# EISAI PRESENTS NEW FINDINGS ON LECANEMAB'S INVESTIGATIONAL SUBCUTANEOUS FORMULATION AND MODELING SIMULATION OF APOE4 GENOTYPE ON ARIA-E INCIDENCE AT THE ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE (AAIC) 2022

August 3, 2022

TOKYO and CAMBRIDGE, Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") and Biogen Inc. (Nasdaq: BIIB, Corporate headquarters: Cambridge, Massachusetts, CEO: Michel Vounatsos, "Biogen") announced that Eisai presented new findings on a subcutaneous formulation of lecanemab (BAN2401) and the modeling simulation of the impact of ApoE4 genotype on the incidence of amyloid- related imaging abnormalities – edema/effusion (ARIA-E) – in subjects treated with lecanemab, an investigational anti-amyloid beta (Aβ) protofibril antibody for the treatment of mild cognitive impairment (MCI) due to Alzheimer's disease (AD) and mild AD (collectively known as early AD) with confirmed presence of amyloid pathology in the brain. The data were shared at the Alzheimer's Association International Conference (AAIC) in San Diego, CA.

Key Eisai presentations include:

**Eisai Abstract #69438: Absolute Bioavailability of a Single, Fixed Subcutaneous Dose of Lecanemab in Healthy Subjects**

This Phase 1 study was an open-label, parallel-group study conducted in healthy subjects: 30 subjects were randomized into a 10 mg/kg intravenous (IV) dose group and 29 subjects (5 of which were Japanese) were randomized into a single fixed 700mg SC dose group. The absolute bioavailability of lecanemab following a single SC injection was 49.7% (90% CI: 43.54 – 56.83). After SC dosing, the Cmax was observed 72 hours post-dose and was 4-fold lower compared to IV infusion, which reflects the relatively long absorption phase following SC dose administration compared with 1-hour IV infusion. Lecanemab's half-life (~7 days) was similar following SC and IV administrations. The incidence of adverse events was similar between SC and IV administrations. No positive results for neutralizing antibodies (NAb) were recorded in this study. Lecanemab PK for the 5 Japanese subjects was similar to that of the non-Japanese subjects following a single subcutaneous dose administration.

**Eisai Abstract #69429: Subcutaneous Dose Selection of Lecanemab for Treatment of Subjects with Early Alzheimer's Disease**

In this analysis, modeling and simulation was conducted to evaluate the equivalence of a fixed weekly SC dose to a body weight-based 10 mg/kg IV bi-weekly dose with regard to lecanemab exposure. The analysis showed that a fixed lecanemab SC dose of 720 mg administered weekly may potentially result in comparable exposure (AUC) and efficacy as measured by reduction in amyloid PET SUVr to 10mg/kg IV dose administered bi-weekly. The exposure-response model is based on the established correlation between ARIA-E and Cmax. SC lecanemab dose is predicted to have a lower incidence of ARIA-E compared to IV lecanemab due to lower Cmax following SC administration.

**Eisai Virtual Developing Topics Presentation Abstract #69402 / Session VDT-4-29: Modeled Impact of ApoE4 Genotype on ARIA-E Incidence in Patients Treated with Lecanemab**

In this analysis, the results of the Phase 2 (Study 201) core study were used to explore the effect of ApoE4 genotype on ARIA-E incidence by modeling and simulation. The model predictions were compared to the ARIA-E incidence observed in subjects newly initiated on lecanemab 10 mg/kg bi- weekly in the Phase 2 (Study 201) open-label long-term study (OLE study). The effect of the ApoE4 genotype was analyzed in the exposure-ARIA-E model with three categorical covariates (homozygous carriers, heterozygous carriers, and noncarriers) using the results of the Phase 2 (Study 201) core study. ApoE4 genotype (homozygous) was a significant covariate in the exposure-ARIA-E model, and the incidence of ARIA-E correlated best with Cmax at steady state. On the other hand, there was no statistically significant difference in ARIA-E incidence between ApoE4 noncarriers and heterozygous
carriers. The predicted incidence of ARIA-E when lecanemab was dosed at 10 mg/kg bi-weekly was
22.5% in ApoE4 homozygous carriers, 6.8% in heterozygous carriers, and 5.4% in ApoE4 noncarriers. In the OLE study, the incidence of ARIA-E observed in ApoE4 homozygotes newly initiated on lecanemab 10 mg/kg bi-weekly treatment was 25% (1 out of 4), comparable to the model prediction of 22.5%. Amyloid-related imaging abnormalities (ARIA) are an adverse event associated with amyloid-lowering therapies, and it is important to monitor for and manage during treatment.

