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12TH INTERNATIONAL CONFERENCE ON ALZHEIMER'S DISEASE (ICAD) 2009: EMERGING THERAPEUTIC STRATEGIES, DIAGNOSTIC TECHNIQUES AND IMAGING TECHNOLOGIES FOR AD

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ABSTRACT

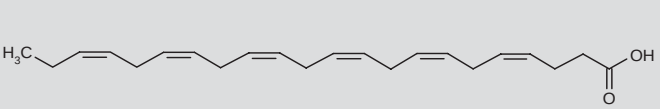
The annual Alzheimer's Association International Conference on Alzheimer's Disease (ICAD) has provided a platform for the presentation and sharing of the latest advances in Alzheimer's disease (AD) research from the world's leading scientists in the field of dementia for the past 11 years. This year's 12th ICAD meeting was held in Vienna on July 11-16, where 3,800 international attendees were given the opportunity to disclose, discuss and discover the latest thoughts, theories and findings in current research focusing on AD and related cognitive disorders. This report will mainly focus on therapeutics and therapeutic strategies, diagnostics and means to control disease progression. It will provide a summary of clinical trial results, novel targets and immunotherapies, and discuss the emergence of new diagnostic techniques and imaging technologies for the monitoring, prevention and potential treatment of AD.

INTRODUCTION

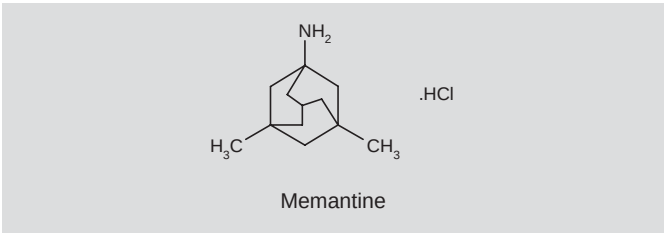
The Alzheimer's Association is a leading voluntary health organization in Alzheimer's disease (AD) care, support and research with an ideal vision: "A world without Alzheimer's". Its mission is to eliminate AD through the advancement of research for both the treatment and prevention of dementia by promoting brain health. Its principal aim is to enhance the care and support for all those affected by the disease, including patients, their families and healthcare professionals. AD represents a progressive neurodegenerative condition with no effective cure at present, which severely impacts on the quality of life of all those affected directly or indirectly by the disease and poses a significant economic burden on healthcare systems. ICAD, the annual meeting sponsored by the Alzheimer's Association, focuses on the acceleration of the development of potential treatments for AD by mediating the sharing of knowledge from scientific experts in the field of dementia research. An overview of the latest advances in preclinical and clinical development of emerging treatments for AD is presented in this report.

CLINICAL TRIAL RESULTS

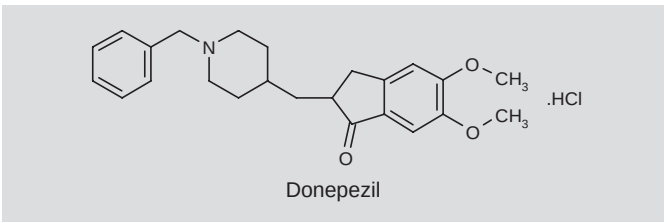
Two large clinical studies evaluating the potential neuroprotective effect of oral supplementation with **docosahexaenoic acid** (DHA; Martek Biosciences) yielded mixed results, which may potentially be attributable to differences in the study populations. The first trial, conducted by the Alzheimer's Disease Cooperative Study (ADCS) and supported by the National Institute on Aging (NIA), was performed in patients with mild to moderate AD and revealed no significant difference in the rate of mexmory worsening following 18 months of DHA administration at 2 g/day compared to placebo. In this study DHA also displayed no significant effect on behavioral symptoms or global disease severity compared to placebo (1). The Memory Improvement with DHA Study (MIDAS) supported by Martek Biosciences, however, revealed that treatment of healthy



Docosahexaenoic acid



Memantine

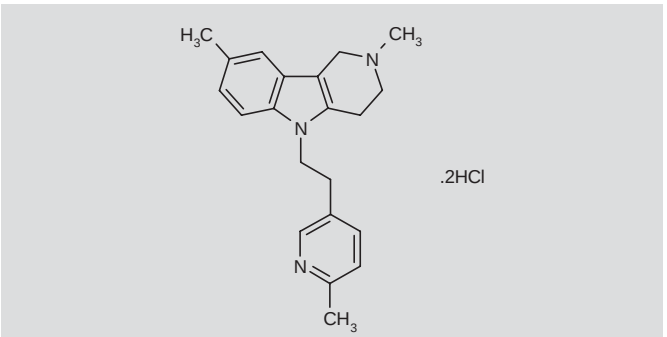


Donepezil

individuals with DHA at a lower dose (900 mg/day) resulted in a significant improvement in memory function; significantly fewer errors were made on the Paired Associate Learning test (PAL) with DHA versus placebo compared to baseline (difference in score: –1.63 ± 0.76; $P < 0.03$). A significant decrease was seen in heart rate with DHA (change from baseline of –3.2 beats/min compared to –1 beat/min on placebo; $P < 0.03$), which correlated with DHA plasma levels at week 24 ($P < 0.01$) (2). The outcome of both studies may suggest that earlier detection and intervention in AD could enhance treatment efficacy.

The safety and efficacy of **memantine** (Merz, Lundbeck) in patients with moderate to severe AD were evaluated in a number of studies presented at ICAD. Treatment with a once-daily regimen of memantine (20 mg) was found to be safe and significantly improved cognition and functional communication skills as early as 4 weeks following treatment initiation in patients with moderate to severe AD in a 16-week, multinational, single-arm, open-label trial (3). In a 12-week, randomized, placebo-controlled trial, memantine (20 mg/day) displayed a statistically significant improvement on the Functional Linguistic Communication Inventory at weeks 4 and 8 compared to placebo ($P = 0.028$ and 0.023, respectively). The incidence of treatment-emergent adverse events was similar between the memantine and placebo groups, with dizziness and restlessness being the most frequent adverse events in memantine-treated patients (4). Treatment with memantine for 6 months caused a significant increase in default mode network (DMN) activity in the precuneus compared to placebo ($P < 0.05$) in a resting-state functional MRI study (5). In two observational studies, 6 months of treatment with memantine correlated with improvement (71% and 66% of patients, respectively) or stabilization (11% of patients) in Mini-Mental State Examination (MMSE) scores (6, 7).

