

1\textsuperscript{st} CTAD Asia - China Conference
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Shanghai- P.R.C

- Epidemiology
- Biomarkers
- Intervention
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Supplement

ABSTRACTS
The Chinese population has been aging rapidly and the country’s economy has experienced exponential growth. We performed a population-based cross-sectional survey with a multistage cluster sampling design. Residents aged 65 years and older were drawn from 30 urban (n=6096) and 45 rural (n=54180) communities across China. We found the prevalence of dementia, AD, and VaD among individuals were 5.14%, 3.21%, and 1.50%, respectively. The prevalence of dementia was significantly higher in rural areas than in urban ones, and education might be an important reason for the urban–rural differences. Based on this, it is estimated that there are about 8 million dementia patients in China. The prevalences of overall MCI, MCI caused by prodromal Alzheimer’s disease, MCI resulting from cerebrovascular disease, MCI with vascular risk factors, and MCI caused by other diseases among individuals aged 65 years and older were 20.8%, 6.1%, 3.8%, 4.9%, and 5.9%, respectively. Participants were assessed with a series of clinical examinations and neuropsychological measures. Dementia, AD, and VaD were diagnosed according to established criteria via standard diagnostic procedures. The rural population had a higher prevalence of overall MCI. It is suggested that there are 24 million MCI patients in the elderly in China. The status of dementia diagnosis and treatment of neurology outpatients in general hospitals in China remains unclear. Our team evaluated dementia diagnoses and treatments in the neurology outpatient departments of 36 randomly selected tier 3 hospitals throughout China, and interventions were initiated to remedy the problems identified. After intervention, all 36 hospitals had established memory clinics (205 dementia doctors) compared with only 6 (47 dementia doctors) before intervention. The percentage of patients diagnosed with dementia significantly increased from 0.10% (536 dementia patients of 553,986 outpatients) to 0.41% (2482 dementia patients of 599,214 outpatients). The socioeconomic costs of Alzheimer’s disease (AD) in China and its impact on global economic burden remain uncertain. We collected data from 3098 patients with AD in 81 representative centers across China and estimated AD costs for individual patient and total patients in China in 2015. We found the annual socioeconomic cost per patient was US $19,144.36, and total costs were US$167.74 billion in 2015. The annual total costs are predicted to reach US $507.49 billion in 2030 and US $1.89 trillion in 2050. Based on our results, the global estimates of costs for dementia were US $957.56 billion in 2015, and will be US $2.54 trillion in 2030, and US $9.12 trillion in 2050, much more than the predictions by the World Alzheimer Report 2015. China bears a heavy burden of AD costs, which greatly change the estimates of AD cost worldwide. Through clinical trials, we have proved that the two Chinese new drugs have definite effect on vascular dementia. In this randomized, double-blind, placebo-controlled trial, we enrolled patients aged 50–70 years who had a diagnosis of subcortical Vascular cognitive impairment without dementia at 15 academic medical centers in China. Over the 6-month treatment period, DL-3-n-butylphthalide (NBP) was effective for improving cognitive and global functioning in patients with subcortical vascular cognitive impairment without dementia and exhibited good safety. Another modern Chinese compound medicine called SaiLuo Tong has also been demonstrated to be an effective treatment for VaD.
OC2: COGNITIVE EVALUATION OF TREATMENT EFFECTS OF THE BROMODOMAIN AND EXTRATERMINAL DOMAIN INHIBITOR APABETALONE; DESIGN AND BASELINE DATA OF THE COGNITION SUBSTUDY OF THE BETONMACE PHASE 3 CARDIOVASCULAR TRIAL. J. Cummings1, J. Johansson2, E. Kulikowski3, N.C. Wong4, C. Halliday3, S.J. Nicholls5, G.G. Schwartz6, K.K. Ray7, M. Sweeney2, (1) Cleveland Clinic Lou Ruvo, Center for Brain Health, Las Vegas, USA; (2) Resverlogix Corp., Research and Development, San Francisco, USA; (3) Resverlogix Corp., Research and Development, Calgary, Canada; (4) Karolinska Institute, Department of NVS, Division of Neurogeriatrics, Huddinge, Sweden; (5) Sahlgrenska Academy at the University of Gothenburg, Department of Psychiatry and Neurochemistry- Institute of Neuroscience and Physiology, Gothenburg, Sweden; (6) School of Medicine, Division of Nephrology & Hypertension, Irvine, USA; (7) University of Adelaide, South Australian Health & Medical Research, Adelaide, Australia; (8) University of Colorado, School of Medicine, Denver, USA; (9) Imperial College, Department of Primary Care and Public Health, London, United Kingdom

Background: Type II Diabetes Mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD) are associated with vascular cognitive impairment. Apabetalone is a selective bromodomain 2 BET inhibitor (BETi) which inhibits the interaction between BET protein and acetylated lysines on histones or transcription factors. BET proteins control the recruitment of the transcriptional machinery to coordinate gene transcription of BET sensitive genes, including factors relevant to ASCVD and dementia. In Phase 2 trials, apabetalone treatment was associated with significant reduction in major adverse cardiovascular event (MACE) reduction. The MACE outcomes trial was most pronounced in patients with diabetes and elevated inflammation as indicated by increased high sensitive C-reactive protein. In the ongoing confirmatory pivotal phase 3 MACE outcomes trial - BETonMACE cognition is being assessed by the Montreal Cognitive Assessment (MoCA) in patients 70 years and older. BETonMACE is an international, multi-center, double blind, randomized (1:1), placebo controlled trial of apabetalone (100 mg orally bid) in 2,400 patients with a recent (7-90 days) acute coronary syndrome, type 2 diabetes, and low HDL-cholesterol. All patients receive high intensity statin treatment as well as other evidence-based standard of care treatments. The primary outcome is time to first occurrence of CVD death, myocardial infarction, or stroke. Objective: To investigate the effect of BETi on cognition in the BETonMACE study, the MoCA will be performed to compare the change from baseline in apabetalone and placebo treated groups, adjusted for age, education, and baseline MoCA score. A subgroup of patients with MoCA score ≤25 will be analyzed separately. Adjudicated MACE events will also be collected in this population. Methods: A pre-specified sub-study analysis of BETonMACE will examine the effects of apabetalone on cognitive function by MoCA in patients with ASCVD, T2DM and low HDL over the age of 70. The MoCA is designed as a rapid screening instrument sensitive to mild cognitive impairment and changes thereof. It assesses multiple cognitive domains including attention and concentration, executive functions, memory, language, visualconstructional skills, conceptual thinking, calculations, and orientation. A score of 26 or above is considered normal. In patients at least 70 years of age the MoCA is administered at randomization, yearly, and at termination of the trial. Archived blood samples have been collected for analysis of biomarkers. Results: To date, 2,418 patients have been randomized in the BETonMACE study, of which 20% are 70 years and older. The MoCA test (Versions 7.1, 7.2, and 7.3) has been administered by trained and certified site investigators across 195 sites in 13 countries and 17 languages. Baseline characteristics of patients who have completed a baseline MoCA test include (median): age 73 years, male 65%, MoCA 25, HDL 34 mg/dL, ApoA-I 121 mg/dL, LDL 63.5 mg/dL, hsCRP 2.5 mg/L, NLR 2.8 and ALP 76.5 U/L. Almost half of the patients taking the MoCA test have a baseline score below 26 indicating some form of cognitive impairment. Upon completion of the study, it is estimated that approximately 450 patients will have undergone MoCA testing with a median exposure to study treatment of 18 months (range 6-36). Conclusions: Cognitive assessment, by MoCA, is being evaluated in participants ≥70 years of age in BETonMACE, a Phase 3 trial testing the effect of a first-in-class BET-inhibitor, apabetalone, on cardiovascular outcomes. The cognitive assessment will provide insights about the therapeutic potential of BETi on vascular cognitive impairment and on Aβ mediated dementia. Archived serum samples will provide the opportunity to assess involvement of Aβ metabolism in BETi effects on cognition.

OC3: CHINESE VERSION OF THE BAYLOR PROFOUNDED MENTAL STATUS EXAMINATION. Xue Fu1, Meiling Ke2, Weihua Yu2, Xia Wang1, Qian Xiao1, Min Gu1, Jia Zhang1, Tao Luo1, Paul J. Massman3,4, Rachelle S. Doody1, Yang Lü1, (1) Department of Geriatrics, The First Affiliated Hospital of Chongqing Medical University, Chongqing China; (2) Institute of Neuroscience, Chongqing Medical University, Chongqing, China; (3) Department of Neurology, Baylor College of Medicine, Houston, TX USA at the time this work was done. Now Gencentre/Roche, Basel, Switzerland; (4) Department of Psychology, University of Houston, Houston, TX, USA

