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

LEQEMBI®: Providing clinical benefit for patients with mild cognitive impairment (MCI) due to Alzheimer's disease (AD) and mild AD dementia

Eisai Biogen

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Patient journey to treatment with LEQEMBI®

Renard, actual patient with AD.
Patient not on LEQEMBI.

- Recognizing the signs of early AD
- Diagnosis of early AD
- Selecting LEQEMBI for appropriate patients
- Initiating LEQEMBI
- Monitoring for safety

AD=Alzheimer's disease.

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Recognizing the signs of early AD

AD=Alzheimer's disease.

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AD is a growing public health crisis and represents a crucial unmet need in healthcare[1]

- AD is a progressive, fatal neurodegenerative disease that accounts for **60% to 80%** of dementia cases*[1]
- **7th** leading cause of death in the US in 2020 and 2021† and **5th** leading cause of death in those ≥65 years old in 2019[1]
- **4.6 million** people in the US have **MCI due to AD or mild AD dementia**, but only **2.28 million** of patients with MCI due to AD or mild AD dementia are **diagnosed**[2]
- About **one-third** of people with MCI due to AD develop AD dementia within 5 years[1,3]

*Dementia refers to a group of symptoms, including difficulties with memory, language, and problem-solving, that affect a person's ability to perform daily activities.[1] †When COVID-19 entered the ranks of the top 10 causes of death.[1]
AD=Alzheimer's disease; MCI=mild cognitive impairment.

1. Alzheimer's Association. 2023 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2023;19(4):1598-1695. **2.** ICER.org. Accessed November 8, 2022. https://icer.org/wp-content/uploads/2020/10/ICER_ALZ_Final_Report_080521.pdf. **3.** Alzheimer's Association. New Alzheimer's Association report finds doctors and the public face challenges in understanding and distinguishing early Alzheimer's development from 'normal aging'. Updated March 15, 2022. Accessed January 20, 2023. https://www.alz.org/news/2022/facts-figures-alzheimers-mild-cognitive-impairment.

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In early stages of AD, patients and their care partners may initially notice subtle changes that continue to worsen as AD progresses[1]

AD continuum[1]

	Preclinical AD	MCI due to AD	Mild AD dementia	Moderate AD dementia	Severe AD dementia
Duration in stage	*2-15 years*[2]	*3-7 years*[2]	*2-6 years*[2]	*1-7 years*[2]	
Cognitive	› Appears normal[1]	› Subtle problems with memory, language, and thinking[1]	› Losing or misplacing a valuable object[5] › Forgetting material that was just read[5]	› More problems with memory and language[1] › More likely to become confused[1] › Forgetful of events or personal history[4]	› Ability to communicate verbally is greatly diminished[1] › Loses awareness of recent experiences[5]
Neuropsychologic	› Appears normal[1]	› Subclinical changes: depression, anxiety, irritability, and aggression[3]	› Anxiety[6] › Apathy[6] › Irritability[6] › Depressive symptoms[6]	› Suspicious and agitated[1] › Moody or withdrawn[5] › Delusions or compulsive, repetitive behavior[5]	› Worsening hallucinations and agitation[7]
Functional	› Appears normal[1]	› Symptoms may not interfere with daily activities[1] › Able to maintain hobbies[4]	› Can function independently, but likely requires assistance[1] › May still be able to drive[1] › Difficulty performing tasks in social or work settings[5]	› Difficulty bathing, dressing, and maintaining a home[1,4] › Trouble controlling bladder/bowels[5] › Changes in sleep pattern[5]	› Difficulty eating, drinking, and walking[1,4] › Becoming bedbound and more susceptible to physical complications[1] › Needs around-the-clock assistance[5]

Slowing progression in earlier stages of AD may allow patients to retain crucial cognitive, neuropsychological, and functional abilities.[8,9]

AD=Alzheimer's disease; MCI=mild cognitive impairment.

1. Alzheimer's Association. 2023 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2023;19(4):1598-1695. **2.** Vermunt L et al. *Alzheimers Dement.* 2019;15(7):888-898. **3.** Caselli RJ et al. *J Am Geriatr Soc.* 2018;66(4):671-678. **4.** Cohen S et al. *J Prev Alzheimers Dis.* 2022;9(3):507-522. **5.** Alzheimer's Association. Stages of Alzheimer's. Accessed November 16, 2022. https://www.alz.org/alzheimers-dementia/stages. **6.** Zvěřová M. *Clin Biochem.* 2019;72:3-6. **7.** Jicha GA, Carr SA. *J Alzheimers Dis.* 2010;19(1):253-272. **8.** Alzheimer's Association. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2022;18(4):700-789. **9.** Christensen DD. *Prim Care Companion J Clin Psychiatry.* 2002;4(2):63-69.

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Diagnosis of early AD

AD=Alzheimer's disease.

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Cognitive screening and structural imaging are key first steps in early AD diagnosis[1]

Patient presents with suspected cognitive changes

Assess with calibrated diagnostic tools that are sensitive to MCI and mild AD dementia

(eg, MoCA, Qmci screen, MMSE, Mini-Cog, SLUMS, and AD8)[1-4]

Use structural imaging to rule out other conditions that may cause symptoms similar to AD

(eg, MRI and CT scans)[2]

AD=Alzheimer's disease; AD8=Eight-Item Informant Interview to Differentiate Aging and Dementia; CT=computed tomography; MCI=mild cognitive impairment; MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; MRI=magnetic resonance imaging; Qmci=Quick Mild Cognitive Impairment; SLUMS=Saint Louis University Mental Status.

1. Alzheimer's Association. Medical tests for diagnosing Alzheimer's. Accessed April 8, 2022. https://www.alz.org/alzheimers-dementia/diagnosis/medical_tests. **2.** O'Caoimh R et al. *J Alzheimers Dis*. 2016;51(2):619-629. **3.** Tariq SH et al. *Am J Geriatr Psychiatry*. 2006;14(11):900-910. **4.** Usarel C et al. *Int Psychogeriatr*. 2019;31(2):223-229.

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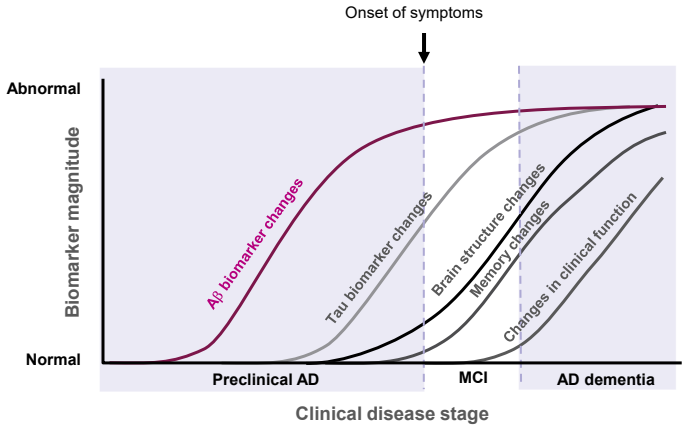
Biomarker-confirmed AD diagnosis enables the identification of patients who may be appropriate for Aβ-targeting therapies[1]

- Amyloid biomarkers are the first biomarkers to present abnormally in the course of AD[2]
- Elevated levels of Aβ can be determined 15 years before the onset of symptoms with a PET scan and 20 years before the onset of MCI with a CSF assay[3,4]
- Aβ biomarkers can help detect AD in early stages and enable planning for earlier intervention[1,5]



Aβ=amyloid beta; AD=Alzheimer's disease; CSF=cerebrospinal fluid; MCI=mild cognitive impairment; PET=positron emission tomography.