Donepezil (Aricept; Eisai, Pfizer) was also the focus of several studies disclosed at this year's ICAD. A Taiwanese study performed in 81 newly diagnosed patients with mild AD receiving 5 mg/day donepezil concluded that higher plasma donepezil concentrations did not correlate with improvements in cognitive function, as evaluated by MMSE and the Clinical Dementia Rating (CDR) scale. *APOE4* genotype status was also found not to be associated with the therapeutic response to donepezil in AD (8). Three-month treatment



Dimebon

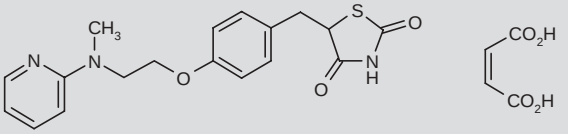
with donepezil (10 mg/day) demonstrated an improvement in the global functional connectivity (fc) from baseline ($P < 0.013$) in the neural network of patients with AD (n = 20) and mild AD (n = 14), as assessed by a global regions of interest (ROI)-based fcMRI analysis, which also allowed the discrimination between AD and control subjects with high specificity and sensitivity (9). Arterial spin-labeling perfusion MRI (ASL-MRI) assessment of 14 newly diagnosed patients with AD receiving a 3-month treatment with donepezil (10 mg/day) revealed a significant increase in regional cerebral blood flow in regions of the right cingulated cortex, right inferior frontal gyrus, right inferior parietal gyrus and the left insular, which correlated with changes in MMSE (10). Treatment of AD patients with donepezil resulted in a significant delay in the emergence/exacerbation of apathy, one of the most common behavioral symptoms in AD ($P = 0.0126$ vs. placebo), as revealed in a pooled analysis of data from two 24-week, double-blind, placebo-controlled trials. The analysis also found that a significantly smaller proportion of AD patients receiving donepezil exhibited apathy exacerbation/emergence at the study endpoint compared to those receiving placebo (10.2% vs. 16.5%; $P = 0.0277$). This effect of donepezil on apathy symptoms may potentially delay functional impairments in AD (11). An open, randomized, 40-week comparative study between donepezil (5-10 mg/day) and memantine (20 mg/day) in moderate to severe AD patients revealed a faster onset of efficacy for donepezil (2 weeks of treatment); however, memantine displayed a better response rate (89.3% vs 40%) and demonstrated a better total reduction in the CareGiver Burden Scale (CGBS) score from baseline to the end of study compared to donepezil (40 vs. 27.2) (12).

Dimebon (PF-01913539; Medivation, Pfizer) is a novel treatment in phase III trials for AD and Huntington's disease (HD). The possibility of combined use of dimebon with acetylcholinesterase (AChE) inhibitors to enhance treatment efficacy in AD was evaluated in a randomized, double-blind, placebo-controlled phase I trial in AD patients previously treated with a stable dose of 10 mg/day of the AChE inhibitor donepezil for at least 60 days. Following oral dosing, dimebon was rapidly absorbed, with a median time to maximum plasma concentration (t_{max}) of 2-4 h. The pharmacokinetic properties of donepezil were not affected by dimebon administration. Dimebon was found to be well tolerated in patients pretreated with donepezil, with no serious adverse events (AEs) or deaths being reported during the study. The most commonly reported AEs in the dimebon group included fatigue (20%) and abdominal distension, dizziness, falls, hyperkalemia and nightmares (13% for all). Concomi-

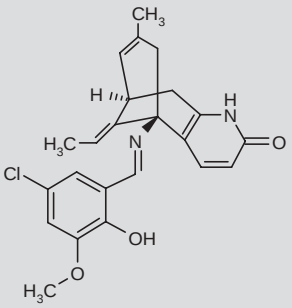
tant treatment with dimebon and donepezil is being evaluated in an ongoing phase III trial in 750 patients. Another ongoing phase III trial, CONCERT, aims to study the efficacy and safety of dimebon in 1,050 patients with mild to moderate AD on stable doses of donepezil (13).

Cerebrolysin (Ebewe), a peptide mixture with neurotrophic activity, was also evaluated in combination with donepezil in a randomized, double-blind clinical trial in patients with mild to moderate AD (N = 197). Patients were randomized to receive i.v. infusions of Cerebrolysin (10 mL) or placebo (saline) for 5 days/week on weeks 1-4 and 13-16 (a total of 40 infusions) in combination with either donepezil (5 mg for 4 weeks and 10 mg thereafter) or placebo. Following 28 weeks of treatment, patients receiving the combination therapy displayed higher scores in the Clinician's Interview Based Impression of Change (CIBIC-Plus) responders rate ($P < 0.01$). They also showed almost significant differences in CIBIC-Plus score ($P = 0.068$) and in Alzheimer's Disease Assessment Scale (ADAS-Cog) and CIBIC-Plus responders rate ($P = 0.056$). Patients receiving Cerebrolysin alone or in combination with donepezil were cognitively stable compared to those receiving only donepezil, who deteriorated after week 16 (14). Analysis of neuropsychiatric symptoms in the same trial revealed that Cerebrolysin monotherapy was superior to donepezil and to the combination treatment. Treatment-related AEs occurred with the same frequency in the different groups. Gastrointestinal symptoms were more commonly seen with donepezil (alone or in combination), nervous system disorders were mostly observed with Cerebrolysin (monotherapy or in combination), whereas the combination therapy was most frequently associated with the incidence of psychiatric conditions (15). In a separate randomized, placebo-controlled trial, Cerebrolysin (20 mL i.v.) given as add-on therapy to 100 mg acetylsalicylic acid significantly improved clinical outcomes (ADAS-Cog and CIBIC-Plus improved by –10,628 and –0.84, respectively; $P < 0.0001$ vs. placebo for both measures), showing beneficial effects lasting for at least 6 months in patients (N = 217) with vascular dementia. Cerebrolysin was safe and well tolerated in this study (16).

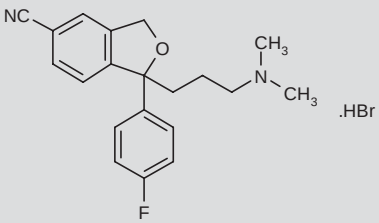
Rosiglitazone (GlaxoSmithKline) was reported to have no significant effect on cognition and overall clinical response in the full population or in *APOE4* genotype subgroups in a phase III study conducted in 579 patients with mild to moderate AD. Subjects in this randomized, double-blind, placebo-controlled, 24-week study were genotyped and stratified into *APOE4*-positive and *APOE4*-negative groups. The active treatments studied were extended-release rosiglitazone (rosiglitazone XR) 2 or 8 mg/day and donepezil 10 mg/day. Analysis of secondary endpoints revealed no effects of rosiglitazone XR 2 or 8 mg on Disability Assessment for Dementia (DAD) or Neuropsychiatric Inventory (NPI) scores at week 24 in *APOE4*-negative subjects, all subjects except those carrying two *APOE4* alleles and the full population. An analysis of changes from baseline in ADAS-Cog scores at week 24 revealed higher rates of responders with rosiglitazone XR 2 mg than with the higher rosiglitazone dose or donepezil in these three study populations. Rosiglitazone XR 2 mg and donepezil were also associated with significant reductions in caregiver hours spent on basic activities in the three populations (17). Both doses of rosiglitazone XR were well tolerated in this study, with safety profiles being similar among *APOE* subgroups and the full population (18).