"In an effort to simplify the patient journey and fulfill our human health care mission, Eisai is developing a subcutaneous formulation of lecanemab that patients may be able to use at home," said Michael Irizarry, M.D., Senior Vice President, Deputy Chief Clinical Officer, Alzheimer's Disease and Brain Health, Eisai Inc. "The new data Eisai presented today about the bioavailability of subcutaneous dosing, and comparability with intravenous dosing, was used by Eisai to define the appropriate subcutaneous dosing that is currently being tested in the Phase 3 Clarity AD open-label extension. In addition, Eisai has expanded on the previous modeling that explored the effect of the ApoE4 genotype on ARIA-E to further our understanding of patient populations who are most impacted by ARIA-E in the lecanemab clinical trials. The modeling will be updated with data from Eisai's Phase 3 Clarity AD confirmatory study reading out in fall 2022."

"We will continue to inform the treatment of patients with Alzheimer's disease and further our development of new therapies," said Dominic Walsh, Head of Neurodegenerative Research Unit at Biogen. "Subcutaneous administration may provide a convenient option for patients and their caregivers in the future, and we look forward to a continued co-development with Eisai on this formulation."

On July 5, 2022, Eisai announced the U.S. Food and Drug Administration (FDA) accepted the Biologics License Application (BLA) for lecanemab under the accelerated approval pathway and was granted priority review, with a Prescription Drug User Fee Act (PDUFA) action date of January 6, 2023. The readout of the primary endpoint data of Clarity AD will occur in the fall of 2022. The FDA has agreed that the results of Clarity AD when completed, can serve as the confirmatory study to verify the clinical benefit of lecanemab.

This release discusses investigational uses of an agent in development and is not intended to convey conclusions about efficacy or safety. There is no guarantee that such an investigational agent will successfully complete clinical development or gain health authority approval.

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**[Notes to editors]**

**1. About Lecanemab (BAN2401)**
Lecanemab is an investigational humanized monoclonal antibody for Alzheimer's disease (AD) that is the result of a strategic research alliance between Eisai and BioArctic. Lecanemab selectively binds to neutralize and eliminate soluble, toxic amyloid-beta (Aβ) aggregates (protofibrils) that are thought to contribute to the neurodegenerative process in AD. As such, lecanemab may have the potential to have an effect on disease pathology and to slow down the progression of the disease. Currently, lecanemab is being developed as the only anti- Aβ antibody that can be used for the treatment of early AD without the need for titration. With regard to the results from pre-specified analysis at 18 months of treatment, Study 201 demonstrated reduction of brain Aβ accumulation ($P<0.0001$) and slowing of disease progression measured by ADCOMS* ($P<0.05$) in early AD subjects. The study did not achieve its primary outcome measure** at 12 months of treatment. The Study 201 open-label extension was initiated after completion of the Core period and a Gap period off treatment of 9-59 months (average of 24 months, n=180 from core study enrolled) to evaluate safety and efficacy is underway.

