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Eisai Co., Ltd

EISAI TO PRESENT UPDATED DUAL-ACTING LECANEMAB DATA, RESEARCH ON BLOOD BIOMARKERS FOR PREDICTING PRESENCE OF AMYLOID IN THE BRAIN AND NEW FINDINGS ON THE ANTI-MTBR (MICROTUBULE BINDING REGION) TAU ANTIBODY E2814 AT THE 17TH CLINICAL TRIALS FOR ALZHEIMER'S DISEASE CONFERENCE (CTAD)

Eisai Co. Ltd (Headquarters: Tokyo, CEO: Haruo Naito, “Eisai”) announced today that the company will present the latest findings on its Alzheimer’s disease (AD) pipeline and research, including our dual-acting, anti-amyloid beta (Aβ) protofibril* antibody for the treatment of AD, lecanemab (generic name, U.S. brand name: LEQEMBI®), at the Clinical Trials for Alzheimer's Disease Conference (CTAD). The conference will be held in Madrid, Spain, and virtually from October 29 to November 1, 2024. Eisai will present data and research in 4 oral and 6 poster presentations at the meeting, and three symposiums on lecanemab will be held, including the importance of continued treatment of AD, a progressive neurodegenerative disease that begins before plaque deposition and continues after plaque removal. Additional findings from Eisai’s robust Alzheimer’s disease (AD) pipeline will be shared.

Blood Biomarkers

Late Breaking Symposium 1: The AHEAD 3-45 Study: Design and Results of a Novel Screening Process for a Preclinical AD Trial

- On October 29 (Tuesday) from 6:10 to 6:50 p.m. Central European Time (CET), this symposium will present the design of the AHEAD 3-45 trial focused on lecanemab in preclinical AD and the findings on use of plasma biomarkers, amyloid and tau PET imaging in screening.

Lecanemab in Clinical Practice

Late Breaking Symposium 2: One-Year Experience on the Use of Lecanemab in Clinical Practice

- On October 30 (Wednesday) from 3:30 to 4:10 p.m. (CET), this symposium will be discussed real-world evidence from clinical practice with lecanemab in the U.S. and Japan. Eisai will present Real World Settings in the U.S.

Lecanemab Long-Term Benefits

Symposium 1: Does the Current Evidence Base Support Continued Dosing with Lecanemab for Early Alzheimer's Disease?

- The symposium, scheduled for October 30 (Wednesday) from 9:40 to 10:20 a.m. (CET), is an update of the Perspectives sessions conducted at AAIC 2024.

Keynote Presentation 1 ‘Lecanemab: From a Mutation to a Treatment for Alzheimer's Disease’ by Professor emeritus Lars Lannfelt of Uppsala University, founder of BioArctic, will occur October 29 (Tuesday) at 4:30 p.m. (CET). Eisai and BioArctic have had a long-term collaboration regarding the development and commercialization of AD treatments.

“At CTAD 2024, Eisai will present the latest information on the use of dual-acting lecanemab in clinical practice, the use of plasma biomarkers in the AHEAD 3-45 trial to screen for preclinical AD, and the latest data on our anti-MTBR (Microtubule binding region) tau antibody E2814,” said Michael Irizarry, M.D., Deputy Chief Clinical Officer and Senior Vice President of Clinical Research at Eisai Inc. “Alzheimer’s disease is a relentlessly progressive disease caused by a continuous underlying neurotoxic process. There is an urgency to diagnose at the early symptomatic stages because appropriate and continuous treatment can slow the progression of Alzheimer’s disease. The earlier mild cognitive impairment due to AD and mild AD dementia are diagnosed and treated, the greater the opportunity for the patient to benefit.”

Key Presentation

■ Late Breaking Symposium 1:

The AHEAD 3-45 Study: Design and Results of a Novel Screening Process for a Preclinical AD Trial

From 6:10 to 6:50 p.m. (CET) on October 29 (Tuesday)

Presentation Title
The AHEAD 3-45 Study: Adaptation to Challenges
Screening Plasma Biomarkers, Amyloid and Tau PET Imaging in the AHEAD 3-45 Study
Racial and Ethnic Differences in Plasma P-tau217 Biomarker Eligibility Rates in a Preclinical AD Trial
Q&A

■ Late Breaking Symposium 2:

One-Year Experience on the Use of Lecanemab in Clinical Practice

From 3:30 to 4:10 p.m. (CET), on October 30 (Wednesday)

Presentation Title
Lecanemab Treatment in Real World Settings in the United States
Lecanemab Use in Clinical Practice at an Academic Medical Center (Independent to Eisai)
Lecanemab Use in Clinical Practice in Japan (Independent to Eisai)
Q&A

■ Symposium 1

Does the Current Evidence Base Support Continued Dosing with Lecanemab for Early Alzheimer's Disease?

