NAMCP Medical Directors Spotlight Guide: An Intervention for Early Alzheimer's Disease

Considerations for Alzheimer's Disease Management for Medical Directors of Purchasers, Health Plans, and Providers

JOURNAL of MANAGED CARE MEDICINE

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Mission Statement

The mission of the National Association of Managed Care Physicians (NAMCP) Medical Directors Institute is to open the lines of communication between medical directors in managed care and treating physicians to help them jointly better navigate and understand what is happening in managed care and the daily management and practice of disease. The NAMCP Medical Directors Institute brings resources and updates, strategic reviews, and key information to medical directors for insurers, employers, providers, and integrated delivery networks. Unique Executive Councils focus on emerging technologies, oncology and value-based contracting for manufacturers and managed market leaders.

This guide presents an overview of the emerging landscape in Alzheimer's Disease and the recent approval of LEQEMBI® (lecanemab-irmb). It discusses managed care treatment and policy in the context of the current indication and emerging landscape. This guide discusses awareness of Alzheimer's Disease and the role that early diagnosis, testing and treatment can have on both patients and their care partners. Early intervention can impact the total costs of care as well as patient access to needed care and wellbeing. This guide is part of a series of activities and initiatives within the NAMCP Institute to support medical directors from purchasers, plans, and provider systems, and to eventually achieve greater collaboration leading to improved patient outcomes.

INDICATION[1]

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.

SELECT SAFETY INFORMATION: Boxed WARNING

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®

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

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JMCM
JOURNAL
OF MANAGED CARE
MEDICINE

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ISSN: 1094-1525. The *Journal of Managed Care Medicine* is published by NAMCP Medical Directors Institute. Corporate and Circulation offices: 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060; Tel (804) 527-1905; Fax (804) 747-5316. Editorial and Production offices: P.O. Box 71895, Richmond, VA 23255-1895; Tel (804) 387-7580; Fax (703) 997-5842. Advertising offices: Sloane Reed, 4435 Waterfront Drive Ste 101, Glen Allen, VA 23060 Tel (804) 527-1905, Fax (804) 747-5316.

POSTMASTER: Send address changes to The Journal of Managed Care Medicine, 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060.

JOURNAL of MANAGED CARE MEDICINE

The Official Journal of the NAMCP MEDICAL DIRECTORS INSTITUTE

A Peer-Reviewed Publication

Intervention for Alzheimer's Disease 2023

Funded by Eisai and Biogen

TABLE OF CONTENTS

NAMCP Medical Directors Spotlight Guide: An Intervention for Early Alzheimer's Disease

Considerations for Alzheimer's Disease Management for Medical Directors of Purchasers, Health Plans, and Providers

Dawn Holcombe, MBA, FACMPE, ACHE

Understanding Alzheimer's Disease

Alzheimer's Disease is a Progressive[2] and Relentless Disease and Represents a Crucial Unmet Need in Healthcare[1,3-5,62]

Alzheimer's Disease (AD) is a progressive[3], fatal[3] neurodegenerative disease that accounts for 60 to 80 percent of dementia[3] (a group of symptoms, including difficulties with memory, language and problem-solving, that affect a person's ability to perform daily activities) cases.[3] AD was the fifth leading cause of death in those aged 65 and older in 2019 and is the seventh leading cause of death in the United States (U.S.) in 2020 and 2021, after COVID entered the ranks of the top 10 leading causes of death.[3,4]

Four million six-hundred thousand people in the U.S. (an estimate made by the Institute for Clinical and Economic Review (ICER) based on 2019 data) have mild cognitive impairment (MCI) due to AD or mild AD dementia, but only 2.28 million patients with MCI due to AD or mild AD dementia are diagnosed.[4,6] About one-third of people with MCI due to AD develop AD dementia within five years.[3] MCI can be caused by many processes, including cerebrovascular disease and other causes, but more than 60 percent of cases are due to AD.[5]

The federal government recognized the need to prevent and effectively treat AD and related dementias (ADRD) and created the National Plan to Address Alzheimer's Disease in 2012 with regular updates, the most recent being in 2022. This national plan declares that "AD/ADRD is a major public health issue and will increasingly affect the health and well-being of the population. Unless the diseases can be effectively treated or prevented, the number of Americans with AD/ADRD will increase significantly in the next two decades as the population ages."[7]

Multiple Factors May Increase the Risk of AD[3,8]

Multiple factors may increase the risk of AD, including both fixed and modifiable risk factors.[7,9]
Fixed risk factors may include:

- Age – Most individuals with AD are aged 65 and older. After age 65, the risk of AD doubles every 10 years.[3,8]
- Genetics – Genetic mutations can lead to early-onset AD, the symptoms of which can start as young as age 30. The apolipoprotein E (*ApoE4*) variant has been linked to AD.[3,8]
- Race – Whites make up the majority of the over five million people in the U.S. with AD, but available studies show that African Americans and Hispanics are at higher risk. African Americans are twice as likely to have AD compared to white Americans. Hispanics are about one and one-half times more likely than whites to have AD and other dementias.[3,8,66]
- Sex – Two-thirds of people with AD are women.[3,8,61]

As shown in Exhibit 1, modifiable risk factors may include major lifestyle factors[3,9] and cardiovascular comorbidities.[3,8]

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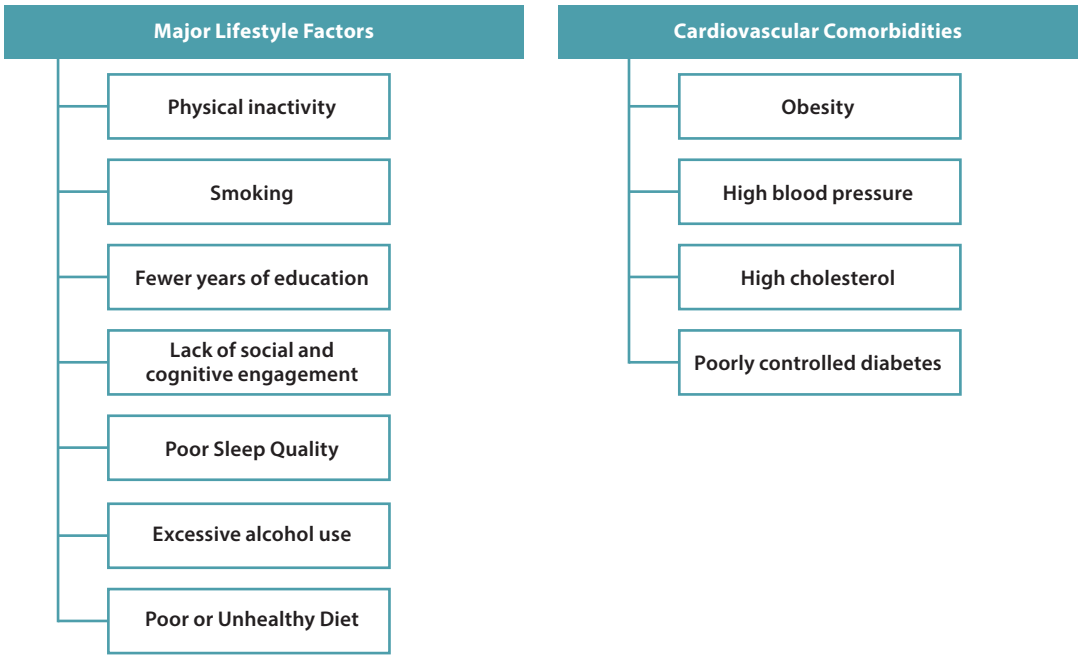
Exhibit 1: Modifiable Factors That May Increase the Risk of AD[3,8]



Importance of Early Intervention and Key Considerations Throughout the Patient Journey

