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2012: A Pivotal Year for Alzheimer's Disease Drug Development

Alzheimer's disease (AD) is named after the German physician Alois Alzheimer, who in 1906 discovered amyloid plaques and neurofibrillary tangles in the brain of a 51-year old female patient, Auguste D, who died from severe dementia[1]. After more than a century, the exact causes of AD are not yet understood[2].

According to the Alzheimer's Association, AD is the sixth-leading cause of death in the country and the only cause of death among the top 10 in the United States that cannot be prevented, cured or even slowed. Estimates vary, but experts suggest that as many as 5.4 million Americans may have AD[3].

A fatal form of dementia, AD is a chronic neurogenetic disorder that results in a progressive decline in cognitive functions including memory, judgment, decision-making, orientation to physical surroundings and language[4]. With the increasing life expectancy and the accelerated aging of the population, there is an urgent need to develop treatments for AD.

As of 2010, there are an estimated 36 million people in the world with dementia and this number is expected to increase to 66 million in 2030 and 115 million in 2050[5]. As many as 28 million of the world's 36 million people with dementia have yet to receive a diagnosis, and therefore do not have access to treatment, information, and care.

Most people with dementia will be cared for at home by a family member[6]. Caring for a person with such a disease can cause emotional, psychological and physical problems[7].

Due in part to the high projected cost of the treatment, supportive care, and the emotional stress on families, in 2011 the US Congress passed and President Obama signed the National Alzheimer's Project Act that instructs the US government to develop a strategic plan to slow the progression, delay the onset, and prevent AD by 2025[8].

New federal funding has been committed prior to the completion of the strategic plan. In February 2012, the Obama administration announced it plans to spend an additional $50 million this year and will seek an extra $80 million in fiscal 2013 to bolster research for AD[9]. An additional $26 million will be allocated to goals outside pure research, including public awareness and support for caregivers. The National Alzheimer's Project Act also established an Advisory Council on AD research, which brings together some of the foremost experts in the field. The next meeting for the Advisory Council is scheduled for April 17, 2012, and the plan is expected to be completed in 2012.

Beyond the government initiatives, 2012 represents a pivotal year for AD drug development, especially in view of expected results from ongoing Phase 3 trials. Accordingly, the purpose of this report is to provide an overview of products in clinical trials and the companies developing novel therapies for AD.

Approved Therapies

Current treatment options are limited to drugs that treat the symptoms and do not slow or reverse the progression of the disease. The neuropathology of AD is characterized by early loss of basal forebrain cholinergic

neurons, leading to decreased cholinergic transmission[10]. These symptoms can be improved with acetyl-cholinesterase inhibitors (AChEI). Approved products include donepezil, rivastigmine, galantamine, and huperzine-A[11]. Apart from these approved agents, there has been little development of cholinergic drugs. One exception is Posiphen®, which has been demonstrated to be an ineffective AChEI, but is being developed for its ability to substantially decrease production of the amyloid precursor protein (APP) and tau[12].

The United States Food and Drug Administration (FDA) has not approved any new drugs for the treatment of AD since Forest Laboratories' Namenda® (memantine hydrochloride), an N-methyl D-aspartate (NMDA) antagonist, in 2003. In 2011, the FDA approved a new formulation of Eisai Inc.'s (ESALY.PK) Aricept® (donepezil hydrochloride), a 23mg continuous release pill.

Investigative Approaches

In recent years there have been a number of product candidates that have advanced into randomized controlled trials that have not demonstrated efficacy in treating AD. While research efforts have not yet determined the cause of AD, the field is moving toward treatment of the disease in earlier stages. This is due to the fact that studies are demonstrating that the disease begins long before the symptoms develop. The field is also moving toward combination treatments.

Aside from agents that treat AD symptoms, drugs in development to slow or reverse the progression of AD are mainly addressing one of two controversial hypotheses, amyloid or tau, and can be divided into five major categories with distinct mechanisms of action*:

1. Drugs to reduce beta-amyloid (known as β-amyloid, Abeta, or Aβ) production, notably secretase inhibitors,
2. Drugs to reduce beta-amyloid plaque burden via inhibition of aggregation or disruption of aggregates,
3. Drugs to promote beta-amyloid clearance via active or passive immunotherapy,
4. Drugs to prevent tau protein phosphorylation or aggregation, and
5. Others

The first three categories are driven by the "amyloid hypothesis," which has been the dominant focus of research and development for the treatment of AD for nearly thirty years[13]. The hypothesis is based on the belief that there is a fault with the processing of APP in the brain that leads to the production of a short fragment of APP known as beta-amyloid, which mainly consists of two peptides - one that is 40 amino acid units long (Ab40) and one 42 units long (Ab42)[14]. Accumulation of this sticky protein fragment in the brain triggers the disruption and destruction of nerve cells that causes AD.

The accumulated clumps of beta amyloid are known as amyloid plaques. The hypothesis is thus that there is a fault with the over production of beta amyloid or with the mechanism that usually clears it from the brain, or possibly both[15].

While the chain of events that leads to the development of AD is still unclear, the accumulation of beta-amyloid and the resulting formation of amyloid plaques are considered hallmarks of the disease pathology. The majority of product candidates that have advanced into randomized controlled trials for AD target beta-amyloid, which represents a major focus of this report.

In view of the fact that the amyloid hypothesis represents the dominant focus of research and development in AD, the majority of product candidate failures have also been in this area. These include Myriad Genetics, Inc.'s (MYGN) Flurizan® (r-flurbiprofen) , Eli Lilly & Co.'s (LLY) semagacestat (LY450139), Neurochem Inc.'s tramiprosate (Alzhemed™), Elan Corporation, plc's (ELN) ELND006 and AN1792, Pfizer Inc.'s (PFE) ponezumab and PF-04494700, and others. However, there are many different approaches for targeting beta-amyloid and the hypothesis hasn't been discounted as of yet.

In fact, recent results of a study by researchers from Case Western Reserve University demonstrated that an oncology drug bexarotene (Targretin® by Eisai Inc.) reduced beta-amyloid plaques in the brain of mice suffering from an AD-like condition[16]. Bexarotene activates retinoid receptors on brain cells that increase production of a fat-protein complex, apolipoprotein E that helps rid excess amyloid in the fluid-filled space between neurons. It also appears to enhance another cleanup process, called phagocytosis. Bexarotene is used to treat cutaneous T-cell lymphoma, or CTCL, a type of skin cancer.

* Adapted from Lancet Neurol. 2010 Jul;9(7):702-16.

> **"This is the first time clinical results of a beta-secretase inhibitor have been reported at a large scientific conference in the U.S."**

According to results of the study, after fourteen days of treatment with bexarotene, beta-amyloid plaque levels decreased by 75%. In the study, the mice treated with bexarotene showed an improvement in their behavior based on several different behavioral and cognitive tests such as ability to make nests for sleeping and sense of smell. The results of this animal study lend further support to and provides clear direction for continued testing of the amyloid hypothesis as a way to address this devastating illness.

1) Drugs to reduce beta-amyloid production

Beta-secretase inhibitors

Beta-secretase (β-secretase) is an enzyme in the central nervous system (CNS) critically involved in the pathogenesis of AD[17]. This enzyme is responsible for the cleavage of APP and the associated creation of beta-amyloid, a neurotoxic peptide believed to be causally linked to AD[18]. Inhibition of beta-secretase is therefore an appropriate therapeutic strategy for treating this disease[19].

