PERIPHERAL AND CENTRAL NERVOUS SYSTEM (PCNS) DRUGS ADVISORY COMMITTEE MEETING

EISAI, INC. BRIEFING DOCUMENT

LEQEMBI® (lecanemab-irmb)

BLA 761269 S-001

LEQEMBI is indicated for the treatment of Alzheimer's disease. Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with LEQEMBI. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.

MEETING DATE: 09 Jun 2023

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
Aβ	amyloid beta
Aβ[1-40]	amyloid beta monomer from amino acid 1 to 40
Aβ[1-42]	amyloid beta monomer from amino acid 1 to 42
Aβ42/40	ratio of Aβ[1-42] to Aβ[1-40]
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADA	anti-drug antibodies
ADAS-Cog14	Alzheimer's Disease Assessment Scale – Cognitive subscale with 14 tasks
ADCOMS	Alzheimer's Disease Composite Score
ADCS MCI-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale for Mild Cognitive Impairment
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADR	adverse drug reaction
AE	adverse event
ANCOVA	analysis of covariance
APOE	apolipoprotein E
APOE4	apolipoprotein E4
APP	amyloid precursor protein
ARIA	amyloid-related imaging abnormalities
ARIA-E	amyloid-related imaging abnormalities-edema/effusion
ARIA-H	amyloid-related imaging abnormalities-hemorrhage
AUC	area under the plasma concentration versus time curve
BLA	Biologics License Application
BTD	Breakthrough Therapy designation
CAA	cerebral amyloid angiopathy
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating – Sum of Boxes
CFR	Code of Federal Regulations
C_{max}	peak concentration
CMC	Chemical, Manufacturing, and Control
COVID-19	coronavirus disease of 2019
CRO	contract research organization
CSF	cerebrospinal fluid

Abbreviation	Term
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
eCRF	electronic case report form
EMA	European Medicines Agency
EOP2	end-of-phase 2
EQ-5D-5L	European Quality of Life-5 Dimensions 5 Level version
FAS	full analysis set
FcγR	Fc gamma receptor
FDA	Food and Drug Administration
GFAP	glial fibrillary acidic protein
HR	hazard ratio
IgG	immunoglobulin G
IND	Investigational New Drug
IV	intravenous
mAb	monoclonal antibody
mAb158	murine version of lecanemab
MAR	missing at random
MCI	mild cognitive impairment
MCID	minimally clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
Nab	neutralizing antibodies
NfL	neurofilament light chain
NIA-AA	National Institute of Aging–Alzheimer's Association
OLE	open-label extension
PD	pharmacodynamic(s)
PET	positron emission tomography
PK	pharmacokinetic(s)
PMR	postmarketing requirement
p-tau	human tau protein
p-tau181	human tau protein phosphorylated at threonine in position 181
QoL	quality of life

Abbreviation	Term
QoL-AD	Quality of Life in Alzheimer's Disease
ROI	region of interest
SAE	serious adverse event
SAP	statistical analysis plan
sBLA	supplemental Biologics License Application
SD	standard deviation
SE	standard error
SMQ	Standardized MedDRA Query
SOC	system organ class
SUVR	standard uptake value ratio
tPA	tissue plasminogen activator
t-tau	total tau
US	United States
USPI	United States prescribing information
vMRI	volumetric magnetic resonance imaging
VAS	visual analog scale

1 EXECUTIVE SUMMARY

1.1 Introduction

On 06 Jan 2023, lecanemab was approved under 21 Code of Federal Regulations (CFR) 314.500 (subpart H, accelerated approval regulations) based on the results from an 856-patient Phase 2 proof of concept Study 201. The approved indication is:

"LEQEMBI is indicated for the treatment of Alzheimer's disease. Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with LEQEMBI [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial."

Products approved under accelerated approval may require further adequate and well-controlled clinical trial(s) to verify and describe clinical benefit. In Dec 2022 there was agreement between Eisai and the Food and Drug Administration (FDA) on the following postmarketing requirement (PMR) study to verify and describe the clinical benefit of lecanemab, to be fulfilled by Phase 3 Study 301 (Clarity AD):

> 4384-1: In order to verify the clinical benefit of lecanemab-irmb, conduct a randomized, controlled trial to evaluate the efficacy of lecanemab-irmb compared to an appropriate control for the treatment of Alzheimer's disease. The trial should be of sufficient duration to observe changes on an acceptable endpoint in the patient population enrolled in the trial.

On the same day as accelerated approval (06 Jan 2023) Eisai submitted a supplementary Biologics License Application (BLA 761269 S-001) containing results from Phase 3 Study 301.

Study 301 showed highly statistically significant 27% slowing of clinical decline on the Clinical Dementia Rating – Sum of Boxes (CDR-SB) after 18 months of treatment with lecanemab (P=0.00005), as well as highly statistically significant slowing of clinical decline on the Alzheimer's Disease Assessment Scale – Cognitive subscale with 14 tasks (ADAS-Cog14) P=0.00065, Alzheimer's disease Composite Score (ADCOMS) P=0.00002 and functional scale the Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL) P<0.00001. The benefits of lecanemab are supported by consistent results across scales and domains, slowing of progression to the next stage of disease, impact on quality of life (QoL) and care partner burden, and consistency across subgroups. Lecanemab impacted biomarkers of amyloid, tau, and neurodegeneration, providing a biological basis for the treatment effects consistent with slowing of disease progression.

1.2 Alzheimer's Disease

Alzheimer's disease (AD) is a progressive, neurodegenerative disorder of unknown etiology and the most common form of dementia among older people. Lecanemab is approved under the

accelerated approval pathway for use in patients with early AD which is comprised of mild cognitive impairment (MCI) due to AD and mild AD dementia (mild AD). In the United States (US), it is estimated that there are 6-7 million people over 50 years of age with MCI due to AD and 2.5 million with mild AD (Gillis, et al., 2022, Alzheimer's Association, 2023). AD is the sixth-leading cause of death in the US and the fifth leading cause for people 65 years and older (Xu, et al., 2020).

AD is defined biologically by the presence of 2 abnormal protein deposits: amyloid plaques (extracellular deposits of brain amyloid comprising β-amyloid [Aβ] peptides) and neurofibrillary tangles (comprising abnormal tau protein). Biomarker (Jack, et al., 2013), clinicopathological (Delacourte, et al., 2002), and cohort (Amieva, et al., 2008) studies indicate that the disease process commences 10 to 20 years before the clinical onset of symptoms.

The disease is characterized clinically by a global decline of cognitive function that progresses slowly and for many patients, results in spending a significant period of their remaining life in the severe disabling disease state (Rizzuto, et al., 2012). Patients with AD typically survive for only 3 to 10 years after symptom onset (Hebert, et al., 2003).

In addition to the effect on patients, AD places a significant burden on families and care partners. Increased care demands result in increased financial, psychological, physical stress and lost productivity for the care partner (Alzheimer's Association, 2023; Suehs, et al., 2014).

1.3 Current Treatment Options and Unmet Need

Current therapeutic agents for patients with mild, moderate, and severe AD dementia consist of symptomatic therapies that include acetylcholinesterase inhibitors (AChEIs), such as donepezil, and the N-methyl-D-aspartate receptor antagonist, memantine. These therapies have been approved for use in mild, moderate, or severe AD and are directed at treating cognitive symptoms by addressing imbalances in neurotransmitter function caused by neurodegeneration in later stages of disease. Symptomatic treatments provide modest, temporary benefit to symptoms at best, which is rapidly lost after treatment discontinuation (Birks, 2006; McShane, et al., 2006). There are no therapies approved for the mild cognitive impairment (MCI) stage of AD.

None of the currently approved symptomatic treatments slow the amyloid accumulation, spread of neurofibrillary tangles and neuronal and synaptic loss that leads to relentless disease progression.

There are 2 products approved in the US under the accelerated approval pathway for the treatment of AD based on a reduction in amyloid beta (Aβ) plaques: lecanemab (LEQEMBI®) and aducanumab (Aduhelm®).

1.4 Lecanemab for Alzheimer's Disease

Lecanemab has been developed under the hypothesis that targeting soluble aggregated forms of Aβ and brain amyloid will attenuate the disease course of AD and thereby slow clinical progression.

Lecanemab is a novel humanized immunoglobulin G1 monoclonal antibody (mAb) that was developed against Aβ protofibrils, based on the observation that the 'Arctic' mutation in Swedish patients with familial AD had an increased propensity for aggregation of Aβ to form protofibrils (Nilsberth, et al., 2001; Tucker, et al., 2015). Aβ peptides exist in many different conformational states including monomeric Aβ peptide, soluble Aβ aggregates of increasing size ranging from small dimers and trimers to larger oligomers and protofibrils, and insoluble fibrils. Aβ protofibrils have been implicated in altering synaptic function and mediating neurotoxicity leading to cognitive decline and dementia observed in AD. Lecanemab was designed to selectively target these large soluble protofibrils relative to monomers (greater than 1000-fold over Aβ monomers), while it also interacts with the insoluble fibrils that are a major component of brain amyloid.

Lecanemab mediates Fc gamma receptor (FcγR)-mediated clearance of Aβ aggregates in primary microglia culture (Kaplow, et al., 2013; Swanson, et al., 2013). The murine version of lecanemab (mAb158) has been shown to remove Aβ protofibrils and reduce brain amyloid in amyloid precursor protein (APP) transgenic mice and prevents initial brain amyloid formation in ArcSwe mouse (Tucker, et al., 2015; Söllvander, et al., 2018). Binding of lecanemab to protofibrils and fibrils (the components of brain amyloid) enhances their FcγR mediated clearance by microglia, with expected subsequent neutralization of toxicity to neurons and removal from the brain resulting in slowing of disease progression.

1.5 Clinical Pharmacology

Steady state concentrations of lecanemab were reached after 6 weeks of 10 mg/kg administered every 2 weeks and systemic accumulation was 1.4-fold. The peak concentration (C_{max}) and area under the plasma concentration versus time curve (AUC) of lecanemab increased dose proportionally in the dose range of 0.3 to 15 mg/kg following single dose.

Distribution: The mean value (95% CI) for central volume of distribution at steady-state is 3.22 (3.15-3.28) L.

Elimination: Lecanemab is degraded by proteolytic enzymes in the same manner as endogenous immunoglobulin G (IgGs). The clearance of lecanemab (95% CI) is 0.434 (0.420-0.451) L/day. The terminal half-life is 5 to 7 days.

Specific Populations: Sex, body weight, and albumin were found to impact exposure to lecanemab. However, none of these covariates were found to be clinically significant.

Patients with Renal or Hepatic Impairment: No clinical studies were conducted to evaluate the pharmacokinetics of lecanemab in patients with renal or hepatic impairment. Lecanemab is degraded by proteolytic enzymes and is not expected to undergo renal elimination or metabolism by hepatic enzymes.

1.6 Confirmatory Phase 3 Study to Verify and Describe the Clinical Benefit of Lecanemab – Study 301

1.6.1 Study Design

Study 301 is a global, multicenter, double-blind, placebo-controlled, parallel-group study to demonstrate the superiority of lecanemab 10 mg/kg biweekly (lecanemab) vs placebo with an open-label extension (OLE) Phase (Figure 1). Eligible patients were randomized in a 1:1 ratio to receive either placebo or lecanemab for an 18-month double-blind treatment duration followed by a 3-month Follow-up Period or an optional 4-year OLE Phase. The study population met the National Institute of Aging – Alzheimer's Association (NIA-AA) clinical criteria for MCI due to AD or mild AD, collectively designated as early AD. The presence of brain amyloid pathology was confirmed in all patients as measured by amyloid PET or CSF total tau (t-tau)/Aβ[1-42]. Study 301 included 3 longitudinal substudies: amyloid PET, CSF biomarker assessments, and tau PET. Participation in these substudies was optional.

Study 301 was carefully designed to reflect a diverse patient population and current community practice through the inclusion of:

- A representative early AD population (MCI and mild AD) based on clinical evaluation and confirmation of elevated amyloid by amyloid PET visual read (per approved PET tracer label) or validated CSF assay
- Usual care settings: Study 301 included a wide range of study sites, from private centers to academic medical centers, including both community- and hospital-based sites of treatment. The sites were located in different types of geographic areas (urban, suburban and rural).
- Patients with a range of comorbidities and concomitant medications
- Diverse racial and ethnic elderly patient populations that generally reflect that of the US Medicare population

Study 301 randomized 1795 patients across 2 treatment groups: placebo (n=897), lecanemab (n=898). Approximately 70% of patients randomized were apolipoprotein E4 (*APOE4)* carriers. All of the randomized patients received at least 1 dose of study drug.

As of 01 Dec 2022, 1385 patients had entered Study 301 OLE Phase. Cumulatively, a total of 1612 patients have been treated with lecanemab in Study 301 (either double-blind or OLE Phase).

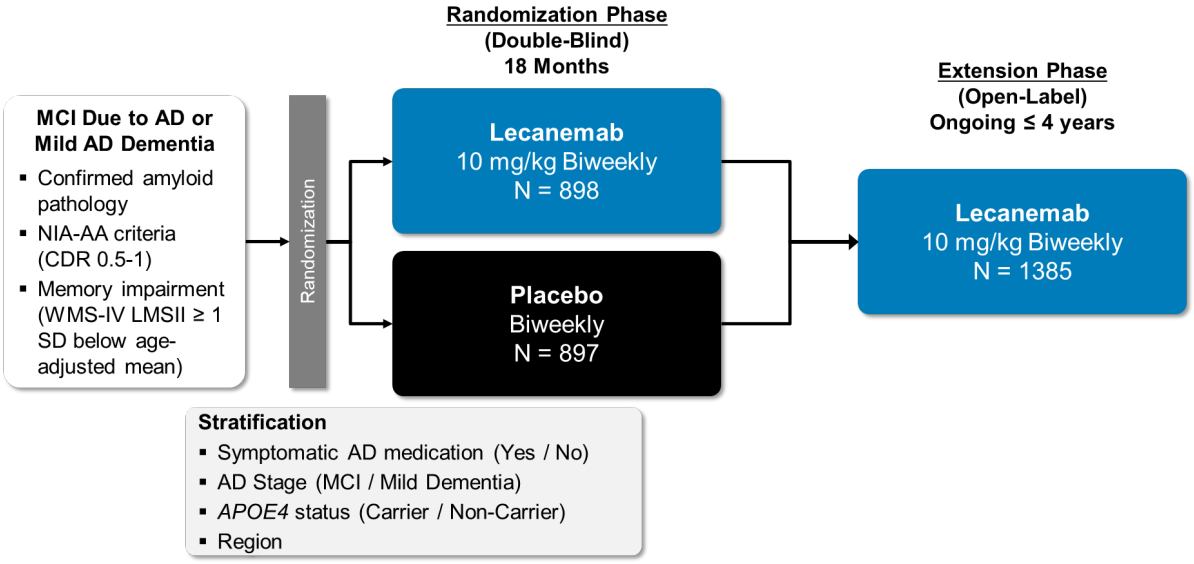

Figure 1 Study Design for Study 301

NIA-AA = National Institute on Aging and Alzheimer's Association; WMS-IV LMSII = Wechsler Memory Scale IV-Logical Memory (subscale) II.

1.6.2 Study Population

The inclusion/exclusion criteria used in Study 301 supported recruitment of an early AD patient population with a range of comorbidities and concomitant medications. Eligible patients were 50 to 90 years of age and met diagnostic criteria for early AD (MCI due to AD or mild AD). All patients were confirmed for brain amyloid pathology as measured by amyloid PET or CSF t-tau/Aβ[1-42]. Mini mental state exam (MMSE) ranged between ≥22 and ≤30 at Baseline and global Clinical Dementia Rating (CDR) score was 0.5 to 1.0. All patients met NIA-AA diagnostic criteria for MCI or mild AD, and the Wechsler memory scale was used to confirm episodic memory impairment. Patients on symptomatic AD medication were permitted in the study if they were on a stable dose for at least 12 weeks before Baseline. Patients were excluded if they had any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the patient's AD. Patients with a history of transient ischemic attack, stroke, or seizures within 12 months of Screening were also excluded.

Eisai's recruitment strategy for Study 301 ensured greater inclusion of ethnic and racial populations in the US that have historically been underrepresented in clinical studies. Approximately 25% of the US patients enrolled identified as Hispanic and/or Black or African American patients living with early AD.

Additional information on the study population is provided in Section 4.1.2.

1.6.3 Dose Selection

Lecanemab 10 mg/kg biweekly was selected as the dose for evaluation in Study 301 and this is the same dose approved under the accelerated approval pathway based on the results from the large, dose-ranging Phase 2 proof of concept Study 201.

1.6.4 Operational Measures Taken to Ensure Blinding

In Study 301 the clinician responsible for CDR assessment did not participate in the medical management of the patients and was blinded to results of safety assessments (including but not limited to results of safety magnetic resonance imaging (MRI), clinical laboratory assessments, and adverse events [AEs]), except for the results of the Columbia-Suicide Severity Rating Scale (C-SSRS). Additionally, for any given patient, every effort was made to ensure that the raters for the CDR, ADAS-Cog14, and MMSE remained unchanged throughout the study. No one rater performed all clinical assessments at a given visit. There was a central review of ratings for CDR, ADAS-Cog14, and MMSE, and for consistency these assessments were reviewed by local language speaking central clinical reviewers at all visits.

In addition to activities at the site level, operationally Eisai's conventional study team members were firewalled to AEs that could be potentially unblinding. Additional information is provided in Section 4.1.4

1.6.5 Assessments

CLINICAL AND QUALITY OF LIFE ASSESSMENTS

The CDR and ADAS-Cog14 are well-accepted and validated clinical scales for use in AD research. The ADCS MCI-ADL is a well-known instrument for the assessment of activities of daily living in AD. The ADCOMS was included in Study 301 to bridge back to the Phase 2 Study 201, which used ADCOMS as the primary endpoint.

The primary endpoint was change from baseline in the CDR-SB at 18 months. Key secondary endpoints were change from baseline at 18 months for amyloid PET using Centiloids (a standardized measurement of amyloid PET imaging [Salvado, et. al., 2019]), ADAS-Cog14, ADCOMS, and ADCS MCI-ADL. Other prespecified exploratory endpoints included the rate of change over time (18 months) for CDR-SB, time to worsening of global CDR score by 18 months and health-related quality of life (QoL) outcome measures (European Quality of Life-5 Dimensions 5 Level version [EQ-5D-5L]; Quality of Life in Alzheimer's disease [QoL-AD] and the Zarit Burden Interview). These scales have a wide range that cover the entire clinical course of an AD patient. For example, the CDR-SB overall score ranges from 0 to 18 and is intended to capture the entire clinical course of AD (which can be over 10 years) and ranges from unimpaired (0) to bedridden (18). Patients with early AD are typically in the range of 0.5 to 6 on the overall CDR-SB. The mean placebo rate of decline in 18-month clinical studies of early AD is 1.5 to 2 on change from baseline CDR-SB (Swanson, et. al., 2021; Budd Haeberlein, et. al., 2022; Teng, et. al., 2022). Therefore, for assessment of slowing disease progression, only a narrow range of the scales are applicable. Additional information is provided in Sections 4.1.5.1 (endpoints) and 4.1.5.2 (assessments).

Table 1 Clinical Assessments in Study 301

Assessment	Evaluation	No. of Domains or Items	Source	Score Range	Worsening Score	Timing of Assessments
CDR-SB	Cognition and function	6 domains	Patient and care partner	0-18 Early AD: ~0.5-6	Higher	Baseline and every 3 months
ADAS-Cog14	Cognition	14 items	Patient	0-90 Early AD: ~10-30	Higher	Baseline and every 3 months
ADCS MCI-ADL	Daily activities	24 items	Care partner	0-53 Early AD: ~35-45	Lower	Baseline and every 6 months
ADCOMS	Cognition and function	12 items	Composite[a]	0-1.97	Higher	Baseline and every 3 months

CDR-SB = Clinical Dementia Rating-Sum of Boxes, ADAS-Cog14 = Alzheimer's Disease Assessment Scale–cognitive subscale, ADCOMS = Alzheimer's Disease Composite Score, ADCS ADL-MCI = Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for mild cognitive impairment (MCI) patients.
a: ADCOMS is a composite of CDR-SB, ADAS-Cog14 and MMSE

Table 2 Quality of Life Assessments in Study 301

Assessment	Evaluation	No. of Domains or Items	Source	Score Range	Worsening Score	Timing of Assessments
EQ-5D-5L	5 Health Dimensions (Mobility, Self-care, Usual Activities, Pain/Discomfort, Anxiety/Depression)	5 dimensions, each with 5 levels of severity	Patient	0-100	Lower	Baseline; every 6 months
QoL-AD	Quality of life of patient with AD	13-item questionnaire, each with 4 levels of severity	Patient	13-52	Lower	Baseline; every 6 months
Zarit Burden Interview	Stresses experienced by care partners of patients with dementia	22-item instrument, each with 5 levels of severity	Care Partner	0-88	Higher	Baseline; every 6 months

EQ-5D-5L = European Quality of Life-5 Dimensions 5 Level version, QoL-AD = Quality of Life in Alzheimer's disease

BIOMARKER ASSESSMENTS

Study 301 assessed CSF, plasma, and imaging biomarker endpoints of amyloid, tau, and neurodegeneration/gliosis. Additional information is provided in Section 4.1.5.3.

Table 3 Biomarker Assessments in Study 301

	Assessment	Biomarker Change in AD	Timing of Assessments	Assay
Amyloid	Amyloid PET	Increased	Baseline, 3, 6, 12 and 18 months	N/A
	CSF Aβ[1-42]	Decreased	Baseline, 12 and 18 months	Fujirebio Lumipulse
	Plasma Aβ42/40 ratio	Decreased	Baseline; every 6 months	C2N Precivity AD-Aβ
Tau	CSF p-tau181	Increased	Baseline, 12 and 18 months	Fujirebio Lumipulse
	Plasma p-tau181	Increased	Baseline; every 6 months	Quanterix Simoa
	Tau PET	Increased	Baseline, 13 and 18 months	MK-6240
Neuro-degeneration / Gliosis	CSF t-tau	Increased	Baseline, 12 and 18 months	Fujirebio Lumipulse
	CSF neurogranin	Increased	Baseline, 12 and 18 months	Euroimmune ELISA
	CSF NfL	Inconsistent	Baseline, 12 and 18 months	Quanterix Simoa
	Plasma NfL	Inconsistent	Baseline; every 6 months	Quanterix Simoa
	Plasma GFAP	Increased	Baseline; every 6 months	Quanterix Simoa

Aβ42/40 = ratio of Aβ[1-42] to Aβ[1-40], Aβ[1-40] = amyloid beta monomer from amino acid 1 to 40, Aβ[1-42] = amyloid beta monomer from amino acid 1 to 42, CSF = cerebrospinal fluid, NfL = neurofilament light chain.

SELECTED ADVERSE EVENTS OF INTEREST TO THE PROPOSED INDICATION

There are 3 adverse events of interest for lecanemab:

- Infusion-related reactions: Predefined in the Statistical Analysis Plan (SAP) as preferred terms “infusion related reaction” and “infusion site reaction”.
- ARIA-E: Interstitial vasogenic edema or sulcal effusion that manifests as parenchymal or sulcal hyperintensities on MRI.
- ARIA-H: Microhemorrhages or uncommon intracerebral hemorrhage >1cm observed as hypointense hemosiderin deposition in parenchyma or leptomeningeal/subpial space (superficial siderosis) on MRI. In this Briefing Document “ARIA-H” represents the combined preferred terms of cerebral hemorrhage, hemorrhage intracranial, thalamus

hemorrhage, superficial siderosis of central nervous system, amyloid related imaging abnormality-microhemorrhage and hemosiderin deposit, cerebellar microhemorrhage.

Amyloid deposition in blood vessels, called cerebral amyloid angiopathy (CAA), is ubiquitous in AD. It can cause common asymptomatic microhemorrhage and superficial siderosis, and rare lobar macrohemorrhage or inflammatory CAA spontaneously in AD. *APOE4* is a risk factor for CAA and intracerebral hemorrhage due to CAA. Mobilization of amyloid from blood vessels in CAA is the likely mechanism of ARIA observed with anti-amyloid antibodies.

1.6.6 Statistical Methods

There were extensive discussions with the FDA on the SAP for Study 301, with SAP version 2.0 finalized 06 Sep 2022 prior to database lock.

ANALYSIS SETS

The following pre-prespecified analysis sets are used to describe Study 301 (double-blind, hereafter "Study 301") data in this Briefing Document:

- The Randomized Set was the group of patients who were randomized to study drug.
- The Safety Analysis Set was the group of all allocated patients who received at least one dose of study drug.
- The mITT full analysis set+ (mITT FAS+): Randomized patients who received ≥ 1 dose of study drug, and Baseline assessment and ≥ 1 post dose primary efficacy measurement.
- The FDA Full Analysis Set (FDA FAS): As above, but excluded 68 patients at sites closed during peak COVID period in 2020 for 6 or more weeks (equivalent to missing ≥3 consecutive doses during that site's closure period).

Study 301 met the primary endpoint and all key secondary endpoints with a high degree of statistical significance, with consistent results seen across the mITT FAS+ and FDA FAS. For this reason, this Briefing Document presents the mITT FAS+ as it includes all data collected on the efficacy endpoints.

SUBGROUP ANALYSES

For Study 301, prespecified subgroup analyses were performed. Efficacy results are presented for the following randomization strata: use of symptomatic AD medication at baseline (yes/no), clinical subgroup (MCI due to AD, mild AD dementia), *APOE4* carrier status (carriers, noncarriers), and geographical region (North America, Europe, Asia).

SENSITIVITY AND SUPPLEMENTARY ANALYSES

Numerous sensitivity and supplementary analyses were conducted to assess the robustness of the primary analysis, all were prespecified except primary mixed model for repeated measures (MMRM) censoring assessments after occurrence of amyloid-related imaging abnormalities (ARIA) or infusion-related reactions, which were performed at the request of the FDA, and

primary MMRM based on the Randomized Set, which was performed at the request of the European Medicines Agency (EMA). Additional information on statistical methods is provided in Section 4.1.8.

1.6.7 Results

1.6.7.1 Disposition, Demographics and Baseline Characteristics

DISPOSITION

In Study 301, a total of 1795 patients were randomized into the study to receive either placebo (897 patients) or lecanemab (898 patients). Of these, 1486 patients (placebo 757; lecanemab 729) completed the double-blind treatment period Study 301 (Table 4). Among the patients who discontinued the study (placebo 140 [15.6%]; lecanemab 169 [18.8%]), reasons for discontinuation were similar, with the most common reasons being withdrawal of consent and AE. The AEs driving the higher discontinuation with lecanemab treatment were infusion-related reactions and ARIA. After excluding these events, the discontinuation rate and timing of discontinuation of lecanemab are similar with placebo. Patients who discontinued study treatment were encouraged to continue in the study and complete scheduled assessments.

Table 4 Patient Disposition and Primary and Other Reasons for Discontinuation From Study – Study 301 Double-Blind (Randomized Set)

	Placebo	Lecanemab	Total
Randomized, n	897	898	1795
Not treated, n	0	0	0
Treated, n (%)	897 (100)	898 (100)	1795 (100)
Completed Double-blind, n (%)	757 (84.4)	729 (81.2)	1486 (82.8)
Discontinued from Double-blind, n (%)	140 (15.6)	169 (18.8)	309 (17.2)
Primary reason for discontinuation, n (%)			
Adverse event	28 (3.1)	51 (5.7)	79 (4.4)
Patient choice	24 (2.7)	26 (2.9)	50 (2.8)
Pregnancy	0	0	0
Inadequate therapeutic effect	0	0	0
Lost to follow-up	5 (0.6)	4 (0.4)	9 (0.5)
Withdrawal of consent	67 (7.5)	69 (7.7)	136 (7.6)
Other	16 (1.8)	19 (2.1)	35 (1.9)

Percentages are based on the number of patients treated in the relevant treatment group. Patients who completed Visit 42 (18-month visit) are considered as the patients who completed the double-blind treatment period. If patients have missing primary reason for discontinuation, they are counted under 'Other'.

DEMOGRAPHICS

In Study 301, demographic and other Baseline characteristics were similar between placebo and lecanemab and reflect the target patient population of early AD.

Overall, the median age was 72 (range: 50 to 90) years. There was a similar proportion of male (857 [47.7%]) and female (938 [52.3%]) patients. Over 75% of patients were White, with 16.9% Asian (with the breakdown of 8.5% Japanese, 7.2% South Korean, 0.7% Chinese and 0.4% Other), and 2.6% Black or African American, and for ethnicity, 12.9% were Hispanic. The study included patients from North America (1072 [59.7%]), Europe (including Australia) (429 [23.9%]), and Asia (excluding China) (294 [16.4%]).

Of the 947 patients in the United States, 895 (94.5%) were White, 7 (0.7%) were Asian, 43 (4.5%) were Black or African American, and for ethnicity, 213 (22.5%) were Hispanic.

The median age (range) was the same for placebo and lecanemab (72.0 [50 to 90] years). Sex was balanced between placebo (421 [46.9%] males) and lecanemab (436 [48.6%] males). Overall, race was balanced between placebo and lecanemab.

DISEASE-RELATED BASELINE CHARACTERISTICS

The characteristics of primary disease diagnosis were similar between placebo and lecanemab. For the clinical diagnosis of early AD, 61.7% patients had a diagnosis of MCI due to AD, and 38.3% patients had mild AD, consistent with the study design. Symptomatic AD medication at baseline was taken by 52.5% of patients overall. The majority of patients in Study 301 were *APOE4* carriers (1231 [68.6%] overall; 957 [53.3%] heterozygous *APOE4* carriers, 274 [15.3%] homozygous *APOE4* carriers) with the remainder *APOE4* noncarriers (564 [31.4%]). The *APOE4* carrier status (*APOE4* carrier or *APOE4* noncarrier) was similar for placebo and lecanemab, per the randomization strata.

BASELINE CLINICAL OUTCOME SCORES

Baseline values for clinical outcome scores (CDR-SB, ADAS-Cog14, ADCOMS, ADCS MCI-ADL, and MMSE) were similar between placebo and lecanemab. The mean Baseline value and standard deviation (SD) for CDR-SB was similar between placebo (3.22 [1.336]) and lecanemab (3.18 [1.344]). Eligibility criteria for Study 301 included patients with a global CDR score of 0.5 (MCI) and 0.5 to 1.0 (mild AD). The proportion of patients with a global CDR score of 0.5 was consistent between placebo (80.8%) and lecanemab (80.5%).

COMORBIDITIES AND CONCOMITANT MEDICATIONS

Eligibility criteria allowed inclusion of patients with a range of comorbidities and concomitant medications, with over 50% of patients reporting hypertension or hyperlipidemia, 15% ischemic heart disease or diabetes. Fifty-percent of patients reported multiple comorbidities.

Since antithrombotic agents (antiplatelet and anticoagulant medications) are common concomitant mediations in this population, it is important to understand benefit-risk for patients on these agents. Patients on stable doses of these medications were eligible to participate. At Baseline, 5% were on anticoagulants and 27% (33% in US patients) were on antiplatelet agents.

1.6.7.2 Efficacy Results

CDR-SB

In Study 301, there was a highly statistically significant difference between placebo and lecanemab on change from Baseline of CDR-SB at 18 months, demonstrating slowing of disease progression, with an adjusted mean treatment difference of -0.451, 27.1% less decline with lecanemab compared to placebo, P=0.00005 (Figure 2). Starting as early as 6 months (P<0.01) and across all subsequent time points, lecanemab showed highly statistically significant changes in CDR-SB from Baseline compared to placebo (all P<0.01). The absolute treatment difference increases over time (Month 12: -0.366; Month 18 -0.451).

Sensitivity and supplementary analyses were also conducted with all results consistent (P<0.001) with the mITT FAS+ analysis (Table 17).

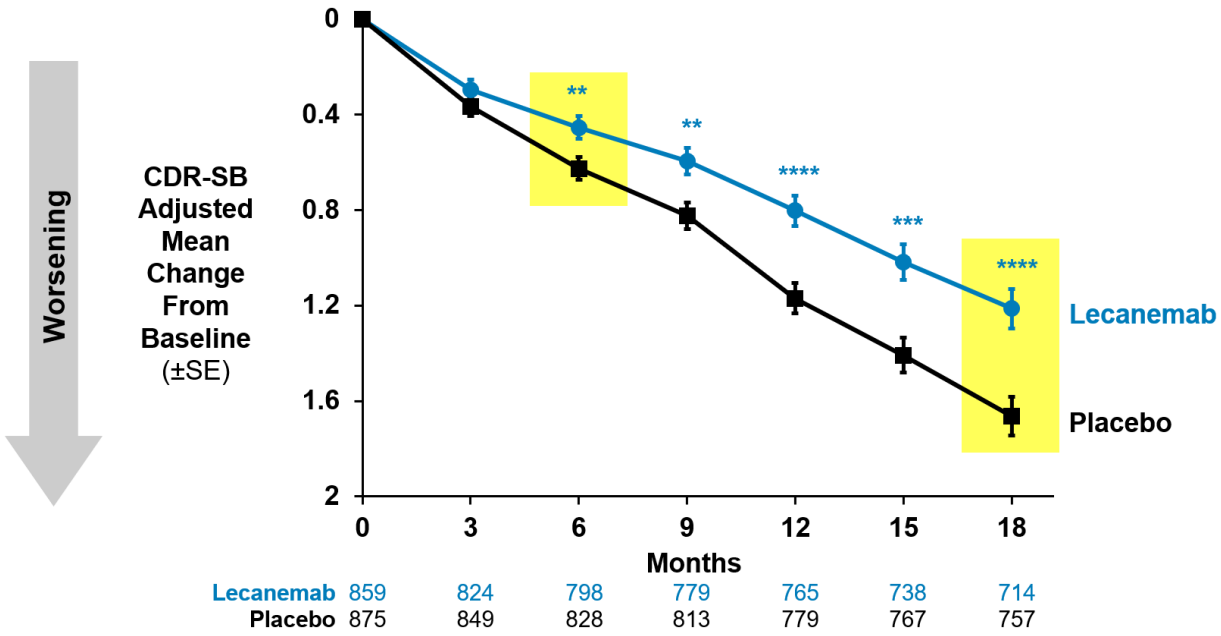

Figure 2 Plot of Adjusted Mean Change from Baseline in CDR-SB – Study 301 Double-Blind (mITT FAS+)

Adjusted means are provided by the MMRM with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of AD symptomatic medication at Baseline, *APOE4* carrier status, region, Baseline value by visit interaction as fixed effects, and Baseline value as covariate.
The observations described at all post-treatment visits are included in MMRM to provide the adjusted mean at each post-treatment visit.
AD = Alzheimer's disease, *APOE4* = apolipoprotein E4, CDR-SB = Clinical Dementia Rating – Sum of Boxes, MMRM = mixed model for repeated measures, SE = standard error.
Statistical scale: * P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001.