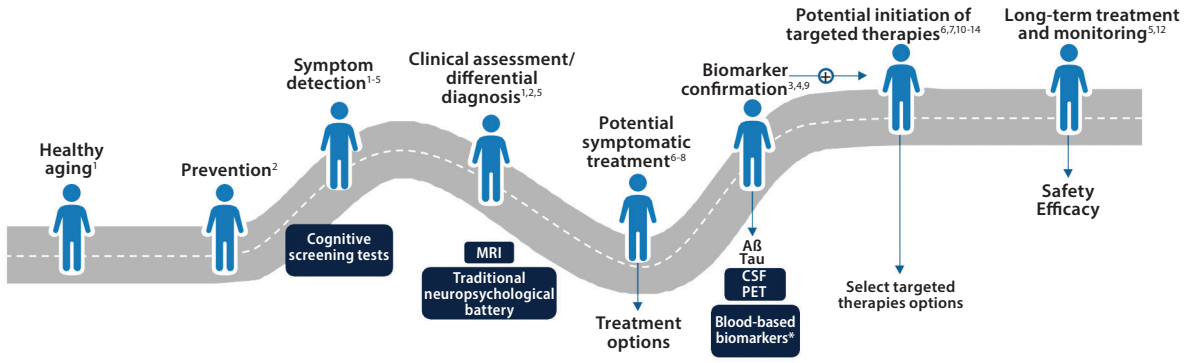
Early AD Patient Journey Involves Multiple Phases Between Symptom Detection and Potential Treatment Initiation[9]

Patients typically go through multiple phases for symptom detection, diagnosis, and potential treatment initiation of AD.[8,9] A 2017 Rand research report projected the average wait time between the clinical diagnosis and treatment phases to be 18.6 months in 2020.[8,9]

In analyzing the preparedness of the U.S. healthcare system infrastructure for an AD treatment, a Rand research report summarized that some earlier clinical trials led to the hypothesis that AD needs to be prevented rather than cured due to the lack of therapies that reverse dementia. Availability of therapies for early AD presents a health systems challenge in that a substantial number of existing cases of early AD would need to be screened, diagnosed, and potentially treated to slow disease progression.[9] The availability of a anti-amyloid treatment will increase the need for routine screening and testing along the Alzheimer's continuum.[9] Given the potential for such a therapy, early screening and diagnosis will be needed to ensure disease identification in a timely manner.[9]

As a response to the detrimental impacts and costs of misdiagnosed or undiagnosed AD, new practice guidelines for the clinical evaluation of AD in primary and specialty care settings were released at the 2018 Alzheimer's Association International Conference. Intended to guide and support treating physicians as well as health plans and other payers, these guidelines provide recommendations for appropriate, timely evaluation and assessment, and highlight the importance of including the caregiver in all aspects of AD care.[13] Exhibit 2 depicts the phases of the early AD patient journey.

Exhibit 2: Early AD Patient Journey Phases[8]



* Blood-based biomarkers analysis is currently under investigation as a newer alternative to PET imaging and CSF-based testing methods for AD.
Aß = amyloid beta; AchEI = acetylcholine esterase inhibitor; AD = Alzheimer's disease;
CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; PET = positron emission tomography.

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The Earlier MCI Due to AD and Mild AD Dementia Are Diagnosed and Treated, The Greater the Opportunity for Benefit[5]

About one-third of people with MCI due to AD develop AD dementia within five years.[2,3,4] They begin to experience subtle deterioration in memory and judgement/problem-solving skills, although symptoms may not interfere with daily activities as yet.[2,8,11,15]

Additionally, one in two people with AD have mild disease.[4,8,16] Associated symptoms include noticeable cognitive changes (memory and judgement/problem-solving). They may also experience declines in community affairs functions (performing tasks in social and work settings).[8,11]

In early stages of AD, patients and their care partners may initially notice subtle changes that continue to worsen as AD progresses. MCI due to AD and mild AD dementia are different stages and are critical points for intervention.[2] Exhibit 3 illustrates the continuum of AD from preclinical, mild cognitive impairment (MCI), mild AD dementia, moderate AD dementia, to severe AD dementia.

Exhibit 3: Alzheimer's Disease Continuum[2,4,11,12,60,64-67]

AD continuum[1]

	Preclinical AD	MCI due to AD	Mild AD dementia	Moderate AD dementia	Severe AD dementia
Duration in stage	2 to 15 years[2]	3 to 7 years[2]	2 to 6 years[2]	1 to 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]

AD = Alzheimer's disease; MC I= mild cognitive impairment.

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To Identify AD Early, Cognitive Screening and Structural Imaging Are Key First Steps[4,8,17]

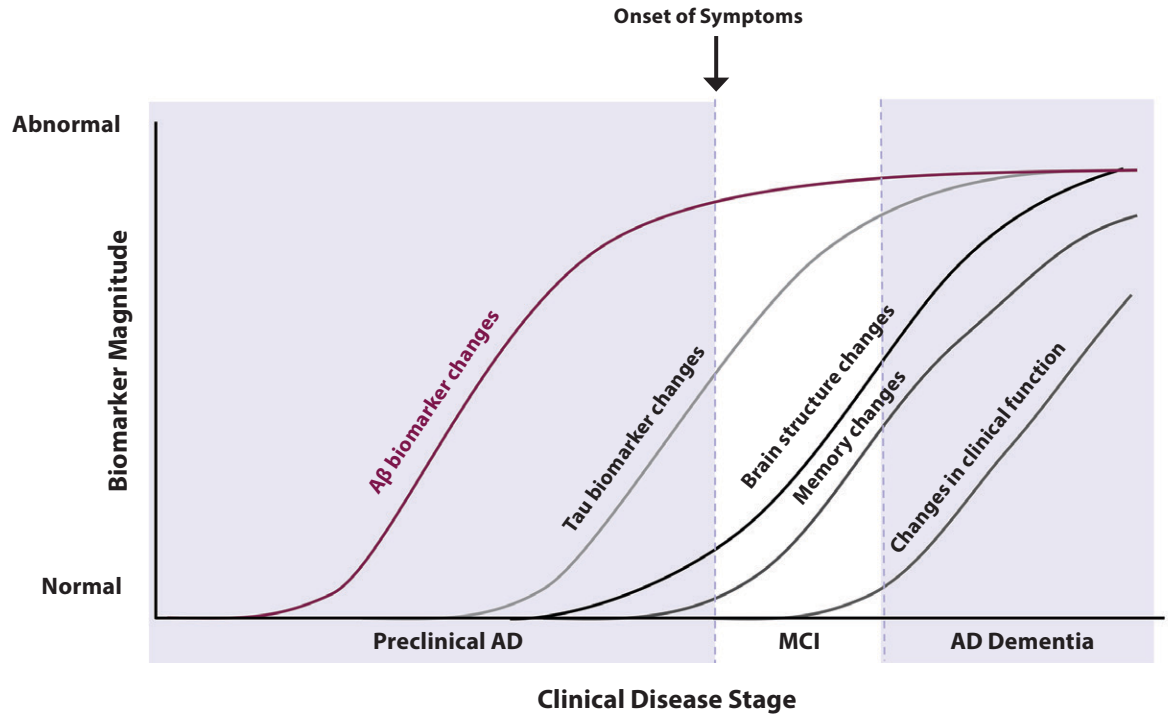
Intervening early can delay progression.[2] To identify AD early, cognitive screening and structural imaging are key first steps. Both treating physicians and managed care plans can support patients with flexibility to accommodate a variety of diagnostic tools.[17] Treating physicians will be most familiar with the options for diagnosis and may express a preference for specific tools to inform individual patient diagnosis based on familiarity and/or preference of the health system or practice.[4,17] Health plans will benefit from collaboration and close communication with treating providers regarding the physician's preferences and utilization of diagnostic tools. After a patient has presented with suspected cognitive changes, they may be assessed with calibrated diagnostic tools that are sensitive to MCI and mild AD dementia.[4,17] Such tools may include: the Montreal Cognitive Assessment (MoCA), the Quick Mild Cognitive Impairment (QMCI) screen, the Mini-Mental State Examination (MMSE), the Mini-Cog, the Saint Louis University Mental Status (SLUMS), and the Eight Item Informant Interview to Differentiate Aging and Dementia (AD8). Structural imaging, such as MRI and CT scans, may also be used to rule out other conditions that may cause symptoms similar to AD.[4,17,18]