Based in Oklahoma City, privately-held biotech company CoMentis, Inc. presented human data of the company's beta-secretase inhibitor CTS-21166 at the 2011 Alzheimer's Association International Conference (AAIC). In a first proof-of-concept human study, the compound appeared safe and reduced plasma beta-amyloid levels substantially for an extended period of time.

When intraperitioneally (i.p.) injected (4 mg/kg over six weeks) into an aggressive APP transgenic mouse (expressing both the Swedish and missense London mutations), CTS-21166 reduced brain beta-amyloid levels by over 35% and plaque load by 40%. The data from human Phase 1 studies suggested that this compound was safe at doses as high as 225mg and when intravenously (i.v.) injected into AD patients, it caused a dose-dependent reduction of plasma beta-amyloid levels for an extended period of time. This is the first time clinical results of a beta-secretase inhibitor have been reported at a large scientific conference in the U.S.

More thorough clinical evaluation of CTS-21166 is underway by CoMentis in a partnership with Astellas Pharma, Inc. (ALPMY.PK) in Japan. In 2008, CoMentis entered into an exclusive worldwide collaboration agreement worth more than $760 million with Astellas Pharma to develop and commercialize products from CoMentis' beta-secretase inhibitor program, including CTS-21166. CoMentis received an upfront payment of $80 million and an equity investment of $20 million. CoMentis has the opportunity to receive up to $660 million in development milestones and may also receive performance-based commercialization milestones. In addition, CoMentis has the right to receive development milestones for next- generation beta-secretase inhibitors discovered under the terms of the research collaboration. Astellas will fund 100% of the pre-Phase 3 global development costs and CoMentis will share the Phase 3 development costs. Astellas has exclusive worldwide commercialization rights while CoMentis retains the right to co-promote in the U.S., where profit will be shared. CoMentis will receive royalties on sales outside the U.S.

Other beta-secretase inhibitors are in development and more clinical data will likely be available for these agents in the near future. For example, at the JP Morgan Healthcare Conference in January 2012, Merck & Co. Inc. (MRK) announced data for the first time of its lead beta-amyloid cleaving enzyme-1 (BACE1) inhibitor, MK-8931. In a once-daily oral, single and multi-dose Phase 1 clinical trial in healthy volunteers, MK-8931 reduced the cerebral spinal fluid (CSF) amyloid-beta-peptide by greater than 90% in healthy volunteers without observing dose limiting side effects in this study. Merck expects to initiate Phase 2 studies in patients with AD in 2012.

Results from a Phase 1 trial of Eli Lilly's orally available non-peptidic BACE1 inhibitor called LY2811376 demonstrated that the agent lowered the levels of beta-amyloid in blood plasma and cerebrospinal fluid. The inhibitor proved more successful than other current drugs at lowering amyloid-beta levels in healthy volunteers[20].

Takeda Pharmaceutical Company Limited (TKPHF.PK) has also discovered a non-peptidic compound, TAK-070, that inhibits BACE1 in a noncompetitive manner. TAK-070 binds to full-length BACE1, but not to truncated BACE1 lacking the transmembrane domain. In preclinical studies, short-term oral administration of TAK-070 decreased the brain levels of soluble beta-amyloid and normalized the behavioral impairments in cognitive tests in Tg2576 mice, an APP transgenic mouse model of AD[21]. Six-month chronic treatment decreased cerebral beta-amyloid deposition by approximately 60%, preserving the pharmacological efficacy on soluble beta-amyloid. These results support the feasibility of BACE1 inhibition with TAK-070 and clinical trials are ongoing.

AC Immune SA is a Swiss-based biopharmaceutical company developing innovative therapeutics with "best in class" potential against AD along three axes: vaccines, antibodies and small molecules. The company's most clinically advanced agent is an oral small molecule ACI-91 that acts indirectly on beta-secretase in a Phase 2 multi-center double blind, placebo controlled trial for the treatment of mild to moderate AD. The study will evaluate the compound's safety, tolerability and efficacy of twelve months of treatment. ACI-91 has the potential to prevent or slow down AD by a dual mechanism of neuroprotection and plaque reduction correlated with an inhibition of beta-secretase. ACI-91 was in-licensed from an unnamed company, which has gained approval in a different indication. According to the company, the compound has an outstanding safety profile due to its long history of safe use in people. ACI-91 entered Phase 2 clinical studies in 2008, which are currently ongoing.

Gamma-secretase inhibitors and modulators

Formation of beta-amyloid is catalyzed by gamma secretase (γ-secretase), a protease with numerous substrates[22]. Accordingly, gamma-secretase inhibitors are designed for selective inhibition of beta-amyloid synthesis.

In August 2010, Eli Lilly & Company (LLY) announced that the company would halt development of semagacestat, a gamma-secretase inhibitor, when preliminary results from two ongoing long-term Phase 3 studies showed it did not slow disease progression and was associated with worsening of clinical measures of cognition and the ability to perform activities of daily living.

During the plenary session at the 2011 AAIC, Eli Lilly presented data from a thirty-two week follow-up period after dosing with semagacestat was halted. The preliminary results of the two Phase 3 trials that resulted in discontinuation of the dosing demonstrated semagacestat did not slow the progression of the disease and was associated with worsening of clinical measures of cognition and the ability to perform activities of daily living. However, by these same measures, patients treated with semagacestat worsened to a statistically significantly greater degree than those treated with placebo. In addition, data showed semagacestat is associated with an increased risk of skin cancer compared with those who received placebo.

The unfavorable results of semagacestat raise questions about other drugs in the same class under development. Myriad Genetics, Inc.'s (MYGN) Flurizan® (r-flurbiprofen) was the first gamma-secretase that was stopped in Phase 3 clinical trials. Other gamma secretase programs currently in clinical development include Bristol-Myers Squib's (BMY) avagacestat (BMS-708163), Merck's (MRK) MK-0752, and EnVivo Pharmaceuticals' EVP-0962, a small molecule selective gamma secretase modulator (GSM).

EVP-0962 was designed to target certain gamma secretase functions and does not inhibit the enzyme all together. EVP-0962 selectively inhibits the production of the toxic aggregated amyloid Ab42 peptide without affecting the total amount of beta-amyloid. EVP-0962 is a selective GSM and does not inhibit other gamma secretase substrates required for normal function (such as Notch). EVP-0962 has the potential to demonstrate comparable efficacy to gamma secretase inhibitors, but with a more attractive safety profile.

Gamma-secretase provides additional functions, besides contributing to the buildup of amyloid plaques in the brain, which may explain some of the side effects experienced with semagacestat. The enzyme is critical for the processing of Notch, a protein that controls cell differentiation and communication. In a one-year preclinical study in transgenic Alzheimer's models presented at the Alzheimer's Association 2010 International Conference on Alzheimer's' Disease (ICAD), EVP-0962 reduced Ab42 peptide levels, decreased amyloid plaque build up, reversed behavioral deficits and reduced brain inflammation associated with Alzheimer's disease. In animal trials, EVP-0962 appeared to have a better safety profile than other gamma secretase inhibitors. In June 2011, EnVivo Pharmaceuticals initiated a Phase 1 trial to study multiple doses of EVP-0962 in healthy volunteers to determine the safety profile. The trial is a double-blind, ascending single and multiple dose study designed to assess the safety, tolerability, pharmacokinetics, pharmacodynamics and food effect of EVP-0962.

