DIVERSE APPROACHES TO ALZHEIMER’S THERAPIES CONTINUE TO SHOW PROGRESS AT ICAD

- Plus, Taking Antidementia Drugs Extends Lifespan Three Years in Alzheimer’s -

CHICAGO, July 30, 2008 – Results from clinical trials of three potential Alzheimer’s therapies raise hope for new and better treatments of the disease, according to data reported today at the 2008 Alzheimer’s Association International Conference on Alzheimer’s Disease (ICAD 2008) in Chicago.

A related study showed that taking antidementia drugs appears to have a positive impact on extending lifespan in those with Alzheimer’s.

These reports included:
• Eighteen-month data from an open-label extension of a pivotal trial of Dimebon (Medivation) in mild to moderate Alzheimer’s.
• Nine-month data from an interim analysis of the first U.S. Phase II trial of intravenous immunoglobulin, or IVIg (Baxter), in Alzheimer’s.
• Results of a Phase II study of a monoclonal antibody (LY2062430, Lilly) in mild to moderate Alzheimer’s.
• Research suggesting that persistent antidementia drug use increases survival in people with Alzheimer’s.

“Therapies targeting amyloid in Alzheimer’s disease must continue to be thoroughly tested,” said William Thies, PhD, Alzheimer’s Association vice president for Medical and Scientific Relations. “At the same time, we know that Alzheimer’s is a complex disease and that better treatments and preventions will likely also be complex, so we must investigate every promising drug target looking eventually towards the possibility of a multi-strategy approach.”

18-Month Data from an Extension of a Pivotal Trial of Dimebon in Alzheimer’s
In a study recently reported, Dimebon (Medivation) improved cognition and memory, activities of daily living, and behavior in a one-year placebo-controlled trial of patients with mild to moderate Alzheimer’s. At ICAD 2008, Jeffrey L. Cummings, M.D., the Augustus S. Rose Professor of Neurology, and Professor of Psychiatry and Biobehavioral Sciences, at UCLA, and colleagues reported on an open-label extension of the trial to 18 months.
One hundred eighty-three (183) people with mild-to-moderate Alzheimer’s were initially randomized into a six-month placebo-controlled study of Dimebon. Patients completing six months of treatment were offered the opportunity to re-consent for an additional six months of controlled treatment in their originally randomized group, followed by an open-label extension (OLE). Data presented at ICAD 2008 include only the 104 OLE participants (54 Dimebon, 50 placebo). All were given Dimebon for the OLE, not placebo, at a dose of 20 mg three times per day. Ninety-two (92) (88.5%) patients enrolling into OLE completed six months of treatment.

Patients originally receiving Dimebon for 12 months who continued on Dimebon for an additional six months in the OLE phase had preservation of function close to their starting baselines on the key signs and symptoms of Alzheimer’s disease 18 months after starting the study. Patients originally on placebo for 12 months who were then crossed over to Dimebon on the OLE phase also stabilized across all key measures tested. Since these patients had declined over the previous 12 months while on placebo, they stabilized at a lower level of function than those treated with Dimebon for the full 18 months.

Dimebon was well-tolerated through 18 months. Adverse events that occurred more often with dimebon compared to placebo were dry mouth, sweating and depressed mood/sadness.

“People initially treated with placebo and then crossed over to Dimebon did not show the same level of benefit as those people who took Dimebon for the full 18 months,” Cummings said. “This emphasizes the benefit of earlier treatment, and suggests the possibility that Dimebon may slow of the progression of Alzheimer’s. However, open-label extensions are not that same as placebo-controlled trials, and extrapolation of the treatment results should be done with caution. Patients are being screened now for the Phase III clinical trials.”

“Dimebon appears to work through a mechanism of action that is distinct from currently marketed Alzheimer’s drugs. Dimebon improves impaired mitochondrial function. Mitochondria are the central energy source of all cells and impaired mitochondrial function may play a significant role in the loss of brain cell function in Alzheimer’s,” Cummings added.

