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CLINICAL TRIALS RESULTS AND NEW DATA ANALYSES IN AMYLOID-RELATED THERAPIES FROM THE ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE 2015

- Longer-Term Analysis of Phase 3 Solanezumab (Lilly) Up to 3.5 Years -
- Biomarker Results from Phase 3 Gantenerumab (Roche) Trial -
- New Data from Aducanumab (Biogen) Phase 1b Study -

WASHINGTON, DC, July 22, 2015 – Clinical trial results from three studies of investigational therapies related to amyloid protein were presented today at the Alzheimer's Association International Conference® 2015 (AAIC® 2015) in Washington, D.C.

They included:

- A new "delayed-start" analysis of negative Phase 3 clinical trials of solanezumab (Lilly) which suggests that the drug may slow the progression of mild Alzheimer's disease.
- A biomarker-only analysis of a discontinued Phase 3 clinical trial of gantenerumab (Roche) that shows the drug engaged its target in the brain and generated positive biological changes.
- New data from PRIME, the Phase 1b study of aducanumab (Biogen).

Two abnormal structures called amyloid plaques and tau tangles are prime suspects in damaging and killing brain cells in Alzheimer's disease and other dementias. Plaques are deposits of a protein fragment called beta-amyloid that build up in the spaces between nerve cells. Tangles are twisted fibers of another protein called tau that build up inside cells.

"The data from these new analyses present exciting possibilities, and we look forward to the results of future studies in these experimental drugs," said Maria Carrillo, PhD, Chief Science Officer, Alzheimer's Association. "For the delayed-start analysis in particular, if it proves to be true, it is the strongest argument to date for early Alzheimer's diagnosis, because getting the drug earlier makes a significant difference in the outcome."

"Last month, we witnessed historic bipartisan support in both cham
in Alzheimer's research funding to date. This included a call for a 6
$350 million for Alzheimer's research by the Senate Appropriations
even with the proposed increase, Alzheimer's funding still receives f
required to meet the primary goal of the National Plan to Address A

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effectively treat Alzheimer's by 2025. Leading experts convened by the Alzheimer's Association stated that $2 billion per year is needed to make real advances in treating and preventing Alzheimer's."

Delayed-Start Analysis of Solanezumab (Lilly) Up To 3.5 Years

Showing that an investigational treatment has slowed the progression of a degenerative brain disease like Alzheimer's is extremely challenging. Researchers have proposed overcoming this problem with a type of study called a "delayed-start" trial. In delayed-start studies, patients are randomly assigned to start active treatment at the beginning of the study or are placed in a "delayed-start" group that receives a placebo treatment for a period of time before being given the active experimental therapy. Researchers then compare the two groups at a later, pre-defined point in time to assess their response to the treatment.

- If the experimental treatment is limited to reducing Alzheimer's symptoms, both early-start and delayed-start participants should experience the same benefit. For example, if a treatment is maximally effective after two months, it would take both groups two months from the time they first receive it to have comparable reductions in their symptoms, and the delayed start group would "catch up" to the early start group and be functioning at a similar level.
- If the treatment can actually slow disease progression, both groups will benefit, but the group that started active treatment later in the study will have progressed further in the disease before they got the drug – while they were on placebo. As a result, the late starters will not be able to "catch up" to the group whose disease progression was slowed for the full duration of the study.

At AAIC 2015, Hong Liu-Seifert, PhD, Research Advisor for the Alzheimer's Disease Global Development Team at Eli Lilly and Company, Indianapolis, Indiana; Paul Aisen, MD, Director of the Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego; and colleagues shared results of a new statistical approach to delayed-start analysis for the experimental drug solanezumab (Lilly). Their presentation was based on a pooled analysis of 1,322 people enrolled in the completed, 18-month EXPEDITION (EXP) and EXPEDITION2 (EXP2) placebo-controlled clinical trials, and a two-year extension trial known as EXPEDITION-EXT (EXP-EXT). EXP and EXP2 did not achieve statistical significance on their primary endpoints.

In EXP-EXT, all participants receive solanezumab, but patients and site personnel remain blinded to original treatment assignment, preserving the randomized, double-blind nature of the entire 3.5-year delayed-start design. The primary time point assessment for the delayed-start analyses was pre-specified at 28 weeks into the delayed-start period.

The researchers found that:

- Treatment differences at 28 weeks in EXP-EXT between the early start and delayed start groups for cognition (ADAS-Cog14) and function (ADCS-iADL) were similar to differences at the end of the placebo-controlled period, within a pre-defined margin. In other words, the delayed starters did not "catch up."
- Treatment differences between the early start and delayed start groups for ADAS-Cog14 and ADCS-iADL remained significant through 52 weeks.