While there are many cognitive assessment options for screening and testing to assess AD, it is not necessary to conduct all of them for assessment. Health plans are recognizing the value of allowing diagnosis with just one or two tests selected by the physician as appropriate for a given patient, thus avoiding the time delays, possible redundancy, and additional costs of requiring all the available tests.[19,20]

Biomarker-Confirmed AD Diagnosis Enables the Identification of Patients Who Would Be Appropriate for Aβ-Targeting Therapy[4,8]

Biomarker-confirmed AD diagnoses enable the early identification of patients who may be appropriate for amyloid beta (Aβ) targeting therapies.[4,8,22] Aβ biomarkers are the first biomarkers to present abnormally in the course of AD and can be measured by CSF Aβ42 or amyloid PET.[4,8,22,25] Elevated levels of Aβ can be determined 15 years before the onset of symptoms with a position emission tomography (PET) scan[4,8,21] and 20 years before the onset of MCI with a cerebrospinal fluid (CSF) assay.[4,8,22,24,25] Exhibit 4 presents the biomarker magnitude over the course of AD.[4,8,22]

Exhibit 4: Presence of Amyloid Biomarkers in the Course of Alzheimer's Disease[4,8,22]



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

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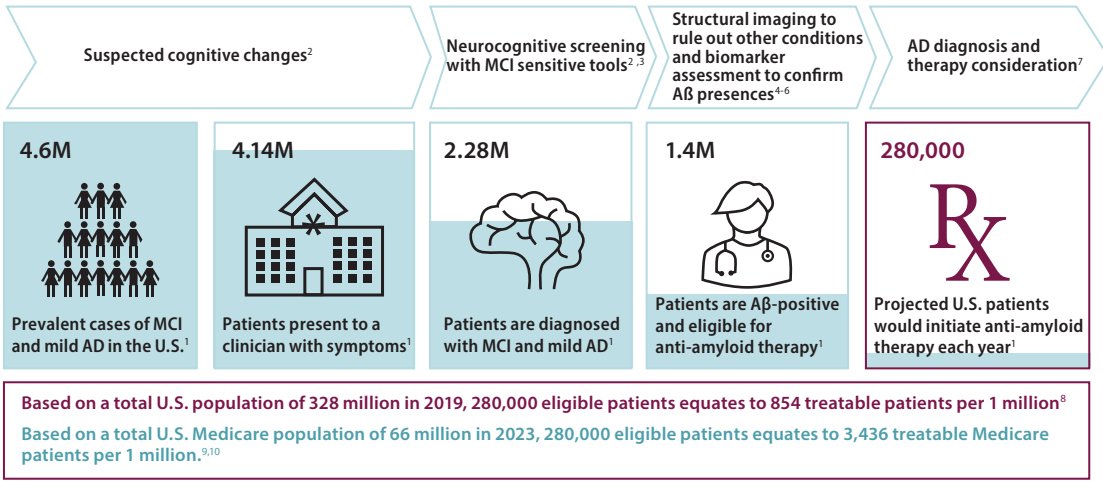
Diagnostic resources can enable the identification of patients who would be appropriate for Aβ-targeting therapy.[2,22,63] However, if testing and coverage limits by health plans do not correlate with diagnostic advances and guidelines followed by the treating provider, patient care and timely access to care may be adversely affected.[8,9] Consequences may lead to reduced early diagnostic utilization and could further restrict patient access to needed biomarker testing.

- Positron emission tomography (PET) scan. The PET is a well-established tool to confirm the presence of Aβ, 15 years before the onset of AD symptoms. It may have limited availability since it requires high-cost equipment, which can raise access issues for rural patients.[8,21,24,25,26]
- Cerebrospinal Fluid (CSF). The CSF Assay is a well-established tool that can determine levels of Aβ, 20 years before the onset of MCI.[24,25,26]
- Blood-based biomarkers. These are attractive due to the accessible, less invasive, and relatively inexpensive nature of blood assays.[8,24,27] Once clinically validated for diagnostic use, they may help inform therapeutic decision-making. Currently available tests are C2N PrecivityAD™ [28] and Quest AD-Detect™.[8,28,29] Blood-based biomarker analysis is currently under investigation as a newer alternative to PET imaging and CSF-based testing methods for AD.

A Subset of All Patients with MCI due to AD or Mild AD are potentially Treatable with an Amyloid-Targeted Therapy [4,8]

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 in the U.S. Using the patient journey scenarios depicted below in Exhibit 5, projections lead to approximately 280,000 potential patients initiating anti-amyloid therapy each year.[31]

Exhibit 5: A Subset of all Patients with MCI due to AD or Mild AD are Potentially Treatable with an Amyloid-Targeted Therapy [4,8,31]



* 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 U.S. 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 Aß-positive to arrive at 1.4 million patients eligible for treatment that targets Aß. Of these 1.4 million patients, 20% were assumed to initiate treatment each year over the course of five years, or approximately 280,000 patients per year.

Aß = amyloid beta; AD = Alzheimer's disease; ICER = Institute for Clinical and Economic Review; MCI = mild cognitive impairment.

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

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Choose a Treatment Option for Early Alzheimer's Disease

LEQEMBI® is an option for early AD that could change the course of AD for managed care, providers and most important, patients and their caregivers.[4,62]

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.[1,4]

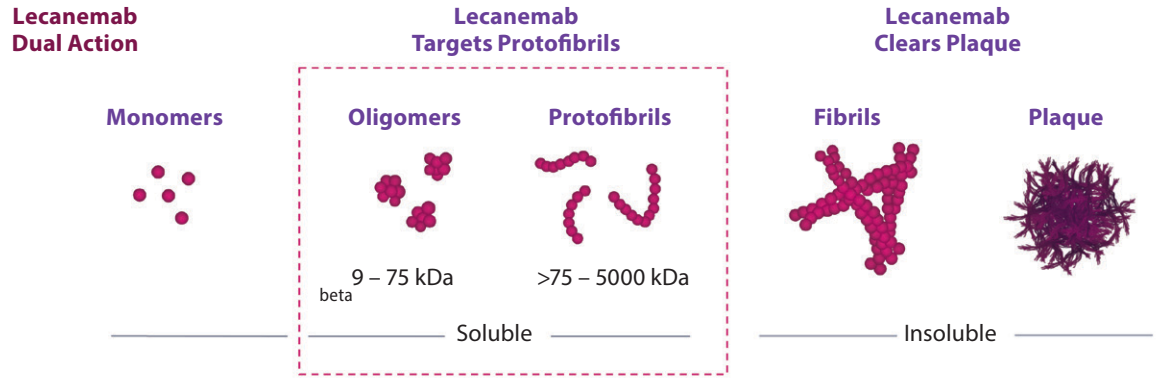
Mechanism of Action

LEQEMBI® Clears More Than Just Plaque.[1,5,32,33] Dual Acting[1] LEQEMBI® Also Supports Neuronal Function By Clearing[1,5,32,34] Highly Toxic Protofibrils That Can Continue to Cause Neuronal Injury and Death Even After Plaques Are Cleared.[1,5,32,35-39]

AD is an ongoing neurotoxic process that begins before and continues after plaque deposition.[1,5,24,35,36,37,39] Aβ dynamically evolves through different conformational states, including soluble monomers, dimers, oligomers, and protofibrils and insoluble fibrils and plaques.[35] The accumulation of Aβ plaques in the brain is a defining pathophysiological feature of AD.[1]

The Aβ cascade also triggers downstream molecular pathways, including tau pathology, which further contribute to neurodegeneration.[1,5,32,35]

Exhibit 6: 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



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

SELECT SAFETY INFORMATION (continued)

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.