AMYLOID PET

For Study 301, Centiloid values are presented by combining data across all tracers. The extent of amyloid reduction is dependent on Baseline amyloid levels.

In the PET substudy (for MMRM analysis: placebo 344 patients, lecanemab 354 patients), treatment with lecanemab reduced amyloid plaque burden at all timepoints, starting at 3 months (P<0.001) (Figure 3). At 18 months of treatment, lecanemab demonstrated a statistically significant reduction in amyloid PET using Centiloids versus placebo. Adjusted mean change in Centiloids at 18 months was -55.5 and 3.6 for lecanemab and placebo, respectively (adjusted mean treatment difference: -59.1; P<0.00001).

The mean level at Baseline for lecanemab was 77.9 Centiloids, and at the end of the study was 23.0 Centiloids, which is below the threshold for amyloid positivity of approximately 30 Centiloids.

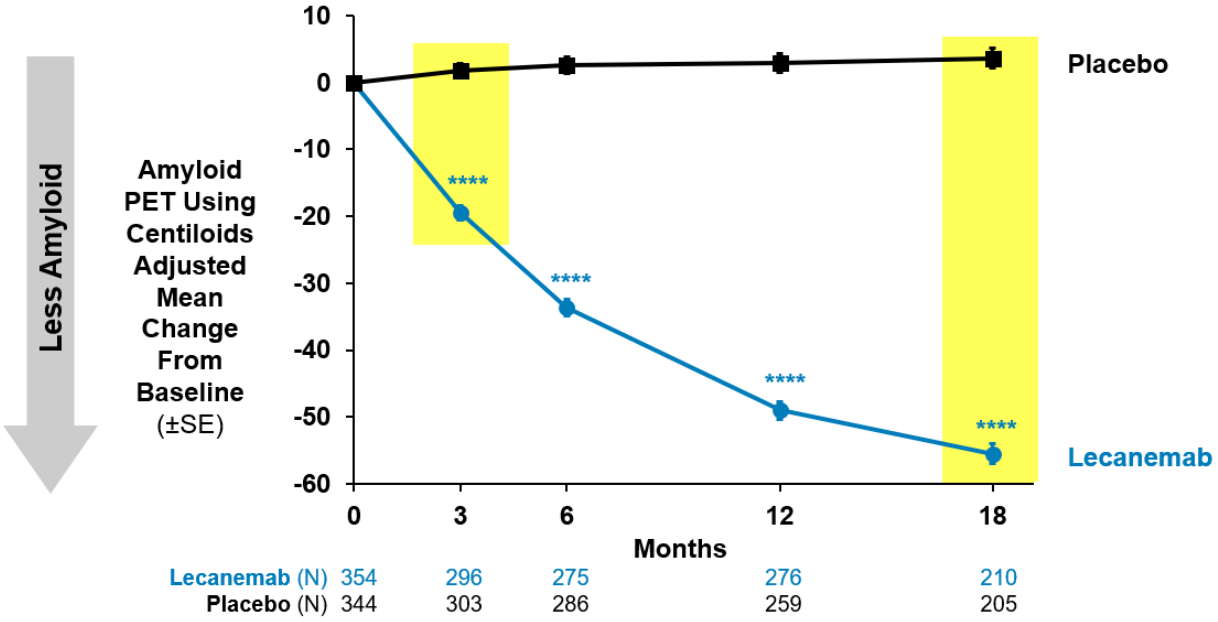

Figure 3 Plot of Adjusted Mean (±SE) of Change from Baseline in Amyloid PET Using Centiloids for Brain Amyloid Levels – Study 301 Double-Blind (PD Analysis Set [Amyloid PET])

Note: At 18 month timepoint 73 patients not included (per SAP) since their PET assessments performed after receiving lecanemab in the OLE Phase.
The observations described at all post-treatment visits are included in MMRM to provide the adjusted mean at each post-treatment visit.
AD = Alzheimer's disease, *APOE4* = apolipoprotein E4, MMRM = mixed model for repeated measures, PD = pharmacodynamic, PET = positron emission tomography, SE = standard error.
Statistical scale: * P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001.

ADAS-Cog14

In Study 301, there was a highly statistically significant difference between placebo and lecanemab on change from Baseline of ADAS-Cog14 at 18 months, demonstrating slowing of disease progression, with an adjusted mean treatment difference of -1.442, and 25.8% less decline with lecanemab compared to placebo, P=0.00065 (Figure 4). Starting as early as 6 months (P<0.05) and across all subsequent time points, lecanemab showed highly statistically significant changes from Baseline in ADAS-Cog14 compared to placebo (all P<0.001). The absolute treatment difference tends to increase over time (Month 12: -1.351; Month 18: -1.442).

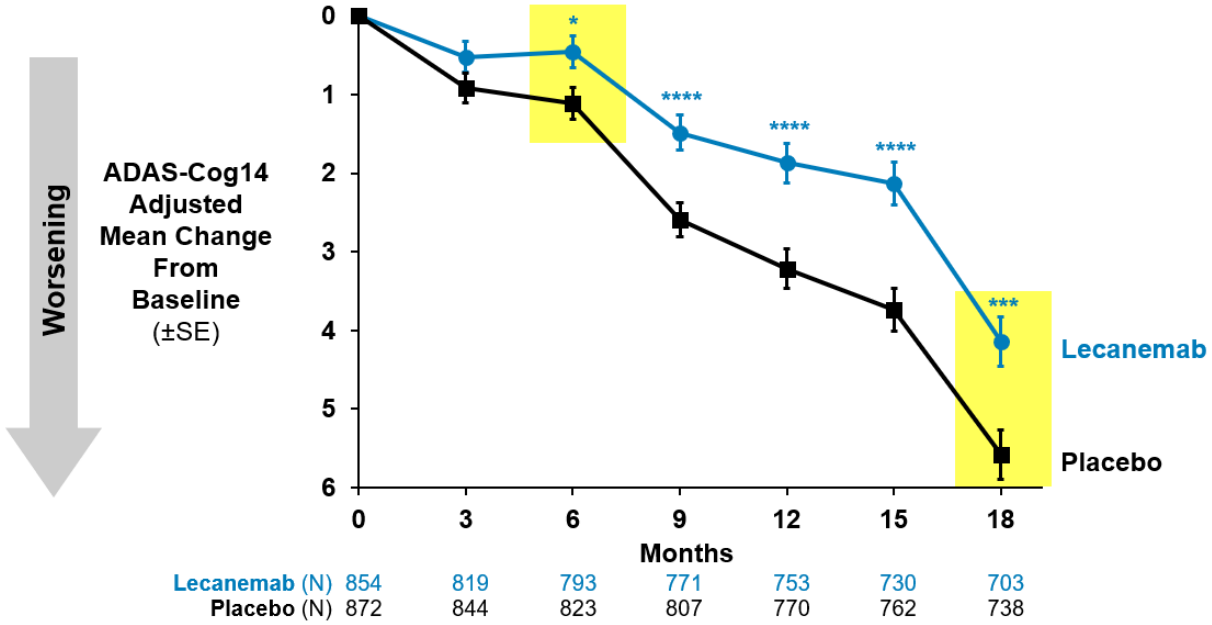

Figure 4 Change from Baseline in ADAS-Cog14 – Study 301 Double-Blind (mITT FAS+)

The observations described at all post-treatment visits are included in MMRM to provide the adjusted mean at each post-treatment visit.
AD = Alzheimer's disease, ADAS-Cog14 = Alzheimer's Disease Assessment Scale - Cognitive Subscale 14-item version, *APOE4* = apolipoprotein E4, MMRM = mixed model for repeated measures, SE = standard error.
Statistical scale: * P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001.

ADCOMS

In Study 301, there was a highly statistically significant difference between placebo and lecanemab on change from Baseline of ADCOMS at 18 months, demonstrating slowing of disease progression, with an adjusted mean treatment difference of -0.050, 23.5% less decline with lecanemab compared to placebo, P=0.00002 (Figure 5). Starting as early as 6 months (P<0.05) and across all subsequent time points, lecanemab showed highly statistically significant changes from Baseline in ADCOMS compared to placebo (all P<0.001). The absolute treatment difference increases over time (Month 12: -0.047; Month 18: -0.050).

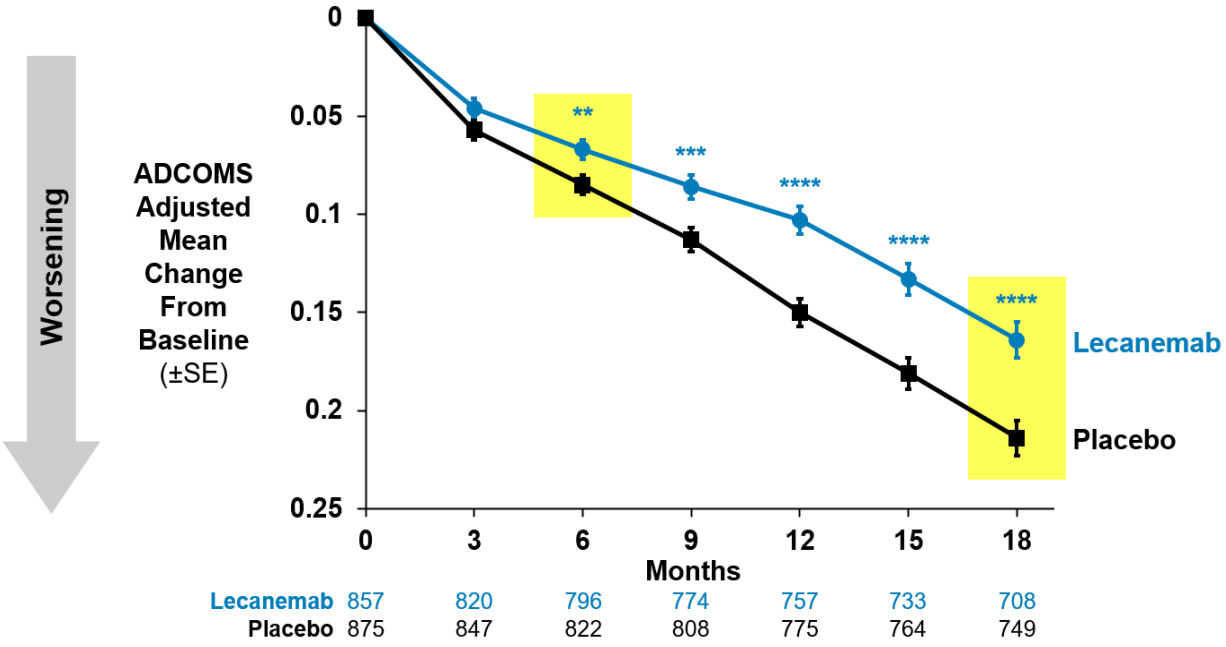

Figure 5 Change from Baseline in ADCOMS – Study 301 Double-Blind (mITT FAS+)

The observations described at all post-treatment visits are included in MMRM to provide the adjusted mean at each post-treatment visit.
AD = Alzheimer's disease, ADCOMS = Alzheimer's Disease Composite Score, *APOE4* = apolipoprotein E4, MMRM = mixed model for repeated measures, SE = standard error.
Statistical scale: * P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001.

ADCS MCI-ADL

In Study 301, there was a highly statistically significant difference between placebo and lecanemab on change from Baseline of ADCS MCI-ADL at 18 months, demonstrating slowing of disease progression, with an adjusted mean treatment difference of 2.016, 36.6% less decline with lecanemab compared to placebo, $P<0.00001$ (Figure 6). Starting as early as the first assessment at 6 months ($P<0.01$) and across all subsequent time points, lecanemab showed highly statistically significant changes in ADCS MCI-ADL from Baseline compared to placebo (all $P<0.0001$). The absolute treatment difference increases over time (Month 12: 1.550; Month 18: 2.016).

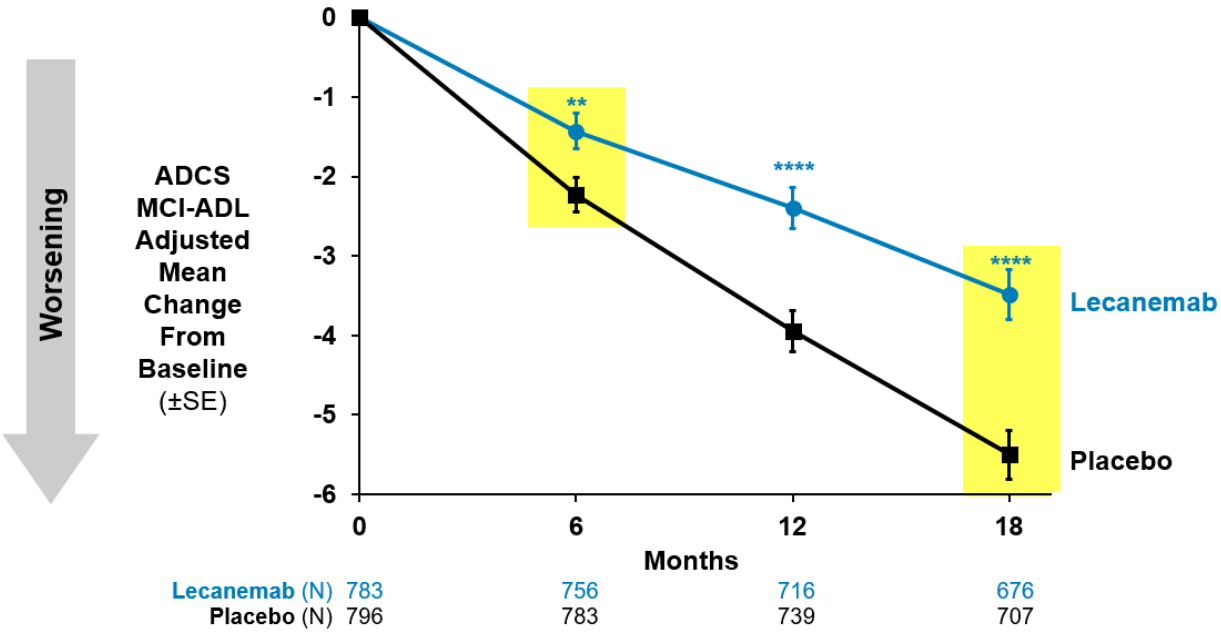

Figure 6 Change from Baseline in ADCS MCI-ADL – Study 301 Double-Blind (mITT FAS+)

The observations described at all post-treatment visits are included in MMRM to provide the adjusted mean at each post-treatment visit. This assessment is administered to the care partner to evaluate the patient status.
AD = Alzheimer's disease, ADCS MCI-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale for Mild Cognitive Impairment, *APOE4* = apolipoprotein E4, MMRM = mixed model for repeated measures, SE = standard error.
Statistical scale: * $P<0.05$, ** $P<0.01$, *** $P<0.001$, **** $P<0.0001$.

RATE OF CHANGE OVER TIME FOR CDR-SB

There is increasing separation over time for CDR-SB between placebo and lecanemab, with a 29.3% slowing of slope on lecanemab annually ([95% CI: 16.1% to 42.4%], *P*=0.00001) versus placebo (Figure 7). This suggests the preservation of CDR-SB by approximately 5.3 months relative to placebo at 18 months. Furthermore, it is projected that lecanemab would not reach the 18-month placebo level of worsening until 7.5 months later, indicating increasing treatment effect over time. Lecanemab would take 25.5 months to reach the same level of placebo at 18 months, per the projection of the slope analysis (same annual slope assumption).

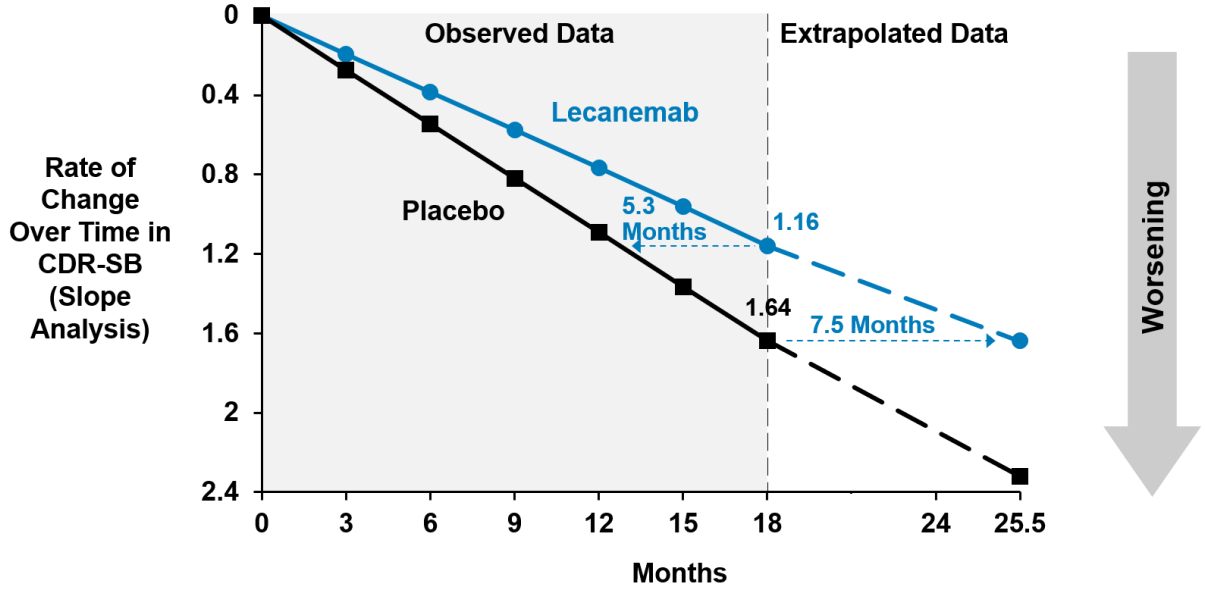

Figure 7 Analysis of Rate of Change over Time of CDR-SB – Study 301 Double-Blind (mITT FAS+)

CDR-SB = Clinical Dementia Rating – Sum of Boxes.

TIME TO WORSENING OF GLOBAL CDR SCORE

The global CDR score provides a staging system for AD, from 0.5 (consistent with MCI), to 1 (mild AD), 2 (moderate AD), and 3 (severe AD). Lecanemab reduced the risk of progression to the next stage of AD on the global CDR score by 31%. The hazard ratio of disease progression on the global CDR score is 0.69 (95% CI [0.572, 0.833], *P*=0.00011). Time to worsening of a global CDR score was defined as time from randomization to worsening of the global CDR score (ie, the first worsening where there is an increase from Baseline by at least 0.5 points on the global CDR score in 2 consecutive visits) (Figure 8).

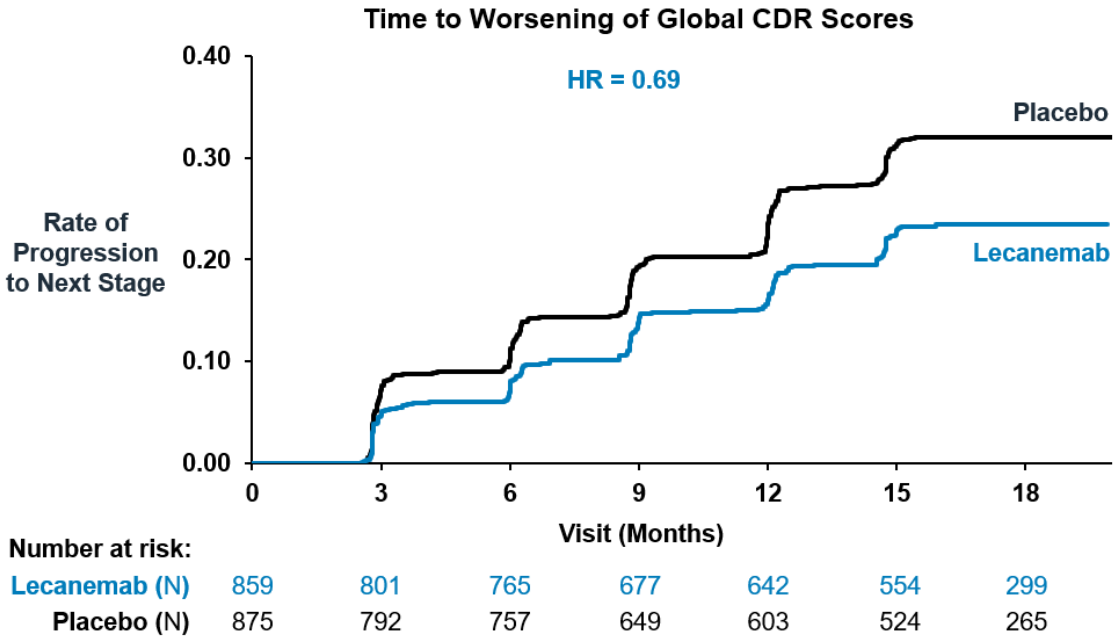

Figure 8 Kaplan–Meier Curves for Time to Worsening of Global CDR Scores – Study 301 Double-Blind (mITT FAS+)

Time to worsening of global CDR scores is defined as time in days from randomization to a confirmed worsening of the CDR scores (ie, the first worsening where there is an increase from Baseline by at least 0.5 points on the global CDR score, in 2 consecutive visits). Time to worsening of global CDR scores will be censored at the date of last CDR assessment if no event. Time in months is calculated by time in days divided by 30.417.
CDR = Clinical Dementia Rating.

HEALTH-RELATED QUALITY OF LIFE

In Study 301, for all key health-related QoL outcomes there was a highly statistically significant difference between placebo and lecanemab (Figure 9). In the early stage of AD, patients are the best informant for assessing their own QoL (rather than by care partner proxy) (Hauber, et al., 2023). Therefore, the summaries of EQ-5D-5L and QoL-AD are focused on the patient's own assessment. The Zarit Burden Interview of Study Partner Score is presented to capture the care partner QoL.

There was a highly statistically significant difference between placebo and lecanemab on change from Baseline for EQ-5D-5L Health Today Patient at 18 months, with an adjusted mean treatment difference of 2.017, 49.1% less decline with lecanemab compared to placebo, *P*=0.00383. There was a highly statistically significant difference between placebo and lecanemab on change from Baseline for QoL-AD Total Score (adjusted mean treatment difference of 0.657, 55.6% less decline, *P*=0.00231). There was a highly statistically significant difference between placebo and lecanemab on change from Baseline for Zarit Burden Interview of Study Partner Score (adjusted mean treatment difference of -2.211, 38.4% less decline, *P*=0.00002.

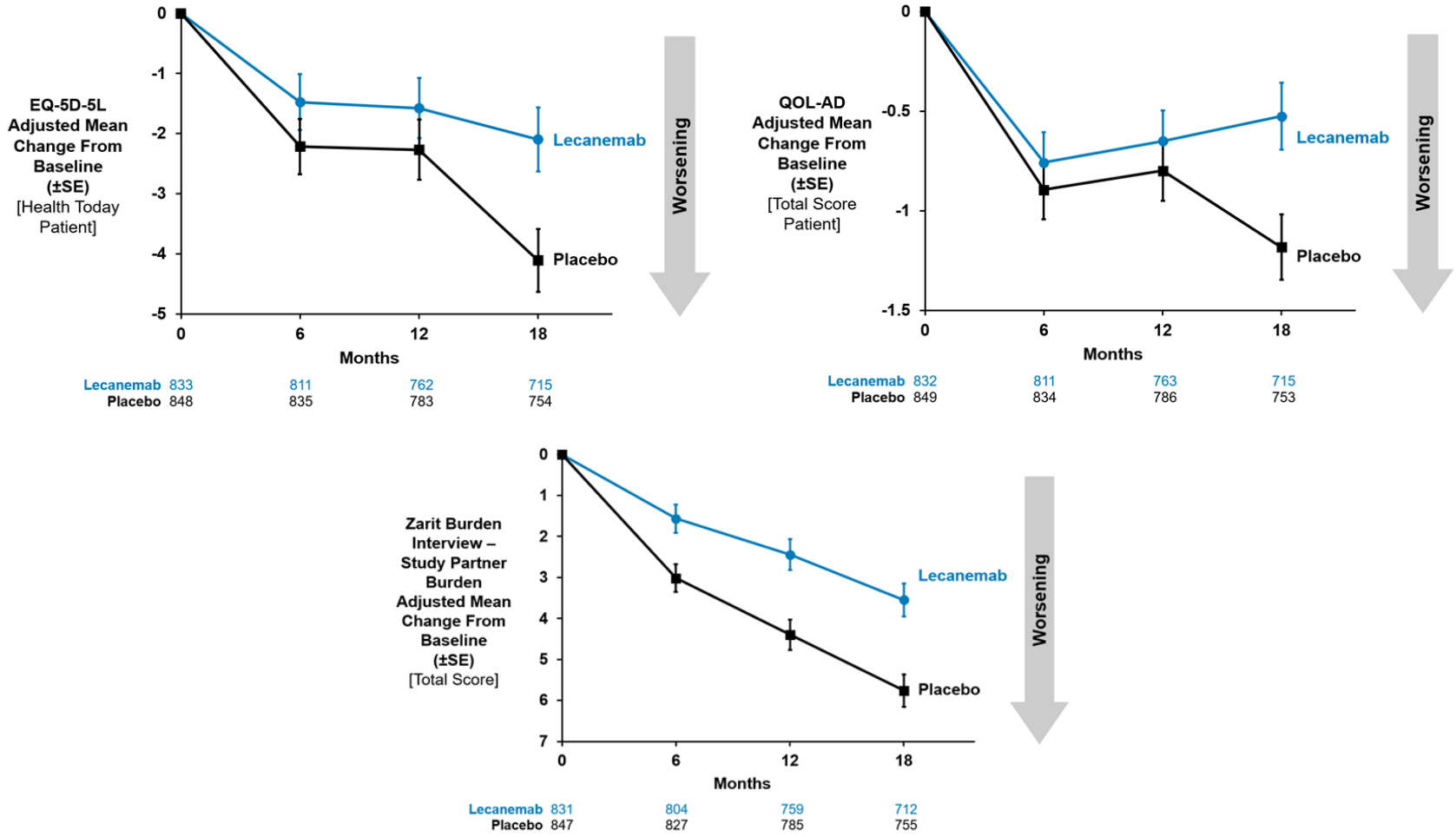

Figure 9 Health-Related Quality of Life Measures: EQ-5D-5L Health Today Patient, QoL-AD Total Score Patient and Zarit Burden Interview –Study 301 Double-Blind (mITT FAS+)

The observations described at all post-treatment visits are included in MMRM to provide the adjusted mean at each post-treatment visit. *APOE4* = apolipoprotein E4, MMRM = mixed model for repeated measures, SE = standard error.
EQ-5D-5L = European Quality of Life–5 Dimensions 5 Level version; QoL-AD = Quality of Life in Alzheimer's Disease.

COMPARISON OF RESULTS IN SUBGROUPS

In Study 301, randomization was stratified by use of symptomatic AD medication at baseline (yes/no), clinical subgroup (MCI due to AD, mild AD dementia), *APOE4* carrier status (carriers, noncarriers), and geographical region (North America, Europe, Asia).

The results of subgroup analyses for 4 clinical endpoints (CDR-SB, ADAS-Cog14, ADCOMS, ADCS MCI-ADL) at 18 months showed results favoring lecanemab and were similar to the results for the overall population. Additional information on subgroups is provided in Section 4.3.1.10.

1.6.7.3 Biomarkers

Alzheimer's disease is characterized by early accumulation of amyloid, then development of neurofibrillary tangles, neurodegeneration, and gliosis/inflammatory changes. The favorable effects of lecanemab treatment on most biomarkers of amyloid, tau, neurodegeneration, and gliosis provide a biological basis for lecanemab's treatment effect and are consistent with slowing of disease progression. Additional information on biomarker results is provided in Section 4.3.2.

1.6.7.4 Safety Results

EXPOSURE

In Study 301, 897 patients were randomized to placebo and 898 to lecanemab. All randomized patients were treated. A total of 816 patients were exposed to lecanemab for at least 6 months, 765 patients were exposed to lecanemab for at least 12 months, and 698 patients were exposed to lecanemab for at least 18 months.

Overall, in Study 301, the mean duration of exposure was 16.49 months for placebo and 15.74 months for lecanemab.

ADVERSE EVENTS

In Study 301, the overall incidence of AEs was lower in placebo (82.2%) than lecanemab (89.1%) (Table 5). Excluding infusion-related reactions, amyloid-related imaging abnormalities-edema/effusion (ARIA-E), and amyloid-related imaging abnormalities-hemorrhage (ARIA-H), the incidence was similar between placebo (80.4%) and lecanemab (83.4%).

The incidence of AEs leading to study drug discontinuation was lower in placebo 28 (3.1%) than lecanemab 65 (6.9%). Excluding the infusion-related reactions, ARIA-E, and ARIA-H, the incidence of AEs leading to study drug discontinuation was similar between placebo (2.9%) and lecanemab (3.3%).

Table 5 Summary of Adverse Events - Study 301 (Safety Analysis Set)

Category	Placebo (N=897) n (%)	Lecanemab (N=898) n (%)
AEs	737 (82.2)	800 (89.1)
Deaths	7 (0.8)	6 (0.7)
Serious AEs	101 (11.3)	126 (14.0)
AEs leading to study drug withdrawal	28 (3.1)	65 (7.2)
AEs leading to study drug dose interruption	72 (8.0)	175 (19.5)
AEs leading to infusion interruption	11 (1.2)	22 (2.4)
AEs of special interest	156 (17.4)	379 (42.2)

For each row category, a patient with two or more adverse events in that category is counted only once.
AE = adverse event.

The incidence of the most common (≥5%) AEs based on individual preferred term include:

- Infusion related reaction: placebo 7.1% and lecanemab 26.3%
- Amyloid-related imaging abnormality-microhemorrhage and hemosiderin deposit (a preferred term for cerebral microhemorrhage): placebo 7.7% and lecanemab 14.0%
- ARIA-E: placebo 1.7% and lecanemab 12.6%. The incidence of symptomatic ARIA-E was low, with no patients in placebo and 25/898 (2.8%) in lecanemab overall.
- Headache: placebo 8.1% and lecanemab 11.2%

DEATHS

In Study 301, there were 7 deaths in placebo (7 [0.8%]) and 6 in lecanemab (6 [0.7%]). There were 2 additional deaths that, although the patients were still in the study, the deaths occurred more than 30 days after last study treatment administration (placebo 1, lecanemab 1). None of the deaths were considered related to study drug. The rate of death per patient year was 0.0065 placebo and 0.0059 lecanemab. The rate of death per patient year with concurrent ARIA irrespective of the ARIA being the cause of death was 0.0008 placebo and none for lecanemab.

In Study 301 OLE Phase (lecanemab Treated Period), there were 9 deaths as of 01 Dec 2022. Additional information is provided in Section 4.4.3. The rate of death per patient year on lecanemab (double-blind + OLE Phase) was 0.0069. The rate of death per patient year with concurrent ARIA, irrespective of the cause of death, on lecanemab (double-blind + OLE Phase) was 0.0013.

Of the 24 deaths in Study 301 (double blind + OLE Phase), 3 were due to intracerebral hemorrhage: 1 in Study 301 double-blind (placebo), and 2 in Study 301 OLE Phase (lecanemab, 1 on tissue plasminogen activator [tPA] and 1 on anticoagulant therapy).

SERIOUS ADVERSE EVENTS

In Study 301, the incidence of serious AEs was lower in placebo (11.3%) than lecanemab (14.0%). Excluding events of infusion related reactions, ARIA-E, and ARIA-H, the incidence of

serious AEs was similar between placebo (11.3%) and lecanemab (12.4%). The majority of serious AEs occurred in 2 or fewer patients. The incidence of laboratory abnormalities considered serious AEs were similar between placebo (7 [0.8%]) and lecanemab (8 [0.9%]). Additional information is provided in Section 4.4.4.

DISCONTINUATIONS DUE TO ADVERSE EVENTS AND/OR LABORATORY ABNORMALITIES

In Study 301, the incidence of AEs leading to discontinuation of study drug was lower in placebo (3.1%) than lecanemab (7.2%). Excluding discontinuations due to events of infusion-related reactions, ARIA-E, and ARIA-H, the incidence of AEs leading to discontinuation of study drug was similar between placebo (26 [2.9%]) and lecanemab (30 [3.3%]). There were 3 discontinuations due to laboratory abnormalities. Additional information is provided in Section 4.4.5.

SELECTED ADVERSE EVENTS OF INTEREST TO THE PROPOSED INDICATION

Infusion-Related Reaction

Investigators were instructed that infusion-related reactions were AEs of special interest and to collect these data with heightened vigilance on a dedicated electronic case report form (eCRF) page to collect symptoms of the reaction. This increased vigilance is illustrated by the 7.4% rate reported for placebo.

The incidence of infusion-related reactions (predefined in the SAP as preferred terms “infusion related reaction” and “infusion site reaction”) was lower in placebo (66/897 [7.4%]) than lecanemab (237/898 [26.4%]). In the overall population, most AEs of infusion-related reactions were mild or moderate in severity with most being Grade 1 (placebo 41/897 [4.6%]; lecanemab 78/898 [8.7%]) or Grade 2 (placebo 25/897 [2.8%]; lecanemab 149/898 [16.6%]). No patient in placebo reported Grade 3 or Grade 4 infusion-related reactions. In the overall lecanemab population, 6/898 (0.7%) patients and 1/898 (0.1%) patients reported Grade 3 or Grade 4 infusion-related reactions, respectively. Of these Grade 3 or Grade 4 infusion-related reactions, 6 occurred with the first dose.