"The results support the potential benefit of starting treatment with solanezumab earlier rather than later in disease progression, and suggest there is persistence of treatment effect even after the delayed-start patients are given the drug," Aisen said. "This analysis method is also planned for the ongoing EXPEDITION3 study."

Simultaneously with presentation at AAIC 2015, results from the delayed-start analysis of solanezumab in mild Alzheimer's will be published in *Alzheimer's & Dementia: Translational Research & Clinical Investigations*.

Biomarker Results from Phase 3 Gantenerumab (Roche) Trial in Early Alzheimer's

In December 2014, dosing of gantenerumab (Roche) in the two-year, Phase 3 SCarlet RoAD trial in people with early symptoms of Alzheimer's was stopped based on preliminary results that indicated the chance of successful completion was very low; patients in the study continue to be followed.

Gantenerumab is a human monoclonal antibody that binds to, and may stimulate the removal of, aggregated forms of beta amyloid protein in the brain. In SCarlet RoAD, people with amyloid build-up in the brain and some signs of impairment of mental processes (such as memory difficulties) received once-monthly placebo or one of two doses of gantenerumab (105 mg or 225 mg).

Overall, patients treated with gantenerumab did not experience cognitive benefit compared to patients treated with placebo, but there was evidence of efficacy in patients with faster progressing disease who had higher exposure to the drug. At AAIC 2015, researchers reported data about the biological activity of the drug. According to the researchers, gantenerumab produced dose-related reductions on levels of amyloid (not statistically significant), as measured by brain amyloid PET scans, and tau (statistically significant), a protein marker of brain cell degeneration that can be measured in the cerebrospinal fluid.

- CSF p-Tau mean % change from baseline at Week 104: placebo (n=63) +2.62 ± 21.89; 105 mg gantenerumab (n=62) -4.85 ± 12.42; 225 mg gantenerumab (n=58) -7.52 ± 9.85.
- CSF t-Tau: mean % change from baseline at Week 104: placebo (n=62) +3.11 ± 21.12; 105 mg gantenerumab (n=60) -1.45 ± 13.55; 225 mg gantenerumab (n=57) -2.94 ± 10.37.
- No changes in CSF Abeta 42 levels were found.
- Amyloid-PET observed mean % change from baseline in cortical composite SUVr at Week 100: placebo (n=20) -1.11 ± 8.02; 105 mg gantenerumab (n=11) +0.19 ± 12.70; 225 mg gantenerumab (n=18) -5.37 ± 7.92.

"This is the first study showing clear changes on both standard biomarkers in people with very early Alzheimer's," said Philip Scheltens, MD, PhD, professor of cognitive neurology and director of the Alzheimer's Center at the VU University Medical Center in Amsterdam, Netherlands and a principal investigator of SCarlet RoAD. "These findings are consistent with brain amyloid clearance and an effect on downstream markers of neurodegeneration. They also suggest that the gantenerumab dose in the Phase 3 Scarlet RoAD trial likely was too low. Future trials should examine higher doses of the drug."

New Data from Phase 1b Study of Aducanumab (Biogen) in Prodromal or Mild Alzheimer's

Aducanumab (BIIB037) is a monoclonal antibody targeting aggregated forms of amyloid beta protein – a hallmark of Alzheimer's disease progression is the accumulation of beta amyloid in the brain.

At AAIC 2015, Biogen presented new results from a prespecified interim analysis of PRIME, the Phase 1b study of aducanumab in patients with prodromal or mild Alzheimer's. The data included results from patients treated up to 54 weeks with the 6 mg/kg dose.

Earlier this year, Biogen announced interim results from the 1, 3 and 10 mg/kg arms of PRIME after one year of treatment as well as the 6 mg/kg arm up to 30 weeks. Those results marked the first time an investigational drug for Alzheimer's demonstrated a statistically significant reduction on amyloid plaque as

well as a statistically significant slowing of clinical impairment in patients with prodromal or mild disease. These promising early results must be expanded and replicated in larger populations.

PRIME is the ongoing Phase 1b randomized, double-blind, placebo-controlled, multiple-dose study evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics of aducanumab in patients with prodromal or mild Alzheimer's. Biogen required patients enrolled in PRIME to have evidence of beta amyloid accumulation (detected by PET scan) and to have met clinical criteria for prodromal or mild Alzheimer's.

About AAIC

The Alzheimer's Association International Conference (AAIC) is the world's largest gathering of researchers from around the world focused on Alzheimer's and other dementias. As a part of the Alzheimer's Association's research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.
AAIC 2015 home page: www.alz.org/aaic/
AAIC 2015 newsroom: www.alz.org/aaic/press.asp

About the Alzheimer's Association®

The Alzheimer's Association is the leading voluntary health organization in Alzheimer's care, support and research. Our mission is to eliminate Alzheimer's disease through the advancement of research, to provide and enhance care and support for all affected, and to reduce the risk of dementia through the promotion of brain health. Our vision is a world without Alzheimer's. Visit alz.org or call 800.272.3900.

