Latest Findings on Lecanemab - Clinical Efficacy, Aria Rates, Biomarkers Relationship to Clinical Outcomes and Dosing Regimens - Presented at AD/PD™ 2022 Annual Meeting

March 21, 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 today that the latest findings on lecanemab, an investigational anti-amyloid-beta (Aβ) protofibril antibody being developed for the treatment of early Alzheimer's disease (AD), were presented at the Aβ Targeted Therapies in AD 2 Symposium at the 2022 International Conference on Alzheimer's and Parkinson's Diseases (AD/PD™) March 15-20 in Barcelona, Spain and virtually.

Four key symposium presentations explored how lecanemab's clinical efficacy data, overall amyloid-related imaging abnormality (ARIA) rates, biomarker relationships to clinical outcomes, potential dosing regimens, and administration have the potential to benefit people living with early AD.

1. Science of the Amyloid Cascade and Distinct Mechanism of Action (MoA) of Lecanemab

- BioArctic's Professor Lars Lannfelt presented the science of the amyloid cascade and studies evaluating lecanemab's distinct binding profile to antibodies created from patented sequences of two other clinical antibodies, aducanumab and gantenerumab. The three antibodies have different binding profiles to Aβ species. All three antibodies bind to fibrils, but with different selectivity. Lecanemab was the strongest Aβ binder and prefers protofibrils. Lecanemab's binding profile is critical to enriching our understanding of the features in clinical outcomes and safety. BioArctic has had a long-term collaboration with Eisai regarding the development and commercialization of drugs for the treatment of AD.

2. Key Trial Design Aspects and Clinical Outcomes of the Lecanemab Phase 2b (Study 201) Trial and Open-Label Extension (OLE) in Early AD

- **Innovative Bayesian Adaptive Randomization Design and Dose Regimen-Finding Study with OLE** – Study 201 (published by Eisai in Alz Res Therapy 13;21) was prospectively designed as a blinded 18-month study. To accelerate the development program, Eisai used a Bayesian adaptive design with a prespecified 12-month Bayesian primary endpoint in addition to the prespecified traditional analysis at the end of the 18-month treatment period. The OLE evaluated the long-term safety and tolerability of lecanemab and the effect of lecanemab on amyloid PET over 12 months of treatment, which looked at treatment naïve patients (those on placebo during the core study) and those patients who had previously been treated with lecanemab, including earlier time points (3 and 6 months) than in the core phase (12 and 18 months). Eisai's study design provided the opportunity to explore the biomarker and clinical effects of stopping and restarting lecanemab across five years of disease trajectory.
- **Rapid and Thorough Amyloid Clearance Correlates with Clinical Benefit** – By using the Bayesian study design across a broad range of doses, researchers were able to efficiently and effectively identify the most effective dose, 10 mg/kg biweekly, to produce rapid and thorough amyloid clearance and potential clinical efficacy. Of the approximately 12 treatment-naïve patients in the OLE (those who received placebo in the Core study), more than 40 percent were amyloid negative as early as 3 months and more than 80% were amyloid negative by 12 months as measured by PET image (visual read).1 The OLE results are consistent with core phase results in which 65% were amyloid negative at 12 months1 and 81% of participants were amyloid negative at 18 months as measured by PET image (visual read) in 161 subjects treated with 10 mg/kg biweekly dose. Robust amyloid reduction in those receiving lecanemab in the Core study was maintained while off-treatment over the Gap period. Despite the small number of participants in the OLE, findings help confirm the results from the Core study: lecanemab rapidly and thoroughly cleared amyloid plaque from the brain. Study 201 established 10 mg/kg biweekly as the most effective dose of lecanemab based on ADCOMS. Lecanemab could potentially be administered at 10mg/kg on the first day of treatment and continue at biweekly intervals without titration.
- **ARIA Incidence, Frequency, Severity and Modeling**
  ARIA-E is an important adverse event of amyloid-lowering therapies that is critical to monitor and manage during treatment.
  Study 201 Core ARIA-E Rates
  ARIA-E was observed in allele groups administered 10 mg/kg biweekly at the following rates: overall ApoE4 carriers 14.3% (7/49), ApoE4 carriers homozygous 50% (5/10), ApoE4 carriers heterozygous 5.1% (2/39) and ApoE4 non-carriers 8.0% (9/112). The overall ARIA-E rate in the Core study was 9.9% (16/161) of patients treated with lecanemab 10 mg/kg biweekly compared with 0.8% (2/245) of placebo patients.
  Study 201 OLE ARIA-E Rates
  Although ApoE carriers were underrepresented in the 10 mg/kg biweekly group in Study 201 Core, all participants entering Study 201 OLE (69.4% of whom were ApoE4 carriers) were treated with 10 mg/kg biweekly, and ARIA rates were consistent with those in the Core study. Forty-five participants who received placebo in the Core study joined the OLE. ARIA-E was observed in allele groups newly treated with 10 mg/kg biweekly in the OLE at the following rates: overall ApoE4 carriers 12.9% (4/31), ApE4 carriers homozygous 25.0% (1/4), ApoE4 carriers heterozygous 11.1% (3/27) and ApoE4 negative 0.0% (0/14). In the OLE study, overall ARIA-E rates were as follows: ApoE4 carriers 10.4% (13/125), ApoE4 carriers homozygous 14.3% (4/28), ApoE4 carriers heterozygous 9.3% (9/97) and ApoE4 non-carriers 1.8% (1/55).