The majority of infusion-related reactions in lecanemab occurred with the first infusion, (placebo 26/66 [39.4%]; lecanemab 178/237 [75.1%]). Most patients who reported infusion-related reactions returned for the next study visit/next infusion (placebo 64/66 [97.0%]; lecanemab 222/237 [93.7%]). Some patients received premedication either before infusion or during infusion reactions (eg, ibuprofen, paracetamol, and diphenhydramine). These medications did not impact the rate of recurrence or severity of subsequent infusion reactions.

Of the 898 patients treated with lecanemab, 7 (0.8%) patients experienced severe infusion-related reactions and almost all resolved between Days 1 and 4 post reaction, and all were discharged without further incident. All were discontinued from study drug per protocol. No placebo patients experienced severe infusion-related reactions. Addition information is provided in Section 4.4.6.1.

ARIA-E

In Study 301, the overall incidence of ARIA-E was lower in placebo (15 [1.7%]) than lecanemab (113/898 [12.6%]).

In placebo and lecanemab, the incidence of ARIA-E was higher in *APOE4* carriers (placebo 14/611 [2.3%]; lecanemab 98/620 [15.8%]) than *APOE4* noncarriers (placebo 1/286 [0.3%]; lecanemab 15/278 [5.4%]). Of the *APOE4* carriers, the incidence of ARIA-E was lower in heterozygous *APOE4* carriers (placebo 9/478 [1.9%]; lecanemab 52/479 [10.9%]) than in homozygous *APOE4* carriers (placebo 5/133 [3.8%]; lecanemab 46/141 [32.6%]).

ARIA-E events in placebo were randomly distributed over the course of treatment. For the first episode of ARIA-E, most cases of lecanemab ARIA-E occurred within the first 3 months of treatment (lecanemab 80/113 [70.8%]) and the time to occurrence was similar by *APOE4* carrier status and genotype (Figure 10).

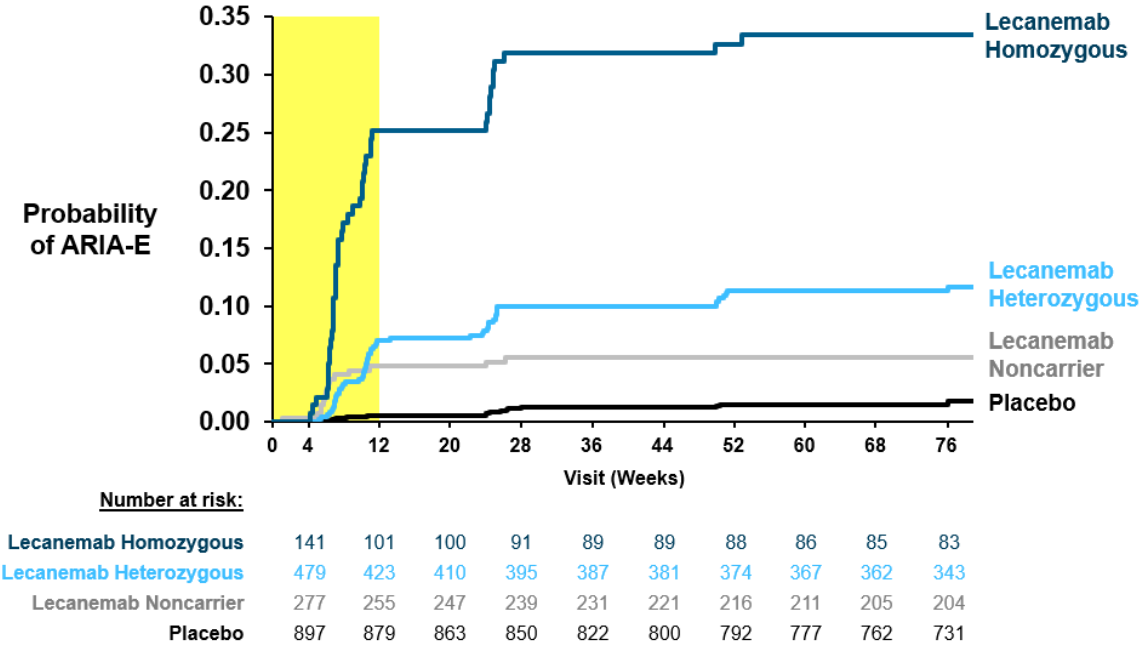

Figure 10 Kaplan-Meier Curve of Time to First ARIA-E Event – Study 301 Double-Blind (Safety Analysis Set)

ARIA-E = amyloid-related imaging abnormality-edema/effusion.

Most ARIA-E were radiographically mild in severity (placebo 9/897 [1.0%]; lecanemab 37/898 [4.1%]) or moderate (placebo 6/897 [0.7%]; lecanemab 66/898 [7.3%]); with no patients in placebo and 9 (1.0%) in lecanemab categorized as having radiographically severe ARIA-E.

The incidence of symptomatic ARIA-E was low, with no patients in placebo and 25/898 (2.8%) in lecanemab overall.

In the overall patient population, there were no serious AEs due to ARIA-E in placebo and the rates were 7/898 (0.8%) in lecanemab (*APOE4* noncarriers 2/278 [0.7%]; heterozygous *APOE4* carriers 2/479 [0.4%], homozygous *APOE4* carriers 3/141 [2.1%]).

There were no cases of ARIA-E leading to study discontinuation in placebo and 14/898 (1.6%) in lecanemab.

In both treatment groups, most patients who experienced ARIA-E did not have a recurrence.

Resolution is defined by resolution of both radiographic and clinical signs and symptoms of ARIA-E. The majority (81%) of ARIA-E resolved by 4 months from initial diagnosis. All 113 cases of first ARIA-E in patients treated with lecanemab resolved. In placebo, of the 15 patients experiencing first ARIA-E, 12 resolved and 3 remained ongoing.

Per protocol, patients with asymptomatic and radiographically mild ARIA-E could continue to receive study drug administration without interruptions. In lecanemab, approximately one-third (34/113) of patients with ARIA-E continued dosing during the first ARIA-E with resolution occurring while dosing continued. The remainder (68/113) of patients with ARIA-E had dose interruption. Of patients who continued dosing, time to resolution was similar to those patients who interrupted dosing. In placebo, approximately one half (9/15) of patients with ARIA-E continued dosing during the first ARIA-E with resolution. The remainder (6/15) of patients with ARIA-E had dose interruption.

The overall incidence of ARIA-E by the subgroup analyses of age (<65 years, ≥65 years), sex (male, female), and race (White, Black or African American, Asian) was generally similar among these subgroups. Addition information is provided in Section 4.4.6.2.

ARIA-H and Intracerebral Hemorrhage

ARIA-H is comprised of microhemorrhage, superficial siderosis, and uncommon intracerebral hemorrhage. ARIA-H can occur with or without concurrent ARIA-E. ARIA-H that occurs without ARIA-E is known as isolated ARIA-H. For Study 301, ARIA-H is described in this section as 1) isolated ARIA-H events not associated with ARIA-E; 2) ARIA-H concurrent with ARIA-E; and 3) overall ARIA-H.

Isolated ARIA-H

In Study 301, the incidences of isolated ARIA-H were similar in placebo (70/897 [7.8%]) and lecanemab (80/898 [8.9%]). For placebo, the incidence of isolated ARIA-H increased with increasing number of E4 alleles: *APOE4* noncarriers (11/286 [3.8%]), heterozygous *APOE4* carriers (35/478 [7.8%]) homozygous *APOE4* carriers (24/133 [18.0%]). Lecanemab showed a similar pattern of increasing frequency based on increasing number of E4 alleles. Isolated ARIA-H events occur throughout the course of treatment with similar rates in placebo and lecanemab. Rates for symptomatic isolated ARIA-H were similar between placebo (2/897 [0.2%] and lecanemab (4/898 [0.4%]). Therefore, isolated ARIA-H has similar incidence, timing, and risk factors (*APOE4*) for lecanemab and placebo, without a lecanemab-related increase in incidence.

Concurrent ARIA-E and ARIA-H

The overall incidence of concurrent ARIA-E and ARIA-H was lower in placebo (9/897 [1.0%]) than lecanemab (74/897 [8.2%]). For placebo, the incidence of concurrent ARIA-E and ARIA-H increased with increasing number of E4 alleles: *APOE4* noncarriers (1/286 [0.3%]), heterozygous *APOE4* carriers (5/478 [1.0%]), and homozygous *APOE4* carriers (3/133 [2.3%]). Lecanemab showed a similar pattern of increasing frequency based on increasing number of E4 alleles.

The onset time, distributions, and symptoms of concurrent ARIA-E and ARIA-H follow the pattern of ARIA-E. The excess incidence of ARIA-H in lecanemab is most likely due to ARIA-H that occurs during the onset or resolution of ARIA-E.

Overall ARIA-H

The overall incidence of ARIA-H was lower in placebo (81/897 [9.0%]) than lecanemab (155/898 [17.3%]).

For lecanemab patients experiencing ARIA-H, 33/278 (11.9%) patients were *APOE4* noncarriers, 67/479 (14.0%) were heterozygous *APOE4* carriers, and 55/141 (39.0%) were homozygous *APOE4* carriers.

The incidence of ARIA–H leading to discontinuation of study drug in lecanemab was higher in *APOE4* carriers (lecanemab 16 [2.3%]) than in *APOE4* noncarriers (lecanemab 2 [0.4%]). The incidence of ARIA-H leading to discontinuation of study drug in lecanemab was higher in *APOE4* carriers (lecanemab 16 [2.6%]) than in *APOE4* noncarriers (lecanemab 2 [0.7%]).

The overall incidence of serious AEs due to ARIA-H were 1/897 (0.1%) in placebo and 5/898 (0.6%) in lecanemab. The incidence of serious ARIA-H was lower in the heterozygous *APOE4* carriers (placebo 0/478; lecanemab 1/479 [0.2%]) and *APOE4* noncarriers (placebo 1/286 [0.3%]; lecanemab 2/278 [0.7%]) than in homozygous *APOE4* carriers (placebo 0/133 [0%]; lecanemab 2/141 [1.4%]).

Most ARIA-H events were radiographically mild (placebo 73/897 [8.1%]; lecanemab 97/898 [10.8%]) to moderate (placebo 5/897 [0.6%]; lecanemab 26/898 [2.9%]) in severity; with 3 (0.3%) patients in placebo and 32 (3.6%) in lecanemab reporting severe ARIA-H, mostly driven by any microhemorrhage event that resulted in a cumulative number greater than 10 microhemorrhages (27/898 [3.0%]). Similar trends were observed in all ARIA-H subcategories.

In both treatment groups, most ARIA-H was asymptomatic overall and across the subtypes.

For the entire study population, symptomatic ARIA-H was reported in 2/897 (0.2%) patients in placebo and 13/898 (1.4%) patients in lecanemab. For lecanemab patients with ARIA-H 13/155 (8.4%) were symptomatic. Most symptomatic cases were concurrent ARIA-E and ARIA-H. Preferred terms for symptoms occurring in more than 1 patient in lecanemab were headache (4 patients), dizziness (3 patients), and confusional state (2 patients).

Most study drug dose interruptions due to ARIA-H occurred in lecanemab patients.

Most cases of ARIA-H with placebo or lecanemab were ongoing at the end of the double-blind treatment period. All cases of intracerebral hemorrhage with placebo or lecanemab were ongoing, which was expected as events of ARIA-H tend not to resolve radiographically.

The overall incidence of ARIA-H by the subgroup analyses of age (<65 years, ≥65 years), sex (male, female), race (White, Black or African American, Asian) was generally similar among these subgroups. Additional information is provided in Section 4.4.6.3.

ARIA-E, ARIA-H and Intracerebral Hemorrhage and Concurrent Antithrombotic Use

There was no increase in ARIA-E or ARIA-H in patients who were on lecanemab and antithrombotics relative to those that were on lecanemab alone. The number of intracerebral hemorrhage cases was small, limiting risk assessment of concomitant use of antithrombotics Additional information is provided in Section 4.4.6.4

IMMUNOGENICITY

Analyses demonstrate that efficacy and safety were not impacted by the presence of anti-drug antibodies (ADA) or neutralizing antibodies (NAb).

In Study 301 at Baseline, the ADA prevalence rate was 5.0%, with the NAb prevalence rate of 0.3%. This indicates a background pre-existence of immune response in the study population. The incidence of positive ADA in lecanemab was 5.5% and titers were low (first quartile [Q1] and third quartile [Q3] of maximum ADA titers were 16 and 400, with 3 patients having a titer ≥2000). The NAb prevalence rate was 0.3% with a maximum titer of 270 reported for a single patient. This patient at Visit 3 Week 1 (Baseline – prior to start of treatment) was ADA positive with a high titer of 50,000 and NAb positive with a high titer of 270. No information was available about prior exposure to any immunotherapeutics. Additional information is provided in Section 4.6.

1.7 Overall Benefit-Risk Assessment

1.7.1 Clinical Interpretation of Study 301 Results

Study 301 demonstrated that lecanemab reduced progression of AD on validated global, functional, cognitive, and QoL outcomes. These outcomes are clinically meaningful when considered across the patient and care partner perspective, and the clinician treating the patient.

The primary outcome measure is the global scale of cognition and function CDR-SB. The CDR-SB involves an interview of the patient and care partner evaluating 6 domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care). Each domain is scored on the following scale of impairment: 0 (none), 0.5 (questionable), 1 (mild), 2 (moderate), and 3 (severe). The CDR-SB overall score is intended to capture the entire clinical course of AD (which can be over 10 years) and ranges from unimpaired (0) to bedridden (18). Patients with early AD are typically in the range of 0.5 to 6 on the overall CDR-SB. Typically in early AD, natural disease progression within 18 months is at most an

average of 2 points on CDR-SB (example ADNI and other clinical studies). Moving from 0 to 0.5 in any domain can mean progressing from unimpaired to impaired in that domain. Moving from 0.5 to 1 can mean progressing from slight impairment to loss of independence in a domain. For example, in the community affairs CDR domain, a rating of 0.5 is "slight impairment in these activities" while a rating of 1.0 is "unable to function independently at these activities". In Study 301, the rate of progression in early AD was 1.66 in placebo; therefore, for assessment of slowing disease progression, a treatment effect can only be between the range 0 to 1.66 on CDR-SB at 18 months.

From the perspective of the clinician, thresholds (referred to as the minimally important clinical difference [MCID]) are an important approach to help contextualize study results and demonstrate meaningful treatment benefit (Lansdall, et al., 2023, Liu, et al., 2021; Andrews, et al., 2021). The MCID is based on clinician assessment and indicates a clinically meaningful change whereby the patient is expected to require either additional treatment or additional supportive care. While literature attempting to define a meaningful score change for individual patients on clinical outcome assessments exist, there are important limitations and misinterpretations. The MCIDs proposed for the CDR-SB in early AD range from 0.50 to 0.98 for MCI and up to 1.63 for mild AD (Lansdall, et al., 2022; Andrews, et al., 2019). Given the limited treatment options for AD, clinicians are likely to underestimate the progression noted by patients or care partners that they identify as important (DiBenedetti, et al., 2020). Furthermore, the patient populations used to derive these do not have confirmed elevated amyloid, introducing significant variability in progression that inflates the MCID, and limits generalizability to a contemporary biomarker confirmed early AD population (Assunção, et al., 2022).

The clinically meaningful change for a clinician following a patient (MCID) has been misapplied as being a threshold for differences between treatment groups in clinical studies. MCID is typically anchored on progression to the next stage of AD, whereby the patient requires either additional treatment or additional supportive care. The appropriate application of MCID to AD clinical study results is to demonstrate the delay in clinically meaningful worsening (Dickson, et al., 2023; Lau Raket 2022; Wessels, et al., 2023; Petersen, et al., 2023). This has been demonstrated by lecanemab in several analyses:

- The CDR assessment provides a global CDR rating that establishes the overall clinical stage of AD, and ranges from 0 (unimpaired), 0.5 (mild cognitive impairment), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia). In Study 301, 81% of patients were CDR 0.5 at baseline. Study 301 results directly show a delay in the relative rate of progression to the next stage of disease of 31% versus the group who did not receive lecanemab.
- In slope analysis, the placebo group reaches a decline of 1.11 on CDR-SB at 12.7 months while the lecanemab treatment group experiences a delay of 5.3 months until a similar level of decline becomes evident at 18 months. By 18 months placebo will have further declined by 1.66 from baseline. As with other therapies, it is expected that a treatment that slows disease progression has an effect that continues to expand over time. Projecting across the entire AD course, this can translate to patients remaining in the early stages of AD for an additional 2 to 3 years (Tahami, et al., 2023; Tahami, et al., 2022).

Thus, treatment with lecanemab can help individuals remain in earlier stages of AD for a longer period. Patients value preservation of function and slowing of decline, and patient focus groups have indicated that personal meaningfulness should be considered alongside clinical meaningfulness when assessing treatments (Moreno, et al., 2023). The patient and care partner information assessed in the CDR-SB, ADCS-ADL-MCI and QoL measures in Study 301 are reflective of items of importance to patients and care partners (Hauber, et al., 2023; DiBenedetti, et al., 2020). Impact on cognition and function are accompanied by improvement in QoL life directly assessed by the patient in both general health related QoL scales (ie, EQ-5D-5L) as well as AD-specific scales (ie, QoL-AD). The use of the Zarit-Burden interview in Study 301 indicates direct effects on improvement in care partner burden with lecanemab relative to placebo.

Acknowledging the limitations cited above, it is generally accepted in peer-reviewed publications and other scientific sources that a 20% to 30% slowing of the CDR-SB differences is clinically meaningful (Abushakra et al, 2016; Petersen, et al., 2023). The 27% reduction in clinical decline from baseline in CDR-SB seen in Study 301 is consistent with a clinically meaningful difference on that scale based on the AD peer-reviewed literature, statistical principles, and guidance from the regulatory authorities under which Study 301 was designed. The highly statistically significant results in ADAS-Cog14 and ADCS MCI-ADL provide reinforcing independent evidence of clinically relevant impact on cognition and function.

Clinically meaningful benefits are based on a comprehensive assessment of impact of the treatment on cognition, function, QoL, care partner burden, and slowing progression of disease from the perspective of the patient, care partner, and clinician (Rentz, et al., 2021, Cohen, et al., 2022, Assunção, et al., 2022). The clinical importance of the treatment difference in CDR-SB is reinforced by the consistency and strength of evidence from Study 301:

- Consistent results across scales of cognition and function (26%-37% slowing), across domains within scales, and across clinically relevant subgroups
- Delay in progression by slope analysis of CDR-SB (delay of 5.3 months over the 18-month study), and by time-to-event analysis of progression to next stage of AD (HR 0.69)
- 38%-56% slowing of decline in health-related QoL measures and 38% slowing of care partner burden
- Lecanemab effects on biomarkers of amyloid, tau, neurodegeneration, and gliosis, provide a biological basis for the treatment effects.

1.7.2 Benefit-Risk Conclusion

AD is a progressive, neurodegenerative disorder that is the most common form of dementia among older people. In the US, it is estimated that there are 6-7 million people over 50 years of age with MCI due to AD and 2.5 million with mild AD (Gillis, et al., 2022, Alzheimer's Association, 2023). AD is the sixth-leading cause of death in the US (Xu, et al., 2020).

The disease is characterized clinically by a global decline of cognitive function that progresses slowly and for many patients, results in spending a significant period of their remaining life in the severe disabling disease state (Rizzuto, et al., 2012). Patients with AD typically survive for

only 3 to 10 years after symptom onset (Hebert, et al., 2003). In addition to the effect on patients, AD places a significant burden on families and care partners (Alzheimer's Association, 2023; Suehs, et al., 2014).

Current therapeutic agents for patients with mild, moderate, and severe AD dementia consist of symptomatic therapies. These therapies provide modest, temporary benefit to symptoms which is rapidly lost after treatment discontinuation (Birks, 2006; McShane, et al., 2006). None of the currently approved symptomatic treatments slow the amyloid accumulation, spread of neurofibrillary tangles and neuronal and synaptic loss that leads to relentless disease progression.

Patients value preservation of function and slowing of decline, and patient focus groups have indicated that personal meaningfulness should be considered alongside clinical meaningfulness when assessing treatments. Treatment with lecanemab can help individuals remain in earlier stages of AD for a longer period as demonstrated by a comprehensive assessment of cognition, function, QoL, care partner burden, and slowing progression of disease.

Safety data from over 1612 patients in Study 301 (double-blind + OLE Phase) demonstrate that lecanemab is generally well-tolerated in patients with early AD, with the AE profile (type and rate) observed in Study 301 consistent with the approved US prescribing information (USPI). The safety profile of lecanemab in patients with early AD has been evaluated with a placebo comparator for up to 18 months of exposure in Study 301 and up to 5 years exposure overall in lecanemab studies.

Adverse events of special interest for lecanemab (infusion-related reaction, amyloid related imaging abnormality microhemorrhages and hemosiderin deposits [a preferred term for ARIA-H cerebral microhemorrhage], and amyloid related imaging abnormality-oedema/effusion) generally occurred at a higher rate than placebo (except isolated ARIA-H which occurred the same rate as placebo). Most of these events were mild to moderate, and those related to lecanemab occurred early in the course of treatment. Serious infusion related reactions and ARIA events were reported infrequently. This profile allows the additional vigilance and MRI monitoring to be concentrated early, where it is most likely to be beneficial. The results of 301 support the safety profile and monitoring recommendations contained in the current USPI for lecanemab.

The findings from Study 301 are consistent with the known safety profile of lecanemab. There were no additional safety issues that would preclude use in the intended population and the risks associated with lecanemab treatment can be adequately described in the USPI to allow for safe use.

Taken together, the consistency and strength of evidence demonstrate that the slowing of disease progression and slowing of decline in QoL measures with lecanemab support a positive benefit-risk profile for the treatment of early AD.

2 BACKGROUND ON ALZHEIMER'S DISEASE

Summary

- AD is a disease with a complex clinical and biological continuum; biological disease begins 10-20 years before symptom onset; amyloid accumulation is the earliest detectable event, followed by tau hyperphosphorylation, together leading to synaptic and neuronal loss
- Cognitive impairment, limitations in daily function, and neuropsychiatric symptoms increase as the disease progresses and the complexity of care and cost burdens rise as disease worsens
  - Severe impact on patients, families, and healthcare systems
- Established treatments are insufficient; provide modest, temporary benefit to symptoms only and do not alter underlying disease pathophysiology
  - No treatments approved for the pre-dementia (MCI) stage of AD

2.1 Alzheimer's Disease

2.1.1 Disease Etiology

AD is a progressive, neurodegenerative disorder of unknown etiology and the most common form of dementia among older people. Lecanemab is approved for use in patients with early AD which is comprised of MCI due to AD and mild AD. In the US, it is estimated that there are 6-7 million people over 50 years of age with MCI due to AD and 2.5 million with mild AD (Gillis, et al., 2022, Alzheimer's Association, 2023). AD is the sixth-leading cause of death in the US and the fifth leading cause for people 65 years and older (Xu, et al., 2020).

The disease is characterized clinically by a global decline of cognitive function that progresses slowly and for many patients, results in spending a significant period of their remaining life in the severe disabling disease state (Rizzuto, et al., 2012). Patients with AD typically survive for only 3 to 10 years after symptom onset (Hebert, et al., 2003).

In addition to the effect on patients, AD places a significant burden on families and care partners. Informal caregiving for patients with Alzheimer's disease or dementia has been estimated at 18 billion hours per year in the US, valued at $339.5 billion annually (Alzheimer's Association, 2023). Increased care demands result in increased financial, psychological, physical stress and lost productivity for the care partner (Alzheimer's Association, 2023; Suehs, et al., 2014).

Risk factors for AD are increasing age, genetic factors, and family history. Age specific prevalence almost doubles every 5 years after age 65 (Alzheimer's Association, 2023). While several genes increase the risk of AD, the ε4 allele of the *APOE* gene is the strongest known genetic risk factor (Elias-Sonnenschein, et al., 2011; Mattsson, et al., 2018). Compared with the most common *APOE* genotype of ε3/ε3, ε4 heterozygosity increases risk of AD by 3 to 4 times, and ε4 homozygosity increases risk by 8 to 12 times (Alzheimer's Association, 2023). Approximately two-thirds of pathology confirmed AD cases are ε4 positive (heterozygous or

homozygous), compared with about 15% to 20% of the general population (Mattsson, et al., 2017).

Current understanding is that AD begins with structural and biological changes in the brain many years before the emergence of clinical symptoms. This was recognized in the 2007 International Working Group on research diagnostic criteria for AD and the NIA-AA (published 2011), where both adopted the concept of a pathophysiological continuum anchored to the presence of biomarkers preceding clinical diagnosis. AD is defined biologically by the presence of 2 abnormal protein deposits: amyloid plaques (extracellular deposits of brain amyloid comprising β-amyloid [Aβ] peptides) and neurofibrillary tangles (comprising abnormal tau protein). Biomarker (Jack, et al., 2013), clinicopathological (Delacourte, et al., 2002), and cohort (Amieva, et al., 2008) studies indicate that the disease process commences 10 to 20 years before the clinical onset of symptoms.

With the understanding that the disease process commences before the onset of clinical symptoms, a diagnostic framework of the disease has been developed to include predementia stages of AD (Dubois, et al., 2010; Sperling, et al., 2011; Jack, et al., 2018) as well as the mild, moderate, and severe dementia stages of AD (McKhann, et al., 2011). Biological classification of AD involves biomarker evidence of AD pathology (Jack, et al., 2018; Dubois, et al., 2021) such as confirmation of brain amyloid accumulation by use of PET or CSF.

Today, AD clinical research focuses on the earlier stages of the disease continuum in the belief that patients in the early stage of the disease are more likely to benefit from a therapy intended to slow progression of disease.

2.1.2 Current Treatment Options

Current therapeutic agents for patients with mild, moderate, and severe AD dementia consist of symptomatic therapies that include AChEIs, such as donepezil, and the N-methyl-D-aspartate receptor antagonist, memantine. These therapies have been approved for use in mild, moderate, or severe AD and are directed at treating cognitive and behavioral symptoms by addressing imbalances in neurotransmitter function caused by neurodegeneration. Symptomatic treatments provide modest, temporary benefit to symptoms at best, which is rapidly lost after treatment discontinuation (Birks, 2006; McShane, et al., 2006). There are no therapies approved for the pre-dementia (MCI) stage of AD.

None of the currently approved symptomatic treatments slow the amyloid accumulation, spread of neurofibrillary tangles and neuronal and synaptic loss that leads to relentless disease progression.

There are 2 products approved in the US under the accelerated approval pathway for the treatment of AD based on a reduction in Aβ plaques: lecanemab (LEQEMBI®) and aducanumab (Aduhelm®).

3 LECANEMAB FOR ALZHEIMER'S DISEASE

Summary

- Lecanemab is a novel humanized immunoglobulin G1 mAb that selectively targets Aβ protofibrils
- Targeting aggregated forms of Aβ and brain amyloid with lecanemab attenuates the disease course of AD and thereby slows clinical progression
- Lecanemab was approved under the accelerated approval pathway for the treatment of AD based on the results of an 856-patient Phase 2 study
- Study 301 is the FDA-agreed confirmatory study to verify and describe the clinical benefit of lecanemab

3.1 Lecanemab Overview

Lecanemab has been developed under the hypothesis that targeting soluble aggregated forms of Aβ and brain amyloid will attenuate the disease course of AD and thereby slow clinical progression.

Lecanemab is a novel humanized immunoglobulin G1 mAb that was developed against Aβ protofibrils, based on the observation that the 'Arctic' mutation in Swedish patients with familial AD had an increased propensity for aggregation of Aβ to form protofibrils (Nilsberth, et al., 2001; Tucker, et al., 2015). Aβ peptides exist in many different conformational states including monomeric Aβ peptide, soluble Aβ aggregates of increasing size ranging from small dimers and trimers to larger oligomers and protofibrils, and insoluble fibrils. Aβ protofibrils have been implicated in altering synaptic function and mediating neurotoxicity leading to cognitive decline and dementia observed in AD. Lecanemab was designed to selectively target these large soluble protofibrils relative to monomers (greater than 1000-fold over Aβ monomers), while it also interacts with the insoluble fibrils that are a major component of brain amyloid.

Lecanemab mediates FcγR-mediated clearance of Aβ aggregates in primary microglia culture (Kaplow, et al., 2013; Swanson, et al., 2013). The murine version of lecanemab (mAb158) has been shown to remove Aβ protofibrils and reduce brain amyloid in APP transgenic mice and prevents initial brain amyloid formation in ArcSwe mouse (Tucker, et al., 2015; Söllvander, et al., 2018). Binding of lecanemab to protofibrils and fibrils (the components of brain amyloid) enhances their FcγR mediated clearance by microglia, with expected subsequent neutralization of toxicity to neurons and removal from the brain resulting in slowing of disease progression.

3.2 Clinical Pharmacology

Steady state concentrations of lecanemab were reached after 6 weeks of 10 mg/kg administered every 2 weeks and systemic accumulation was 1.4-fold. The C_{max} and AUC of lecanemab increased dose proportionally in the dose range of 0.3 to 15 mg/kg following single dose.

Distribution: The mean value (95% CI) for central volume of distribution at steady-state is 3.22 (3.15-3.28) L.

Elimination: Lecanemab is degraded by proteolytic enzymes in the same manner as endogenous IgGs. The clearance of lecanemab (95% CI) is 0.434 (0.420-0.451) L/day. The terminal half-life is 5 to 7 days.

Specific Populations: Sex, body weight, and albumin were found to impact exposure to lecanemab. However, none of these covariates were found to be clinically significant.

Patients with Renal or Hepatic Impairment: No clinical studies were conducted to evaluate the pharmacokinetics of lecanemab in patients with renal or hepatic impairment. Lecanemab is degraded by proteolytic enzymes and is not expected to undergo renal elimination or metabolism by hepatic enzymes.

3.3 Current Indication

Lecanemab is currently approved under the accelerated approval pathway:

"LEQEMBI is indicated for the treatment of Alzheimer's disease. Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with LEQEMBI. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial."

3.4 Regulatory History

The Investigational New Drug Application (IND) for lecanemab was cleared to proceed in Jul 2010, with Breakthrough Therapy designation (BTD) granted Jun 2021 and Fast Track designation granted Dec 2021.

A rolling Biologics License Application (BLA) under 21CFR 314.500 (subpart H, accelerated approval regulations) was initiated Sep 2021 based on the results from Phase 2 proof of concept Study 201 and approved Jan 2023. A supplemental BLA (sBLA) containing the confirmatory study to verify and describe the clinical benefit of lecanemab (Study 301 Clarity AD) was submitted Jan 2023 and accepted under priority review in Mar 2023.

The lecanemab clinical development program was designed with input from the FDA through a series of formal meetings and in line with the FDA's draft Guidance for Industry *Early Alzheimer's Disease: Developing Drugs for Treatment* (FDA, 2018). A summary of key clinical interactions with the FDA for the early AD indication is provided in Table 6.

Table 6 Lecanemab Milestones and Key Interactions/Discussions with the FDA

Meeting Type / Interaction	Date	Topics Discussed
Type B: Pre- IND Meeting	Jun 2009	• Proposed CMC, nonclinical and clinical programs • Proposed dosing in single-dose clinical study
Type B: End-of-Phase 2A (EOP2) Meeting	Nov 2012	• Phase 2 proof of concept Study 201
Study 201 Original Protocol Submission	Nov 2012	• Submission of original protocol for Study 201
Study 201 Initiated	Dec 2012	• First patient in for Study 201
Study 201 Completed	Jul 2018	• Last patient out for Study 201
Type B: EOP2 Meeting	Oct 2018	• Results from Phase 2 proof of concept Study 201 • Proposed Phase 3 program including study design elements • Potential BTD Request
Study 201 OLE Phase Initiated	Dec 2018	• OLE Phase initiated for Study 201 after discussion with the FDA
Type C: Mechanism of Action Meeting	Jan 2019	• Reduction of brain amyloid as predictive of clinical benefit

BTD = Breakthrough Therapy designation, CMC = Chemical, Manufacturing, and Control, EOP2 = end of Phase 2, FDA = Food and Drug Administration, IND= Investigational New Drug; OLE=Open Label Extension.

3.5 Confirmatory Trial(s) to Verify Clinical Benefit for Drugs Approved Under the Accelerated Approval Pathway

As summarized in the FDA Guidance for Industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (FDA 2014), products approved under accelerated approval may require further adequate and well-controlled clinical trial(s) to verify and describe clinical benefit. In Dec 2022 there was agreement between Eisai and the FDA on the following postmarketing requirement (PMR) trial to verify and describe the clinical benefit of lecanemab. Study 301 was confirmed as the trial to fulfill this PMR:

4384-1: In order to verify the clinical benefit of lecanemab-irmb, conduct a randomized, controlled trial to evaluate the efficacy of lecanemab-irmb compared to an appropriate control for the treatment of Alzheimer's disease. The trial should be of sufficient duration to observe changes on an acceptable endpoint in the patient population enrolled in the trial.

Key interactions with the FDA for Study 301 are described in Table 7.