LEQEMBI® (lecanemab-irmb) 100 mg/mL
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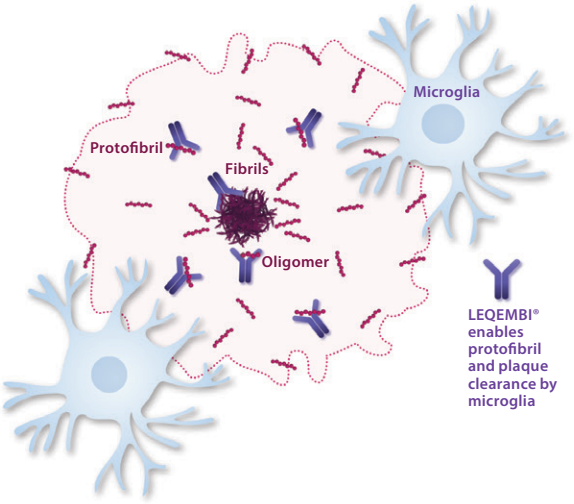
As shown in Exhibits 6 and 7, LEQEMBI® selectively targets the most neurotoxic Aβ aggregates, oligomers and protofibrils, preventing Aβ deposition before plaques develop and removing existing plaques.[1,5,35,41-45]

- Lecanemab-irmb is a humanized immunoglobulin gamma 1 (lgG1) monoclonal antibody directed against aggregated soluble (oligomers and protofibrils) and insoluble (fibrils and plaques) forms of Aβ.[1,5,35]
- LEQEMBI® is the only monoclonal antibody that preferentially binds with highest affinity to toxic protofibrils (with 10 to 15 times higher selectivity over fibrils, and greater than 1,000-fold selectivity over monomers).[34,45-47,33]

Exhibit 7: LEQEMBI® Selectively Targets the Most Neurotoxic Aβ Aggregates, Oligomers and Protofibrils[4,5,34,35,41-44,47]



*LEQEMBI® mechanism of action data are from in vitro studies and in vivo animal models.[1,5]

Aß = amyloid beta; AD = Alzheimer's disease; IgG1 = immunoglobulin gamma 1

SELECT SAFETY INFORMATION

WARNINGS & PRECAUTIONS (continued)

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.

LEQEMBI® (lecanemab-irmb) 100 mg/mL
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Clarity AD Trial

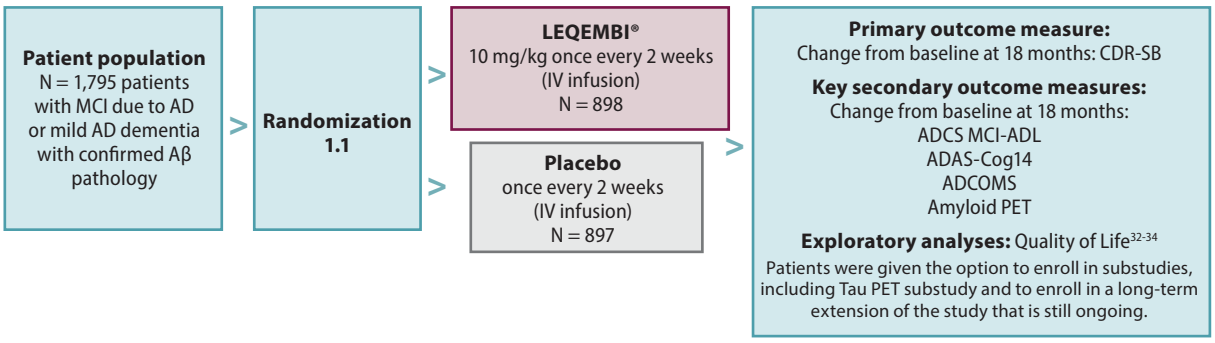
Clarity AD: A Pivotal Study Evaluating Key Primary and Secondary Endpoints in Patients with MCI Due to AD and Mild AD Dementia Across a Variety of Practice Settings[1,4]

Clarity AD (Study 2) is an 18-month, global, placebo-controlled, double-blind, parallel-group randomized study.[4,32] Exhibit 8 shows the process of patient randomization for the study. This pivotal study evaluated key primary and secondary endpoints in patients with MCI due to AD and mild AD dementia.[1,4,32] The study was conducted across a variety of practice settings, including private and hospital- and community-based academic centers located in urban, suburban, and rural areas.[48]

The Clarity AD study randomization was stratified according to:[1,4,32]

- Clinical subgroup (MCI due to AD or mild AD dementia) [1,4,32]
- Presence or absence of ongoing approved AD treatment (e.g., Acetylcholinesterase inhibitors, memantine, or both)[1,4,32]
- ApoE ε4 status (i.e., carriers or noncarriers)[1,4,32]
- Geographical region[1,4,32]

Exhibit 8: Clarity AD (Study 2) Patient Randomization[4,32]



Aβ = amyloid beta; 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; ADCOMS = Alzheimer's Disease Composite Score; CDR-SB = Clinical Dementia Rating-Sum of Boxes;

Clarity AD Inclusion and Exclusion Criteria[1,4,32]

Exhibit 9 provides more detailed inclusion and exclusion criteria for Clarity AD.[1,4,32]

Exhibit 9: Inclusion and Exclusion Criteria for Clarity AD[1,4,32]

Select key inclusion criteria[1,2]	Select key exclusion criteria[1]
• 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	• 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[1,4,32]

The baseline characteristics of the Clarity AD study, outlined in Exhibit 10, included a broad population, representative of patients with MCI due to AD and mild AD dementia, including a higher percentage of patients with MCI due to AD compared with mild AD. Approximately 27 percent of the total enrollment in the U.S. was Hispanic (22.5%) and Black (4.5%) people.[1,4,34] In the U.S., the population studied was generally reflective of the Medicare population and included patients who had at least two comorbid conditions (63.7%), and patients that received anticoagulants (5.7%). Comorbid conditions included hyperlipidemia, ischemic heart disease, hypertension, diabetes, and obesity.[4,34] Additionally, 5.7% of patients received anticoagulants.[4,34]

Because intracerebral hemorrhages greater than 1cm 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®.[4]

Exhibit 10: Clarity AD Trial Baseline Characteristics[1,4,32,34]

	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 (53.0)	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)

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.

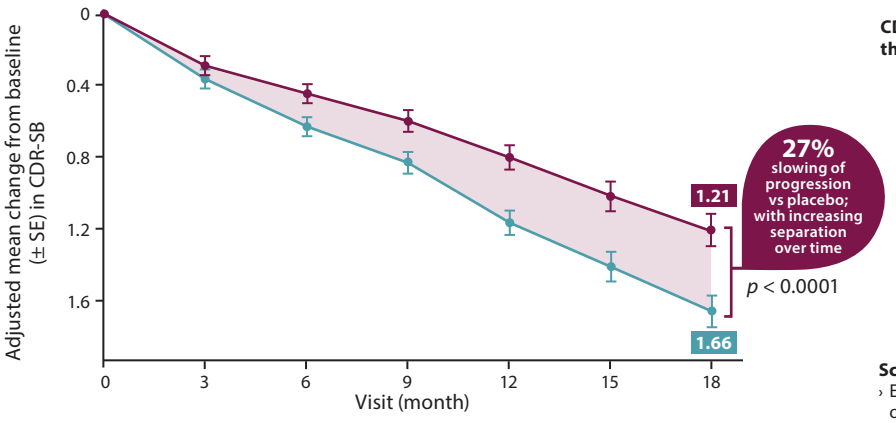
1. LEQEMBI® (lecanemab-irmb) [Prescribing Information]. Nutley, NJ: Eisai Inc.
2. van Dyck CH et al. *N Engl J Med.* 2023;388(1):9-21.
3. Eisai Inc. Presented at: Clinical Trials on Alzheimer's Disease; November 29-December 2, 2022; San Francisco, CA.
4. CCW. Accessed June 16, 2023. https://www2.ccwdata.org/documents/10280/19096644/ccw-website-table-a1a.pdf.
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.

