BIOARCTIC

Press release

Latest analysis of lecanemab's effect on biomarkers as well as new data on subcutaneous dosing presented at the AAIC 2023 Alzheimer conference

Stockholm, July 20, 2023 – BioArctic AB's (publ) (Nasdaq Stockholm: BIOA B) partner Eisai announced today that the results of a detailed analysis of the Phase 3 Clarity AD study, presented at the Alzheimer's Association International Conference (AAIC) 2023, demonstrated that lecanemab-irmb (generic name, U.S. brand name: LEQEMBI®) treatment showed benefits on both amyloid-beta (Aβ) and tau pathology as well as other downstream biomarker changes. In addition, new data on subcutaneous (SC) formulation shows promising PK/PD data modeling on efficacy and safety, representing a potential new option for administering therapy. The U.S. Food and Drug Administration (FDA) granted traditional approval for LEQEMBI for the treatment of Alzheimer's disease (AD) on July 6, 2023

Clarity AD was a global confirmatory Phase 3 placebo-controlled, double-blind, parallel-group, randomized study in 1,795 people with early AD (lecanemab group: 10 mg/kg bi-weekly IV treatment: 898, placebo group: 897). Lecanemab met the primary endpoint (change from baseline at 18 months on the global cognitive and functional scale, Clinical Dementia Rating-Sum of Boxes [CDR-SB]) and all key secondary endpoints with statistically significant results. In November 2022, results of the Clarity AD study were presented at the *Clinical Trials on Alzheimer's Disease (CTAD)* conference and simultaneously published in the peer-reviewed medical journal, *The New England Journal of Medicine*.

Lecanemab: Amyloid Reduction and Evidence of Downstream Biomarker Modification
In addition to the key secondary endpoint of lecanemab's effect on amyloid accumulation in the brain as measured by amyloid positron emission tomography (PET), the Clarity AD study also measured multiple A/T/N+ (amyloid, tau, neurodegeneration) biomarkers involved in the pathophysiology of AD such as amyloid (Aβ1-42 in CSF, Aβ42/40 ratio in plasma), tau (p-Tau181 in cerebral spinal fluid [CSF] and plasma), neurodegeneration (total tau [t-tau] in CSF and neurofilament light [NfL] in CSF and plasma), astrocyte activation (plasma GFAP: glial fibrillary acidic protein) and synaptic dysfunction (neurogranin in CSF).

An increase in plasma Aβ42/40 ratio was observed with lecanemab compared to placebo (adjusted mean change from baseline of lecanemab: 0.008, placebo: 0.001, $p<0.0001$). A reduction in plasma p-Tau181 was observed with lecanemab compared to placebo (adjusted mean change from baseline of lecanemab: -0.575pg/mL, placebo: 0.201pg/mL, $p<0.0001$). The other biomarkers also improved after treatment with lecanemab. These outcomes suggested lecanemab impacts A/T/N+ biomarkers involved in the AD pathophysiology and exerts biological effects that demonstrate slowing of disease progression.

Baseline characteristics and initial results were presented from the tau PET substudy of Clarity AD. Lecanemab administration slowed the accumulation of tau pathology in the temporal lobe. Additionally, lecanemab administration showed a clinical effect in the overall population of the tau PET substudy, and a large effect size was observed in the low tau population[1] defined in this presentation, which represents the early phase of AD.

Subcutaneous (SC) Lecanemab is Predicted to Achieve Comparable Efficacy and Improved Safety Compared to Lecanemab IV in Early AD
In an exposure/bioavailability and modeling study comparing intravenous (IV) and subcutaneous (SC) dosing of lecanemab, the bioavailability of SC dosing of lecanemab was shown to be approximately 50% of that of IV dosing. Further analysis using the PK/PD model showed that a fixed lecanemab SC dose of 720 mg administered weekly may potentially result in comparable exposure over time (area under the curve [AUC]) in blood and efficacy as measured by reduction in amyloid PET SUVr to 10 mg/kg IV dose administered bi-weekly. Models developed with data following IV administration show that amyloid-related imaging abnormalities with edema/effusion (ARIA-E) are more related to the peak concentrations of lecanemab in blood, with maximum blood concentrations being the best predictor of ARIA-E. Because SC dosing will have lower maximum blood concentrations than IV dosing, SC dosing is predicted to have a lower incidence of ARIA-E, if the relationship is the same for SC dosing.

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 the right to commercialize lecanemab in the Nordic region and currently Eisai and BioArctic are preparing for a joint commercialization in the region.

The presentation materials of this release will be posted on the investors section of the Eisai's corporate website at 01:30 on July 21 CET (8:30 on July 21 in Japan time).

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.

The information was released for public disclosure, through the agency of the contact person below, on July 20, 2023, at 01.30 a.m. CET.

