# EISAI SUBMITS MARKETING AUTHORIZATION APPLICATION FOR LECANEMAB AS TREATMENT FOR EARLY ALZHEIMER'S DISEASE IN EUROPE

January 10, 2023

**TOKYO and CAMBRIDGE, Mass., January 10, 2023 –** Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") and Biogen Inc. (Nasdaq: BIIB, Corporate headquarters: Cambridge, Massachusetts, CEO: Christopher A. Viehbacher, "Biogen") announced today that Eisai has submitted a marketing authorization application (MAA) for lecanemab (Brand Name in the U.S.: LEQEMBI™), an investigational anti-amyloid beta (Aβ) protofibril antibody, for the treatment of early Alzheimer's disease (mild cognitive impairment due to Alzheimer's disease (AD) and mild AD dementia) to the European Medicines Agency (EMA). This application is based on the results of the Phase III Clarity AD study and the Phase IIb clinical study (Study 201), which demonstrated that lecanemab treatment showed a reduction of clinical decline in early AD, and is subject to a validation to determine whether the EMA accepts the application for review.

The Clarity AD study met its primary endpoint (CDR-SB[1]: Clinical Dementia Rating-Sum of Boxes) and all key secondary endpoints with highly statistically significant results. 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 2022, the results of the Clarity AD study were presented at the 2022 Clinical Trials on Alzheimer's Disease (CTAD) conference , and simultaneously published in *the New England Journal of Medicine*, peer-reviewed medical journals.

In the U.S., lecanemab was granted accelerated approval as a treatment for AD by the U.S. Food and Drug Administration (FDA) on January 6, 2023. Eisai submitted a Supplemental Biologics License Application (sBLA) to the FDA for approval under the traditional pathway on the same day. In China, Eisai has initiated submission of data for BLA to the National Medical Products Administration (NMPA) of China in December 2022. In Japan, Eisai plans to submit a marketing authorization application by the end of Eisai's fiscal year 2022, which ends March 31, 2023.

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.

[1] CDR-SB is a numeric scale used to quantify the various severity of symptoms of dementia. Based on interviews of people living with AD and family/caregivers, qualified healthcare professionals assess cognitive and functional performance in six areas: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The total score of the six areas is the score of CDR-SB, and CDR-SB is also used as an appropriate item for evaluating the effectiveness of therapeutic drugs targeting the early stages of AD.


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**[Notes to editors]**

1. **INDICATION, DOSAGE AND ADMINISTRATION, AND IMPORTANT SAFETY INFORMATION IN THE U.S.**

**INDICATION**

LEQEMBI is indicated for the treatment of Alzheimer's disease. Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with LEQEMBI. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS**

**Amyloid Related Imaging Abnormalities**

LEQEMBI can cause amyloid related imaging abnormalities-edema (ARIA-E) and -hemosiderin deposition (ARIA-H). ARIA-E can be observed on MRI as brain edema or sulcal effusions, and ARIA-H as microhemorrhage and superficial siderosis. ARIA is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. Reported symptoms associated with ARIA may include headache, confusion, visual changes, dizziness, nausea, and gait difficulty. Focal neurologic deficits may also occur. Symptoms associated with ARIA usually resolve over time.

**ARIA Monitoring and Dose Management Guidelines**

- Obtain recent (within one year) brain magnetic resonance imaging (MRI) prior to initiating treatment with LEQEMBI. Obtain an MRI prior to the 5th, 7th, and 14th infusions.
- Recommendations for dosing in patients with ARIA-E and ARIA-H depend on clinical symptoms and radiographic severity. Depending on ARIA severity, use clinical judgment in considering whether to continue dosing, temporarily discontinue treatment, or permanently discontinue LEQEMBI.
- Enhanced clinical vigilance for ARIA is recommended during the first 14 weeks of treatment with LEQEMBI. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI if indicated. If ARIA is observed on MRI, careful clinical evaluation should be performed prior to continuing treatment.
- There is no experience in patients who continued dosing through symptomatic ARIA-E or through asymptomatic, but radiographically severe, ARIA-E. There is limited experience in patients who continued dosing through asymptomatic but radiographically mild to moderate ARIA-E. There are limited data in dosing patients who experienced recurrent ARIA-E.