1. Alzheimer's Association. 2023 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2023;19(4):1598-1695. **2.** Jack CR Jr et al. *Lancet Neurol*. 2013;12(2):207-216. **3.** Bateman RJ et al. *N Engl J Med*. 2012;367(9):795-804. **4.** Jack CR Jr et al. *Alzheimers Dement*. 2011;7(3):257-262. **5.** Alzheimer's Association. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2022;18(4):700-789.

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A subset of all patients with MCI due to AD or mild AD are potentially treatable with an amyloid-targeted therapy

The ICER estimate of the number of treatable patients may be calculated by following the patient journey*[1]

Suspected cognitive changes[2]	Neurocognitive screening with MCI sensitive tools[2,3]	Structural imaging to rule out other conditions and biomarker assessment to confirm Aβ presence[4-6]	AD diagnosis and therapy consideration[7]
4.6M prevalent cases of MCI and mild AD in the US[1]	**4.14M** patients present to a clinician with symptoms[1]	**2.28M** patients are diagnosed with MCI and mild AD[1]	**1.4M** patients are Aβ-positive and eligible for anti-amyloid therapy[1]	**280,000** **Projected US patients would initiate anti-amyloid therapy each year[1]**

Based on a total US population of 328 million in 2019, 280,000 eligible patients equates to 854 treatable patients per 1 million[8]

Based on a total US Medicare population of 66 million in 2023, 280,000 eligible patients equates to 3,436 treatable Medicare patients per 1 million.[9,10]

*Based on ICER budget impact model using an unpublished analysis based on 2019 data. A scenario begins with 4.6 million prevalent cases of MCI and mild AD in the US. From there, one could assume that 90% of prevalent cases present to a clinician with symptoms and of those, 55% are diagnosed. Of those presenting to a clinician and who are diagnosed with MCI, 61.5% were assumed to be Aβ-positive to arrive at 1.4 million patients eligible for treatment that targets Aβ. Of these 1.4 million patients, 20% were assumed to initiate treatment each year over the course of 5 years, or approximately 280,000 patients per year.
Aβ=amyloid beta; AD=Alzheimer's disease; ICER=Institute for Clinical and Economic Review; MCI=mild cognitive impairment.

1. ICER.org. Accessed June 17, 2023. https://icer.org/wp-content/uploads/2020/10/ICER_ALZ_Final_Report_080521.pdf. **2.** O'Caoimh R et al. *J Alzheimers Dis*. 2016;51(2):619-629. **3.** Maruff P et al. *BMC Pharmacol Toxicol*. 2013;1(1):1-11. **4.** Alzheimer's Association. Medical tests for diagnosing Alzheimer's. Accessed June 17, 2023. https://www.alz.org/alzheimers-dementia/diagnosis/medical_tests. **5.** Hampel H et al. *Nat Rev Neurol*. 2018;14(11):639-652. **6.** Hlavka JP et al. *Rand Health Q*. 2019;8(3):2. **7.** Alzheimer's Association. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2022;18(4):700-789. **8.** United States Census Bureau. ACS Demographic and Housing Estimates. 2019. Accessed March 9, 2022. https://data.census.gov/cedsci/table?d=ACS%201-Year%20Estimates%20Data%20Profiles&tid=ACSDP1Y2019.DP05. **9.** Center for Medicare Advocacy. Accessed July 24, 2023. https://medicareadvocacy.org/medicare-enrollment-numbers/. **10.** LEQEMBI (lecanemab-irmb) [Prescribing Information]. Nutley, NJ: Eisai Inc.

Renard, actual patient with AD, with his son RJ.
Patient not on LEQEMBI.

Selecting LEQEMBI® for appropriate patients

AD=Alzheimer's disease.

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LEQEMBI® 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.

LEQEMBI (lecanemab-irmb) [Prescribing Information]. Nutley, NJ: Eisai Inc.

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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.**

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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.

Select Safety Information

WARNINGS AND PRECAUTIONS (CONT'D)

AMYLOID RELATED IMAGING ABNORMALITIES (CONT'D)

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.

Select Safety Information

WARNINGS AND PRECAUTIONS (CONT'D)

AMYLOID RELATED IMAGING ABNORMALITIES (CONT'D)

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% of 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).

Select Safety Information

WARNINGS AND PRECAUTIONS (CONT'D)

AMYLOID RELATED IMAGING ABNORMALITIES (CONT'D)

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.

Select Safety Information

WARNINGS AND PRECAUTIONS (CONT'D)

AMYLOID RELATED IMAGING ABNORMALITIES (CONT'D)

Intracerebral Hemorrhage (Cont'd)

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.

Select Safety Information

WARNINGS AND PRECAUTIONS (CONT'D)

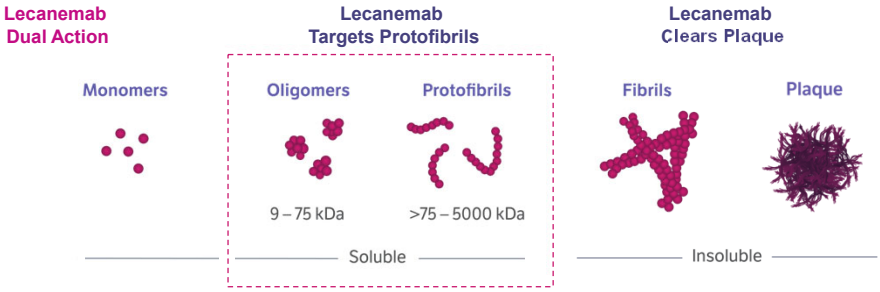
INFUSION-RELATED REACTIONS

- 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%).

LEQEMBI® clears more than just plaque.
Dual-acting LEQEMBI also supports neuronal function by clearing highly toxic protofibrils that continue to cause neuronal injury and death even after plaques are cleared[1-8]



Aβ pathway in AD

- Aβ dynamically evolves through different conformational states, including[4]:
  - Soluble monomers, dimers, oligomers, and protofibrils
  - Insoluble fibrils and plaques
- The accumulation of Aβ plaques in the brain is a defining pathophysiological feature of AD[1]

LEQEMBI initiates microglial clearance of Aβ protofibrils and plaques[9-11]

- LEQEMBI-irmb is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble (oligomers and protofibrils) and insoluble (fibrils) forms of Aβ[1,4]
- LEQEMBI is the only monoclonal antibody that preferentially binds with highest affinity to toxic protofibrils (with 10-15x higher selectivity over fibrils, and >1000-fold selectivity over monomers)[8,12-14]

Aβ=amyloid beta; AD=Alzheimer's disease.