Currently, lecanemab is being studied in a confirmatory Phase 3 clinical study in symptomatic early AD (Clarity-AD), following the outcome of the Phase 2 clinical study (Study 201). Since July 2020 the Phase 3 clinical study (AHEAD 3- 45) for individuals with preclinical AD, meaning they are clinically normal and have intermediate or elevated levels of amyloid in their brains, is ongoing. AHEAD 3-45 is conducted as a public-private partnership between the Alzheimer's Clinical Trial Consortium that provides the infrastructure for academic clinical trials in Alzheimer's Disease and related dementias in the U.S, funded by the National Institute on Aging, part of the National Institutes of Health, Eisai and Biogen. Furthermore, Eisai has initiated a lecanemab subcutaneous dosing Phase 1 study.
* Developed by Eisai, ADCOMS (AD Composite Score) combines items from the ADAS-Cog (Alzheimer's Disease Assessment Scale-cognitive subscale), CDR (Clinical Dementia Rating) and the MMSE (Mini-Mental State Examination) scales to enable a sensitive detection of changes in clinical functions of early AD symptoms and changes in memory. The ADCOMS scale ranges from a score of 0.00 to 1.97, with higher score indicating greater impairment.
** An 80% or higher estimated probability of demonstrating 25% or greater slowing in clinical decline at 12 months treatment measured by ADCOMS from baseline compared to placebo.

**2. About the Collaboration between Eisai and Biogen for Alzheimer's Disease**
Eisai and Biogen have been collaborating on the joint development and commercialization of AD treatments since 2014. Eisai serves as the lead of lecanemab development and regulatory submissions globally with both companies co- commercializing and co-promoting the product and Eisai having final decision-making authority.

**3. About the Collaboration between Eisai and BioArctic for Alzheimer's Disease**
Since 2005, Eisai and BioArctic have had a long-term collaboration regarding the development and commercialization of AD treatments. Eisai obtained the global rights to study, develop, manufacture and market lecanemab for the treatment of AD pursuant to an agreement concluded with BioArctic in December 2007. The development and commercialization agreement on the antibody lecanemab back-up was signed in May 2015.

**4. About Eisai Co., Ltd.**
Eisai's Corporate Concept is "to give first thought to patients and people in the daily living domain, and to increase the benefits that health care provides." Under this Concept (also known as human health care (hhc) Concept), we aim to effectively achieve social good in the form of relieving anxiety over health and reducing health disparities. With a global network of R&D facilities, manufacturing sites and marketing subsidiaries, we strive to create and deliver innovative products to target diseases with high unmet medical needs, with a particular focus in our strategic areas of Neurology and Oncology.

In addition, we demonstrate our commitment to the elimination of neglected tropical diseases (NTDs), which is a target (3.3) of the United Nations Sustainable Development Goals (SDGs), with working on various activities together with global partners.

For more information about Eisai, please visit www.eisai.com (for global headquarters: Eisai Co., Ltd.), and connect with us on Twitter @Eisai_SDGs.

**5. About Eisai Inc.**
At Eisai Inc., human health care (hhc) is our mission and is the shared purpose that connects us to those we serve creating a network of powerful relationships that enables us to identify, understand and work to address the needs of people throughout their lives. We boldly push past the boundaries of science and aim to deliver life-changing therapies and health-related solutions that matter to people and society. We bring together science, technology and real-world expertise to pursue a world free from cancer, Alzheimer's disease and other neurodegenerative diseases.

Everything we do is guided by the simple principle that patients and their families come first, and we have a responsibility to listen to and learn from them.

Eisai Inc. is the U.S. pharmaceutical subsidiary of Tokyo-based Eisai Co., Ltd. The company's presence in the U.S. includes three discovery centers as well as commercial, clinical development and global demand organizations. To learn more about Eisai, please visit us at www.eisai.com/US and follow us on Twitter and LinkedIn. For more information on our work in neurology, please visit the Eisai U.S. Neurology LinkedIn page.

Eisai Co., Ltd. is a leading global pharmaceutical company headquartered in Japan. Eisai's corporate philosophy is based on the human health care (hhc) concept, which is to give first thought to patients and their families, and to increase the benefits that health care provides to them. With a global network of R&D facilities, manufacturing sites and marketing subsidiaries, we strive to realize our hhc philosophy by delivering innovative products to target diseases with high unmet medical needs, with a particular focus in our strategic areas of Neurology and Oncology.