Clinical Results

LEQEMBI® is Proven to Slow Progression Across the Stages of Early AD

Intervening with LEQEMBI® changes the disease course, slowing cognitive and functional decline with continued treatment.[1,2,32] As shown in Exhibit 11, the Clarity AD trial primary endpoint, clinical Dementia Rating-Sum of Boxes (CDR-SB) showed statistical significance for LEQEMBI® at all time points beginning at six months, and continued treatment demonstrated clinically meaningful slowing of cognitive and functional decline with increasing separation versus placebo through 18 months.[1]

Exhibit 11: Clarity AD Primary Endpoint, CDR-SB: Change from Baseline at 18 Months[1,4,50]



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.

SELECT SAFETY INFORMATION

WARNINGS & PRECAUTIONS (continued)

Intracerebral Hemorrhage (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.

LEQEMBI® (lecanemab-irmb) 100 mg/mL
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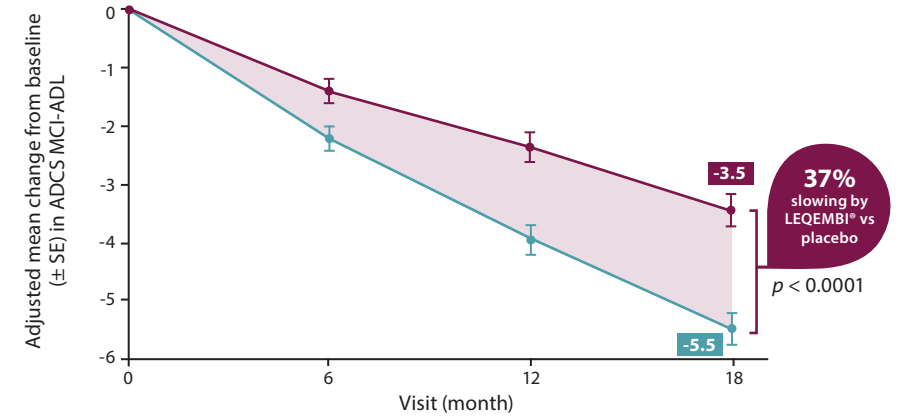
LEQEMBI® Significantly Slowed Disease Progression by 37 Percent on the ADCS MCI-ADL Scale at 18 Months[4]

Exhibit 12 shares a Clarity AD trial secondary endpoint, the Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL) impact. Slowing of functional decline was statistically significant at all time points beginning at six months, becoming more pronounced over time.[1,4]

Exhibit 12: Clarity AD Trial Secondary Endpoint, ADCS MCI-ADL Shows Significant Slowing of Functional Decline through 18 Months[1,4,50]



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

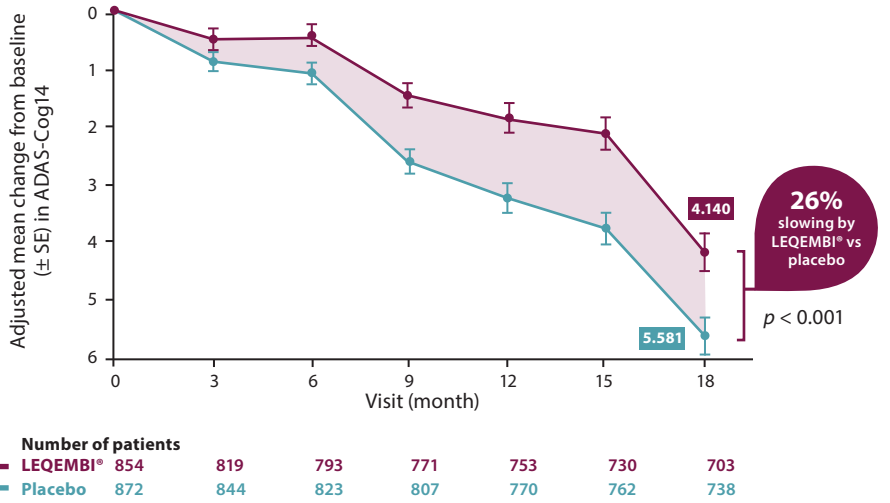
ADCS MCI-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; SE = standard error.

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.

LEQEMBI® Significantly Slowed Disease Progression by 26 Percent on ADAS-Cog14 Scale at 18 Months[1,4]

A Clarity AD trial secondary endpoint, the Alzheimer's Disease Assessment Scale-Cognitive Subscale 14-item version (ADAS-Cog14) reflects in Exhibit 13 that slowing of cognitive loss was statistically significant at all time points beginning at six months through 18 months.

Exhibit 13: Clarity AD Trial Secondary Endpoint ADAS-Cog 14 is Statistically Significant Through 18 Months[1,4,53]



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]

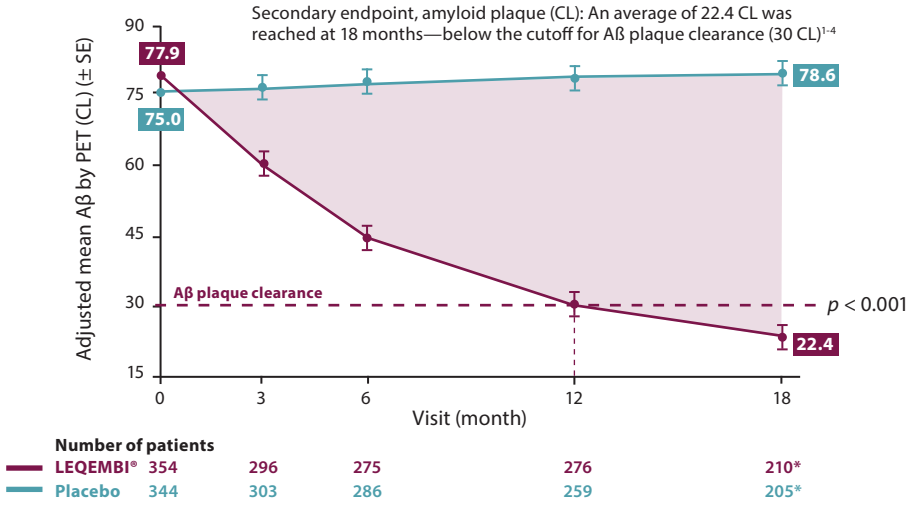
- 0 to 90 points (a composite of 14 items with varying scores)
- Higher scores indicate greater impairment

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 Alzheimer's Dis. 2018;63(2):423-444.
5. Wessels AM et al. J Prev Alzheimer's 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 Centiloid and Achieved Amyloid Plaque Clearance in 68 Percent of Patients[1,4,32,34]

A Clarity AD secondary endpoint was measurement of amyloid plaque using the Centiloid (CL) scale, as demonstrated in Exhibit 14.[1] At 12 months, plaque clearance decreased to under the cutoff for Aβ plaque clearance (30 CL). Sixty-eight percent of 210 patients on LEQEMBI® achieved plaque clearance at 18 months compared to 16 percent of 205 patients on placebo, and an average of 22.4 CL was reached at 18 months (further below the plaque clearance cutoff than was reached at 12 months).[1,4,32,34]

Exhibit 14: Amyloid Plaque, a Secondary Endpoint, Reached an Average of 22.4 CL at 18 Months—Below the cutoff for Aβ Plaque Clearance (30CL)[1,4,32]