Rosiglitazone



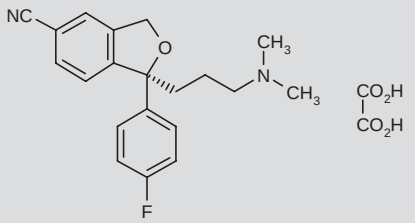
Mimopezil



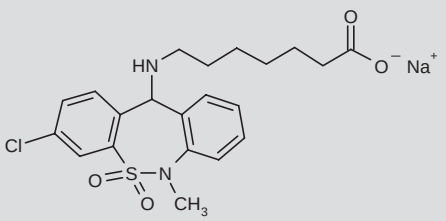
Citalopram

Mimopezil (Debio-9902; Debiopharm) is a potent and selective AChE inhibitor with a demonstrated ability to delay cognitive decline in patients with mild to moderate AD following daily oral administration. In an attempt to overcome problems arising from poor compliance associated with oral treatment in AD, Debiopharm is currently developing a sustained-release formulation of mimopezil (implants for s.c. injection releasing the drug over a period of 28 days). Preliminary results from a recent double-blind phase IIb safety and efficacy trial (BRAINz study) in 158 AD patients randomized to receive either mimopezil or donepezil for 6 months were presented at ICAD. Mimopezil was administered as a daily oral dose of 1 mg during the 1-month titration period and as s.c. implants of 9 and 12 mg in the 1- and 4-month maintenance periods, respectively. The comparator donepezil was given as an oral dose of 5 mg during the titration period and subsequently at 10 mg during both maintenance periods. Mimopezil implantations (800 procedures conducted to date in this ongoing trial) were found to be well tolerated, with no local AEs. ADAS-Cog evaluation revealed no statistically significant difference between mimopezil and donepezil treatment. The clinical benefit of mimopezil was less apparent in *APOE4*-positive patients (19).

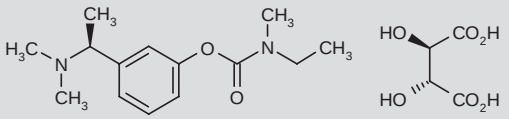
The antidepressant **citalopram** (Lundbeck) was evaluated in AD patients with psychosis or aggressive/agitated behavior (who did not



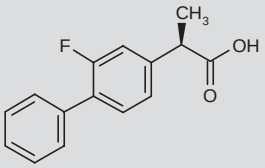
Escitalopram oxalate



Tianeptine sodium



Rivastigmine tartrate



Tarenflurbil

benefit from previous treatment with atypical antipsychotics) in the CATIE-AD study; a double-blind, randomized phase II trial, results from which were disclosed at ICAD. AD patients who discontinued initial treatment with olanzapine, quetiapine, risperidone or placebo were randomized to treatment with another atypical antipsychotic (n = 165) or citalopram (n = 87). Analyses were stratified based on whether previous treatment involved an antipsychotic or placebo. The study reported no significant difference in the time to all-cause discontinuation between treatment with citalopram and any of the three antipsychotics used in the trial (P = 0.22). There was also no difference in the time of discontinuation due to intolerability or lack of efficacy between groups and previous treatment with placebo had no effect on the outcome of subsequent active treatment. Generally, mild improvements were observed overall in rating scales during active treatment; however, these improvements did not significantly differ between antipsychotics and citalopram (20).

A study conducted by scientists in Korea revealed no significant differences in efficacy and tolerability between treatment with the selective serotonin reuptake inhibitor (SSRI) **escitalopram oxalate** (Lundbeck) and the serotonin reuptake enhancer **tianeptine sodium** (Servier) in older depressed patients with or without executive dysfunction. Depressive symptoms measured on the Montgomery-Asberg Depression Rating Scale (MADRS) at study endpoint (12 weeks) demonstrated a similar change from baseline of –20.2 and –22.4 for patients treated with escitalopram (n = 48) and tianepine (n = 37), respectively. An unfavorable response of geriatric depression to both escitalopram and tianepine was observed in the Controlled Oral Word Association and the Korean Stroop Color-Word tests for executive functions (21).

Several clinical studies presented at ICAD evaluated the dual butyrylcholinesterase (BuChE) and AChE inhibitor **rivastigmine tartrate** (Novartis). Retrospective analysis from a 3-4-year, randomized, placebo-controlled trial of rivastigmine (3-12 mg/day) in 241 subjects with mild cognitive impairment (MCI) who underwent pharmacogenetic testing and MRI scans revealed a significant reduction in the decline in white matter volume in rivastigmine-treated female subjects with a wild-type *BCHE* genotype compared to placebo (3.0% vs. 6.8%; P = 0.027), which suggests that dual cholinesterase inhibition may affect white matter volume in MCI subjects and that gender may be an influencing factor on the conversion from MCI to AD (22). A 6-month, open-label, naturalistic study on the use of rivastigmine transdermal patches (9.5 mg/24 h, 10 cm^2) in 103 AD outpatients in Austria showed favorable tolerability, with mild skin reactions mostly developing after 3 months of treatment. An improvement in MMSE scores from 19.8 to 20.5 points (P = 0.01) was seen over the course of the study. Skin adhesion of the patch was described as very good or good in 85% of study participants (23). Administration of a rivastigmine patch to 65 AD outpatients in Greece was not associated with side effects in 37 patients, whereas side effects were reported in 27 patients, 15 of whom discontinued use. The majority of patients exhibiting side effects (70%) displayed skin disorders at the site of application, including pruritus and erythema. Less frequent side effects were anxiety, mild depression, gastrointestinal discomfort, headache and malaise (7%, 7%, 7%, 4% and 4%, respectively) (24). Additional evaluation of treatment compliance with a rivastigmine patch in a 24-week, multicenter, open-label study, in which patients received a 4.6 mg/24 h rivastigmine patch for 4 weeks followed by a 9.5 mg/24 h patch, was reported to be currently ongoing. The study will assess adherence to treatment for at least 8 weeks, as well as MMSE, Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC), Alzheimer's Disease Caregiver Preference Questionnaire (ADCPQ) and caregiver burden parameters (25).

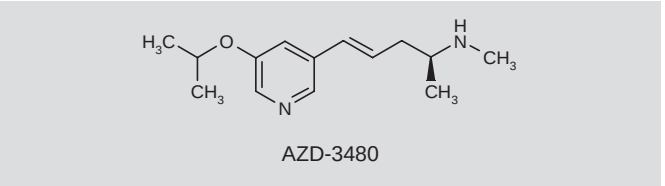
Tarenflurbil (Myriad Pharmaceuticals), a γ-secretase inhibitor shown to reduce the production of β-amyloid ($A\beta_{42}$) peptides both in vitro and in vivo, failed to display efficacy in an international, randomized, double-blind, placebo-controlled phase III trial following administration at 800 mg b.i.d. for 18 months to patients with mild AD. The study reported no statistically significant differences in ADAS-Cog, Alzheimer's Disease Cooperative Study-Activities of Daily Living (ACDS-ADL) and CDR-sum of boxes (CDR-sb) measurements between treatment with tarenflurbil and placebo. The trial

was prematurely terminated for 300 patients based on recommendations of the Data Monitoring Committee (26).

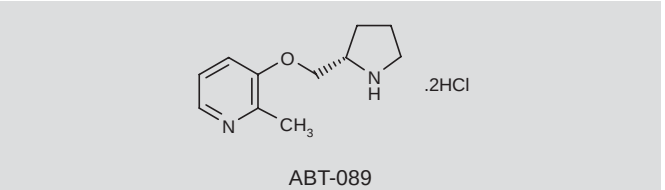
AstraZeneca's **AZD-3480** (ispronicline, TC-1734), a selective agonist of the central α4β2 and α2β2 neuronal nicotinic receptors (NNRs), also failed to meet the primary outcome of ADAS-Cog improvement at week 12 in a multicenter, double-blind, placebo-controlled phase IIb proof-of-concept study in 567 patients with mild to moderate AD, randomized to receive one of three doses of AZD-3480 (5, 20 and 35 or 100 mg, depending on the CYP2D6 metabolic status), donepezil (10 mg) or placebo once daily for 12 weeks. AZD-3480 also displayed no improvement on the CDR computerized test battery compared to placebo. An improvement versus placebo was seen on the 20-mg AZD-3480 dose on the ADCS-CGIC and MMSE scales (–0.5, $P < 0.001$ and 0.9, $P = 0.009$, respectively). Treatment with AZD-3480 was well tolerated but the study was deemed inconclusive due to the failure of AZD-3480 and donepezil to achieve statistical significance on ADAS-Cog compared to placebo (27).