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- Hong Liu-Seifert, PhD; Paul Aisen, MD; et al. Delayed-Start Analyses of up to 3.5 Years in the Phase 3 Solanezumab Expedition Program in Mild Alzheimer's Disease. (Funder: Eli Lilly and Company)
- Philip Scheltens, MD, PhD, et al. Biomarker Data from SCarlet RoAd - a Global Phase 3 Study of Gantenerumab in Patients with Prodromal AD (Funder: Roche)
- Jeff Sevigny, MD, et al. Aducanumab (BIIB037), an Anti-Amyloid Beta Monoclonal Antibody, in Patients with Prodromal or Mild Alzheimer's Disease: Interim Results of a Randomized, Double-Blind, Placebo-Controlled, Phase 1B Study. (Funder: Biogen Idec)

F4-03-02
Wednesday, July 22, 2015, 8-09:30 AM, Walter E. Washington Convention Center, Ballroom A

Delayed-Start Analyses of up to 3.5 Years in the Phase 3 Solanezumab Expedition Program in Mild Alzheimer's Disease

FRS Topic: Delayed Start Studies in the Assessment of Potential Disease Modifying Effect

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Presented by Paul Aisen, MD
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Background: The methods to assess effects of investigational drugs for Alzheimer's disease (AD) on underlying disease progression are not well established. As stated in 2013 FDA draft guidance on early AD clinical trial development, one such method is a delayed-start design: a placebo-controlled period followed by a delayed-start period wherein all patients receive active treatment.

Methods: EXPEDITION and EXPEDITION2 were Phase 3, 18-month, placebo-controlled studies investigating solanezumab. EXPEDITION-EXT is an ongoing extension study available for patients who completed EXPEDITION or EXPEDITION2. In these analyses, all patients completed at least 2 years in EXPEDITION-EXT or discontinued. In EXPEDITION-EXT, all patients receive solanezumab, but patients and site personnel remain blinded to original treatment assignment, preserving the randomized, double-blind nature of the entire 3.5-year delayed-start design. We applied a new statistical methodology to assess possible disease-modifying effects of solanezumab in mild AD dementia using a noninferiority test of treatment differences during the delayed-start period compared with the end of the placebo-controlled period. The primary time point assessment for the delayed-start analyses was prespecified at 28 weeks in the delayed-start period.

Results: Approximately 95% of patients with mild AD who completed EXPEDITION and EXPEDTION2 elected to enter EXPEDITION-EXT. Treatment differences between solanezumab and placebo at 28 weeks in EXPEDITION-EXT (Δ_2) for ADAS-Cog14 and ADCS-iADL were similar to differences at the end of the placebo-controlled period (Figure and Table 1). Noninferiority was met, indicating treatment differences in cognition and function at the end of the placebo-controlled studies were preserved after 28 weeks in the delayed-start period within a pre-defined margin. Throughout the remainder of the 2-year delayed-start period, treatment differences for ADAS-Cog14 were significant through 80 weeks and noninferiority was met through 52 weeks. For ADCS-iADL, treatment differences were significant and noninferiority was met through 52 weeks.

Conclusions: These results are consistent with a potential disease-modifying effect of solanezumab on underlying disease progression. As shown by our data, benefits observed during the placebo-controlled period could not be recovered by the later introduction of solanezumab at the onset of EXPEDITION-EXT.

DT-01-02
Oral session, Wednesday, July 22, 2-3:30 pm, Hall E
Topic Selection: Identifying and Treating Alzheimer's Disease

Biomarker Data from SCarlet RoAd – a Global Phase 3 Study of Gantenerumab in Patients with Prodromal AD

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Background: Gantenerumab, a human anti-Abeta antibody designed to bind aggregated Abeta and promote plaque removal, was studied in SCarlet RoAD (NCT01224106; WN25203)—a Phase 3, multicenter, randomized, double-blind, placebo-controlled, 2-year trial in prodromal AD. Dosing was terminated in December 2014 following a pre-planned futility analysis; patients continue to be followed. CSF biomarker data and amyloid PET sub-study results are presented (patients completing 2-year treatment).