Table 7 Lecanemab Milestones and Key Interactions/Discussions with the FDA for Study 301

Meeting Type / Interaction	Date	Topics Discussed
Study 301 Original Protocol Submission	Feb 2019	• Submission of original protocol for Study 301
Study 301 Initiated	Mar 2019	• First patient in for Study 301
Type C: Study 301 Meeting	Dec 2020	• Approaches for ongoing Study 301 related to COVID-19 pandemic • Statistical analysis approach for Study 301
Type B: BTD Multidisciplinary Meeting	Sep 2021	• Overall development program (early AD), including ongoing studies (early AD and preclinical AD) • Potential BLA submission under accelerated approval pathway via rolling review, including format and content of BLA • Study 301 proposed as the confirmatory study if accelerated approval was granted
Type B: Study 301	Dec 2021	• Statistical analysis approach for Study 301
Study 301 SAP	Jun 2022	• Follow-up on SAP for Study 301
Type B: pre sBLA Meeting for Study 301	Jul 2022	• Content and format of the sBLA for Study 301 intended to verify and describe the clinical benefit of lecanemab to support traditional approval • Follow-up on SAP for Study 301 • Data Submission Plan for sBLA
FDA Feedback on Study 301 Statistical Analysis	Aug 2022	• Statistical analysis approach for Study 301
Study 301 Completed	Aug 2022	• Last patient out
Study 301 OLE Phase SAP	Sep 2022	• Statistical analysis approach for Study 301 OLE Phase

AD = Alzheimer's disease, BLA = Biologics License Application, BTD = Breakthrough Therapy designation, EOP2 = end of Phase 2, FDA = Food and Drug Administration, IND = Investigational New Drug; OLE = Open Label Extension, SAP = statistical analysis plan

4 CONFIRMATORY PHASE 3 STUDY TO VERIFY AND DESCRIBE THE CLINICAL BENEFIT OF LECANEMAB – STUDY 301

4.1 Study Design

Summary

- Study 301 is the FDA-agreed confirmatory trial to verify and describe the clinical benefit of lecanemab
  - Global, multicenter, double-blind, placebo-controlled, parallel-group study to demonstrate the superiority of lecanemab vs placebo with an OLE Phase
  - Patient population was early AD; patients with MCI and mild AD dementia
  - Inclusion/exclusion criteria supported recruitment of patients with a range of comorbidities and concomitant medications
  - The study utilized globally established and validated measures of cognition, and function in early AD. QoL outcomes and biomarkers were also assessed.
  - Primary and key secondary endpoints: CDR-SB, amyloid PET, ADAS-Cog14, ADCOMS, ADCS MCI-ADL were tested per a pre-specified testing hierarchy

Study 301 is a global, multicenter, double-blind, placebo-controlled, parallel-group study to demonstrate the superiority of lecanemab vs placebo with an OLE Phase. Eligible patients were randomized in a 1:1 ratio to receive either placebo or lecanemab for an 18-month double-blind treatment duration followed by a 3-month Follow-up Period or an optional 4-year OLE Phase. The study population met the NIA-AA clinical criteria for MCI due to AD or mild AD, collectively designated as early AD. The presence of brain amyloid pathology was confirmed in all patients as measured by amyloid PET or CSF t-tau/Aβ[1-42]. Study 301 included 3 longitudinal substudies: amyloid PET, CSF biomarker assessments, and tau PET. Participation in these substudies was optional.

Study 301 was carefully designed to reflect a diverse patient population and current community practice through the inclusion of:

- A representative early AD population (MCI and mild AD) based on clinical evaluation and confirmation of elevated amyloid by amyloid PET visual read (per approved PET tracer label) or validated CSF assay
- Usual care settings: Study 301 included a wide range of study sites, from private centers to academic medical centers, including both community- and hospital-based sites of treatment. The sites were located in different types of geographic areas (urban, suburban and rural). The principal investigators at sites included a range of practitioner types, including neurologists, internists, psychiatrists, and geriatricians. Coordinators and raters served as site staff, while radiology professionals were involved in central reads of MRIs.
- Patients with a range of comorbidities: eligibility criteria allowed inclusion of patients with a range of comorbidities, including hypertension, diabetes, heart disease, obesity (Section 4.1.2).

- Patients with a range of concomitant medications: eligibility criteria allowed for inclusion of patients on symptomatic AD medication (randomization strata), antiplatelet and anticoagulant agents, and anti-depressants (Section 4.1.2).
- Diverse racial and ethnic elderly patient populations that generally reflect that of the US Medicare population: Eisai's recruitment strategy for Study 301 ensured greater inclusion of ethnic and racial populations in the US, resulting in approximately 25% of the total US enrollment including Hispanic and African American patients living with early AD (Section 4.2.2).

Study 301 randomized 1795 patients across 2 treatment groups: placebo (n=897), lecanemab (n=898). Approximately 70% of patients randomized were *APOE4* carriers. All of the randomized patients received at least 1 dose of study drug.

As of 01 Dec 2022, 1385 patients had entered Study 301 OLE Phase. Cumulatively, a total of 1612 patients have been treated with lecanemab in Study 301 (either in the double-blind or OLE Phase). An overview of the study design is presented in Executive Summary Figure 1.

4.1.1 Optional Substudies

There were 3 optional longitudinal substudies in Study 301. Patients were able to participate in 1 or more substudies.

- Longitudinal amyloid PET substudy: Longitudinal amyloid PET assessments were conducted at 3, 6, 12, and 18 months of treatment to demonstrate target engagement and to assess amyloid clearance
- Longitudinal CSF biomarker assessments substudy: Longitudinal CSF assessments were performed at 12 and 18 months of treatment for soluble biomarker analysis (eg, Aβ[1-42], Aβ[1-40], neurogranin, neurofilament light chain (NfL), t-tau, and p-tau181 to assess effects on indicators of disease pathology. Patients who were on anticoagulant therapy were not eligible to participate in this substudy.
- Longitudinal tau PET substudy: Longitudinal tau PET assessments were performed at 13 and 18 months of treatment. This substudy was offered only to patients who 1) enrolled at sites able to participate and 2) had an amyloid positive study-specific PET scan at Baseline.

For any given patient participating in the imaging substudies (amyloid PET and/or tau PET), the same PET tracer was used at the Baseline and post-Baseline assessments.

Patients can continue their participation in the 3 optional longitudinal substudies during the Study 301 OLE Phase.

There are 2 additional optional substudies to the Study 301 OLE Phase that are exploring the subcutaneous administration of lecanemab. BLA 761269 S-001 does not seek approval of subcutaneous administration.

4.1.2 Study Population Demographic and Baseline Characteristics

Per protocol, 50% of the total number of patients were to have MCI due to AD and 70% of the total number of patients were to be *APOE4* carriers. The definitions used to define the early AD subpopulations of MCI due to AD and mild AD are provided in Table 8.

The inclusion/exclusion criteria used in Study 301 (Table 9) supported recruitment of an early AD patient population with a range of comorbidities and concomitant medications (Section 4.2.6).

Table 8 Disease Characteristics of Early AD Subpopulations

Early AD Subpopulation	Disease Characteristics
MCI due to AD	Intermediate likelihood, defined as: NIA-AA core clinical criteria for MCI due to AD – intermediate likelihood (McKhann, et al., 2011); a global CDR score of 0.5 and a Memory Box score of 0.5 or greater at Screening and Baseline; and a history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening
Mild AD	Defined as meeting the NIA-AA core clinical criteria for probable AD dementia; and a global CDR score of 0.5 to 1.0 and a Memory Box score of 0.5 or greater at Screening and Baseline.

AD = Alzheimer's disease, CDR = Clinical Dementia Rating, MCI = mild cognitive impairment, NIA-AA = National Institute on Aging and the Alzheimer's Association.

Table 9 Key Inclusion/Exclusion Criteria – Study 301

Inclusion Criteria	
Ages for Inclusion	• Male/female patients 50 – 90 years of age, inclusive
Diagnostic AD Criteria	• MCI due to AD intermediate likelihood and mild AD • MMSE score ≥22 and ≤30 at Screening and Baseline • Global CDR score 0.5 to 1.0
Impairment in Episodic Memory	At least 1 SD below age-adjusted mean in the WMS-IV LM II[a]
Positive Amyloid Load Criteria	PET assessment of imaging agent uptake into brain or CSF assessment of t-tau/Aβ[1-42]
AD Symptomatic Medication	Stable dose for at least 12 weeks before Baseline. Treatment-naïve patients for AD can be entered into the study. Use of memantine was not allowed for patients in Japan.

Table 9 Key Inclusion/Exclusion Criteria – Study 301

Exclusion Criteria	
Exclusionary Neurological	• Had any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the patient's AD • History of TIA, stroke, or seizures within 12 months of Screening • Had any psychiatric diagnosis or symptoms, that could interfere with study procedures • GDS score ≥8 at Screening • Evidence of other clinically significant lesions on brain MRI at Screening that could indicate a dementia diagnosis other than AD Other significant pathological findings on brain MRI at Screening, including but not limited to: more than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter); a single intracerebral hemorrhage greater than 10 mm at greatest diameter; an area of superficial siderosis; evidence of vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter were not exclusionary)

Aβ[1-42] = amyloid beta monomer from amino acid 1 to 42, AD = Alzheimer's disease, CDR = Clinical Dementia Rating, CSF = cerebrospinal fluid, GDS = geriatric depression scale, MCI = mild cognitive impairment, MMSE = Mini-Mental State Examination, MRI = magnetic resonance imaging, TIA = transient ischemic attacks, t-tau = total tau, WMS-IV LM II = Wechsler Memory Scale-IV Logical Memory (subscale) II.
a: ≤15 for age 50 to 64 years, ≤12 for age 65 to 69 years; ≤11 for age 70 to 74 years; ≤9 for age 75 to 79 years; and ≤7 for age 80 to 90 years.

4.1.3 Dose Selection

Lecanemab 10 mg/kg biweekly was selected as the dose for evaluation in Study 301 and is the same dose approved under the accelerated approval pathway, based on the results from the large, dose-ranging Phase 2 proof of concept Study 201.

4.1.4 Operational Measures Taken to Ensure Blinding

In Study 301 the clinician responsible for CDR assessment did not participate in the medical management of the patients and was blinded to results of safety assessments (including but not limited to results of safety MRI, clinical laboratory assessments, and AEs), except for the results of the Columbia-Suicide Severity Rating Scale (C-SSRS). Additionally, for any given patient, every effort was made to ensure that the raters for the CDR, ADAS-Cog14, and MMSE remained unchanged throughout the study. No one rater performed all clinical assessments at a given visit. There was a central review of ratings for CDR, ADAS-Cog14, and MMSE, and for consistency these assessments were reviewed by local language speaking central clinical reviewers at all visits.

In addition to activities at the site level, operationally Eisai's conventional study team members were firewalled to AEs that could be potentially unblinding, which included ARIA-E, ARIA-H, skin rash or other hypersensitivity reactions including infusion-related reactions, related concomitant medications and all postbaseline safety MRI data. These data were stored in a

separate independent firewalled database with limited access, which was monitored by an independent medical monitoring team, managed by an external contract research organization (CRO).

COVID-19 vaccinations, vaccine related AEs and related concomitant medications were also stored in the separate independent firewalled database with limited access, as some COVID-19 related AEs may have been similar to infusion-related reactions observed following study drug administration.

This independent database was merged with the overall clinical database by an independent Eisai Data operations member and sent to independent statistical vendor to prepare the Data Safety Monitoring Board (DSMB) outputs.

Sensitivity analyses to assess for potential unblinding due to medical management (ARIA-E, ARIA-H, infusion-related reactions) (Section 4.3.1.9) confirm that there was no impact on efficacy due to any of these adverse events.

4.1.5 Assessments

4.1.5.1 Clinical Endpoints

The CDR and ADAS-Cog14 are well-established and validated clinical scales for use in the research assessment of AD, and the ADCS MCI-ADL is a well-known instrument for the assessment of activities of daily living in AD. The ADCOMS was included in Study 301 to bridge back to the Phase 2 Study 201, which used ADCOMS as the primary endpoint.

PRIMARY ENDPOINT

- Change from baseline in the CDR-SB at 18 months

KEY SECONDARY ENDPOINTS

- Change from baseline in amyloid PET using Centiloids at 18 months for brain amyloid levels
- Change from baseline in ADAS-Cog14 at 18 months
- Change from baseline in ADCOMS at 18 months
- Change from baseline in ADCS MCI-ADL at 18 months

OTHER SECONDARY/EXPLORATORY ENDPOINTS

- Incidence of AEs and change in vital signs, electrocardiograms (ECGs), laboratory safety tests, suicidality assessments, and MRI safety parameters
- Rate of change over time (mean slope) based on CDR-SB score over 18 months of treatment
- Time to worsening of global CDR score by 18 months

- Overall health-related QoL at 18 months of treatment as measured by the following outcome measures:
  - EQ-5D; 5 Level version (EQ-5D-5L)
  - QoL-AD
  - Zarit Burden Interview

4.1.5.2 Clinical Assessments

A tabular summary of the clinical assessments used in Study 301 is provided in Executive Summary Table 1.

CDR-SB

The CDR is a validated clinical scale that describes 5 degrees of impairment in performance on each of 6 categories of cognition/function including memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care (Berg, et al., 1988). The CDR assessment provides a global CDR rating that establishes the overall clinical stage of AD, and ranges from 0 (unimpaired), 0.5 (mild cognitive impairment), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia).

The CDR-SB sums each of the domain scores and is the gold standard validated outcome measure for AD clinical studies. Each domain is scored on the following scale of impairment: 0 (none), 0.5 (questionable), 1 (mild), 2 (moderate), 3 (severe). The CDR-SB overall score ranges from 0 to 18 and is intended to capture the entire clinical course of AD (which can be over 10 years) and ranges from unimpaired (0) to bedridden (18). Patients with early AD are typically in the range of 0.5-6 on the overall CDR-SB. In early AD, moving from 0 to 0.5 in any domain can mean progressing from unimpaired to impaired in that domain. Moving from 0.5 to 1 can mean progressing from slight impairment to loss of independence in a domain. In the 2013 draft Guidance for Industry *Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease*, CDR-SB was specifically suggested as an example of a single primary outcome measure that assesses both cognition and function in patients with early AD (FDA, 2013).

The mean placebo rate of decline in 18-month clinical studies of early AD is 1.5 to 2 on change from baseline CDR-SB (Swanson, et. al., 2021; Budd Haeberlein, et. al., 2022; Teng, et al., 2022). Therefore, for assessment of slowing disease progression, only a narrow range of the scale is applicable.

In order to assure optimal validity and reliability of the CDR measurements, Study 301 required a qualified healthcare professional to serve as rater. A specialist third party provided oversight of rater training and rater eligibility. All CDR raters had appropriate education, clinical experience with dementia, and previous experience with administering the CDR.

AMYLOID PET

Brain amyloid status at study entry was assessed by PET visual read; brain amyloid reduction was assessed using Centiloid scale, and PET SUVR. Several 18F amyloid tracers, including florbetapir, florbetaben, and flutemetamol (Vandenberghe, et al., 2010) have been approved by the FDA.

The quantitative threshold for amyloid positivity for florbetapir was defined as amyloid PET SUVR=1.17, corresponding to Centiloid cut-off of approximately 30 Centiloid (Fleisher, et al., 2011). This Centiloid cut off of 30 Centiloids lies within the 25 to 35.7 Centiloid range for agreement with visual read (Rowe, et al., 2018; Amadoru, et al., 2020; Roé-Vellvé, et al., 2020; Bullich, et al., 2021), and is aligned with both Centiloid cut offs for 'established Aβ pathology' as determined by histopathology (Rowe, et al., 2017), and p-tau/Aβ42 and CSF t-tau/Aβ42 cut offs (Salvadó, et al., 2019).

While a Centiloid score ≥30 is the quantitative threshold for elevated amyloid, the inclusion criteria are based on visual read (based on the label for approved amyloid PET tracers), which is considered positive even if there are very focal areas of amyloid accumulation, but where the Centiloid value which is calculated across the entire cortical region could be <30.

ADAS-COG14

The ADAS-Cog14 is a cognitive scale widely used in AD studies. It is a structured scale that evaluates memory (word recall, delayed word recall, and word recognition), reasoning (following commands), language (naming, comprehension), orientation, ideational praxis (placing letter in envelope), and constructional praxis (copying geometric designs) (Rosen, et al., 1984). Ratings of spoken language, language comprehension, word finding difficulty, ability to remember test instructions, maze, and number cancellation are also obtained. The modified version used in Study 301 is scored from 0 to 90 points with a score of 0 indicating no impairment and a score of 90 indicating maximum impairment. This range is for the entire disease stage, from unimpaired to moderate or severe AD. However, as stated above for CDR-SB, placebo progression for ADAS-Cog14 in early AD stage has been approximately 6 points over 18 months in early AD clinical studies (Swanson, et. al., 2021; Budd Haeberlein, et. al., 2022; Teng, et. al., 2022).

ADCOMS

The ADCOMS is a composite scale consisting of selected items (12 total) from the CDR (all 6 items), the ADAS-Cog14 (4 items), and the MMSE (2 items). ADCOMS is more sensitive to clinical progression (assessed by mean to standard deviation ratios) compared to currently existing clinical batteries (Wang, et al., 2016). As such, ADCOMS requires smaller sample sizes for clinical studies in early AD, and it facilitated the response adaptive component of the Bayesian design for Study 201. The ADCOMS was included in Study 301 to demonstrate reproducibility and consistency of results.

ADCS MCI-ADL

The ADCS MCI-ADL is a functional scale based on information provided by an informant/care partner that evaluates the level of performance of patients in several activities of daily living. The scale has 24 items that include assessment of the extent to which the patient performs the home and community activities, and whether they can be performed independently or with support (such as shopping, preparing meals, and using household appliances) together with 1 basic item (getting dressed) and is used in clinical studies with participants with early AD to provide an assessment of change in functional state over time (Egan, et al., 2019; Galasko, et al., 1997; Pedrosa, et al., 2010). The total score can range between 0 and 53, with lower values indicating greater impairment. This range is for the entire disease stage, from unimpaired to moderate AD. However, as stated above, placebo progression for ADCS MCI-ADL in early AD stage has been at most 6 points over 18 months in early AD clinical studies (Swanson, et. al., 2021; Budd Haeberlein, et. al., 2022; Teng, et. al., 2022). A single point change in an activity can mean moving from performing it unsupervised to requiring supervision, or from an activity requiring supervision to requiring physical assistance by the care partner.

HEALTH-RELATED QUALITY OF LIFE

The health-related QoL outcomes included the EQ-5D-5L, the QoL-AD, and the Zarit Burden Interview (Executive Summary Table 2).

EQ-5D-5L is a descriptive system that covers 5 dimensions of health (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) with 5 levels of severity in each dimension (no problems, slight problems, moderate problems, severe problems, and unable to perform or extreme problems) as well as Visual Analog Scale (VAS) for overall current health, which are evaluated by a patient, a care partner as a proxy, and a care partner. The score range is from 0 (worst imaginable health state) to 100 (best imaginable health state).

QoL-AD is a 13-item questionnaire designed to provide both a patient and a care partner report of the QoL for patients who have been diagnosed with AD. The total score range is 13-52, with a scale of 1-4 (poor, fair, good, or excellent) for each of 13 items.

The Zarit Burden Interview is a 22-item instrument used in dementia caregiving research, to assess the stresses experienced by study partners of patients with dementia. The total score range: 0 to 88; with 0-21: no to mild burden; 21-40: mild to moderate burden; 41-60: moderate to severe burden, and ≥ 61: severe burden.

4.1.5.3 Biomarker Endpoints and Assessments

Study 301 assessed a number of CSF, plasma, and imaging biomarker endpoints of amyloid, tau, and neurodegeneration/gliosis. The assessments, timepoints and assays used are described in Executive Summary Table 3.

4.1.5.4 Selected Adverse Events of Interest to the Proposed Indication

There are 3 adverse events of interest for lecanemab:

- Infusion-related reactions: Predefined in the SAP as preferred terms "infusion related reaction" and "infusion site reaction".
- ARIA-E: Interstitial vasogenic edema or sulcal effusion that manifests as parenchymal or sulcal hyperintensities on MRI.
- ARIA-H: Microhemorrhages or uncommon intracerebral hemorrhage >1cm observed as hypointense hemosiderin deposition in parenchyma or leptomeningeal/subpial space (superficial siderosis) on MRI. In this document "ARIA-H" represents the combined preferred terms of cerebral hemorrhage, hemorrhage intracranial, thalamus hemorrhage, superficial siderosis of central nervous system, amyloid related imaging abnormality-microhemorrhage and hemosiderin deposit, cerebellar microhemorrhage.

Amyloid deposition in blood vessels, called CAA, is ubiquitous in AD. It can cause common asymptomatic microhemorrhage and asymptomatic superficial siderosis, and rare lobar macrohemorrhage or inflammatory CAA spontaneously in AD. *APOE4* is a risk factor for CAA and intracerebral hemorrhage due to CAA. Mobilization of amyloid from blood vessels in CAA is the likely mechanism of ARIA observed with anti-amyloid antibodies.

4.1.6 Treatment Duration

The double-blind treatment duration for Study 301 was 18 months plus 3 months of follow-up off treatment for those not continuing into the OLE Phase. Eighteen months was selected as this was considered the optimal treatment duration to demonstrate slowing of disease progression based on clinical and biomarker data from Study 201 and given that lecanemab is administered at the therapeutic dose from the first dose without titration. The treatment duration for Study 301 OLE Phase will last up to 4 years.

4.1.7 Randomization

Randomization was stratified by use of symptomatic AD medication at baseline (yes/no), clinical subgroup (MCI due to AD, mild AD dementia), *APOE4* carrier status (carriers, noncarriers), and region (North America, Europe [including Australia] Asia Pacific [excluding China]).

4.1.8 Statistical Methods

There were extensive discussions with the FDA on the SAP for Study 301 (Table 6), with SAP version 2.0 finalized 06 Sep 2022 prior to database lock.

4.1.8.1 Analysis Sets

Below are the pre-prespecified analysis sets used to describe Study 301 (double-blind, hereafter "Study 301") data in this Briefing Document:

- The Randomized Set was the group of patients who were randomized to study drug.
- The Safety Analysis Set was the group of all allocated patients who received at least one dose of study drug.
- The mITT full analysis set+ (mITT FAS+): Randomized patients who received ≥ 1 dose of study drug, and Baseline assessment and ≥1 post dose primary efficacy measurement.
- The FDA Full Analysis Set (FDA FAS): As above, but excluded 68 patients at sites closed during peak COVID period in 2020 for 6 or more weeks (equivalent to missing ≥ 3 consecutive doses during that site's closure period).

Study 301 met the primary endpoint and all key secondary endpoints with a high degree of statistical significance, with consistent results seen across the mITT FAS+ and FDA FAS. For this reason, this Briefing Document presents the mITT FAS+ as it includes all data collected on the efficacy endpoints.

4.1.8.2 Subgroup Analyses

For Study 301, prespecified subgroup analyses were performed. Efficacy results are presented for randomization strata:

- Use of AD symptomatic medication at Baseline (yes or no)
- Clinical subgroup (MCI due to AD, mild AD dementia)
- *APOE4* carrier status (noncarrier, carrier)
- Region (North America, Europe [including Australia] Asia Pacific [excluding China])

4.1.8.3 Sensitivity and Supplementary Analyses

Sensitivity and supplementary analyses (Table 17) were conducted to assess the robustness of the primary analysis. Aall were prespecified except primary MMRM censoring assessments after occurrence of ARIA or infusion-related reactions, which were performed at the request of the FDA, and primary MMRM based on the Randomized Set, which was performed at the request of the EMA.

4.2 Disposition, Demographics and Baseline Characteristics

Summary

- Overall, 80% of patients completed 18 months of treatment
- Disposition, demographics and baseline clinical characteristics were similar in placebo and lecanemab
  - Approximately 60% had MCI and 40% had mild AD dementia
  - *APOE4* distribution reflected the general AD population with approximately 30% of the population being *APOE4* noncarriers, 55% heterozygous *APOE4* carriers and 15% homozygous *APOE4* carriers. This is important as *APOE4* is a risk factor for AD, including an earlier age of onset and is also associated with cerebral amyloid angiopathy and spontaneous intracerebral hemorrhage due to CAA. *APOE4 is* also associated with increased risk of ARIA with anti-amyloid therapies.
  - Approximately 50% of patients were on symptomatic AD medication at baseline.
  - Comorbidities included hypertension (55%), hyperlipidemia (60%), ischemic heart disease (16%), obesity (17%) and diabetes (15%)
  - Concomitant medications included antidepressants (29%), antiplatelet therapy (27%) and anticoagulants (5%)

4.2.1 Patient Disposition

In Study 301, a total of 1795 patients were randomized into the study to receive either placebo (897 patients) or lecanemab (898 patients). Of these, 1486 patients (placebo 757; lecanemab 729) completed Study 301 (Executive Summary Table 4). Among the patients who discontinued the study (placebo 140 [15.6%]; lecanemab 169 [18.8%]), reasons for discontinuation were similar, with the most common reasons being withdrawal of consent and AE. The AEs driving the higher discontinuation with lecanemab treatment were infusion-related reactions and ARIA. After excluding these events, the discontinuation rate and timing of discontinuation of lecanemab are similar with placebo. Patients who discontinued study treatment were encouraged to continue in the study and complete scheduled assessments.

4.2.2 Demographics

In Study 301, demographic and other Baseline characteristics were similar between placebo and lecanemab and reflect the target patient population of early AD (Table 10).

Overall, the median age was 72 (range: 50 to 90) years. There was a similar proportion of male (857 [47.7%]) and female (938 [52.3%]) patients. Over 75% of patients were White, with 16.9% Asian (with the breakdown of 8.5% Japanese, 7.2% South Korean, and 0.7% Chinese and 0.4% Other), and 2.6% Black or African American, and for ethnicity, 12.9% were Hispanic. The study included patients from North America (1072 [59.7%]), Europe (including Australia) (429 [23.9%]), and Asia (excluding China) (294 [16.4%]).

Of the 947 patients in the United States, 895 (94.5%) were White, 7 (0.7%) were Asian, 43 (4.5%) were Black or African American, and for ethnicity, 213 (22.5%) were Hispanic.

The median age (range) was the same for placebo and lecanemab (72.0 [50 to 90] years). Sex was balanced between placebo (421 [46.9%] males) and lecanemab (436 [48.6%] males). Overall, race was balanced between placebo and lecanemab.

Table 10 Demography and Baseline Characteristics – Study 301 Double-Blind (Safety Analysis Set)

Category	Placebo (N=897)	Lecanemab (N=898)	Combined Total (N=1795)
Age (year)			
Mean (SD)	71.1 (7.79)	71.4 (7.88)	71.3 (7.83)
Min, Max	50, 90	50, 90	50, 90
Sex, n (%)			
Male	421 (46.9)	436 (48.6)	857 (47.7)
Female	476 (53.1)	462 (51.4)	938 (52.3)
Race, n (%)			
White	696 (77.6)	685 (76.3)	1381 (76.9)
Black or African American	25 (2.8)	22 (2.4)	47 (2.6)
Asian	150 (16.7)	153 (17.0)	303 (16.9)
Other	26 (2.9)	38 (4.2)	64 (3.6)
APOE4 carrier status (Laboratory), n (%)			
Carriers	611 (68.1)	620 (69.0)	1231 (68.6)
Heterozygous	478 (53.3)	479 (53.3)	957 (53.3)
Homozygous	133 (14.8)	141 (15.7)	274 (15.3)
Noncarriers	286 (31.9)	278 (31.0)	564 (31.4)
Use of AD symptomatic medication at Baseline (CRF), n (%)			
Yes	477 (53.2)	466 (51.9)	943 (52.5)
No	420 (46.8)	432 (48.1)	852 (47.5)
Clinical subgroup (CRF), n (%)			
MCI due to AD	555 (61.9)	552 (61.5)	1107 (61.7)
Mild AD dementia	342 (38.1)	346 (38.5)	688 (38.3)
Number of years of disease since diagnosis			
N	895	898	1793
Missing	2	0	2
Mean (SD)	1.34 (1.538)	1.43 (1.527)	1.38 (1.533)
Median	0.80	0.80	0.80
Min, Max	0, 11.2	0, 10	0, 11.2
Age at onset of symptoms (Years)			
N	897	897	1794
Missing	0	1	1
Mean (SD)	67.6 (8.04)	68.0 (8.08)	67.8 (8.06)
Median	68.3	68.8	68.6
Min, Max	29.9, 86.9	38, 85.7	29.9, 86.9

Percentages are based on the total number of patients in relevant treatment group.
AD = Alzheimer's disease, *APOE4* = apolipoprotein E4, CRF = case report form, MCI = mild cognitive impairment, Min = minimum, Max = maximum, SD = standard deviation.

4.2.3 Disease-related Baseline Characteristics

The characteristics of primary disease diagnosis were similar between placebo and lecanemab.

Overall, the mean time since disease diagnosis was 1.38 (range: 0 to 11.2) years and the mean age at onset of symptoms was 67.8 (range: 29.9 to 86.9) years. For the clinical diagnosis of early AD, 61.7% patients had a diagnosis of MCI due to AD, and 38.3% patients had mild AD, consistent with the study design. Symptomatic AD medication at baseline was taken by 52.5% of patients overall (Table 10).

4.2.4 *APOE4* Carrier Status

The majority of patients in Study 301 were *APOE4* carriers (1231 [68.6%]; 957 [53.3%] heterozygous *APOE4* carriers, 274 [15.3%] homozygous *APOE4* carriers) with the remainder *APOE4* noncarriers (564 [31.4%]). The *APOE4* carrier status was similar for placebo and lecanemab (Table 10), per the randomization strata.

4.2.5 Baseline Clinical Outcome Scores

Baseline values for clinical outcome scores CDR-SB, ADAS-Cog14, ADCOMS, ADCS MCI-ADL, and MMSE) were similar between placebo and lecanemab. The mean Baseline value (and SD) for CDR-SB was similar between placebo (3.22 [1.336]) and lecanemab (3.18 [1.344]).

Eligibility criteria for Study 301 included patients with a global CDR score of 0.5 (MCI) and 0.5 to 1.0 (mild AD). The proportion of patients with a global CDR score of 0.5 was consistent between placebo (80.8%) and lecanemab (80.5%).

4.2.6 Comorbidities and Concomitant Medications

The inclusion/exclusion criterion used in Study 301 (Section 4.1.2) supported recruitment of an early AD patient population with a range of comorbidities and concomitant medications (Table 11). Over 50% of patients reporting hypertension or hyperlipidemia, 15% ischemic heart disease or diabetes. Fifty-percent of patients reported multiple comorbidities. Since antithrombotic agents (antiplatelet and anticoagulant medications) are common concomitant mediations in this population, it is important to understand benefit-risk for patients on these agents. Patients on stable doses of these medications were eligible to participate. At Baseline, 5% were on anticoagulants and 27% (33% in US patients) were on antiplatelet agents.

Table 11 Comorbidities and Concomitant Medications at Baseline – Study 301 Double-Blind (Safety Analysis Set)

Category	Combined Total Global Population (N=1795)	Combined Total US Population (N=947)
Comorbidities		
Hypertension, n (%)	990 (55.2)	611 (64.5%)
Hyperlipidemia, n (%)	1084 (60.4)	672 (71.0%)
Ischemic Heart Disease, n (%)	283 (15.8)	186 (19.6%)
Diabetes, n (%)	270 (15.0)	179 (18.9%)
Obesity, n (%)	297 (16.5)	228 (24.1%)
At least 2 comorbidities above, n (%)	916 (51.0)	603 (63.7%)
At least 3 comorbidities above, n (%)	435 (24.2)	314 (33.2%)
At least 4 comorbidities above, n (%)	139 (7.7)	111 (11.7%)
At least 5 comorbidities above, n (%)	25 (1.4)	22 (2.3%)
Concomitant Medications		
Anticoagulants	88 (4.9%)	60 (6.3%)
Antiplatelet therapy	492 (27.4%)	313 (33.1%)
Antidepressants	514 (28.6%)	285 (30.1%)

US = United States.

4.3 Efficacy Results

Summary

- Lecanemab treatment met the primary and secondary endpoints vs placebo at 18-months, with highly significant differences starting at 6 months (all $P<0.05$):
  - Reduced clinical decline by 27% (CDR-SB)
  - Reduced brain amyloid starting at 3 months (amyloid PET)
  - Slowed cognition loss by 26% (ADAS-Cog14)
  - Slowed functional decline by 37% (ADCS MCI-ADL)
- Consistent benefit (38%-56%) seen across multiple QoL assessments, including care partner burden
- All sensitivity and supplementary analyses show highly statistically significant results
  - ARIA, infusion-related reactions, intercurrent events (discontinuations, change in use of symptomatic AD medication) had no impact on efficacy results
- Results were consistent across range of endpoints and subgroups

Study 301 achieved its primary objective of demonstrating superiority of lecanemab over placebo for change from Baseline in CDR-SB score at 18 months. The Phase 3 confirmatory study met the primary outcome and all key secondary outcomes with a high degree of statistical significance.

There was internal consistency of the data in Study 301, with highly statistically significant results (all $P<0.001$) seen for all endpoints, which measure cognition and function, as early as 6 months. Statistically significant results were seen in QoL measurements obtained from the patient or informant (Table 12). Sensitivity and supplementary analyses were also conducted for CDR-SB and other endpoints, with all results consistent with the main analysis. Other outcome measures also demonstrated consistency.

Table 12 Convergence of Evidence Across Multiple Independent Measures of Cognition, Function, Disease Progression and QoL Measures – Study 301 Double-Blind

Endpoint	Measurement	Measurement Required Input From Patient or Informant	Study 301 Outcome vs placebo at 18 months	*P* Value
Primary and Key Secondary Endpoints				
CDR-SB	Cognition and function	Patient and Care partner	27% slowing of decline	*P*=0.00005
Amyloid PET	Biomarker	N/A	59.1 centiloid reduction	*P*<0.00001
ADAS-Cog14	Cognition	Patient	26% slowing of decline	*P*=0.00065
ADCOMS	Cognition and function	Patient and Care partner	24% slowing of decline	*P*=0.00002
ADCS MCI-ADL	Function	Care partner	37% slowing of decline	*P*<0.00001
Quality of Life Endpoints				
EQ-5D-5L Dimensions	Patient |VAS	Patient	49% improvement in QoL	*P*=0.00383
Zarit Burden Interview	Care partner burden	Care partner	38% improvement in burden	*P*=0.00002
QoL-AD (Patient)	QoL	Patient	56% improvement in QoL	*P*=0.00231

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, CDR-SB = Clinical Dementia Rating – Sum of Boxes, EQ-5D-5L = European Quality of Life–5 Dimensions 5 Level version; QoL-AD = Quality of Life in Alzheimer's Disease

4.3.1 Clinical Results

4.3.1.1 CDR-SB

In Study 301, there was a highly statistically significant difference between placebo and lecanemab on change from Baseline of CDR-SB at 18 months, demonstrating slowing of disease progression, with an adjusted mean treatment difference of -0.451, 27.1% less decline with lecanemab compared to placebo, P=0.00005 (Executive Summary Figure 2 and Table 13). Starting as early as 6 months (P<0.01) and across all subsequent time points, lecanemab showed

highly statistically significant changes in CDR-SB from Baseline compared to placebo (all $P<0.01$). The absolute treatment difference increases over time (Month 12: -0.366; Month 18 -0.451). Subgroup analyses are presented in Section 4.3.1.10.

