questionnaire. Each discourse of patients and controls was recorded during 20 minutes and analyzed by the computational tool Stablex, based on mathematical-statistical-computer assisted program which mainly distinguish the results of preferential, basic and differential vocabulary. After that, we compared the results and verify the abstract, concrete and the most used words the AD patients conveyed to use in the social interactions. Results: The results showed that the patients have more non living and abstract words preserved and the frequency analysis of the words in the discourses also showed that using linguistic strategies can be effective to enhance and improve communication. Conclusion: Using the words that are more frequent and preserved can be effective tools to socialize until the patients reach severe stage. It is also required to do more studies for the effectiveness of improvement and increasing verbal communication between Alzheimer's disease patients and caregivers.

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