Background: Currently, China is facing serious issues related to having an aging population. The prevalence of senile dementia (age of onset ≥ 65 years) is about 6% in China, and AD makes up about 65% of all dementia cases. Most of the Chinese people have an inadequate awareness of AD and dementia, resulting in failure to timely diagnose AD patients and provide appropriate treatment. Therefore, many AD patients do not see a doctor until the moderate to severe stage of the disease, and better instruments are needed to correctly assess these more severely affected patients. Doody RS et al., have designed the Baylor Profound Mental State Examination (BPMSE), a simplified scale that has proved to be a reliable and valid tool for evaluating moderate to severe AD patients. Objectives: To validate the Chinese version of the Baylor Profound Mental Status Examination (BPMSE-Ch). Methods: The Baylor Profound Mental Status Examination (BPMSE) was translated into Chinese and back-translated. The BPMSE-Ch was administered to 102 AD patients with a Mini-Mental State Examination (MMSE) score below 17. We assessed the internal consistency, reliability (inter-rater reliability and test-retest reliability), and construct validity between the BPMSE-Ch and MMSE, Severe Impairment Battery (SIB), Global Deterioration Scale (GDS1), Geriatric Depression Scale (GDS2), Instrumental Activities of Daily Living (IADL), Physical Self-Maintenance Scale (PSMS), Neuropsychiatric Inventory (NPI) and Clinical Dementia Rating (CDR). Results: The BPMSE-Ch showed good internal consistency (α = 0.87); and inter-rater and test-retest reliability were both excellent, ranging from 0.91 to 0.99 (p < 0.001). The construct validity of the measure was also supported by significant correlations with MMSE, SIB, GDS1, IADL, PSMS, NPI and CDR (p < 0.001). Moreover, Table 1 shows that the BPMSE-Ch-cog differentiated patients belonging to different severity groups according to MMSE cut-offs (F = 56.7, p < 0.001). Importantly, it was found that the differences in total BPMSE-Ch-cog score as well as in its four
subcomponents scores between Group 2 and Group 3 were significant (p < 0.001). It suggested that the BPMSE-Ch had a lower floor effect than the MMSE, but a ceiling effect existed for patients with MMSE scores above 11. As shown in Table 2, BPMSE-Ch-cog scores differentiated the patients into groups according to the CDR stage (F = 16.0, p < 0.001). The mean BPMSE-Ch-cog and subcomponents scores declined as the CDR stage increased. It was observed that as the CDR stage increased, the corresponding range of BPMSE-Ch-cog became wider. Notably, Groups 3 and 4 differed significantly for the total BPMSE-Ch-cog score and the subcomponents scores, demonstrating the sensitivity of the BPMSE-Ch to different degrees of cognitive impairment among severely affected patients. Conclusions: The BPMSE-Ch is a reliable and valid tool for evaluating cognitive function in Chinese patients with severe AD.

**Table 1**

| Group | (n=50) | (n=36) | (n=16) | p values of paired comparisons
|-------|--------|--------|--------|------------------------
| MMSE (range) | 16-12 | 7-11 | 0-6 | Group 1-2 Group 2-3
| BPMSE-Ch-cog (mean ± SD) | 4.52 ± 0.50 | 4.00 ± 0.86 | 2.56 ± 1.36 | NS <0.001
| Orientation | 10.00 ± 0.86 | 9.25 ± 1.63 | 7.55 ± 3.45 | NS <0.001
| Language | 4.35 ± 0.58 | 3.95 ± 0.58 | 3.69 ± 0.57 | NS <0.001
| Attention | 4.35 ± 0.58 | 4.35 ± 0.58 | 2.56 ± 1.26 | NS <0.001
| Motor | 4.35 ± 0.58 | 4.35 ± 0.58 | 2.56 ± 1.26 | NS <0.001

a = Number of patients. One-way ANOVA test: NS = Not significant. 1 By Scheffé’s analysis.

**Table 2**

| Group | (n=45) | (n=36) | (n=10) | p values of paired comparisons
|-------|--------|--------|--------|------------------------
| MMSE (mean ± SD) | 13.67 ± 1.29 | 12.34 ± 1.82 | 9.73 ± 1.92 | Group 1-2 Group 2-3 Group 3-4
| BPMSE-Ch-cog (mean ± SD) | 23.08 ± 1.58 | 21.25 ± 2.22 | 12.50 ± 3.92 | NS <0.001
| Orientation | 4.52 ± 0.58 | 4.45 ± 0.55 | 3.98 ± 0.58 | NS NS <0.001
| Language | 10.00 ± 0.58 | 9.89 ± 0.89 | 8.68 ± 1.55 | NS NS NS <0.001
| Attention | 4.00 ± 0.00 | 3.77 ± 0.42 | 3.60 ± 1.55 | NS NS NS <0.001
| Motor | 5.00 ± 0.00 | 4.64 ± 0.65 | 4.09 ± 1.29 | NS NS NS <0.001

a = Number of patients. NS = Not significant using one-way ANOVA test; 1 By Scheffé’s analysis.

**OC4: CONSORTIUM FOR DEMENTIA PREVENTION IN CHINESE POPULATIONS (CDPCP): A PROPOSED PLATFORM FOR INFORMATION-SHARING AND RESEARCH COLLABORATIONS.** Lei Feng1, Juan Li2, Jin-Tai Yu3, Can Zhang4, Chunbo Li5, Bruno Vellas6 (1) Department of Psychological Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; (2) Department of Neurology, Qingshao Municipal Hospital, Qingshao University, Qingshao, Shandong, China; (3) Institute of Psychology, the Chinese Academy of Sciences, Beijing, China; (4) Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, U.S.A.; (5) Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China; (6) Department of Geriatric & Internal Medicine, Toulouse University, France)

**Background:** Dementia prevalence and incidence is on the rise in mainland China and other Chinese populations. To date, the majority of research has been conducted on western populations. It is urgent and important to promote research and practice of dementia prevention in Chinese populations. **Objective:** To highlight the importance of dementia prevention in Chinese populations and propose a large Consortium as a collaborative information-sharing platform for the promotion of both scientific research and real-world implementation of dementia prevention in China and other major Chinese populations. **Methods:** We used population projection from the United Nations (UN) and age-specific prevalence rate of Alzheimer’s disease (AD) in China to estimate the future number of patients with Alzheimer’s disease in mainland China by 2050. We summarized current status of dementia research in China from the perspectives of epidemiology, biomarkers, and interventional studies. **Results:** We estimated that in 2050 China would have over 21 million AD patients. At least 23 population-based prospective studies from 13 cohorts were published; those studies have helped in establishing causal relationship between potential modifiable risk and protective factors. Studies on biomarkers and interventions have been conducted in Chinese populations. However, previous studies have limitations in sample size and duration of intervention. No studies are at the scale comparable with the major prevention trials that have been conducted in western countries (FINGER, MAPT, preDIVA, etc.). However, there are emerging new studies on AD prevention and it is a good time to join forces for a bigger impact. More high-quality research should be conducted to provide evidence for real-world implementation of prevention programs. To serve this purpose, we propose to form the Consortium for Dementia Prevention in Chinese Populations (CDPCP), which will function as a platform for information-sharing and collaborations. **Conclusion:** With rising tide of Alzheimer’s disease and other forms of dementia in Chinese populations, it is important to join forces to promote high-quality research and real-world implementations. We believe this proposed Consortium for Dementia Prevention in Chinese Populations (CDPCP) will be able to make important contributions and invite like-minded researchers and practitioners to join the consortium.

**Background:** Neuropsychiatric symptoms (NPSs) are common in both mild cognitive impairment (MCI) and Alzheimer’s disease (AD). **Objectives:** To investigate the prevalence of neuropsychiatric symptoms in patients with MCI and AD from the memory clinic of The First Affiliated Hospital of Chongqing Medical University. **Methods:** We selected patients who attended the memory clinic of The First Affiliated Hospital of Chongqing Medical University. Patients and their caregivers underwent neuropsychological examinations, and the demographics of all patients were recorded. Neuropsychiatric symptoms (NPSs) were assessed by the Neuropsychiatric Inventory (NPI), and Clinical Dementia Rating (CDR) was used to classify the severity of AD. **Results:** 169 patients with MCI and 308 patients with AD (192 were classified as mild, 84 as moderate, and 32 as severe) were included in this study. 49.1% of patients with MCI, 79.7% of patients with mild AD, 96.4% of patients with moderate AD, and 100.0% of patients with severe AD exhibited one or more...
NPSs. In patients with MCI, the most frequent NPSs were depression, irritability, apathy, and anxiety. In patients with mild AD, the most common disturbances were irritability, apathy, anxiety, and delusions. In patients with moderate AD, the most frequent NPSs were delusions, apathy, hallucinations, and anxiety. In patients with severe AD, the most frequent NPSs were sleep disturbance, aberrant motor activity, hallucinations, and apathy. The prevalence of delusions, hallucinations, anxiety, apathy, irritability, and aberrant motor activity in mild AD were significant higher than that in the MCI group ($\chi^2=19.448$, 7.873, 12.386, 11.756, 7.743, 13.390, all $P<0.0167$). The prevalence of all symptoms in the moderate AD group was significantly higher than that in the mild AD group except for irritability (all $P<0.0167$). The prevalence of aberrant motor activity, sleep disturbance, and disinhibition in the severe AD group was significant higher than in the moderate AD group ($\chi^2=17.673$, 9.995, 16.987, all $P<0.0167$). There was no statistically significant difference in NPSs between women and men in MCI patients ($P>0.05$). However, in AD patients, the prevalence of delusions and depression in women was significantly higher than in men ($\chi^2=8.609$, 23.560, both $P<0.05$). Conclusions: The prevalence and severity of NPSs gradually increases alongside cognitive impairment increase. Women with AD are more prone to have delusions and depression than men. Key words: memory clinic, mild cognitive impairment, Alzheimer’s disease, Neuropsychiatric symptoms

**OC6: SAFETY, TOLERABILITY AND PHARMACOKINETICS OF CRENEZUMAB IN MILD-TO-MODERATE AD PATIENTS TREATED WITH ESCALATING DOSES FOR UP TO 32.3 MONTHS.** Helen Lin1, Andres Schneider2, Angelica Quartino1, Tobias Bittner2, Nan Hu1, Jillian Smith3, William Cho1, Susanne Ostrowitzki4,5,6 (1) Genentech, Inc. – South San Francisco, CA, US; (2) Hoffmann-La Roche AG – Basel, Switzerland; (3) F. Hoffmann-La Roche Ltd – Basel, Switzerland