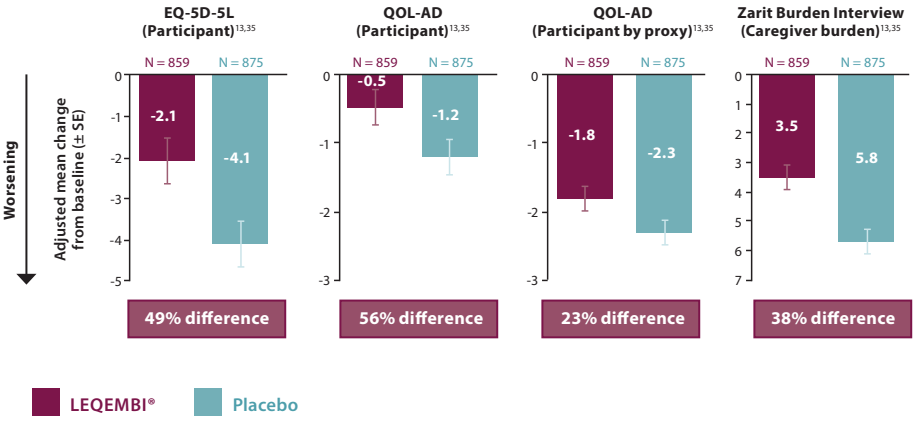
Based on pharmacodynamic analysis population (amyloid PET sub-study population). Adjusted mean change from baseline, SE, and *p* value were derived using MMRM with treatment group, visit, treatment-group-by-visit interaction, clinical subgroup, use of AD symptomatic medication at baseline, ApoE ε4 carrier 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]
Aß = 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[4]

The Clarity AD trial also considered measures of patient health-related Quality of Life (QOL) and caregiver burden at 18 months.[4,54] Comparative measures shown in Exhibit 15 included the European Quality of Life-5 Dimensions (5 level version) (EQ-5D-5L) [34], the Quality of Life in Alzheimer's Disease (QOL-AD) [34] and the Zarit Burden Interview for Caregiver Burden.[34]

Exhibit 15: Clarity AD Trial Measures of Patient Health-Related QOL and Caregiver Burden at 18 Months[4,32,55]



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

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

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

A Post-Hoc Analysis Evaluated CDR-SB Scores in a Tau PET Sub-study [5,53,56]

Tau protein aggregates are a predictive biomarker for Alzheimer's disease that is closely linked to emergence of neurodegeneration and manifestation of clinical symptoms.[53]

A predefined optional tau PET sub-study looked at outcomes stratified by the participant's 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). Of the total population included in this analysis (MK-6240 tau PET whole cortical gray matter), 141 patients (41.2%) had low tau levels (SUVR < 1.06), 191 (55.8%) had intermediate tau levels (SUVR ≥ 1.06, ≤ 2.91), and 10 (2.9%) had high tau levels (SUVR > 2.91). Exhibit 16 illustrates the similar baseline characteristics of patients across tau populations with the exception of amyloid load. Of the patients who had low tau levels, 61 percent (n = 86/141) were considered to have MCI. [5,32,53,56]

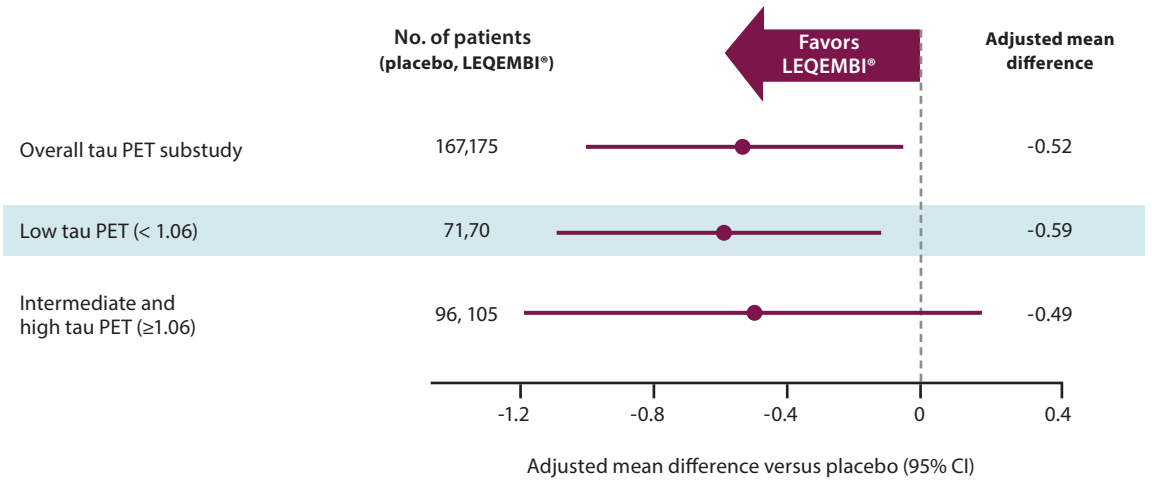
Exhibit 16: Baseline Characteristics are Generally Similar Across Tau Populations with the Exception of Amyloid Loads[5,56]

	Tau PET sub-study		Low tau		Intermediate/high tau	
	LEQEMBI® (N=175)	**Placebo** (N=175)	**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)

Aβ = amyloid beta; AChEIs = acetylcholinesterase inhibitors; CDR-SB = Clinical Dementia Rating-Sum of Boxes; CI=confidence interval; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; PET = positron emission tomography; SD = standard deviation; SUVR = standard uptake value ratio.

An exploratory post-hoc analysis of early AD patients with varying tau levels and the effect of LEQEMBI® 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. Exhibit 17 illustrates the mean differences in the CDR-SB results across tau levels.

Exhibit 17: The CDR-SB Results Across Tau Levels[5,56]



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.[5,56]

SELECT SAFETY INFORMATION (continued)

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.

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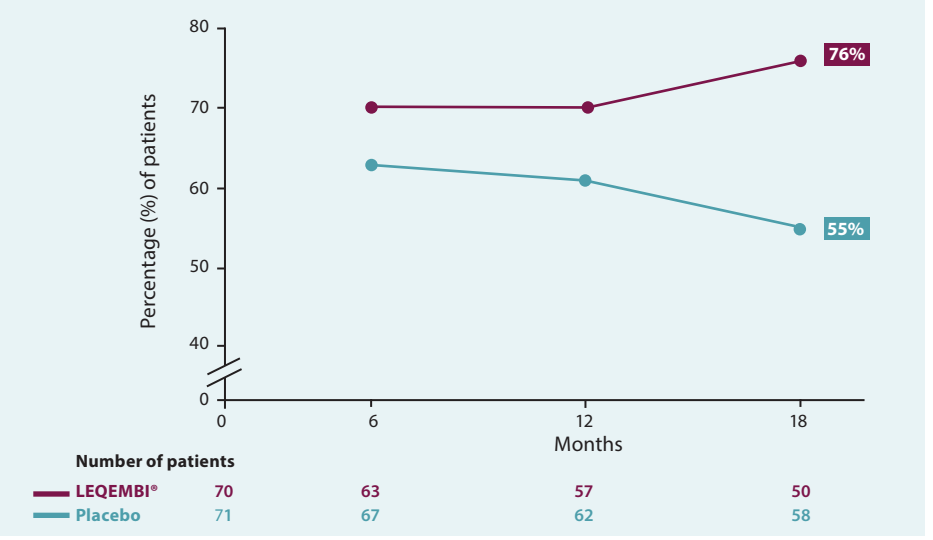
Exhibit 18 and 19 present post-hoc analyses that evaluated CDR-SB in a low tau patient population.[5,57] Exhibit 18 presents an evaluation of observed worsening measured by CDR-SB over time in the low-tau PET group. Exhibit 19 presents an evaluation of observed improvement measured by CDR-SB in the low-tau PET group. The CDR-SB measures cognition and function. An increase in scores equals increased impairment and a decrease in scores equals decreased impairment.[5,53,56]

Exhibit 18: Observed Rates of No Worsening as Measured By the CDR-SB in the Low-Tau PET Group at 18 Months[5,53,56]

76% of patients with early AD and low tau levels showed no worsening in CDR-SB scores compared to baseline[53,56]



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.