Study 201 Core and OLE Pooled ARIA-E Rates

In the Core and the OLE, ARIA-E was observed in allele groups administered 10 mg/kg biweekly at the following rates: ApoE4 carriers 13.8% (11/80), ApoE4 carriers homozygous 42.9% (6/14), ApoE4 carriers heterozygous 7.6% (5/66) and ApoE non-carriers 7.1% (9/126). The overall ARIA-E rate was 9.7% (20/206) of patients treated with lecanemab 10 mg/kg biweekly.

ARIA-E Rates Frequency and Severity

In the Core study and OLE, the majority of ARIA-E events occurred within the first 3 months of treatment (75% [12/16]) and resolved within 4 months of onset. For the majority of patients, the radiographic severity was mild or moderate; severe radiographic severity was reported in 1.2% (2/161) of patients. The majority of ARIA-E was asymptomatic; with symptomatic ARIA-E reported in 1.9% (3/161) of patients. Symptoms reported in association with ARIA-E included headache, visual disturbance, confusion, aphasia. There has been a single case of ARIA-E associated with seizure in the Core study and OLE to date.

Exposure-Response Model Predicted and Observed ARIA-E vs. Cmax for APOE 4

The PK/PD exposure-ARIA-E model was developed from the Core study utilizing data from all doses and demonstrated that ARIA-E is driven primarily by Cmax. The ApoE4 genotype is a significant covariate in the model. The PK/PD model predicted ARIA-E by Cmax at the 10 mg/kg biweekly dose in the Core study by allele group as follows: ApoE4 carriers homozygous 22.5%, ApoE4 carriers heterozygous 6.8% and ApoE4 non-carriers 5.4%. In addition to the modeling predicting ARIA-E by Cmax in the Core study, it confirmed the observed ARIA-E in the OLE. Given the small data set for ApoE4 homozygous patients, this will be evaluated in Eisai's Phase 3 Clarity AD clinical trial.

ARIA-H Rates

In the Core study, the incidence was higher in ApoE4 homozygous carriers than in ApoE4 heterozygous carriers and non-carriers. ARIA-H was observed in 6.2% (10/161) of patients treated with lecanemab 10 mg/kg biweekly compared with 4.9% (12/245) of placebo patients. The rate of ARIA-H was higher in ApoE4 carriers (12.2% [6/49] vs placebo 5.2% [9/174]), than in ApoE 4 non-carriers (3.6% [4/112] vs placebo 4.2% [3/71]). All patients with microhemorrhage or superficial siderosis were asymptomatic. There has been one report of symptomatic cerebral macrohemorrhage. These data are hypothesis-generating and will be further evaluated in Clarity AD.

3. Phase 2b (Study 201) Lecanemab Early AD Study Biomarker Results, Correlations with Clinical Outcomes and Potential Less-Frequent Maintenance Dosing

- Aβ42/40 and P-Tau181 are plasma biomarkers that signal sequential changes in AD progression. Lecanemab has an effect on these plasma biomarkers as amyloid plaque reduction is related to soluble amyloid and P-Tau. Lecanemab has a dose- and time-dependent reduction of amyloid plaques with a correlated increase in plasma Aβ42/40 and a decrease in plasma P-Tau181. Changes in plasma Aβ42/40 and P-Tau18 also correlate with change from baseline Clinical Dementia Rating scale Sum of Boxes (CDR-SB). In the Core study, a correlation in change from baseline in amyloid PET SUVR and plasma Aβ42/40 ratio and plasma P-tau181 was observed at 18 months, indicating that plasma biomarkers could potentially help with measuring clinical changes.
- When lecanemab treatment was discontinued at the end of the Core study, changes in the plasma Aβ42/40 (47%), P-Tau18 (24%), and amyloid PET SUVR (21%), gradually began to reverse, suggesting stopping therapy prematurely may potentially allow re-accumulation of pathology. Less frequent maintenance treatment to prevent re-accumulation may be possible based on data and modeling. Eisai will further explore maintenance dosing in the subcutaneous substudy of the Study 201 OLE, which will evaluate alternative dosing every 4 weeks or every 12 weeks.
- Increasing strong evidence highlights the role of amyloid plaques in triggering tau dysregulation and researchers optimize tau therapeutics by removing a key driver of tau dyshomeostasis (amyloid). For this reason, the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU), led by Washington University School of Medicine in St. Louis, selected lecanemab as the backbone anti-amyloid therapy for anti-tau combination for the ongoing component of the Tau NexGen clinical study, which continues enrollment efforts.