In July 2011, Bristol-Myers Squibb Company (BMY) announced the results of a Phase 2 study evaluating the safety and tolerability of the investigational oral gamma secretase inhibitor avagacestat (BMS-708163) in patients with mild-to-moderate AD. The randomized, double-blind, placebo-controlled study demonstrated that avagacestat doses below 100 mg/day provide a potential therapeutic window for further evaluation in Phase 3 registrational studies. The Phase 2 study results were presented at the 2011 AAIC.

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People with mild cognitive impairment (MCI) usually have impaired memory or show impairment in other areas of their brain function, such as planning things or paying attention, but do not have significant problems in everyday living. A sub-group of people with MCI may have what is now known as prodromal Alzheimer's disease (prodromal AD). Bristol Myers is also conducting a Phase 2 study of avagacestat for the treatment of patients with prodromal AD.

Merck's (MRK) gamma-secretase inhibitor MK-0752 was initially aimed at treating AD, but in early studies the drug demonstrated a significant reduction in stem cells in tumors[23] and is currently being studied for the treatment of breast and pancreatic cancer.

2) Drugs to prevent beta-amyloid aggregation

A loss of metal homeostasis is also an important event in AD and metal dyshomeostasis may contribute to development of beta-amyloid, tau and oxidative stress biology of AD[24].

Prana Biotechnology Ltd. (PRAN) is developing PBT2, a second-generation oral inhibitor of metal-induced beta-amyloid aggregation. Unlike other approaches to the treatment of AD, PBT2 targets one of the initial disease progression steps, which is the interaction with metals in the brain that result in beta-amyloid becoming toxic. With age, tight controls on metal distribution and homeostasis fatigue enabling beta-amyloid oligomers to form in synapses impairing neuronal transmission. Published preclinical data demonstrates that PBT2 prevents the interaction of synaptic zinc and copper with beta-amyloid to prevent it from becoming toxic.

PBT2 has been shown to redistribute metals that were previously trapped in the brain by beta-amyloid deposits , thus restoring neuronal function[25]. The compound uniquely addresses a mechanism of beta-amyloid deposition involving the sequestration of metals that are essential for neural health. One of the functions of APP ensures that iron is able to move out of neurons.

In a double blind multi-center Phase 2a clinical trial, 78 patients in Sweden and Australia were randomized to receive either a placebo, PBT2 50mg or PBT2 250mg capsule once per day for 12 weeks[26]. Analysis of the trial data demonstrated that the safety and tolerability profile of PBT2 at both doses was indistinguishable from that of placebo. There were no study withdrawals related to adverse events. There was no serious adverse event (SAE) in any PBT2 treated patient. The study demonstrated the impact of PBT2 on reducing Ab42 in the cerebrospinal fluid (CSF) that surrounds the brain and spinal cord. PBT2 at the 250mg dose showed a highly significant reduction in CSF Ab42 compared to placebo ($p=0.006$). The effect of PBT2 was dose related.

Encouraging signs of cognitive improvement, as measured by the Neuropsychological Test Battery (NTB), were also observed[27]. Statistically significant improvement was evident in two of the four Executive Function NTB tests: the Category Fluency Test ($p=0.028$) and the Trail Making Test part B ($p=0.005$), both after 12 weeks of treatment at the 250mg dose compared to placebo. The NTB is a test of cognition that is more sensitive to the changes in executive function that are seen in the early stage of AD.

In March 2012, Prana Biotechnology dosed its first patient in its twelve month Phase 2 double blind , placebo controlled trial imaging trial testing PBT2 (IMAGINE trial) . The trial is being conducted in 40 patients with prodromal or mild AD to assess the effects of PBT2 on the distribution of amyloid in the brain and cognitive function improvement.

Elan Corporation, plc (ELN) is developing ELND005 (scyllo-inositol), an oral small molecule beta-amyloid anti-aggregation agent for AD. ELN005 is specifically designed to target the abnormal forms of beta-amyloid. In preclinical studies, ELND005 has been shown to stop and/or reverse the progression of AD pathologies and symptoms by neutralizing beta-amyloid oligomers, inhibiting toxic effects of beta-amyloid oligomers on neuron-to-neuron communication, preventing the formation of beta-amyloid fibrils, and breaking down existing fibrils. The studies demonstrate that ELND005 reduces beta-amyloid burden, neuro-inflammation and vascular amyloid loads

In August 2010, top line results of a Phase 2 clinical study (study AD201) were announced. Study AD201 was a Phase 2 placebo controlled study in 351 patients with mild to moderate AD who received study drug (250mg twice daily; 1,000mg twice daily; 2,000mg twice daily; or placebo) for up to 18 months. The two higher dose groups were discontinued in December 2009.

The study did not achieve significance on co-primary outcome measures NTB and Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL), which measures the ability to independently perform daily activities such as eating, bathing, and using the telephone. The 250mg twice daily dose demonstrated

a biological effect on beta-amyloid protein in the CSF, in a subgroup of patients who provided CSF samples. This dose achieved targeted drug levels in the CSF previously associated with therapeutic effects in animal models, and showed some effects on clinical endpoints in an exploratory analysis.

After reviewing the final safety data with the study's Independent Safety Monitoring Committee, it was concluded that the 250mg twice daily dose has acceptable safety and tolerability. FDA has granted Fast Track Designation of ELND005 for the treatment of AD.

In September 2006, Elan and Transition Therapeutics Inc. (TTHI) entered into an exclusive, worldwide collaboration agreement for the joint development and commercialization of Transition's ELND005 product candidate. In December 2010, Elan modified its Collaboration Agreement with Transition Therapeutics for the development and commercialization of ELND005. As a consequence of Transition's decision to exercise its opt-out right, Transition is not funding any continuing development or commercialization of ELND005 and has also relinquished its 30% ownership of ELND005 to Elan. Elan has until December 2012 to advance the asset in clinical trials or Elan must terminate the collaboration agreement, unless Elan plays Transition Therapeutics $11 million by January 31, 2013.

Under the modified agreement, Elan paid Transition $9.0 million in January 2011. Consistent with the terms of the original agreement, following its opt-out decision, Transition will be entitled to receive milestone payments of up to $93.0 million (in addition to the $11.0 million described above), along with tiered royalty payments on net sales of ELND005 ranging in percentage from a high single digit to the mid teens, depending on the level of sales.

In March 2012 at the 27th Conference of Alzheimer's Disease International (ADI), Elan presented data from a post hoc analyses of the AD201 study, which randomized 353 patients with mild to moderate AD to placebo. In mild AD, ELND005 decreased the emergence of new neuropsychiatric symptoms driven by depression and anxiety, and to a lesser degree by apathy and appetite.

3) Drugs to promote beta-amyloid clearance

Passive immunotherapy

Another approach under development for the treatment of AD is to reduce the build up of amyloid plaque using monoclonal antibodies, also known as passive immunotherapy. In 2012, clinical trial results from two late stage monoclonal antibodies for the treatment of mild to moderate AD are expected: Eli Lilly's solanezumab and Janssen Alzheimer Immunotherapy Research & Development, LLC's (JAIRD) bapineuzumab. JAIRD is a subsidiary of Johnson & Johnson (JNJ). Results of the Phase 3 trials for solanezumab and bapineuzumab are expected in the second quarter and third quarter of 2012, respectively.