Background: Crenezumab is a humanized anti-amyloid beta monoclonal antibody in development for the treatment of Alzheimer’s disease (AD). This study (GN29632) was designed to evaluate the safety and tolerability of crenezumab at doses up to 120 mg/kg intravenously (IV) every 4 weeks (q4w). A secondary objective was to characterize the serum pharmacokinetics (PK) of crenezumab at the doses investigated. Exploratory objectives were to assess clinical efficacy and effects on imaging and plasma biomarkers. Objective: To assess the long-term safety and tolerability of crenezumab and serum PK in patients with mild-to-moderate AD. Methods: Patients with mild-to-moderate AD (aged 50–90 years) with an amyloid-positive positron emission tomography scan were enrolled in three consecutive cohorts and administered four infusions of 30 or 45 (cohort 1, n = 26), 60 (cohort 2, n = 26) or 120 (cohort 3, n = 23) mg/kg crenezumab or corresponding placebo IV q4w (5:1 ratio). After completing the double-blind, placebo-controlled portion of the study, patients were offered to continue on active drug at the dose assigned at randomization, except for patients in cohort 3, who would receive 60 mg/kg. Recently, the protocol was amended to now offer 60 mg/kg IV q4w to all patients in the active extension. All patients undergo regular brain magnetic resonance imaging to monitor for amyloid-related imaging abnormalities (ARIA) related to edema (ARIA-E) and hemosiderosis (ARIA-H). Results: Safety and tolerability data collected as of 30 November 2017 and PK data will be presented: patients will have been exposed to crenezumab for up to 32.3, 27.8 or 17.5 months in cohorts 1, 2 and 3, respectively. Conclusions: The long-term safety and tolerability of crenezumab is being evaluated in patients with mild-to-moderate AD. Updated safety and crenezumab serum concentration data will be presented.

**OC7: COMPARATIVE SAFETY AND EFFECTIVENESS OF CHOLINESTERASE INHIBITORS AND MEMANTINE FOR ALZHEIMER’S DISEASE: A NETWORK META-ANALYSIS OF 41 RANDOMIZED CONTROLLED TRIALS.** Kai-Xin Dou1, Meng-Shan Tan1, Chen-Chen Tan1, Xi-Peng Cao2, Xiao-He Hou1, Qi-Hao Guo3, Lan Tan1, Vincent Mok4,5,6, Jin-Tai Yu1,2 (1) Department of Neurology, Qingdao Municipal Hospital, Qingdao, China; (2) Clinical Research Center, Qingdao Municipal Hospital, Qingdao University, Qingdao, China; (3) Department of Neurology & Institute of Neurology, Huashan Hospital, Fudan University, WHO Collaborating Center for Research and Training in Neurosciences, Shanghai, China; (4) Division of Neurology, Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China; (5) Therese Pei Fong Chow Research Center for Prevention of Dementia, The Chinese University of Hong Kong, Hong Kong, China; (6) Gerald Choa Neuroscience Centre, Lai Che Woo Institute of Innovative Medicine, The Chinese University of Hong Kong, Hong Kong, China

Background: Alzheimer’s disease (AD), a progressive neurodegenerative disorder, is the most common of dementia affecting 46.8 million people with an enormous public health impact. Currently, there are no therapeutic interventions that can delay the disease progression, but available medications have provided symptomatic benefits. Two main classes of drugs are recommended by the US Food and Drug Administration (FDA) for pharmacological management of AD: cholinesterase inhibitors (ChEIs) donepezil, galantamine, and rivastigmine and glutamate antagonist memantine. But there has been no consensus about the choice of various types and doses of drugs at different stages and previous meta-analyses lack direct comparative evidence among available drugs. Objective: We conducted a comprehensive network meta-analysis to compare and rank different types and dosages of cognitive enhancers at different clinical stages for guiding treatment decisions. Methods: We searched PubMed, the Cochrane Central Register of Controlled Trials, and Embase for randomized controlled trials (RCTs) published from the database inception to July 21, 2017. Recruited studies met the inclusion criteria of double-blind trials by randomly assigning to patients the four primary FDA-approved treatments (donepezil, galantamine, rivastigmine, and memantine) given alone or in combination within the therapeutic dose range. The primary outcomes were the mean overall changes in cognitive function and the responders who had any adverse events. Secondary outcomes included daily functions, neuropsychiatric symptoms, and the global assessment of changes. We conducted a pairwise meta-analysis using the random effects model and then performed a random effects model Bayesian network meta-analysis. Results: Forty-one randomized controlled trials were included in this study. Compared with placebo, galantamine 32 mg daily (standardized mean difference [SMD] -0.51, 95% credible interval [CrI] -0.67 to -0.35), 24 mg daily (-0.50, -0.61 to -0.40) and donepezil 10 mg daily (-0.40, 0.51 to -0.29) were probably the most effective agents on cognition for mild to moderate AD, and memantine 20 mg combined with donepezil 10 mg (0.76, 0.39 to 1.11) was recommended for moderate to severe patients. Memantine showed the best profile of acceptability. Rivastigmine transdermal patch 15 cm² was the best optional treatment both in function and global changes. This analysis showed that none of these medicines were likely to improve neuropsychiatric symptoms. Conclusions: Pharmacological interventions have beneficial effects on cognition, function and global changes, but not on neuropsychiatric symptoms as evidenced by current network meta-analysis. Although the clinical effects are uncertain in the multi-factor environment, those findings are helpful for guiding treatment decisions. Choice of drugs
may mainly depend on the disease severity and clinical symptoms. Hopefully, further research should try to differentiate more clearly the effects of monotherapy versus combined therapies.

Figure 1
Comparative efficacy and tolerability for mild to moderate AD in the network meta-analysis: Comparisons should be read from left to right. The efficacy and tolerability estimate is located at the intersection of the column-defining treatment and the row-defining treatment. For efficacy (mean changes of cognition), an SMD below 0 favors the column-defining treatment. For tolerability (all-cause adverse events), an OR below 1 favors the row-defining treatment. Significant results are in bold and underlined. PBO = placebo; DON = donepezil; GAL = galantamine; RIV = rivastigmine; MEM = memantine; SMD = standardized mean difference; OR = odds ratios; CrI = credible intervals

OC8: MODELS FOR PREDICTING RISK OF DEMENTIA: A SYSTEMATIC REVIEW. Xiao-He Hou1, Lei Feng2, Can Zhang3, Xi-Peng Cao4, Lan Tan1, Jin-Tai Yu1 (1) Department of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao, China; (2) Department of Psychological Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; (3) Genetics and Aging Research Unit, Mass General Institute for Neurodegenerative Diseases (MIND), Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA; (4) Clinical Research Center, Qingdao Municipal Hospital, Qingdao University, Qingdao, China

Background: Dementia is a significant public health problem associated with disability, institutionalization and mortality among elderly individuals. The prevalence of dementia in the world has been reported to be approximately 5%–7% among people aged 60 years and older. Accurate identification of individuals with high risk of dementia is important for early diagnosis and intervention, such as close monitoring, improved care and risk factor-targeted intervention. Information from well-established dementia risk models can guide targeted intervention to prevent dementia, in addition to the main purpose of quantifying the probability of developing dementia in the future. Objective: To evaluate the predictive performances of existing models. Methods: We conducted a systematic review of published studies on existing dementia risk models. The models were assessed by sensitivity, specificity, and area under the curve (AUC) from receiver operating characteristic (ROC) analysis. Results: Out of 8462 studies reviewed, 61 articles describing dementia risk models were identified, with the majority articles modeling late life risk (n=39), followed by those modeling prediction mild cognitive impairment (n=15), midlife risk (n=4) and patients with diabetes (n=3). Sample sizes of the studies included ranged from 40 to 930,395. Follow-up duration ranged from 1 year to 39.1 years. (Figure 2) Age, sex, education, Mini Mental State Examination, the Consortium to Establish a Registry for Alzheimer’s Disease neuropsychological assessment battery, Alzheimer’s Disease Assessment Scale-cognitive subscale, BMI, alcohol intake and genetic variables are most common predictors included in the models. (Figure 2) Most risk models had moderate-to-high predictive ability (AUC >0.70). The highest AUC value (0.932) was produced from a risk model developed for mild cognitive impairment patients. Conclusion: Many risk prediction models have been developed, but only a handful of them have been externally validated. The predictive ability of the existing dementia risk models is acceptable, but the lack of validation limited the extensive application of the models for dementia risk prediction in general population or across subgroups in the population. In the eight models which have been validated, CAIDE score is a good tool for mid-life dementia risk prediction. FCSRT-FR showed relatively better predictive accuracy than the other late life risk models. It can be recommended for widely use. The Disease State Index showed consistently moderate accuracy in different cohorts, so it is a good choice for predicting dementia risk for patients with MCI despite the high cost of calculating the model. The DSDRS could be recommended for patients with diabetes.