**Incidence of ARIA**

- In Study 1 (Study 201), symptomatic ARIA occurred in 3% (5/161) of LEQEMBI-treated patients. Clinical symptoms associated with ARIA resolved in 80% of patients during the period of observation.
- Including asymptomatic cases, ARIA was observed in LEQEMBI: 12% (20/161); placebo: 5% (13/245). ARIA-E was observed in LEQEMBI: 10% (16/161); placebo: 1% (2/245). ARIA-H was observed in LEQEMBI: 6% (10/161); placebo: 5% (12/245). There was no increase in isolated ARIA-H for LEQEMBI compared to placebo.
- Intracerebral hemorrhage >1 cm in diameter was reported after one treatment in LEQEMBI: 1 patient; placebo: zero patients. Events of intracerebral hemorrhage, including fatal events, in patients taking LEQEMBI have also been reported in other studies.

**Apolipoprotein E ε4 (ApoE ε4) Carrier Status and Risk of ARIA**

- In Study 1, 6% (10/161) of patients in the LEQEMBI group were ApoE ε4 homozygotes, 24% (39/161) were heterozygotes, and 70% (112/161) were noncarriers.
- The incidence of ARIA was higher in ApoE ε4 homozygotes than in heterozygotes and noncarriers among patients treated with LEQEMBI. Of the 5 LEQEMBI-treated patients who had symptomatic ARIA, 4 were ApoE ε4 homozygotes, 2 of whom experienced severe symptoms. An increased incidence of symptomatic and overall ARIA in ApoE ε4 homozygotes compared to heterozygotes and noncarriers in LEQEMBI-treated patients has been reported in other studies.
- The recommendations on management of ARIA do not differ between ApoE ε4 carriers and noncarriers.
- Consider testing for ApoE ε4 status to inform the risk of developing ARIA when deciding to initiate treatment with LEQEMBI.

**Radiographic Findings**

- The majority of ARIA-E radiographic events occurred early in treatment (within the first 7 doses), although ARIA can occur at any time and patients can have more than 1 episode. The maximum radiographic severity of ARIA-E in patients treated with LEQEMBI was mild in 4% (7/161) of patients, moderate in 4% (7/161) of patients, and severe in 1% (2/161) of patients. Resolution on MRI occurred in 62% of ARIA-E patients by 12 weeks, 81% by 21 weeks, and 94% overall after detection. The maximum radiographic severity of ARIA-H microhemorrhage in patients treated with LEQEMBI was mild in 4% (7/161) of patients and severe in 1% (2/161) of patients; 1 of the 10 patients with ARIA-H had mild superficial siderosis.

**Concomitant Antithrombotic Medication and Other Risk Factors for Intracerebral Hemorrhage**

- Patients were excluded from enrollment in Study 1 for baseline use of anticoagulant medications. Antiplatelet medications such as aspirin and clopidogrel were allowed. If anticoagulant medication was used because of intercurrent medical events that required treatment for ≤4 weeks, treatment with LEQEMBI was to be temporarily suspended.
- Most exposures to antithrombotic medications were to aspirin; few patients were exposed to other antiplatelet drugs or anticoagulants, limiting any meaningful conclusions about the risk of ARIA or intracerebral hemorrhage in patients taking other antiplatelet drugs or anticoagulants. Because intracerebral hemorrhages >1 cm in diameter have been observed in patients taking LEQEMBI, additional caution should be exercised when considering the administration of antithrombotics or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with LEQEMBI.
- Patients were excluded from enrollment in Study 1 for the following risk factors for intracerebral hemorrhage: prior cerebral hemorrhage >1 cm in greatest diameter, more than 4 microhemorrhages, superficial siderosis, evidence of vasogenic edema, evidence of cerebral contusion, aneurysm, vascular malformation, infective lesions, multiple lacunar infarcts or stroke involving a major vascular territory, and severe small vessel or white matter disease. Caution should be exercised when considering the use of LEQEMBI in patients with these risk factors.

