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FOUR ALZHEIMER'S CLINICAL TRIALS ADDRESS A VARIETY OF TREATMENT TARGETS – AMYLOID, TAU, SYNAPSE FORMATION

- Unsuccessful Phase III Study Does Not Mean the End of Anti-Amyloid Therapies -

CHICAGO, IL, July 29, 2008 – Results from four studies of potential new treatments for Alzheimer's – even an unsuccessful late stage clinical trial – increase the field's knowledge and point scientists toward advances in therapies for the disease, according to research reported today at the 2008 Alzheimer's Association International Conference on Alzheimer's Disease (ICAD 2008), in Chicago.

The reports included data from:

- A Phase III trial of tarenflurbil (Flurizan, Myriad), an anti-amyloid therapy, that failed to achieve its primary endpoints.
- A 12-week, Phase IIa trial of PBT2 (Prana Biotechnology), which reduces the toxic form of amyloid by preventing the interaction of amyloid with copper and zinc in the brain.
- A 84-week, Phase II trial of methylthioninium chloride (remember™, TauRx Therapeutics), a tau aggregation inhibitor that targets toxic tau aggregates, or "tangles." Tangles of tau in the brain are another characteristic hallmark of Alzheimer's.
- A proof of concept clinical trial in mild Alzheimer's of Souvenaid (Danone Research-Centre for Specialised Nutrition), a "medical food" product that encourages the formation of brain synapses and may reduce beta amyloid.

"While researchers continue to investigate amyloid as a target for Alzheimer's therapies – it is the most mature theory being pursued – we must also examine other potential avenues given the urgency of conquering this disease," said Samuel Gandy, MD, PhD, chair of the Alzheimer's Association's Medical and Scientific Advisory Council. "We can't leave any stone unturned if we hope to aid the 5 million people currently living with Alzheimer's and the millions more that will be devastated by this epidemic."

While currently approved treatment options for Alzheimer's offer some relief of symptoms for perhaps a year or two, they do not change the underlying course of the disease. It is widely hoped that the next generation of therapies will be disease modifying, that is, they will slow or stop the brain cell death and loss of function caused by Alzheimer's.

"We must develop better treatments for Alzheimer's that go beyond improving symptoms to drugs that actually change the course of the disease. Delaying the onset of Alzheimer's and slowing the progression of the disease means that millions of people would not get Alzheimer's, and that many who do get the disease might only experience mild symptoms. In addition, delaying the onset and slowing the progression of

Alzheimer's in the next five years could generate billions of dollars annually in Medicare and Medicaid savings for nursing home care alone," Gandy said.

Dr. Gandy is Mount Sinai Professor of Alzheimer's Disease Research, Professor of Neurology and Psychiatry, and Associate Director of the Alzheimer's Disease Research Center at the Mount Sinai School of Medicine, New York City.

18-Month Phase III Trial Results for Tarenflurbil (Flurizan)

Myriad Genetics announced on June 30, 2008, that its Phase III trial of tarenflurbil (Flurizan) had failed to achieve statistical significance on either of its two primary endpoints, and that the company was abandoning development of the compound for Alzheimer's disease.

"While the results of the trial were certainly disappointing, just because the Flurizan Phase III clinical trial failed, doesn't mean that other amyloid-targeted therapies in the clinical trial pipeline aren't valid. We learn a great deal from every clinical study," Gandy said. "There are many ways to impact amyloid and its role in Alzheimer's. There are other drugs in development that target amyloid with mechanisms of action that are different from this one. One or more of these drugs may ultimately prove successful."

At ICAD 2008, detailed data and results from the trial were presented for the first time by Robert C. Green, MD, MPH, of Boston University School of Medicine. Tarenflurbil is classified as a selective amyloid lowering agent, which was shown in nonclinical studies to modulate gamma secretase activity. The drug was in trials in people with mild Alzheimer's to determine if its ability to lower the amount of toxic beta-amyloid would slow or stop the course of the disease.