1. LEQEMBI (lecanemab-irmb) [Prescribing Information]. Nutley, NJ: Eisai Inc. **2.** van Dyck CH et al. *N Engl J Med*. 2023;388(1):9-21. **3.** Brendza RP et al. *J Clin Invest*. 2005;115(2):428-433. **4.** Hampel H et al. *Mol Psychiatry*. 2021;26(10):5481-5503. **5.** Ono K et al. *Int J Mol Sci*. 2020;21(5):952. **6.** Söllvander S et al. *Mol Neurodegener*. 2016;11(1):38. **7.** Hartley DM et al. *J Neurosci*. 1999;19(20):8876-8884. **8.** Eisai Inc. Presented at: Clinical Trials on Alzheimer's Disease; November 29-December 2, 2022; San Francisco, CA. **9.** Eisai Inc. Presented at: Clinical Trials on Alzheimer's Disease; October 24-October 27, 202; Boston, MA. **10.** Swanson CJ et al. Poster presented at: Alzheimer's Association International Conference; July 13-18, 2013, Boston, MA. Poster P4-286. **11.** Swanson CJ et al. Poster presentation at: Alzheimer's Association International Conference; July 16-20, 2017. London, UK. Poster P2-055. **12.** Kaplow JM et al. *Alzheimers Dement*. 2013;9:P807-P808. **13.** Swanson CJ et al. *Alzheimers Res Ther*. 2021;13(1):80. **14.** Data on file. Eisai Inc. Nutley, NJ. **15.** Lannfelt L et al. *Alzheimers Res Ther*. 2014;6(2):16.

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Clarity AD: A pivotal study evaluating a breadth of endpoints in patients with MCI due to AD and mild AD dementia across a variety of practice settings[1,2]

Clarity AD (Study 2) is an 18-month, global, placebo-controlled, double-blind, parallel-group randomized study.[1,3]

Randomization phase[1,3]

Patient population
- N=1795 patients with MCI due to AD or mild AD dementia with confirmed Aβ pathology

Randomization
1:1

LEQEMBI®
10 mg/kg once every 2 weeks
(IV infusion)
N=898

Placebo
once every 2 weeks
(IV infusion)
N=897

Primary outcome measure:
Change from baseline at 18 months: CDR-SB

Key secondary outcome measures:
Change from baseline at 18 months:
ADCS MCI-ADL
ADAS-Cog14
ADCOMS
Amyloid PET

Exploratory analyses: Quality of Life[3-5]

Patients were given the option to enroll in substudies, including Tau PET substudy and to enroll in a long-term extension of the study that is still ongoing.

Randomization stratified according to[1,3]:

- Clinical subgroup (MCI due to AD or mild AD dementia)
- Presence or absence of ongoing approved AD treatment (eg, acetylcholinesterase inhibitors, memantine, or both)
- ApoE ε4 status (ie, carriers or noncarriers)
- Geographical region

Variety of practice settings[2]:

Included a wide range of study sites

- Private and hospital- and community-based academic centers
- Located in urban, suburban, and rural areas

Aβ=amyloid beta; AChEI=acetylcholinesterase inhibitor; AD=Alzheimer's disease; ADAS-Cog14=Alzheimer's Disease Assessment Scale-Cognitive Subscale 14-item version; ADCOMS=Alzheimer's Disease Composite Score; ADCS MCI-ADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; ApoE ε4=apolipoprotein E ε4; CDR-SB=Clinical Dementia Rating-Sum of Boxes; IV=intravenous; MCI=mild cognitive impairment; PET=positron emission tomography.

1. LEQEMBI (lecanemab-irmb) [Prescribing Information]. Nutley, NJ: Eisai Inc. **2.** US Food and Drug Administration. Updated June 9, 2023. Accessed June 28, 2023. https://www.fda.gov/media/169263/download. **3.** van Dyck CH et al. *N Engl J Med*. 2023;388(1):9-21. **4.** Eisai Inc. Presented at: Clinical Trials on Alzheimer's Disease; November 29-December 2, 2022; San Francisco, CA. **5.** Eisai Inc. Presented at: Clinical Trials on Alzheimer's Disease; October 24-October 27, 202; Boston, MA.

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Clarity AD inclusion and exclusion criteria

Select key inclusion criteria[1,2]

- Patients with MCI due to AD or mild AD dementia
  - Global CDR score of 0.5 or 1.0 and CDR Memory Box score ≥0.5
  - MMSE score ≥22 and ≤30
  - WMS-IV LMII score ≥1 SD below age-adjusted mean
- Amyloid pathology confirmed
- Aged 50 to 90 years

Select key exclusion criteria[1]

- Serious hypersensitivity to lecanemab-irmb or to any of the excipients of LEQEMBI
- Risk factors for intracerebral hemorrhage: neuroimaging 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)

AD=Alzheimer's disease; CDR=Clinical Dementia Rating; MCI=mild cognitive impairment; MMSE=Mini-Mental State Examination; SD=standard deviation; WMS-IV LMII=Wechsler Memory Scale IV-Logical Memory (subscale) II.

1. LEQEMBI (lecanemab-irmb) [Prescribing Information]. Nutley, NJ: Eisai Inc. **2.** van Dyck CH et al. *N Engl J Med*. 2023;388(1):9-21.

Baseline characteristics: A broad population, representative of patients with MCI due to AD and mild AD dementia[1]

	LEQEMBI® 10 mg/kg once every 2 weeks (N=859)	Placebo (N=875)
Age, mean (SD), years	71.4 (7.9)	71.0 (7.8)
Female, n (%)	443 (51.6)	464 (53.0)
White, n (%)	655 (76.3)	677 (77.4)
Years since diagnosis, mean (SD)	1.41 (1.51)	1.34 (1.54)
Years since onset of symptoms, mean (SD)	4.13 (2.35)	4.15 (2.53)
CDR global score=0.5, n (%)	694 (80.8)	706 (80.7)
Mild dementia due to AD, n (%)	331 (38.5)	331 (37.8)
ApoE ε4 status, n (%)		
Noncarrier	267 (31.1)	275 (31.4)
Carrier	592 (68.9)	600 (68.6)
Heterozygote	456 (53.1)	468 (53.5)
Homozygote	136 (15.8)	132 (15.1)
On AChEIs and/or memantine, n (%)	447 (52.0)	468 (53.5)
CDR-SB, mean (SD)	3.17 (1.34)	3.22 (1.34)
PET Centiloids, mean (SD)	77.92 (44.84)	75.03 (41.82)
ADAS-Cog14, mean (SD)	24.45 (7.08)	24.37 (7.56)
ADCOMS, mean (SD)	0.398 (0.147)	0.400 (0.147)
ADCS MCI-ADL, mean (SD)	41.2 (6.6)	40.9 (6.9)
MMSE, mean (SD)	25.5 (2.2)	25.6 (2.2)

In the US, the population studied was generally reflective of the Medicare population[3-6]:

- Approximately 27% of total enrollment in the US were Hispanic (22.5%) and Black (4.5%) people[3]
- 63.7% of patients had at least 2 comorbid conditions*[3]
- 5.7% received anticoagulants[3]
  - 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 (eg, tissue plasminogen activator) to a patient already being treated with LEQEMBI[1]

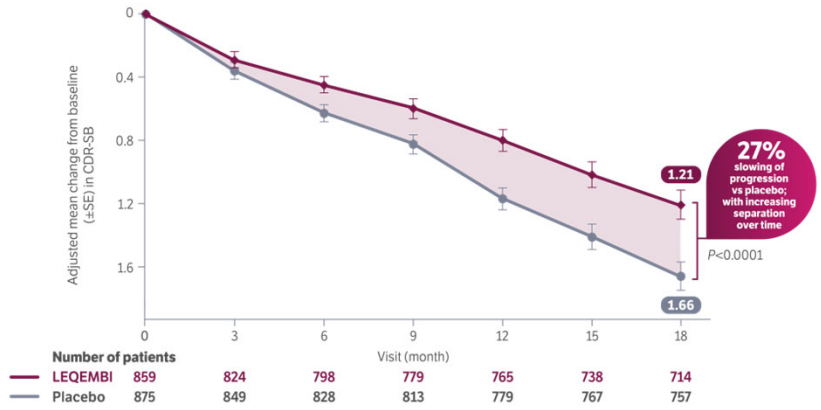
*Comorbid conditions include hypertension, hyperlipidemia, ischemic heart disease, and obesity[3]

AChEI=acetylcholinesterase inhibitor; AD=Alzheimer's disease; ADAS-Cog14=Alzheimer's Disease Assessment Scale-Cognitive Subscale 14-item version; ADCS MCI-ADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; ApoE ε4=apolipoprotein E ε4; CDR=Clinical Dementia Rating; CDR-SB=Clinical Dementia Rating-Sum of Boxes; MCI=mild cognitive impairment; MMSE=Mini-Mental State Examination; PET=positron emission tomography; SD=standard deviation.