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[1] Using the MK6240 tau PET probe, tau accumulation in the brain was defined as low tau accumulation group (MK6240 cutoff value <1.06, 141 subjects), intermediate accumulation group (MK6240 cutoff value between 1.06 and 2.91, 191 subjects), and high accumulation group (MK6240 cutoff value >2.91, 10 subjects).

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.

IMPORTANT SAFETY INFORMATION

WARNING: AMYLOID RELATED IMAGING ABNORMALITIES (ARIA)

- **Monoclonal antibodies directed against aggregated forms of amyloid beta, including LEQEMBI, can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). Incidence and timing of ARIA vary among treatments. ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events rarely can occur. Serious intracerebral hemorrhages >1 cm, some of which have been fatal, have been observed in patients treated with this class of medications.**
    - **Apolipoprotein E ε4 (ApoE ε4) Homozygotes: Patients who are ApoE ε4 homozygotes (approximately 15% of Alzheimer's disease patients) treated with this class of medications, including LEQEMBI, have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results. Prescribers should inform patients that if genotype testing is not performed, they can still be treated with LEQEMBI; however, it cannot be determined if they are ApoE ε4 homozygotes and at higher risk for ARIA.**
- **Consider the benefit of LEQEMBI for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with LEQEMBI**

CONTRAINDICATION

LEQEMBI is contraindicated in patients with serious hypersensitivity to lecanemab-irmb or to any of the excipients of LEQEMBI. Reactions have included angioedema and anaphylaxis.

WARNINGS AND PRECAUTIONS

AMYLOID RELATED IMAGING ABNORMALITIES

- LEQEMBI can cause ARIA-E and ARIA-H. ARIA-E can be observed on MRI as brain edema or sulcal effusions, and ARIA-H as microhemorrhage and superficial siderosis. ARIA can occur spontaneously in patients with Alzheimer's disease. ARIA-H associated with monoclonal antibodies directed against aggregated forms of beta amyloid generally occurs in association with an occurrence of ARIA-E. ARIA-H and ARIA-E can occur together. ARIA usually occurs early in treatment and 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 baseline 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 2, symptomatic ARIA occurred in 3% (29/898) of LEQEMBI-treated patients. Serious symptoms associated with ARIA were reported in 0.7% (6/898) of patients treated with LEQEMBI. Clinical symptoms associated with ARIA resolved in 79% (23/29) of patients during the period of observation.
- Including asymptomatic radiographic events, ARIA was observed in LEQEMBI: 21% (191/898); placebo: 9% (84/897). ARIA-E was observed in LEQEMBI: 13% (113/898); placebo: 2% (15/897). ARIA-H was observed in LEQEMBI: 17% (152/898); placebo: 9% (80/897). There was no increase in isolated ARIA-H for LEQEMBI vs placebo.

ApoE ε4 Carrier Status and Risk of ARIA

- In Study 2, 16% (141/898) of patients in the LEQEMBI arm were ApoE ε4 homozygotes, 53% (479/898) were heterozygotes, and 31% (278/898) were noncarriers.
- The incidence of ARIA was higher in ApoE ε4 homozygotes (LEQEMBI: 45%; placebo: 22%) than in heterozygotes (LEQEMBI: 19%; placebo: 9%) and noncarriers (LEQEMBI: 13%; placebo: 4%). Among patients treated with LEQEMBI, symptomatic ARIA-E occurred in 9% of ApoE ε4 homozygotes compared with 2% of heterozygotes and 1% noncarriers. Serious events of ARIA occurred in 3% of ApoE ε4 homozygotes, and approximately 1% of heterozygotes and noncarriers.
- The recommendations on management of ARIA do not differ between ApoE ε4 carriers and noncarriers.

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% (37/898), moderate in 7% (66/898), and severe in 1% (9/898). Resolution on MRI occurred in 52% of ARIA-E patients by 12 weeks, 81% by 17 weeks, and 100% overall after detection. The maximum radiographic severity of ARIA-H microhemorrhage in LEQEMBI-treated patients was mild in 9% (79/898), moderate in 2% (19/898), and severe in 3% (28/898) of patients; superficial siderosis was mild in 4% (38/898), moderate in 1% (8/898), and severe in 0.4% (4/898). Among LEQEMBI-treated patients, the rate of severe radiographic ARIA-E was highest in ApoE ε4 homozygotes 5% (7/141), compared to heterozygotes 0.4% (2/479) or noncarriers 0% (0/278). Among LEQEMBI-treated patients, the rate of severe radiographic ARIA-H was highest in ApoE ε4 homozygotes 13.5% (19/141), compared to heterozygotes 2.1% (10/479) or noncarriers 1.1% (3/278).

Intracerebral Hemorrhage

- Intracerebral hemorrhage >1 cm in diameter was reported in 0.7% (6/898) of patients in Study 2 after treatment with LEQEMBI compared to 0.1% (1/897) on placebo. Fatal events of intracerebral hemorrhage in patients taking LEQEMBI have been reported.