**First U.S. Double-Blind Phase II Clinical Trial of IVlg (Immunotherapy) in Alzheimer’s**

IVlg is under investigation by Baxter International as a potential anti-amyloid immunotherapy for Alzheimer’s. It contains a broad spectrum of antibodies, and is currently indicated as a therapy for people with primary immunodeficiency disorders. IVlg contains antibodies that bind to the beta amyloid aggregates that are thought to be central to Alzheimer’s. In two previous open-label studies, patients with mild to moderate Alzheimer’s showed cognitive improvement when treated with IVlg for six months.

Diamanto Tsakanikas, PhD, Norman Relkin, MD, PhD, and colleagues at Well Cornell Medical College carried out a six-month Phase II double-blind, placebo-controlled study of IVlg for Alzheimer’s followed by a 12-month, rater-blinded extension study. At ICAD 2008, they reported an interim analysis of uninterrupted IVlg treatment for 9 months.

Twenty-four people with mild to moderate Alzheimer’s (MMSE 14-26) participated in the trial. For the first six months, eight participants received placebo and 16 received IVlg at four doses ranging from 0.2 grams IVlg per kilogram of body weight every two weeks to 0.8 grams IVlg per kilogram of body weight given once per month (four people each at the four different doses). After six months, all subjects were given IVlg with the raters blinded to dose. The primary outcome measures were two standard measures of cognition and the clinician’s observation of change (a seven point scale from “markedly improved”=+3 to “marked worsening”=-3), respectively the ADAS-cog and the ADCS-CGIC, which were administered at baseline and three-month intervals thereafter.

In the total group, the researchers found statistically significant differences favoring IVlg treatment on the CGIC at three, six and nine months. At nine months, the IVlg group averaged 1.5 points higher on the
CGIC. On the ADAS-cog, scores favoring IVIg reached statistical significance at nine months. The average change in ADAS-Cog score at nine months favored IVIg treatment by 5.4 ADAS points. Uninterrupted IVIg treatment also produced sustained benefits relative to initial placebo treatment in activities of daily living.

When the results for each dose were analyzed individually, subjects receiving 0.4 grams of IVIg per kilogram of body weight given every two weeks improved over baseline on ADAS-Cog, ADCS-CGIC, and a measure of daily functioning. The researchers identified this as the best dose. None of the subjects given placebo showed comparable improvements.

Treatment-related adverse events that occurred at a greater frequency with IVIg treatment as compared to placebo were rash and a transient drop in blood count. In contrast, there were more behavioral disturbances in placebo-treated patients than those who received IVIg.

“While there were relatively small numbers of participants in this study, we were nonetheless able to demonstrate that people with Alzheimer’s who get uninterrupted treatment with IVIg for nine months have statistically significant and clinically relevant improvements on both cognitive and global clinical measures,” Tsakanikas said. “A large-scale, 18-month, multicenter Phase III clinical trial of IVIg in Alzheimer’s is now getting underway, sponsored by Baxter and the National Institutes of Health, that will test whether IVIg immunotherapy provides long-term benefits and has a disease-modifying effect.”

**Phase II Immunotherapy Trial with LY2062430 in Mild to Moderate Alzheimer’s**

Previous research has shown that antibodies that bind to beta amyloid can be given intravenously. By binding to beta amyloid and increasing the rate of its removal from the body, these antibody infusions may slow the progression of Alzheimer’s.

Eric Siemers, MD, Medical Director of the Alzheimer’s Disease Research Team at Eli Lilly and Company, and colleagues conducted a Phase II trial of a monoclonal antibody, known as LY2062430, that binds to the mid-domain of beta amyloid.