SELECT SAFETY INFORMATION

WARNINGS & PRECAUTIONS (continued)

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.

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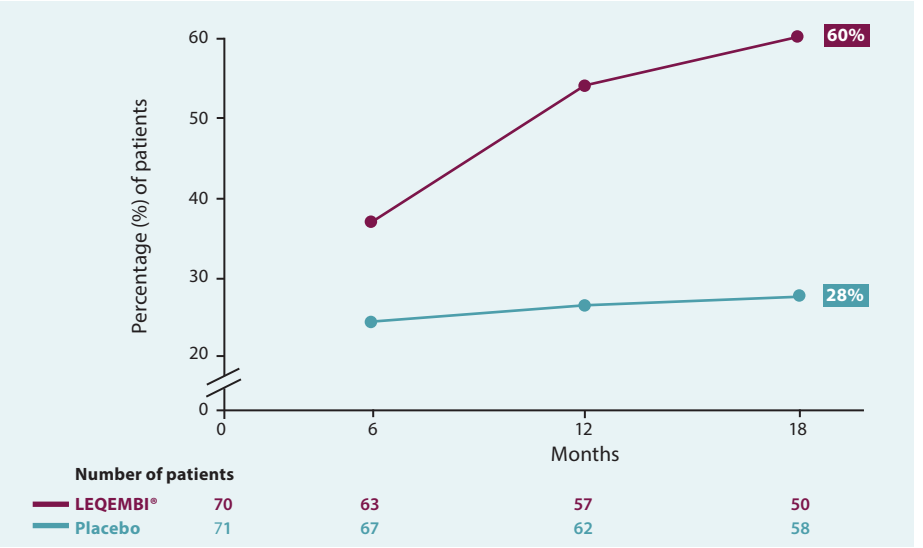
Exhibit 19: Observed Rates of Improvement as Measured By the CDR-SB in the Low-Tau PET Group at 18 Months[5,56]

60% of patients with early AD and low tau levels showed an improvement as measured by the CDR-SB compared with baseline[53,56]



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.[5,56]

Now that LEQEMBI® Clarity AD trial efficacy data has been discussed, we will explore some of the safety data that was identified.

SELECT SAFETY INFORMATION

WARNINGS & PRECAUTIONS (continued)

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.

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Safety Matters. The Incidence and Timing of ARIA Varies Among Treatments: Amyloid Related Imaging Abnormalities (ARIA)[4,5,32]

ARIA is a consequence of amyloid presence in blood vessel walls that can occur spontaneously in patients with AD or because of treatment with a monoclonal antibody (including LEQEMBI®) that removes amyloid.[1,4,5,57,58] ARIA with edema, or ARIA-E, can be observed on MRI as brain edema or sulcal effusions. (4; 1) ARIA with hemosiderin deposition, or ARIA-H, includes microhemorrhage and superficial siderosis.[2,4]

Exhibit 20 presents the incidence of ARIA in LEQEMBI and placebo. Overall, symptomatic ARIA occurred in 3 percent (29/898) of patients treated with LEQEMBI®.[1,4,5] Serious symptoms associated with ARIA were reported in 0.7 percent (6/898) of patients treated with LEQEMBI®.[1,4,5] Clinical symptoms associated with ARIA resolved in 79 percent (23/29) of patients during the period of observation.[4,5,59] In patients with symptomatic ARIA, commonly reported symptoms include headache, confusion, visual changes, dizziness, nausea, and gait difficulty.[1,4] ARIA-H that occurred with ARIA-E tended to occur early (within 6 months).[4,5,32] There was no increase in isolated ARIA-H (i.e., ARIA-H in patients who did not also experience ARIA-E) for LEQEMBI® compared to placebo.[4,5,32]

Exhibit 20: Study 2: Incidence of ARIA[4,5,32]

ARIA Incidence	LEQEMBI® (N = 898) % (n)	Placebo (N = 897) % (n)
ARIA-E or ARIA-H*	21 (191)	9 (84)
ARIA-E1	13 (113)	2 (15)
ARIA-H	17 (152)	9 (80)
Isolated ARIA-H	8.9 (80)	7.8 (70)

* Including asymptomatic radiographic events

Factors to Consider For ARIA

Exhibit 21 reviews the incidence of ApoE ε4 status and risk of ARIA in CLARITY AD. Serious events of ARIA occurred in 3 percent of ApoE ε4 homozygotes and approximately 1 percent of heterozygotes and noncarriers.[1,4,5]

Exhibit 21: The Incidence of ApoE ε4 Status and Risk of ARIA in Study[1,4,5]

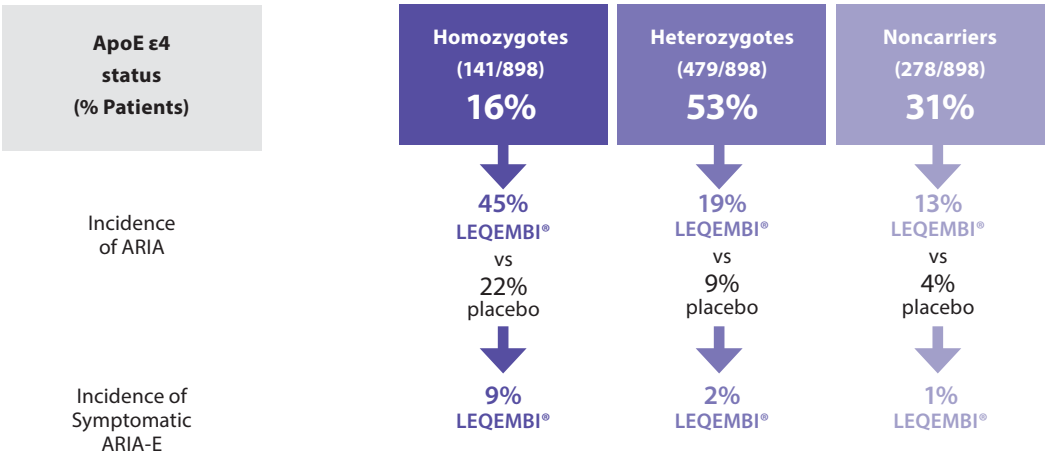

Exhibit 22: Role of Risk Factors for ARIA and Intracerebral Hemorrhage

✓ **ApoE ε4 status:**

- Before treatment, test for ApoE ε4 status to inform the risk for developing ARIA
- Prior to testing, explain to patients that if ApoE ε4 (genotype) testing is not done, they can still be treated with LEQEMBI; however, it will not be known if they are at higher risk of ARIA
- The presence of an ApoE ε4 allele is also associated with cerebral amyloid angiopathy, which increases the risk for intracerebral hemorrhage

✓ **Concomitant use of antiplatelet or anticoagulant and additional risk factors:** 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 or a thrombolytic agent (eg, tissue plasminogen activator)

ApoE ε4=apolipoproteln E ε4; ARIA=amylold-related Imaging abnormality.

Exhibit 23: Study 2 – Most Common Adverse Reactions with LEQEMBI®[1,4]

Adverse reaction	LEQEMBI® 10 mg/kg once every 2 weeks (N = 898) %	Placebo (N = 897) % (n)
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.

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

MOST COMMON ADVERSE REACTIONS[4]

Exhibit 23 presents the most common adverse reactions in ≥5% of patients treated with LEQEMBI 10 mg/kg every 2 weeks and ≥2% higher than placebo in CLARITY AD. Seven percent of patients discontinued LEQEMBI® due to an adverse reaction compared to 3 percent of patients on placebo. The most common adverse reaction leading to discontinuation of LEQEMBI® was ARIA-H microhemorrhages that led to discontinuation in 2 percent (15/898) of patients treated with LEQEMBI® compared to 1 percent (1/897) of patients on placebo.[1,4,34]

Initiating LEQEMBI®[4]

After Confirming Patient is Appropriate for Treatment and Deciding to Initiate Therapy, LEQEMBI® is Administered as a Titration-Free Infusion Over One Hour, Once Every Two Weeks[1,4,5]

Once the physician has determined that LEQEMBI® would be the desired treatment for a given patient, the following steps would be taken to confirm and document that the patient is appropriate for LEQMBI®.

