referral processes. It was launched in 2007. Potential participants (PP) > age 49, with or without cognitive concerns, access the Registry via outreach events, telephone, or the Internet (www.registry.azalz.org). An initial intake form is completed and questions are addressed by telephone. Interested PP's receive a welcome packet, consent form, and medical history form; these are reviewed by telephone upon their return. Cognitive screening occurs via a cognitive and functional questionnaire and the modified Telephone Interview based Cognitive Screen (TICSm); those with ambiguous scores undergo a version of the Auditory Verbal Learning Task (Rey AVLT). Based on review of medical information and testing, PP's are categorized as probably cognitively normal, possibly cognitively impaired, or probably demented, and referred to existing AAC studies or held for future referral. **Results:** The database stores PP contact information, research interest, cognitive status, demographics and referral information. After consent, it is used to track and facilitate PP enrollment and contacts, store comprehensive medical information, facilitate cognitive testing, and initiate and track study referrals with the AAC. It also catalogues clinical study and site information for all AAC sites. **Conclusions:** A companion presentation (Arizona Alzheimer's Registry II: Progress and Data from Year 1; Holt et al) summarizes the unexpected early success of this initiative, which may offer a model for other organizations.

P4-397 MEMANTINE TREATMENT PREVENTS CLINICAL WORSENING: A POOLED ANALYSIS OF PATIENTS WITH MODERATE TO SEVERE ALZHEIMER'S DISEASE

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Background: Memantine, a moderate-affinity, uncompetitive NMDA receptor antagonist, is approved in several countries, including the U.S. and those in the European Union, for the treatment of moderate to severe Alzheimer's disease (AD). This analysis sought to combine the data from three double-blind, placebo-controlled trials in moderate to severe AD and to compare the numbers of memantine (10 mg, BID)- and placebo-treated patients who demonstrated a clinical decline from baseline on measures of cognition (SIB), function ($ADCS\text{-}ADL_{19}$), global status (CIBIC-Plus), and behavior (NPI). In the context of this progressive neurodegenerative disease, focusing on prevention of worsening may provide more realistic treatment expectations for patients and clinicians. **Methods:** The data were pooled from 3 clinical trials in moderate to severe AD (2 memantine monotherapy studies, MEM-MD-01 and MRZ-90001-9605, and 1 memantine plus donepezil combination study, MEM-MD-02). For each outcome measure, we used a generalized estimating equations model to compare the proportions of memantine- and placebo-treated patients (observed cases) who experienced a decline from baseline at Week 12, Week 24/28 (study endpoint), and across the entire trial (overall). **Results:** On all outcome measures, significantly fewer memantine-treated patients experienced clinical decline at Week 12, Week 24/28, and overall, compared to placebo-treated patients. At Week 24/28, the percentages of placebo- and memantine-treated patients who demonstrated clinical worsening were, respectively: 55.8% vs 44.7% on the SIB ($P=0.001$), 65.6% vs 56.2% on the ADCS-ADL ($P=0.006$), 53.2% vs 42.2% on the CIBIC-Plus ($P=0.002$), and 46.8% vs 39.7% on the NPI ($P=0.048$). **Conclusions:** The current study suggests that significantly fewer patients treated with memantine demonstrate clinical worsening after 6 months of treatment, compared to patients treated with placebo. These findings lend further support to the efficacy of memantine treatment in patients with moderate to severe AD.

P4-398 IDENTIFYING COGNITIVE ENHANCEMENT IN MAN: ADDING TESTING TO ROUTINE PHASE I TRIALS

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Background: One of the challenges for translational medicine over the last three decades has been to convince skeptics that cognitive function can be improved in healthy young volunteers. Now that an incontrovertible body of evidence has accumulated to show that this is possible, the opportunity to add cognitive testing to routine Phase I studies in order to identify potential cognition enhancement is becoming routine practice. **Methods:** This paper will review the use of the Cognitive Drug Research (CDR) computerized assessment system in over 25 such studies, and will identify the core aspects of test design which makes possible this integration of pharmacodynamic testing into trials whose primary purpose is safety and tolerability. **Results:** The trials reviewed will all have involved the simple addition of CDR testing to routine single and multiple dose trials, without an increase in subject number, study duration or at the expense of the primary objectives of such work - the safety of the volunteers and the identification of the tolerability of the compounds. Drugs with a diverse range of mechanisms of action will be covered, but special attention will be devoted to several of the selective nicotinic acetylcholine receptor agonists which are under development, including TC1734/AZD3480 and MEM3454. **Conclusions:** The paper will conclude that adding cognitive testing to routine Phase I trials is fast becoming a routine tool in translational medicine which has repeatedly shown its value, not only by identifying suitable targets for further development, but also by facilitating co-licensing deals.