  Concomitant Antithrombotic Medication:
  - In Study 2, baseline use of antithrombotic medication (aspirin, other antiplatelets, or anticoagulants) was allowed if the patient was on a stable dose. The majority of exposures to antithrombotic medications were to aspirin. Antithrombotic medications did not increase the risk of ARIA with LEQEMBI. The incidence of intracerebral hemorrhage was 0.9% (3/328 patients) in patients taking LEQEMBI with a concomitant antithrombotic medication at the time of the event compared to 0.6% (3/545 patients) in those who did not receive an antithrombotic. Patients taking LEQEMBI with an anticoagulant alone or combined with an antiplatelet medication or aspirin had an incidence of intracerebral hemorrhage of 2.5% (2/79 patients) compared to none in patients who received placebo.
  - Because intracerebral hemorrhages >1 cm in diameter have been observed in patients taking LEQEMBI, additional caution should be exercised when considering the administration of anticoagulants or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with LEQEMBI.

  Other Risk Factors for Intracerebral Hemorrhage:
  - Patients were excluded from enrollment in Study 2 for findings on neuroimaging that indicated an increased risk for intracerebral hemorrhage. These included findings suggestive of cerebral amyloid angiopathy (prior cerebral hemorrhage >1 cm in greatest diameter, >4 microhemorrhages, superficial siderosis, vasogenic edema) or other lesions (aneurysm, vascular malformation) that could potentially increase the risk of intracerebral hemorrhage. The presence of an ApoE ε4 allele is also associated with cerebral amyloid angiopathy, which has an increased risk for intracerebral hemorrhage. Caution should be exercised when considering the use of LEQEMBI in patients with factors that indicate an increased risk for intracerebral hemorrhage and in particular for patients who need to be on anticoagulant therapy.

HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions, including angioedema, bronchospasm, and anaphylaxis, have occurred in LEQEMBI-treated patients. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction, and initiate appropriate therapy.

INFUSION-RELATED REACTIONS

- In Study 2, infusion-related reactions were observed in LEQEMBI: 26% (237/898); placebo: 7% (66/897), and the majority of cases in LEQEMBI-treated patients (75%, 178/237) occurred with the first infusion. Infusion-related reactions were mostly mild (69%) or moderate (28%) in severity. Infusion-related reactions resulted in discontinuations in 1% (12/898) of LEQEMBI-treated patients. 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.
- 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 2, the most common adverse reactions leading to discontinuation of LEQEMBI was ARIA-H microhemorrhages that led to discontinuation in 2% (15/898) of patients treated with LEQEMBI compared to <1% (1/897) of patients on placebo.
- In Study 2, the most common adverse reactions reported in ≥5% of patients treated with LEQEMBI (N=898) and ≥2% higher than placebo (N=897) were infusion-related reactions (LEQEMBI: 26%; placebo: 7%), ARIA-H (LEQEMBI: 14%; placebo: 8%), ARIA-E (LEQEMBI: 13%; placebo: 2%), headache (LEQEMBI: 11%; placebo: 8%), superficial siderosis of central nervous system (LEQEMBI: 6%; placebo: 3%), rash (LEQEMBI: 6%; placebo: 4%), and nausea/vomiting (LEQEMBI: 6%; placebo: 4%).

Please see full US Prescribing Information for LEQEMBI, including Boxed WARNING.

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About LEQEMBI® (lecanemab-irmb)
LEQEMBI® (lecanemab-irmb) is the result of a strategic research alliance between BioArctic and Eisai. LEQEMBI is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble (protofibril) and insoluble forms of amyloid-beta (Aβ). LEQEMBI is an amyloid beta-directed antibody indicated as a disease-modifying treatment for Alzheimer's disease (AD). In the US, LEQEMBI was granted accelerated approval by the US Food and Drug Administration (FDA) on January 6, 2023, and traditional approval on July 6, 2023. 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.

Please see full Prescribing Information, including Boxed WARNING in the United States.

Eisai has also submitted applications for approval of lecanemab in Japan, EU, China, Canada, Great Britain and South Korea. In Japan and China, the applications have been designated for priority review, and in Great Britain, lecanemab has been designated for the Innovative Licensing and Access Pathway (ILAP), which aims to reduce the time to market for innovative medicines.

Eisai has completed lecanemab subcutaneous bioavailability study, and subcutaneous dosing is currently being evaluated in the Clarity AD (Study 301) OLE. A maintenance dosing regimen has been evaluated as part of Study 201 as well as the Clarity AD (Study 301) OLE.

Since July 2020 the lecanemab 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), including lecanemab and an anti-tau treatment, that is conducted by Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU), led by Washington University School of Medicine in St. Louis, is ongoing.

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 2007, and the

Development and Commercialization agreement for the antibody BAN2401 back-up for Alzheimer's disease, which was signed 2015. In 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.