Results from the first-in-man phase I multiple-ascending-dose trial of the potent and selective, orally active serotonin inhibitor **SUVN-502** (Suven) in healthy volunteers were also presented. SUVN-502, currently in development for the treatment of symptomatic dementia in AD, was administered as a single ascending dose (5, 15, 50, 100 and 200 mg) or multiple ascending doses (50, 100 and 150 mg) to healthy male subjects (n = 6/cohort). Treatment with SUVN-502 was well tolerated up to the highest dose, with no serious AEs or changes in vital sign parameters (28). The single-ascending-dose regimen revealed no study medication-related abnormalities and demonstrated favorable pharmacokinetics that supported potential once-daily dosing of the drug (29). Physical and clinical chemistry examinations, hematology, urinalysis and ECG assessments throughout the multiple-ascending-dose trial revealed a favorable safety and toxicology profile, which supported further evaluation of SUVN-502 in proof-of-concept studies for cognitive dysfunction (30).

The acetylcholine receptor modulator **ABT-089** (Abbott) was reported to reverse a number of scopolamine-induced cognitive deficits in a single-center, multiple-dose, randomized, double-blind, placebo-controlled phase I trial in healthy subjects. Treatment with ABT-089 (5, 15 and 40 mg/day for 6 days) was found to significantly reduce scopolamine-induced deficits in attention measures estimated in the CDR and CogState batteries ($P < 0.05$). ABT-089 also demonstrated the ability to improve cognitive performance, including speed of memory and spatial working memory at steady state (day 4 of the study) in the absence of scopolamine, suggesting that the compound may potentially be used for the treatment of impaired cognition associated with AD (31).



AZD-3480



ABT-089

IMMUNOTHERAPY

A series of oral presentations on the development of immunotherapeutic approaches included the disclosure of clinical data from the first-in-man study with the active Aβ immunotherapeutic vaccine **CAD-106** (Cytos Biotechnology, Novartis). The CAD-106 vaccine comprises the $A\beta_{1-6}$ peptide coupled to the *Escherichia coli* phage Qbeta, designed to induce the production of antibodies against Aβ protein and inhibit the formation of plaques in the brain of AD patients. A 52-week, two-center, randomized, double-blind, placebo-controlled, parallel-group trial in patients with mild to moderate AD (N = 58) involved the administration of CAD-106 in two cohorts of patients. In cohort I, 24 patients received a dose of 50 µg or placebo on weeks 0, 6 and 8, whereas 22 patients in cohort II were given 150 µg or placebo on weeks 0, 2 and 6. CAD-106 induced a measurable antibody response against Aβ in 16 and 18 patients, respectively, in cohorts I and II, with peak mean Aβ IgG titers seen at week 8 in both cohorts. AEs were described as mild, with the most common being injection-site erythema (4% and 64%, respectively, in cohorts I and II) (32). In a preclinical study, immunization of APP transgenic mice (APP23 and APP24) with CAD-106 correlated with an efficient reduction in parenchymal (total) amyloid. In APP24 mice (but not APP23 mice) there was a significant increase in vascular Aβ, which represents a risk factor for the development of microhemorrhages. However, the observed elevation in vascular Aβ was not followed by increases in brain hemorrhages, which may be a result of the diffuse, nonfibrillar nature of the deposited vascular Aβ peptide (33).

Scientists from Affiris reported on the development of the AFFITOPE-based **MimoVax** vaccine designed to target truncated and modified oligomers of Aβ, which are considered a major cause of the synaptic alterations and cognitive malfunctions manifested in AD. Immunization of mice overexpressing human APP with MimoVax correlated with a significant reduction in amyloid plaque load and in Aβ-associated pathological alterations in the brain. Treated animals did not display Aβ-specific T cells. MimoVax may represent a novel therapeutic strategy with improved safety and efficacy for the treatment of AD patients (34).

ACI-24, an oligo-specific liposome-based vaccine bearing a tetrapalmitoylated $A\beta_{1-15}$ peptide, developed using AC Immune's Supramolecular Technology as a potential therapeutic candidate for AD, was evaluated for safety in the APPxPS1 mouse model of AD. Intraperitoneal (i.p.) injection to APPxPS1 mice (27-28 months old) of five doses of ACI-24 at 2-week intervals correlated with the induction of anti-Aβ antibody titers (IgG_{2b} and IgG_3 isotypes), which displayed high specificity for oligomeric Aβ species. This response, which is indicative of a preferential Th2 profile, was not seen in mice injected with empty liposomes. Following ACI-24 vaccination, a significant decrease in the amount of insoluble $A\beta_{1-40}$ and in soluble and insoluble $A\beta_{1-42}$ was observed, which did not correlate with the incidence of activated microglia, T-cell infiltration or astrogliosis in the brains of the injected animals. There was no significant increase

in the levels of TNF-α, IL-6, IL-1β or interferon gamma in the brains of ACI-24-vaccinated mice. Perl's Iron histological staining of brain tissues revealed no microhemorrhages following ACI-24 immunization, which also correlated with a reduced number of large hemorrhages compared to vehicle control vaccination. The data obtained in this study indicate a low risk for the development of encephalitis and suggest a positive safety profile for ACI-24 in an AD rodent model (35).

The murine monoclonal antibody **A-887755** (Abbott), raised against *N*-terminal truncated $A\beta_{20-42}$ globulomer, was found to display a more favorable profile compared to nonselective Aβ peptide antibodies (passive immunotherapy) in a preclinical study. In cultured primary hippocampal neurons preincubation with A-887755 at equimolar concentrations resulted in inhibition of $A\beta_{20-42}$ globulomer binding to the dendritic processes of neurons, even in the presence of excess $A\beta_{40/42}$ monomer. Passive immunotherapy with unselective antibodies at 18-fold higher concentrations was unable to prevent $A\beta_{20-42}$ globulomer binding to neurons and was also associated with recognition of Aβ fibrils and Aβ monomer. The specificity of A-887755 for targeting Aβ oligomers also reduced the risk of potential side effects arising from binding to other Aβ species, including Aβ monomer, sAPPα and Aβ fibrils. Future development of A-887755 as a potential immunotherapeutic agent for the treatment of AD is supported by the results obtained in this study (36).

Preliminary results from a safety and pharmacokinetic (PK) evaluation of the humanized monoclonal $IgG_{2\zeta A}$ isotype antibody **PF-04360365** (Pfizer) in a recent double-blind, placebo-controlled, dose-escalation (0.1-10 mg/kg) study in patients with mild to moderate AD were also presented. PF-04360365 is raised against amino acids 33-40 of the $A\beta_{1-40}$ peptide and is currently under clinical development (phase II) by Pfizer for the i.v. treatment of Alzheimer's-type dementia. Treatment with PF-04360365 was found to be well tolerated at the dose range used, with the most common AEs being upper respiratory tract infection, headache and diarrhea. All AEs were deemed mild to moderate in severity. There was no clinical or imaging evidence of microhemorrhage, vasogenic edema or encephalitis in any of the participants. PK analysis revealed a linear profile with approximately dose-proportional increases in C_{max} and AUC parameters, and evidence of mild central permeability (37).