Solanezumab (LY2062430), is a humanized monoclonal antibody that recognizes the middle region of beta-amyloid and binds soluble forms of the peptide. The drug is being developed by Eli Lilly, which currently holds a license to the PDL BioPharma Queen et al patents with respect to solanezumab.

Bapineuzumab, a humanized monoclonal antibody against the N-terminus of beta-amyloid, is designed to bind and remove the beta-amyloid peptide that accumulates in the brain. It was originally developed at Elan. In September 2009, JAIRD acquired substantially all of the assets and rights of Elan related to its Alzheimer's Immunotherapy Program (AIP), including bapineuzumab. Elan holds a 49.9% equity interest in JAIRD, and will be entitled to a 49.9% share of the profits and certain royalty payments upon the commercialization of AIP products. Perhaps signaling renewed investor optimism for bapineuzumab, Elan's stock price recently traded at its highest level since mid-2008.

JAIRD is continuing the AIP activities with Pfizer, Inc. (PFE), which acquired Wyeth in 2009, to research, develop and commercialize selective products for the treatment and/or prevention of neurodegenerative conditions, including AD. The program includes multiple compounds being evaluated for slowing the progression of AD including the lead compound bapineuzumab and a potentially superior active immunotherapy product candidate (ACC-001).

Comparing and contrasting the two monoclonal antibodies, bapineuzumab binds to aggregated beta-amyloid, which is found primarily in the brain, while solanezumab binds to monomeric beta-amyloid, found throughout the body. Solanezumab differs from bapineuzumab in several ways[28]:

- it recognizes a distinct epitope in the central portion of the peptide;
- whereas bapineuzumab binds amyloid plaques more strongly than soluble beta-amyloid,

solanezumab selectively binds to soluble beta-amyloid with little to no affinity for the fibrillar form; and

- it seems that solanezumab presents less CNS adverse events than bapineuzumab.

Eli Lilly is conducting two separate but identical multi-center, randomized, double-blind, placebo-controlled Phase 3 clinical trials of solanezumab as a potential treatment to delay the progression of mild to moderate AD. The trials, called EXPEDITION and EXPEDITION2, each include a treatment period that lasts 18 months and are expected to enroll a total of 2,000 patients age 55 and older from 16 countries.

Patients enrolled in the trials are randomized in a 1:1 ratio (500 patients in each trial arm) to receive intravenous infusions of either placebo or 400 mg of solanezumab once every four weeks. Patients who are taking currently available symptomatic treatments for AD can continue treatment during their participation in the EXPEDITION trials. The primary objective of both trials is to test whether solanezumab will slow the cognitive and functional decline of AD patients as compared with placebo. These outcomes will be analyzed using measures of the Alzheimer's Disease Assessment Scale-Cognitive subscore [ADAS-COG], which measures cognitive function with an emphasis on memory, and the Alzheimer's Disease Cooperative Study - Activities of Daily Living scale (ADCS-ADL). Secondary objectives of the trials include different clinical benefits as measured by several brain-scanning and biochemical biomarkers and ratings scales, and quality of life impact.

Eli Lilly has indicated that so far no more than 1% of patients treated with solanezumab have developed vasogenic edema in Phase 2 and Phase 3 trials, about the same rate seen in baseline brain scans. The difference in vasogenic edema rates between bapineuzumab and solanezumab could be a consequence of the different mechanisms of action. Vasogenic edema is thought to arise from the accumulation of monoclonal antibody-antigen complexes in the brain vasculature.

In a January 31, 2012 conference call, Eli Lilly announced that EXPEDITION and EXPEDITION2 trials of solanezumab would continue as planned, based on a data-monitoring committee assessment of safety and futility data.

Bapineuzumab is the subject of two ongoing Phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety trials in patients with mild to moderate AD. One of the trials is in patients who are Apolipoprotein E4 (ApoE4) carriers (NCT00575055) and the second trial is in patients who are ApoE4 non-carriers (NCT00574132). In both trials, the primary outcome measures are cognitive and functional and the secondary outcome measures are cognitive and global. Both the primary and secondary outcome measures are evaluated at 18-months.

In the ApoE4 carrier trial, patients received either of bapineuzumab or placebo, given by infusion every 13 weeks for a total of 6 infusions. This Phase 3 trial included approximately 1,000 patients and each patient was followed for 18 months. The Phase 3 ApoE4 carrier trial of bapineuzumab was completed in 2010 and results have not been reported.

In the ApoE4 non-carriers trial, patients will receive one of two different doses of bapineuzumab or placebo, given by infusion every 13 weeks for a total of 6 infusions. This Phase 3 trial will include approximately 1,300 patients and each patient will be followed for 18 months.

In the Phase 2 trial bapineuzumab in mild to moderate AD did not meet its primary efficacy endpoint. Additional data from the trial indicate possible benefits with the drug, particularly among ApoE4 non-carriers[29].

Among the ApoE4 non-carriers, the exploratory analysis demonstrated a significant difference between bapineuzumab and placebo in ADAS-Cog scores (P=.026), NTB scores (p=.006), MMSE scores (p=.043), and CDR-SB scores (p=.04), all of which favored active treatment. There were no significant differences between active and placebo treatment among the carriers of ApoE4.

It has been suggested that bapineuzumab may be safer than originally thought. Published data demonstrated that a brain swelling condition called vasogenic edema, now called ARIA-E or Amyloid Related Imaging Abnormalities with Parenchymal Edema, may decrease over time[30].

Data presented at the 2010 AAIC indicated that bapineuzumab lowers the levels of tau, a protein which aggregates inside the brain cells of people with Alzheimer's forming neurofibrillary tangles. A more recent study also supports the finding that bapineuzumab results in decreases in CSF total-tau and phosphorylated-tau, which may indicate downstream effects on the degenerative process[31].

> **"If the results from the Phase 3 trial of bapineuzumab are positive, it is reasonable to expect that JAIRD would continue the clinical development of ACC-001..."**

While less clinically advanced than solanezumab and bapineuzumab, Roche Holding AG (RHHBY.PK) is developing a monoclonal antibody, gantenerumab (RO4909832), for the treatment of early stages of AD. Gantenerumab is a fully human anti-beta-amyloid antibody that has a high capacity to specifically bind to cerebral amyloid plaques. In October 2011, the first clinical data regarding gantenerumab were published[32]. Results from Phase 1 clinical trials and *ex vivo* studies demonstrated that gantenerumab treatment results in a dose-dependent reduction of brain amyloid, possibly through phagocytosis via brain microglial cells, whereas amyloid load increased in patients receiving placebo treatment.

Roche's "Scarlet Road" study is currently recruiting 360 patients in 15 countries to investigate the efficacy and safety of gantenerumab in patients in the early or prodromal stage of AD. The Phase 2 study is a multi-center, randomized, double-blind, placebo-controlled, parallel-group two year study to evaluate the effect of subcutaneous gantenerumab on cognition and function in prodromal AD. The study will look at the effects that gantenerumab has on participants' ability to remember information, to solve problems and to go about day-to-day activities.

In 2006, AC Immune SA licensed its anti-beta-amyloid antibody crenezumab (MABT5102A) to Genentech, a member of the Roche Group. The agreement provides AC Immune with potential revenues of more than $300 million in payments upon successful completion of clinical and regulatory milestones in AD and additional applications plus royalties upon commercialization. Genentech has full ownership and global responsibility for clinical development, manufacturing and commercialization of the antibody, including all regulatory activities. AC Immune received an upfront payment, a milestone payment when the first patient was dosed under the Phase 1 clinical trial, and another payment upon the start of the Phase 2 trial.