Sensitivity and supplementary analyses were also conducted with all results consistent ($P<0.001$) with the mITT FAS+ analysis (Table 17).

Table 13 Change from Baseline in CDR-SB Score at 18 Months – Study 301 Double-Blind (mITT FAS+)

Parameter Visit Statistic	Placebo (N=875)	Lecanemab (N=859)
CDR-SB		
Week 79		
M	875	859
N	757	714
Adjusted mean (SE)	1.663 (0.080)	1.213 (0.082)
Adjusted mean difference: Lecanemab - Placebo		-0.451
95% Confidence interval for differences		-0.669, -0.233
P value		0.00005
% Difference vs. Placebo		-27.1%

m shows the number of patients who are included in MMRM, n shows the number of patients at each visit.
Missing values are not imputed and assumed to be missing at random.
% difference is calculated as adjusted mean difference divided by adjusted mean for placebo group.
AD = Alzheimer's disease, *APOE4* = apolipoprotein E4, CDR-SB = Clinical Dementia Rating – Sum of Boxes, MMRM = mixed model for repeated measures, N = number of patients in treatment group, SE = standard error.

4.3.1.2 Amyloid PET

For Study 301, Centiloid values are presented by combining data across all tracers. The extent of amyloid reduction is dependent on Baseline amyloid levels.

In the PET substudy (for MMRM analysis: placebo 344 patients, lecanemab 354 patients), treatment with lecanemab reduced amyloid plaque burden at all timepoints, starting at 3 months ($P<0.001$) (Executive Summary Figure 3). At 18 months of treatment, lecanemab demonstrated a statistically significant reduction in amyloid PET using Centiloids versus placebo. Adjusted mean change in Centiloids at 18 months was -55.5 and 3.6 for lecanemab and placebo, respectively (adjusted mean treatment difference: -59.1; $P<0.00001$.

The mean level at Baseline for lecanemab was 77.9 Centiloids, and at the end of the study the level for lecanemab was 23.0 Centiloids, which is below the threshold for amyloid positivity of approximately 30 Centiloids.

4.3.1.3 ADAS-Cog14

In Study 301, there was a highly statistically significant difference between placebo and lecanemab on change from Baseline of ADAS-Cog14 at 18 months, demonstrating slowing of disease progression, with an adjusted mean treatment difference of -1.442, and 25.8% less decline with lecanemab compared to placebo, *P*=0.00065 (Executive Summary Figure 4, Table 14). Starting as early as 6 months (*P*<0.05) and across all subsequent time points, lecanemab showed highly statistically significant changes from Baseline in ADAS-Cog14 compared to placebo (all *P*<0.001). The absolute treatment difference tends to increase over time (Month 12: -1.351; Month 18: -1.442). Subgroup analyses are presented in Section 4.3.1.10.

Table 14 Change from Baseline in ADAS-Cog14 at 18 Months – Study 301 Double-Blind (mITT FAS+)

Parameter Visit Statistic	Placebo (N=875)	Lecanemab (N=859)
ADAS-Cog14		
Week 79		
m	872	854
n	738	703
Adjusted mean (SE)	5.581 (0.309)	4.140 (0.314)
Adjusted mean difference: Lecanemab - Placebo		-1.442
95% Confidence interval for differences		-2.270, -0.613
P value		0.00065
% Difference vs. Placebo		-25.8%

m shows the number of patients who are included in MMRM, n shows the number of patients at each visit.
The change from Baseline for overall population is analyzed using the MMRM with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of AD symptomatic medication at Baseline, *APOE4* carrier status, region, Baseline value by visit interaction as fixed effects, and Baseline value as covariate. Missing values are not imputed and assumed to be missing at random. % difference is calculated as adjusted mean difference divided by adjusted mean for placebo group.
AD = Alzheimer's disease, ADAS-Cog14 = Alzheimer's Disease Assessment Scale - Cognitive Subscale 14-item version, *APOE4* = apolipoprotein E4, MMRM = mixed model for repeated measures, N = number of patients in treatment group, SE = standard error.

4.3.1.4 ADCOMS

In Study 301, there was a highly statistically significant difference between placebo and lecanemab on change from Baseline of ADCOMS at 18 months, demonstrating slowing of disease progression, with an adjusted mean treatment difference of -0.050, 23.5% less decline with lecanemab compared to placebo, *P*=0.00002 (Executive Summary Figure 5 and Table 15). Starting as early as 6 months (*P*<0.05) and across all subsequent time points, lecanemab showed highly statistically significant changes from Baseline in ADCOMS compared to placebo (all *P*<0.001). The absolute treatment difference increases over time (Month 12: -0.047; Month 18: -0.050).

Table 15 Change from Baseline in ADCOMS at 18 Months – Study 301 Double-Blind (mITT FAS+)

Parameter Visit Statistic	Placebo (N=875)	Lecanemab (N=859)
ADCOMS		
Week 79		
m	875	857
n	749	708
Adjusted mean (SE)	0.214 (0.009)	0.164 (0.009)
Adjusted mean difference: Lecanemab - Placebo		-0.050
95% Confidence interval for differences		-0.074, -0.027
P value		0.00002
% Difference vs. Placebo		-23.5%

m shows the number of patients who are included in MMRM, n shows the number of patients at each visit.
Missing values are not imputed and assumed to be missing at random.
% difference is calculated as adjusted mean difference divided by adjusted mean for placebo group.
AD = Alzheimer's disease, ADCOMS = Alzheimer's Disease Composite Score, *APOE4* = apolipoprotein E4, MMRM = mixed model for repeated measures, N = number of patients in treatment group, SE = standard error.

4.3.1.5 ADCS MCI-ADL

In Study 301, there was a highly statistically significant difference between placebo and lecanemab on change from Baseline of ADCS MCI-ADL at 18 months, demonstrating slowing of disease progression, with an adjusted mean treatment difference of 2.016, 36.6% less decline with lecanemab compared to placebo, $P<0.00001$ (Executive Summary Figure 6 and Table 16). Starting as early as the first assessment at 6 months ($P<0.01$) and across all subsequent time points, lecanemab showed highly statistically significant changes in ADCS MCI-ADL from Baseline compared to placebo (all $P<0.0001$). The absolute treatment difference increases over time (Month 12: 1.550; Month 18: 2.016). Subgroup analyses are presented in Section 4.3.1.10.

Table 16 Change from Baseline in ADCS MCI-ADL at 18 Months – Study 301 Double-Blind (mITT FAS+)

Parameter Visit Statistic	Placebo (N=875)	Lecanemab (N=859)
ADCS MCI-ADL		
Week 79		
m	796	783
n	707	676
Adjusted mean (SE)	-5.500 (0.308)	-3.484 (0.313)
Adjusted mean difference: Lecanemab - Placebo		2.016
95% Confidence interval for differences		1.208, 2.823
P value		<.00001
% Difference vs. Placebo		-36.6%

m shows the number of patients who are included in MMRM, n shows the number of patients at each visit.
Missing values are not imputed and assumed to be missing at random.
% difference is calculated as adjusted mean difference divided by adjusted mean for placebo group.
AD = Alzheimer's disease, ADCS MCI-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale for Mild Cognitive Impairment, *APOE4* = apolipoprotein E4, MMRM = mixed model for repeated measures, N = number of patients in treatment group, SE = standard error.

4.3.1.6 Rate of Change Over Time for CDR-SB

There is increasing separation over time for CDR-SB between placebo and lecanemab, with a 29.3% slowing of slope on lecanemab annually ([95% CI: 16.1% to 42.4%], *P*=0.00001) versus placebo (Executive Summary Figure 7). This suggests the preservation of CDR-SB by approximately 5.3 months relative to placebo at 18 months. Furthermore, it is projected that lecanemab would not reach the 18-month placebo level of worsening until 7.5 months later, indicating increasing treatment effect over time. Lecanemab would take 25.5 months to reach the same level of placebo at 18 months, per the projection of the slope analysis (same annual slope assumption).

4.3.1.7 Time to Worsening of Global CDR Score

The global CDR score provides a staging system for AD, from 0.5 (consistent with MCI), to 1 (mild AD), 2 (moderate AD), and 3 (severe AD). Lecanemab reduced the risk of progression to the next stage of AD on the global CDR score by 31%. The hazard ratio of disease progression on the global CDR score is 0.69 (95% CI [0.572, 0.833], *P*=0.00011). Time to worsening of a global CDR score was defined as time from randomization to worsening of the global CDR score (ie, the first worsening where there is an increase from Baseline by at least 0.5 points on the global CDR score in 2 consecutive visits) (Executive Summary Figure 8).

4.3.1.8 Health-Related Quality of Life Outcomes

In Study 301, for all key health-related QoL outcomes there was a highly statistically significant difference between placebo and lecanemab (Executive Summary Figure 9). In the early stage of AD, patients are the best informant for assessing their own QoL (rather than by care partner proxy) (Hauber, et al., 2023). Therefore, the summaries of EQ-5D-5L and QoL-AD are focused

on the patient's own assessment. The Zarit Burden Interview of Study Partner Score is presented to capture the care partner QoL.

There was a highly statistically significant difference between placebo and lecanemab on change from Baseline for EQ-5D-5L Health Today Patient at 18 months, with an adjusted mean treatment difference of 2.017, 49.1% less decline with lecanemab compared to placebo, *P*=0.00383. There was a highly statistically significant difference between placebo and lecanemab on change from Baseline for QoL-AD Total Score (adjusted mean treatment difference of 0.657, 55.6% less decline, *P*=0.00231). There was a highly statistically significant difference between placebo and lecanemab on change from Baseline for Zarit Burden Interview of Study Partner Score (adjusted mean treatment difference of -2.211, 38.4% less decline, *P*=0.00002).

4.3.1.9 Sensitivity and Supplementary Analyses

Sensitivity and supplementary analyses were also conducted for the mITT FAS+, with all results consistent (*P*<0.001) with the main analysis for the mITT FAS+ (Table 17).

The tipping point analysis assessed how severe departures must be from the missing at random (MAR) assumption to overturn the conclusion of the primary analysis. Adding the shift parameter (delta) to only lecanemab created a missing not at random trajectory in which lecanemab patients performed worse post discontinuation than was predicted by the observed data based on the MAR assumption. The delta required to overturn the primary analysis (tipping point) was 1.5. With delta=1.0, statistically significant difference between placebo and lecanemab was still seen (*P*<0.05). A tipping point of 1.5 implies that patients who discontinued from study in lecanemab must progress far faster than placebo patients in order to reach a non-significant result (ie, mean change of 2.7 for lecanemab subjects who discontinued versus 1.66 mean change of placebo). Similarly, statistical significance was overturned when improvement of 1.5 was added to placebo patients that discontinued from study. This suggests placebo patients who discontinued from the study must show far more slowing than mean placebo (0.16 for placebo patients who discontinued vs 1.66 mean change of placebo). Because the deltas associated with the tipping points were not plausible, results from the primary analysis were robust to plausible departures from MAR.

Table 17 Change from Baseline in CDR-SB Score at 18 Months – Sensitivity and Supplementary Analyses – Study 301 Double-Blind

Type of Sensitivity or Supplementary Analysis	Adjusted Mean Change From Baseline for Placebo	Adjusted Mean Change From Baseline for Lecanemab	Adjusted Mean Difference (Lecanemab – Placebo)	95% CI for Difference	*P*-value
Rank ANCOVA with missing data imputed via multiple imputation approach Analysis set = mITT FAS+	NA	NA	-0.456*	(-0.737, -0.176)**	<0.001
Primary MMRM on all randomized patients*** Analysis set = Randomized Set	1.659	1.225	-0.434	(-0.644, -0.224)	<0.001
Primary MMRM with randomization stratification variables based on IxRS classification Analysis set = mITT FAS+	1.669	1.217	-0.452	(-0.670, -0.234)	<0.001
Primary MMRM with log-transformed endpoint as response variable Analysis set = mITT FAS+	1.456	1.039	-0.416	NA	<0.001
Primary MMRM censoring assessments after initiation/dose adjustment of symptomatic AD drug or treatment discontinuation Analysis set = mITT FAS+	1.543	1.137	-0.406	(-0.623, -0.189)	<0.001
Primary MMRM on per-protocol participants Analysis set = per-protocol	1.578	1.141	-0.436	(-0.657, -0.216)	<0.001
Primary MMRM censoring assessments after occurrence of ARIA (ARIA-E or ARIA-H) Analysis set = mITT FAS+	1.675	1.151	-0.524	(-0.750, -0.298)	<0.001
Primary MMRM censoring assessments after occurrence of ARIA-E Analysis set = mITT FAS+	1.672	1.169	-0.503	(-0.726, -0.279)	<0.001
Primary MMRM censoring assessments after occurrence of ARIA-H Analysis set = mITT FAS+	1.661	1.162	-0.499	(-0.721, -0.277)	<0.001
Primary MMRM censoring assessments after occurrence of infusion-related reactions Analysis set = mITT FAS+	1.720	1.269	-0.451	(-0.694, -0.208)	<0.001
Primary MMRM with imputation by placebo after study discontinuation due to treatment-related adverse events Analysis set = mITT FAS+	1.649	1.182	-0.468	(-0.683, -0.252)	<0.001
Primary MMRM repeated to evaluate impact of COVID Analysis set = FDA FAS	1.603	1.208	-0.394	(-0.613, -0.176)	<0.001

AD = Alzheimer's disease, ANCOVA = analysis of covariance, ARIA = amyloid-related imaging abnormalities, ARIA-E = amyloid-related imaging abnormality-edema/effusion, ARIA-H = amyloid-related imaging abnormality-microhemorrhage and hemosiderin deposit, CDR-SB = Clinical Dementia Rating - Sum of Boxes, COVID = coronavirus disease, mITT = modified intent-to-treat, FAS+ = Full Analysis Set+, IxRS = interactive voice and web response system, NA = Not applicable, MMRM = mixed model for repeated measures.
*Hodges-Lehmann nonparametric estimate of median difference; ** Hodges-Lehmann non-parametric estimate of median difference and asymptotic standard error are calculated and then combined using Rubin's rules to compute the CI. ***All randomized patients (N=1795) are included. Missing values for randomized patients but not in mITT FAS+ are imputed using placebo means at each visit.

4.3.1.10 Comparison of Results in Subgroups

In Study 301, randomization was stratified by use of symptomatic AD medication at baseline (yes/no), clinical subgroup (MCI due to AD, mild AD dementia), *APOE4* carrier status (carriers, noncarriers), and geographical region (North America, Europe, Asia).

The results of subgroup analyses for 4 clinical endpoints (CDR-SB, ADAS-Cog14, ADCOMS, ADCS MCI-ADL) at 18 months showed results favoring lecanemab and were similar to the results for the overall population (mITT FAS+ [Figure 11] ADCOMS not shown).

- Analysis by use of symptomatic AD medication at Baseline (yes/no) was consistent, with a similar magnitude of effect of lecanemab over placebo for all 4 clinical endpoints.
- Analysis by clinical subgroup (MCI due to AD, mild AD) were consistent, with a similar magnitude of effect of lecanemab over placebo for all 4 clinical endpoints (CDR-SB, ADAS-Cog14, ADCOMS, ADCS MCI-ADL).
- Analysis by *APOE4* carrier status (*APOE4* carriers, *APOE4* noncarriers,) favored lecanemab for both subgroups at 18 months for all 4 clinical endpoints (CDR-SB, ADAS-Cog14, ADCOMS, ADCS MCI-ADL).
- Results favored lecanemab over placebo for all 4 clinical endpoints across all regions (North America, Europe, and Asia) with varying magnitude of effect by endpoint.

Figure 11 Lecanemab Versus Placebo by Randomization Strata – Study 301 Double-Blind (mITT FAS+)

AD = Alzheimer's Disease, ADAS-Cog14 = Alzheimer's Disease Assessment Scale - Cognitive Subscale with 14 tasks, ADCOMS = Alzheimer's Disease Composite Score, *APOE4* = apolipoprotein E4, CDR-SB = clinical dementia rating – sum of boxes, CI = confidence interval, mITT = modified intent to treat, FAS+ = full analysis set+, MCI = mild cognitive impairment.

4.3.2 Biomarker Results

Summary

- Study 301 employed a comprehensive assessment of blood, CSF, and imaging biomarkers of amyloid, tau, neurodegeneration, and gliosis
- Lecanemab improvements on biomarkers of amyloid, tau, neurodegeneration, and gliosis provide a biological basis for lecanemab's treatment effect and are consistent with slowing of disease progression

AD is characterized by early accumulation of amyloid, then development of neurofibrillary tangles, neurodegeneration, and gliosis/inflammatory changes. Study 301 employed a comprehensive assessment of blood, CSF and imaging biomarkers of amyloid, tau, neurodegeneration, and gliosis to provide the biologic rationale of the observed clinical outcomes. Together with the clinical data, the favorable effects of lecanemab treatment on most biomarkers of amyloid, tau, neurodegeneration, and gliosis provide a biological basis for lecanemab's treatment effect and are consistent with slowing of disease progression.

4.3.2.1 Amyloid

Lecanemab improved markers of amyloid with reduction of brain amyloid by PET in as early as 3 months (Executive Summary Figure 3) and improvement in CSF Aβ[1–42] and plasma Aβ42/40 (Figure 12).

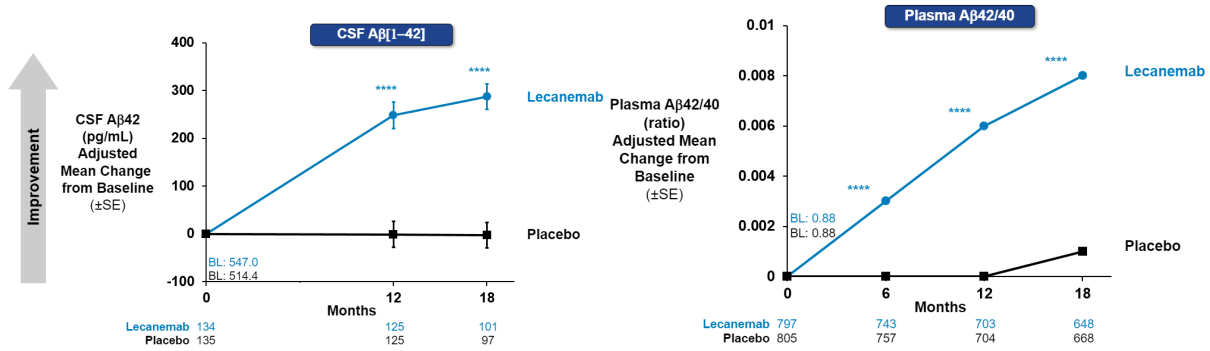

Figure 12 Adjusted Mean (± SE) Change from Baseline in CSF Aβ[1-42] (left) and Plasma Aβ42/40 (right) by Visit – Study 301 Double-Blind (PD Analysis Set)

Aβ42/40 = ratio of Aβ[1-42] to Aβ[1-40], Aβ[1-40] = amyloid beta monomer from amino acid 1 to 40, Aβ[1-42] = amyloid beta monomer from amino acid 1 to 42, CSF = cerebrospinal fluid, PD = pharmacodynamics, SE = standard error.
Statistical scale: * P<0.05, ** P <0.01, *** P <0.001, **** P <0.0001, ***** P <0.00001.

4.3.2.2 Tau

Biomarkers of tau showed improvement in CSF and plasma p-tau181 (Figure 13).

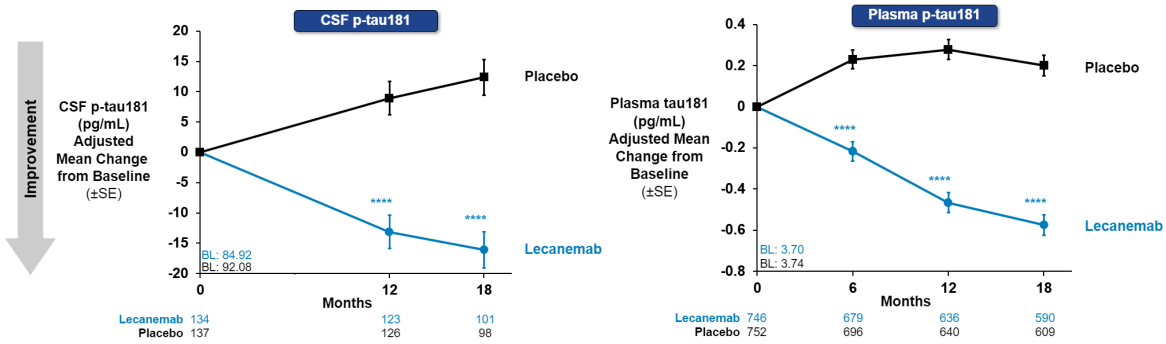

Figure 13 Adjusted Mean (± SE) Change from Baseline in CSF p-tau181 (left) and Plasma p-tau181 (right) by Visit – Study 301 Double-Blind (PD Analysis Set)

CSF = cerebrospinal fluid, PD = pharmacodynamics, p tau181 = human tau protein phosphorylated at threonine in position 181, SE = standard error.
Statistical scale: * P <0.05, ** P <0.01, *** P <0.001, **** P <0.0001, ***** P <0.00001.

TAU PET

In Study 301, there was a statistically significant difference in the change from Baseline in brain tau pathology in 3 composite regions known to accumulate tau early in the disease (ie, temporal, medial temporal, and meta-temporal) as measured by tau PET SUVR (ventral cerebellum reference region) at 18 months in lecanemab compared to placebo (medial temporal region of interest (ROI): adjusted mean treatment difference -0.068, P=0.00237; meta-temporal ROI: adjusted mean treatment difference -0.071, P=0.01195; temporal ROI: adjusted mean treatment difference 0.065, P=0.01619), and the difference was seen as early as 13 months, the first timepoint measured (Figure 14).

These temporal regions, known to accumulate tau early in the disease process, had the highest tau PET SUVR levels at Baseline compared to other brain regions in both placebo and lecanemab.

No statistically significant effects were observed at 18 months on the global tau load on the change from Baseline in occipital, parietal, cingulate, and frontal regions or in the whole cortical gray matter.

Extent of treatment effect is proportional to Baseline level of Tau signal. In placebo, the regions with higher Tau accumulation are those with higher Baseline Tau, ie, temporal regions have the highest Baseline Tau levels ad greatest Tau accumulation at 18 months. Lecanemab slows down Tau accumulation at 18 months in all regions, and this is statistically significant for temporal regions.

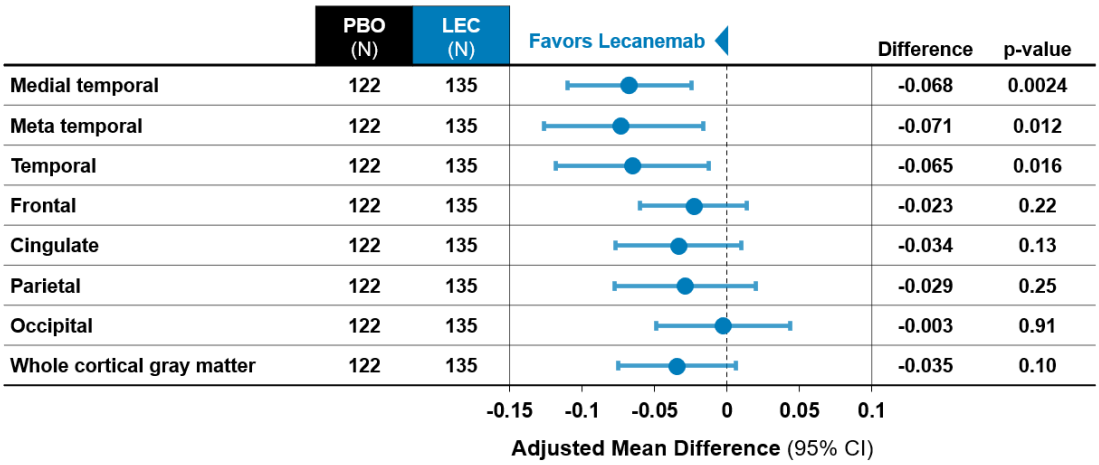

Figure 14 Adjusted Mean (± SE) Change from Baseline in tau PET SUVR Composite for Brain Tau Levels at 18 Months – Study 301 Double-Blind (PD Analysis Set [Tau PET])

Only PET data using 18F-MK6240 tracer is included.
PD = pharmacodynamics, PET = positron emission tomography, ROI = region of interest, SE = standard error.
SUVR = standard uptake value ratio.

4.3.2.3 Neurodegeneration/Gliosis

For biomarkers of neurodegeneration and gliosis, while there were no significant differences between lecanemab and placebo in CSF or plasma NfL (Figure 15) there was improvement in CSF t-tau, CSF neurogranin, and plasma glial fibrillary acidic protein (GFAP) (Figure 16).

Lecanemab demonstrated inconsistent findings with brain volume, with slight preservation of hippocampal volume, but reduction in cortical volume. Volume loss in the absence of neurodegeneration has been termed "pseudoatrophy", attributed to volume reduction from reductions in plaque, dystrophic neurites, and inflammation (astrocytosis, microgliosis); there may also be antibody mediated fluid shifts (AlzForum, 2023).

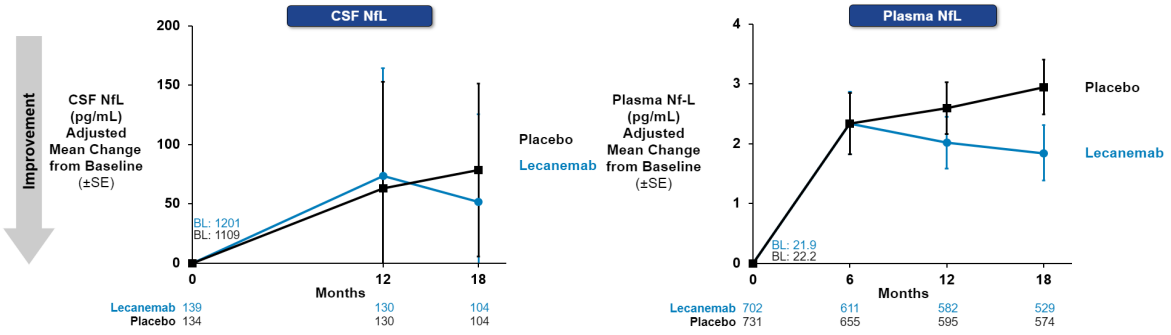

Figure 15 Adjusted Mean (± SE) Change from Baseline in CSF NfL (left) and Plasma NfL (right) – Study 301 Double-Blind (PD Analysis Set)

CSF = cerebrospinal fluid, NfL = neurofilament light chain, PD = pharmacodynamics, SE = standard error.
Statistical scale: * $P<0.05$, ** $P<0.01$, *** $P<0.001$, **** $P<0.0001$.

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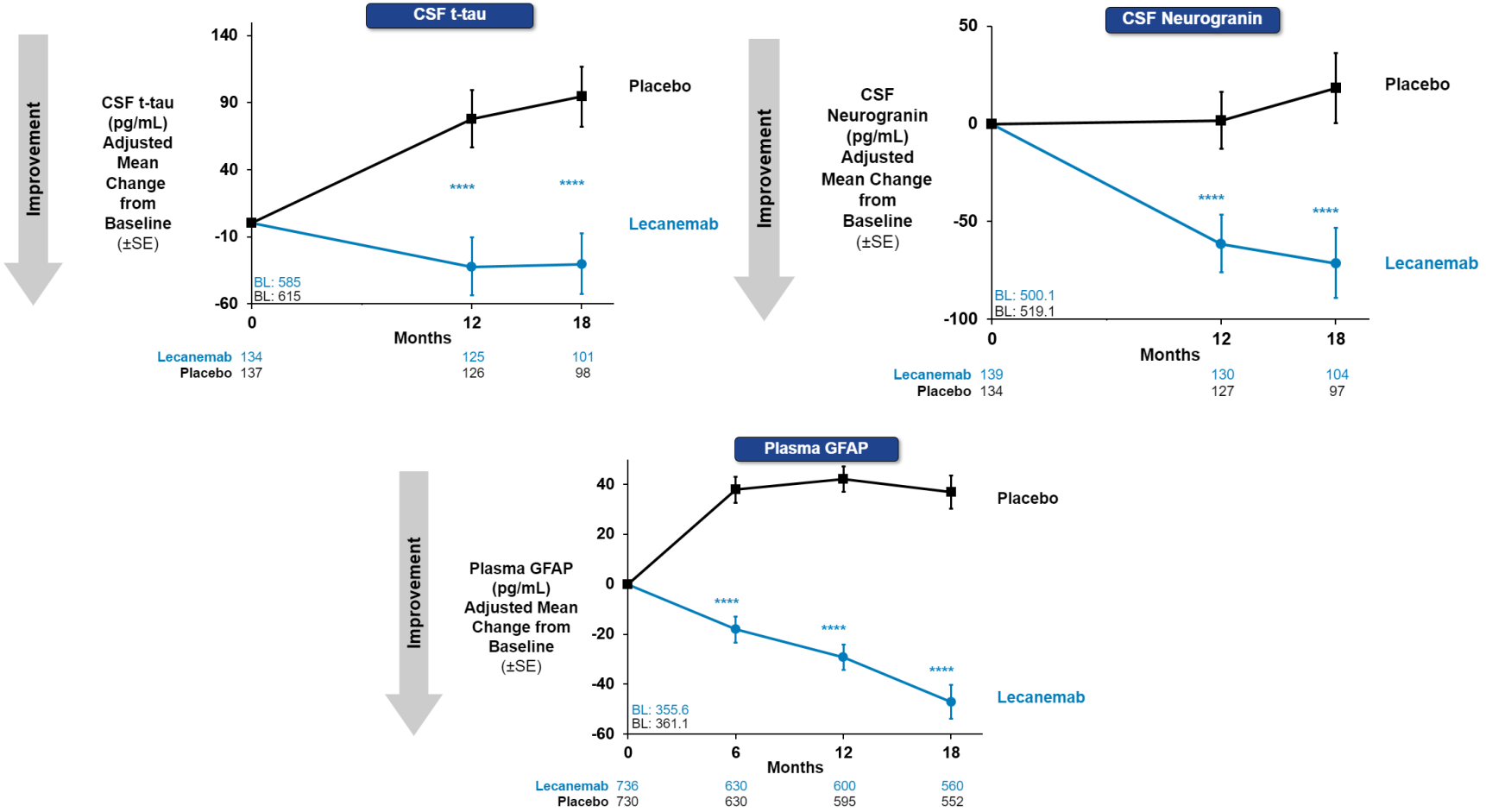

Figure 16 Adjusted Mean (± SE) Change from Baseline in CSF T-tau (top left) CSF Neurogranin (top right) and Plasma GFAP (bottom) by Visit – Study 301 Double-Blind (PD Analysis Set)

CSF = cerebrospinal fluid, GFAP = glial fibrillary acidic protein, PD = pharmacodynamics, SE = standard error, t-tau = total tau.
Statistical scale: * $P<0.05$, ** $P<0.01$, *** $P<0.001$, **** $P<0.0001$.

4.4 Safety Results

Summary

- Safety results from Study 301 confirm the safety profile in the approved USPI, including the known adverse drug reactions (ADRs) of infusion-related reaction, ARIA-E, and ARIA-H
- Excluding ADRs, the incidence of AEs, serious AEs and AEs leading to discontinuation were similar between placebo and lecanemab
- No differences were seen in the type and rate of AEs observed during the course of long-term treatment with lecanemab with the exception of infusion-related reactions and ARIA-E, both of which occurred early during treatment
- The incidence of deaths were similar in placebo and lecanemab

4.4.1 Exposure

In Study 301, 897 patients were randomized to placebo and 898 to lecanemab. All randomized patients were treated. A total of 816 patients were exposed to lecanemab for at least 6 months, 765 patients were exposed to lecanemab for at least 12 months, and 698 patients were exposed to lecanemab for at least 18 months. Overall, in Study 301, the mean duration of exposure was 16.49 months for placebo and 15.74 months for lecanemab (Table 18).

Table 18 Cumulative Extent of Exposure – Study 301 Double-Blind (Safety Analysis Set)

Extent of Exposure	Placebo (N=897)	Lecanemab (N=898)
Duration (months[a]), n (%)		
>0 weeks	897 (100.0)	898 (100.0)
≥3 months	880 (98.1)	841 (93.7)
≥6 months	860 (95.9)	816 (90.9)
≥12 months	800 (89.2)	765 (85.2)
≥18 months	731 (81.5)	698 (77.7)
Duration of exposure (months)		
n	897	898
Mean (SD)	16.49 (3.928)	15.74 (5.040)
Median	18.03	18.03
Min, Max	0.5, 20.0	0.5, 18.8
Total duration (patient-years)[b]	1232.99	1177.92

Max = maximum, Min = minimum, SD = standard deviation.
a: Duration (months) = ([date of last dose – date of first dose +1]/ 7 + 1 treatment cycle)/ 52*12. Treatment cycle is 2 weeks. Extent of exposure for ≥3 months, ≥6 months, ≥12 months, ≥18 months use 2-weeks window (ie, 2.538 months, 5.538 months, 11.538 months, 17.538 months, respectively).
b: Total duration (patient-years) = summation over all patients' exposure durations.

4.4.2 Adverse Events

In Study 301, the overall incidence of AEs was lower in placebo (82.2%) than lecanemab (89.1%) (Executive Summary Table 5). Excluding infusion-related reactions, ARIA-E, and ARIA-H, the incidence was similar between placebo (80.4%) and lecanemab (83.4%).

The incidence of AEs leading to study drug discontinuation was lower in placebo 28 (3.1%) than lecanemab 65 (7.2%). This lower incidence in placebo is expected due to the management of infusion-related reactions and ARIA-E, which were less common in placebo than lecanemab. Excluding the infusion-related reactions, ARIA-E, and ARIA-H, the incidence of AEs leading to study drug discontinuation was similar between placebo (2.9%) and lecanemab (3.3%).