In the randomized, double-blind, placebo-controlled trial, 1,649 individuals with mild Alzheimer's (mean MMSE in both groups = 23.3) were randomized 1:1 to receive tarenflurbil 800 mg twice-a-day or placebo for 18 months. The co-primary outcome measures of efficacy were two standard measures of cognition and the ability to accomplish activities of daily living, respectively the ADAS-cog and the ADCS-ADL, with assessments conducted every three months. The secondary outcome measure was the Clinical Dementia Rating scale. Exploratory outcomes included the Neuropsychiatric Inventory (NPI), Quality of Life-Alzheimer's test, and Caregiver Burden Inventory.

The researchers found that the drug did not achieve statistical significance in either of its primary endpoints of cognition and activities of daily living. Also, it did not achieve statistical significance on the secondary endpoint. By the end of the 18-month trial, patients in both the tarenflurbil and placebo groups had declined approximately seven points on the ADAS-cog scale and 10 points on the ADCS-ADL scale.

According to the researchers, the reported adverse effects reflect the expected profile of the elderly population with Alzheimer's and, in most participants, symptoms were well balanced between the tarenflurbil and placebo groups. However, in the tarenflurbil treatment group, there was increased frequency of anemia (9.7 percent vs. 4.5 percent), infections (pneumonia, H. zoster, sepsis) (6.9 percent vs. 2.9 percent), and gastrointestinal ulcers (1.7 percent vs. 0.4 percent).

"This was the largest and longest placebo-controlled AD treatment trial ever completed," Green said. "While the trial did not meet its endpoints, it was well-designed and executed, and it provided clear answers regarding Flurizan's lack of efficacy and its safety."

"The fact that both the drug-treated and placebo groups declined over the course of the trial – and that the placebo-treated patients declined at the expected rate – shows that we can do this type of trial in people with mild Alzheimer's. As the first trial to ever study a large population of mild Alzheimer's patients, we've collected very valuable data on the progression of the disease in its earliest stages. We are confident that the

results of this study will help researchers in their quest to develop new and better treatments for Alzheimer's," Green added.

"This drug candidate, in this dose, in this group did not work. But, like much good science, the study raises as many questions as it does provide answers. Was the dose right? Was the study long enough? Did they start the intervention early enough in the course of the disease? Designing and executing clinical studies that answer these questions will help us defeat Alzheimer's disease," Gandy said. "The only way we are going to solve the problem of Alzheimer's is for scientists and companies to have the courage to make significant investments in these large scale trials – which may or may not work. This was a very well done study and the company and scientists are to be commended for that."

Phase IIa Trial of PBT2, a Metal-Protein Attenuating Compound, in Mild Alzheimer's

PBT2 is a metal-protein attenuating compound (MPAC) being developed by Prana Biotechnology as a potential Alzheimer's therapy. In previous research, ions of copper and zinc were found to play a role in the aggregation of beta amyloid protein, which is believed to cause functional damage in Alzheimer's. According to Prana, PBT2 reduces the toxic form of beta amyloid by preventing the interaction of beta amyloid with copper and zinc. MPACs have been shown to restore normal function to beta amyloid-impaired synapses and improve cognitive performance in mouse models of Alzheimer's.

Jeffrey L. Cummings, MD, of the David Geffen School of Medicine at UCLA, Los Angeles, CA, reports on a Phase IIa randomised, double-blind, placebo-controlled trial of PBT2 to assess the safety, tolerability, biochemical impact on the body, and preliminary efficacy of two different doses of the compound in patients with early Alzheimer's. This was done by (1) looking at how treatment with PBT2 changed the levels of proteins that are believed to be linked to Alzheimer's in the blood and spinal fluid (CSF) and (2) using memory and thinking tests to assess any change in the participants' mental capacity.

Seventy-eight (78) people with mild Alzheimer's (mean MMSE=22.9) were randomized to receive placebo (n=29), PBT2 50mg (n=20) or PBT2 250mg (n=29) capsules orally, once per day for 12 weeks. Biomarker assessment included the mean change from baseline to week 12 of proteins A β 42 and A β 40 in CSF. Preliminary efficacy assessments included the mean change from baseline to week 12 on a Neuropsychological Test Battery (NTB) and the ADAS-cog.