Prior to Initiating LEQEMBI®:[4,5,59]

NOTE: The following steps may have been performed during the AD diagnosis process.[4,5,59]

- Confirm the presence of amyloid beta pathology – confirmation of tau pathology is not required.[4,5,59]
- Obtain a recent baseline brain MRI prior to initiating treatment with LEQEMBI®.[4,5,59]
- Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing amyloid-related imaging abnormality (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.[4,5,59]

After confirming the patient is appropriate for treatment and deciding to initiate therapy, LEQEMBI® is administered as a titration-free infusion over one hour, once every two weeks.[4,5,59]

Dosage and Administration of LEQEMBI® (LEQEMBI® (lecanemab-irmb)[4,5,59]

- The recommended dosage of LEQEMBI® is 10 mg/kg

- LEQEMBI® is administered via IV infusion over approximately one hour, once every two weeks
- If an infusion is missed, the next dose should be administered as soon as possible.

Concomitant Medications[4,5,59]

- Baseline use of antithrombotic medications (aspirin, other antiplatelets, or anticoagulants) was allowed in Study 2 if the patient was on a stable dose.[4,5,59]
- Most exposures to an antithrombotic medication were to aspirin.[4,5,59]
- Antithrombotic medications taken with LEQEMBI® did not increase the risk of ARIA.[4,5,59]
- Intracerebral hemorrhage occurred in 0.9 percent (3/328) of patients taking LEQEMBI® with a concomitant antithrombotic medication at the time of the event compared to 0.6 percent (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 percent (2/79 patients) compared to none in patients on placebo.[4,5,59]

CMS Has Updated Guidelines on Coverage for Anti-Amyloid mAb Therapies Indicated for AD[4,5]

When considering initiation of LEQEMBI®, the Centers for Medicare and Medicaid Services (CMS) has identified coverage information that can inform appropriate access/patient identification. CMS has now released information regarding coverage of new Alzheimer's drugs for Medicare patients. For more information, go to https://qualitynet.cms.gov/alzheimers-ced-registry.[4,5]

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WARNINGS & PRECAUTIONS (continued)

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.

LEQEMBI® (lecanemab-irmb) 100 mg/mL
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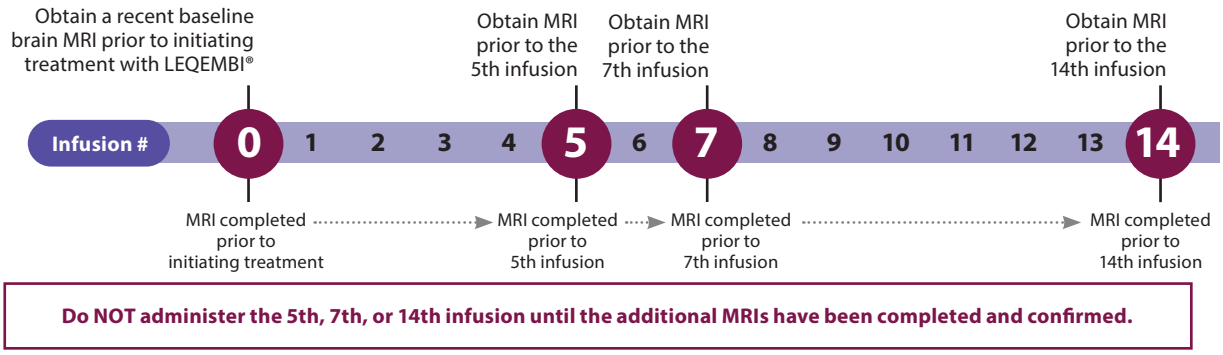
Monitoring the Safety of Your Patients

LEQEMBI® PI Provides Detailed ARIA Screening and Management Strategies to Help Monitor the Safety of Patients from the Start, as shown in Exhibit 24[1,4,5]

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.[1,4,5]

Exhibit 24: Monitoring Patients for Safety with LEQEMBI®[1,4,5]



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

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WARNINGS & PRECAUTIONS (continued)

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).

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Exhibit 25: Dosing Interruptions for Patients who Experience ARIA-E or ARIA-H[1,4,5]

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 judgement		
Moderate or severe	Suspend dosing†		

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

‡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]

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

Dosing Interruptions for Patients Who Experience ARIA-E or ARIA-H Depend on Clinical Symptomatic and Radiographic Severity[1,4,5]

Dosing was able to be continued in most patients with ARIA. Dosing interruptions for patients who experience amyloid-related imaging abnormality-edema (ARIA-E) or amyloid-related imaging abnormality-hemosiderin deposition (ARIA-H) will depend on clinical symptomatic and radiographic severity, as shown in Exhibit 25. 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. The recommendations on management of ARIA do not differ between ApoE ε4 carriers and noncarriers.[1,4,5]

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.[1,4,5]

In patients who develop intracerebral hemorrhage greater than 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®.[1,4,5]

In Patients with MCI due to AD and Mild AD Dementia, Get Ahead and Stay Ahead for Longer, Demonstrated vs Placebo Through 18 Months in Clarity AD[4,5]

Early and Ongoing Treatment Can Slow the Progression of AD. AD is a Progressive, Relentless Disease Caused by a Continuous Underlying Neurotoxic Process[3,5,35]

- The earlier MCI due to AD and mild AD dementia are diagnosed and treated, the greater the opportunity for benefit.[2,5]

LEQEMBI® Clears More Than Just Plaque[1,3,5,33]

- Dual-acting LEQEMBI® supports neuronal functional in AD by continually clearing highly toxic protofibrils that can continue to cause neuronal injury and death well after plaques are cleared.

LEQEMBI® was Studied in the Earliest Stages of Symptomatic AD[3,5,56]

- The majority of patients were in the earliest symptomatic stage, MCI due to AD.[5]

LEQEMBI® is Proven to Slow Progression Across the Stages of Early Alzheimer's Disease[1,3,5,60]

Intervening with LEQEMBI® changes the disease course, slowing cognitive and functional decline with treatment. Results from baseline at 18 months versus placebo included:[1,3,5,32,60,61]

- 27 percent slowing of cognitive and functional decline ($p < 0.0001$) on CDR-SB [5,59]
- 37 percent slowing of functional decline ($p < 0.0001$) on ADCS MCI-ADL [1,5,32,33]
- 26 percent slowing of cognitive decline ($p < 0.001$) on ADAS-Cog14[1,5,32,33]
- 56 CL reduction in amyloid burden with 68 percent of 210 patients achieving plaque clearance [5,33,60]
- Starting at six months, across all time points, LEQEMBI® treatment showed statistically significant changes in the primary and all key secondary endpoints from baseline compared to placebo [1,5]

Safety Matters. The Incidence and Timing of ARIA Varies Among Treatments[5]

- ARIA-E occurred in 13 percent of patients and ARIA-H occurred in 17 percent of patients taking LEQEMBI®
- Symptomatic ARIA occurred in 3 percent of patients treated with LEQEMBI® [1,5]
- The most common adverse reactions reported in ≥ 5 percent of patients treated with LEQEMBI® (N = 898) and ≥ 2 percent 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%)[1,5]
- The most common adverse reaction leading to discontinuation of LEQEMBI® was ARIA-H microhemorrhages that led to discontinuation in 2 percent (15/898) of patients treated with LEQEMBI® compared to < 1% (1/897) of patients on placebo.[1,5]

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WARNINGS & PRECAUTIONS (continued)

Intracerebral Hemorrhage (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.

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

Please see Important Safety Information throughout this article and accompanying full Prescribing Information, including Boxed WARNING.

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