Figure 1 Comparison of AUCs, numbers of variables and follow-up length in different studies. The length of the bars on the left represents the AUC values of the models in different studies. The length of the bars on the right represents the follow-up years in different studies. *The follow-up length was not available or not applicable. AD, Alzheimer’s disease; AUC, area under the curve; MCI, mild cognitive impairment
OC9: OPTIMIZING THE GANTENERUMAB PHASE III DOsing REGIMEN THROUGH PK/PD MODELING AND CLINICAL TRIAL SIMULATIONS. Carsten Hofmann¹, Ronald Gieschke¹, Sylvie Retout¹, Smiljana Ristic², Nicola Voyle³, Paul Delmar², Daniel Serafin¹ ((1) Clinical Pharmacology and Bioanalytical R&D, Roche Pharma Research and Early Development – Basel, Switzerland; (2) Neuroscience, Roche Product Development – Basel, Switzerland; (3) Neuroscience, Roche Product Development – Weibyn, UK)

Background: Following a futility assessment of one gantenerumab Phase III study (Scarlet RoAD [NCT01224106]) in 2015, a strategy to select a potentially efficacious and safe dosing regimen for gantenerumab had to be developed. Objective: To combine available internal and external information and generate additional clinical safety data to confirm prior modeling assumptions. Methods: Mathematical pharmacokinetics/pharmacodynamics (PK/PD) models for positron emission tomography (PET; surrogate for efficacy) and amyloid-related imaging abnormalities (ARIA; safety) were developed to create a hypothesis for an optimal dosing regimen in patients. Subsequently, several dosing regimens were tested in open-label extension (OLE) phases of former Phase III studies to assess the safety of higher doses and to inform the PK/PD models. The updated models were used to simulate different Phase III titration regimens with the aim of finding a safe, potentially efficacious and simple dosing regimen for all patients, irrespective of apolipoprotein E4 (ApoE4) genotype status. Results: Actual clinical data from the OLEs and PK/PD modeling data indicated that doubling the dose every 3 months until the final dose is reached provides the best results in terms of benefit, risk and simplicity. Conclusions: The holistic approach of combining available internal and external data, through PK/PD modeling and generating new clinical data, to confirm the model assumption allowed the team to develop an optimized dosing regimen for the new gantenerumab Phase III studies in a very short time.

OC10: STRATEGY OF RESEARCH NEW DRUGS AGAINST AD. Cuibai Wei¹, Jianping Jia¹, Jihui Lv², Yujing Zhang¹ ((1) Neurology Department, Xuan Wu Hospital, Capital Medical University, Beijing, China; (2) Neurology Department, Beijing Geriatric Hospital, Beijing, China)

Background: It has been reported that over 46 million people live with dementia worldwide. This number is estimated to increase to 131.5 million by 2050. Specifically, 94% of people with dementia live in low and middle-income countries. It also estimated how these numbers will increase in the future, dementia including Alzheimer’s disease (AD) and other causes, is one of the biggest public health and social care challenges facing the world today and in the future. People with dementia have poor access to appropriate healthcare, even in most high-income country settings, where only around 50% of people with dementia receive therapy. Currently Cholinesterase inhibitors and NMDA receptor antagonist are the main medicines, but only to be used as symptomatic drugs. No modifying–disease drug has been approved for Alzheimer disease. So, the strategy of researching new drug to fight AD is a crucial challenge. Objectives: Many factors may affect results of clinical trials of new drugs, so it is necessary to refine an available strategy for researching new drugs against AD. Methods: We searched and reviewed the relevant literature through the Pubmed database. Results: The choice of drug targets is the first step to achieve effective drugs against AD. Because the pathological mechanism of AD is complex, single target therapy can hardly achieve a curative effect. Therefore, multi-targets intervention strategy should be adopted in AD drug development. Enrolling population is the secondary endpoint for a successful clinical study. Prodromal and mild AD vs. the late stage of dementia constitute better intervention windows, since there are more living neurons. Neuroimaging is convenient and there are available tools to improve homogeneity of populations in AD clinical trials. Cranial MRI and PET scan give an objective reference for AD diagnosis and collect imaging data from patients enrolled in trials. Finally, selecting a right and sensitive measure is also important for a reliable trial. The Alzheimer’s Disease Assessment Scale cognitive subscale (ADAS-cog) is available and general cognitive assessment instruments, but they lack sensitivity in the earlier stages of AD. Some study suggest that the CDR-SB has psychometric properties that could make it attractive as a primary outcome measure in clinical trials of AD to comprehensively assess both cognitive and functional disability in prodromal and mild AD patients. Conclusions: We suggest that the development of novel drugs for AD should be based on an appropriate and comprehensive strategy, including accurate drug targets, proper patient recruitment and using sensitive measurement tools for effective drugs.
Background: Gantenerumab is a fully human monoclonal antibody currently under evaluation for the treatment of early Alzheimer’s disease (AD). In the ongoing, open-label extension (OLE) studies of Scarlet RoAD (SR; NCT01224106) and Marguerite RoAD (MR; NCT02051608), preliminary analysis showed that titrated dosing schemes targeting 1,200 mg/month (high dose) resulted in up to three times more amyloid reduction over 12 months versus 24 months of fixed low-dose treatment (225 mg) in the double-blind (DB) SR study (1). Objective: To discuss the effects of high-dose gantenerumab after 24 months of treatment. Methods: In the SR and MR OLE studies, patients were assigned to one of six titration schedules targeting a dose of 1,200 mg/month. Patients with low cerebrospinal fluid β-amyloid and a positive visual scan at OLE baseline were eligible for the positron emission tomography (PET) substudy; those who reached doses ≥ 900 mg for ≥ 6 months were included in the analysis. Owing to considerable differences in titration schedules and duration of time off treatment between DB and OLE dosing, patients were analyzed in three groups: the MR DB placebo cohort (MR-Pbo), the MR DB gantenerumab (MR-Gant) and an SR DB cohort combining patients originally assigned to placebo or gantenerumab (SR). Change from OLE baseline in amyloid burden was assessed based on global and regional standard uptake value ratio (SUVR) analysis of florbetapir PET at 12 and 24 months. Results: Preliminary analysis of 40 patients (MR-Pbo, 14; MR-Gant, 17; SR, 9) showed mean (SD) 12-month changes in absolute SUVR units of −0.24 (0.21), −0.27 (0.14) and −0.13 (0.16) in the MR-Pbo, MR-Gant and SR groups, respectively. Reductions in amyloid burden and the percentage of patients below the amyloid positivity threshold using an updated data cutoff (30 May 2018) will be reported. Approximately 37 patients (MR-Pbo 12; MR-Gant 12; SR 13), not accounting for patient dropouts, will undergo an OLE 24-month PET scan for this analysis. Conclusions: Updated findings are expected to confirm preliminary results and show a continued reduction in amyloid burden with ongoing treatment up to 24 months. This work supports our planned Phase III program using high doses of gantenerumab. 1. Klein G. Higher dose gantenerumab leads to significant reduction in amyloid plaque burden – results for the Marguerite and Scarlet RoAD open-label extension studies. 10th Clinical Trials on Alzheimer’s Disease (CTAD); 2-4 November 2017; Boston, MA, US.

Background: Deep brain stimulation (DBS), a novel therapy for Alzheimer's disease (AD), has mainly been focused on mild to moderate cases until now. Objectives: This study aimed to give the first evidence of alterations in performance induced by stimulating the fornix in patients with severe AD patients. Methods: The performance of five cases enrolled in the study, were scored with specialized assessments such as Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR), etc. before and at an early stage after DBS. The burden of caregivers was evaluated by Zarit Caregiver Burden Interview (ZBI). Moreover, their changes in certain dimensions, which could not be totally reflected by our assessments, such as mental states and social performance, were reported in this paper. Results: The cognitive performance of the patients remained stable or improved to various degrees as a whole and the caregivers’ burden was decreased. Individually, a better mental state or social performance was observed in 3 cases, case 2 even acquired a remarkable improvement in long-term memory. The conditions of case 4 deteriorated due to inappropriate antipsychotic medications given by his caregivers. Conclusion: DBS, in its early stages, was capable of slowing down or reversing the cognitive deficits in severe AD patients and ameliorating their emotional and social performance to an extent. However, long term effects induced by DBS in severe AD need to be validated further. And more investigations should focus on the definite mechanism of DBS.

**Figure 1**
Indicates severe brain atrophy in the whole brain pre-surgery

**Figure 2**
Indicates the location of electrodes in the fornix

**Figure 3**
Indicates the sites of electrode and leading wires
OC13: YXQN MEDICINE AMELIORATES ALZHEIMER’S DISEASE- COGNITIVE IMPAIRMENT AND PATHOLOGY IN TRANSGENIC MICE. Xiao-meng Li1, Xiao-wan Wang1, Li-chun Wang1, Xu Dong1, Jia-le Li2, Si-tong Liu1, Jiang Li2 (1) The Key Laboratory of Molecular Epigenetics of MOE, Institute of Genetics and Cytology, Northeast Normal University, Changchun, China; (2) Dental Hospital, Jilin University, Changchun, China

Background: Alzheimer’s disease (AD) is the world’s most common form of dementia, in which aggregation of amyloid-β (Ab) is the hallmark. Unfortunately, no medicines are yet available to cure AD. Objectives: Yangxue Qingnian (YXQN) is a Chinese traditional medicine, and its pharmacological effect is improving cerebral blood flow. In this study, we aimed to investigate the possible effects that YXQN reduced AD-like pathology and cognitive impairment in APPswePS1dE9 (APP/PS1) mice with 2 months administration.

Methods: YXQN extract was provided by the TIANJIN TASLY Pharmaceutical Co., LTD. The diluted YXQN medicine and donepezil were used for oral administration in APPswePS1dE9 (APP/PS1) mice of 8-month-old. In all, the drug dosages were YXQN low-dose at 0.69 g/kg, YXQN middle-dose at 2.08 g/kg, YXQN high-dose at 6.24 g/kg, and donepezil at 1.03 mg/kg. During the 2-month administration period, cognitive function of the five groups of APP/PS1 mice was measured by Y-maze at Day 30 and Day 60. The Morris Water Maze (MWM) was also performed at the termination of the drug supplementation. After that, a set of biochemical indices in the brain was investigated. Therefore, all AD pathological indices in this research were determined in 10-month-old APP/PS1 mice.

