LEQEMBI® (lecanemab-irmb) 100 mg/mL
INJECTION FOR INTRAVENOUS USE

Eisai

Biogen

LEQEMBI Phase 3 Clinical Study Fact Sheet

LEQEMBI® (lecanemab-irmb) is the first and only approved treatment shown to reduce the rate of disease progression and slow cognitive and functional decline in people living with Alzheimer's disease (AD).

Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment (MCI) or mild dementia stage of disease, the population in which treatment was initiated in clinical trials.[1]

MCI due to AD and mild AD dementia are different stages within the Alzheimer's disease continuum and critical points for intervention.[2]

On July 6, 2023, the FDA granted LEQEMBI traditional approval. The traditional approval was based on the findings from Eisai's large, global Phase 3 clinical trial of LEQEMBI, Clarity AD. The complete results of the Clarity AD study were presented at the Clinical Trials on Alzheimer's Disease (CTAD) conference in November 2022 and simultaneously published in *The New England Journal of Medicine*.[3]

Below, please find more information about Eisai's Clarity AD clinical study.

Clarity AD (Study 301) NCT03887455

Objectives

- Evaluate efficacy and safety of LEQEMBI 10 mg/kg administered once every 2 weeks in patients with early AD compared with placebo
- In an optional, open-label, long-term extension phase, evaluate the long-term safety and tolerability of LEQEMBI, and whether its treatment effects as measured by Clinical Dementia Rating-Sum of Boxes (CDR-SB) are maintained over time (ongoing)[4]

Design

- Global, confirmatory, placebo-controlled, double-blind, parallel-group, randomized study[4]
- 18-month trial period, followed by an Open Label Extension (OLE) period [Time Frame: Baseline up to Month 45][4*]
- Trial arms:[4]
  - Placebo
  - LEQEMBI 10 mg/kg (once every two weeks)

**OLE is ongoing and data readout is pending.*

Patient population

- Amyloid-positive, with MCI due to AD or mild AD dementia[4]

Enrollment

- Included 1,795 participants[5]
  - Aged 50-90 years (median = 72)[1]
  - 80% of participants 65 years of age or older[5]
  - 52.3% female[5]
  - 38.1% mild AD[5]
- Diversity in U.S. participants
  - 4.5% (43) are Black and 22.5% (213) are Hispanic[5]

Endpoints[4]

- Primary Endpoint:
  - Change from Core Study Baseline in CDR-SB (global cognitive and functional scale) at 18 Months (Core Study)
  - Number of Participants Reporting One or More Treatment-Emergent Adverse Events (TEAEs) (Extension Phase)
  - Change from Core Study Baseline in CDR-SB (Extension Phase)
- Select Key Secondary Endpoints:
  - Change from baseline in Amyloid Positron Emission Tomography (PET) Using Centiloids, Alzheimer's Disease Assessment Scale - Cognitive Subscale 14 (ADAS-Cog14), Alzheimer's Disease Composite Score (ADCOMS) and Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL) at 18 Months (Core Study)

Results[1]

- Efficacy
  - LEQEMBI treatment met the primary endpoint and reduced clinical decline on the global cognitive and functional scale, CDR-SB, compared with placebo at 18 months by 27%, which represents a treatment difference in the score change of -0.45 (p=0.0001)
  - Starting as early as six months, across all time points, LEQEMBI treatment showed statistically significant changes from baseline compared to placebo
  - All key secondary endpoints were also met with statistically significant results compared with placebo
- Safety
  - LEQEMBI is associated with a **Boxed WARNING** and the following Warnings and Precautions: Amyloid Related Imaging Abnormalities (ARIA), Hypersensitivity Reactions and Infusion-Related Reactions.
  - The most common adverse reactions reported in ≥5% of patients treated with LEQEMBI (N=898) and ≥2% higher than placebo (N=897) in Study 301 were infusion-related reactions (LEQEMBI: 26%; placebo: 7%), ARIA-hemosiderin deposition (LEQEMBI: 14%; placebo: 8%), ARIA-edema (LEQEMBI: 13%; placebo: 2%), headache (LEQEMBI: 11%; placebo: 8%), and Superficial siderosis of central nervous system (LEQEMBI: 6%; placebo: 3%), rash (LEQEMBI: 6%; placebo: 4%) and nausea/vomiting (LEQEMBI: 6%; placebo: 4%).
  - In Study 301, 7% of LEQEMBI-treated patients, compared to 3% 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 1% (12/898) of patients treated with LEQEMBI compared to <1% (1/897) of patients on placebo.

Please see additional Important Safety Information continued and click here for full Prescribing Information, including Boxed WARNING.

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.

Please see additional Important Safety Information continued and click here for full Prescribing Information, including Boxed WARNING.

Important Safety Information for LEQEMBI® (lecanemab-irmb) continued

WARNINGS AND PRECAUTIONS (continued)

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 reaction 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 Prescribing Information for LEQEMBI, including Boxed WARNING.

References

1. LEQEMBI. Prescribing Information. Eisai Inc. and Biogen; 2023.
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