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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 (rember™, 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 (9.6 percent vs. 4.4 percent), infections (pneumonia, H. zoster, sepsis) (6.8 percent vs. 2.9 percent), and gastrointestinal ulcers (1.7 percent vs. 0.3 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 Aβ42 and Aβ40 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 Aβ42 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^{TM}) 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 Aβ 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)