No.24-53

July 23, 2024
Eisai Co., Ltd.

EISAI TO PRESENT DUAL-ACTING LECANEMAB THREE YEAR EFFICACY AND SAFETY DATA AND DISCUSS LONG-TERM OUTCOMES OF CONTINUED TREATMENT AT THE ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE 2024

Latest findings from Eisai's robust Alzheimer's disease (AD) pipeline will be shared, including the importance of continued treatment of AD, which is a progressive neurodegenerative disease that begins before plaque deposition and continues after plaque removal

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 Alzheimer's Association International Conference (AAIC). Dual-acting lecanemab is the only early AD treatment available to support neuronal function by clearing the highly toxic protofibrils that continue to cause neuronal injury and death even after plaques have been cleared from the brain. The conference will be held in Philadelphia and virtually from July 28 to August 1, 2024. Eisai will present data and research in four (4) oral and 15 poster presentations at the meeting and will host two (2) sessions on lecanemab.

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

- On July 30 from 4:15 p.m. to 5:45 p.m. EDT, Eisai will present the latest data exploring three critical topics:
  1) Does the current evidence for lecanemab mechanism support a rationale for continued lecanemab dosing?
  2) Is the lecanemab maintenance dosing regimen supported by simulation models?
  3) Is there evidence for a continued benefit for long-term lecanemab treatment?
- Dennis Selkoe, M.D., will focus on the toxicity of soluble aggregated amyloid-beta species, including oligomers, protofibrils and diffusible fibrils. The session will review the latest data on the mechanism of action of lecanemab, which binds to protofibrils and oligomers that continue to be produced even after plaques are cleared. Additional discussion will focus on the potential mechanistic justification for ongoing treatment to maintain clinical and biomarker efficacy.
- Data from an intervening off-treatment period (gap period) occurring after the completion of the core phase of the Phase II Study 201 and before the initiation of the open-label extension (OLE) suggested the importance of continued administration of lecanemab. Youfang Cao, PhD., and Larisa Reyderman, Ph,D., from Eisai will present clinical pharmacology data and clinical pharmacology modeling outcomes that combine the outcomes from Study 201 and the Phase 3 Clarity AD study, which will provide insights into potential lecanemab maintenance dosing.
- Christopher van Dyck, M.D., will present the latest 36-month efficacy and safety data from dual-acting lecanemab's Phase 3 Clarity AD core and OLE studies and panelists will discuss the potential benefits of continuous treatment of AD, which is a progressive, neurodegenerative disease that begins before plaque deposition and continues after plaque removal.

Featured Research Session: Beyond Amyloid Removal with Lecanemab Treatment: Update on Long-Term Imaging and Fluid Biomarkers.

- In this Featured Research session on July 30 from 2:00 PM to 3:30 PM EDT, the latest findings on imaging and fluid biomarkers from dual-acting lecanemab treatment will be presented.
- Brian Willis, PhD., and Arnaud Charil, PhD of Eisai will present the outcomes of recent PK/PD modeling examining the potential connection between dual-acting lecanemab's PK and amyloid PET, CDR-SB, and the outcomes of the tau PET from Carity AD core and OLE studies.
- Nick Fox, M.D., FRCP, FMedSci, will explain the changes in brain volume that occur with anti-amyloid immunotherapy and its potential relationship to amyloid clearance.
- Charlotte Teunissen, PhD., will present data on neurodegenerative biomarkers in plasma as a result of long-term treatment of dual-acting lecanemab, and will also explain the necessity for maintenance treatment from these changes in biomarkers.

"At AAIC 2024, Eisai will present the results from the Phase 2 and Phase 3 lecanemab studies and open label extensions exploring ongoing dosing with dual-acting lecanemab for potential longer-term clinical and biomarker benefit," said Michael Irizarry, M.D., Deputy Chief Clinical Officer and Senior Vice President of Clinical Research at Eisai Inc. "Alzheimer's disease (AD) is a progressive and relentless disease caused by a continuous underlying neurotoxic process. There is an urgency to treat because early and ongoing treatment can slow the progression of Alzheimer's disease. The earlier mild cognitive impairment (MCI) due to AD and mild AD dementia are diagnosed and treated, the greater the opportunity for the patient to benefit."

Key Presentation

■ Perspectives Session:

Does the Current Evidence Base Support Lecanemab Continued Dosing for Early Alzheimer's Disease? From 4:15 PM to 5:45 PM EDT on July 30, 2024

Session Program
Does the Current Evidence for Lecanemab Mechanism Support a Rationale for Continued Lecanemab Dosing?
How Does the Latest Clinical Pharmacology Data & Modeling Support Continued Lecanemab Dosing?
Neuro-Dynamic Quantitative Systems Pharmacology (QSP) Model Supports Continued Lecanemab Treatment With Maintenance Dosing For Alzheimer's Disease
Is there Evidence for a Continued Benefit for Long-Term Lecanemab Treatment? A Benefit/Risk Update from Long-Term Efficacy, Safety and Biomarker Data
Q&A

■ Featured Research Session

Beyond Amyloid Removal with Lecanemab Treatment: Update on Long-Term Imaging and Fluid Biomarkers From 2:00 PM to 3:30 PM EDT on July 30, 2024

Session Program
Amyloid Plaque Reduction as a Biomarker of Efficacy: Assessment of Amyloid PET and Change in CDR-SB Utilizing Semi-Mechanistic Model
Lecanemab Slows Tau PET Accumulation
“Paradoxical” Cerebral Volume Changes in Anti-Amyloid Immunotherapy Trials
Long-Term Effects of Lecanemab on Biomarkers of Neurodegeneration in Plasma
Q&A