1. LEQEMBI (lecanemab-irmb) [Prescribing Information]. Nutley, NJ: Eisai Inc. **2.** van Dyck CH et al. *N Engl J Med*. 2023;388(1):9-21. **3.** Eisai Inc. Presented at: Clinical Trials on Alzheimer's Disease; November 29-December 2, 2022; San Francisco, CA. **4.** CCW. Accessed June 16, 2023. https://www2.ccwdata.org/documents/10280/19096644/ccw-website-table-a1a.pdf. **5.** Center for Medicare & Medicaid Services. Multiple chronic conditions. Updated December 1, 2021. Accessed June 16, 2023. https://www.cms.gov/research-statistics-data-and-systems/statistics-trends-and-reports/chronic-conditions/mcc_main. **6.** Troy A and Anderson TS. *JAMA Health Forum*. 2021;2(7):e211693. doi:10.1001/jamahealthforum.2021.

Intervening with LEQEMBI® changes the disease course, slowing cognitive and functional decline with continued treatment[1]

Primary endpoint, CDR-SB: Change from baseline at 18 months.
LEQEMBI showed statistical significance at all time points beginning at 6 months, and continued treatment demonstrated clinically meaningful slowing of cognitive and functional decline with increasing separation vs placebo through 18 months[1]



CDR-SB is a validated outcome measure that consists of the following domains[2,3]:

Cognition

- Memory (eg, recalling recent/distant events)
- Orientation (eg, time relationships, navigating familiar territory)
- Judgment and problem solving

Function

- Community affairs (eg, ability to work, socialize, and/or shop)
- Home and hobbies (eg, household tasks and activities)
- Personal care (eg dressing, washing, using bathroom)

Scoring[2-4]:

- Each domain can be scored as 0, 0.5, 1, 2, or 3, for a total scale range from 0 to 18
- Higher scores indicate more advanced AD
- MCI due to AD and mild AD dementia tend to score 0.5 or 1 in each domain

AD=Alzheimer's disease; CDR-SB=Clinical Dementia Rating-Sum of Boxes; MCI=mild cognitive impairment; SE=standard error.
1. LEQEMBI (lecanemab-irmb) [Prescribing Information]. Nutley, NJ: Eisai Inc. **2.** van Dyck CH et al. *N Engl J Med*. 2023;388(1):9-21. **3.** Morris JC. *Neurology*. 1993;43(11):2412-2414. **4.** Eisai Inc. Presented at: Clinical Trials on Alzheimer's Disease; November 29-December 2, 2022; San Francisco, CA.

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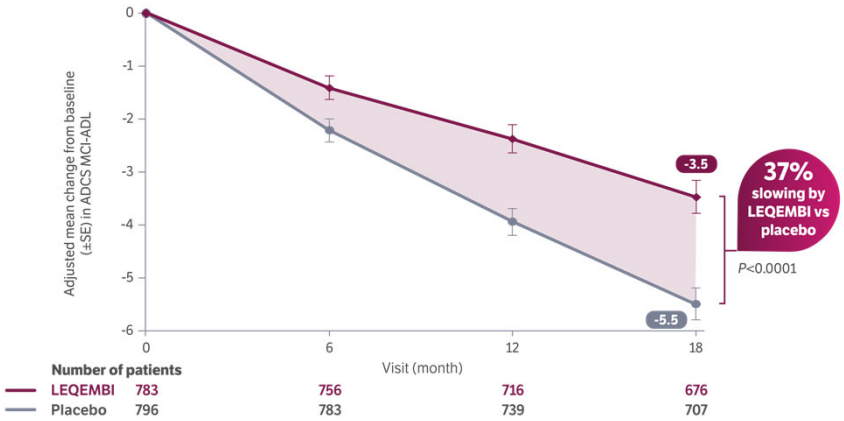
LEQEMBI (lecanemab-irmb) 100 mg/mL INJECTION FOR INTRAVENOUS USE

LEQEMBI® significantly slowed disease progression by 37% on the ADCS MCI-ADL scale at 18 months[1]

Secondary endpoint, ADCS MCI-ADL: Change from baseline at 18 months.
Slowing of functional decline was statistically significant at all time points beginning at 6 months, becoming more pronounced over time[1]



Function

ADCS MCI-ADL measures activities of daily living, including[2,3]:

- Travel
- Go shopping
- Keep appointments
- Make a meal
- Clean room
- Clean laundry
- Balance banking
- Use a telephone
- Left on his/her own
- Use household appliance
- Perform pastime
- Find personal belongings
- Write things down
- Select first set of clothes
- Talk about current events
- Read more than 5 minutes
- Usual dressing
- Watch television

Scoring[2]:

- 0 to 53 points, where lower scores indicate greater impairment

ADCS MCI-ADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; SE=standard error.
1. LEQEMBI (lecanemab-irmb) [Prescribing Information]. Nutley, NJ: Eisai Inc. **2.** van Dyck CH et al. *N Engl J Med*. 2023;388(1):9-21. **3.** Cohen S et al. Presentation presented at: AD/PD Annual Meeting; March 28-April 1, 2023. Gothenburg, Sweden.

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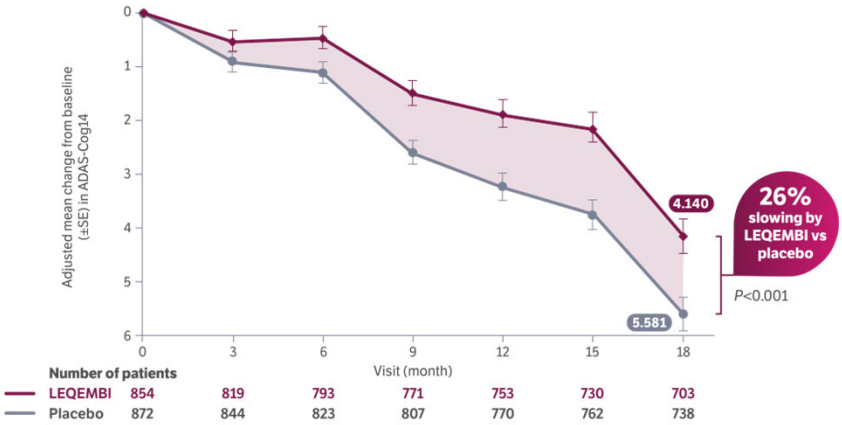
LEQEMBI (lecanemab-irmb) 100 mg/mL INJECTION FOR INTRAVENOUS USE

LEQEMBI® significantly slowed disease progression by 26% on ADAS-Cog14 scale at 18 months[1]

Secondary endpoint, ADAS-Cog14: Change from baseline at 18 months. Slowing of cognitive loss was statistically significant at all time points beginning at 6 months[1,2]