Results: Our data showed that YXQN substantially ameliorated behavioral defects in 10-month-old APP/PS1 mice using Morris Water Maze and Y-maze tests, in which the cognitive ability of YXQN high-dose group was almost similar to control mice. Next, we focused on the brain pathological alterations in the YXQN group by three experiments, including thioflavin-S, congo-red, and Ab-immunohistochemistry staining. The results demonstrated that the high-dose of YXQN dramatically suppressed amyloid plaques in the hippocampus and cortex of APP/PS1 mice, which showed a 47–72% reduction in plaque deposits, relative to the vehicle group. In addition, our data verified that YXQN decreased the cerebral amyloid load by attenuating β-secretase BACE1 and γ-secretase PS1 in the pathological processing of APP and promoted the level of α-secretase ADAM10 in the physiological processing of APP to generate more sAPPa, which combat amyloidosis formation, and also carry out neurotropic and neuroprotective effect. Conclusions: Taken together, our results strongly suggest that YXQN could be a potential medicine for AD and provide new evidence for further AD drug research and development.

OC14: ELENBECESTAT (E2609), A BACE INHIBITOR: RESULTS FROM A PHASE-2 STUDY IN SUBJECTS WITH MILD COGNITIVE IMPAIRMENT (MCI) AND MILD-TO-MODERATE DEMENTIA DUE TO ALZHEIMER’S DISEASE (AD). Shau Yu Lynch, June Kaplow, Jim Zhao, Shobha Dhadda, Johan Luthman, Bruce Albala (Eisai Inc. Woodcliff Lake, NJ, 07677 USA)

Background: This Phase-2, 18-month, placebo-controlled study investigated the safety of elenbecestat in MCI-to-moderate AD subjects and explored its effects on biomarkers and clinical endpoints.

Methods: Subjects were diagnosed as AD (NIA-AA 2011 criteria) and confirmed as amyloid-PET+ before being randomized to placebo, elenbecestat 5, 15, or 50-mg/day. While ongoing, the study was amended; subjects with ≥3 months of treatment remaining were reassigned from elenbecestat 5- and 15-mg/day to 50-mg/day. Subjects who received ≥3 months of elenbecestat 50-mg/day were analyzed as the 50-mg/day Total group. Safety measures included incidences of TEAEs and clinical laboratory assessments. Clinical effectiveness (CDR-SB) and effect on amyloid load (amyloid-PET) were explored by comparing changes from baseline (CBF) to 18 months between 50mg/day Total vs placebo. Longitudinal amyloid-PET was obtained from 28 subjects with flurbetaben and 7 subjects with flortetaipir. Analyses of mean CBF in CDR-SB and mean % CBF in cortical composite PET SUVR values (ratio of average of tracer-specific cortical regions to whole cerebellum) were based on ANCOVA with baseline values as covariates.

Results: This study randomized 70 subjects: 43 (61%) completed the study; 27 (39%) discontinued early. No deaths occurred. Incidences of TEAEs and TEAEs leading to treatment discontinuation were similar for 50-mg/day Total and placebo. No dose-dependent response relationship was observed. No subject discontinued due to liver toxicity. Although sample sizes for PET SUVR analyses were small, statistically significant mean treatment differences of -5.8% (p=0.013) and -13.6% (p=0.014) were observed between 50mg/day Total vs placebo in the flurbetaben (placebo=7; 50-mg/day Total=21) and flortetaipir (placebo=4; 50-mg/day Total=3) subgroups, respectively. The 50mg/day Total group (n=29) demonstrated a mean treatment difference of -0.5 (>30% less decline) in CDR-SB vs placebo (n=12) which was not statistically significant (p=0.55) in this small study. Subgroup analysis of subjects with baseline flortetaipir PET SUVR values within 1.4-1.9, showed that those in the 50-mg/day Total group demonstrated 72% less decline in CDR-SB vs placebo. Conclusions: Elenbecestat was generally well tolerated; no unexpected safety concerns emerged. Although sample sizes were small, statistically significant decreases in PETSUVR were seen. Clinical assessments suggest elenbecestat may have attenuating effects on cognitive decline in MCI-to-moderate AD subjects.

OC15: DEVELOPMENT OF NOVEL PET IMAGING TRACERS FOR NEURODEGENERATIVE DISEASES. Paul Tempest1, Gilles Tamagan1, Ken Marek2, John Seibyl3, Vincent Carroll1, Olivier Barret4, David Algaliê1, Kun-Ju Lin1, Ing-Tsung Hsiao4, Qing-Fang Yang5, Maiko Ono2, Hiroshi Shimada1, Narihiko Sahara2, Ming-Rong Zhang2, Makoto Higuchi2, Chin Yin Tai4, Ming-Kuei Jang1 (1) APRINOIA Therapeutics - Taipei, Taiwan; (2) National Institute for Quantum and Radiological Science and Technology (QST) - Chiba, Japan; (3) Invicro - New Haven, CT USA; (4) Chang Gung Memorial Hospital and Chang Gung University - Tao-Yuan, Taiwan

Background: With the success of amyloid PET imaging in the clinic, demand for imaging agents targeting other CNS located protein aggregates has increased. PET imaging agents can be instrumental in providing a non-invasive method for diagnosis, tracking disease progression or regression, and patient stratification for therapeutic trials. Currently, there is no known PET tracer available for 4R tau based tauopathies. Additionally, there is a substantial unmet need for therapeutics for various pathologies involving tau in the CNS. Objectives: We are seeking to establish utility of our 4R tau tracer, [18F]-APN-1607, for several tauopathies including Alzheimer’s disease (AD), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). Our goal is to provide a single imaging compound able to image multi-isofoms of tau across various tauopathies. Additionally, we hope to leverage our CNS focused, small molecule collection to rapidly provide PET tracers for other protein aggregates such as alpha-synuclein and TDP43. We hope to use these new PET tracers as tools to enable therapeutic programs to rapidly and non-invasively show target engagement and efficacy.

Methods: APRINOIA Therapeutics has operations in Taipei, Suzhou, Tokyo and Boston and, together with our partners, has developed imaging capabilities in Tokyo, Taipei, and New Haven for our second
P1: CHORAL SINGING FOR THE PREVENTION OF DEMENTIA: STUDY DESIGN OF A RANDOMIZED CLINICAL TRIAL. Lei Feng1, Rui Wang2, Iris Rawtaer3, F. H. Maurine Tsakok4, Bernard Lanskey5, Chay Hoon Tan6, Lee-Gan Goh7, Rathi Mahendran1,3, Ee-Heok Kua1,3

**Backgrounds:** The significance of neuroimaging and fluid biomarkers in the prediction of clinical progression during the very early stages of Alzheimer’s disease (AD) is being demonstrated by the results of AD Neuroimaging Initiative (ADNI). We have conducted Japanese (J-) ADNI using almost identical protocols to ADNI’s and compared the results, to ensure international harmonization in global clinical trials of disease-modifying drugs for AD.**Methods:** To characterize the clinical, neuroimaging and biomarker measures in subjects with normal cognition (CN), late amnestic mild cognitive impairment (MCI) or mild AD in the Japanese elderly population diagnosed using the same criteria with ADNI’s, total of 537 subjects (154 CN, 234 late MCI, and 149 AD) from 38 clinical sites were enrolled at baseline and followed for 24-36 months using cognitive and functional measures used in ADNI, 1.5T structural MRI, FDG and 11C-PiB amyloid PET scans, blood and CSF sampling (assayed for Aβ(1-42) and tau by Alzbio3) and APOE genotyping. These subjects were compared with 1004 ADNI participants with Ab biomarker data (400 CN, 355 late MCI, 249 AD). Rate of changes in representative cognitive composite measures were compared for amyloid-positive MCI and mild AD individuals between the J-ADNI and ADNI populations. J-ADNI data have been publicized from the National Bioscience Database Center, Japan (Research ID: hum0043.v1, 2016) and ADNI data were obtained from the ADNI database (http://adni.loni.usc.edu).**Results:** The subjects with late MCI in J-ADNI (total) progressed to dementia in 12 months at a rate of 26.3% per year, more rapidly than in ADNI (13.2%) (log-rank p<0.001). The percentages of APOE ε4-positive individuals in the total CN, MCI and AD in J-ADNI were 24.0, 52.1 and 59.6%, respectively, which were at similar levels to those in ADNI (28, 55 and 67%). Amyloid positivity rates in CN, MCI and AD in J-ADNI were 24, 67 and 93%, respectively, which were not significantly different from those in ADNI (34, 72 and 90%; borderline in CN: p=0.137). Three-year mean changes in MMSE (-1.23/y), CDR-SB (1.12/y) and ADAS-cog13 (2.9/y) in amyloid-positive MCI in J-ADNI were at similar levels to those in ADNI (-1.20/y, 0.73/y, 2.4/y, respectively), with significantly faster declines in MMSE at 6 and 12 months in J-ADNI. Two-year mean changes in MMSE (-1.65/y), CDR-SB (1.25/y) and ADAS-cog13 (2.9/y) in amyloid-positive mild AD in J-ADNI also were similar to those in ADNI (-2.2/y, 1.65/y, 3.9/y, respectively), whereas the baseline mean scores in CDR-SB (3.73) and ADAS-cog13 (27.4) in J-ADNI were significantly lower than those in ADNI (4.41 and 30.4, respectively), and these differences in mild AD were generally sustained during the longitudinal follow-up. Functional Assessment Questionnaire in mild AD showed a similar trend of separation. In contrast, CN populations in J-ADNI and ADNI exhibited minimal movements in the cognitive scores.**Conclusion:** J-ADNI has successfully recruited cohorts of CN, subjects with late amnestic MCI and mild AD with generally comparable baseline characteristics and progression profiles with ADNI. The slightly faster trend of progression in MCI in a subset of measures (e.g., conversion to dementia and decline in MMSE within the 1st year), as well as milder cognitive scores and decline in mild AD of J-ADNI, may reflect (i) relatively narrower disease ranges (i.e., later in MCI and milder in AD) of individuals recruited in J-ADNI, (ii) a minor difference in the dividing line between late MCI and mild AD, with J-ADNI setting a slightly earlier cut-point, (iii) difference in educational length (slightly shorter in J-ADNI), (iii) ethnic differences, or combination of these factors. These results strongly support the successful bridging of clinical trial data between Japan and North America.
importance of nutrition on cognitive health during aging. Neuronal health depends on the adequacy of multiple nutrients. Recently, a treatment with multiple nutrients (Souvenaid) in mild AD has met some success. Souvenaid is a 125 mL (125-kcal) drink, which contains multiple nutrients including uridine monophosphate, phospholipid, choline, omega-3 fatty acids, vitamins and antioxidants. The latter are considered essential for the formation of synaptic membranes and synaptic functioning. In an overseas study, Souvenaid was shown in a 12-week randomized, double-blind controlled trial to benefit the treated mild AD persons. The compliance was 95% and it was well tolerated. However, there was no data on the efficacy or tolerability of Souvenaid in Chinese older adults with mild AD and other dementias, in a real-world setting. As cholinesterase inhibitors (rivastigmine, donepezil, galantamine) and memantine were all currently used treatments, Souvenaid was added onto the current treatments in this real-world clinical study. Objectives: The objective of this study was to explore the effects and tolerability of Souvenaid in Chinese patients with mild AD and other dementias in a real-world outpatient clinic setting. Methods: This was a 3-month open-label case series study, which was conducted in a single memory clinic center from October 2014 to April 2016. The diagnosis of AD was in accordance with the 2011 NIA-AA criteria of probable AD dementia, with MRI brain imaging showing medial temporal atrophy and/or hippocampal atrophy. Results: 37 subjects completed their 3-month follow-up. At baseline, the mean (SD) age was 82.7 (8.5) years, and the mean MMSE score was 19.8: 67.6% of them were women. 91.9% (n=34) of them had AD dementia, and 81.1% (n=3) had vascular dementia (n=2) or alcoholic dementia (n=1). 86.5% of them were on approved symptomatic AD treatments. Souvenaid was well tolerated by 89.2% of the subjects. 10.8% had intolerance with minor GI side effects including diarrhea, and abdominal cramps. Financially, 91.9% could afford the cost. Cognitively, the mean MMSE improved by 1.6 after 3 months (p=0.006, paired t-test), and 60% of them showed improvements (Table 1). Improvements in memory (caregivers’ reports), behavior and daily activity among Chinese patients with mild AD and other dementias, over a 3-month period.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Mean MMSE score</th>
<th>Change</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 months</td>
</tr>
<tr>
<td>Overall (N=37)</td>
<td>19.8 (6.6)</td>
<td>21.5 (7.3)</td>
</tr>
<tr>
<td>AD (n=34)</td>
<td>19.8 (6.8)</td>
<td>21.0 (7.4)</td>
</tr>
<tr>
<td>VaD &amp; other (n=3)</td>
<td>20.3 (3.1)</td>
<td>27.0 (2.0)</td>
</tr>
</tbody>
</table>