Methods: Eligible patients were 50–85 years old, had MMSE scores ≥24, CDR-Global scores of 0.5 (memory box scores of 0.5 or 1.0) and evidence of amyloid pathology (CSF Aβ42 <600 ng/mL, Innotest®), with cognitive and functional performance largely preserved to exclude a diagnosis of dementia. Patients were randomized to monthly subcutaneous injections of placebo, or 105 mg or 225 mg gantenerumab, based on APOEe4 allele status (no APOEe4 homozygotes received 225 mg). CSF biomarkers were analyzed using Elecsys® beta-Amyloid (1–42), tTau and pTau (181P) immunoassays (Roche Diagnostics; these products are in development and not available in the USA). 114 patients were enrolled in a PET sub-study (AmyvidTM). Standardized uptake value (SUVr), normalized to different reference regions, was assessed. Clinical results are presented separately.

Results: Amyloid-PET observed mean % change (± SD) from baseline in cortical composite SUVr (using mean cerebellar grey as reference region) at Week 100: placebo (n=20) -1.11 ± 8.02; 105 mg gantenerumab (n=11) +0.19 ± 12.70; 225 mg gantenerumab (n=18) -5.37 ± 7.92. No changes in CSF Abeta 42 levels were found. CSF p-Tau mean % change (± SD) from baseline at Week 104: placebo (n=63) +2.62 ± 21.89; 105 mg gantenerumab (n=62) -4.85 ± 12.42; 225 mg gantenerumab (n=58) -7.52 ± 9.85. CSF t-Tau: mean % change (± SD) from baseline at Week 104: placebo (n=62) +3.11 ± 21.12; 105 mg gantenerumab (n=60) -1.45 ± 13.55; 225 mg gantenerumab (n=57) -2.94 ± 10.37.

Conclusions: At the doses tested, gantenerumab treatment was associated with dose-dependent reductions in brain Abeta SUVr and CSF p-Tau and t-Tau, compared with placebo. As expected, CSF Abeta 42 levels were unaltered. These findings are consistent with brain amyloid clearance and an effect on downstream markers of neurodegeneration.

Proposal ID: O4-04-05
Oral session. Wednesday, July 22, 2 pm
Theme Selection: Therapeutics
Topic Selection: Clinical: Clinical Trials and Translational Studies Targeting ABeta

Aducanumab (BIIB037), an Anti-Amyloid Beta Monoclonal Antibody, in Patients with Prodromal or Mild Alzheimer's Disease: Interim Results of a Randomized, Double-Blind, Placebo-Controlled, Phase 1B Study

Jeff Sevigny, MD
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Background: Aducanumab (BIIB037) is a human monoclonal antibody selective for aggregated forms of beta-amyloid peptide being investigated as a disease-modifying treatment for AD. This Phase 1b study is evaluating the safety, tolerability, pharmacokinetics, and pharmacodynamics of aducanumab in patients with prodromal or mild AD.

Methods: Patients included in this multicenter, randomized, double-blind, placebo-controlled, multiple-dose study (PRIME; NCT01677572) were aged 50-90 years, had a positive florbetapir (18F-AV-45) PET scan, and met clinical criteria for prodromal or mild AD. During the double-blind, placebo-controlled phase, patients received aducanumab or placebo once every 4 weeks for 52 weeks. In a staggered, ascending-dose design, patients were randomized to 1 of 7 treatment arms stratified by ApoE4 status (carrier/non-carrier). Primary endpoint was safety and tolerability. Secondary endpoints included change from baseline to Week 26 in brain beta-amyloid plaque burden measured by PET imaging. Cognition/functioning, including change from baseline on the Clinical Dementia Rating scale, was an exploratory endpoint. Interim analyses included: (1) subjects in all arms who completed the Week 26 visit, and (2) subjects in all arms who completed the Week 54 visit (results for placebo, 1, 3 and 10 mg/kg aducanumab at Week 54 available here, results for 6 mg/kg at Week 54 will be presented).

Results: Patients (N=166) were randomized to placebo (n=40), 1 (n=31), 3 (n=33), 6 (n=30) or 10 (n=32) mg/kg aducanumab. By Week 54, the most common adverse events (AEs) were amyloid-related imaging abnormalities (ARIA; 6%, 13%, 33% and 47% for 1, 3, 6 and 10 mg/kg aducanumab, respectively, versus 5% for placebo) and headache (16%, 16%, 27% and 28% versus 5%). The most common serious AE was ARIA (3%, 3%, 13% and 16% versus 0%). Treatment-related dose- and time-dependent reductions in brain beta-amyloid plaque (as shown by standard uptake value ratio reduction at Week 26 and further reductions at Week 54) were observed within the doses tested (Figure). There was reduced dose- and time-dependent impairment in measures of cognition.

Conclusions: Dose-dependent ARIA was the main safety and tolerability finding. Aducanumab reduced beta-amyloid plaque in patients with prodromal or mild AD. A clinical signal was observed in exploratory analysis.

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