Fifty-two (52) people with mild to moderate Alzheimer’s and 16 volunteer subjects were studied. Alzheimer’s patients received 12 weekly infusions of placebo or antibody (100 mg every 4 weeks, 100 mg once per week, 400 mg every 4 weeks or 400 mg once per week). Volunteers received a single 100 mg dose of antibody. Safety assessments included brain imaging using magnetic resonance imaging (MRI) and examination of cerebrospinal fluid (CSF, a fluid normally present around the brain and spinal cord). In an optional sub-study, 24 Alzheimer’s patients and 13 volunteers underwent a type of brain imaging known as SPECT using a tracer (known as IMPY) that measures the amount of amyloid plaque present in the brain. Measures of symptom severity were obtained in all AD patients using the Alzheimer’s Disease Assessment Scale - Cognition (ADAS-cog).

The researchers found that following administration of the antibody, the amount of beta amyloid in blood increased substantially after the antibody bound to the beta amyloid protein. A small amount of the antibody enters the CSF, and in the Alzheimer’s patients beta amyloid also increased in CSF, similarly bound to the antibody. For patients treated with 400 mg of the antibody, the amount of the type of beta amyloid primarily found in plaque (known as AB1-42) that appeared in the blood correlated with the amount of amyloid plaque in the brains based on IMPY scans (r=0.65, p=0.02). According to Siemers, this finding suggests that some of the beta amyloid protein present in plaque moves to blood after treatment with the antibody.
Certain other types of beta amyloid thought to be primarily or exclusively found in amyloid plaque are also increased in blood and CSF of study participants. The antibody produced no change in cognitive scores or in the total amount of amyloid plaque based on IMPY scans. Siemers said that this was expected in a study of this duration.

According to the researchers, brain imaging using MRI and CSF safety assessments showed no evidence of inflammation, bleeding or other side effects throughout the trial. No side effects were identified that appeared to be related to antibody treatment.

“We saw an increase in amyloid beta, which is thought to be bound to LY2062430, in both the blood and cerebrospinal fluid of study participants,” Siemers said. “Additionally, after treatment we found a correlation between beta amyloid in blood and the amount of amyloid plaque in brain as determined by IMPY imaging, as well as an increase in blood and CSF in certain types of beta amyloid found in plaques. These biomarker data suggest that amyloid plaques in the brain may begin to ‘dissolve’ after 12 weeks of treatment with this antibody. We’re now planning a Phase III clinical trial of this drug to be started in 2009.”

**Antidementia Drugs Contribute to Longer Life in People with Alzheimer’s**

Survival (life span) in people with Alzheimer’s is recognized to be shorter than what is expected in cognitively normal seniors and is recognized to be influenced by several factors including age, disease severity, general debility, and gender. Approved antidementia drugs have been shown help with the symptoms of Alzheimer’s but their influence on life span is not known.

At ICAD 2008, Susan Rountree, MD, of the Alzheimer’s Disease and Memory Disorders Center of Baylor College of Medicine in Houston, Texas, reported on a study of the persistent use of antidementia drugs and their influence on survival.

The researchers followed 641 people diagnosed with Alzheimer’s at an academic medical clinic between 1989 and 2005. These individuals had been on drug therapy over the course of their Alzheimer’s for variable amounts of time and the majority had used one or more of the commercially available antidementia drugs (donepezil, galantamine, rivastigmine, tacrine, or memantine).

Total years on medication was divided by the total years of disease symptoms to determine a persistency score for each individual. Participants were divided into four groups (1st, 2nd, 3rd, 4th quartiles) ranging from the lowest to highest persistency scores and the researchers compared life span among the groups after adjustment for a variety of factors generally recognized to influence survival. The 1st quartile took drug less than 33 percent of the time, 2nd quartile = 34-55 percent of the time, 3rd quartile = 56-70 percent of the time, and the 4th quartile = 71-99 percent of the time.

Over the entire course of the study, 12 percent of participants never took any antidementia drugs. Fifty-three (53) percent of the participants died.