DIAGNOSTICS AND IMAGING TECHNOLOGIES FOR DISEASE PROGRESSION MONITORING

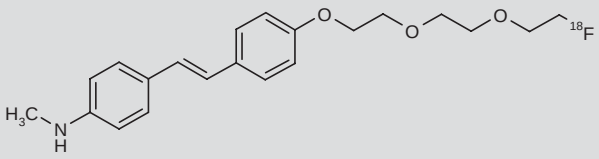
The development of promising novel in vitro and in vivo diagnostic agents for the early and more accurate detection and disease progression monitoring of AD was reported at ICAD.

An optimized formulation of the small, conformationally dynamic, fluorescently labeled **Pronucleon peptides** (Adlyfe) developed to detect soluble Aβ oligomers was described as a potential in vitro diagnostic test for AD. Preliminary experimental evaluation of this new formulation of Pronucleon, devised to maximize stability, enhance solubility and improve the ability to detect oligomers under clinically relevant conditions, was performed using Adlyfe's "misfolded" protein detection (MPD) assay and other independent direct binding methods. The novel Pronucleon formulation was found to be robust and stable for a period of up to 6 months. It was able to specifically interact with two distinct types of soluble Aβ oligomers: SDS-derived and DMEM/F12 media-induced oligomers. The structural properties of the Pronucleon peptides could be controlled by altering the assay conditions. Adlyfe announced its plan to expand the development of stable oligomer products to include other potentially clinically relevant types, such as dimers, in an effort to improve in vitro AD diagnostics (38).

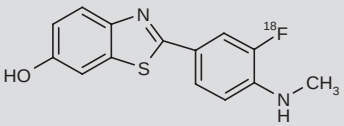
The fluorinated positron emission tomography (PET) radioligand **[^{18}F]-AZD-4694** (AstraZeneca) demonstrated suitability as a potential diagnostic tool for the detection of Aβ deposits in cynomolgus monkeys in a recent study conducted in Sweden. [^{18}F]-AZD-4694 was observed to rapidly enter the monkey brain, with an exposure of approximately 5% of the total injected dose. Uptake of the radioligand in the brain peaked at 2 min postinjection and subsequently cleared to a homogeneous low level after 50 min. AstraZeneca investigators maintained that these in vivo properties of [^{18}F]-AZD-4694 would support its further development as a PET tracer for the visualization of Aβ deposits in the living human brain (39).

Scientists from Bayer Schering Pharma presented encouraging phase II data on the sensitivity and specificity of the PET tracer **[^{18}F]-BAY-94-9172** in the diagnostic imaging of AD. [^{18}F]-BAY-94-9172 was evaluated in 10 AD patients and 10 age-matched healthy controls for its ability to differentiate between subjects with AD and controls based on visual assessment of PET scans. The study found positive Aβ loads in the brains of 9 of 10 AD patients and in only 1 of 10 healthy controls ($P < 0.001$). A tendency towards a higher frequency of *APOE*-positive genotypes in the Aβ-positive versus Aβ-negative PET scans was observed for all study participants (40). Test-retest static [^{18}F]-BAY-94-9172 PET scans obtained from 7 AD patients and 8 age-matched healthy controls at 2-4 weeks apart revealed a higher cortical retention of [^{18}F]-BAY-94-9172 in AD patients compared to healthy controls. Cortical standardized uptake volume ratios (SUVR) test-retest variability was estimated at 6.8% and 2.9%, respectively, in AD patients and healthy controls and did not appear to be affected by the range of specific activity that is likely to be seen in clinical practice (41).

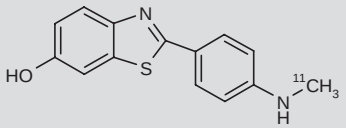
[^{18}F]-GE-067 (University of Pittsburgh, GE Healthcare), a fluorinated derivative of **Pittsburgh Compound B** ([^{11}C]-PIB) originally developed by scientists at the University of Pittsburgh for the detection of



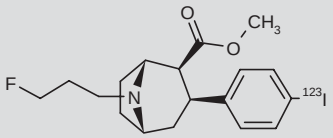
[^{18}F]-BAY-94-9172



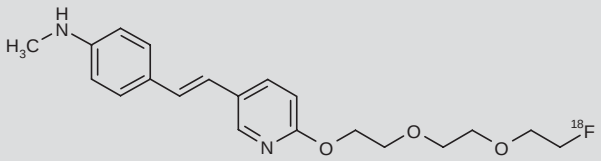
[^{18}F]-GE-067



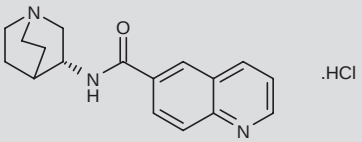
Pittsburgh Compound B



Ioflupane (I123)



Florpiramine F 18



EVP-5141

Aβ peptides, is currently under development as an AD diagnostic and a potential radiopharmaceutical for brain imaging. [^{18}F]-GE-067 was evaluated for its ability to discriminate between subjects with clinically probable AD and cognitively intact healthy volunteers following injection into 25 AD patients, 20 individuals with mild cognitive impairment (MCI) and healthy volunteers above and below 55 years of age (n = 15 and 10, respectively) at a dose of 177.3 MBq. Analysis of PET images revealed the discriminatory power of [^{18}F]-GE-067, with little overlap between the probable AD and healthy subject cohorts (42). [^{18}F]-GE-067 (170 MBq) and [^{11}C]-PIB (327 MBq) displayed similar tracer binding abilities in individuals with clinically probable AD and in MCI subjects in a phase II clinical trial (43). Pharmacological and pharmacokinetic equivalence studies of [^{18}F]-GE-067 and [^{11}C]-PIB suggested a highly similar manner of binding to Aβ deposition exhibited by these agents. Nearly identical brain uptake (5 min) was seen in all subjects with either agent (44).

Florpiramine F 18 (^{18}F-AV-45; Avid Radiopharmaceuticals) is an amyloid imaging biomarker developed to detect cerebral amyloid deposition and thus distinguish between individuals with substantial Aβ deposition in an AD-like pattern from those with AD-free pathology. Preliminary PET results from a recent phase II study aiming to evaluate the performance characteristics of ^{18}F-AV-45 (370 MBq) in subjects with probable AD, MCI and cognitively normal control (NC) elderly individuals revealed a significant difference in ^{18}F-AV-45 retention in the cortical gray matter in the NC and AD groups ($P <$ 0.001). ^{18}F-AV-45 retention values in the MCI group were intermediate between those recorded in the NC and AD groups. Generally, there was a trend for increased biomarker retention with increasing subject age, which supports the potential clinical utility of ^{18}F-AV-45 as an imaging biomarker to distinguish between AD patients and elderly individuals with normal cognitive abilities (45).