The researchers found that PBT2 250mg demonstrated a statistically significant reduction of CSF A β 42 after 12 weeks of treatment compared with placebo (p=0.006), which was dose-dependent (p=0.023). PBT2 250mg demonstrated statistically significant improvements in both the Trail Making Test Part B and the Category Fluency Test (components of the NTB related to executive function) compared with placebo (p=0.009 and p=0.041, respectively). PBT2 had no effect on the ADAS-cog in this trial.

The researchers found the safety and tolerability profile to be similar between PBT2 and placebo. The overall withdrawal rate in the study was 5 percent, with no withdrawals attributed to adverse events. There were no serious adverse events reported with PBT2.

"These results indicate that PBT2 is having an impact on the underlying biology of Alzheimer's, which is very exciting," Cummings said. "This is a critical proof of concept, and the safety and efficacy demonstrated by PBT2 in this study warrant evaluation in larger scale clinical trials in Alzheimer's."

A Phase IIb trial of a Tau Aggregation Inhibitor Therapy

As an alternative to anti-amyloid therapies for Alzheimer's, researchers continue to examine a variety of treatments and targets with the potential to curb the disease. This includes presenting data supporting the viability of therapies targeting tau protein and its aggregation into the "tangles" originally discovered by Alois Alzheimer.

Previous research has shown that the buildup of brain lesions known as neurofibrillary tangles, which are composed of a short fragment of a protein called tau, is correlated with increasing levels of dementia symptoms. And, these tangles first appear in the brain long before symptoms of the disease become clinically apparent. Methylthioninium chloride (MTC, or brand name rember™) has been shown in the test tube to dissolve tau tangle filaments and prevent aggregation of tau into tangles. MTC has also been shown to block the toxic effects of aggregated tau in cells. In animal models, MTC has demonstrated cognitive and behavioral benefits in line with reduced tau pathology.

In research reported at ICAD 2008, Claude M. Wischik, Professor in Mental Health, University of Aberdeen, United Kingdom and Chairman, TauRx Therapeutics, Singapore, and colleagues conducted a 24-week, double-blind, randomized, dose-ranging, parallel design trial of MTC monotherapy in 321 people with Alzheimer's at 17 centers in the United Kingdom and Singapore, followed by a 60-week, blinded, active treatment extension. The control group received placebo for the initial 24 weeks and then a minimal efficacy dose subsequently. The primary objective was to investigate the effects of oral MTC at 30, 60 and 100 mg doses three times per day, compared with placebo, over 24 weeks on cognitive function as measured by the ADAS-cog in patients with mild or moderate Alzheimer's, stratified by stage of the disease. Another objective was to determine MTC's potential to modify the course of Alzheimer's over 19 months. Imaging results from SPECT and PET scans were collected at baseline and after 24 weeks of treatment.

The researchers found that, at 24 weeks, MTC produced a significant improvement relative to placebo of -5.5 ADAS-cog units in moderate subjects at the 60 mg dose ($p = 0.0208$). There was no placebo decline in people with mild Alzheimer's in the control group over the first 24 weeks preventing initial efficacy analysis, although efficacy was demonstrated in mild Alzheimer's by SPECT-scan outcomes over the same period. MTC stabilized the progression of Alzheimer's over 50 weeks in both mild and moderate Alzheimer's. The overall effect size was -6.8 ADAS-cog units vs. decline of 7.8 units in the control arm ($p < 0.0001$), with significant efficacy demonstrated separately in mild and moderate subgroups.

According to the researchers, as a first approximation to supporting disease modifying efficacy, treatment with MTC at the 60mg dose produced a significantly larger effect size at 50 weeks than at 24 weeks implying an effect on the rate of cognitive decline ($p = 0.0014$). This was confirmed in a mixed effects slope analysis, showing an 81 percent reduction of long run rate of progression of decline over 50 weeks ($p < 0.0001$). The final 84-week analysis confirmed the long term effect of the 60mg dose in subjects remaining on treatment, with apparent decline still not significantly different from baseline at the final assessment, whereas there was significant decline in the other study arms.

The researchers added that brain imaging using SPECT and PET confirmed the clinical trial results. SPECT measures regional cerebral blood flow (rCBF) which is closely related to brain cell activity. The study showed that treatment with MTC at the 60mg dose eliminated the rCBF decline that was seen in control subjects. The effect was greatest in brain regions that had the most severe tau aggregation pathology, namely the hippocampus and the entorhinal cortex, which are regions affected early and most severely in Alzheimer's.