4. Update on Lecanemab Clinical Development, Including New Subcutaneous Formulation

Eisai's Dr. Michael Irizarry Senior VP of Clinical Research and Deputy Chief Clinical Officer presented updates on key lecanemab clinical trials.

- Clarity AD Phase 3: The innovative Bayesian design of lecanemab's robust dose-ranging Phase 2b study allowed Eisai to design the Phase 3 confirmatory Clarity AD clinical trial to verify lecanemab's clinical efficacy and safety in early AD. Enrollment is complete with 1,795 participants globally. Additionally, Eisai's recruitment strategy for the Clarity AD clinical trial ensured greater inclusion of ethnic and racial populations in the U.S., resulting in approximately 25% of the total U.S. enrollment including Hispanic (22.5%) and African American (4.5%) persons living with early AD, which mirrors the U.S. Medicare population. The readout will occur in Fall 2022.
- AHEAD3-45 Phase 3 Study in Preclinical AD: As of March 2022, there were over 2,900 people screened, resulting in 287 participants enrolled.
- Clarity AD Subcutaneous Substudy: Eisai is developing a subcutaneous formulation of lecanemab with the potential to be administered at home by the patient or caregiver via an auto-injector with a more rapid administration than the IV formulation (<15 second SC injection versus ~1h infusion). PK/PD modeling of Study 201 suggests that the average lecanemab concentration (Cave) predicts amyloid clearance while the maximal lecanemab concentration (Cmax) predicts ARIA-E rate. Since subcutaneous administration results in a blunted Cmax, the SC dose with comparable Cave to 10 mg/kg IV is hypothesized to have similar amyloid reduction with potentially reduced incidence of ARIA-E relative to IV but less than half the ARIA-E rate as IV. Eisai is evaluating the SC formulation in the Clarity AD OLE.

"The invited lecanemab presentations at AD/PD™ provide new and exciting insights into how the mechanism of action of late-stage anti-amyloid antibodies differ and how that may help simplify the patient journey by offering a less frequent dosing regimen while providing long-term benefit," said Lynn Kramer, M.D., Chief Clinical Officer, Neurology Business Group, Eisai. "Eisai aims to bring these potential innovations to people living with early AD and healthcare providers as quickly as possible as we work to fulfill our *human health care* mission."

Lecanemab was granted Breakthrough Therapy and Fast Track designations by the U.S. Food and Drug Administration (FDA) in June and December 2021, respectively. Eisai anticipates completing lecanemab's rolling submission of a Biologics License Application for the treatment of early AD to the FDA under the accelerated approval pathway. Eisai expects to complete this rolling submission in the first quarter of our fiscal year 2022, which begins April 1, 2022. Eisai initiated a submission to the Pharmaceuticals and Medical Devices Agency (PMDA) of application data of lecanemab under the prior assessment consultation system in Japan in March 2022. Additionally, the readout of the Phase 3 confirmatory Clarity AD clinical trial will occur in the Fall of 2022. 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.

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 patients. 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, and 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 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 Alzheimer's disease (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. 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. In March 2014 Eisai and Biogen entered into a joint development and commercialization agreement for lecanemab and the parties amended that agreement in March 2022.

* Developed by Eisai, ADCOMS (AD Composite Score) combines items from the ADAS-Cog (AD Assessment Scale-cognitive subscale), Clinical Dementia Rating (CDR) 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 are collaborating on the joint development and commercialization of AD treatments. Eisai serves as the lead of lecanemab development and regulatory submissions globally with both companies co-commercializing and co-promoting the product.

3. About the Collaboration between Eisai and BioArctic for Alzheimer's Disease
Since 2005, BioArctic has had a long-term collaboration with Eisai regarding the development and commercialization of drugs for the treatment of AD.

The commercialization agreement on the lecanemab antibody was signed in December 2007, and the development and commercialization agreement on the antibody lecanemab back-up for AD, which was signed in May 2015. Eisai is responsible for the clinical development, application for market approval and commercialization of the products for AD. BioArctic has no development costs for lecanemab in AD.

4. About Eisai Co., Ltd.
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.

5. 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 is providing the first and only approved treatment to address a defining pathology of Alzheimer's disease. Biogen is also commercializing biosimilars and focusing on advancing the industry's most diversified pipeline 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.
The company routinely post information that may be important to investors on our website at www.biogen.com. To learn more, please visit www.biogen.com and 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 ADUHELM or 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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