**Infusion-Related Reactions**

- Infusion-related reactions were observed in LEQEMBI: 20% (32/161); placebo: 3% (8/245), and the majority of cases in LEQEMBI-treated patients (88%, 28/32) occurred with the first infusion. All infusion-related reactions were mild (56%) or moderate (44%) in severity. Infusion-related reactions resulted in discontinuations in 2% (4/161) of patients treated with LEQEMBI. Symptoms of infusion-related reactions included fever and flu-like symptoms (chills, generalized aches, feeling shaky, and joint pain), nausea, vomiting, hypotension, hypertension, and oxygen desaturation.
- After the first infusion, 38% of LEQEMBI-treated patients had transient decreased lymphocyte counts to <0.9 x109/L compared to 2% on placebo, and 22% of LEQEMBI-treated patients had transient increased neutrophil counts to >7.9 x109/L compared to 1% on placebo.
- In the event of an infusion-related reaction, the infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy initiated as clinically indicated. Prophylactic treatment with antihistamines, acetaminophen, nonsteroidal anti-inflammatory drugs, or corticosteroids prior to future infusions may be considered.

**ADVERSE REACTIONS**

- In Study 1, 15% of LEQEMBI-treated patients, compared to 6% of placebo-treated patients, stopped study treatment because of an adverse reaction. The most common adverse reaction leading to discontinuation of LEQEMBI was infusion-related reactions that led to discontinuation in 2% (4/161) of patients treated with LEQEMBI compared to 1% (2/245) of patients on placebo.
- The most common adverse reactions reported in ≥5% of patients treated with LEQEMBI (N=161) and ≥2% higher than placebo (N=245) in Study 1 were infusion-related reactions (LEQEMBI: 20%; placebo: 3%), headache (LEQEMBI: 14%; placebo: 10%), ARIA-E (LEQEMBI: 10%; placebo: 1%), cough (LEQEMBI: 9%; placebo: 5%), and diarrhea (LEQEMBI: 8%; placebo: 5%).

**Please see full Prescribing Information.**

## 2. About Lecanemab

Lecanemab (Brand Name in the U.S.: LEQEMBI™) is the result of a strategic research alliance between Eisai and BioArctic. Lecanemab is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble (protofibril) and insoluble forms of amyloid-beta (Aβ). In the U.S., LEQEMBI was granted accelerated approval by the U.S. Food and Drug Administration (FDA) on January 6, 2023. LEQEMBI is indicated for the treatment of Alzheimer's disease (AD) in the U.S. Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in Aβ plaques observed in patients treated with LEQEMBI. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.

Eisai has completed lecanemab subcutaneous bioavailability study, and subcutaneous dosing is currently being evaluated in the Clarity AD (Study 301) OLE.

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.

## 3. About Phase IIb (Study 201) study and Phase III Clarity AD study

Phase IIb clinical study (Study 201) was conducted as a double-blind, parallel-group, dose-finding study of lecanemab or placebo for 18 months in 856 people living with early AD. Lecanemab treatment resulted in a dose-dependent, longitudinal, and significant reduction in PET SUVR, which assesses amyloid-β accumulation in the brain, compared to placebo. At 18 months, ADCOMS[2], CDR-SB, and ADAS-cog14[3] showed a dose-dependent reduction in clinical decline, with suppression rates of 29.7%, 26.5%, and 47.2% in the 10 mg/kg bi-weekly treatment, respectively. The study did not achieve its primary outcome measure[4] at 12 months of treatment. The most common adverse events occurring in the 10 mg/kg biweekly group (incidence ≥ 5% and more frequent than in the placebo group) were infusion reactions (19.9%), headache (13.7%), ARIA-E (9.9%), cough (8.7%), diarrhea (8.1%), dizziness (7.5%), cerebral microhemorrhages (5.6%).