AD: Alzheimer’s disease; MMSE, mini-mental state examination; VaD, vascular dementia

### P3: COMPARISON OF THE USEFULNESS OF BRAIN PERFUSION SPECT, DAT-SPECT, AND MIBG SCINTIGRAPHY FOR THE DIAGNOSIS OF DEMENTIA WITH LEWY BODIES.

#### Backgrounds:
Current diagnostic criteria recommend neuroimaging as a diagnostic support tool for the clinical diagnosis of dementia with Lewy bodies (DLB). Because DLB causes characteristic impairments and disabilities, such as neuroleptic hypersensitivity, which may significantly increase morbidity and mortality, its prompt and correct diagnosis is very important. The aim of this study was to evaluate the utility with which diagnostic accuracy can be increased using a combination of brain perfusion SPECT (bpSPECT), 123I-metaiodobenzylguanidine myocardial scintigraphy (MIBG scintigraphy), and DATSPECT. Taking finances and patient burden into consideration, we compared the tests to determine priority. Methods: Thirty-four patients with probable DLB (75.0 ± 8.3 years old, 14 male: 20 female) underwent bpSPECT, MIBG myocardial scintigraphy, and DATSPECT. Results: Our comparison of three functional imaging techniques indicated that MIBG scintigraphy (79%) or DATSPECT (79%) had better sensitivity for characteristic abnormalities in DLB than bpSPECT (53%). The combination of the three modalities could increase sensitivity for diagnosis of DLB to 100%. Additionally the ratio of patients with rapid eye movement sleep behavior disorder (RBD) was significantly higher in MIBG (+) group than in MIBG (-) group. Conclusions: In the stand-alone diagnostic means, priority should be placed on MIBG scintigraphy or DAT-SPECT for the diagnosis of DLB. However, our results suggest that the combination of bpSPECT, MIBG scintigraphy, and DATSPECT increased accuracy of the clinical diagnosis of DLB.

### Table 2

<table>
<thead>
<tr>
<th>Subjects (N=37), %</th>
<th>Much improved</th>
<th>Improved</th>
<th>Unchanged</th>
<th>Worsened</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caregiver report</td>
<td>16</td>
<td>30</td>
<td>41</td>
<td>13</td>
</tr>
<tr>
<td>Self-report</td>
<td>16</td>
<td>27</td>
<td>49</td>
<td>8</td>
</tr>
<tr>
<td>Cognitive orientation (Caregiver report)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persons</td>
<td>–</td>
<td>43</td>
<td>51</td>
<td>6</td>
</tr>
<tr>
<td>Place</td>
<td>–</td>
<td>27</td>
<td>62</td>
<td>11</td>
</tr>
</tbody>
</table>

**Methods:** The objective of this study was to explore the effects and tolerability of Souvenaid in Chinese patients with mild AD and other dementias in a real-world outpatient clinic setting. **Results:** 37 subjects completed their 3-month follow-up. At baseline, the mean (SD) age was 82.7 (8.5) years, and the mean MMSE score was 19.8: 67.6% of them were women. 91.9% (n=34) of them had AD dementia, and 81.1% (n=3) had vascular dementia (n=2) or alcoholic dementia (n=1). 86.5% of them were on approved symptomatic AD treatments. Souvenaid was well tolerated by 89.2% of the subjects. 10.8% had intolerance with minor GI side effects including diarrhea, and abdominal cramps. Financially, 91.9% could afford the cost. Cognitively, the mean MMSE improved by 1.6 after 3 months (p=0.006, paired t-test), and 60% of them showed improvements (Table 1). Improvements in memory (caregivers’ reports), behavior and daily activity among Chinese patients with mild AD and other dementias, over a 3-month period.

### Table 2

<table>
<thead>
<tr>
<th>Cognitive outcomes after 3 months of Souvenaid supplementation</th>
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<tbody>
<tr>
<td>Subjects (N=37), %</td>
</tr>
<tr>
<td>Much improved</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Caregiver report</td>
</tr>
<tr>
<td>Self-report</td>
</tr>
<tr>
<td>Cognitive orientation (Caregiver report)</td>
</tr>
<tr>
<td>Persons</td>
</tr>
<tr>
<td>Place</td>
</tr>
</tbody>
</table>

**Background:** Alzheimer's disease (AD) typically affects individuals who are aged 60 or above and quickly becomes one of the most prevalent neurodegenerative diseases worldwide. Thus, a non-invasive, serum-based diagnostic platform is eagerly awaited. The goal of
this study was to identify a serum-based biomarker panel using a predictive protein-based algorithm able to confidently differentiate AD patients from control subjects. Methods: One hundred and fifty-six patients with AD and the same number of gender- and age-matched control participants with standardized clinical assessments and neuroimaging measures were evaluated. Serum proteins of interest were quantified using a magnetic bead based immunofluorescent assay and a total of 33 analytes were examined. All of the subjects were then randomized into a training set containing 70% of the total samples and a validation set containing 30%, with each containing an equal number of AD and normal samples. Logistic regression and Random Forest analysis were then applied to develop a desirable algorithm for AD detection. Results: Of the 33 analyses examined, 17 were found to be significantly differentially expressed between AD and control samples. The Random Forest method was found to generate a more robust predictive model than the logistic regression analysis. Furthermore, an 8-protein-based algorithm was found to be the most robust with a sensitivity of 97.7%, specificity of 88.6%, and AUC of 99%. Conclusions: Our study developed a novel 8-protein biomarker panel that can be used to distinguish AD and control multi-source candidates regardless of age. It is hoped that these results provide further insight into the applicability of serum-based screening methods and contribute to the development of lower cost, less invasive methods for diagnosing AD and monitoring progression.