“This is the first instance of a disease-modifying Alzheimer's therapy that has attained its primary, pre-specified cognitive efficacy target in a clinical trial,” said Wischik. “This trial therefore provides the first clinical trial evidence that an Alzheimer's therapy aimed at blocking tau aggregation may be a viable disease-modifying treatment. We now need to confirm this in a larger Phase III trial.”

“Our results appear to meet the draft EMEA clinical guidelines for disease-modifying therapy, supported by SPECT and PET evidence of efficacy in brain regions heavily affected by tau pathology,” Wischik added.

Proof of Concept Clinical Trial of Souvenaid™: A Medical Nutrition Approach to Mild Alzheimer's

People with Alzheimer's exhibit a significant loss of brain synapses, and this loss correlates with the loss of cognitive function. Pre-clinical research using a technique invented by Massachusetts Institute of Technology (MIT) has shown that specific combinations of nutrients can increase synapse formation. Now a double-blind, controlled study with Souvenaid™, including these nutrients, has shown it may help patients with mild Alzheimer's Disease.

Souvenaid™, developed by Danone Research – Centre for Specialised Nutrition, is designed to improve synapse formation and synaptic transmission via the synergistic action of a combination of nutrients (specifically, it contains uridine monophosphate, choline, the omega-3 fatty acids (EPA, DHA), phospholipids, B vitamins and antioxidants). Pre-clinical research has shown that specific combinations of certain nutrients interact to enhance brain cell outgrowth, synapse formation, and neurotransmitter release and also improved cognitive function in several pre-clinical models. This specific combination of nutrients showed also reduced amyloid production and toxicity in the pre-clinical models.

At ICAD 2008, Philip Scheltens, MD, PhD, of the Alzheimer Center of the VU University Medical Centre, Amsterdam, the Netherlands reported the results of a randomised, double-blind, controlled 12-week trial, sponsored by Danone Research, to assess the safety and effect of Souvenaid™ on memory and cognitive performance in people with mild Alzheimer's (MMSE 20-26, mean=23.9) who had never taken any Alzheimer's drugs.

Two hundred twelve (212) people with mild Alzheimer's were recruited for the trial at 28 sites mainly in the Netherlands, Germany, and Belgium, with a single site in the U.S.; 106 were assigned to Souvenaid™, a 125 ml (125 kcal) once-a-day drink, and 106 to control in the 12-week study. Primary outcome measures were a delayed verbal memory task derived from the Wechsler Memory Scale-revised and the 13-item modified ADAS-cog. Secondary outcomes included the MMSE, 23-item Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (ADCS-ADL), 12-item Neuropsychiatric Inventory (NPI), Clinician's Interview Based Impression of Change plus Caregiver Input (CIBIC-plus) and Quality of Life in Alzheimer's Disease (QOL-AD). A separate analysis was performed on a pre-specified subgroup of very mild Alzheimer's (MMSE>23). In an optional, double-blind, 12-week extension phase, patients continued to receive the same study product (85 percent of the week 12 completers continued into the extension phase).

The investigators found a statistically significant benefit in mild Alzheimer's patients on the delayed verbal memory task in the Souvenaid™ group, and also a significant effect in the subgroup of very mild patients. The unadjusted analyses showed no significant effect on the modified ADAS-cog. However, the baseline modified ADAS-cog score was a predictor for the intervention effect. Thus, patients with a higher baseline score showed a greater effect of Souvenaid™ on cognition. The investigators noted that there was no decline in modified ADAS-cog and verbal memory in the control group during the 12 weeks of the study.

According to the investigators, Souvenaid™ was well tolerated (compliance=94 percent) and showed a good safety profile. The drop-out rate in the study was low – 6.6 percent in first 12 weeks, 4.8 percent in the 12-week extension. They found no significant difference in adverse effects between the study groups throughout the study period.