The researchers found an inverse and statistically significant relationship between the overall risk of death and the persistency of drug use. Those in the lowest persistency group (1st quartile) were 2.4 times more likely to die than those in the highest persistency group (4th quartile). Those with intermediate drug exposure had increased risk of death of 2.2 times (2nd quartile) and 1.5 times (3rd quartile) compared to the most persistent users. More persistent therapy was associated with a longer median survival time; the median survival between the lowest quartile group and the most persistent users was 3.12 years.
“In our study, people with Alzheimer’s who took antidementia drugs more persistently lived longer than those who took the medications for shorter time intervals,” Rountree said. “In an earlier study involving this group, we reported that persistency of treatment was also associated with long term cognitive and functional benefits. Persistent drug therapy appears to help Alzheimer’s patients live longer and the mechanism may be related to overall improvement of cognition and function resulting from current symptomatic therapies.”

**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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- Jeffrey Cummings. “18-Month data from an open-label extension of a one-year controlled trial of dimebon in patient with mild-to-moderate Alzheimer's disease.” (Funder: Medivation)
- Diamanto Tsakanikas. – “Effects of uninterrupted intravenous immunoglobulin treatment of Alzheimer's disease for 9 months.” (Funder: Baxter International)
- Eric R. Siemers. – “Safety, tolerability and biomarker effects of an Abeta monoclonal antibody administered to patients with Alzheimer's disease.” (Funder: Eli Lilly and Company)
- Susan Rountree. – “Persistent Antidementia Drug Treatment and Survival in an Alzheimer’s Disease Cohort.” (Funders: Forest Research Institute and The Cynthia and George Mitchell Foundation)
18-month data from an open-label extension of a one-year controlled trial of dimebon in patients with mild-to-moderate Alzheimer's disease

Jeffrey Cummings1, Rachelle Doody2, Svetlana Gavrilova3, Mary Sano4, Paul Aisen5, Lynn Seely6, David Hung6
1University of California, Los Angeles Alzheimer's Disease Center, Los Angeles, CA, USA; 2Baylor College of Medicine, Houston, TX, USA; 3Russian Academy of Medical Sciences, Moscow, Russian Federation; 4Mount Sinai Medical Center, New York City, NY, USA; 5University of California, San Diego School of Medicine, San Diego, CA, USA; 6Medivation, Inc., San Francisco, CA, USA.
Contact e-mail: jcummings@mednet.ucla.edu

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Background: Dimebon is a novel small molecule which improved cognition and memory, activities of daily living, and behavior in a one-year placebo-controlled trial of patients with mild-to-moderate Alzheimer's disease (AD).

Objective: This study evaluates the continued effectiveness of Dimebon in an open-label extension for 18 months.

Methods: 183 patients with mild-to-moderate AD were initially randomized into a 6-month placebo-controlled study of Dimebon. Patients completing 6 months of treatment were offered the opportunity to re-consent for an additional 6 months of controlled treatment in their originally randomized group, followed by an open-label extension. Data presented are from observed case analyses of the OLE including only the 104 OLE patients. Projected placebo decline was estimated using simple linear regression on data from weeks 1-52.

Results: 120 patients completed one year of treatment; 104 re-enrolled into the OLE (54 Dimebon, 50 placebo). 92 (88.5%) patients enrolling into OLE completed 6 months of treatment. Patients treated with Dimebon for 18 months continued to show benefit on all endpoints in mean change from baseline over the projected placebo decline of the patients enrolling into the OLE study: ADAS-cog (2.1 vs. 7.6), CIBIC-plus (4.3 vs. 5.1), ADCS-ADL (-3.1 vs. -4.7), NPI (0.72 vs. 3.7), and MMSE (0.0 vs. -2.1). Patients originally randomized to placebo then crossed over to Dimebon treatment for 6 months had stabilization of their previously documented decline on all five endpoints. Patients treated with Dimebon for 18 months continued to show benefit over the group crossed over to Dimebon treatment for 6 months on the ADAS-cog (p = 0.05) and CIBIC-plus (p = 0.02). Dimebon was well-tolerated through 18 months.