Cognition

ADAS-Cog14 measures activities of cognition, including[3-5]:

- Memory
- Orientation
- Attention
- Executive function
- Language
- Praxis (practical application of knowledge/skills)

Scoring[2,6]:

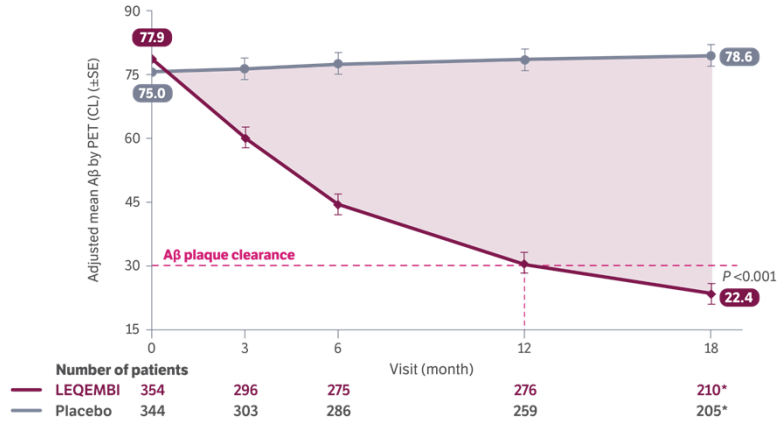
- 0 to 90 points (a composite of 14 items with varying scores)
- Higher scores indicate greater impairment

ADAS-Cog14=Alzheimer's Disease Assessment Scale-Cognitive Subscale 14-item version; SE=standard error.

1. LEQEMBI (lecanemab-irmb) [Prescribing Information]. Nutley, NJ: Eisai Inc. **2.** van Dyck CH et al. *N Engl J Med*. 2023;388(1):9-21. **3.** van Dyck CH et al. *N Engl J Med*. 2023;388(protocol 1):9-21. **4.** Kueper JK et al. *J Alzheimers Dis*. 2018;63(2):423-444. **5.** Wessels AM et al. *J Prev Alzheimers Dis*. 2018;5(1):15-20. **6.** Eisai Inc. Presented at: Clinical Trials on Alzheimer's Disease; November 29-December 2, 2022; San Francisco, CA.

At 18 months, LEQEMBI® reduced amyloid burden by an average of 56 CL and achieved amyloid plaque clearance in 68% of patients[1,2]

Secondary endpoint, amyloid plaque (CL): An average of 22.4 CL was reached at 18 months—below the cutoff for Aβ plaque clearance (30 CL)[1-4]



Adjusted mean Aβ by PET (CL):

- Plaque clearance reached at 12 months—below the cutoff for Aβ plaque clearance (30 CL)
- 68% of 210 patients on LEQEMBI compared to 16% of 205 patients on placebo achieved plaque clearance at 18 months
- 22.4 CL was reached at 18 months

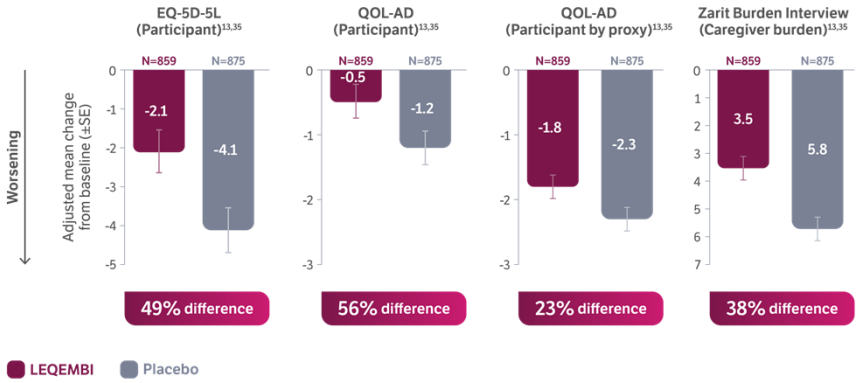
Based on pharmacodynamic analysis population (amyloid PET substudy population). Adjusted mean change from baseline, SE, and *P* value were derived using MMRM with treatment group, visit, treatment-group-by-visit interaction, clinical subgroup, use of AD symptomatic medication at baseline, ApoE ε4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.[2]

*73 subjects were not included at 18 months (per SAP) since their PET assessments were performed after receiving LEQEMBI in the extension phase.[2]
Aβ=amyloid beta; AD=Alzheimer's disease; ApoE ε4=apolipoprotein E ε4; CL=Centiloid; MMRM=Mixed Models for Repeated Measures; PET=positron emission tomography; SAP=statistical analysis plan; SE=standard error.

1. van Dyck CH et al. *N Engl J Med*. 2023;388(1):9-21. **2.** Eisai Inc. Presented at: Clinical Trials on Alzheimer's Disease; November 29-December 2, 2022; San Francisco, CA. **3.** LEQEMBI (lecanemab-irmb) [Prescribing Information]. Nutley, NJ: Eisai Inc. **4.** Data on file. Eisai Inc. Nutley, NJ.

LEQEMBI®: Evaluation of impact on patient quality of life and caregiver burden

Exploratory analyses: Measures of patient health-related QOL and caregiver burden at 18 months[1-3]



Limitations: Prespecified exploratory endpoints were not adjusted for multiplicity; therefore, no conclusions can be drawn[1]

European Quality of Life–5 Dimensions (5-level version) (EQ-5D-5L)[2]:

- Covers 5 dimensions of health:
  - Mobility, self-care, usual activities, pain or discomfort, and anxiety or depression
- Covers 5 levels of severity in each dimension:
  - No problems, slight problems, moderate problems, severe problems, and unable to perform or extreme problems
- The score being presented is the Health Today VAS (Visual Analog Scale subtotal)

Quality of Life in Alzheimer's Disease (QOL-AD)[2]:

- A 13-item questionnaire designed to provide both a patient and a caregiver report of the QOL for patients who have been diagnosed with AD

Zarit Burden Interview[2]:

- The 22-item instrument used in dementia caregiving research to assess the stresses experienced by study partners of subjects with dementia

AD=Alzheimer's disease; QOL=quality of life; SE=standard error.
1. van Dyck CH et al. *N Engl J Med*. 2023;388(protocol 1):9-21. **2.** Eisai Inc. Presented at: Clinical Trials on Alzheimer's Disease; November 29-December 2, 2022; San Francisco, CA. **3.** Data on file. Eisai Inc. Nutley, NJ.