“We're very excited by these results and we look forward to further research on this product,” Scheltens said. “This is an innovative, completely different approach and we believe that medical foods such as Souvenaid™ can be a valuable part of Alzheimer's disease management. We're committed to a high level of scientific rigor in the next trial to further test Souvenaid™.”

“Souvenaid™ is a medical food product backed by 10 years of research. Much of the conceptual work and early pre-clinical work was done at MIT under Professor Richard Wurtman, and supported principally by the National Institutes of Health,” Scheltens added.

About ICAD 2008

The 2008 Alzheimer’s Association International Conference on Alzheimer’s Disease (ICAD 2008) is the largest gathering of international leaders in Alzheimer research and care ever convened. At ICAD 2008, more than 5,000 researchers from 60 countries will share groundbreaking information and resources on the cause, diagnosis, treatment and prevention of Alzheimer’s and related disorders. As a part of the Association’s research program, ICAD serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community. ICAD 2008 will be held in Chicago at McCormick Place, Lake Side Center from July 26–31.

About the Alzheimer’s Association

The Alzheimer’s Association is the leading voluntary health organization in Alzheimer’s research, care and support. Our mission is to eliminate Alzheimer’s disease through the advancement of research, provide and enhance care and support for all affected, and reduce the risk of dementia through the promotion of brain health. Our vision is a world without Alzheimer’s. For more information, visit www.alz.org.

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- Robert C. Green. “Safety and efficacy of tarenflurbil in subjects with mild Alzheimer’s disease: Results from an 18- month multi-center phase 3 trial.” (Funder: Myriad Pharmaceuticals)
- Jeff Cummings. “Targeting A β as a modifying therapy of Alzheimer’s disease: Safety, efficacy and biomarker findings of a phase 2a randomised, double-blind, placebo-controlled trial of PBT2.” (Funder: Prana Biotechnology Limited)
- Claude M. Wischik. “Tau aggregation inhibitor (TAI) therapy with rember™ arrests disease progression in mild and moderate Alzheimer’s disease over 50 weeks.” (Funder: TauRx Therapeutics)
- Philip Scheltens. “The efficacy Of Souvenaid in mild Alzheimer’s disease: A randomized, controlled, double-blind, parallel Group, multi-centre, multi-country clinical trial.” (Funder: Danone Research)

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Control #: 08-A-2170-ALZ

O3-04 - Drug Discovery: Clinical Trials TUESDAY

(Presentation #: O3-04-01; 7/29/2008 3:00:00 PM - 3:15:00 PM)

Safety and efficacy of tarenflurbil in subjects with mild Alzheimer's disease: Results from an 18- month multi-center phase 3 trial

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Background: Tarenflurbil is a selective A β 42-lowering agent that modulates γ -secretase activity to preferentially reduce production of A β 42 in vivo and in vitro. Preliminary evidence for potential benefit of tarenflurbil 800 mg bid in subjects with mild AD was recently observed in a randomized, double-blind Phase 2 trial. This multi-center Phase 3 study assessed the safety and efficacy of tarenflurbil in subjects with mild Alzheimer's disease (AD).

Methods: In this randomized, double-blind, placebo-controlled trial, individuals with mild AD (MMSE score 20-26, inclusive) were randomized (1:1) to receive tarenflurbil 800 mg bid or placebo for 18 months. Randomization was stratified according to use/non-use of acetylcholinesterase inhibitors and/or memantine. The co-primary outcome measures of efficacy were the ADAS-cog and the ADCS-ADL, with assessments conducted every 3 months. The secondary outcome was the CDR-sb, and exploratory outcomes included the NPI, Quality of Life-AD, and Caregiver Burden Inventory. Analysis was conducted by comparing the rate of change (slope) in the outcome measures between treatment and placebo arms. Adverse events were monitored throughout the study.

Results: The study was originally powered for 1600 participants, and 1684 participants were randomized at 133 sites throughout the US between Feb 21, 2005 and Sep 1, 2006, of which 1653 had mild AD and are included in the primary analysis. At baseline, participants were 51.1% female, had a mean age (\pm standard deviation, range) of 74.6 (\pm 8.3, 53-94) and mean MMSE score of 23.3 (\pm 2.0, 20-26).