Conclusions: Dimebon treatment for 18 months continued to improve the clinical course of patients with AD, with beneficial effect seen in cognition and memory, activities of daily living, and behavior. Patients treated with placebo and then crossed over to Dimebon did not show the same benefit as those patients originally treated with Dimebon suggesting the possibility that Dimebon treatment may result in disease modification. Open-label extensions are not placebo-controlled and extrapolation of the treatment results should be done with caution.
Effects of uninterrupted intravenous immunoglobulin treatment of Alzheimer's disease for 9 months

Diamanto Tsakanikas, Kavita Shah, Carolina Flores, Stephanie Assuras, Norman R. Relkin
Weill Medical College of Cornell University, New York, NY, USA.
Contact e-mail: dit2003@med.cornell.edu

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Background: To examine whether IVIg provides symptomatic improvement to AD patients when treatment is uninterrupted over 9 months. IVIG is currently under investigation as a potential anti-amyloid immunotherapy for AD. In two previous open-label studies, patients with mild-moderate AD improved cognitively when treated with IVIg for 6 months. Although treatment was extended to 18 months in one study, outcome was altered by interruption of IVIg administration between 6 and 9 months for washout studies. We carried out a 6-month Phase II double-blind, placebo-controlled study of IVIg for AD followed by a 12 month rater-blinded extension that did not include any washout period. In this interim analysis, we examine the symptomatic effects of uninterrupted IVIg treatment for 9 months.

Methods: 24 subjects with mild to moderate AD participated. For 6 months, 8 participants received placebo and 16 received IVIg at various doses. After 6 months, all subjects were given IVIg with the raters blinded to dose. The primary outcome measures were the ADAS-Cog and the ADCS-CGIC, which were administered at baseline and three-month intervals thereafter. Both parametric (T-test) and non-parametric (K-W, Median) statistical tests were applied to the data.

Results: At baseline, there were no significant demographic or performance differences between the IVIg and placebo groups. Statistically significant differences favoring IVIg treatment were observed on the CGIC at 3, 6, and 9 months. On the ADAS Cog, change scores numerically favored the IVIg-treatment at 3,6, and 9 months, and the difference reached statistical significance at 3 and 9 months. At 9 months, the IVIg group also improved relative to initially placebo treated patients in activities of daily living. In an analysis by dose arm, subjects receiving 0.4g IVIg /kg/2 weeks improved over baseline on ADAS-Cog scores, global outcome and daily functioning. None of the subjects given placebo showed comparable improvements.

Conclusions: While a past study suggested symptomatic improvement from IVIg peak at 6 months, the present study demonstrates that uninterrupted treatment of AD patients for 9 months can result in further improvements on cognitive and global measures and daily functioning. A large, multicenter clinical trial is now getting underway that will further test whether IVIg provides long-term benefits in AD consistent with a disease-modifying effect.
Safety, tolerability and biomarker effects of an Abeta monoclonal antibody administered to patients with Alzheimer’s disease

Eric R. Siemers1, Stuart Friedrich1, Robert A. Dean1, Gopalan Sethuraman1, Ronald DeMattos1, Danna Jennings2, Gilles Tamagnan2, Kenneth Marek2, John Seibyl2
1Eli Lilly and Company, Indianapolis, IN, USA; 2Molecular NeuroImaging, New Haven, CT.
Contact e-mail: esiemers@lilly.com


Background: Passive immunization with a monoclonal antibody binding the mid-domain of Aβ may slow the progression of Alzheimer’s Disease (AD).

Methods: 52 mild to moderate AD patients and 16 volunteer subjects were studied in a phase II clinical trial. AD patients received 12 weekly infusions of placebo or antibody (100 mg Q 4 weeks, 100 mg Q week, 400 mg Q 4 weeks or 400 mg Q week). Volunteers received a single 100 mg dose of antibody. Safety assessments included magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) examinations. Plasma and CSF Aβ concentrations were measured by ELISA. A sub-study of 24 AD patients and 13 volunteers underwent single photon emission tomography (SPECT) scanning after injection of [123I] 6-iodo-2-(4-dimethylamino-)phenyl-imidazo[1,2-a]pyridine (IMPY) to assess amyloid plaque burden. The primary imaging outcome was the regional IMPY activity compared to cerebellum. Alzheimer’s Disease Assessment Scale - Cognition (ADAS-cog) scores were determined in all patients pre- and post-treatment.