Scientists from the University of Sassari, Italy, presented single photon emission computed tomography (SPECT) data supporting the potential use of **ioflupane (I123)** (DaTSCAN®; GE Healthcare) for the differential diagnosis of AD and probable dementia with Lewy bodies (LBD). Differential diagnosis of AD and LBD was evaluated in 39 consecutive patients aged 52-84 years with cognitive disorders for at least 1 year and clinical criteria insufficient for differentiation following i.v. injection of 148 MBq ioflupane (I123). Ioflupane (I123) SPECT images were qualitatively and quanitatively classified as normal and pathological. Qualitative and quantitative analyses were able to differentiate AD and LBD in 8 and 13 patients, respectively (46).

The development of a **biomarker-based diagnostic** method for the early clinical detection of very mild AD was reported by scientists from Trinity College, University of Dublin, as a means to enhance diagnostic accuracy at an early disease stage. The model's predictor variables included a combination of memory tests such as the Rey Auditory Verbal Learning Test (RAVLT) and ADAS delayed recall, cerebrospinal fluid (CSF) concentration ratios of total tau, p-tau181 and $A\beta_{1\text{-}42}$ and MRI volumetric measures of the left and right hippocampus and entorhinal cortex. Cross-validation of the model revealed a classification accuracy of 95.69% (47).

NOVEL TARGETS IN PRECLINICAL/EARLY CLINICAL DEVELOPMENT

Results from in vitro and in vivo studies, as well as preliminary data from early clinical evaluation investigating the potential therapeutic effects of novel agents for the treatment of AD, were disclosed at this year's ICAD.

Researchers from EnVivo Pharmaceuticals described the development of γ-secretase modulators with encouraging preclinical activity in cell culture and rodents. Chronic dosing of one such agent, **EVP-0962**, in a transgenic AD mouse model resulted in the reversal of hippocampal memory deficits on a contextual fear conditioning task. In this mouse model, EVP-0962 reduced production of $A\beta_{42}$ in the brain after 2 months of daily oral administration. $A\beta_{42}$ production was also found to be decreased in multiple cell lines and normal rodent brains following EVP-0962 administration. EVP-0962 is expected to begin clinical evaluation in 2010.

EnVivo Pharmaceuticals, in collaboration with Bayer Schering Pharma, is also developing **EVP-5141**, a new α7 nicotinic acetylcholine receptor (nAChR) agonist, which has shown promising in vivo efficacy in rodents and is expected to provide a novel therapeutic strategy for the treatment of cognitive deficits in AD and schizophrenia. In

rats the compound (dose range of 0.3-3 mg/kg) caused improvements in the social recognition test and antagonized scopolamine-induced deficits in acquisition and retrieval processes in the passive avoidance task at 0.3 mg/kg p.o. It was also found to improve spatial working memory of aged rats in a water maze task at 1 mg/kg i.p. In mice object and social recognition abilities were improved following EVP-5141 administration at 0.3 mg/kg (48).

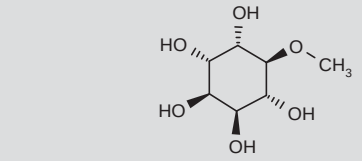
Investigators from AC Immune and Genentech presented preclinical data on **MABT-5102-A**, a humanized monoclonal antibody binding to Aβ. MABT-5102-A was found to bind with high affinity to monomer-, oligomer- and fiber-enriched preparations of $A\beta_{1-42}$, inhibited self-association and aggregation of Aβ peptides into protofibrillar conformations, disaggregated preformed $A\beta_{1-42}$ protofibrils and blocked Aβ oligomer-induced toxicity in primary neurons (49). Evaluation of the pharmacokinetics (PK) and pharmacodynamics (PD) and distribution of MABT-5102-A in human APP transgenic (Tg) mice, non-Tg mice and cynomolgus monkeys revealed dose-proportional PK in both species. Clearance was doubled in Tg versus non-Tg mice. In mice and monkeys, plasma total Aβ levels increased dose-dependently. Tissue distribution was similar in Tg and non-Tg mice. MABT-5102-A uptake into brain and cerebrospinal fluid (CSF) represented under 0.2% w/w of the administered dose. A PK/PD model linked MABT-5102-A disposition with plasma total Aβ levels in both species (50). MABT-5102-A has been selected for further clinical development. A phase I study is currently enrolling patients with mild to moderate AD.

Exebryl-1, a small-molecule compound under development by ProteoTech, demonstrated efficacy in lowering Aβ peptide, plaque and tangle load, which are hallmarks of AD, in a preclinical study presented at ICAD. In vivo in APP transgenic mouse models, i.p. administration of Exebryl-1 (50 mg/kg/day) for 90 days was associated with a marked reduction (approximately 45%) in the formation of APP deposits. Significant decreases in the amount of soluble and insoluble $A\beta_{42}$ (51.7% and 77.5%, respectively; $P < 0.01$ for both compared to vehicle control) were seen following 3 months of i.p. administration at 50 mg/kg/day. Reductions in Aβ load and in amyloid plaque number of 46.6% and 41%, respectively, were noted in APP transgenic mice following oral administration at 150-200 mg/kg/day. Assessments of spatial learning and memory in the Morris water maze revealed a 69.5% and 67.5% improvement, respectively, on days 1 and 4. A first-in-man phase Ia clinical trial of Exebryl-1 was completed in the autumn of 2008. Preliminary data analysis has shown a favorable safety profile at the dose range tested (20-600 mg). Pharmacokinetic analyses from this trial are still pending (51).

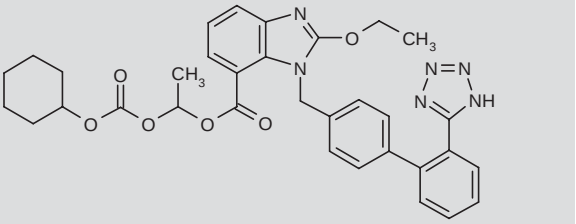
ANTIDIABETIC AND ANTIHYPERTENSIVE AGENTS FOR THE TREATMENT OF AD

Preliminary results from preclinical and clinical evaluations presented at the congress support the potential therapeutic application of antidiabetic and antihypertensive agents for the prevention of cognitive decline associated with AD.

The natural antidiabetic substance NIC5-15 (**pinitol**) has demonstrated the ability to reduce the production of $A\beta_{1-42}$ peptide through Notch-sparing γ-secretase inhibition. The compound was found to be well tolerated in 9 of 10 AD subjects who completed the full protocol in a double-blind, placebo-controlled, multiple-dose-escalation (1500, 3000 and 5000 mg) trial conducted by scientists from Humanetics and Mount Sinai School of Medicine aiming to evaluate the safety, tolerability and pharmacokinetics of NIC5-15. The most common possibly treatment-related AEs reported were hypoglycemia, anemia and diarrhea. Pharmacokinetic analysis is still ongoing (52). Ongoing analyses of data obtained in this trial imply possible correlations between measures of cognitive performance such as ADAS, ADCS-ADL and MMSE with Aβ and other biomarkers of AD neurodegeneration (53).