The incidence of the most common (≥5%) AEs are listed in Table 19 and include:

- Infusion related reaction: placebo 7.1%, and lecanemab 26.3%
- Amyloid-related imaging abnormality-microhemorrhage and hemosiderin deposit (a preferred term for cerebral microhemorrhage): placebo 7.7% and lecanemab 14.0% with exposure-adjusted rates (patient-years) of placebo 0.06, and lecanemab 0.11
- ARIA-E: placebo 1.7%, and lecanemab 12.6%. Symptomatic ARIA-E was reported by 2.8% of patients overall.
- Headache: placebo 8.1%, and lecanemab 11.2%

Table 19 Adverse Events With Incidence in at Least 5% of Patients in any Treatment Group By Decreasing Frequency – Study 301 Double-Blind (Safety Analysis Set)

MedDRA Preferred Term	Placebo (N = 897) n(%)	Lecanemab (N = 898) n(%)
Patients with any AE	737 (82.2)	800 (89.1)
Infusion related reaction[a]	64 (7.1)	236 (26.3)
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	69 (7.7)	126 (14.0)
Amyloid related imaging abnormality-oedema/effusion	15 (1.7)	113 (12.6)
Headache	73 (8.1)	101 (11.2)
Fall	87 (9.7)	94 (10.5)
Urinary tract infection	82 (9.1)	78 (8.7)
COVID-19	61 (6.8)	63 (7.0)
Back pain	52 (5.8)	60 (6.7)
Arthralgia	62 (6.9)	53 (5.9)
Superficial siderosis of central nervous system	22 (2.5)	50 (5.6)
Diarrhea	58 (6.5)	49 (5.5)
Dizziness	46 (5.1)	49 (5.5)
Anxiety	39 (4.3)	45 (5.0)

Cerebral microhemorrhages include those deemed not ARIA-H by investigator.
AEs are ordered by decreasing frequency in lecanemab, then placebo group.
AE = adverse event, COVID-19 = Coronavirus disease of 2019, MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients in treatment group, n = number of patients with an event in each category.

4.4.3 Deaths

In Study 301, there were 7 deaths in placebo (7 [0.8%]) and 6 in lecanemab (6 [0.7%]). There were 2 additional deaths that, although the patients were still in the study, the deaths occurred more than 30 days after last study treatment administration (placebo 1, lecanemab 1). None of the deaths were considered related to study drug. The rate of death per patient year was 0.0065 placebo and 0.0059 lecanemab. The rate of death per patient year with concurrent ARIA irrespective of the ARIA being the cause of death was 0.0008 placebo and none for lecanemab.

In Study 301 OLE Phase (lecanemab Treated Period), there were 9 deaths as of 01 Dec 2022. The rate of death per patient year on lecanemab (double-blind + OLE Phase) was 0.0069. The rate of death per patient year with concurrent ARIA, irrespective of the cause of death, on lecanemab (double-blind + OLE Phase) was 0.0013.

Of the 24 deaths in Study 301 (double blind + OLE Phase), 3 were due to intracerebral hemorrhage: 1 in Study 301 double-blind (placebo), and 2 in Study 301 OLE Phase (lecanemab, 1 on tissue plasminogen activator (tPA) and 1 on anticoagulant therapy). Additional details on deaths reported in Study 301 are provided in Appendix 1.

4.4.4 Serious Adverse Events

In Study 301, the incidence of serious AEs was similar between placebo (11.3%) and lecanemab (14.0%) (Table 20). Excluding events of infusion related reactions, ARIA-E, and ARIA-H, the incidence of serious AEs was similar between placebo (11.3%) and lecanemab (12.4%). The majority of serious AEs occurred in 2 or fewer patients.

Laboratory abnormalities considered serious AEs in the lecanemab clinical program included System Organ Classes (SOCs) of blood and lymphatic system disorders, investigations, and metabolism and nutrition disorders. In Study 301, the incidence of laboratory abnormalities considered serious AEs were similar between placebo (7 [0.8%]) and lecanemab (8 [0.9%]).

Table 20 Serious Adverse Events Occurring in ≥3 Patients by Decreasing Frequency – Study 301 Double-Blind (Safety Analysis Set)

MedDRA Preferred Term	Placebo (N = 897) n (%)	Lecanemab (N = 898) n (%)
Patients with any Serious AE	101 (11.3)	126 (14.0)
Infusion-related reaction	0	11 (1.2)
Amyloid related imaging abnormality-oedema/effusion	0	7 (0.8)
Atrial fibrillation	3 (0.3)	6 (0.7)
Syncope	2 (0.2)	6 (0.7)
Angina pectoris	0	6 (0.7)
Diverticulitis	1 (0.1)	4 (0.4)
Non-cardiac chest pain	0	4 (0.4)
Pneumonia	3 (0.3)	3 (0.3)
Subdural hematoma	3 (0.3)	3 (0.3)
Hip fracture	2 (0.2)	3 (0.3)
Inguinal hernia	2 (0.2)	3 (0.3)
Transient ischemic attack	2 (0.2)	3 (0.3)
Fall	1 (0.1)	3 (0.3)
Cerebral hemorrhage	0	3 (0.3)
Acute respiratory failure	3 (0.3)	2 (0.2)
Osteoarthritis	3 (0.3)	2 (0.2)
COVID-19	2 (0.2)	2 (0.2)
Dehydration	2 (0.2)	2 (0.2)
Cerebrovascular accident	1 (0.1)	2 (0.2)
Femoral neck fracture	1 (0.1)	2 (0.2)
Ankle fracture	3 (0.3)	1 (0.1)
Prostate cancer	3 (0.3)	1 (0.1)
Pulmonary embolism	3 (0.3)	1 (0.1)
Myocardial infarction	2 (0.2)	1 (0.1)
Confusional state	3 (0.3)	0
Spinal compression fracture	3 (0.3)	0

Patient with two or more AEs with the same preferred term was counted only once for that preferred term.
Cerebral microhemorrhages include those deemed not ARIA-H by investigator.
AEs were ordered by decreasing frequency in the lecanemab group, then the placebo group.

4.4.5 Discontinuations Due to Adverse Events and/or Laboratory Abnormalities

In Study 301, the incidence of AEs leading to discontinuation of study drug was lower in placebo (3.1%) than lecanemab (7.2%) (Table 21). Excluding discontinuations due to events of infusion-related reactions, ARIA-E, and ARIA-H, the incidence of AEs leading to discontinuation of study drug was similar between placebo (26 [2.9%]) and lecanemab (30 [3.3%]).

The most common (≥2 patients in either placebo or lecanemab) AEs leading to discontinuation of study drug are listed below.

- Placebo: myocardial infarction (2 [0.2%]), subdural hematoma (2 [0.2%])
- Lecanemab: depression (2 [0.2%]), superficial siderosis of central nervous system (4 [0.4%]), amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits (a PT for cerebral microhemorrhage) (15 [1.7%]), ARIA-E (14 [1.6%]), infusion related reaction (12 [1.3%])

There were 3 discontinuations due to laboratory abnormalities reported, including 1 event of hepatic enzyme increased (placebo 1 [0.1%]), 1 event of hyperglycemia (lecanemab 1 [0.1%]), and 1 event of thrombocytopenia (lecanemab 1 [0.1%]).

Table 21 Adverse Events Leading to Discontinuation of Study Drug by System Organ Class and Preferred Term Occurring in ≥2 Patients in Any Treatment Group – Study 301 Double-Blind (Safety Analysis Set)

MedDRA System Organ Class Preferred Term	Placebo (N=897) n (%)	Lecanemab (N=898) n (%)
Patients with any AE leading to discontinuation from study drug	28 (3.1)	65 (7.2)
Cardiac disorders		
Myocardial infarction	2 (0.2)	1 (0.1)
Injury, poisoning and procedural complications		
Infusion related reaction	1 (0.1)	12 (1.3)
Subdural hematoma	2 (0.2)	1 (0.1)
Nervous system disorders		
Amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits	1 (0.1)	15 (1.7)
Amyloid related imaging abnormality-oedema/effusion	0	14 (1.6)
Superficial siderosis of central nervous system	0	4 (0.4)
Psychiatric disorders		
Depression	0	2 (0.2)

Patient with 2 or more AEs in the same system organ class (or with the same preferred term) was counted only once for that system organ class (or preferred term). Cerebral microhemorrhages include those deemed not ARIA-H by investigator.
AE = adverse event, ARIA–H = amyloid-related imaging abnormality-hemorrhage, MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients in treatment group, n = number of patients with an event in each category.

4.4.6 Selected Adverse Events of Interest to the Proposed Indication

Summary

- Infusion-related reactions reported with lecanemab are typically of lower grades of severity, generally occurred only with the first infusion, led to low rates of discontinuation, and have a low recurrence rate
- ARIA-E occurs early in treatment, is mostly asymptomatic, resolves spontaneously regardless of radiographic severity, and asymptomatic radiographically mild ARIA-E can be dosed through without interruption.
- Increasing number of E4 alleles is a risk factor for ARIA-E; however, the clinical course of ARIA-E remains unchanged.
- Consistent with the approved USPI, most ARIA-E occurred within the first 3 months of treatment, irrespective of *APOE4* genotype, and the majority resolved radiographically by 4 months.
- The incidence of symptomatic ARIA-E was low (~3%) in patients treated with lecanemab.
- ARIA-H events tend to occur concurrently with ARIA-E events.
  - Isolated ARIA-H (ARIA-H in patients who did not also experience ARIA-E) consisting of microhemorrhage and superficial siderosis and excluding intracerebral hemorrhage is randomly distributed throughout the treatment period, were similar to placebo in frequency and distribution, almost always asymptomatic, and do not require alterations in dosing.
  - Increasing number of E4 alleles is a risk factor for ARIA-H; however, the clinical course of ARIA-H remains unchanged.
- There was no increase in ARIA-E, ARIA-H in patients who were on lecanemab and antithrombotics relative to those on lecanemab alone. The number of intracerebral hemorrhage cases was small, limiting risk assessment of concomitant antithrombotics.

4.4.6.1 Infusion-Related Reactions

Investigators were instructed that infusion related reactions were AEs of special interest and to collect these data with heightened vigilance on a dedicated eCRF page to collect symptoms of the reaction. This increased vigilance is illustrated by the 7.4% rate reported for placebo.

The incidence of infusion-related reactions (predefined in the SAP as preferred terms “infusion related reaction” and “infusion site reaction”) was lower in placebo (66/897 [7.4%]) than lecanemab (237/898 [26.4%]). In the overall population, most AEs of infusion-related reactions were mild or moderate in severity with most being Grade 1 (placebo 41/897 [4.6%]; lecanemab 78/898 [8.7%]) or Grade 2 (placebo 25/897 [2.8%]; lecanemab 149/898 [16.6%]) (Table 22). No patient in placebo reported Grade 3 or Grade 4 infusion-related reactions. In the overall lecanemab population, 6/898 (0.7%) patients and 1/898 (0.1%) patients reported Grade 3 or Grade 4 infusion-related reactions, respectively. Of these Grade 3 or Grade 4 infusion-related reactions, 6 occurred with the first dose.

The majority of infusion-related reactions in lecanemab occurred with the first infusion, (placebo 26/66 [39.4%]; lecanemab 178/237 [75.1%]). Most patients who reported infusion-related reactions returned for the next study visit/next infusion (placebo 64/66 [97.0%]; lecanemab 222/237 [93.7%]). Some patients received premedication medications either before infusion or during infusion reactions (eg, ibuprofen, paracetamol, and diphenhydramine). These medications did not impact the rate of recurrence or severity of infusion reactions.

Table 22 Summary of Infusion-Related Reactions by Maximum Grade – Study 301 Double-Blind (Safety Analysis Set)

NCI-CTCAE Grade	Placebo (N = 897) n (%)	Lecanemab (N = 898) n (%)
Any grade	66 (7.4)	237 (26.4)
Grade 1	41 (4.6)	78 (8.7)
Grade 2	25 (2.8)	149 (16.6)
Grade 3	0	6 (0.7)
Grade 4	0	1 (0.1)
Grade 5	0	0
Missing	0	3 (0.3)

Grade 1: mild reaction, infusion interruption not indicated, intervention not indicated, Grade 2: infusion interruption or treatment indicated, but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDs], IV fluids); prophylactic medications indicated for <24 hours, Grade 3: prolonged (eg, not rapidly responsive to symptomatic medications and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization required for clinical sequelae (eg, renal impairment), Grade 4: life-threatening consequences; urgent treatment needed (eg, vasopressor or ventilatory support), Grade 5: death.
A patient with multiple severity grades within category was only counted under the maximum grade in each relevant category.
AE = adverse event, NCI-CTCAE = Common Terminology Criteria for Adverse Events, IV = intravenous, MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients in treatment group, n = number of patients with an event in each category.

Of the 898 patients treated with lecanemab, 7 (0.8%) patients experienced severe infusion-related reactions and almost all resolved between Days 1 and 4 post reaction, and all were discharged without further incident. All were discontinued from study drug per protocol. No placebo patients experienced severe infusion-related reactions.

Details of the Grade 3 or Grade 4 infusion-related reactions are provided in Appendix 2.

There were few AEs of infusion-related reaction leading to study drug interruption (placebo 6/897 [0.7%], lecanemab 14/898 [1.6%]) or infusion interruption (placebo 1/897 [0.1%], lecanemab 9/898 [1.0%]); these patients received subsequent infusions.

Infusion-related reactions were reported for 237 lecanemab patients, 222 who continued to next visit for a subsequent infusion.

Of these 222 patients, 97/222 (43.7%) received at least 1 premedication with subsequent infusions. Of these 97 patients, 36/97 (37.1%) had subsequent infusion-related reactions and 61/97 (62.9%) did not have subsequent infusion-related reactions.

Of these 222 patients, 125 (125/222 [56.3%]) did not receive a premedication with subsequent infusions. Of these 125 patients, 44/125 (35.2%) had subsequent infusion-related reactions and 81/125 (64.8%) did not have subsequent infusion-related reactions.

There was a similar rate of recurrence regardless of use of premedication. Comparing patients who took premedication with the first infusion-related reaction with those who did not, there was no difference in preventing subsequent infusion-related reactions nor in severity of subsequent infusion-related reactions.

Infusion-related reactions were reported for 66 placebo patients, of these, 64 patients continued to next visit.

Of these 64 patients, 7/64 (10.9%) patients received at least 1 premedication prior to subsequent infusions and of these, 2/7 (28.6%) patients did not have subsequent infusion-related reaction. The remaining 57/64 (89.1%) patients did not receive a premedication prior to subsequent infusions. Of these 57 patients, 39/57 (68.4%) did not have subsequent infusion-related reactions.

4.4.6.2 ARIA-E

In Study 301, the overall incidence of ARIA-E was lower in placebo (15 [1.7%]) than lecanemab (113/898 [12.6%]) (Table 23).

In placebo and lecanemab, the incidence of ARIA-E was higher in *APOE4* carriers (placebo 14/611 [2.3%]; lecanemab 98/620 [15.8%]) than *APOE4* noncarriers (placebo 1/286 [0.3%]; lecanemab 15/278 [5.4%]). Of the *APOE4* carriers, the incidence of ARIA-E was lower in heterozygous *APOE4* carriers (placebo 9/478 [1.9%]; lecanemab 52/479 [10.9%]) than in homozygous *APOE4* carriers (placebo 5/133 [3.8%]; lecanemab 46/141 [32.6%]).

Table 23 Summary of ARIA-E – Study 301 Double-Blind (Safety Analysis Set)

ARIA Term	Placebo (N = 897) n/m (%)	Lecanemab (N = 898) n/m (%)
ARIA-E	15 (1.7)	113 (12.6)
APOE4 noncarriers	1/286 (0.3)	15/278 (5.4)
APOE4 carriers	14/611 (2.3)	98/620 (15.8)
APOE4 heterozygous carriers	9/478 (1.9)	52/479 (10.9)
APOE4 homozygous carriers	5/133 (3.8)	46/141 (32.6)

A patient with 2 or more events is counted only once for that event.
APOE4 carrier and noncarrier status and genotype are based on actual lab data.
AE = adverse event, *APOE4* = apolipoprotein E4, ARIA = amyloid-related imaging abnormalities, ARIA-E = amyloid-related imaging abnormality-edema/effusion, m = number of patients in each category, N = number of patients in treatment group, n = number of patients with an event in each category.

ARIA-E events in placebo were randomly distributed over the course of treatment. For the first episode of ARIA-E, most cases of lecanemab ARIA-E occurred within the first 3 months of treatment (lecanemab 80/113 [70.8%]) and the time to occurrence was similar by *APOE4* carrier status and genotype (Executive Summary Figure 10).

Most ARIA-E were radiographically mild in severity (placebo 9/897 [1.0%]; lecanemab 37/898 [4.1%]) or moderate (placebo 6/897 [0.7%]; lecanemab 66/898 [7.3%]); with no patients in placebo and 9 (1.0%) in lecanemab categorized as having radiographically severe

ARIA-E. The percentage of radiographically moderate ARIA-E was higher in the homozygous *APOE4* carriers.

Of the 113 lecanemab patients who were diagnosed with ARIA-E, radiographic severity was as follows (note 1 subject had missing radiographic severity):

- Mild: 37/113 (32.7%)
- Moderate: 66/113 (58.4%)
- Severe: 9/113 (8.0%)
- *APOE4* noncarriers (15 total): moderate ARIA-E, 9/15 [60%] and no severe ARIA-E
- Heterozygous *APOE4* carriers (52 total): moderate ARIA-E, 24/52 (46.2%); severe ARIA-E, 2/52 (3.84%)
- Homozygous *APOE4* carriers (46 total): moderate ARIA-E, 33/46 (71.7%); severe ARIA-E, 7/46 (15.2%)

The incidence of symptomatic ARIA-E was low, with no patients in placebo and 25/898 (2.8%) in lecanemab overall.

Of the 25 lecanemab patients who were reported to have symptomatic ARIA-E, the distribution of clinical severity was similar across genotypes:

- *APOE4* noncarriers (4 symptomatic cases in 278 noncarriers): 3 moderate ARIA-E and no severe ARIA-E
- Heterozygous *APOE4* carriers (8 symptomatic cases in 479 heterozygous *APOE4* carriers): 2 moderate ARIA-E and 2 severe ARIA-E
- Homozygous *APOE4* carriers (13 symptomatic cases in 141 homozygous *APOE4* carriers): 7 moderate ARIA-E and 1 severe ARIA-E

Symptoms associated with ARIA-E AEs were not captured as separate AEs in the study database but were captured in ARIA-E CRFs. Preferred terms for symptoms occurring in more than 1 patient in lecanemab with ARIA-E were headache (12 patients), confusional state (4 patients), dizziness (3 patients), and nausea (3 patients).

In the overall patient population, there were no serious AEs due to ARIA-E in placebo and 7/898 (0.8%) in lecanemab (*APOE4* noncarriers 2/278 [0.7%]; heterozygous *APOE4* carriers 2/479 [0.4%], homozygous *APOE4* carriers 3/141 [2.1%]).

There were no cases of ARIA-E leading to study discontinuation in placebo and 14/898 (1.6%) in lecanemab.

In both treatment groups, most patients experienced ARIA-E without recurrence, with 1/897 (0.1%) placebo patient and 28/898 (3.1%) lecanemab patients experiencing a second event. No placebo patients and 4/898 (0.4%) lecanemab patients experienced a third occurrence. One (1/898 [0.1%]) lecanemab patient experienced 4 episodes of ARIA-E.

The recurrence rate by *APOE4* genotype was:

- Placebo 1/897 (0.1%), lecanemab 28/898 (3.1%)
- Homozygous carriers: placebo 1/133 (0.8%), lecanemab 20/141 (14.2%)
- Heterozygous carriers: placebo 0/487 (0%), lecanemab 7/479 (1.5%)
- Noncarriers carriers: placebo 0/286 (0%), lecanemab 1/278 (0.4%)

Resolution is defined by resolution of both radiographic and clinical signs and symptoms of ARIA-E. The majority (81%) of ARIA-E resolved by 4 months from initial diagnosis. All 113 cases of first ARIA-E in patients treated with lecanemab resolved. In placebo, of the 15 patients experiencing first ARIA-E, 12 resolved and 3 remained ongoing.

Per protocol, patients with asymptomatic and radiographically mild ARIA-E could continue to receive study drug administration without interruptions. In lecanemab, approximately one-third (34/113) of patients with ARIA-E continued dosing during the first ARIA-E with resolution while dosing continued. The remainder (68/113) of patients with ARIA-E had dose interruption. Of patients who continued dosing, time to resolution was similar to those patients who interrupted dosing. In placebo, approximately one half (9/15) of patients with ARIA-E continued dosing during the first ARIA-E with resolution. The remainder (6/15) of patients with ARIA-E had dose interruption.

- Of the 68 lecanemab patients who interrupted dosing, most (62/68) resumed dosing during the study with a mean time to resolution of 2.9 months.

Investigators were permitted to continue dosing without interruption for radiographically mild asymptomatic ARIA-E. Fifty-four patients had radiographically mild ARIA-E at onset:

- 10 of the 54 patients had dose interruption, per investigator decision, after the first MRI with ARIA-E, and the ARIA-E resolved
- 32 of the 54 patients had ARIA-E that resolved spontaneously without dose interruption
- 12 of the 54 patients continued dosing after the first MRI with ARIA-E, the ARIA-E became radiographically moderate and had dose interruptions, then the patients' ARIA-E resolved
- All 54 patients' ARIA-E resolved

The overall incidence of ARIA-E by the subgroup analyses of age (<65 years, ≥65 years), sex (male, female), race (White, Black or African American, Asian) was generally similar:

- By age: the incidence of ARIA-E for lecanemab was similar across age strata (<65 years 14.3% and ≥65 years 12.2%)
- By sex: the incidence of ARIA-E for lecanemab was similar by sex (males 11.7%, females 13.4%)
- By race: the rates of ARIA-E for lecanemab were lower in Asians (6.5%) and Black or African American patients (a much smaller group) (9.1%) than White patients (13.6%)

4.4.6.3 ARIA-H and Intracerebral Hemorrhage

ARIA-H is comprised of microhemorrhage, superficial siderosis, and uncommon intracerebral hemorrhage. ARIA-H can occur with or without concurrent ARIA-E. ARIA-H that occurs without ARIA-E is known as isolated ARIA-H. For Study 301, ARIA-H is described in this section as 1) isolated ARIA-H events not associated with ARIA-E and 2) ARIA-H concurrent with ARIA-E, with detailed characterization of overall ARIA-H.

Isolated ARIA-H

In Study 301, the incidences of isolated ARIA-H were similar in placebo (70/897 [7.8%]) and lecanemab (80/898 [8.9%]) (Table 24). For placebo, the incidence of isolated ARIA-H increased with increasing number of E4 alleles: *APOE4* noncarriers (11/286 [3.8%]), heterozygous *APOE4* carriers (35/478 [7.8%]) homozygous *APOE4* carriers (24/133 [18.0%]). Lecanemab showed a similar pattern of increasing frequency based on increasing number of E4 alleles. Isolated ARIA-H events occur throughout the course of treatment with similar rates in placebo and lecanemab. Rates for symptomatic isolated ARIA-H were similar between placebo (2/897 [0.2%] and lecanemab (4/898 [0.4%]). Therefore, isolated ARIA-H has similar incidence, timing, and risk factors (*APOE4*) for lecanemab and placebo, without a lecanemab related increase in incidence.

Table 24 Isolated ARIA-H – Study 301 Double-Blind (Safety Analysis Set)

ARIA Term	Placebo (N = 897) n/m (%)	Lecanemab (N = 898) n/m (%)
Isolated ARIA-H (only ARIA-H, no ARIA-E)	70 (7.8)	80 (8.9)
APOE4 noncarriers	11/286 (3.8)	23/278 (8.3)
APOE4 carriers	59/611 (9.7)	57/620 (9.2)
APOE4 heterozygous carriers	35/478 (7.3)	40/479 (8.4)
APOE4 homozygous carriers	24/133 (18.0)	17/141 (12.1)

A patient with 2 or more events is counted only once for that event.
APOE4 carrier and noncarrier status and genotype are based on actual lab data.
AE = adverse event, *APOE4* = apolipoprotein E4, ARIA = amyloid-related imaging abnormalities, ARIA-E = amyloid-related imaging abnormality-edema/effusion, ARIA-H = amyloid-related imaging abnormality-hemorrhage, m = number of patients in each category, N = number of patients in treatment group, n = number of patients with an event in each category.

Concurrent ARIA-E and ARIA-H

The overall incidence of concurrent ARIA-E and ARIA-H was lower in placebo (9/897 [1.0%]) than lecanemab (74/897 [8.2%]) (Table 25). For placebo, the incidence of concurrent ARIA-E and ARIA-H increased with increasing number of E4 alleles: *APOE4* noncarriers (1/286 [0.3%]), heterozygous *APOE4* carriers (5/478 [1.0%]), and homozygous *APOE4* carriers (3/133 [2.3%]). Lecanemab showed a similar pattern of increasing frequency based on increasing number of E4 alleles.

The onset time, distributions, and symptoms of concurrent ARIA-E and ARIA-H follow the pattern of ARIA-E. The excess incidence of ARIA-H in lecanemab is most likely due to

ARIA-H that occurs during the onset or resolution of ARIA-E.

Table 25 Concurrent ARIA-E and ARIA-H – Study 301 Double-Blind (Safety Analysis Set)

ARIA Term	Placebo (N = 897) n/m (%)	Lecanemab (N = 898) n/m (%)
Concurrent ARIA-E and ARIA-H[a]	9 (1.0)	74 (8.2)
APOE4 noncarriers	1/286 (0.3)	10/278 (3.6)
APOE4 carriers	8/611 (1.3)	64/620 (10.3)
APOE4 heterozygous carriers	5/478 (1.0)	26/479 (5.4)
APOE4 homozygous carriers	3/133 (2.3)	38/141 (27.0)

A patient with 2 or more events is counted only once for that event.
APOE4 carrier and noncarrier status and genotype are based on actual lab data.
AE = adverse event, *APOE4* = apolipoprotein E4, ARIA = amyloid-related imaging abnormalities, ARIA-E = amyloid-related imaging abnormality-edema/effusion, ARIA-H = amyloid-related imaging abnormality-hemorrhage, m = number of patients in each category N = number of patients in treatment group, n = number of patients with an event in each category.
a: Concurrent is defined as overlapping in the AE duration of 2 ARIA events.

Overall ARIA-H

The overall incidence of ARIA-H was lower in placebo (81/897 [9.0%]) than lecanemab (155/898 [17.3%]) (Table 26).

Table 26 ARIA-H Subcategories - Study 301 Double-Blind (Safety Analysis Set)

	Total		Isolated	
	Placebo (N=897) n (%)	Lecanemab (N=898) n (%)	Placebo (N=897) n (%)	Lecanemab (N=898) n (%)
ARIA-H (micro, macro, superficial)	81 (9.0)	155 (17.3)	70 (7.8)	80 (8.9)
Cerebral microhemorrhage	68 (7.6)	126 (14.0)	63 (7.0)	60 (6.7)
Superficial siderosis	21 (2.3)	50 (5.6)	13 (1.4)	23 (2.6)
Intracerebral hemorrhage[a]	2 (0.2)	6 (0.7)	1 (0.1)	4 (0.4)
Symptomatic ARIA-H	2 (0.2)	13 (1.4)	2 (0.2)	4 (0.4)
ARIA-H by *APOE4* genotype				
APOE4 noncarrier, n/m (%)	12/286 (4.2)	33/278 (11.9)	11/286 (3.8)	23/278 (8.3)
APOE4 carrier, n/m (%)	69/611 (11.3)	122/620 (19.7)	59/611 (9.7)	57/620 (9.2)
APOE4 heterozygote, n/m (%)	41/478 (8.6)	67/479 (14.0)	35/478 (7.3)	40/479 (8.4)
APOE4 homozygote, n/m (%)	28/133 (21.1)	55/141 (39.0)	24/133 (18.0)	17/141 (12.1)

APOE4 = apolipoprotein E4, ARIA = amyloid-related imaging abnormalities, ARIA-H = amyloid-related imaging abnormality-hemorrhage, N = number of patients in treatment group, n = number of patients with an event in each category, m = number of patients in each category.
a: Includes one case on placebo and one case on lecanemab with intracerebral hemorrhage > 30 days after discontinuing study medication.

A breakdown of subtypes of ARIA-H overall and by *APOE4* genotype is as follows:

- Superficial siderosis: placebo 21/897 (2.3%); lecanemab 50/898 (5.6%), with exposure adjusted rates of placebo 0.02 and lecanemab 0.04.
  - Placebo: 2/286 (0.7%) *APOE4* noncarriers, 13/478 (2.7%) heterozygous *APOE4* carriers, and 6/133 (4.5%) homozygous *APOE4* carriers
  - Lecanemab: 13/278 (4.7%) *APOE4* noncarriers, 19/479 (4.0%) heterozygous *APOE4* carriers, and 18/141 (12.8%) homozygous *APOE4* carriers
- Cerebral microhemorrhage (preferred term of amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits): placebo 68/897 (7.6%); lecanemab 126/898 (14%), with exposure adjusted rates of placebo 0.06 and lecanemab 0.11.
  - Placebo: 9/286 (3.1%) *APOE4* noncarriers, 34/478 (7.1%) were heterozygous *APOE4* carriers, and 25/133 (18.8%) were homozygous *APOE4* carriers
  - Lecanemab: 20/278 (7.2%) *APOE4* noncarriers, 58/479 (12.1%) heterozygous *APOE4* carriers, and 48/141 (34.0%) homozygous *APOE4* carriers
- Cerebral microhemorrhage >10: placebo 1/897 (0.1%); lecanemab 27/898 (3.0%)
  - Placebo: 0/286 (0%) *APOE4* noncarriers, 1/478 (0.2%) *APOE4* carriers, and 0/133 (0%) homozygous *APOE4* carriers
  - Lecanemab: 0/278 (0%) *APOE4* noncarriers, 8/479 (1.7%) heterozygous *APOE4* carriers, and 19/141 (13.5%) homozygous *APOE4* carriers
- Cerebral microhemorrhage ≤10: placebo 68/897 (7.6%); lecanemab 119/898 (13.3%)
  - Placebo: 9/286 (3.1%) *APOE4* noncarriers, 34/478 (7.1%) *APOE4* carriers, and 25/133 (18.8%) homozygous *APOE4* carriers
  - Lecanemab: 20/278 (7.2%) patients were *APOE4* noncarriers, 57/479 (11.9%) were heterozygous *APOE4* carriers, and 42/141 (29.8%) were homozygous *APOE4* carriers
- Intracerebral hemorrhage (includes one case on placebo and one case on lecanemab with event >30 days after discontinuing study medication): placebo 2/897 (0.2%); lecanemab 6/898 (0.7%)
  - Placebo: 1/286 (0.3%) patient was *APOE4* noncarrier, 1/478 (0.2%) patient was heterozygous *APOE4* carriers and there were none on homozygous *APOE4* carriers
  - Lecanemab: 1/278 (0.4%) patient was noncarrier, 3/479 (0.6%) were heterozygous *APOE4* carriers, and 2/141 (1.4%) were homozygous *APOE4* carriers
- Intracerebral hemorrhage both on placebo and lecanemab occurred randomly throughout the course of treatment (Table 27). One intracerebral hemorrhage occurred with lecanemab and concurrent anticoagulant medication (warfarin). Two patients had intracerebral hemorrhage during follow up (≥30 days after last dose of study drug): one placebo patient had intracerebral hemorrhage 128 days after placebo discontinuation (last dose Day 239 – event Day 367). One lecanemab patient on anticoagulation had intracerebral hemorrhage 41 days after drug discontinuation for ARIA-E (last dose Day 46 – event Day 85).

Table 27 ARIA-H Intracerebral Hemorrhages > 1cm – Study 301 Double-Blind (Safety Analysis Set)

Patient Identifier	Treatment Group	Treatment Emergent	Anticoagulant	Antiplatelet	ASA	Isolated ARIA-H or Concurrent with ARIA-E	*APOE4* Carrier Status (genotype)	Onset Day	Outcome	Symptomatic (Y/N)
1	Lecanemab	Y	N	Y	N	Concurrent	+/+	48	Not recovered/not resolved	N
2	Placebo	N (stopped for ARIA 61 days before)	N	N	N	Concurrent	+/-	300	Recovering/Resolving	Y
3	Lecanemab	Y	N	N	N	Isolated	+/-	441	Not resolved	Y
4	Placebo	Y	N	N	Y	Isolated	-/-	unknown	Fatal	N
5	Lecanemab	N (stopped for ARIA 39 days before)	Y	N	N	Concurrent	+/-	85	Recovering/Resolving	Y
6	Lecanemab	Y	N	N	N	Isolated	-/-	439	Not resolved	Y
7	Lecanemab	Y	Y	N	Y	Isolated	+/+	175	Recovering/Resolving	N
8	Lecanemab	Y	N	N	N	Isolated	+/-	173	Recovering/Resolving	N

Concurrent is defined as overlapping in the AE duration of 2 ARIA events. Antiplatelet use excludes aspirin. Aspirin use is designated in ASA column.
APOE4 = apolipoprotein E4, ARIA = amyloid-related imaging abnormalities, ARIA-H = amyloid-related imaging abnormality-hemorrhage, ASA = aspirin.

For lecanemab patients experiencing ARIA-H, 33/278 (11.9%) patients were *APOE4* noncarriers, 67/479 (14.0%) were heterozygous *APOE4* carriers, and 55/141 (39.0%) were homozygous *APOE4* carriers. The incidence of ARIA-H leading to discontinuation of study drug in lecanemab was higher in *APOE4* carriers (lecanemab 16 [2.6%]) than in *APOE4* noncarriers (lecanemab 2 [0.7%]).