Roche's second anti-beta amyloid antibody in clinical development, crenezumab, is a fully humanized IgG4 monoclonal antibody to beta-amyloid that binds both monomeric and oligomeric forms of beta-amyloid, inhibits beta-amyloid aggregation and promotes beta-amyloid disaggregation. Crenezumab in a Phase 2 randomized, double-blind, parallel group, placebo controlled study clinical trail in mild to moderate AD.

In the Phase 1 trial that concluded in 2010, crenezumab demonstrated encouraging safety data in patients with mild to moderate AD, with no signs of vasogenic edema in any of the subjects. Dose proportional pharmacokinetics were observed following both single and multiple doses. The plasma beta-amyloid levels correlated with serum crenezumab concentration. The ongoing Phase 2 trial will enroll more than 370 patients in multiple centers globally. The primary outcome measures cognitive and global function.

Another passive immunotherapy in a Phase 3 clinical trial is Baxter International Inc.'s (BAX) Gammagard Liquid [Immune Globulin Infusion (Human)] 10%. Gammagard Liquid is indicated as replacement therapy for primary humoral immunodeficiency in adult and pediatric patients two years of age or older. The company plans to initiate a second, confirmatory Phase 3 trial in the first quarter of 2012, having satisfactorily completed a futility analysis in its first Phase 3 trial. The patient enrollment in the first Phase 3 was completed in June 2011. The primary endpoint of the Phase 3 studies are to evaluate the effectiveness of Gammagard Liquid on preserving cognitive performance and functional activities in patients with mild to moderate AD, as compared to standard of care, over an 18-month period.

Gammagard Liquid is made from human plasma that is donated by healthy people. The product contains naturally occurring antibodies that directly bind to different forms of beta-amyloid protein, including oligomers and fibrils. In a 24 patient Phase 2 study in mild to moderate AD treated for 18 months, Gammagard Liquid demonstrated better cognitive function and less brain enlargement than those given a placebo.

Patients with mild to moderate AD who received the intravenous medication in a Phase 2 study averaged about 1.36 points higher than patients who initially received a placebo on a standard test of mental abilities (Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change). On a second cognitive performance test, patients who received Gammagard Liquid declined by about 9.15 fewer points than placebo patients. MRI analyses also showed patients treated with Gammagard Liquid saw a 6.7 percent decrease in annual ventricular enlargement in their brains, compared to a 12.3 percent rate in patients on a placebo.

Active immunotherapy

Currently, at least five active immunotherapies are in development to slow or reverse the progression of AD by inhibiting generation of toxic beta-amyloid and removing soluble and aggregated beta-amyloid.

"The second target that is being pursued in the research and development to slow or reverse the progression of AD is tau."

Beyond bapineuzumab, JAIRD is developing ACC-001, a second-generation beta-amyloid vaccine intended to induce a highly specific antibody response by the patient's immune system to beta-amyloid. ACC-001, is an Aβ(1-6) attached to a carrier protein, using Agenus Inc.'s (AGEN) surface-active saponin adjuvant QS-21. ACC-001, an amino-terminal immunoconjugate, was shown to be safe in a phase 1 study and is currently being evaluated in Phase 2 clinical studies by JAIRD. ACC-001 has also been granted fast track designation by the FDA.

If the results from the Phase 3 trial of bapineuzumab are positive, it is reasonable to expect that JAIRD would continue the clinical development of ACC-001 due to its potential advantages over bapineuzumab. For example, ACC-001 would require less frequent injections and follow-up visits. Further, the addition of the QS-21 adjuvant to the vaccine has the potential to enhance the immune response - both B-cell and T-cell responses.

Another beta-amyloid vaccine in Phase 2 clinical trials is CAD106, which is being evaluated in elderly patients with mild AD. In 2001, Cytos Biotechnology AG (CYTN.SW) announced the development of CAD106 in collaboration with Novartis Pharma AG (NVS). CAD106 is an immunotherapeutic product in development for the treatment of AD that is designed to induce antibodies against the beta-amyloid protein. CAD106 consists of two components, the Immunodrug™ carrier Qb coupled with a fragment of the beta-amyloid protein. In animal studies it has been shown that treatment with CAD106 can block the formation of beta-amyloid plaques in the brain.

The first Phase 2 trial is designed to be a randomized, double blind, placebo-controlled, parallel group study. The phase 2 trial is to evaluate the safety and tolerability of CAD106 when administered as repeated subcutaneous injections in subjects with mild AD. The second study for the evaluation of CAD106 is also in its Phase 2. This study is designed to be a non-randomized, open label, double blind, placebo controlled, single group assignment. The study is to evaluate the safety and tolerability of CAD106 in patients with AD.

In 2003, Novartis executed a commercial license for Cytos' Immunodrug™ against AD. Terms include an upfront payment, annual license fees and a milestone payment to Cytos. In 2004, Cytos entered into a supply and amendment agreement with Novartis. Under the terms of the agreement, Cytos will provide Novartis with GMP-grade drug substance for the Immunodrug™ candidate CAD106 against AD for early clinical development studies. In return, Cytos will receive supply fees and has the potential to earn additional revenues under the supply and amendment agreement with Novartis.

Affiris AG is a Vienna-based biotechnology company using its patented AFFITOME® technology to tailor vaccines to develop peptide-based targeting to AD, Parkinson's disease, atherosclerosis, high blood pressure and other diseases with unmet medical needs.

In 2008, GlaxoSmithKline plc (GSK) obtained exclusive rights from Affiris for various AD vaccines in clinical development. Affiris' technology is being combined with GlaxoSmithKline's expertise in innovative adjuvant systems to improve the chance of success in the discovery of new treatments against AD. The agreement was valued at approximately $553 million.

Based on interim analyses of the secondary endpoints, Affiris decided to focus first on AFFITOPE® AD02 and started a Phase 2 study in late 2010. This multi-center, European project recruits 420 patients with early AD, who will be vaccinated repeatedly. The clinical activity of AFFITOPE® AD02 will be assessed on efficacy parameters suggested by the regulatory authority over a period of 12 months.

Aside from the company's license agreement with Genentech/Roche for crenezumab, AC Immune SA is developing ACI-24, an active oligo-specific amyloid vaccine stimulating the patient's immune system to produce beta-sheet conformation-specific antibodies that prevent plaque deposition or enhance clearance of plaques. The vaccine is designed to break immune tolerance. During preclinical development, ACI-24 has shown high efficacy *in vivo* by memory restoration and plaque reduction. The vaccine is also characterized by a very high specificity due to generating a conformation-specific antibody response. The favorable safety profile of ACI-24 is underlined through the absence of local inflammation in relevant models as well as its T-cell independent mechanism shown in preclinical development.

United Biomedical, Inc. is developing UB-311, a novel immunotherapeutic for the treatment of AD. The UBI vaccine employs the company's UBITh helper T cell technology and a particular site-specific epitope to target the amyloid-beta peptide. UB-311 has successfully completed clinical Phase 1 study, demonstrating safety

and tolerability. UBI is initiating a Phase 2 study in early 2012.

