Eisai Initiates BLA Submission of Data for Lecanemab in China

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TOKYO and CAMBRIDGE, 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 initiated submission of data for Biologics License Application (BLA) to the National Medical Products Administration (NMPA) of China for lecanemab (development code: BAN2401), an investigational anti-amyloid beta (Aβ) protofibril antibody.

The registration category of lecanemab was designated as a Category 1 drug (innovative biologics not approved in China or any other countries).
The data submitted in this package includes data from the Phase II clinical trial (Study 201) in mild cognitive impairment (MCI) due to Alzheimer's disease (AD) and mild AD (collectively known as early AD) with confirmed Aβ accumulation in the brain and the top-line data of the large global Phase III Clarity AD study. Eisai will submit additional data including full data of the Clarity AD study, as directed by the NMPA.

Lecanemab selectively binds and eliminates soluble, toxic Aβ aggregates (protofibrils) that are thought to contribute to the neurotoxicity 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. The Clarity AD study of lecanemab met its primary endpoint and all key secondary endpoints with highly statistically significant results. 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 Breakthrough Therapy and Fast Track designations by the U.S. Food and Drug Administration (FDA) in June and December 2021, respectively. In July 2022, the FDA accepted Eisai's BLA for lecanemab under the accelerated approval pathway and granted it Priority Review. The Prescription Drug User Fee Act (PDUFA) action date is January 6, 2023. Eisai aims to file for traditional approval in the U.S. and for marketing authorization applications in Japan and the Europe by the end of Eisai's FY2022, 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.

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[Notes to editors]

1. About Lecanemab

Lecanemab is an investigational humanized monoclonal antibody for AD that is the result of a strategic research alliance between Eisai and BioArctic. Lecanemab selectively binds and eliminates soluble, toxic amyloid-beta (Aβ) aggregates (protofibrils) that are thought to contribute to the neurotoxicity 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.
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.
Furthermore, Eisai has initiated a lecanemab subcutaneous dosing Phase 1 study.

2. About Phase II (Study 201) study and Phase III Clarity AD study

Phase II 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[1], CDR-SB[2], and ADAS-cog14[3] showed a dose-dependent reducing 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%), microhemorrhages (5.6%).

[1] ADCOMS is 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

[2] 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.

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 (Study 201). 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.

3. About Registration Categories of Biological Agents (Therapeutic Use) in China

The registration categories of biologics (therapeutic use) in China include categories 1 through 3. Category 1 is for innovative biologics that have not been approved in China or in any other countries; Category 2 is for biologics that improve on products approved in China or any other countries, improving safety, efficacy, quality, and having clear therapeutic superiority; and Category 3 is for biologics that have been approved in China or any other countries. Applications under Category 1 are more likely to receive priority review designation, which is expected to shorten the review period.

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 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.

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.

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