Leveraging the experience gained from the development and marketing of a treatment for Alzheimer's disease, Eisai aims to establish the "Eisai Dementia Platform." Through this platform, Eisai plans to deliver novel benefits to those living with dementia and their families through constructing a "Dementia Ecosystem," by collaborating with partners such as medical organizations, diagnostic development companies, research organizations, and bio-ventures in addition to private insurance agencies, finance industries, fitness clubs, automobile makers, retailers, and care facilities. For more information about Eisai Co., Ltd., please visit https://www.eisai.com.

**6. About Biogen**

As pioneers in neuroscience, Biogen discovers, develops, and delivers worldwide innovative therapies for people living with serious neurological diseases as well as related therapeutic adjacencies. One of the world's first global biotechnology companies, Biogen was founded in 1978 by Charles Weissmann, Heinz Schaller, Sir Kenneth Murray, and Nobel Prize winners Walter Gilbert and Phillip Sharp. Today, Biogen has a leading portfolio of medicines to treat multiple sclerosis, has introduced the first approved treatment for spinal muscular atrophy, and developed the first and only approved treatment to address a defining pathology of Alzheimer's disease. Biogen is also commercializing biosimilars and focusing on advancing one of the industry's most diversified pipelines in neuroscience that will transform the standard of care for patients in several areas of high unmet need.

In 2020, Biogen launched a bold 20-year, $250 million initiative to address the deeply interrelated issues of climate, health, and equity. Healthy Climate, Healthy Lives™ aims to eliminate fossil fuels across the company's operations, build collaborations with renowned institutions to advance the science to improve human health outcomes, and support underserved communities.

We routinely post information that may be important to investors on our website at www.biogen.com. Follow us on social media - Twitter, LinkedIn, Facebook, YouTube.

**Biogen Safe Harbor**

This news release contains forward-looking statements, including statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, about the potential clinical effects of lecanemab; the potential benefits, safety and efficacy of lecanemab; potential regulatory discussions, submissions and approvals and the timing thereof; the expected data readout for the Clarity AD study; the treatment of Alzheimer's disease; the anticipated benefits and potential of Biogen's collaboration arrangements with Eisai; the potential of Biogen's commercial business and pipeline programs, including lecanemab; and risks and uncertainties associated with drug development and commercialization. These statements may be identified by words such as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "intend," "may," "plan," "possible," "potential," "will," "would" and other words and terms of similar meaning. Drug development and commercialization involve a high degree of risk, and only a small number of research and development programs result in commercialization of a product. Results in early-stage clinical studies may not be indicative of full results or results from later stage or larger scale clinical studies and do not ensure regulatory approval. You should not place undue reliance on these statements or the scientific data presented.

These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including without limitation unexpected concerns that may arise from additional data, analysis or results obtained during clinical studies, including the Clarity AD clinical trial and AHEAD 3-45 study; the occurrence of adverse safety events; risks of unexpected costs or delays; the risk of other unexpected hurdles; regulatory submissions may take longer or be more difficult to complete than expected; regulatory authorities may require additional information or further studies, or may fail or refuse to approve or may delay approval of Biogen's drug candidates, including lecanemab; actual timing and content of submissions to and decisions made by the regulatory authorities regarding lecanemab; uncertainty of success in the development and potential commercialization of lecanemab; failure to protect and enforce Biogen's data, intellectual property and other proprietary rights and uncertainties relating to intellectual property claims and challenges; product liability claims; third party collaboration risks; and the direct and indirect impacts of the ongoing COVID-19 pandemic on Biogen's business, results of operations and financial condition. The foregoing sets forth many, but not all, of the factors that could cause actual results to differ from Biogen's expectations in any forward-looking statement. Investors should consider this cautionary statement as well as the risk factors identified in Biogen's most recent annual or quarterly report and in other reports Biogen has filed with the U.S. Securities and Exchange Commission. These statements are based on Biogen's current beliefs and expectations and speak only as of the date of this news release. Biogen does not undertake any obligation to publicly update any forward-looking statements, whether as a result of new information, future developments or otherwise.

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