**P5: EFFECT OF THE BET PROTEIN INHIBITOR APABETALONE ON SERUM MARKERS OF POTENTIAL IMPORTANCE FOR COGNITIVE DECLINE IN CARDIOVASCULAR DISEASE PATIENTS.** J. Cummings1,2, J. Johansson2, E. Kulikowski1, N.C. Wong3, C. Halliday1, K. Lebioda1, A. Khan1, B. Winblad4, H. Zetterberg4, M. Sweeny5 (1) Cleveland Clinic Lou Ruvo, Center for Brain Health, Las Vegas, USA; (2) Resverlogix Corp., Research and Development, San Francisco, USA; (3) Resverlogix Corp., Research and Development, Calgary, Canada; (4) Karolinska Institute, Dept NVS, Div. of Neurogeriatrics, Huddinge, Sweden; (5) Sahlgrenska Academy at the University of Gothenburg, Department of Psychiatry and Neurochemistry- Institute of Neuroscience and Physiology, Gothenburg, Sweden)

Background: Preventing and treating vascular cognitive impairment (VCI) has been challenging and thus novel therapeutic targets and approaches are currently being explored. Recent findings indicate a potential role of bromodomain and extramitral (BET) proteins in VCI pathogenesis and Aβ metabolism. Apabetalone (RVX-208) has previously been shown to downregulate markers of vascular inflammation, vascular calcification, complement and coagulation contributing to their effects on vascular disease pathogenesis. Apabetalone inhibits the interaction between BET protein bromodomains (BD) and acetylated lysine on histones or transcription factors. Apabetalone is a selective (BD2) BET inhibitor (BETi). BET proteins control the recruitment of the transcriptional machinery to coordinate gene transcription of BET sensitive genes, including factors responsive to inflammatory insult. Less is known about direct or indirect effects of BETi on Aβ metabolism. In phase 2 trials apabetalone treatment showed a significant reduction in major adverse cardiovascular events (MACE). The MACE reduction was most pronounced in patients with diabetes and elevated inflammation. Therefore a phase 3 outcomes trial - BETonMACE - has been initiated in post-acute coronary syndrome (ACS) patients with diabetes. The primary endpoint is time to cardiovascular disease (CVD)-related death, non-fatal myocardial infarct or stroke. Cognition assessment by Montreal Cognitive Assessment (MoCA) is being evaluated in patients ≥70 years of age in BETonMACE. Effects of apabetalone on MoCA will provide insights about the potential for BETi to modulate cognitive function in elderly patients with cardiovascular disease and diabetes. Objective: We investigated the effect of apabetalone on serum markers of cognitive decline and neurodegenerative disease progression from archived serum samples from a phase 2 trial in patients with CVD. These findings provide rationale for a cognition sub-study of the ongoing BETonMACE clinical trial. Methods: Serum Aβ42 was assessed in apabetalone phase 1 and 2 clinical trials. Serum Aβ40 was analyzed in phase 2 clinical dose-response trial ASSERT before and after 12 weeks treatment in a stable coronary artery disease population of 299 patients using Invitrogen ELISA assay. In addition, SOMAscan™ proteomic analysis was performed on serum from the Phase 2b ASSURE clinical trial to assess levels of ~300 proteins in the plasma following 26 weeks of treatment. Proteins of interest were selected based on literature describing their link to pathogenesis of VCI, MCI and/or AD. Results: In a Phase 1 clinical trial (test study) 8 mg/kg treatment per day for 7 days resulted in an 11.4% (SD 3.0) increase in serum Aβ40 vs. 2.2% (SD 5.8) for placebo. In the ASSERT Phase 2 trial (confirmation study), in patients with the lowest serum Aβ40 level at baseline (below median), treated with a dose of 150 mg, b.i.d., a significant increase of +7.7% in serum Aβ40 was observed in the apabetalone-treatment group (n=30) compared to placebo (n=30). At doses of 50 mg b.i.d. and 100 mg b.i.d. serum Aβ40 increases of +0.8% and +4.5% were observed, respectively. The Invitrogen ELISA method for Aβ42 used was not sufficiently sensitive for detecting serum levels. We have previously reported changes in the plasma proteome of patients treated with apabetalone in the complement and coagulation pathways, the acute phase response and vascular inflammation. Here we report, for the first time, changes in proteins linked to cognitive decline and neurodegenerative disease. In the atherosclerosis regression phase 2 ASSURE trial, proteomic analysis demonstrated significant increases in the apabetalone (n=47) group (100 mg b.i.d.), versus placebo treated (n=47) patients in the following markers; ATP synthase subunit O-mitochondrial (ATP5O) +45%; Amyloid Beta A4 Protein (APP) +33%; Brain-Derived Neurotrophic Factor (BDNF) +28%; Annexin A1 +9%; and Gelsolin, +5% (p<0.05 for all markers, except BDNF, which had p<0.1). The following markers were decreased versus placebo: Serum Amyloid P-Component (APC) -11%; tyrosine (Y), lysine (K) and leucine (L) 40kDa (YKL-40) (CH3L1), -18.5%; and C-Reactive Protein (CRP), -21% (p<0.05 for APCS and CRP; YKL-40 p<0.1).

Conclusions: In CVD patients, BETi by apabetalone increases serum Aβ40 and modulates cardiometabolic markers. Here we report effects on serum protein markers of cognitive decline and neurodegenerative disease. These BETi effects provide rationale to explore apabetalone as a potential therapeutic for VCI and neurodegenerative disease. Cognition assessment using the MoCA in patients ≥70 years of age is currently being performed as a substudy in the BETonMACE Phase 3 CVD outcomes trial. Favorable effects on cognition coupled with mechanistic understanding would open developmental paths for confirmatory trials in VCI and neurodegenerative disorders.

**P6: ASSESSMENT INSTRUMENTS USED IN NEW DRUG PHASE III RANDOMIZED CLINICAL TRIALS FOR ALZHEIMER DISEASE.** Hai-Ning He1, Shi-Fu Xiao1 Tao Wang1 (1) Department of Geriatric Psychiatry, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine; Alzheimer’s Disease and Related Disorders Center, Shanghai Jiao Tong University - China)

Background: Backgrounds Alzheimer’s disease (AD) is increasing in prevalence and social burden every year throughout the world without effective therapies that slow or prevent disease progression.
Therefore, the development of new drugs for AD has become a global challenge. In recent years, with the constant emergence of pathology-targeted drugs, some of them have entered phase III clinical trials, therefore assessment instruments used in the protocols of new drug clinical trials need to be summarized. Objectives: An overview of the assessment instruments used in phase III clinical trials was made to provide guidance for future clinical trials. Methods: We retrieved published phase III clinical trials through standardized search strategies in PubMed and Embase. Simultaneously, the protocols were searched in ClinicalTrials.gov. Both primary outcome measures and secondary outcome measures were analyzed and summarized from the studies. Our search covered all trials available up to April 21, 2018. Results: We screened a total of 10 drugs, including symptom-based drugs (Tacrine, Donepezil, Galantamine, Rivastigmine and Huperzine A) and pathogenesis-based drugs (Solanezumab, Bapineuzumab, Gantenerumab, Crenezumab and LMTM). Among them, Gantenerumab and Crenezumab have not had results published yet. We searched their protocols in clinicaltrials.gov to analyze their outcome measures. The majority of Phase III clinical trials of symptom-based drugs used Alzheimer’s Disease Assessment Scale Cognitive Subscale (ADAS-cog) and/or Clinician’s Interview-Based Impression of Change Plus (CIBIC plus) as the primary outcome measure, while a minority of trials used Severe Impairment Battery (SIB) and/or Alzheimer’s Disease Cooperative Study-Activities of Daily Living (ADCS-ADL). Meanwhile, secondary outcome measures varied. ADCS-Instrumental Activities of Daily Living (ADCS-IADL), Neuropsychological Inventory (NPI), Assessment of Subject Accommodation Status and Caregiver Burden (APAS-CarB), EuroQol 5-Dimensional Health-Related Quality of Life Scale (EQ-5D) and Quality of Life in Alzheimer’s Disease (QoL-AD) were used to assess daily function, while Mini-Mental State Examination (MMSE), ADCS-Clinical Global Impression of Change (ADCS-CGIC), Clinical Global Impression Scale (CGIS), Clinical Global Impression of Improvement (CGI-I) and Clinical Dementia Rating-Sum of Boxes (CDR-SB) were used to assess global function. Compared with symptom-based drugs, in addition to the above-mentioned clinical measurements, clinical trials of amyloid-beta targeted drugs introduced biomarkers and imaging markers as secondary outcome measures to assess potential therapeutic effects. According to their pharmacological mechanism, available biomarkers were plasma Aβ (Aβ1-40 and Aβ1-42), cerebrospinal fluid (CSF) Aβ/Aβ1-40 and Aβ1-42, CSF tau and CSF phospho-tau. In some studies, volumetric MRI (vMRI) were used to measure changes in lateral ventricular volume, temporoparietal volume, whole brain volume, and hippocampal volume. Furthermore, Amyloid-PET and Tau-PET were used to provide information about brain amyloid and tau load over time, respectively. These measurements were assessed at baseline, at mid-term follow-up visit and at endpoint of the study (or at early termination), and to provide information on whether the drug has therapeutic effects in human bodies through comparing changes from baseline. Conclusions: Phase III clinical trials of both symptom-based drugs and pathogenesis-based drugs mostly used ADAS-cog, CIBIC plus and CDR-SB as primary outcome measures. Daily functional assessment scales, as well as global functional assessment scales and psychotic symptoms scales were used as secondary outcome measures. The improvement of these measurements is in good agreement with the improvement of clinical symptoms. Meanwhile, biomarkers were the key secondary outcome measures in clinical trials of pathogenesis-based drugs. In the future studies, imaging data could be acquired at multi follow-up visits if available, proving information on brain progression in AD patients.