Conclusions: This Phase 3 protocol was powered to evaluate the efficacy of tarenflurbil with respect to the primary outcomes using an analytic strategy comparing rate of change. Results for primary and secondary efficacy outcomes will be presented, along with safety results including adverse events and lab parameters.

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Control Number: 08-HT-3522-ALZ

Pres Pref: Oral

Targeting $\text{a}\beta$ As A Modifying Therapy Of Alzheimer'S Disease: Safety, Efficacy And Biomarker Findings Of A Phase 2a Randomised, Double-blind Placebo-controlled Trial Of Pbt2

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Background: PBT2 is a Metal-Protein Attenuating Compound (MPAC) designed to impact upon the Cu^{2+} - and Zn^{2+} - mediated toxic oligomerization of $\text{A}\beta$ that causes functional damage in Alzheimer's disease (AD). PBT2 is being developed as a potential therapy.

Objective: To assess the safety, tolerability, pharmacodynamics (PD) and preliminary efficacy of PBT2 in patients with early AD.

Methods: In this double-blind, multicenter study, 78 patients with early AD were randomized to receive placebo (n=29), PBT2 50mg (n=20) or PBT2 250mg (n=20) capsules orally once per day for 12 weeks. PD biomarker assessment included the mean change from baseline to week 12 of $\text{A}\beta_{42}$ and $\text{A}\beta_{40}$ in cerebrospinal fluid (CSF). Preliminary efficacy assessments included the mean change from baseline to week 12 on the Neuropsychological Test Battery (NTB).

Conclusion: The range of mean patient baseline characteristics across treatment groups was: age, 72.1 to 72.6 years; % females, 45 to 52%; ADAS-Cog, 18.7 to 18.9; MMSE, 22.2 to 23.5; no. patients with ApoE e4, 72.4% to 80%. Overall withdrawal rate was 7.7%, with no withdrawals attributed to adverse events. There were no serious adverse events reported with PBT2 and treatment emergent adverse events were evenly distributed amongst the three treatment arms. PBT2 250mg demonstrated a statistically significant reduction of CSF $\text{A}\beta_{42}$ after 12 weeks of treatment compared with placebo (p=0.006, ITT) which was dose-dependent (p=0.023). Similarly, PBT2 250mg demonstrated a reduction of $\text{A}\beta_{40}$ levels in CSF, however this did not reach statistical significance compared with placebo (p=0.092). In addition, 250mg PBT2 demonstrated statistically significant improvements in both the Trail Making Test Part B and the Category Fluency Test (components of the NTB) after 12 weeks of treatment compared with placebo (p=0.009 and p=0.041, respectively (ITT)). PBT2 was safe and well tolerated in this study in patients with mild AD. PBT2 significantly reduced the level of $\text{A}\beta_{42}$ in CSF, a key protein implicated in the pathology/etiology of AD. Furthermore, PBT2 was shown to have an effect on measures of executive function. The safety and efficacy demonstrated in this study would warrant evaluation in larger scale clinical trials in AD patients.

Disclosures: J. Cummings, Abbot, Acadia, ADAMAS, Astellas, CoMentis, Eisai, EnVivo, Forest, Janssen, Lundbeck, Lilly, Medivation, Merck, Merz, Myriad, Novartis, Pfizer, Prana, Sonexa, Takeda Pharmaceutical Companies; ADAMAS, Prana; Eisai, Forest, Janssen, Novartis, Pfizer, Lundbeck, Merz; Dr Cummings owns the copyright for the Neuropsychiatric Inventory.

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Control #: 08-A-2332-ALZ

O3-04 - Drug Discovery: Clinical Trials TUESDAY

(Presentation #: O3-04-07; 7/29/2008 4:30:00 PM - 4:45:00 PM)

Tau aggregation inhibitor (TAI) therapy with rember™ arrests disease progression in mild and moderate Alzheimer's disease over 50 weeks

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Background: Neurofibrillary degeneration is correlated with clinical dementia. Methylthioninium chloride (MTC, rember™) dissolves Tau polymers (Paired Helical Filaments) isolated from AD brain, and prevents Tau aggregation in cell models at the nanomolar range (0.15 - 0.58 μM). MTC has efficacy in Tau transgenic animal models, reversing cognitive and other behavioural defects, and reversing Tau pathology in the brain.