4) Drugs to prevent tau protein phosphorylation or aggregation

The second target that is being pursued in the research and development to slow or reverse the progression of AD is *tau*. In addition to the beta-amyloid plaques found in the brains of AD patients, "tangles" or clumps of an abnormal form of the protein tau are present. Tau is a ubiquitous protein that clearly binds to and stabilizes microtubules. Hyperphosphorylation of tau disrupts its normal function in regulating axonal transport and leads to the accumulation of neurofibrillary tangles and toxic species of soluble tau. The phosphorylation state of tau played a critical role in mediating tau mislocalization and subsequent impairment of synaptic communication. Furthermore, degradation of hyperphosphorylated tau by the proteasome is inhibited by the actions of beta-amyloid.

Beta-amyloid interacts with the signaling pathways that regulate the phosphorylation of the microtubule-associated protein tau. These two proteins and their associated signaling pathways therefore represent important therapeutic targets for AD.

Published findings suggest how tau disrupts neuronal communication at the synapses. Researchers found that early accumulation of hyperphosphorylated tau in dendrites and dendritic spines, the site where there is a synapse between two neurons, disrupted communication coming in from other neurons[33].

Several life science companies are developing compounds that target tau, including Allon Therapeutics (NPC.TO), Noscira, and TauRx Pharmaceuticals.

Allon Therapeutics has an ongoing Phase 2a clinical trial for davunetide, a peptide derived from a naturally occurring neuroprotective brain protein, activity dependent neuroprotective protein (ADNP). Davunetide has demonstrated activity in preclinical models of tauopathies. Although MCI can present with a variety of symptoms, when memory loss is the predominant symptom it is termed "amnestic MCI" and is frequently a prodromal state of AD[34]. Davunetide has shown statistically significant efficacy in amnestic MCI.

The Phase 2 trial was a double-blind, randomized, placebo-controlled, multiple-dose study to evaluate the safety, tolerability and effect on cognitive function of davunetide after 12 weeks of intranasal administration in patients with amnestic MCI.

The trial was conducted at 15 sites in the United States in 144 patients aged 55 to 85 years old and evenly divided between genders. Three groups of patients received either placebo, low dose of davunetide (5 mg, once a day) or high dose (15 mg, twice a day) intranasally for 12 weeks. The safety results of this study indicate that davunetide was generally well tolerated. The rate of adverse events was equally distributed between the placebo and treated groups.

A significant, dose-dependent and durable improvement was seen in two tests that measure short-term recall and working memory — delayed-match-to-sample (DMTS) and digit span. The DMTS task is a test of simultaneous and delayed sample matching assessing both visual matching ability and delayed visual recognition memory. The high dose (15 mg twice daily) group showed a significant 62.4% improvement from baseline ($p=0.038$, versus placebo) in the DMTS 12-second delay test by the end of the trial. The effects of davunetide on DMTS performance were selective and dose-dependent.

Digit span is a sensitive test of working memory, which is necessary for holding and manipulating information. A significant improvement on the digit span test is consistent with a clinically meaningful impact in AD. At both 4-weeks and 16-weeks the high dose resulted in a 11.7 percent and 17.2 percent change from baseline, which was statistically significant compared to placebo ($p=0.037$ and 0.028, respectively versus placebo). The mean improvement of the low dose was better than placebo at all assessments, but not statistically significant.

The primary end-point for the trial was a composite of several cognitive tests (composite cognitive memory score, or CCMS) that measured memory and executive function. Patients treated with davunetide showed statistically significant improvement on tests that measured short-term recall and working memory, but no improvement on tests that involved executive functions, such as planning, cognitive flexibility and abstract thinking.

Allon is currently enrolling patients in a Phase 2/3 study of davunetide for progressive supranuclear palsy (PSP), a form of frontotemporal dementia (FTD).

TauRx Pharmaceuticals Ltd. has evaluated its first generation tau aggregation inhibitor (TAI), rember™, in a large, double-blind, long-duration international phase 2

clinical trial in 321 patients with mild or moderate AD. The active compound in rember™ is methylthioninium chloride (MTC), a reducing agent better known as methylene blue. Methylene blue colors the urine green, raising the question of how a study with this substance can stay blinded at all.

In the Phase 2 trial that was conducted in the UK and Singapore, rember™ showed evidence of a significant reduction in the rate of clinical decline: 80% by weeks 50 and 102 of this trial, relative to controls, as measured using psychometric tools. Functional neuroimaging results from the trial supported the psychometric data: in patients exposed to rember™, the loss of function occurring in the areas of the brain known to be particularly affected by the Tau-tangle pathology of disease was eliminated over 6 months. Functional brain scan benefits seen at 6 months were predictive of clinical benefit at 12 months.

Disappointingly, the highest dose of the original rember™ did not perform well in the Phase 2 trial, leading scientists to change the formulation so that it could be better taken up by the body, without prohibitive side-effects.

The clinical tolerability profile of TauRx's lead "second generation" TAI called LMTX, is currently being investigated in trials under a US IND. LMTX has the same active moiety, methylthionine chloride, as TauRx's first generation product rember™. TauRx last reported that LMTX was preparing to advance into pivotal international Phase 3 trials in mild and moderate AD and related neurodegenerative diseases following an agreement with INC Research via a Letter of Intent. However, no update could be found on the company's website.

Noscira, a biopharmaceutical subsidiary of Grupo Zeltia (ZEL.MC), is in a Phase 2 clinical trial with tideglusib (Nypta®/Zentylor™), which is an orally bioavailable glycagen synthetase kinase-3 (GSK-3) inhibitor for the treatment of AD. Overexpression of GSK-3 leads to hyperphosphorylation of the tau protein. Tideglusib is a member of the thiadiazolindindione family of the GSK-3 inhibitors with non-ATP competitive mechanism of action[35]. It is hypothesized that GSK-3 plays a key role in the pathogenesis of AD and probably the link between beta amyloid and tau pathology[36].

According to the company, in experimental models tideglusib has demonstrated positive activity against histeopathological lesions associated with AD. For example, it reduces phosphrylation of the tau protein and hippocampal and entorhinal cortex neuron loss, improves spatial memory deficits and significantly reduces the accumulation of amyloid plaques in the brain. The compound also provides neuroprotection and reduces neuroimflammation.

In three Phase 1 studies, more than 150 healthy young and elderly patients were treated with tideglusib administered orally and the drug was well tolerated. During the 2010 ICAD, data from the phase 2a double-blind, placebo controlled, escalating doses trial of tideglusib in 30 mild to moderate AD patients were reported showing a trend in the cognitive increase of the mild to moderate AD patients treated for 20 weeks. Patients treated with tideglusib in addition to an acetylcholinesterase inhibitor showed an improvement in four of the five clinical efficacy variables that were assessed: Mini Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale (ADAS-COG), Geriatric Depression State and Global Clinical Assessment. The patients treated with the active compound exhibited a benefit of more than 4 points in the ADAS-cog cognitive scale compared with those treated with placebo. The number of subjects was too small to be statistically significant.