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In Clarity AD: Tau PET substudy and a post hoc analysis

Study description: The predefined optional tau PET substudy looked at outcomes stratified by the participants' level of the brain tau aggregates (tau PET) as well as correlations of tau data to clinical outcomes. Post hoc analyses stratified patients by low, intermediate, and high levels of brain tau aggregates using the Cerveau database of tau PET (N=342). An exploratory post hoc analysis of early AD patients with varying tau levels and the effect on their CDR-SB scores was performed. Further analyses were conducted in the low tau group to measure the change from baseline on the CDR-SB.[1-3]

Baseline characteristics generally similar across tau populations with exception of amyloid load[1]

	Tau PET substudy		Low tau		Intermediate/high tau*	
	LEQEMBI® (n=175)	Placebo (n=167)	LEQEMBI (n=70)	Placebo (n=71)	LEQEMBI (n=105)	Placebo (n=96)
Age, mean (SD), years	71.8 (7.8)	72.4 (7.8)	72.6 (7.6)	71.8 (8.6)	71.2 (7.9)	72.8 (7.1)
Years since onset of symptoms	4.32 (2.443)	4.21 (3.042)	4.77 (2.488)	3.81 (2.027)	4.01 (2.377)	4.51 (3.596)
On AChEIs and/or memantine	71 (40.6)	66 (39.5)	24 (34.3)	31 (43.7)	47 (44.8)	35 (36.5)
Aβ PET Centiloids, mean (SD)	70.65 (46.844)	73.84 (41.032)	36.35 (35.790)	50.36 (37.637)	93.51 (38.753)	90.96 (34.536)
MMSE, mean (SD)	25.62 (2.178)	25.65 (2.094)	25.46 (2.012)	25.92 (2.136)	25.72 (2.285)	25.45 (2.051)
CDR-SB, mean (SD)	3.40 (1.307)	3.31 (1.332)	3.44 (1.424)	3.20 (1.369)	3.38 (1.230)	3.40 (1.304)

Of the patients who had low tau levels, 61% (n=86/141) were considered to have MCI due to AD[1]

*191 (55.8%) had intermediate tau levels and 10 (2.9%) had high tau levels
Aβ=amyloid beta; AChEI=acetylcholinesterase inhibitor; AD=Alzheimer's disease; CDR-SB=Clinical Dementia Rating-Sum of Boxes; MCI=mild cognitive impairment; MMSE=Mini-Mental State Examination; PET=positron emission tomography; SD=standard deviation.

1. Johnson K. Biomarker assessments from Clarity AD: downstream implications of targeting protofibrils and tau as a predictive biomarker. Presented at: Clinical Trials on Alzheimer's Disease; October 24-27, 2023; Boston, MA. **2.** van Dyck CH et al. *N Engl J Med*. 2023;388(1):9-21. **3.** Johnson K, Li D, Dhadda S, et al. Biomarker assessments from Clarity AD: downstream implications of targeting protofibrils and tau as a predictive biomarker. Abstract presented at: Clinical Trials on Alzheimer's Disease; October 24-27, 2023; Boston, MA.

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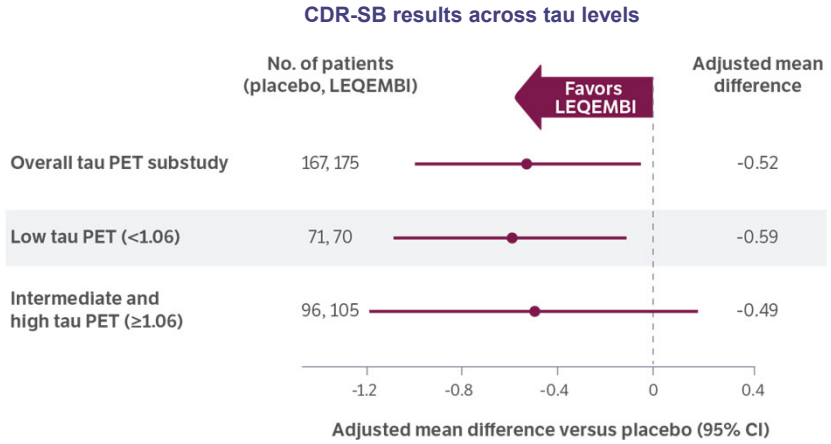
In Clarity AD, a post hoc analysis evaluated CDR-SB scores in a tau PET substudy



Limitations: These post hoc exploratory analyses reflect data from the tau PET subgroup of the Clarity AD study. The analyses were limited by small sample size and were not adjusted for multiplicity; as such no conclusions can be drawn.

CDR-SB=Clinical Dementia Rating-Sum of Boxes; PET=positron emission tomography.

Johnson K. Biomarker assessments from Clarity AD: downstream implications of targeting protofibrils and tau as a predictive biomarker. Presented at: Clinical Trials on Alzheimer's Disease; October 24-27, 2023; Boston, MA.

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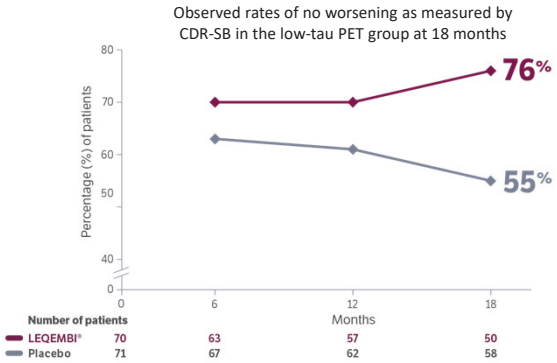
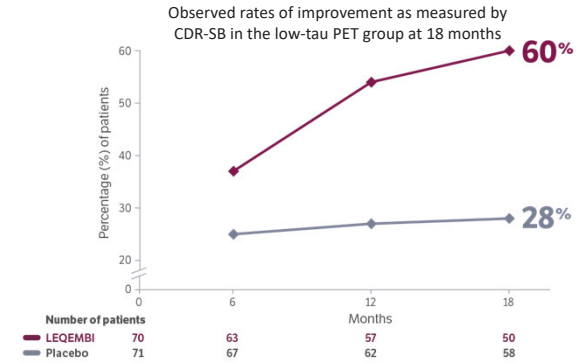
In Clarity AD, post hoc analyses evaluated CDR-SB in a low-tau patient population[1]

CDR-SB measures cognition and function. An increase in score=increased impairment, and a decrease in score=decreased impairment[2]

76% of patients with early AD and low tau levels showed no worsening in CDR-SB scores compared to baseline[1,3]



60% of patients with early AD and low tau levels showed an improvement as measured by the CDR-SB compared with baseline[1,3]



Limitations: These post hoc exploratory analyses reflect data from the tau PET subgroup of the Clarity AD study. The analyses were limited by small sample size and were not adjusted for multiplicity; as such no conclusions can be drawn.[3]

AD=Alzheimer's disease; CDR-SB=Clinical Dementia Rating-Sum of Boxes; IV=intravenous; MCI=mild cognitive impairment; PET=positron emission tomography.

1. Johnson K, Li D, Dhadda S, et al. Biomarker assessments from Clarity AD: downstream implications of targeting protofibrils and tau as a predictive biomarker. Abstract presented at: Clinical Trials on Alzheimer's Disease; October 24-27, 2023; Boston, MA. **2.** van Dyck CH et al. *N Engl J Med*. 2023;388(1):9-21. **3.** Johnson K. Biomarker assessments from Clarity AD: downstream implications of targeting protofibrils and tau as a predictive biomarker. Presented at: Clinical Trials on Alzheimer's Disease; October 24-27, 2023; Boston, MA.