Methods: An exploratory, dose-range finding, parallel design, double-blind, randomised, placebo-controlled trial of rember™ monotherapy was conducted in 332 subjects meeting DSM-IV and NINCDS-ADRDA for probable AD in UK and Singapore. The primary objective was to investigate the effects of oral MTC at 30, 60 and 100 mg three times per day, compared with placebo, on cognitive function (ADAS-cog) in patients with mild or moderate AD stratified by CDR. The 100mg dose was found to have a formulation defect limiting release of the therapeutic form of MTC. Secondary outcomes included MMSE, CDRsb, CGIC, ADFACS and NPI. Nested studies of SPECT- and PET-scan outcomes at 6 months are reported separately.

Results: In the prespecified analysis at 24 weeks, rember™ produced a significant improvement relative to placebo of -5.4 ADAS-cog units in CDR-moderate subjects at the 60mg dose. There was no placebo decline in CDR-mild AD over the first 24 weeks preventing initial efficacy analysis, although efficacy was demonstrated in mild AD by the SPECT-scan outcomes. rember™ stabilised the progression of AD over 50 weeks in both mild and moderate AD. The overall effect size was -6.8 ADAS-cog units vs. decline of 7.8 units in the placebo/comparator arm, with significant efficacy demonstrated separately in mild and moderate subgroups. rember™ efficacy was confirmed on all secondary outcomes. The rember™ efficacy analysis met new EMEA guidelines for disease-modifying therapy by slope analysis and two-time-point analysis, supported by SPECT and PET evidence of efficacy in brain regions strongly affected by Tau pathology.

Conclusions: This represents the first evidence that TAI monotherapy with rember™ is a viable disease-modifying treatment for mild and moderate AD which may also have preventative application at preclinical Braak stages of AD.

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Control #: 08-HT-3476-ALZ

The Efficacy Of Souvenaid* In Mild Alzheimer's Disease: A Randomized, Controlled, Double-blind, Parallel Group, Multi-centre, Multi-country Clinical Trial

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Disclosure Block: P. Scheltens, Danone Research, Consultant.

Background: Increasing evidence shows a role of nutrients in Alzheimer's Disease (AD). Extensive preclinical studies have demonstrated that a combination of nutrients increases synapse formation and reduces the production of beta-amyloid.

Objective: To assess the effect of an intervention with a medical food on memory and cognitive performance in drug naïve mild AD patients.

Methods: Drug naïve mild AD patients (MMSE 20-26) were randomly allocated to receive Souvenaid, a 125ml (125kcal) once-a-day milk-based drink containing FortasynTM Connect [a specific combination of nutrients] or an iso-caloric control drink in a double-blind 12 weeks study. Primary outcome measures were a delayed verbal memory task (derived from Wechsler Memory Scale-revised) and the 13-item modified ADAS-cog at 12 weeks. In a double-blind 12 week extension phase patients continued to receive the same study product. A repeated-measures mixed model analysis was performed on the intention to treat population and a pre-specified subgroup of very mild AD (MMSE>23). The trial was preregistered with the Dutch Trial Register (#ISRCTN72254645).

Results: Of 212 enrolled study patients (mean MMSE 23.9, mean age 73.7, male 50%), 106 were assigned to Souvenaid and 106 to control. No significant baseline differences were detected between the groups. There was no decline in modified ADAS-cog and verbal memory in the control group. In the Souvenaid group a clear trend towards an effect on the delayed verbal memory task was observed while a significant benefit was found in very mild AD patients. The unadjusted analyses showed no significant effect on the modified ADAS-cog. However, the baseline modified ADAS-cog score was a predictor for the intervention effect, i.e. patients with a higher baseline score showed a greater effect of Souvenaid. Intervention with Souvenaid was well tolerated (compliance was 95%) and safe. There was no significant difference in (S)AEs between the study groups throughout the study period.

Conclusion: Souvenaid is safe and well tolerated. This proof of concept study demonstrates that Souvenaid given for 12 weeks improves memory in very mild AD. These findings justify further studies with Souvenaid in patients with AD disease.

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