Results: Baseline MMSE score in AD patients was 20.2 + 3.8. MRI and CSF safety assessments were unremarkable throughout the trial. No adverse events appeared related to antibody treatment. Antibody infusion increased total (bound + unbound) plasma Aβ1-40 and Aβ1-42 in a dose-dependent manner. In patients, antibody treatment similarly increased total CSF Aβ1-40 and Aβ1-42. In patients taking 400 mg Q week, antibody treatment decreased unbound CSF Aβ1-40 (p<0.01), but unbound CSF Aβ1-42 was increased in a dose-dependent manner. For patients treated with 400 mg, baseline IMPY cingulate cortex signal correlated with plasma Aβ1-42 concentrations 7 days after the first infusion (r=0.65, p=0.02). Antibody produced no baseline to endpoint change in ADAS-cog or IMPY scans.

Conclusions: Antibody was well tolerated using doses up to 400 mg Q week. The correlation between total plasma Aβ1-42 after treatment and baseline amyloid plaque burden by IMPY, together with the dose-dependent increase in unbound CSF Aβ1-42, suggest that this antibody may mobilize Aβ1-42 in AD plaque, and normalize soluble CSF Aβ1-42 in AD patients.
Persistent antiamnestic drug treatment and survival in an Alzheimer's disease (AD) cohort

Susan Rountree1, Valory Pavlik1, Wenyaw Chan2, Rachelle Doody1
1Baylor College of Medicine, Houston, TX, USA; 2University of Texas School of Public Health, Houston, TX, USA.
Contact e-mail: rountree@bcm.edu

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Background: The current antiamnestic drugs ameliorate symptoms of AD but it is unknown what effect they have on survival.

Methods: 641 AD patients were followed prospectively at an academic center over a 20 year period. Drug exposure (donepezil, galantamine, rivastigmine, tacrine, memantine) was calculated by a persistency index (PI) reflecting total years of drug use/total years with disease symptoms. Time on drug was recorded without regard to whether the patient was on one or more than one drug. Drug use, neuropsychological tests, clinical assessments, and vital status were maintained in an electronic database according to standardized protocols. Patients were followed to death or censoring on December 31, 2005. We used proportional hazards regression to assess the association of greater persistent therapy, coded as quartile of the PI, on all-cause mortality, using the upper quartile as the reference group. Adjustments were made for baseline disease severity categorized by the MMSE score (mild, moderate, severe), age, sex, years of education, duration of symptoms and exposure to antiamnestic drugs prior to the initial visit.

Results: 53% of the cohort died and 47% were censored with a mean follow-up time of 3.0 ± 1.9 years. Male sex (p<.0001), age (p<.0001), moderate vs. mild (p<.01) and severe vs. mild (p<.01) stage disease, drug use before the initial visit (p<.0001) were associated with higher mortality. Patients whose PI fell in the lowest three quartiles had a significantly increased relative risk of death compared to the highest quartile of drug use, with adjustments: HR(1st) = 2.4 (95%CI 1.7-3.5, p<.0001); HR(2nd) = 2.2 (95%CI 1.5-3.2, p<.0001); HR(3rd) = 1.5 (95%CI 1.0-2.2, p<.05). Patients drug naïve at the initial visit (n=368) whose PI was below the median (first two quartiles) had significantly increased relative risk of death compared to those in the upper quartile of drug use, with adjustments: HR(1st) = 2.5 (95%CI 1.4-4.2, p<.01); HR(2nd) = 2.5 (95%CI 1.4-4.5, p<.01); HR(3rd) = 1.4 (95%CI 0.8-2.6, p=0.24).

Conclusions: Greater persistent therapy with antiamnestic drugs was significantly associated with prolonged survival in an AD cohort. Additional studies are needed to confirm these results.