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Warnings and precautions: ARIA

- Symptomatic ARIA occurred in 3% (29/898) of patients treated with LEQEMBI[1]
- Serious symptoms associated with ARIA were reported in 0.7% (6/898) of patients treated with LEQEMBI[1]
- Clinical symptoms associated with ARIA resolved in 79% (23/29) of patients during the period of observation[1]
- In patients with symptomatic ARIA, commonly reported symptoms include headache, confusion, visual changes, dizziness, nausea, and gait difficulty[1]
- ARIA-H that occurred with ARIA-E tended to occur early (within 6 months)[2]
- There was no increase in isolated ARIA-H (ie, ARIA-H in patients who did not also experience ARIA-E) for LEQEMBI compared to placebo[1]

Study 2: Incidence of ARIA

ARIA incidence	LEQEMBI® (N=898) % (n)	Placebo (N=897) % (n)
ARIA-E or ARIA-H*[1]	21 (191)	9 (84)
ARIA-E[1]	13 (113)	2 (15)
ARIA-H[1]	17 (152)	9 (80)
Isolated ARIA-H[2]	8.9 (80)	7.8 (70)

*Including asymptomatic radiographic events.[1]

ARIA is a consequence of amyloid presence in blood vessel walls that can occur spontaneously in patients with AD or as a result of treatment with a monoclonal antibody (including LEQEMBI®) that removes amyloid.[1,3,4]

ARIA with edema, or ARIA-E, can be observed on MRI as brain edema or sulcal effusions. ARIA with hemosiderin deposition, or ARIA-H, includes microhemorrhage and superficial siderosis.[1]

AD=Alzheimer's disease; ARIA=amyloid-related imaging abnormality; ARIA-E=amyloid-related imaging abnormality-edema; ARIA-H=amyloid-related imaging abnormality-hemosiderin deposition.

1. LEQEMBI (lecanemab-irmb) [Prescribing Information]. Nutley, NJ: Eisai Inc. **2.** van Dyck CH et al. *N Engl J Med*. 2023;388:9-21. **3.** Barakos J et al. *J Prev Alz Dis*. 2022;2(9):211-220. **4.** Cogswell PM et al. *Am J Neuroradiol*. 2022;43:E19-E35.

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Warnings and precautions: ARIA (cont'd)

The incidence of radiographic ARIA-E in Study 2

Radiographic ARIA with LEQEMBI®

	LEQEMBI		
	ARIA-E % (n/N)	ARIA-H % (n/N)	
Maximum radiographic severity of ARIA		Microhemorrhage	Superficial siderosis
Mild	4 (37/898)	9 (79/898)	4 (38/898)
Moderate	7 (66/898)	2 (19/898)	1 (8/898)
Severe	1 (9/898)	3 (28/898)	0.4 (4/898)
Severe radiographic ARIA	**ARIA-E % (n/N)**	**ARIA-H % (n/N)**	
ApoE ε4 homozygotes	5 (7/141)	13.5 (19/141)	
ApoE ε4 heterozygotes	0.4 (2/479)	2.1 (10/479)	
Noncarriers	0 (0/278)	1.1 (3/278)	

- The majority of ARIA-E radiographic events occurred within the first 7 doses of treatment, although ARIA can occur at any time and patients can have more than 1 episode
- Resolution of ARIA-E on MRI occurred in 52% by 12 weeks, 81% by 17 weeks, and 100% overall after detection

The incidence of ApoE ε4 status and risk of ARIA in Study 2

- 16% of patients were ApoE ε4 homozygotes (141/898):
  - The incidence of ARIA was 45% for LEQEMBI vs 22% for placebo
- 53% of patients were ApoE ε4 heterozygotes (479/898):
  - The incidence of ARIA was 19% for LEQEMBI vs 9% for placebo
- 31% of patients were noncarriers (278/898):
  - The incidence of ARIA was 13% for LEQEMBI vs 4% for placebo
- Among patients treated with LEQEMBI, symptomatic ARIA occurred in 9% of ApoE ε4 homozygotes compared with 2% of heterozygotes and 1% of noncarriers. Serious events of ARIA occurred in 3% of ApoE ε4 homozygotes and approximately 1% of heterozygotes and noncarriers

ApoE ε4=apolipoprotein E ε4; ARIA=amyloid-related imaging abnormality; ARIA-E=amyloid-related imaging abnormality-edema; ARIA-H=amyloid-related imaging abnormality-hemosiderin deposition. LEQEMBI (lecanemab-irmb) [Prescribing Information]. Nutley, NJ: Eisai Inc.

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Warnings and Precautions and most common adverse reactions

Hypersensitivity reactions[1]

- Hypersensitivity reactions, including angioedema, bronchospasm, and anaphylaxis, have occurred in patients who were treated with LEQEMBI®
- Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction, and initiate appropriate therapy
- LEQEMBI is contraindicated in patients with a history of serious hypersensitivity to lecanemab-irmb or to any of the excipients of LEQEMBI

Infusion-related reaction

- The majority of IRRs were mild (69%, 163/237) or moderate (28%, 67/237) and occurred within the first infusion (75%, 178/237)[1,2]
- IRRs resulted in discontinuations in 1% (12/898) of patients treated with LEQEMBI[1]

Study 2: Adverse reactions reported in ≥5% of patients treated with LEQEMBI 10 mg/kg every 2 weeks and ≥2% higher than placebo in Study 2[1]

Adverse reaction	LEQEMBI 10 mg/kg once every 2 weeks (N=898) %	Placebo (N=897) %
IRRs	26	7
ARIA-H	14	8
ARIA-E	13	2
Headache	11	8
Superficial siderosis of CNS	6	3
Rash*	6	4
Nausea/vomiting	6	4

* Rash includes acne, erythema, infusion site rash, injection site rash, rash, rash erythematous, rash pruritic, skin reactions, and urticaria.

Discontinuation due to ARs[1]

- 7% of patients discontinued LEQEMBI due to an adverse reaction compared to 3% of patients on placebo
- 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

ARIA-E=amyloid-related imaging abnormality-edema; ARIA-H=amyloid related imaging abnormality-hemosiderin deposition; CNS=central nervous system; IRR=infusion-related reaction.

1. LEQEMBI (lecanemab-irmb) [Prescribing Information]. Nutley, NJ: Eisai Inc. **2.** Eisai Inc. Presented at: Clinical Trials on Alzheimer's Disease; November 29-December 2, 2022; San Francisco, CA.

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Kay, actual patient with AD.
Patient not on LEQEMBI.

Initiating LEQEMBI®

AD=Alzheimer's disease.

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After confirming patient is appropriate for treatment and deciding to initiate therapy, LEQEMBI® is administered as a titration-free infusion over 1 hour, once every 2 weeks

Prior to initiating LEQEMBI

- Confirm the presence of amyloid beta pathology
  - Confirmation of tau pathology is not required
- Obtain a recent baseline brain MRI prior to initiating treatment with LEQEMBI
- 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 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

Note: the above steps may have been performed during the AD diagnosis process.

Dosage and administration of LEQEMBI

- The recommended dosage of LEQEMBI is 10 mg/kg
- LEQEMBI is administered via IV infusion over approximately 1 hour, once every 2 weeks
- If an infusion is missed, the next dose should be administered as soon as possible

Concomitant medications

- Baseline use of antithrombotic medications (aspirin, other antiplatelets, or anticoagulants) was allowed in Study 2 if the patient was on a stable dose
- Most exposures to an antithrombotic medication were to aspirin
- Antithrombotic medications taken with LEQEMBI did not increase the risk of ARIA
- Intracerebral hemorrhage occurred in 0.9% (3/328) of patients taking LEQEMBI with a concomitant antithrombotic medication at the time of the event compared to 0.6% (3/545) of 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 on placebo

AD=Alzheimer's disease; ApoE ε4=apolipoprotein E ε4; ARIA=amyloid-related imaging abnormality; IV=intravenous; MRI=magnetic resonance imaging.

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For anti-amyloid mAb therapies indicated for AD, the CMS has updated guidance on coverage

The Centers for Medicare & Medicaid Services (CMS) has released information regarding coverage of new Alzheimer's drugs for Medicare patients.