[2] Developed by Eisai, ADCOMS combines items from the ADAS-Cog scale for assessing cognitive functions, MMSE and the CDR scale for evaluating the severity of dementia to enable highly sensitive detection of changes in clinical functions of early AD symptoms and changes in memory

[3] ADAS-Cog is the most common cognitive assessment instrument used in AD clinical trials all over the world. ADAS-Cog14 consists of 14 competencies: word recall, commands, constructional praxis, object and finger naming, ideational praxis, orientation, word recognition, remembering word recognition instructions, comprehension of spoken language, word finding difficulty, spoken language ability, delayed word recall, number cancellation, and maze task. ADAS-Cog has been used in clinical trials for earlier stages of AD including MCI.

[4] 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.

Phase III Clarity AD study was conducted as a placebo-controlled, double-blind, parallel-group, randomized study of lecanemab 10 mg/kg or placebo administered bi-weekly for 18 months in 1,795 people living with early AD. Mean change of CDR-SB from baseline at 18 months as the primary endpoint was 1.21 and 1.66 for lecanemab and placebo groups, respectively. Lecanemab treatment resulted in highly statistically significant results, reducing clinical decline on the global cognitive and functional scale, compared with placebo at 18 months by -0.45 (95% Confidence Interval (CI): -0.67, -0.23; P=0.00005), representing a 27% slowing of decline. Starting as early as six months (difference: -0.17 [95% CI: -0.29, -0.05]; P<0.01), and increasing in absolute difference over time across all time points every 3 months, the treatment showed highly statistically significant changes in CDR-SB from baseline compared to placebo (all p-values are less than 0.01). All key secondary endpoints, amyloid Positron Emission Tomography (PET) using Centiloids, ADAS-Cog14, ADCOMS and ADCS MCI-ADL[5], also showed highly statistically significant results compared with placebo (P<0.001).

The most common adverse events (>10%) in the lecanemab group were infusion reactions (lecanemab: 26.4%; placebo: 7.4%), ARIA-H (combined cerebral microhemorrhages, cerebral macrohemorrhages, and superficial siderosis; lecanemab: 17.3%; placebo: 9.0%), ARIA-E (edema/effusion; lecanemab: 12.6%; placebo: 1.7%), headache (lecanemab: 11.1%; placebo: 8.1%), and fall (lecanemab: 10.4%; placebo: 9.6%). Infusion reactions were largely mild-to-moderate (grade 1-2: 96%) and occurred on the first dose (75%).

During the study period, deaths occurred in 0.7% and 0.8% of participants in the lecanemab and placebo groups, respectively and no deaths were related to lecanemab or occurred with amyloid-related imaging abnormalities (ARIA) in 18-month double-blind study period. Serious adverse events were experienced by 14.0% of participants in the lecanemab group and 11.3% of participants in the placebo group. Treatment-emergent adverse events occurred in 88.9% and 81.9% of participants in the lecanemab and placebo groups, respectively. Treatment-emergent adverse events leading to drug withdrawal occurred in 6.9% and 2.9% of participants in the lecanemab and placebo groups, respectively.

Overall, lecanemab's ARIA incidence profile was within expectations based on the Phase 2 trial results. ARIA-E events were largely mild-to-moderate radiographically (91% of those who had ARIA-E), asymptomatic (78% of those who had ARIA-E), occurred within the first 3 months of treatment (71% of those who had ARIA-E) and resolved within 4 months of detection (81% of those who had ARIA-E). Among the 2.8% of lecanemab-treated subjects with symptomatic ARIA-E, the most commonly reported symptoms were headache, visual disturbance, and confusion. The incidence of symptomatic ARIA-H was 0.7% in the lecanemab group and 0.2% in the placebo group. No imbalance was observed in isolated ARIA-H (i.e., ARIA-H in participants who did not also experience ARIA-E) between lecanemab (8.9%) and placebo (7.8%).

[5] ADCS MCI-ADL assesses the competence of patients with MCI in activities of daily living (ADLs), based on 24 questions to the patient's partner about actual recent activities of daily living.

## 4. About the Collaboration between Eisai and Biogen for AD

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.

## 5. About the Collaboration between Eisai and BioArctic for AD

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.

## 6. 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.

## 7. 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 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.

The company routinely posts information that may be important to investors on its website at www.biogen.com. Follow Biogen 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 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.