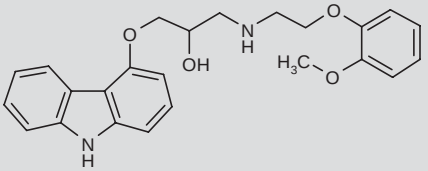
Pinitol



Candesartan

The potential use of the angiotensin receptor blocker **candesartan** (AstraZeneca, Takeda) in the prevention of cognitive decline was evaluated in a substudy of the Study on Cognition and Prognosis in the Elderly (SCOPE) involving elderly hypertensive (n = 257) and normotensive (n = 256) subjects. Annual assessment of cognition (mean follow-up 43 months) was performed using the CDR computerized assessment battery, as well as additional tests of executive function. Treatment with candesartan was associated with significantly less decline in attention and episodic memory and correlated with a trend towards less decline in speed of cognition compared to placebo. Treatment effect sizes were small to medium within the hypertensive group (0.26-0.28); however, larger effect sizes were seen in the context of changes in the normotensive subjects. The small to medium effect sizes seen in this trial may be clinically relevant following prolonged treatment with candesartan, favoring the potential application of antihypertensive therapy for the primary prevention of dementia (54).

Another clinically prescribed agent for the treatment of hypertension and congestive heart failure, **carvedilol**, was reported by scientists from Mount Sinai School of Medicine and Johns Hopkins University to significantly reduce Aβ peptide oligomerization and result in attenuation of cognitive deterioration in a mouse model of AD. Treatment of TgCRND8 mice with oral carvedilol (1.5 mg/kg/day, equivalent to 8.5 mg/day in humans) administered continuously for 5 months correlated with an 80% increase in survival at 18 weeks of age compared to a 50% increase seen in the control group. There



Carvedilol

was no change in body weight and no effect on blood pressure in carvedilol-treated animals compared to controls. Statistically significant reductions of 40% and 60%, respectively, in $A\beta_{1-40}$ and $A\beta_{1-42}$ peptide content were seen in the carvedilol-treated group, and these were associated with improvements in performance in the Morris water maze test. Based on favorable preclinical data, carvedilol is currently being evaluated in an ongoing 6-month, randomized, placebo-controlled pilot trial in patients with mild to moderate AD (N = 50). The effect of carvedilol on cognition is the primary outcome measure of this trial, with secondary outcome measures including the effect on neuropsychiatric symptoms, brain metabolism, plasma amyloid levels and general function as measured by the CDR scale. Results from this trial are expected to provide valuable information on the potential development of carvedilol as a novel disease-modifying treatment for AD (55).

CONCLUDING REMARKS

The 12th ICAD meeting offered a week of intensive exposure to the latest scientific efforts and achievements in the research of AD and related cognitive disorders. Breakthroughs from both academic and pharmaceutical industry sources, including the development of new technologies to detect and/or prevent disease progression, were presented. Leading scientists in the area of dementia research shared their views and findings and explored collaborative opportunities aiming to advance the understanding of AD and increase the chances of discovery of effective treatments.

REFERENCES

1. Quinn, J.F., Raman, R., Thomas, R.G. et al. *A clinical trial of docosahexanoic acid (DHA) for the treatment of Alzheimer's disease.* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst O1-04-02.
2. Yurko-Mauro, K., McCarthy, D., Bailey-Hall, D. et al. *Results of the MIDAS Trial: Effects of docosahexaenoic acid on physiological and safety parameters in age-related cognitive Decline*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst O1-04-01.
3. Schulz, J., Rainer, M., Klünemann, H.-H. et al. *Once-daily memantine treatment improves cognition and functional communication in patients with moderate to severe AD: Results of a 16-week single-arm, open-label trial.* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P1-257.
4. Hofbauer, R.K., Saxton, J., Woodward, M. et al. *Effects of memantine on functional communication in patients with moderate AD: Results of a 12-week placebo-controlled trial*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P1-271.
5. Lorenzi, M., Beltramello, A., Zoccatelli, G. et al. *Effect of memantine on the activity of the default mode network. A resting fMRI study.* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P1-108.
6. Riepe, M.W., Hartmann, S., Lambert-Baumann, J. et al. *Memantine in Alzheimer´s disease - Results of an observational study in nursing home patients.* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P1-249.
7. Frölich, L., Hartmann, S., Lambert-Baumann, J. et al. *Efficacy and tolerability of Memantine in Alzheimer´s disease - Results of an observational study*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P1-247.
8. Yang, Y.-H., Chen, S.-H., Chou, M.-C. et al. *Concentration of donepezil to therapeutic response in Alzheimer's disease.* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P2-218.
9. Li, S.-J., Ward, D.B., Wu, Z. et al. *Detection of changes in functional connectivity following Aricept treatment in mild Alzheimer disease subjects.* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P2-228.
10. Antuono, P., Jones, J., Wu, Z. et al. *Detection of changes in cerebral blood flow perfusion following Aricept® treatment in mild Alzheimer's disease subjects*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disords (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P2-229.
11. Waldemar, G., Gauthier, S., Wilkinson, D. et al. *The effects of donepezil on apathy in patients with Alzheimer's disease.* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P3-223.
12. Haridas, K.M. *A randomised study to compare the efficacy, tolerability and safety between memantine and donepezil in moderate to severe Alzheimer's disease*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P2-203.
13. Tariot, P., Sabbagh, M., Flitman, S. et al. *A safety, tolerability and pharmacokinetic study of dimebon in patients with Alzheimer's disease already receiving donepezil*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P1-254.
14. Alvarez, A., Cacabelos, A., Aleixandre, M. et al. *Combined treatment with Cerebrolysin and donepezil in mild to moderate Alzheimer's disease: Results of a double-blind, randomized clinical trial*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P1-244.
15. Doppler, E., Alvarez, A., Cacabelos, A. et al. *Synergistic treatment effects with Cerebrolysin and donepezil: Results from a randomized, double-blind, multicenter trial to compare safety and efficacy of Cerebrolysin, donepezil and a combination treatment in patients with probable Alzheimer's disease.* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P1-246.
16. Novak, P.H., Moessler, H., Gusev, E.I. et al. *Cerebrolysin in vascular dementia: A randomized, placebo controlled study*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P1-248.
17. Alderton, C., Zvartau-Hind, M., Ritchie, S. et al. *Secondary endpoint and responder analyses in a study of rosiglitazone XR in APOE4-stratified subjects with mild-to-moderate Alzheimer's disease*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P1-263.
18. Zvartau-Hind, M., Alderton, C., Ritchie, S. et al. *Safety and tolerability of rosiglitazone XR in a randomised, placebo-controlled study in APOE4-stratified subjects with mild-to-moderate Alzheimer's disease*. Alzheimer's

& Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P1-245.