In April 2011, Noscira commenced a Phase 2b clinical trial of tideglusib for the treatment of AD. In September 2011, a satisfactory report was received from the first Data & Safety Monitoring Board (DSMB). In January 2012, Noscira announced the completion of the randomization of patients with AD for the Phase 2 trial, called Alzheimer's Research in GSK-3 modulation (ARGO), of tideglusib. The trial involves 308 patients, aged 50 to 85, with a score between 14 and 26 on the MMSE and treatment in stable well-tolerated doses with an acetylcholinesterase inhibitor and/or memantine. The drug is administered orally in daily doses. The patients in both groups receive baseline treatment with the commercially available drugs for AD. The main purpose of this multi-center, double-blind, randomized, placebo controlled, 4 arm study is to evaluate the cognitive changes after administration of tideglusib versus placebo at two oral doses and two treatment regimes for 26 weeks with a possibility of an extension of the double-blind trial for up to 15 months. The primary efficacy criteria in the ARGO trial is the comparison of the change with respect to the basal situation in the ADAS- Cog plus scale in groups with the active treatment versus the placebo group. The study will also analyze secondary cognitive, functional and quality of life variables. Preliminary

results of the ARGO trial are expected by the end of 2012.

In December 2011, Reuters reported that a Phase 2 trial of tideglusib for PSP did not meet the primary endpoint of improvement at clinical stage[37].

5) Other Therapies

In addition to developing EVP-0962, EnVivo Pharmaceuticals' more advanced compound is designed to treat the symptoms of AD versus the underlying disease. The product candidate is an alpha-7 agonist called EVP-6124, which is a selective, potent, brain penetrant oral compound that offers a novel mechanism of action. EVP-6124 enhances synaptic transmission in the brain and acts as a co-agonist in combination with Acetylcholine (ACh) to enhance cognition. By sensitizing the alpha-7 receptor, EVP-6124 makes it possible for smaller amounts of naturally occurring ACh to be effective in activating the A7 receptor. This mechanism could potentially alleviate the undesirable side effects caused by other systemic compounds, such as AChEIs, which are dose-limited by toxic side effects. A multi-center, multinational, double-blind, placebo-controlled Phase 2b study of EVP-6124 is currently ongoing in AD, with data expected in early 2012.

Based in Pennsylvania, privately held QR Pharma, Inc. is developing Posiphen®, a cholinergically inactive enantiomer of phenserine[38], for the treatment of AD. Posiphen® is a small, orally available molecule with a high blood brain barrier permeability that may provide benefits beyond those realized by compounds that target beta-amyloid via its multiple mechanisms. For example, the compound inhibits the synthesis of APP, which in turn decreases the levels of N-APP, Ab and C31, all three toxic peptides derived from the precursor. Posiphen® also targets Tau, which further contributes to the toxicity in AD, and alpha synuclein (α-Synuclein).

QR Pharma conducted a trial in 30 patients with mild cognitive impairment to confirm Posiphen®'s mechanism of action in humans and correlate it with the pharmacokinetics of the compound and its metabolites in CSF and plasma. The results from this biomarker human trial demonstrated Posiphen® was able to reverse the degenerative biochemistry found in the brain of AD patients back to a healthy state. Posiphen® lowers levels of APP, tau and inflammation by about 50%, approaching the levels found in healthy volunteers. Ten day treatment with Posiphen® reduces tau/Ab42 ratio back to the ratio found for healthy volunteers. Over 120 people have been tested in short term studies with Posiphen® and in all cases the compound was found to be safe.

Anavex Life Science Corp. (AVXL.OB) is developing ANAVEX 2-73, a novel sigma 1 receptor agonist targeting AD. In AD, ANAVEX 2-73 has shown a best-in class profile, due to its potency in validated animal models, no toxicity to date in exhaustive animal testing, novel mode of action and its potential to blunt endoplasmic reticulum (ER) stress, mitochondrial stress and oxidative stress, thought to be contributory causes of AD. Research in recent years indicates that oxidative stress is a precursor to amyloid-beta plaques and tau (Neuro-Fibrillary Tangles or NFT), and that protecting against oxidative stress may help to prevent or slow the disease.

Anavex conducted a randomized, placebo-controlled Phase 1 study to initially test ANAVEX 2-73 as a single, ascending oral dose in healthy male volunteers between the ages of 18 and 55. In this Phase 1 study, the maximum tolerated single dose was defined per protocol as 55-60 mg. This dose is above the equivalent dose shown to have positive effects in mouse models of AD. There were no significant changes in laboratory or electrocardiogram (ECG) parameters. ANAVEX 2-73 was well tolerated below the 55-60 mg dose with only mild adverse events in some volunteers. Observed adverse events at doses above the maximum tolerated single dose included headache and dizziness, which were moderate in severity and reversible. Anavex plans to begin a multiple ascending dose trial of ANAVEX 2-73.

Curaxis Pharmaceutical Corp (CURX.PK) is a specialty pharmaceutical company advancing the use of leuprolide acetate to treat women with mild to moderate AD. The company's scientific hypothesis is that several components of AD pathology may result from the abnormal entry of neurons, which typically do not divide, into the cell division cycle. Instead of successfully completing cell division, these terminally differentiated neurons die, and this neuronal cell death is believed to produce the clinical deficits observed in AD patients. Curaxis' researchers believe that luteinizing hormone (LH) is a stimulus that promotes neurons to attempt to divide and have demonstrated that LH is elevated in AD patients and is also present in brain structures that are pathologically affected by AD[39]. Curaxis' drug that addresses the pathologies of AD through multiple pathways, including beta amyloid, tau phosphorylation, inflammation and aberrant cell cycling, as a unique clinical approach in targeting the brain disorder.

> **"Key readouts from a number of promising agents for AD are expected in 2012, including solanezumab, bapineuzumab, and tideglusib."**

Curaxis' most advanced product candidate for AD is Memryte (VP4896), a proprietary, small, biodegradable implant that is comprised of leuprolide acetate and a polymer. Memryte decreases the amount of LH released by the pituitary gland. Published reports demonstrate that leuprolide treatment in mice dramatically and significantly reduced the concentrations of brain Ab42 by 40% after four weeks, and by 71% after eight weeks[40].

Curaxis' Memryte utilizes DURECT Corporation's (DRRX) proprietary DURIN technology to provide sustained release of the peptide leuprolide acetate. DURECT will receive milestone payments if specified development milestones are achieved, and, if commercialized, royalties based on sale of the resulting product anywhere in the world.

Curaxis previously conducted several clinical studies to test leuprolide acetate and Memryte for the treatment of mild to moderate AD. It branded its clinical trial program as "Antigonadotropin-Leuprolide in Alzheimer's Disease Drug Investigation," for which it used the acronym ALADDIN. Curaxis' clinical program includes: a completed Phase 1 safety and pharmacokinetic study of Memryte, ALADDIN 105; and three Phase 2 clinical trials, two of which used an injectable formulation of leuprolide acetate and one of which used the proprietary implant, Memryte, which Curaxis was forced to terminate in 2006 due to financial constraints. Since terminating those trials, Curaxis had been unable to advance the clinical development of its AD candidate due to a lack of financial resources.

Ceregene, Inc., a private, San Diego-based biotechnology company focused on the treatment of major neurodegenerative disorders using the delivery of nervous system growth factors, has an entirely different approach with CERE-110 for the treatment of mild to moderate AD. CERE-110 is a gene therapy product designed to deliver nerve growth factor (NGF). CERE-110 is composed of an adeno-associated viral (AAV) vector carrying the gene for NGF and is surgically injected into the Nucleus Basalis of Meynet (NGB). The product has the potential to induce sustained expression of NGF, which may result in a long lasting restoration of function, protection of neurons and slowing the progression of AD. The Phase 1 open label study in 10 patients with mild to moderate AD demonstrated that CERE-110 was safe and well-tolerated. Increases in brain metabolism were observed in several cortical regions at six and 12 months in four patients as compared to severity-matched individuals with AD.