From 9:40 to 10:20 a.m. (CET) on October 30 (Wednesday)

Presentation Title
Mechanistic Rationale for Continued Lecanemab Dosing
Pharmacologic Support for a Maintenance Dosing Regimen with Lecanemab: An Update on the Latest Clinical Pharmacology Data and Modeling
Evidence for a Continued Benefit for Long-Term Lecanemab Treatment: A Benefit/Risk Update from Long-Term Efficacy, Safety and Biomarker Data
Q&A

■ **Roundtable:**

Advancing Combination Therapy: Discussion on Key Considerations, Perspectives, and Promising Avenues for the Future of Alzheimer's Treatments

From 1:45 to 2:15 p.m. (CET) on October 30 (Wednesday)

■ **Oral Presentations**

Asset/Project, Presentation Date and Time (CET)	**Presentation Number, Title**
Lecanemab Oct 30 (Wed) 11:20 – 11:35 a.m.	LB6 Lecanemab for the Treatment of Mild Cognitive Impairment and Mild Dementia Due to Alzheimer's Disease in Adults That Are Apolipoprotein E ε4 Heterozygotes or Non-Carriers
Lecanemab Oct 31 (Wed) 3:25 – 3:40 p.m.	LB18 AI-Derived Prognostic Covariates Enhance the Precision of Lecanemab Efficacy Assessments and Optimize Alzheimer's Disease Clinical Trials
E2814 Oct 29 (Tue) 5:40 – 5:55 p.m.	OC4 Anti-Tau Therapeutic Antibody, E2814, Reduces Early and Late Tau Pathology Biomarkers in Patients with DIAD
Biomarker Nov 1 (Fri) 3:40 – 3:55 p.m.	LB29 The Use of Plasma Biomarkers for the Prediction of Amyloid Positivity

■ **Poster Presentations**

Asset/Project, Presentation Date	**Presentation Number, Title**
Lecanemab Oct 29 (Tue) – Oct 30 (Wed)	LP017 Transitioning from Clinical Trial to Clinical Practice for Long-Term Lecanemab Treatment in Early Alzheimer's Disease: Perspectives from an Alzheimer's Disease Treatment Center
Biomarker Oct 29 (Tue) – Oct 30 (Wed)	P007 Using Plasma pTau217 to Forecast Longitudinal Progression Substantially Increases the Efficiency of AD Clinical Trials
Biomarker Oct 29 (Tue) – Oct 30 (Wed)	P009 Assessing the Feasibility of Implementing Blood-Based Biomarkers as Confirmatory Diagnostic Tools for Early Alzheimer's Disease in Real-World Clinical Practice: A Prospective, Multi-Clinic Implementation Science and Observational Study
Imaging/Biomarker Oct 31 (Thu)	P098 Enhancing the Effectiveness of Alzheimer's Disease Drug Development by Assessing Tau PET as a Promising Surrogate Endpoint Within the Pre-Competitive Critical Path for Alzheimer's Disease (CPAD) Consortium

AD General Nov 1 (Fri)	P206 Risk Prediction Models of Mild Cognitive Impairment Using Electronic Health Record Data
AD General Nov 1 (Fri)	P217 All-Cause Mortality Increased with Intracerebral Hemorrhage in the United States Medicare Beneficiaries 65 Years or Older with Mild Cognitive Impairment or Alzheimer's Dementia

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

* Protofibrils are believed to contribute to the brain injury that occurs with AD and are considered to be the most toxic form of Aβ, having a primary role in the cognitive decline associated with this progressive, debilitating condition.[1] Protofibrils cause injury to neurons in the brain, which in turn, can negatively impact cognitive function via multiple mechanisms, not only increasing the development of insoluble Aβ plaques but also increasing direct damage to brain cell membranes and the connections that transmit signals between nerve cells or nerve cells and other cells. It is believed the reduction of protofibrils may prevent the progression of AD by reducing damage to neurons in the brain and cognitive dysfunction.[2]

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[Notes to editors]

1. **About Lecanemab (LEQEMBI®)**

Lecanemab is the result of a strategic research alliance between Eisai and BioArctic. It is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble (protofibril) and insoluble forms of amyloid-beta (Aβ). Lecanemab is approved in the U.S., Japan, China, South Korea, Hong Kong, Israel, the United Arab Emirates and Great Britain. Eisai has also submitted applications for approval of lecanemab in 10 countries and regions, including the European Union (EU).