■ Oral Presentations

Asset/Project, Presentation Date and Time (EDT, U.S)	Topic, Abstract number
Lecanemab July 30 (Tue) 2:42 PM – 2:49 PM	Examining Lecanemab-Associated Amyloid-Beta Protofibril as a Proximal Biomarker of Neurodegeneration Unlike Other Plaque-Associated Biomarkers Abstract ID #94585
Lecanemab July 30 (Tue) 2:49 PM – 2:56 PM	Lecanemab, Amyloid-Induced Tau Pathology as Supported CSF MTBR-tau243 in Clarity AD Abstract ID #95507
E2027 July 31 (Wed) 5:05 PM – 5:15 PM	The Effects of the Novel Phosphodiesterase 9 (pde9) Inhibitor E2027 (irsenontrine) on CSF Proteomics Profile in Amyloid Positive and Amyloid Negative Lewy Body Dementia Abstract ID #91293
General AD July 29 (Mon) 8:00 AM - 8:10 AM	Unmet Needs in the Diagnosis and Management of Early AD in Community-Based Settings in the United States Abstract ID #89135

■ Poster Presentations

Asset/Project, Presentation Date and Time (EDT, U.S)	Topic, Abstract number
Lecanemab July 28 (Sun)	Model-Based Assessment of Lecanemab Maintenance Dosing Regimen and Potential for Continued Suppression of Amyloid Plaque, Disease Progression Abstract ID #89308
E2814 July 30 (Tue)	Crystal Structure of E2814 Bound to Tau Abstract ID #94773
E2511 July 28 (Sun)	Non-Clinical Evidence for Modulating Synaptic CSF Biomarkers by E2511: A Novel Small Compound TrkA Biased Positive Allosteric Modulator Abstract ID #95071

E2025 July 28 (Sun)	E2025, A Novel Anti-EphA4 Antibody, Enhances EphA4 Cleavage, and Suppresses Tau Pathologies in a Transgenic Model of AD Abstract ID #94810
Biomarker July 29 (Mon)	Prediction of Regional Brain Tau Levels in Early Alzheimer's Disease Using Plasma pTau217 Abstract ID #95793
Biomarker July 31 (Wed)	A Prospective Multi-Clinic Implementation Science Study to Evaluate Use of Blood- Based Biomarkers as Confirmatory Diagnostic Tools for Early Alzheimer's Disease in Real-World Clinical Practice Abstract ID #88784
Biomarkers July 30 (Tue)	Advancing Early Detection of Alzheimer's Disease in the Primary Care Setting in the United States Abstract ID #86582
Imaging July 31 (Wed)	Volumes of Specific Substrates Within the Amygdala and Hippocampus are Impacted by Brain Amyloid-β Abstract ID #92024
General AD July 28 (Sun)	Total Healthcare Costs Across the Alzheimer's Disease Continuum in the United States (US) Abstract ID #86386
General AD July 29 (Mon)	Risk Factors for Mild Cognitive Impairment: Prediction Models Developed with Electronic Health Record Data Abstract ID #85564
General AD July 29 (Mon)	Patterns in the Diagnosis and Management of Early AD in Community-Based Settings in the United States Abstract ID #92630
General AD July 30 (Tue)	Usage Patterns of Anticoagulant Therapy in Patients with Mild Cognitive Impairment or Alzheimer's Disease Abstract ID #86110
General AD July 30 (Tue)	Adapting Healthcare Infrastructure for Disease-Modification in Early Alzheimer's Disease Abstract ID #94773
General AD July 31 (Wed)	Critical Path for Alzheimer's Disease (CPAD) Consortium: Data-Driven Solutions for Clinical Trial Design and Informed Decision Making Abstract ID #86145
General AD July 29 (Mon)	Expectations and Perspectives of Patients and Physicians on New Treatment for Early Alzheimer's Disease: Results of a Physician Survey and Patient Focus Group Interview Abstract ID #86956

Poster viewing time is set from 3:30PM to 4:15PM, during break and lunch time on the date of presentation.

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]

Media Inquiries:
Eisai Co., Ltd.
Public Relations Department
TEL: +81 (0)3-3817-5120

Eisai Inc. (U.S.)
Libby Holman
+1-201-753-1945
Libby_Holman@Eisai.com

Eisai Europe, Ltd. (UK, Europe, Australia, New Zealand and Russia)
EMEA Communications Department
+44 (0) 786 601 1272
EMEA-comms@eisai.net

[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 and Israel. Eisai has also submitted applications for approval of lecanemab in 12 countries and regions, including the European Union (EU).

LEQEMBI's FDA approval was 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 November 2023, Eisai presented 24-month data from the Phase 3 Clarity AD open Label Extension Study demonstrating that LEQEMBI-treated patients continued to show benefit at 24 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.

These results suggest that LEQEMBI treatment may affect clinical outcomes through improvement of AD pathology. 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, a Phase II/III Tau NexGen study for the treatment of dominantly inherited Alzheimer's disease (DIAD), conducted by the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) led by Washington University School of Medicine in St. Louis (St. Louis, MO, USA), is underway.

3. About E2511

E2511 is Eisai’s in-house discovered and developed investigational novel molecule that directly binds to tropomyosin receptor kinase A (TrkA); a nerve growth factor (NGF) located on the neural cell membrane. E2511 could potentially promote recovery and synaptic remodeling of damaged cholinergic neurons. A Phase 1 study for E2511 is underway.

4. About E2025

E2025 is Eisai’s in-house discovered and developed investigational novel anti-EphA4 (Erythropoietin-producing hepatocellular receptor A4) antibody that enhances EphA4 cleavage. E2025 could potentially promote synaptic remodeling of glutamic neurons. A Phase 1 study for E2025 is underway.

5. 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.

6. 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.co.jp/news/2022/news202285.html
4. van Dyck, H., 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.