Ceregene has initiated a multi-center, controlled Phase 2 clinical trial in collaboration with the Alzheimer's Disease Cooperative Study (ADCS). The randomized, controlled double-blinded Phase 2 study of CERE-110 will examine the safety and effectiveness of NGF on AD in 50 patients with mild to moderate AD at 10 research sites throughout the United States. Participants will be randomized equally to one of two treatment groups: half of the subjects will initially receive placebo surgery, but no administration of gene therapy. In the other half, CERE-110 will be injected into the NBM of the brain. At the completion of the trial, subjects in the placebo arm will be given the opportunity to switch to the active treatment protocol if the efficacy and safety data are supportive. The study will evaluate the treatment arm versus the control arm with respect to safety, cognitive function and quality of life at two years.

One challenge with CERE-110 is that precise brain surgery is required to deliver the gene for NGF to the specific subset of neurons most affected by the disease. NGF is a large protein, which does not pass through the blood brain barrier. However, CERE-110 has the potential to provide a sustained expression of NGF to meaningfully enhance neurons enough to slow the decline with one treatment.

Conclusion

The number of product candidates that have advanced into randomized controlled trials yet failed to demonstrate efficacy in AD, combined with the fact that the biology of the disease and what causes this fatal disorder has not been elucidated, has resulted in a high degree of skepticism for the field. However, as noted by Dennis J. Selkoe, M.D., the Vincent and Stella Coates Professor of Neurologic Diseases at Harvard Medical School and member of the Board of Directors at Elan, "Rigorous preclinical validation of mechanism-based therapeutic agents followed by meticulously designed trials that focus on the cardinal cognitive symptoms and their associated biomarkers in the mild or presymptomatic phases of Alzheimer's disease are likely to lead to success, perhaps in the not-too-distant future.[41]"

Importantly, key readouts from a number of promising agents for AD are expected beginning in the second quarter of 2012, including solanezumab, bapineuzumab, and tideglusib. Many of these clinical trials are being conducted in earlier stages of AD (mild to moderate versus moderate to severe) in the hopes of a disease modifying effect or slowing the progression of the disease. The majority of these compounds with the

potential to have a disease modifying effect have originated from emerging biotech companies.

Positive results from other ongoing clinical trials, the introduction of new tools for detection, such as Eli Lilly's Amyvid™ imaging agent, and advances in understanding the causes and biology of AD could also enhance interest and much needed investment in the life science companies developing treatments for this disease.

Additional data should be available for some of the other compounds in clinical development at the two main AD conferences in 2012. The AAIC annual meeting is being held July 14-19, 2012 in Vancouver, British Columbia, Canada. The ICAD annual meeting is being held October 8-9, 2012 in Dubai, United Arab Emirates.

AD will likely be making headlines around the next meeting of the National Alzheimer's Project Act Advisory Council, which is scheduled for April 17, 2012. The strategic plan to slow the progression, delay the onset and prevent AD by 2025 is expected to be completed by the end of this year.

In the absence of new medical breakthroughs in 2012 and beyond, the cost of AD in the United States is expected to rise (in current dollars) to $1.1 trillion a year by 2050 from $183 billion today[42]. Accordingly, clinical success from any of the more than 30 life science companies advancing promising AD treatments (**see Table 1**) would be a welcome event, providing new hope to patients, physicians, family caregivers, and investors. In view of recent progress, we believe that therapeutic success in AD could indeed occur as early as this year.

Table 1. Companies with AD programs mentioned in this report

Company	Product(s)	Category*	Clinical Stage(s) for AD
AC Immune SA	ACI-91, ACI-24, crenezumab	1, 3	Phase 2, Phase 1, Phase 2
Affiris AG	AD01, AD02, AD03	3	Phase 1, Phase 2, Phase 1
Agenus Inc. (AGEN)	QS-21 adjuvant with ACC-001	3	Phase 2
Allon Therapeutics (NPC.TO)	davunetide	4	Phase 2
Anavex Life Science Corp. (AVXL.OB)	ANAVEX 2-73	5	Phase 1
Astellas Pharma (ALPMY.PK)	CTS-21166	1	Phase 1
Baxter International Inc. (BAX)	Gammagard Liquid	3	Phase 3
Bristol-Myers Squibb (BMY)	avagacestat (BMS-708163)	1	Phase 2
Ceregene Inc.	CERE-110	5	Phase 2
CoMentis, Inc.	CTS-21166	1	Phase 1
Curaxis Pharmaceutical Corp (CURX.PK)	Memryte	5	Phase 2 (not active)
Cytos Biotechnology AG (CYTN.SW)	CAD106	3	Phase 2
DURECT Corporation (DRRX)	Memryte	5	Phase 2 (not active)
Eisai Inc. (ESALY.PK)	Aricept®, bexarotene (Targretin®)	1, 5	Marketed, preclinical
Elan Corporation plc (ELN)	bapineuzumab, ACC-001, ELND005	2, 3	Phase 3, Phase 2, Phase 2
Eli Lilly & Co. (LLY)	solanezumab	3	Phase 3
EnVivo Pharmaceuticals	EVP-0962, EVP-6124	1,5	Phase 1, Phase 2b
Forest Laboratories (FRX)	Namenda® (memantine hydrochloride)	5	Marketed
GlaxoSmithKline (GSK)	AD01, AD02, AD03	3	Phase 1, Phase 2, Phase 1
Johnson & Johnson (JNJ)	bapineuzumab, ACC-001	3	Phase 3, Phase 2
Merck (MRK)	MK-0752, MK-8931	1	Phase 1, Phase 1
Myriad Genetics (MYGN)	Flurizan® (r-flurbiprofen)	1	Failed in Phase 3
Neurochem	Tramiprosate (Alzhemed™)	1	Failed in Phase 3
Noscira/Grupo Zeltia	tideglusib (Nypta®/Zentylor™)	4	Phase 2
Novartis AG (NVS)	CAD106	3	Phase 2
Pfizer Inc. (PFE)	Aricept®, ponezumab, PF-04494700, bapineuzumab, ACC-001	3, 5	Marketed, Failed in Phase 2, Failed in Phase 2, Phase 3, Phase 2
Prana Biotechnology Ltd. (PRAN)	PBT2	2	Phase 2
QR Pharma, Inc.	Posiphen®	5	Phase 2
Roche Holding AG (RHHBY.PK)	gantenerumab, crenezumab	3	Phase 2, Phase 2
Takeda Pharmaceutical Co. (TKPHF.PK)	TAK-070	1	Phase 1
TauRx Pharmaceuticals Ltd.	LMTX	4	Phase 3 (not active)
Transition Therapeutics (TTHI)	ELND005	2	Phase 2
United Biomedical, Inc.	UB-311	3	Phase 1

*Category key: 1) Drugs to reduce beta-amyloid (know as β-amyloid, or Aβ) production, 2) Drugs to reduce beta-amyloid plaque burden via inhibition of aggregation or disruption of aggregates, 3) Drugs to promote beta-amyloid clearance via active or passive immunotherapy, 4) Drugs to prevent tau protein phosphorylation or aggregation, and 5) Others.

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Appendix

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