LEQEMBI's approvals in these countries were based on Phase 3 data from Eisai's, global Clarity AD clinical trial, in which it met its primary endpoint and all key secondary endpoints with statistically significant results. The primary

endpoint was the global cognitive and functional scale, Clinical Dementia Rating Sum of Boxes (CDR-SB). In the Clarity AD clinical trial, treatment with lecanemab reduced clinical decline on CDR-SB by 27% at 18 months compared to placebo.[3,4] The mean CDR-SB score at baseline was approximately 3.2 in both groups. The adjusted least-squares mean change from baseline at 18 months was 1.21 with lecanemab and 1.66 with placebo (difference, −0.45; 95% confidence interval [CI], −0.67 to −0.23; P<0.001). In addition, the secondary endpoint from the AD Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL), which measures information provided by people caring for patients with AD, noted a statistically significant benefit of 37% compared to placebo. The adjusted mean change from baseline at 18 months in the ADCS-MCI-ADL score was −3.5 in the lecanemab group and −5.5 in the placebo group (difference, 2.0; 95% CI, 1.2 to 2.8; P<0.001). The ADCS MCI-ADL assesses the ability of patients to function independently, including being able to dress, feed themselves and participate in community activities. The most common adverse events (>10%) in the lecanemab group were infusion reactions, ARIA-H (combined cerebral microhemorrhages, cerebral macrohemorrhages, and superficial siderosis), ARIA-E (edema/effusion), headache, and fall.

In July 2024 Eisai presented 36-month data from the Phase 3 Clarity AD Open-Label Extension Study demonstrating that LEQEMBI-treated patients continued to show benefit at 36 months of treatment. In the 18-month core study of Clarity AD, there was a statistically significant difference in global cognition and function as measured by CDR-SB between the LEQEMBI and placebo groups. The separation in CDR-SB between the group that continued to receive LEQEMBI (early start group) and the group who switched from placebo to LEQEMBI (delayed start group) was maintained during the 6-month OLE following the core study. This indicates that similar disease trajectory for both early and delayed start groups occurred with LEQEMBI administration. The blood biomarker results (plasma Aβ42/40 ratio, ptau181, GFAP and NfL) showed improvement even after delayed initiation of treatment with LEQEMBI.

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 AD and related dementias in the U.S, funded by the National Institute on Aging, part of the National Institutes of Health, Eisai and Biogen. Since January 2022, the Tau NexGen clinical study for Dominantly Inherited AD (DIAD), that is conducted by Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU), led by Washington University School of Medicine in St. Louis, is ongoing and includes lecanemab as the backbone anti-amyloid therapy.

2. About E2814

An investigational anti-microtubule binding region (MTBR) tau antibody, E2814, is being developed as a disease-modifying agent for tauopathies including sporadic AD. Phase I clinical studies are underway. E2814 was discovered as part of the research collaboration between Eisai and University College London. E2814 is designed to prevent the spreading of tau seeds within the brains of affected individuals. In addition, E2814 has been selected as an anti-tau therapy in a Phase II/III Tau NexGen study for the treatment of DIAD, conducted by DIAN-TU led by Washington University School of Medicine in St. Louis, is underway.

3. 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 Eisai and Biogen co-commercializing and co-promoting the product and Eisai having final decision-making authority.

4. 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 with BioArctic in December 2007. The development and commercialization agreement on the antibody lecanemab back-up was signed in May 2015.

References

1. Amin L, Harris DA. Aβ receptors specifically recognize molecular features displayed by fibril ends and neurotoxic oligomers. *Nat Commun*. 2021;12:3451. doi:10.1038/s41467-021-23507-z
2. Ono K, Tsuji M. Protofibrils of Amyloid-β are Important Targets of a Disease-Modifying Approach for Alzheimer's Disease. *Int J Mol Sci.* 2020;21(3):952. doi: 10.3390/ijms21030952. PMID: 32023927; PMCID: PMC7037706.
3. Eisai presents full results of lecanemab Phase 3 confirmatory Clarity AD study for early Alzheimer's disease at Clinical Trials on Alzheimer's Disease (CTAD) conference. Available at: https://www.eisai.com/news/2022/news202285.html
4. van Dyck, C., et al. Lecanemab in Early Alzheimer's Disease. *New England Journal of Medicine.* 2023;388:9-21. https://www.nejm.org/doi/full/10.1056/NEJMoa2212948.