



Press release

FDA accepts sBLA for traditional approval of LEQEMBI™ (lecanemab-irmb) for the treatment of Alzheimer's disease and grants Priority Review

Stockholm, March 6, 2023 – BioArctic AB's (publ) (Nasdaq Stockholm: BIOA B) partner Eisai announced today that the U.S. Food and Drug Administration (FDA) has accepted Eisai's supplemental Biologics License Application (sBLA) for LEQEMBI™ (lecanemab-irmb) 100 mg/mL injection for intravenous use, supporting the conversion of the accelerated approval of LEQEMBI to a traditional approval. The LEQEMBI application is based on the confirmatory Phase 3 Clarity AD data and has been granted Priority Review, with a Prescription Drug User Fee Act (PDUFA) action date of July 6, 2023. The FDA is currently planning to hold an Advisory Committee to discuss this application but has not yet publicly announced the date of the meeting.

LEQEMBI is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble ("protofibrils")¹ and insoluble forms of amyloid beta (A β), approved under the Accelerated Approval Pathway for the treatment of Alzheimer's Disease (AD) on January 6, 2023. Treatment with LEQEMBI should only be initiated in patients with the mild cognitive impairment or mild dementia stage of disease and confirmed presence of A β pathology. On the same day that LEQEMBI received its accelerated approval, Eisai submitted the sBLA to the FDA for approval under the traditional pathway.

The sBLA is based on the findings from Eisai's recently published large, global confirmatory Phase 3 clinical trial, Clarity AD. LEQEMBI met the 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 peer-reviewed medical journal [New England Journal of Medicine](#).

LEQEMBI was approved under accelerated approval in the U.S. and was launched in the U.S. on January 18, 2023. The accelerated approval was based on Phase 2b data that demonstrated that LEQEMBI reduced the accumulation of A β plaque in the brain, a defining feature of AD, and its continued approval may be contingent upon verification of LEQEMBI's clinical benefit in a confirmatory trial. The FDA has determined that the results of Clarity AD can serve as the confirmatory study to verify the clinical benefit of lecanemab.

¹ Protofibrils are large A β aggregated soluble species of 75-500 Kd



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. BioArctic has right to commercialize lecanemab in the Nordic under certain conditions and is currently preparing for commercialization in the Nordics together with Eisai. BioArctic has no development costs for lecanemab in Alzheimer's disease and is entitled to payments in connection with regulatory approvals and sales milestones as well as royalties on global sales.

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 ϵ 4 (ApoE ϵ 4) Carrier Status and Risk of ARIA

- In Study 1, 6% (10/161) of patients in the LEQEMBI group were ApoE ϵ 4 homozygotes, 24% (39/161) were heterozygotes, and 70% (112/161) were noncarriers.
- The incidence of ARIA was higher in ApoE ϵ 4 homozygotes than in heterozygotes and noncarriers among patients treated with LEQEMBI. Of the 5 LEQEMBI-treated patients who had symptomatic ARIA, 4 were ApoE ϵ 4 homozygotes, 2 of whom experienced severe symptoms. An increased incidence of symptomatic and overall ARIA in ApoE ϵ 4 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 ϵ 4 carriers and noncarriers.
- Consider testing for ApoE ϵ 4 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 $<0.9 \times 10^9/L$ compared to 2% on placebo, and 22% of LEQEMBI-treated patients had transient increased neutrophil counts to $>7.9 \times 10^9/L$ 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 $\geq 5\%$ of patients treated with LEQEMBI (N=161) and $\geq 2\%$ 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 LEQEMBI US [Prescribing Information](#).



This information is information that BioArctic AB (publ) is obliged to disclose pursuant to the EU Market Abuse Regulation. The information was released for public disclosure, through the agency of the contact person below, on March 6, 2023, at 00:30 a.m. CET.

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About lecanemab

Lecanemab (Brand Name in the U.S.: LEQEMBI™) is the result of a strategic research alliance between BioArctic and Eisai. Lecanemab is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble 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.

In the U.S., Eisai submitted a supplemental Biologics License Application (sBLA) to the FDA for approval under the traditional pathway on January 6, 2023. The Clarity AD study of lecanemab met its primary endpoint and all key secondary endpoints with highly statistically significant results. Eisai submitted an application for manufacturing and marketing approval to the Pharmaceuticals and Medical Devices Agency (PMDA) on January 16, 2023, in Japan. The Priority Review was granted by the Ministry of Health, Labour and Welfare (MHLW) on January 26, 2023. Eisai utilized the prior assessment consultation system of PMDA, with the aim of shortening the review period for lecanemab. In Europe, Eisai submitted a marketing authorization application (MAA) to the European Medicines Agency (EMA) on January 9, 2023, and accepted on January 26, 2023. In China, Eisai initiated submission of data for a BLA to the National Medical Products Administration (NMPA) of China in December 2022 and priority review was granted February 27, 2023.

Eisai has completed a LEQEMBI subcutaneous bioavailability study and subcutaneous dosing is currently being evaluated in the Clarity AD open label extension study.

Since July 2020 Eisai's 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 and Eisai.

Since January 2022, the Tau NexGen clinical study for Dominantly Inherited AD (DIAD) is ongoing, where lecanemab is given as a background anti-amyloid treatment when exploring combination therapies with anti-



tau treatments. The study is conducted by Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU), led by Washington University School of Medicine in St. Louis.

About the collaboration between BioArctic and Eisai

Since 2005, BioArctic has a long-term collaboration with Eisai regarding the development and commercialization of drugs for the treatment of Alzheimer's disease. The most important agreements are the Development and Commercialization Agreement for the lecanemab antibody, which was signed in December 2007, and the Development and Commercialization agreement for the antibody BAN2401 back-up for Alzheimer's disease, which was signed in May 2015. In March 2014, Eisai and Biogen entered into a joint development and commercialization agreement for lecanemab. Eisai is responsible for the clinical development, application for market approval and commercialization of the products for Alzheimer's disease. BioArctic has right to commercialize lecanemab in the Nordic under certain conditions and is currently preparing for commercialization in the Nordics together with Eisai. BioArctic has no development costs for lecanemab in Alzheimer's disease and is entitled to payments in connection with regulatory approvals, and sales milestones as well as royalties on global sales.

About BioArctic AB

BioArctic AB (publ) is a Swedish research-based biopharma company focusing on disease-modifying treatments for neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and ALS. BioArctic focuses on innovative treatments in areas with high unmet medical needs. The company was founded in 2003 based on innovative research from Uppsala University, Sweden. Collaborations with universities are of great importance to the company together with its strategically important global partner Eisai in Alzheimer disease. The project portfolio is a combination of fully funded projects run in partnership with global pharmaceutical companies and innovative in-house projects with significant market and out-licensing potential. BioArctic's Class B share is listed on Nasdaq Stockholm Large Cap (ticker: BIOA B). For more information about BioArctic, please visit www.bioarctic.com.