P4-399 THE SOMATOTROPHICS, MEMORY AND AGING RESEARCH TRIAL (SMART): STUDY OF MENTAL ACTIVITY & RESISTANCE TRAINING FOR THE PREVENTION OF COGNITIVE IMPAIRMENT IN AT-RISK OLDER INDIVIDUALS

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Background: Epidemiological, basic science and clinical evidence suggests that cognitive and physical exercise may benefit brain function in late life. Potentially protective neurobiological effects include adaptations in cortical volume, neuropeptides, functional activation, cytokines, body composition and insulin sensitivity. Delaying the onset of dementia and age-related cognitive impairment through cognitive and physical activity may therefore be a realistic goal, however this has yet to be fully tested in a RCT. In particular, the possibility of synergistic effects between cognitive and physical activity has not been robustly evaluated. **Methods:** A fully factorial, double-blind, placebo controlled and longitudinal randomized clinical trial. 182 initially non-demented older individuals at-risk for dementia by virtue of borderline cognitive function will be recruited and randomly assigned to one of four intervention conditions in equal numbers. Eligible individuals will be older than 65 years without dementia or depression, physically and linguistically capable of completing supervised cognitive and physical exercise, and at-risk defined as corrected MMSE 23-27. *Interventions:* 1. Cognitive exercise: 6 months of thrice weekly 1 hour sessions of computer-based multi-modal cognitive exercise plus sham physical exercise (stretching). 2. Physical exercise: 6 months of thrice weekly 1 hour sessions of progressive resistance exercise plus sham cognitive exercise (lectures). 3. Combined exercise: both active cognitive and physical exercise. 4. Double Sham Control group: both sham cognitive and physical exercise. **Results:** Will occur at 0 (baseline), 6 months (immediately after the intervention: proximal follow-up) and 18 months (longitudinal follow-up). These will include: Neuropsychological battery including ADAS-Cog; Neuropsychiatric evaluation; Magnetic Resonance Imaging (MRI) brain scans; Mood and well-being; Physical fitness and functional performance; and Systemic inflammation, metabolism, nutritional biochemistry. **Conclusions:** *Primary*: To determine whether active interventions lead to a differential rate of cognitive decline at longitudinal follow-up compared to the placebo group, and whether combined mental and physical exercise is more effective than either modality alone. *Secondary:* To determine whether active intervention effects are mediated by specific changes in brain structure and function, or via

alterations in metabolism, body composition or systemic inflammation. To determine whether active intervention effects are associated with improved mood and well-being.

P4-400 A RETROSPECTIVE, OBSERVATIONAL STUDY OF COGNITIVE, BEHAVIORAL AND FUNCTIONAL OUTCOMES IN MILD TO MODERATE ALZHEIMER PATIENTS TREATED WITH CHOLINESTERASE INHIBITORS, OR WITH GINGKO BILOBA OR MEMANTINE

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Background: A total of 448 patients were enrolled since December until August 2007 meeting the criteria for dementia of DSM IV, including a recent computerized tomographic scan or magnetic resonance imaging compatible with an AD diagnosis. The distribution of the initial medicatons encompass 42% donepezil, 25% rivastigmine, 23% galantamine, 5% gingko biloba (EGb 761) and 5% memantine. The patients were referred to the neurologic department of a general hospital, and enrolled by Prof. dr. J. De Bleecker, MD and myself. **Methods:** Cognitive, functional and behavioral status measurement using following scales: MMSE,GDS,ADL, IADL and NPI. These measures were obtained at baseline and at 6 months and then each year again. **Results:** Possible differential efficacy of the various medications are currently being analysed by Prof.Georges Van Maele, Dpt Medical Informatics & Statistics, University Hospital 5K3, De Pintelaan 185, 9000 Gent, Belgium. **Conclusions:** we expect to do some inferences concerning the course of the disease and the possible impact of the various medications.