For more information, go to https://qualitynet.cms.gov/alzheimers-ced-registry.

AD=Alzheimer's disease; mAb=monoclonal antibody.

Centers for Medicare & Medicaid Services. Updated July 6, 2023. Accessed July 17, 2023. https://qualitynet.cms.gov/files/64a7151bd15911001c695b32?filename=Provider%20%20Factsheet%20Alzheimers%20Treatment.pdf.

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Miyoko, actual patient with AD, with her daughter Kimiko.
Patient not on LEQEMBI®.

Monitoring for safety

AD=Alzheimer's disease.

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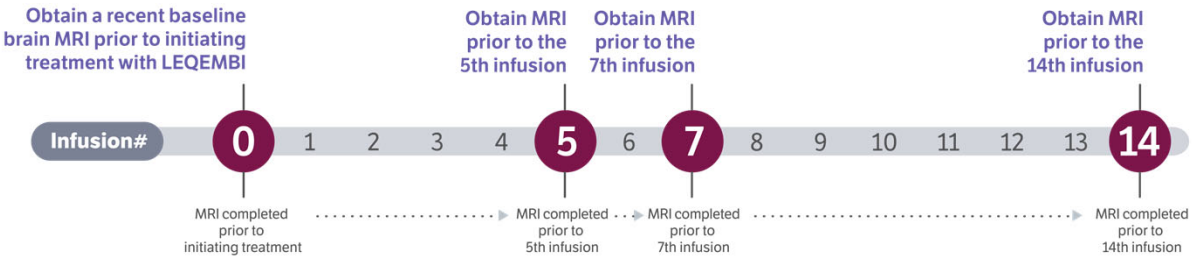
LEQEMBI® PI provides detailed ARIA screening and management strategies to help monitor the safety of patients from the start



Do NOT administer the 5th, 7th, or 14th infusion until the additional MRIs have been completed and confirmed.

› 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

ARIA=amyloid-related imaging abnormality; MRI=magnetic resonance imaging.
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Dosing interruptions for patients who experience ARIA-E or ARIA-H depend on clinical symptomatic and radiographic severity[1]

Clinical symptom severity*	ARIA-E severity on MRI		
	Mild	Moderate	Severe
Asymptomatic	May continue dosing	Suspend dosing†	Suspend dosing†
Mild	May continue dosing based on clinical judgment		
Moderate or severe	Suspend dosing†		

*Mild: discomfort noticed, but no disruption of normal daily activity. Moderate: discomfort sufficient to reduce or affect normal daily activity. Severe: incapacitating, with inability to work or to perform normal daily activity.[1]

†Suspend until MRI demonstrates radiographic resolution and symptoms, if present, resolve; consider a follow-up MRI to assess for resolution 2 to 4 months after initial identification. Resumption of dosing should be guided by clinical judgment.[1]

- Use clinical judgment in considering whether to continue dosing in patients with recurrent ARIA-E[1]
- 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[1]

Clinical symptom severity	ARIA-H severity on MRI		
	Mild	Moderate	Severe
Asymptomatic	May continue dosing	Suspend dosing‡	Suspend dosing§
Symptomatic	Suspend dosing‡		

‡Mild/moderate: Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve; resumption of dosing should be guided by clinical judgment; consider a follow-up MRI to assess for stabilization 2 to 4 months after initial identification.[1]

§Severe: Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve; use clinical judgment in considering whether to continue treatment or permanently discontinue LEQEMBI®.[1]

- In patients who develop intracerebral hemorrhage >1cm in diameter during treatment with LEQEMBI, suspend dosing until MRI demonstrates radiographic stabilization and symptoms, if present, resolve. Use clinical judgment in considering whether to continue treatment after radiographic stabilization and resolution of symptoms or permanently discontinue LEQEMBI[1]

If ARIA is observed on MRI, careful clinical evaluation should be performed prior to continuing treatment. Dosing was able to be continued in most patients with ARIA.[1,2] The recommendations on management of ARIA do not differ between ApoE ε4 carriers and noncarriers.[1,2]

ApoE ε4=apolipoprotein E ε4; ARIA=amyloid-related imaging abnormality; ARIA-E=amyloid-related imaging abnormality-edema; ARIA-H=amyloid-related imaging abnormality-hemosiderin deposition; MRI=magnetic resonance imaging.

1. LEQEMBI (lecanemab-irmb) [Prescribing Information]. Nutley, NJ: Eisai Inc. **2.** Data on file. Eisai Inc. Nutley, NJ.

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In patients with MCI due to AD and mild AD dementia, get ahead and stay ahead for longer*

Early and ongoing treatment can slow the progression of AD[1,2,8]

Early AD is a critical point for intervention[1]

LEQEMBI clears more than just plaque[1,2,8]

Dual-acting LEQEMBI supports neuronal function in AD by clearing highly toxic protofibrils that can continue to cause neuronal injury and death well after plaques are cleared[1-7]

Studied in patients with MCI due to AD and mild AD dementia, including patients in the earliest stages of symptomatic AD[8,9]

- The majority of patients were in the earliest symptomatic stage, MCI due to AD

LEQEMBI is proven to slow progression across all stages of early Alzheimer's disease[1,2,8,9]

Intervening with LEQEMBI changes the disease course, slowing cognitive and functional decline with continued treatment. Results from baseline at 18 months vs placebo:

- 27% slowing of cognitive and functional decline (*P*<0.0001) on CDR-SB
- 37% slowing of functional decline (*P*<0.0001) on ADCS MCI-ADL
- 26% slowing of cognitive decline (*P*<0.001) on ADAS-Cog14
- 56 CL reduction in amyloid burden with 68% of 210 patients achieving plaque clearance
- Starting at 6 months, across all time points, LEQEMBI treatment showed statistically significant changes in the primary and all key secondary endpoints from baseline compared to placebo

Safety matters. The incidence and timing of ARIA vary among treatments[1]

- ARIA-E occurred in 13% of patients and ARIA-H occurred in 17% of patients taking LEQEMBI
- Symptomatic ARIA occurred in 3% of patients treated with LEQEMBI
- 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%)
- 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

*Demonstrated vs placebo through 18 months in Study 2.[1,2]

AD=Alzheimer's disease; ADAS-Cog14=Alzheimer's Disease Assessment Scale-Cognitive Subscale 14-item version; ADCS MCI-ADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; ARIA=amyloid-related imaging abnormality; ARIA-E=amyloid-related imaging abnormality-edema; ARIA-H=amyloid-related imaging abnormality-hemosiderin deposition; CL=Centiloid; CDR-SB=Clinical Dementia Rating-Sum of Boxes; MCI=mild cognitive impairment.

1. LEQEMBI (lecanemab-irmb) [Prescribing Information]. Nutley, NJ: Eisai Inc. **2.** van Dyck CH et al. *N Engl J Med*. 2023;388(1):9-21. **3.** Brendza RP et al. *J Clin Invest*. 2005;115(2):428-433. **4.** Hampel H et al. *Mol Psychiatry*. 2021;26(10):5481-5503. **5.** Ono K, Tsuji M. *Int J Mol Sci*. 2020;21(3):952. **6.** Söllvander S et al. *Mol Neurodegener*. 2016;11(1):38. **7.** Hartley DM et al. *J Neurosci*. 1999;19(20):8876-8884. **8.** Iwatsubo T et al. Presented at: CTAD Conference; November 29-December 2, 2022; San Francisco, CA. **9.** Alzheimer's Association. 2023 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2023;18:1-122.

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