The overall incidence of serious AEs due to ARIA-H were 1/897 (0.1%) in placebo and 5/898 (0.6%) in lecanemab. The incidence of serious ARIA-H was lower in the heterozygous *APOE4* carriers (placebo 0/478; lecanemab 1/479 [0.2%] and *APOE4* noncarriers (placebo 1/286 [0.3%]; lecanemab 2/278 [0.7%]) than in homozygous *APOE4* carriers (placebo 0/133 [0%]; lecanemab 2/141 [1.4%]).

Most ARIA-H events were radiographically mild (placebo 73/897 [8.1%]; lecanemab 97/898 [10.8%]) to moderate (placebo 5/897 [0.6%]; lecanemab 26/898 [2.9%]) in severity; with 3 (0.3%) patients in placebo and 32 (3.6%) in lecanemab reporting severe ARIA-H, mostly driven by any microhemorrhage event that resulted in a cumulative number greater than 10 microhemorrhages (27/898 [3.0%]). Similar trends were observed in all ARIA-H subcategories.

Of those lecanemab patients who reported ARIA-H, radiographic severity was as follows:

- Mild: 97/155 (62.6%)
- Moderate: 26/155 (16.8%)
- Severe: 32/155 (20.6%) on lecanemab reporting severe ARIA-H, mostly driven by any microhemorrhage event that resulted in a cumulative number greater than 10 microhemorrhages (27/155 [17.4%]).

In both treatment groups, most ARIA-H was asymptomatic overall and across the subtypes.

For the entire study population, symptomatic ARIA-H was reported in 2/897 (0.2%) patients in placebo and 13/898 (1.4%) patients in lecanemab. For lecanemab patients with ARIA-H, 13/155 (8.4%) were symptomatic. Most symptomatic cases were concurrent ARIA-E and ARIA-H. Preferred terms for symptoms occurring in more than 1 patient in lecanemab were headache (4 patients), dizziness (3 patients), and confusional state (2 patients).

Most study drug dose interruptions due to ARIA-H occurred in lecanemab patients.

- Isolated intracerebral hemorrhage: lecanemab 3/898 (0.3%) patients had drug interruptions of which 2/898 (0.2%) patients resumed study drug after drug interruption and there was 1/897 (0.1%) patient on placebo and 1/898 (0.1%) patient on lecanemab who discontinued study drug administration
- Isolated superficial siderosis: lecanemab 1/898 (0.1%) patient had drug interruptions but later resumed treatment. There were no patients on placebo with drug interruptions due to superficial siderosis. There were 2/898 (0.2%) patients on lecanemab who discontinued study drug administration and none on placebo.
- Isolated cerebral microhemorrhage: lecanemab 3/898 (0.3%) patients had study drug interruptions but later resumed treatment. In placebo, there were 3/897 (0.3%) patients who

interrupted study drug (of which, 3/897 [0.3%] later resumed treatment) and 1/897 [0.1%] discontinued treatment.

Most cases of ARIA-H with placebo or lecanemab were ongoing at the end of the double-blind treatment period. All cases of intracerebral hemorrhage with placebo or lecanemab were ongoing, which was expected as events of ARIA-H tend not to resolve radiographically.

The overall incidence of ARIA-H by the subgroup analyses of age (<65 years, ≥65 years), sex (male, female), race (white, Black or African American, Asian) was generally similar among these subgroups with some numerical differences (not considered clinically meaningful) as noted below.

- By age: incidence of ARIA-H for lecanemab was lower in patients <65 years (12.6%) compared to patients ≥65 years (18.4%)
- By sex: incidence of ARIA-H for lecanemab was similar by sex (males 18.3%, females 16.2%)
- By race: incidence of ARIA-H for lecanemab was lower in Black or African American patients (a much smaller group) (13.6%) and Asians (14.4%) compared to White patients (18.0%)

4.4.6.4 ARIA-E, ARIA-H (Microhemorrhage and Superficial Siderosis), and Intracerebral Hemorrhage, and Antithrombotic Use

There was no increase in ARIA-E or ARIA-H in patients who were on lecanemab and antithrombotics relative to those that were on lecanemab alone. The number of intracerebral hemorrhage cases was small, limiting risk assessment of concomitant use of antithrombotics (Table 28).

Table 28 ARIA Incidence by Use of Antiplatelet or Anticoagulant Therapy – Study 301 Double-Blind (Safety Analysis Set)

	ARIA-E with Concurrent ARIA-H		ARIA-H (Microhemorrhage or Superficial Siderosis)		Intracerebral Hemorrhage	
	Placebo	Lecanemab	Placebo	Lecanemab	Placebo	Lecanemab
No antiplatelet or anticoagulation at any time	6/585 (1.0%)	46/564 (8.2%)	49/585 (8.4%)	93/564 (16.5%)	1/585 (0.2%)[a]	3/564 (0.5%)
Event post any antiplatelet (aspirin or non-aspirin)	1/236 (0.4%)	19/251 (7.6%)	22/236 (9.3%)	40/251 (15.9%)	1/236 (0.4%)	1/251 (0.4%)
Event post any anticoagulation (alone or with antiplatelet)	1/76 (1.3%)	2/83 (2.4%)	7/76 (9.5%)	9/83 (10.8%)	0/76 (0%)	2/83 (2.4%)[a]

a: Includes one case on placebo and one case on lecanemab with intracerebral hemorrhage > 30 days after discontinuing study medication.

4.4.6.5 Convulsion/Seizure

The risk of convulsions is elevated in AD and convulsions have also been reported as a symptom of severe ARIA-E (Irizarry, et al., 2012). In Study 301, seizures were an infrequent symptom of ARIA-E. There were 9 patients in the study (4 placebo; 5 lecanemab) with AEs in Standardized MedDRA Query (SMQ) of convulsion (narrow). Incidence of AEs in the SMQ of convulsion (ie, seizures) unassociated with ARIA-E or ARIA-H events were infrequent and similar between treatment groups: placebo 3/897 (0.3%) and lecanemab 2/898 (0.2%). With concurrent ARIA-E or ARIA-H events: placebo 1/897 (0.1%) and lecanemab 3/898 (0.3%).

4.5 Treatment-Emergent Adverse Events Based on Exposure to Lecanemab: Long Term Use in Study 301 (Lecanemab Treated Period)

Results relevant to the safety of long-term treatment with lecanemab are derived from ongoing Study 301 OLE Phase (lecanemab Treated Period). Data presented for Study 301 OLE Phase are cumulative for any subject who received at least 1 dose of lecanemab at any time, whether in Study 301 double-blind or OLE Phase. Therefore, these data may be interpreted as a pooled presentation of all lecanemab treated subjects across the total duration of Study 301.

In Study 301 OLE Phase (lecanemab Treated Period) 505 subjects have received lecanemab for at least 24 months (mean treatment duration 17.35 months).

Overall, the most common TEAEs reported in Study 301 OLE Phase (lecanemab Treated Period) were consistent with what was reported in the double-blind:

In Study 301 OLE Phase, the most common (>10%) TEAEs: infusion related reaction (24.5%), amyloid related imaging abnormality-microhemorrhages and hemosiderin deposits (16.0%), COVID-19 (14.7%), amyloid related imaging abnormality-edema/effusion (13.6%), and headache (10.3%). The rates of these most common TEAEs were similar to what was reported for lecanemab in Study 301 double-blind: infusion related reaction (26.3%), amyloid related imaging abnormality- microhemorrhage and hemosiderin deposit (a preferred term for cerebral microhemorrhage) (14.0%), ARIA-E (12.6%), and headache (11.2%).

4.6 Immunogenicity

Summary

- Efficacy and safety were not impacted by the presence of ADA or NAb

In Study 301 ADA data analyses were based on ADA evaluable patients, which are defined as patients who were treated with lecanemab and had valid baseline and at least 1 valid postbaseline ADA sample.

In Study 301 at baseline, the ADA prevalence rates was 5.0%, with the NAb prevalence rate of 0.3%. This indicates a background pre-existence of immune response in the study population. The incidence of positive ADA in lecanemab was 5.5% and titers were low (first quartile [Q1]

and third quartile [Q3] of maximum ADA titers were 16 and 400, with 3 patients having a titer ≥2000). The NAb prevalence rate was 0.3% with a maximum titer of 270 reported for a single patient. This patient at Visit 3 Week 1 (Baseline – prior to start of treatment) was ADA positive with a high titer of 50,000 and NAb positive with a high titer of 270. No information was available about prior exposure to any immunotherapeutics.

4.6.1 Population PK

Population PK analyses indicated ADA status did not meaningfully affect lecanemab serum concentration. Presence of ADA positive samples resulted in a 13% increase in lecanemab clearance, which is within the variability of the clearance parameter estimate and not considered to be clinically meaningful. ADA titer as a continuous time-variant covariate had no significant effect on lecanemab clearance. Lecanemab serum concentrations are therefore concluded not to be affected by ADA titer.

4.6.2 Clinical Efficacy

During treatment with lecanemab in Study 301, there was a clinically meaningful reduced decline in all measures of clinical efficacy relative to placebo that was not affected by the presence of ADA and was independent of ADA status or ADA subgroup. The presence of NAb did not affect efficacy.

4.6.3 Clinical Safety

In Study 301, AEs reported were summarized by SOC and preferred term by ADA status, and no clinically meaningful correlations were observed in the incidence of overall AE occurrence and ADA status, or any single AE and ADA status. The overall AE incidence was similar for both ADA positive and ADA negative conclusive patients (placebo, 82.2% [note: AEs for placebo were not analyzed by ADA status]; lecanemab ADA positive 89.8%, ADA negative conclusive 89.7%).

Incidences of AEs associated with immunological reactions such as infusion-related reactions, and rash were similar between patients with positive ADA and patients with negative conclusive ADA.

4.7 Postmarketing Data

Postmarketing exposure has been limited to date, with the small number of events reported consistent with what has been observed in controlled clinical studies.

4.8 Overall Benefits and Risks Conclusions

Summary

- AD has a severe impact on patients, families, and healthcare systems. Established treatments are insufficient; they provide modest, temporary benefit to symptoms only and do not slow disease progression.
- Study 301 demonstrated highly statistically significant 27% slowing of clinical decline on CDR-SB after 18 months of treatment with lecanemab (*P*=0.00005), as well as highly statistically significant slowing of clinical decline on all clinical efficacy endpoints (ADAS-Cog14 *P*=0.00065) and functional scales (ADCS ADL-MCI P<0.00001).
- The benefits of lecanemab are supported by consistent results across scales and domains, slowing of progression to the next stage of disease, clinically meaningful impact on QoL or care partner burden, and consistency across subgroups.
- Lecanemab impacted biomarkers of amyloid, Tau, and neurodegeneration providing a biological basis for the treatment effects consistent with slowing of disease progression.
- Common ADRs for lecanemab include infusion-related reaction, amyloid related imaging abnormality microhemorrhages and hemosiderin deposits (a preferred term for ARIA-H cerebral microhemorrhage), ARIA-E, headache, and superficial siderosis of the nervous system.
  - The early timing of occurrence, and resolution with appropriate clinical management supports that these events are readily manageable
  - Infusion related reactions are typically of lower grades of severity, have onset with first infusion, have low rates of discontinuation, and have a low recurrence rate (regardless of use of premedication)
  - ARIA-E occurs early in treatment, is mostly asymptomatic, resolves spontaneously regardless of radiographic severity, and asymptomatic radiographically mild ARIA-E can be dosed through without interruption. Increasing number of E4 alleles is a risk factor for ARIA-E; however, the clinical course of ARIA-E remains unchanged.
  - Isolated ARIA-H consisting of microhemorrhage and superficial siderosis is randomly distributed throughout the treatment period, is almost always asymptomatic, and does not require alterations in dosing
  - There was no increase in ARIA-E or ARIA-H in patients who were on lecanemab and antithrombotics relative to those that were on lecanemab alone. The number of intracerebral hemorrhage cases was small, limiting risk assessment of concomitant use of antithrombotics.
- Taken together, the consistency and strength of evidence demonstrate that the slowing of disease progression and slowing of decline in QoL measures with lecanemab support a positive benefit-risk profile for the treatment of early AD.

4.8.1 Therapeutic Context

Current understanding is that AD begins with structural and biological changes in the brain many years before the emergence of clinical symptoms. The main neuropathological hallmark of AD is the presence of 2 abnormal protein deposits: extracellular deposits of amyloid plaques (brain amyloid comprising β-amyloid peptides) and neurofibrillary tangles (comprising abnormal tau protein). Biomarker (Jack, et al., 2013), clinicopathological (Delacourte, et al., 2002) and cohort (Amieva, et al., 2008) studies indicate that the disease process commences 10 to 20 years before the clinical onset of symptoms.

Although the pathogenesis of brain amyloid and neurofibrillary tangles and how they contribute to the clinical syndrome of AD is not yet fully elucidated, the leading hypothesis for pathological initiation is the "amyloid cascade." This hypothesis postulates that neurodegenerative processes in AD are driven by an imbalance between Aβ production and Aβ clearance in the brain (Hardy and Selkoe, 2002).

4.8.2 Benefits of Lecanemab Treatment

The effectiveness of lecanemab as a treatment for early AD is supported by the slowing of clinical decline and the effects on brain amyloid, downstream fluid (plasma and CSF) and imaging biomarkers (tau PET), representing effects on the underlying pathophysiology, and exposure-response relationships from the adequate and well–controlled Phase 3 Study 301.

Study 301 is the confirmatory study to verify and describe the clinical benefit of lecanemab and was designed as a global, multicenter, double-blind, placebo-controlled, parallel-group study to demonstrate the superiority of lecanemab versus placebo. Patients who completed 18 months of double-blind treatment transitioned into the OLE Phase, provided they met the inclusion/exclusion criteria.

The dose of lecanemab selected for evaluation in Study 301 was based on the results of dose range finding Study 201 that showed this was the most efficacious dose, with an acceptable benefit-risk balance. The results from Study 201, which was primary study supporting accelerated approval, demonstrate a dose- and time-dependent relationship between the effect of lecanemab on the reduction of brain amyloid slowing in clinical decline as measured by CDR-SB, ADCOMS, and ADAS-Cog14.

4.8.2.1 Clinical Interpretation of Study 301 Results

Study 301 demonstrated that lecanemab reduced progression of AD on validated global, functional, cognitive, and QoL outcomes. These outcomes are clinically meaningful when considered across the patient and care partner perspective and the clinician treating the patient.

The primary outcome measure is the global scale of cognition and function CDR-SB. The CDR-SB involves an interview of the patient and care partner evaluating 6 domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care). Each domain is scored on the following scale of impairment: 0 (none), 0.5 (questionable), 1 (mild), 2 (moderate), 3 (severe). The CDR-SB overall score is intended to capture the entire clinical course of AD (which can be over 10 years) and ranges from unimpaired (0) to bedridden

(18). Patients with early AD are typically in the range of 0.5 to 6 on the overall CDR-SB. Typically, in early AD natural disease progression within 18 months is at most an average of 2 points on CDR-SB (example ADNI and other clinical studies). Moving from 0 to 0.5 in any domain can mean progressing from unimpaired to impaired in that domain. Moving from 0.5 to 1 can mean progressing from slight impairment to loss of independence in a domain. For example, in the community affairs CDR domain, a rating of 0.5 is "slight impairment in these activities" while a rating of 1.0 is "unable to function independently at these activities. In Study 301, the rate of progression in early AD was 1.66 in lecanemab; therefore, for assessment of slowing disease progression, a treatment effect can only be between the range 0 to 1.66 on CDR-SB at 18 months.

From the perspective of the clinician, thresholds (referred to as the minimally important clinical difference [MCID]) are an important approach to help contextualize study results and demonstrate meaningful treatment benefit (Lansdall, et al., 2023, Liu, et al., 2021; Andrews, et al., 2021). The MCID is based on clinician assessment and indicates a clinically meaningful change whereby the patient is expected to require either additional treatment or additional supportive care. While literature attempting to define a meaningful score change for individual patients on clinical outcome assessments exist, there are important limitations and misinterpretations. The MCIDs proposed for the CDR-SB in early AD range from 0.50 to 0.98 for MCI and up to 1.63 for mild AD (Lansdall, et al., 2022; Andrews, et al., 2019). Given the limited treatment options for AD, clinicians are likely to underestimate the progression noted by patients or care partners that they identify as important (DiBenedetti, et al., 2020). Furthermore, the patient populations used to derive these do not have confirmed elevated amyloid, introducing significant variability in progression that inflates the MCID, and limits generalizability to a contemporary biomarker confirmed early AD population. (Assunção, et al., 2022).

The clinically meaningful change for a clinician following a patient (MCID) has been misapplied as being a threshold for differences between treatment groups in clinical studies. MCID is typically anchored on progression to the next stage of AD, whereby the patient requires either additional treatment or additional supportive care. The appropriate application of MCID to AD clinical study results is to demonstrate the delay in clinically meaningful worsening (Dickson, et al., 2023; Lau Raket 2022; Wessels, et al., 2023; Petersen, et al., et. al., 2023). This has been demonstrated by lecanemab in several analyses:

- The CDR assessment provides a global CDR rating that establishes the overall clinical stage of AD, and ranges from 0 (unimpaired), 0.5 (mild cognitive impairment), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia). In Study 301, 81% of patients were CDR 0.5 at baseline. Study 301 results directly show a delay in the relative rate of progression to the next stage of disease of 31% versus the group who did not receive lecanemab.
- In slope analysis, the placebo group reaches a decline of 1.11 on CDR-SB at 12.7 months while the lecanemab treatment group experiences a delay of 5.3 months until a similar level of decline becomes evident at 18 months. By 18 months placebo will have further declined by 1.66 from baseline. As with other therapies, it is expected that a treatment that slows disease progression has an effect that continues to expand over time. Projecting across the entire AD course, this can translate to patients remaining in the early stages of AD for an additional 2 to 3 years (Tahami, et al., 2023; Tahami, et al., 2022).

Thus, treatment with lecanemab can help individuals remain in earlier stages of AD for a longer period. Patients value preservation of function and slowing of decline, and patient focus groups have indicated that personal meaningfulness should be considered alongside clinical meaningfulness when assessing treatments (Moreno, et al., 2023). The patient and care partner information assessed in the CDR-SB, ADCS-ADL-MCI and QoL measures in Study 301 are reflective of items of importance to patients and care partners (Hauber, et al., 2023; DiBenedetti, et al., 2020). Impact on cognition and function are accompanied by improvement in QoL directly assessed by the patient in both general health related QoL scales (ie, EQ-5D) as well as AD-specific scales (ie, AD-QoL). The use of the Zarit-Burden interview in Study 301 indicates direct effects on improvement in care partner burden with lecanemab relative to placebo.

Acknowledging the limitations cited above, it is generally accepted in peer-reviewed publications and other scientific sources that a 20% to 30% slowing of the CDR-SB differences is clinically meaningful (Abushakra, et al., 2016; Petersen, et al., 2023). The 27% reduction in clinical decline from baseline in CDR-SB seen in Study 301 is consistent with a clinically meaningful difference on that scale based on the AD peer-reviewed literature, statistical principles, and guidance from the regulatory authorities under which Study 301 was designed. The highly statistically significant results in ADAS-Cog14, and ADCS MCI-ADL provide reinforcing independent evidence of clinically relevant impact on cognition and function.

Clinically meaningful benefits are based on a comprehensive assessment of impact of the treatment on cognition, function, QoL, care partner burden, and slowing progression of disease from the perspective of the patient, care partner, and clinician (Rentz, et al., 2021, Cohen, et al., 2022, Assunção, et al., 2022). The clinical importance of the treatment difference in CDR-SB is reinforced by the consistency and strength of evidence of evidence from Study 301:

- Consistent results across scales of cognition and function (26%-37% slowing), across domains within scales, and across clinically relevant subgroups
- Delay in progression by slope analysis of CDR-SB (delay of 5.3 months over the 18-month study), and by time-to-event analysis of progression to next stage of AD (HR 0.69)
- 38%-56% slowing of decline in health-related QoL measures and 38% slowing of care partner burden
- Lecanemab effects on biomarkers of amyloid, tau, neurodegeneration, and gliosis, that provide a biological basis for the treatment effects.

4.8.3 Potential Risks and Limitations

The common ADRs for lecanemab based on Study 301 are infusion-related reaction, amyloid related imaging abnormality microhemorrhages and hemosiderin deposits (a preferred term for ARIA-H cerebral microhemorrhage), amyloid related imaging abnormality-oedema/effusion, headache, and superficial siderosis of central nervous system.

Infusion-related reactions are typically of lower grades of severity, have onset with first infusion, have low rates of discontinuation, and have a low recurrence rate (regardless of use of premedication). In Study 301 there was no difference in use of premedication for preventing

subsequent infusion reactions nor in severity of subsequent infusion reactions, and regardless of use of premedication, most patients did not report further infusion-related reactions.

ARIA-E occurs early in treatment, is mostly asymptomatic, resolves spontaneously regardless of radiographic severity, and asymptomatic radiographically mild ARIA-E can be dosed through without interruption. Increasing number of E4 alleles is a risk factor for ARIA-E; however, the clinical course of ARIA-E remains unchanged.

Isolated ARIA-H (ARIA-H in patients who did not also experience ARIA-E) consisting of microhemorrhage and superficial siderosis and excluding intracerebral hemorrhage, is randomly distributed throughout the Treatment Period, is almost always asymptomatic, and does not require alterations in dosing. Increasing number of E4 alleles is a risk factor for ARIA-H; however, the clinical course of ARIA-H as defined above, remains unchanged.

Cerebral microhemorrhage (ARIA-H) was also seen by itself or in association with ARIA-E. These events were typically asymptomatic, stabilized on follow-up MRI testing, and at a lower incidence than with other comparable treatments.

There was no increase in ARIA-E or ARIA-H in patients who were on lecanemab and antithrombotics relative to those that were on lecanemab alone. The number of intracerebral hemorrhage cases was small, limiting risk assessment of concomitant use of antithrombotics.

Acute thrombolytics are infrequently used and are usually used in life-threatening emergency situations where they are the only option of care. A single case of tPA use in a 65-year-old female homozygous *APOE4* carrier has been reported in Study 301 OLE Phase.

There was an increased risk of intracerebral hemorrhages with lecanemab therapy in the Study 301 (placebo 0.2%; lecanemab 0.7%). Although the risk of intracerebral hemorrhage while on lecanemab is low overall, it is substantially greater for patients on anticoagulants (Study 301: 2.4% for those on anticoagulants). The rates are similar in Study 301 OLE Phase. Furthermore, the relative contribution from lecanemab to this risk is unclear as anticoagulants alone confer a higher risk of intracerebral hemorrhage in non-AD populations. The risk in AD populations with CAA is not known, but is expected to be higher; therefore, any incremental risk cannot be judged. Lecanemab was favored over placebo on CDR-SB in the subgroup of patients taking anticoagulant medications.

4.8.4 Overall Benefit-Risk Assessment

AD is a progressive, neurodegenerative disorder that is the most common form of dementia among older people. In the US, it is estimated that there are 6-7 million people over 50 years of age with MCI due to AD and 2.5 million with mild AD (Gillis, et al., 2022, Alzheimer's Association, 2023). AD is the sixth-leading cause of death in the US (Xu, et al., 2020). The disease is characterized clinically by a global decline of cognitive function that progresses slowly and for many patients, results in spending a significant period of their remaining life in the severe disabling disease state (Rizzuto, et al., 2012). Patients with AD typically survive for only 3 to 10 years after symptom onset (Hebert, et al., 2003). In addition to the effect on patients, AD places a significant burden on families and care partners (Alzheimer's Association, 2023; Suehs, et al., 2014).

Current therapeutic agents for patients with mild, moderate, and severe AD dementia consist of symptomatic therapies. These therapies provide modest, temporary benefit to symptoms which is rapidly lost after treatment discontinuation (Birks, 2006; McShane, et al., 2006). None of the currently approved symptomatic treatments slow the amyloid accumulation, spread of neurofibrillary tangles and neuronal and synaptic loss that leads to relentless disease progression.

Patients value preservation of function and slowing of decline, and patient focus groups have indicated that personal meaningfulness should be considered alongside clinical meaningfulness when assessing treatments. Treatment with lecanemab can help individuals remain in earlier stages of AD for a longer period as demonstrated by a comprehensive assessment of cognition, function, QoL, care partner burden, and slowing progression of disease.

Safety data from over 1612 patients in Study 301 (double-blind + OLE Phase) demonstrate that lecanemab is generally well-tolerated in patients with early AD, with the AE profile (type and rate) observed in Study 301 consistent with the approved USPI. The safety profile of lecanemab in patients with early AD has been evaluated with a placebo comparator for up to 18 months of exposure in Study 301 and up to 5 years exposure overall in lecanemab studies.

Adverse events of special interest for lecanemab (infusion-related reaction, amyloid related imaging abnormality microhemorrhages and hemosiderin deposits [a preferred term for ARIA-H cerebral microhemorrhage], amyloid related imaging abnormality-oedema/effusion) generally occurred at a higher rate than placebo (except isolated ARIA-H which occurred the same rate as placebo). Most of these events were mild to moderate, and those related to lecanemab occurred early in the course of treatment. Serious infusion related reactions and ARIA events were reported infrequently. This profile allows the additional vigilance and MRI monitoring to be concentrated early, where it is most likely to be beneficial. The results of 301 support the safety profile and monitoring recommendations contained in the current US Package Insert for lecanemab.

The findings from Study 301 are consistent with the known safety profile of lecanemab. There were no additional safety issues that would preclude use in the intended population and the risks associated with lecanemab treatment can be adequately described in the USPI to allow for safe use.

Taken together, the consistency and strength of evidence demonstrate that the slowing of disease progression and slowing of decline in QoL measures with lecanemab support a positive benefit-risk profile for the treatment of early AD.

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Appendix 1 Tabular Summary of Deaths in Study 301

Table 29 Deaths – Study 301 Double-Blind and OLE Phase

ID	AE Start Study Day	Study Day of Death	Days Since Last Dose to Death	Fatal Event (Verbatim Term)	Other Relevant Details
Double-blind Placebo					
1	462	462	7	Unknown cause	A 90 year old patient with sudden death of unknown cause. Long cardiac history with previous myocardial infarctions, bundle branch block, aortic stenosis, angina pectoris and multiple concomitant medications for cardiac history. Complaints prior to death of shortness of breath and not feeling well.
2	4	4	4	Acute respiratory failure	A 82 year old patient, no other relevant details.
3	36	37	5	Heart attack	A 79 year old patient, no other relevant details.
4	546	607	76	Bone metastases	A 75 year old patient, no other relevant details.
5	Unknown	402	48	Intracerebral hemorrhage	A 72 year old patient, no other relevant details.
6	404	416	24	COVID-19	A 86 year old patient, no other relevant details.
7	71	319	249	Pancreatic cancer	A 85 year old patient, no other relevant details.
8	301	301	49	Cardiopulmonary arrest[a]	A 79 year old patient, no other relevant details.
Double-blind Lecanemab					
9	434	434	14	Unknown cause	A 85 year old patient, sudden death in a setting of no known serious comorbidities.
10	263	282	46	Stroke, acute, symptomatic	A 79 year old patient, no other relevant details.
11	230	230	11	Suspected myocardial infarction	A 70 year old patient, significant medical history included diabetes, hypertension, coronary artery disease, prior myocardial infarction, and cardiac arrythmia and conduction defects. Experienced dyspnea, collapsed, and died suddenly.

Table 29 Deaths – Study 301 Double-Blind and OLE Phase

ID	AE Start Study Day	Study Day of Death	Days Since Last Dose to Death	Fatal Event (Verbatim Term)	Other Relevant Details
12	351	405	76	Respiratory failure	A 88 year old patient, significant medical history included coronary artery disease, diabetes, hyperlipidemia, hypertension, chronic obstructive pulmonary disease, cardiac dysrhythmia including atrioventricular block with left ventricular hypertrophy. Patient experienced new onset atrial fibrillation with rapid response and a cardiac arrest soon afterwards during an AVM ablation procedure. Immediate sequelae included respiratory failure, intubation, iatrogenic pneumonia, and pulmonary embolism and edema. Patient received a tracheostomy and was transferred to an acute long-term care hospital where she expired.
13	534	563	45	Lymphomatous meningitis	A 77 year old patient, no other relevant details.
14	375	402	23	Respiratory tract infection SARS-CoV19	A 76 year old patient, no other relevant details.
15	526	526	36	DKA (Diabetic ketoacidosis)[b]	A 79 year old patient, no other relevant details.
Open-Label Extension[c]					
16	11	11	11	Myocardial infarction	A 78 year old patient, no other relevant details.
17	103	129	32	COVID-19 with pneumonia	A 68 year old patient, no other relevant details.
18	515	519	15	COVID-19	A 85 year old patient, no other relevant details.
19	188	188	16	Fatal car accident	A 64 year old patient, no other relevant details.
20	777	777	20	Cardiac failure acute	A 81 year old patient, no other relevant details.
21	116	143	46	Left occipital intracerebral hemorrhage (ARIA-H) symptomatic	A 85 year old patient who received placebo in the double-blind Study. Death considered possibly related to study drug by Investigator. Myocardial infarction was considered the proximal cause of death in a setting of atrial fibrillation, anticoagulant therapy with apixaban, falls, macrohemorrhage, and pneumonia. The autopsy confirmed CAA and concluded a terminal cardiopulmonary event was the likely cause of death.

Table 29 Deaths – Study 301 Double-Blind and OLE Phase

ID	AE Start Study Day	Study Day of Death	Days Since Last Dose to Death	Fatal Event (Verbatim Term)	Other Relevant Details
22	38	43	13	Possible Seizure (unknown) (suspected) and possible cerebrovascular accident (unknown) (suspected)	A 77 year old patient who received placebo in the double-blind Study. Death considered possibly related to study drug by Investigator. Patient experienced acute hemiparesis, possible seizure, and hypoxia in a setting of new onset atrial fibrillation and subsequent aspiration pneumonia life support was discontinued and the patient died. Cerebral ischemia, seizure, and ARIA are among the considerations. Additional information including autopsy report have been requested from next of kin.
23	33	37	9	Acute multifocal ICH (Intracerebral hemorrhage) POST TPA	A 63 year old patient who received placebo in the double-blind Study. Death considered possibly related to study drug by Investigator. tPA treatment was administered in the setting of an acute stroke, which was considered the proximal cause of macrohemorrhage and death.
24	695	696	11	Symptomatic suspected cerebral vascular accident	A 72 year old patient who received lecanemab in the double-blind Study. Death considered possibly related to study drug by Investigator.

All deaths occurred during study, with data cut of 01 Dec 2022.
a: Event occurred 49 days since last dose, not included in treatment-emergent adverse event summaries.
b: Event occurred 36 days since last dose, not included in treatment-emergent adverse event summaries.
c: Study Day is based on first infusion date of lecanemab in double blind phase or OLE Phase.

Appendix 2 Narratives for Grade 3 and 4 Infusion-Related Reactions

- Lecanemab: 81-year-old patient had an infusion-related reaction after their first dose of study drug on Day 1 that was considered severe (Grade 3) and related to the study drug. Post-infusion symptoms included a slightly increased BP, pulse rate, and respiration rate and the patient became cyanotic with rigors, chills, and fever. Laboratory tests results taken on Day 1 prior to dosing indicated the patient had pre-existing thrombocytopenia. The patient was transferred to the emergency department for treatment and was hospitalized. The patient was permanently discontinued from the study due to thrombocytopenia and infusion-related reaction. The pre-existing thrombocytopenia was ongoing at the time of discontinuation and the infusion-related reaction resolved on Day 2.
- Lecanemab: 73-year-old patient had an infusion-related reaction during their first dose of study drug on Day 1 that was considered severe (Grade 3) and related to study drug. The infusion was stopped, and the patient transferred to the emergency department and later hospitalized due to acute respiratory failure and hypoxia. Chest x-ray was suggestive of mild pulmonary edema, atelectasis, and aspiration or pneumonia. The patient was permanently discontinued from the study due to the infusion-related reaction that resolved on Day 3.
- Lecanemab: 74-year-old patient had an infusion-related reaction after their first dose of study drug on Day 1 that was considered severe (Grade 4), life-threatening, and related to study drug. Post-infusion symptoms included vomiting, mild nausea, dyspnea with increased respiratory rate, retraction, and basal wheezing (pain) and then later back stiffness and pain, increased chills, and cold extremities. The infusion-related reaction was considered to be an anaphylactic reaction and epinephrine was administered. The patient transferred to the emergency department and further treatment given. The event resolved on Day 2 and the patient was discharged from the emergency room. The patient was permanently discontinued from the study due to the infusion-related reaction on Day 113.
- Lecanemab: 83-year-old had an infusion-related reaction on Day 1 that was considered moderate (Grade 2) and related to study drug. Post-infusion symptoms included cold and shivering. The fever and raised BP were considered resolved on Day 3. Following the infusion on Day 97, the patient had an infusion-related reaction that was considered moderate (Grade 3) and related to study drug. Post-infusion symptoms included fever, increased confusion, and tiredness. The patient received paracetamol 1 g once. The patient was discontinued from study drug on Day 97 but continued in the study and the event was considered resolved on Day 105. On Day 188, the patient was permanently discontinued from the study due to the infusion-related reaction.
- Lecanemab: 66-year-old patient had an infusion-related reaction on Day 1 that was considered severe (Grade 3) and related to study drug. Post-infusion symptoms included a cold sensation in the whole body, headache, and syncope. The patient was treated with furosemide 500 mg IV once, alprazolam once and transferred to the emergency department for further observation. The event was resolved on Day 1 and the patient was discharged from the emergency room. The patient was permanently discontinued from the study due to the infusion-related reaction on Day 43.
- Lecanemab: 79-year-old patient had an infusion-related reaction on Day 1 that was considered moderate (Grade 3) and related to study drug. Post-infusion symptoms included vomiting, nausea, elevated BP, elevated heart rate with chills, and oral temperature of 37.1ºC.

The patient was transferred to the emergency room and further treatment given. An ECG showed sinus tachycardia. The event resolved on Day 4. On Day 4, the patient was noted with atrial fibrillation, was hospitalized, and treated. The event of atrial fibrillation was resolved, and the patient was discharged from the hospital on Day 4. The atrial fibrillation event was considered not related to study drug. The patient was discontinued from study treatment on Day 1 due to patient´s choice and was permanently discontinued from the study on Day 252 due to patient´s choice.