19. Wilkinson, D., Cohen, S., Inglis, F. et al. *Results of a double-blind phase 2b study of monthly mimopezil implants compared to oral donepezil in patients with moderate Alzheimer's Disease (BRAINz study).* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst O1-04-05.
20. Schneider, L.S., Vigen, C.L.P., Mack, W.J. et al. *Citalopram compared to atypical antipsychotics for Alzheimer patients who did not previously benefit from treatment: The CATIE-AD study.* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst O4-04-01.
21. Kwak, K.-P., Lee, D.Y., Han, Y.H. *A comparative study of the efficacy with escitalopram and tianeptine in older depressed patients with or without executive dysfunction*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P4-239.
22. Ferris, S., Darreh-Shori, T., Lane, R. *Effects of rivastigmine on brain white matter volume in mild cognitive impairment (MCI).* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P2-246.
23. Schmidt, R. *A naturalistic study of rivastigmine transdermal patch in outpatient services in Austria.* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P2-245.
24. Tsolaki, M., Ida, E. *Side effects of rivastigmine (Exelon) transdermal patch*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P2-251.
25. Kurz, A., Tracik, F., Articus, K. *Treatment compliance with rivastigmine patch: Does a novel application form lead to enhanced adherence?* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P1-048.
26. Wilcock, G.K., Black, S.E., Balch, A.H. et al. *Safety and efficacy of tarenflurbil in subjects with mild Alzheimer's disease: Results from an 18-month international multi-center phase 3 trial.* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst O1-04-07.
27. Frölich, L., Eckerwal, G., Jonas, N. et al. *A multi-centre, double-blind, placebo-controlled phase IIb proof-of-concept dose-ranging study of AZD3480 and donepezil over 12 weeks in patients with mild to moderate Alzheimer's Disease*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst O1-04-04.
28. Nirogi, R., Kambhampati, R., Shinde, A. et al. *SUVN-502: A safe, potent, selective, brain penetrant and orally active 5-HT$_6$ receptor antagonist - First in human clinical phase-1 study*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P1-251.
29. Nirogi, R., Kandikere, V., Mudigonda, K. et al. *Safety, tolerability and pharmacokinetics of SUVN-502 - A 5-HT$_6$ receptor antagonist, first in human phase-1 single ascending dose (SAD) study.* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P1-252.
30. Nirogi, R., Kandikere, V., Mudigonda, K. et al. *Human phase-1 multiple ascending dose (MAD) study - Safety, tolerability and pharmacokinetics of SUVN-502, a 5-HT$_6$ receptor antagonist.* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P1-253.
31. Baker, J.D., Lenz, R.A., Locke, C. et al. *ABT-089, a neuronal nicotinic receptor partial agonist, reverses scopolamine-induced cognitive deficits in healthy normal subjects.* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P2-221.
32. Winblad,B.G., Minthon, L., Floesser, A. et al. *Results of the first-in-man study with the active Aβ immunotherapy CAD106 in Alzheimer patients.* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1):Abst O2-05-05.
33. Staufenbiel, M., Beibel, M., Danner, S. et al. *Strong parenchymal amyloid reduction following CAD106 immunotherapy is associated with an increase in vascular Aβ but not microhemorrhages*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst O2-05-06.
34. Mandler, M., Santic, R., Weninger, H. et al. *The MimoVax vaccine: A novel AD-treatment strategy targeting truncated Aβ40/42 by active immunization*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst O2-05-08.
35. Pihlgren, M., Madani, R., Hickman, D.T. et al. *The safety profile of ACI-24, an oligo-specific amyloid beta vaccine, demonstrated decrease of large microbleedings in brain of aged Alzheimer's disease mouse model*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P3-281.
36. Barghorn, S., Striebinger, A., Giaisi, S. et al. *Abeta-oligomer selective antibody A-887755 exhibits a favorable profile for Alzheimer's disease immunotherapy compared to Abeta-peptide unselective antibodies*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P3-275.
37. Bednar, M., Zhao, Q., Landen, J.W. et al. *Safety and pharmacokinetics of the anti-amyloid monoclonal antibody PF-04360365 following a single infusion in patients with mild-to-moderate Alzheimer's disease: Preliminary results*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst O4-04-03.
38. Moll, J.R., Soukharev, S., Nelson, C. et al. *Specific detection of soluble amyloid beta oligomers using conformationally dynamic Pronucleon™ peptides*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P1-073.
39. Sundgren-Andersson, A.K., Svensson, S.P.S., Swahn, B.-M. et al. *AZD4694: Fluorinated positron emission tomography (PET) radioligand for detection of β-amyloid deposits*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P2-023.
40. Sabri, O., Barthel, H., Becker, G. et al. *[^{18}F]BAY 94-9172 PET - Towards in vivo quantification of brain β-amyloid plaque load in Alzheimer disease*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P2-002.
41. Rowe, C.C., Pejoska, S., Mulligan, R.S. et al. *Test-retest variability studies in Alzheimer's disease and normal ageing of the new amyloid imaging agent [18F]BAY 94-9172*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P2-009.
42. Vandenberghe, R., Van Laere , K., Ivanoiu, A. et al. *Phase II study of the ^{18}F labelled PiB derivative GE067*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst O1-01-04.
43. Van Laere , K., Vandenberghe, R., Ivanoiu, A. et al. *Correlation between ^{18}F-GE-067 and ^{11}C-PIB uptake in Alzheimer's disease and MCI.* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P2-011.
44. Mathis, C.A., Ikonomovic, M.D., Mason, N.S. et al. *Pharmacologic and pharmacokinetic equivalence studies of GE-067 to PiB*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P2-007.

45. Sperling, R., Johnson, K., Pontecorvo, M.J. et al. *PET imaging of β-amyloid with florpiramine F 18 (18F-AV-45); preliminary results from a phase II study of cognitively normal elderly subjects, individuals with mild cognitive impairment, and patients with a clinical diagnosis of Alzheimer's disease.* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P1-084.

46. Nuvoli, S., Nieddu, A., Rotondo, A. et al. *Alzheimer's disease (AD) and Lewy bodies dementia (LBD) differential diagnosis: A ^{123}ioflupane SPECT study*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P1-078.

47. Ewers, M., Walsh, C., Trojanowski, J.Q. et al. *Biomarker based diagnosis of very mild Alzheimer's disease: A multicenter study.* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P4-332.

48. Boess, F., De Vry, J., Erb, C. et al. *Pharmacological and behavioral profile of EVP-5141, a novel α7 nicotinic acetylcholine receptor agonist*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl.1): Abst P1-234.

49. Watts, R.J., Chen, M., Atwal, J. et al. *Selection of an anti-Abeta antibody that binds various forms of Abeta and blocks toxicity both in vitro and in vivo*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P3-283.

50. Mortensen, D., Deng, R., Adolfsson, O. et al. *Characterization of the pharmacokinetics, pharmacodynamics, and distribution of anti-Abeta antibody, MABT5102A*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P3-259.

51. Snow, A.D., Cummings, J., Lake, T. et al. *Exebryl-1: A novel small molecule currently in human clinical trials as a disease-modifying drug for the treatment of Alzheimer's disease.* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P3-254.

52. Grossman, H., Marzloff, G., Luo, X. et al. *NIC5-15 as a treatment for Alzheimer's: Safety, pharmacokinetics and clinical variables*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P1-279.

53. Pasinetti, G., Rosen, Z., Grossman, H. *Nic5-15 a novel natural gama-secretase inhibitor that attenuates brain beta-amyloid content and improves cognition.* Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P4-331.

54. Saxby, B.K., Wesnes, K.A., McKeith, I.G. et al. *Hypertension as a treatment target for prevention of dementia: Effects of candesartan on cognitive decline in older hypertensives in the SCOPE substudy, and comparison to normotensive controls*. Alzheimer's & Dementia [12th Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P4-088.

55. Pasinetti, G., Rosen, Z., Rosenberg, P. et al. *Carvedilol as a potential novel disease modifying agent for the treatment of Alzheimer's disease.* Alzheimer's & Dementia [12th International Conference on Alzheimer's Disease and Related Disorders (ICAD) (July 11-16, Vienna) 2009] 2009, 5(Suppl. 1): Abst P4-330.