P7: MITOPHAGY IS ASSOCIATED WITH EXERCISE-INDUCED IMPROVEMENT OF MITOCHONDRIAL DYSFUNCTION IN APP/PS1 TRANSGENIC MICE. Na Zhao1,2, Qing-Wei Yan1,2, Ling-Yu Yin1,2, Bo Xu1,2 (1) Key Laboratory of Adolescent Health Assessment and Exercise Intervention of Ministry of Education, East China Normal University, Shanghai, China; (2) School of Physical Education & Health Care, East China Normal University, Shanghai, China; (3) School of Physical Education, Xi zang Minzu University, Xianyang, China

Background: Randomization rates in AD clinical trials are extremely challenging, averaging only about 0.5 participants randomized per study per month at each site. This rate needs to be improved upon if the search for new medicines is going to remain cost effective and new ideas such as trial ready registries are becoming the vogue. But do traditional methods still work? Maybe the attention to recruitment needs more time and focus; something which small clinical centers have less resource to provide, especially if not included in study costs. Methods: Bioclinica Research Network (BRN) sites in Denmark (Ballerup, Vejle, Aalborg) uses Facebook, posters and brochures, advertising in AD magazines, information meetings, social events and collaboration with primary care physicians and dementia nurses to find patients. They also have staff dedicated to filtering all the data collected and identifying prospective participants and approaching them personally. They are currently participating in a large multicenter, multi-national clinical trial of ‘at-risk of AD’ participants. This is known to be a traditionally difficult group to recruit, so BRN sought to benchmark their progress in Denmark at 19 weeks against the rest of the 150 sites performing the study. Results: At 19 weeks. Conclusion: 1) Randomization rates at BRN sites are over four times the reported average for AD studies and 15 times above the average rate for other sites on this trial. 2) At this rate, the BRN sites will recruit to target in 31 weeks. The global study would reach target in 304 weeks. Future initiatives will demonstrate how much further dedicated patients recruit technology on a country / site level will be able to further increase randomization rates. 3) BRN sites would shorten recruitment by more than 5 years providing significant cost savings and supporting faster results for a patient’s population in high demand for effective medication. The opportunity costs alone of a successful study would pay for that study. 4) If the patients in screening at the 19-week point screen fail at 59%, another 43 patients can be potentially randomized; meaning the target will be exceeded by the end of the current screening period. 5) Traditional recruitment methods can attract large numbers of potential participants. 6) Screen fail rates are 7% higher than the other centers average, but less than the predicted screen fail rate for this study. 7) BRN has the capability and capacity to deliver complex AD studies at significantly faster rates than currently reported and accepted.

P8: EXERCISE IMPROVES HIPPOCAMPAL MITOCHONDRIAL MORPHOLOGY IN APP/PS1 TRANSGENIC MICE. Baixia Li1,2, Xiaoyan Ding1,2, Fei Liang1,2, Chenfei Zhang1,2, Bo Xu1,2 (1) Key Laboratory of Adolescent Health Assessment and Exercise Intervention of Ministry of Education, East China Normal University, Shanghai, China; (2) School of Physical Education & Health Care, East China Normal University, Shanghai, China

Background: Backgrounds: Alzheimer’s disease (AD) is a progressive neurodegenerative disease clinically characterized by learning and memory function deterioration. While it is well established that exercise can improve cognitive performance in AD, there have been few basic cellular and molecular mechanisms research
performed to test the interaction between exercise and AD. **Objectives:** In this study, we aimed at investigating whether treadmill exercise improves learning and memory function in APP/PS1 transgenic mouse model of Alzheimer’s disease by improving mitochondrial morphology. **Methods:** Animals: Double-transgenic mice (APP/PS1 mice) were obtained from Nanjing Biomedical Research Institute of Nanjing University. 12 transgenic and 12 wild-type mice were investigated. Throughout the experiments, the animals were kept in plastic cages (6 mice per cage) in a controlled environment (22–24 °C, 40–60% relative humidity, 12-h light–dark cycle), with food and water available ad libitum. All animal experiments were performed in accordance with the care and use of medical laboratory animals (Ministry of Health, Peoples Republic of China) and the guidelines of the laboratory animal ethical standards of East China Normal University. Treadmill exercise protocol: At 3 months of age, the mice were randomly assigned into four groups (n = 6 each): wild-type control group (WC), wild-type exercised group (WE), transgenic control group (TC) and transgenic exercised group (TE). The exercise protocol consisted of 30 min of running (12 m/min at 0% slope). Animals trained 5 times a week for 3 months (from 3 to 6 months of age). The mice in the non-exercise groups were left on the treadmill, without running, for the same period as the exercise groups. Morris water mazes: Learning and memory ability was evaluated by Morris water maze. The whole process included 1-day adaptive phase without platform, a 5-day learning phase with hiding platform, and 1-day exploratory phase after 24h of the last learning phase. In the exploratory experiment, the distances of getting old goal location were recorded to evaluate the learning ability. Transmission Electron Microscopy (TEM): According to the TEM sample preparation method, dissected hippocampus CA1 was quickly cut into 1-mm-thick slices and immediately placed in 3% glutaraldehyde in phosphate buffer for 2h. After washed by PBS, it was fixed by osmic acid (OsO4) and embedded in EPON812 resin. Then it was cut successively to 0.07mm chips. Uranyl and lead citrate were used to stain. And it was observed by Field-emission Scanning Electron Microscopy (Sirion 200 (SEM)& INCA X-Act (EDS)). **Results:** Behavior Change: The platform quadrant distances of TC were considerably lower than WC (p<0.05). The platform quadrant distances were significantly increased in the TE group following a 12-week treadmill exercise (p<0.05). The platform quadrant distances of TC were considerably lower than WC (p<0.05). The platform quadrant distances were significantly increased in the TE group following a 12-week treadmill exercise (p<0.05). Mitochondrial morphology: Many fragmented mitochondria were destroyed by disrupted membranes and without clear cristae appeared in APP/PS1 transgenic mice. After training, the mitochondrial swelling structure of TE and WE disappeared, and the structure of the mitochondria was clear and the number increased. In this study, the mitochondrial area of TC group was lower than that in WE group (p<0.05), and the mitochondrial area increased after exercise intervention, and the mitochondrial area of WE(p<0.01) and TE (p<0.05) group was significantly higher than that of TC group. **Conclusions:** Our results show that, in comparison to wild type mice, transgenic mice were characterized by impaired learning and memory function. Treadmill exercise enhanced learning and memory function in APP/PS1 mice. Hence, this investigation demonstrates that treadmill exercise is an effective therapeutic that alleviate learning and memory decline in APP/PS1 mouse model and improved mitochondrial morphology maybe a cellular mechanism involved in neuropathological course of AD and cognitive improvement induced by exercise.
phase, patients received aducanumab or placebo once every 4 weeks for 52 weeks. In a staggered, parallel-group design, patients were randomized to fixed doses of aducanumab (1-10 mg/kg) stratified by ApoE ε4 status (carrier/non-carrier). After patient enrollment in fixed-dose cohorts was complete, the protocol was amended to include a cohort of ApoE ε4 carriers who received either titrated doses of aducanumab (1 mg/kg [2 doses]; 3 mg/kg [4 doses]; 6 mg/kg [5 doses]; 9 mg/kg thereafter) or placebo. Patients meeting eligibility criteria at Week 56 were enrolled in the LTE, where all patients were assigned to receive aducanumab 3, 6, or 10 mg/kg. LTE dose assignments were as follows: patients initially randomized to the aducanumab titration regimen during the double-blind phase continued at their original dose assignment. By Week 110, average expected dose of the titration arm was 7.6 mg/kg. Patients who received placebo during the double-blind phase were assigned treatment in the LTE to either aducanumab 3 mg/kg, a titration regimen of aducanumab 3 to 6 mg/kg (2 doses of 3 mg/kg followed by subsequent doses of 6 mg/kg), or a titration regimen of aducanumab up to 10 mg/kg (as described above). Patients randomized to aducanumab 1 mg/kg during the double-blind phase subsequently were assigned to receive aducanumab 3 mg/kg in the LTE. All other patients who had received fixed doses of aducanumab (3, 6, or 10 mg/kg) during the double-blind phase continued at their original dose assignment or a reduced dose. In the LTE, with the exception of safety, all endpoints were exploratory and included measurement of Aβ reduction using amyloid PET (as assessed by standard uptake value ratio) and change from baseline in the clinical endpoints Clinical Dementia Rating-Sum of Boxes (CDR-SB) scale and the Mini Mental State Exam (MMSE). A mixed model for repeated measures was used for the analysis of change from baseline in amyloid PET, CDR-SB and MMSE. Results: Of 196 patients randomized and dosed in PRIME within the fixed-dose and titration cohorts, 143 were dosed in the LTE and 115 completed treatment at Month 24. Patients from the titration cohort who continued aducanumab treatment up to 24 months experienced a reduction in brain amyloid plaque burden, as measured by PET, which was consistent with the dose- and time-dependent results observed in fixed-dose cohorts. Decreases in brain amyloid plaque burden were also observed among placebo-treated patients who switched to aducanumab in the LTE. CDR-SB and MMSE data suggest a clinical benefit in patients continuing aducanumab over 24 months. There were no new cases of ARIA-E in patients who continued on the same dose of aducanumab. Four patients experienced more than one episode of ARIA-E over 24 months of treatment, with an additional 2 patients experiencing recurrent ARIA-E after the first year of the LTE. These recurrent events were consistent with other ARIA reported to date; they were typically asymptomatic, and most patients continued in the study. The incidence of ARIA-E in patients switching from placebo to aducanumab was consistent with that reported in the placebo-controlled portion of the study. Conclusions: In the small population of patients from the titration and fixed-dose cohorts who completed the first year of the LTE, amyloid plaque burden continued to decrease in a dose- and time-dependent manner. Analyses of exploratory clinical endpoints, CDR-SB and MMSE, in the titration cohort were consistent with the results from the fixed-dose cohorts and suggest a continued benefit on the rate of clinical decline during the second year of treatment. Recurrent ARIA events were consistent with other ARIA events reported to date. No new safety signals were identified at 24 months. These data support further investigation of the clinical efficacy and safety of aducanumab in patients with early AD in the ENGAGE and EMERGE Phase 3 trials.1. Sevigny J et al. Nature. 2016;537:50-56.