P4-401 IDENTIFYING COGNITIVE ENHANCEMENT IN MAN: IDENTIFYING EFFICACY IN THE DEMENTIAS

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Background: The limitations of the ADAS-cog as a tool to assess the efficacy of drugs to treat Alzheimer's disease are becoming widely recognized. One major deficiency is that it does not assess attention, and this limitation is even more serious in other dementias where deficits to attention are recognized as primary diagnostic symptoms, e.g. Dementia with Lewy bodies and Parkinson's disease dementia. The case for an automated test battery such as the Cognitive Drug Research (CDR) computerized assessment system to replace the ADAS-cog in Phase III trials has been made (Wesnes K, Neurodegenerative Disorders 2008, in press). However, this transition has already started in Phase II, where the ADAS-cog is unarguably unsuitable as it requires studies the size of typical Phase III trials to detect benefits. **Methods:** Data will be presented from a variety of compounds showing the sensitivity of the CDR system in various Phase II studies, including novel data from the first Alzheimer's trial with a selective nicotinic agonist, MEM3454, in which the CDR System was the primary outcome. **Results:** The suitability of the CDR system, even in small Phase IIa trials, makes it particularly suitable for this crucial stage of translational medicine. Work in which the CDR system was a co-primary endpoint in the first randomized trial of an anticholinesterase in Dementia with Lewy bodies will also be reported, as will data from the trial on which the regulatory decision to allow rivastigmine to be prescribed to treat the cognitive deficits in Parkinson's disease dementia was based. **Conclusions:** It is concluded that the use of systems like the CDR which properly and sensitively assess the full range of cognitive deficits in the dementias will help identify the full therapeutic potential of future treatments. This should help avoid a repetition of the widely criticized recommendation by the National Institute for Clinical Excellence that all Alzheimer's drugs should no longer be used in the treatment of mild to moderate Alzheimer's disease in the UK.

P4-402 BASELINE COGNITIVE AND DEMOGRAPHIC CHARACTERISTICS OF WOMEN ENROLLED IN THE KRONOS EARLY ESTROGEN PREVENTION STUDY (KEEPS)

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Background: The KEEPS (Kronos Early Estrogen Prevention Study) Cognitive and Affective Study (KEEPS C/A) is a multisite, randomized, placebo-controlled, double-blind, parallel-group design addressing major hormone-related issues raised by recent findings of WHIMS. The objective of the KEEPS C/A Study is to evaluate differential efficacy of oral conjugated equine estrogen (CEE or Premarin®) and transdermal 17 β-estradiol (tE2) with 12 days/month progesterone (Prometrium®) on mood and cognition in healthy non-hysterectomized, women who are within 6 months - 3 years of menopause. The KEEPS C/A Study will be conducted over 4 years. **Methods:** Outcome measures include cognitive and mood tests administered at baseline and months 18, 36 and 48 during treatment. Of these, month 36 evaluation investigates potential progestational effects while months 18 and 48 examine estrogenic effects. Affective measures include: Profile of Mood States Questionnaire (POMS), Memory Function Questionnaire (MFQ), Beck Depression Inventory (BDI) and PRIME-MD. The cognitive battery includes: Prospective Memory Test, Modified Mini-Mental State Examination (MMSE2), NYU Paragraphs, Stroop, Digit Symbol, WMS-3 Letter-Number Sequencing, California Verbal Learning Test 2 (CVLT-2), Mental Rotation, Visual Search, Benton Visual Retention Test and Verbal Fluency. **Results:** To date, the KEEPS C/A Study has enrolled 671 women, average age (mean $\pm$SD) 53.7$\pm$2.5 years. Approximately 77% of subjects are Caucasians, while 23% are of minority origin. Most participants report an annual income over $40,000 and have at least a high school diploma. At baseline, mean BMI is 26.2 $\pm$ 4.6 kg/mm^2, laboratory values (mg/dL) are: Total cholesterol 215$\pm$31.8, HDL cholesterol 65.0$\pm$17.2, LDL cholesterol 129.9$\pm$29.3, triglycerides 91.2$\pm$51.0, and fasting glucose 89.0$\pm$9.9. All women are cognitively healthy (MMSE2 = 28.9 $\pm$ 2.1). Interestingly, a positive relationship ($r = .150$, $p < .01$) is observed between plasma estradiol and MMSE2 total score. **Conclusions:** Baseline physiological, cognitive and affective data in the KEEPS C/A Study indicate that the cohort is healthy and free of cognitive dysfunction. The correlation between estradiol and MMSE score supports prior data reporting estradiol's salutary effect on cognition.

P4-403 EXTENDED-RELEASE (ER) MEMANTINE CAPSULE (28 MG, ONCE DAILY): A MULTIPLE-DOSE, OPEN-LABEL STUDY EVALUATING STEADY-STATE PHARMACOKINETICS IN HEALTHY VOLUNTEERS

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Background: Memantine is a moderate-affinity, uncompetitive antagonist of N-methyl-D-aspartate (NMDA) receptors, indicated for the treatment of moderate to severe Alzheimer's disease (AD). Approved memantine administration is 10 mg twice daily (20 mg/day), in the form of an immediate-release (IR) tablet or solution. In this study, we investigated the safety, tolerability, and pharmacokinetics of an extended-release (ER) memantine capsule (28 mg) in healthy volunteers. **Methods:** In this Phase I, single-center, open-label study,