- Lecanemab: 77-year-old male had an infusion-related reaction on Day 1 that was considered severe (Grade 3) and related to study drug. Post-infusion symptoms included shivers, vomits and a hypertensive crisis. The patient was treated, and the event resolved on Day 1. The patient was permanently discontinued from the study due to the infusion-related reaction on Day 225.

Appendix 3 Approved USPI for Lecanemab

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LEQEMBI™ safely and effectively. See full prescribing information for LEQEMBI™.

LEQEMBI™ (lecanemab-irmb) injection, for intravenous use
Initial U.S. Approval: 2023

---------- INDICATIONS AND USAGE----------

LEQEMBI is an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease. Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with LEQEMBI. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial. (1)

----------DOSAGE AND ADMINISTRATION----------

- Confirm the presence of amyloid beta pathology prior to initiating treatment. (2.1)
- The recommended dosage is 10 mg/kg that must be diluted then administered as an intravenous infusion over approximately one hour, once every two weeks. (2.2)
- Obtain a recent (within one year) brain MRI prior to initiating treatment to evaluate for pre-existing Amyloid Related Imaging Abnormalities (ARIA). (2.3, 5.1)
- Obtain an MRI prior to the 5th, 7th, and 14th infusions. If radiographically observed ARIA occurs, treatment recommendations are based on type, severity, and presence of symptoms. (2.3, 5.1)
- Dilution in 250 mL of 0.9% Sodium Chloride Injection, USP, is required prior to administration. (2.4)
- Administer as an intravenous infusion over approximately one hour via a terminal low-protein binding 0.2 micron in-line filter. (2.5)

---------- DOSAGE FORMS AND STRENGTHS ----------

Injection:

- 500 mg/5 mL (100 mg/mL) solution in a single-dose vial (3)
- 200 mg/2 mL (100 mg/mL) solution in a single-dose vial (3)

---------- CONTRAINDICATIONS ----------

None. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Amyloid Related Imaging Abnormalities (ARIA): Enhanced clinical vigilance for ARIA is recommended during the first 14 weeks of treatment with LEQEMBI. Risk of ARIA, including symptomatic ARIA, was increased in apolipoprotein E ε4 homozygotes compared to heterozygotes and noncarriers. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI scanning if indicated. (2.3, 5.1)
- Infusion-Related Reactions: The infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy administered as clinically indicated. Consider pre-medication at subsequent dosing with antihistamines, non-steroidal anti-inflammatory drugs, or corticosteroids. (5.2)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (at approximately 10% and higher incidence compared to placebo): infusion-related reactions, headache, and ARIA-edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at 1-888-274-2378 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 1/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LEQEMBI is indicated for the treatment of Alzheimer's disease. Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with LEQEMBI *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Confirm the presence of amyloid beta pathology prior to initiating treatment *[see Clinical Pharmacology (12.1)]*.

2.2 Dosing Instructions

The recommended dosage of LEQEMBI is 10 mg/kg that must be diluted then administered as an intravenous infusion over approximately one hour, once every two weeks.

If an infusion is missed, administer the next dose as soon as possible.

2.3 Monitoring and Dosing Interruption for Amyloid Related Imaging Abnormalities

LEQEMBI can cause amyloid related imaging abnormalities -edema (ARIA-E) and -hemosiderin deposition (ARIA-H) *[see Warnings and Precautions (5.1)]*.

Monitoring for ARIA

Obtain a recent (within one year) brain magnetic resonance imaging (MRI) prior to initiating treatment with LEQEMBI. Obtain an MRI prior to the 5^{th}, 7^{th}, and 14^{th} infusions.

Recommendations for Dosing Interruptions in Patients with ARIA

ARIA-E
The recommendations for dosing interruptions for patients with ARIA-E are provided in Table 1.

Table 1: Dosing Recommendations for Patients with ARIA-E

Clinical Symptom Severity[1]	ARIA-E Severity on MRI		
	Mild	**Moderate**	**Severe**
Asymptomatic	May continue dosing	Suspend dosing[2]	Suspend dosing[2]
Mild	May continue dosing based on clinical judgment	Suspend dosing[2]	
Moderate or Severe	Suspend dosing[2]		

[1] 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.

[2] 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.

ARIA-H

The recommendations for dosing interruptions for patients with ARIA-H are provided in Table 2.

Table 2: Dosing Recommendations for Patients with ARIA-H

Clinical Symptom Severity	ARIA-H Severity on MRI		
	Mild	**Moderate**	**Severe**
Asymptomatic	May continue dosing	Suspend dosing[1]	Suspend dosing[2]
Symptomatic	Suspend dosing[1]	Suspend dosing[1]	

[1] 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.

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

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

2.4 Dilution Instructions

- Prior to administration, LEQEMBI must be diluted in 250 mL of 0.9% Sodium Chloride Injection, USP.
- Use aseptic technique when preparing the LEQEMBI diluted solution for intravenous infusion.
- Calculate the dose (mg), the total volume (mL) of LEQEMBI solution required, and the number of vials needed based on the patient's actual body weight and the recommended dose of 10 mg/kg. Each vial contains a LEQEMBI concentration of 100 mg/mL.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Check that the LEQEMBI solution is clear to opalescent and colorless to pale yellow. Do not use if opaque particles, discoloration, or other foreign particles are present.
- Remove the flip-off cap from the vial. Insert the sterile syringe needle into the vial through the center of the rubber stopper.
- Withdraw the required volume of LEQEMBI from the vial(s) and add to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP.
- Each vial is for one time-use only. Discard any unused portion.
- Gently invert the infusion bag containing the LEQEMBI diluted solution to mix completely. Do not shake.
- After dilution, immediate use is recommended *[see Description (11)]*. If not administered immediately, store LEQEMBI refrigerated at 2°C to 8°C (36°F to 46°F) for up to 4 hours, or at room temperature up to 30°C (86°F) for up to 4 hours. Do not freeze.

2.5 Administration Instructions

- Visually inspect the LEQEMBI diluted solution for particles or discoloration prior to administration. Do not use if it is discolored, or opaque or foreign particles are seen.
- Prior to infusion, allow the LEQEMBI diluted solution to warm to room temperature.
- Infuse the entire volume of the LEQEMBI diluted solution intravenously over approximately one hour through an intravenous line containing a terminal low-protein binding 0.2 micron in-line filter. Flush infusion line to ensure all LEQEMBI is administered.
- Monitor for any signs or symptoms of an infusion-related reaction. The infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy administered as clinically indicated. Consider pre-medication at subsequent dosing with antihistamines, non-steroidal anti-inflammatory drugs, or corticosteroids *[see Warnings and Precautions (5.2)]*.

3 DOSAGE FORMS AND STRENGTHS

LEQEMBI is a clear to opalescent and colorless to pale yellow solution, available as:

- Injection: 500 mg/5 mL (100 mg/mL) in a single-dose vial
- Injection: 200 mg/2 mL (100 mg/mL) in a single-dose vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Amyloid Related Imaging Abnormalities

Monoclonal antibodies directed against aggregated forms of beta amyloid, including LEQEMBI, can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E), which can be

observed on MRI as brain edema or sulcal effusions, and ARIA with hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis. ARIA-H 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 of any cause and ARIA-E can occur together. ARIA is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. When present, 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.

Incidence of ARIA

Symptomatic ARIA occurred in 3% (5/161) of patients treated with LEQEMBI in Study 1 *[see Clinical Studies (14)].* Clinical symptoms associated with ARIA resolved in 80% of patients during the period of observation.

Including asymptomatic radiographic events, ARIA was observed in 12% (20/161) of patients treated with LEQEMBI, compared to 5% (13/245) of patients on placebo in Study 1. ARIA-E was observed in 10% (16/161) of patients treated with LEQEMBI compared with 1% (2/245) of patients on placebo. ARIA-H was observed in 6% (10/161) of patients treated with LEQEMBI compared with 5% (12/245) of patients on placebo. 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.

Intracerebral hemorrhage greater than 1 cm in diameter was reported in one patient in Study 1 after treatment with LEQEMBI compared to none on placebo. Events of intracerebral hemorrhage, including fatal events, in patients taking LEQEMBI have also been reported in other studies.

ApoE ε4 Carrier Status and Risk of ARIA

In Study 1, 6% (10/161) of patients in the LEQEMBI group were apolipoprotein E ε4 (ApoE ε4) homozygotes, 24% (39/161) were heterozygotes, and 70% (112/161) were noncarriers. The incidence of ARIA was higher in ApoE ε4 homozygotes than in heterozygotes and noncarriers among patients treated with LEQEMBI. Of the 5 patients treated with LEQEMBI who had symptomatic ARIA *(see Incidence of ARIA)*, 4 were ApoE ε4 homozygotes, 2 of whom experienced severe symptoms. In addition, an increased incidence of symptomatic and overall ARIA in ApoE ε4 homozygotes compared to heterozygotes and noncarriers in patients taking LEQEMBI has been reported in other studies. The recommendations on management of ARIA do not differ between ApoE ε4 carriers and noncarriers *[see Dosage and Administration (2.3)].* Consider testing for ApoE ε4 status to inform the risk of developing ARIA when deciding to initiate treatment with LEQEMBI.

Radiographic Findings

The radiographic severity of ARIA associated with LEQEMBI was classified by the criteria shown in Table 3.

Table 3: ARIA MRI Classification Criteria

ARIA Type	Radiographic Severity		
	Mild	**Moderate**	**Severe**
ARIA-E	FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter in one location <5 cm	FLAIR hyperintensity 5 to 10 cm in single greatest dimension, or more than 1 site of involvement, each measuring <10 cm	FLAIR hyperintensity >10 cm with associated gyral swelling and sulcal effacement. One or more separate/ independent sites of involvement may be noted.
ARIA-H microhemorrhage	≤ 4 new incident microhemorrhages	5 to 9 new incident microhemorrhages	10 or more new incident microhemorrhages
ARIA-H superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	> 2 areas of superficial siderosis

The majority of ARIA-E radiographic events occurred early in treatment (within the first 7 doses), although ARIA can occur at any time and patients can have more than 1 episode. The maximum radiographic severity of ARIA-E in patients treated with LEQEMBI was mild in 4% (7/161) of patients, moderate in 4% (7/161) of patients, and severe in 1% (2/161) of patients. Resolution on MRI occurred in 62% of ARIA-E patients by 12 weeks, 81% by 21 weeks, and 94% overall after detection. The maximum radiographic severity of ARIA-H microhemorrhage in patients treated with LEQEMBI was mild in 4% (7/161) of patients and severe in 1% (2/161) of patients; 1 of the 10 patients with ARIA-H had mild superficial siderosis.

Concomitant Antithrombotic Medication and Other Risk Factors for Intracerebral Hemorrhage

Patients were excluded from enrollment in Study 1 for baseline use of anticoagulant medications. Antiplatelet medications such as aspirin and clopidogrel were allowed. During the study, if anticoagulant medication was used because of intercurrent medical events that required treatment for 4 weeks or less, treatment with LEQEMBI was to be temporarily suspended. Patients who received LEQEMBI and an antithrombotic medication (aspirin, other antiplatelets, or anticoagulants) did not have an increased risk of ARIA-H compared to patients who received placebo and an antithrombotic medication. The majority of exposures to antithrombotic medications were to aspirin; few patients were exposed to other antiplatelet drugs or anticoagulants, limiting any meaningful conclusions about the risk of ARIA or intracerebral hemorrhage in patients taking other antiplatelet drugs or anticoagulants. Because intracerebral hemorrhages greater than 1 cm in diameter have been observed in patients taking LEQEMBI, additional caution should be exercised when considering the administration of antithrombotics or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with LEQEMBI.

Additionally, patients were excluded from enrollment in Study 1 for the following risk factors for intracerebral hemorrhage: prior cerebral hemorrhage greater than 1 cm in greatest diameter, more than 4 microhemorrhages, superficial siderosis, evidence of vasogenic edema, evidence of cerebral contusion, aneurysm, vascular malformation, infective lesions, multiple lacunar infarcts or stroke involving a major vascular territory, and

severe small vessel or white matter disease. Caution should be exercised when considering the use of LEQEMBI in patients with these risk factors.

Monitoring and Dose Management Guidelines

Recommendations for dosing in patients with ARIA-E depend on clinical symptoms and radiographic severity *[see Dosage and Administration (2.3)].* Recommendations for dosing in patients with ARIA-H depend on the type of ARIA-H and radiographic severity *[see Dosage and Administration (2.3)]*. Use clinical judgment in considering whether to continue dosing in patients with recurrent ARIA-E.

Baseline brain MRI and periodic monitoring with MRI are recommended *[see Dosage and Administration (2.3)]*. 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.

The Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) is a voluntary provider-enrolled patient registry that collects information on treatments for Alzheimer's disease, including LEQEMBI. Providers may obtain information about the registry at www.alz-net.org or contact alz-net@acr.org.

5.2 Infusion-Related Reactions

In Study 1, infusion-related reactions were observed in 20% (32/161) of patients treated with LEQEMBI compared to 3% (8/245) of patients on placebo; and the majority (88%, 28/32) occurred with the first infusion. Infusion-related reactions were mild (56%) or moderate (44%) in severity. Infusion-related reactions resulted in discontinuations in 2% (4/161) of patients treated with LEQEMBI. Symptoms of infusion-related reactions include fever and flu-like symptoms (chills, generalized aches, feeling shaky, and joint pain), nausea, vomiting, hypotension, hypertension, and oxygen desaturation.

After the first infusion, 38% of patients treated with LEQEMBI had transient decreased lymphocyte counts to less than 0.9 $x10^9$/L compared to 2% in patients on placebo, and 22% of patients treated with LEQEMBI had transient increased neutrophil counts to greater 7.9 $x10^9$/L compared to 1% of patients on placebo.

In the event of an infusion-related reaction, the infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy initiated as clinically indicated. Prophylactic treatment with antihistamines, acetaminophen, nonsteroidal anti-inflammatory drugs, or corticosteroids prior to future infusions may be considered.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Amyloid Related Imaging Abnormalities *[see Warnings and Precautions (5.1)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of LEQEMBI has been evaluated in 763 patients who received at least one dose of LEQEMBI. In Study 1 in patients with Alzheimer's disease, 161 patients received LEQEMBI 10 mg/kg every two weeks *[see Clinical Studies (14)]*. Of these 161 patients, 44% were female, 93% were White, 6% were of Hispanic or Latino ethnicity, 4% were Asian, and 2% were Black. The mean age at study entry was 73 years (range from 51 to 88 years).

In the combined double-blind, placebo-controlled period and long-term extension period of Study 1, 237 patients received LEQEMBI for at least 6 months, 217 patients for at least 12 months, and 186 patients for 18 months.

In the double-blind, placebo-controlled period of Study 1, 15% of patients treated with LEQEMBI, compared to 6% of patients on placebo, stopped study treatment because of an adverse reaction. The most common adverse reaction leading to discontinuation of LEQEMBI was infusion-related reactions that led to discontinuation in 2% (4/161) of patients treated with LEQEMBI compared to 1% (2/245) of patients on placebo.

Table 4 shows adverse reactions that were reported in at least 5% of patients treated with LEQEMBI and at least 2% more frequently than in patients on placebo.

Table 4: Adverse Reactions Reported in at Least 5% of Patients Treated with LEQEMBI 10 mg/kg Every Two Weeks and at least 2% Higher than Placebo in Study 1

Adverse Reaction	**LEQEMBI 10 mg/kg Every Two Weeks N=161 %**	**Placebo N=245 %**
Infusion-related reactions	20	3
Headache	14	10
ARIA-E	10	1
Cough	9	5
Diarrhea	8	5

Less Common Adverse Reactions

Atrial fibrillation occurred in 4% of patients treated with LEQEMBI compared to 1% in patients on placebo. Lymphopenia or decreased lymphocyte count were reported in 4% of patients treated with LEQEMBI, all after the first dose, compared to less than 1% of patients on placebo.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on LEQEMBI use in pregnant women to evaluate for a drug associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. No animal studies have been conducted to assess the potential reproductive or developmental toxicity of LEQEMBI.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

8.2 Lactation

Risk Summary

There are no data on the presence of lecanemab-irmb in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Published data from other monoclonal antibodies generally indicate low passage of monoclonal antibodies into human milk and limited systemic exposure in the breastfed infant. The effects of this limited exposure are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LEQEMBI and any potential adverse effects on the breastfed infant from LEQEMBI or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of LEQEMBI in pediatric patients have not been established.

8.5 Geriatric Use

In Study 1, the age of patients exposed to LEQEMBI 10 mg/kg every two weeks ranged from 51 to 88 years, with a mean age of 73 years; 62% were 65 to 80 years, and 21% were 80 years and older. Age-related findings about clinical efficacy and safety are limited by the small numbers of patients less than 65 years of age and 80 years of age and older in clinical studies of LEQEMBI.

11 DESCRIPTION

Lecanemab-irmb is a recombinant humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta, and is expressed in a Chinese hamster ovary cell line. Lecanemab-irmb has an approximate molecular weight of 150 kDa.

LEQEMBI (lecanemab-irmb) injection is a preservative-free, sterile, clear to opalescent and colorless to pale yellow solution for intravenous use by infusion after dilution. LEQEMBI is supplied in single-dose vials available in concentrations of 500 mg/5 mL (100 mg/mL) or 200 mg/2 mL (100 mg/mL).

Each mL of solution contains 100 mg of lecanemab-irmb and arginine hydrochloride (42.13 mg), histidine (0.18 mg), histidine hydrochloride monohydrate (4.99 mg), polysorbate 80 (0.50 mg), and Water for Injection at an approximate pH of 5.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lecanemab-irmb is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta. The accumulation of amyloid beta plaques in the brain is a defining pathophysiological feature of Alzheimer's disease. LEQEMBI reduces amyloid beta plaques, as evaluated in Study 1 *[see Clinical Studies (14)]*.

12.2 Pharmacodynamics

Effect of LEQEMBI on Amyloid Beta Pathology

LEQEMBI reduced amyloid beta plaque in a dose- and time-dependent manner in Study 1, compared with placebo *[see Clinical Studies (14)]*.

The effect of LEQEMBI on amyloid beta plaque levels in the brain was evaluated using PET imaging (^{18}F-florbetapir tracer). The PET signal was quantified using the Standard Uptake Value Ratio (SUVR) method to estimate brain levels of amyloid beta plaque in composites of brain areas expected to be widely affected by Alzheimer's disease pathology (frontal, parietal, lateral temporal, sensorimotor, and anterior and posterior cingulate cortices), compared to a brain region expected to be spared of such pathology (cerebellum). The SUVR was also expressed on the Centiloid scale.

In the double-blind, placebo-controlled period of Study 1, treatment with LEQEMBI 10 mg/kg every two weeks reduced amyloid beta plaque levels in the brain, producing reductions in PET SUVR compared to placebo at both Weeks 53 and 79 ($p<0.001$). The magnitude of the reduction was time- and dose-dependent.

During an off-treatment period (range from 9 to 59 months; mean of 24 months), SUVR and Centiloid values began to increase with a mean rate of increase of 2.6 Centiloids/year, however, treatment difference relative to placebo at the end of the double-blind, placebo-controlled period in Study 1 was maintained.

In the double-blind, placebo-controlled period of Study 1, an increase in plasma Aβ42/40 ratio was observed with LEQEMBI 10 mg/kg every two weeks dosing compared to placebo.

Effect of LEQEMBI on Tau Pathophysiology

A reduction in plasma p-tau181 was observed with LEQEMBI 10 mg/kg every two weeks compared to placebo in the double-blind, placebo-controlled period of Study 1.

Exposure-Response Relationships

Model based exposure-response analyses for Study 1 demonstrated that higher exposures to lecanemab-irmb were associated with greater reduction in clinical decline on CDR-SB and ADAS-Cog14. In addition, higher

exposures to lecanemab-irmb were associated with greater reduction in amyloid beta plaque in Study 1. An association between reduction in amyloid beta plaque and clinical decline on CDR-SB was also observed.

Higher exposures to lecanemab-irmb were also associated with greater increase in plasma Aβ42/40 ratio and greater reduction in plasma p-tau181.

12.3 Pharmacokinetics

Steady state concentrations of lecanemab-irmb were reached after 6 weeks of 10 mg/kg administered every 2 weeks and systemic accumulation was 1.4-fold. The peak concentration (C_{max}) and area under the plasma concentration versus time curve (AUC) of lecanemab-irmb increased dose proportionally in the dose range of 0.3 to 15 mg/kg following single dose.

Distribution

The mean value (95% CI) for central volume of distribution at steady-state is 3.22 (3.15-3.28) L.

Elimination

Lecanemab-irmb is degraded by proteolytic enzymes in the same manner as endogenous IgGs. The clearance of lecanemab-irmb (95% CI) is 0.434 (0.420-0.451) L/day. The terminal half-life is 5 to 7 days.

Specific Populations

Sex, body weight, and albumin were found to impact exposure to lecanemab-irmb. However, none of these covariates were found to be clinically significant.

Patients with Renal or Hepatic Impairment
No clinical studies were conducted to evaluate the pharmacokinetics of lecanemab-irmb in patients with renal or hepatic impairment. Lecanemab-irmb is degraded by proteolytic enzymes and is not expected to undergo renal elimination or metabolism by hepatic enzymes.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of lecanemab-irmb or of other lecanemab products.

During the 18-month treatment period in Study 1, 63/154 (40.9%) of patients treated with LEQEMBI 10 mg/kg every two weeks developed anti-lecanemab-irmb antibodies. Of these patients, neutralizing anti-lecanemab-irmb antibodies were detected in 16/63 (25.4%) patients. However, the assays used to measure anti-lecanemab-irmb antibodies and neutralizing antibodies are subject to interference by serum lecanemab concentrations, possibly resulting in an underestimation of the incidence of antibody formation. Therefore, there is insufficient information to characterize the effects of anti-lecanemab-irmb antibodies on pharmacokinetics, pharmacodynamics, safety, or effectiveness of LEQEMBI.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies have not been conducted.

Mutagenesis

Genotoxicity studies have not been conducted.

Impairment of Fertility

No studies in animals have been conducted to assess the effects of lecanemab-irmb on male or female fertility. No adverse effects on male or female reproductive organs were observed in a 39-week intravenous toxicity study in monkeys administered lecanemab-irmb weekly at doses up to 100 mg/kg. The highest dose tested was associated with plasma exposures (C_{ave}) approximately 24 times that in humans at the recommended human dose (10 mg/kg every two weeks).

14 CLINICAL STUDIES

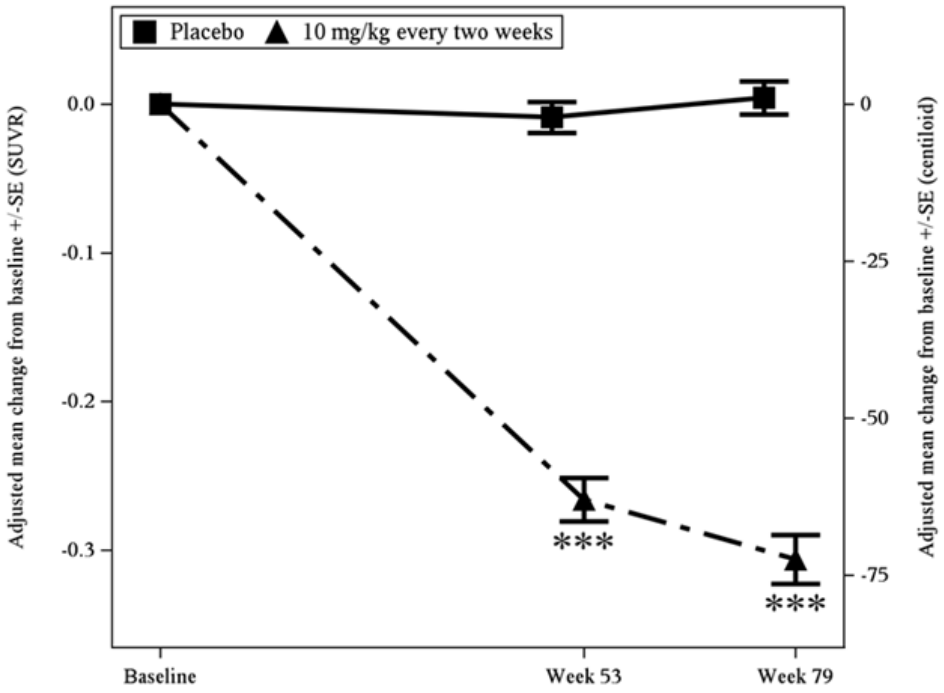
The efficacy of LEQEMBI was evaluated in a double-blind, placebo-controlled, parallel-group, dose finding study (Study 1, NCT01767311) in patients with Alzheimer's disease (patients with confirmed presence of amyloid pathology and mild cognitive impairment [64% of patients] or mild dementia stage of disease [36% of patients], consistent with Stage 3 and Stage 4 Alzheimer's disease). Study 1 had a 79-week double-blind, placebo-controlled period, followed by an open-label extension period for up to 260 weeks, which was initiated after a gap period (range 9 to 59 months; mean 24 months) off treatment.

In Study 1, 856 patients were randomized to receive one of 5 doses (161 of which were randomized to the recommended dosing regimen of 10 mg/kg every two weeks) of LEQEMBI or placebo (n=247). Of the total number of patients randomized, 71.4% were ApoE ε4 carriers and 28.6% were ApoE ε4 non-carriers. During the study the protocol was amended to no longer randomize ApoE ε4 carriers to the 10 mg/kg every two weeks dose arm. ApoE ε4 carriers who had been receiving LEQEMBI 10 mg/kg every two weeks for 6 months or less were discontinued from study drug. As a result, in the LEQEMBI 10 mg/kg every two weeks arm, 30.3% of patients were ApoE ε4 carriers and 69.7% were ApoE ε4 non-carriers. At baseline, the mean age of randomized patients was 71 years, with a range of 50 to 90 years. Fifty percent of patients were male and 90% were White.

Patients were enrolled with a Clinical Dementia Rating (CDR) global score of 0.5 or 1.0 and a Memory Box score of 0.5 or greater. All patients had a Mini-Mental State Examination (MMSE) score of ≥22, had objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the Wechsler-Memory Scale-IV Logical Memory II (subscale) (WMS-IV LMII). Patients were enrolled with or without concomitant approved therapies (cholinesterase inhibitors and the N-methyl-D-aspartate antagonist memantine) for Alzheimer's disease.

In Study 1, a subgroup of 315 patients were enrolled in the amyloid PET substudy; of these, 277 were evaluated at week 79. Results from the amyloid beta PET substudy are described in Figure 1 and Table 5. Plasma biomarkers are described in Table 5.

Figure 1: Reduction in Brain Amyloid Beta Plaque (Adjusted Mean Change from Baseline in Amyloid Beta PET Composite, SUVR and Centiloids) in Study 1



Number of patients			
Placebo	98	96	88
10 mg/kg every two weeks	44	43	37

***P<0.001

Table 5: Biomarker Results of LEQEMBI in Study 1

Biomarker Endpoints[1]	LEQEMBI 10 mg/kg every two weeks	Placebo
Amyloid Beta PET Composite SUVR	N=44	N=98
Mean baseline	1.373	1.402
Adjusted mean change from baseline at Week 79	-0.306	0.004
Difference from placebo	-0.310 (p<0.001)	
Amyloid Beta PET Centiloid	N=44	N=98
Mean baseline	78.0	84.8
Adjusted mean change from baseline at Week 79	-72.5	1.0
Difference from placebo	-73.5 (p<0.001)	
Plasma Aβ42/40[2]	N=43	N=88
Mean baseline	0.0842	0.0855
Adjusted mean change from baseline at Week 79	0.0075	0.0021
Difference from placebo	0.0054 (p=0.0036)	
Plasma p-tau181 (pg/mL)[2]	N=84	N=179
Mean baseline	4.6474	4.435
Adjusted mean change from baseline at Week 79	-1.1127	0.0832
Difference from placebo	-1.1960 (p<0.0001)	

N is the number of patients with baseline value.
[1] P-values were not statistically controlled for multiple comparisons.
[2] Plasma Aβ42/40 and plasma p-tau181 results should be interpreted with caution due to uncertainties in bioanalysis.

The primary endpoint was change from baseline on a weighted composite score consisting of selected items from the CDR-SB, MMSE, and ADAS-Cog 14 at Week 53. LEQEMBI had a 64% likelihood of 25% or greater slowing of progression on the primary endpoint relative to placebo at Week 53, which did not meet the prespecified success criterion of 80%.

Key secondary efficacy endpoints included the change from baseline in amyloid PET SUVR composite at Week 79 and change from baseline in the CDR-SB and ADAS-Cog14 at Week 79. Results for clinical assessments showed less change from baseline in CDR-SB and ADAS-Cog 14 scores at Week 79 in the LEQEMBI group than in patients on placebo (CDR-SB: -0.40 [26%], 90% CI [-0.82, 0.03]; ADAS-Cog 14: -2.31 [47%], 90% CI [-3.91, -0.72].

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

LEQEMBI (lecanemab-irmb) injection is a preservative-free, sterile, clear to opalescent, and colorless to pale yellow solution. LEQEMBI is supplied one vial per carton as follows:

500 mg/5 mL (100 mg/mL) single-dose vial (with white flip cap) – NDC 62856-215-01
200 mg/2 mL (100 mg/mL) single-dose vial (with dark grey flip cap) – NDC 62856-212-01

16.2 Storage and Handling

Unopened Vial

- Store in a refrigerator at 2°C to 8°C (36°F to 46°F).

- Store in the original carton to protect from light.
- Do not freeze or shake.

Diluted Solution

For storage of the diluted infusion solution, *see Dosage and Administration (2.5)*.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide).

Amyloid Related Imaging Abnormalities

Inform patients that LEQEMBI may cause Amyloid Related Imaging Abnormalities or "ARIA". ARIA most commonly presents as a temporary swelling in areas of the brain that usually resolves over time. Some people may also have small spots of bleeding in or on the surface of the brain. Inform patients that most people with swelling in areas of the brain do not experience symptoms, however, some people may experience symptoms such as headache, confusion, dizziness, vision changes, nausea, aphasia, weakness, or seizure. Instruct patients to notify their healthcare provider if these symptoms occur. Inform patients that events of intracerebral hemorrhage greater than 1 cm in diameter have been reported infrequently in patients taking LEQEMBI, and that the use of antithrombotic or thrombolytic medications while taking LEQEMBI may increase the risk of bleeding in the brain. Notify patients that their healthcare provider will perform MRI scans to monitor for ARIA *[see Warnings and Precautions (5.1)]*.

Inform patients that although ARIA can occur in any patient treated with LEQEMBI, there is an increased risk in patients who are ApoE ε4 homozygotes, and that there is a test available to determine ApoE ε4 genotype.

Patient Registry

Advise patients that the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) is a voluntary provider-enrolled patient registry that collects information on treatments for Alzheimer's disease, including LEQEMBI. Encourage patients to participate in the ALZ-NET registry *[see Warnings and Precautions (5.1)]*.

Infusion-Related Reactions

Advise patients of the potential risk of infusion-related reactions, which can include flu-like symptoms, nausea, vomiting, and changes in blood pressure, the majority of which occur with the first infusion *[see Warnings and Precautions (5.2)]*.

Manufactured by:
Eisai Inc.
Nutley, NJ 07110
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MEDICATION GUIDE
LEQEMBI™ (leh-kem'-bee)
(lecanemab-irmb)
injection, for intravenous use

What is the most important information I should know about LEQEMBI?
LEQEMBI can cause serious side effects including:

- **Amyloid Related Imaging Abnormalities or "ARIA". ARIA is a side effect that does not usually cause any symptoms but serious symptoms can occur.** ARIA is most commonly seen as temporary swelling in areas of the brain that usually resolves over time. Some people may also have small spots of bleeding in or on the surface of the brain, and infrequently, larger areas of bleeding in the brain can occur. Most people with this type of swelling in the brain do not get symptoms, however some people may have symptoms, such as:
  - headache
  - confusion
  - dizziness
  - vision changes
  - nausea
  - difficulty walking
  - seizures

Your healthcare provider will do magnetic resonance imaging (MRI) scans before and during your treatment with LEQEMBI to check you for ARIA. Some people have a genetic risk factor (homozygous apolipoprotein E gene carriers) that may cause an increased risk for ARIA. Talk to your healthcare provider about testing to see if you have this risk factor.

Call your healthcare provider or go to the nearest hospital emergency room right away if you have any of the symptoms listed above.

What is LEQEMBI?
LEQEMBI is a prescription medicine used to treat people with Alzheimer's disease.
It is not known if LEQEMBI is safe and effective in children.

Before receiving LEQEMBI, tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. It is not known if LEQEMBI will harm your unborn baby. Tell your healthcare provider if you become pregnant during your treatment with LEQEMBI.
- are breastfeeding or plan to breastfeed. It is not known if lecanemab-irmb (the active ingredient in LEQEMBI) passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while receiving LEQEMBI.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Especially tell your healthcare provider if you take medicines to reduce blood clots from forming (antithrombotic medicines, including aspirin). Ask your healthcare provider for a list of these medicines if you are not sure.
Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How will I receive LEQEMBI?

- LEQEMBI is given by a healthcare provider through a needle placed in your vein (intravenous (IV) infusion) in your arm.
- LEQEMBI is given every 2 weeks. Each infusion will last about 1 hour.
- If you miss an infusion of LEQEMBI, you should receive your next dose as soon as possible.

What are the possible side effects of LEQEMBI?
LEQEMBI can cause serious side effects, including:

- **see "What is the most important information I should know about LEQEMBI?"**
- **infusion-related reactions. Infusion-related reactions are a common side effect which can be serious. Tell your healthcare provider right away if you get these symptoms during an infusion of LEQEMBI:**
  - fever
  - flu-like symptoms (chills, body aches, feeling shaky and joint pain)
  - nausea
  - vomiting
  - dizziness or lightheadedness
  - changes in your heart rate or feel like your chest is pounding
  - difficulty breathing or shortness of breath

If you have an infusion-related reaction, your healthcare provider may give you medicines before your LEQEMBI infusions to decrease your chance of having an infusion-related reaction. These medicines may include antihistamines, anti-inflammatory medicines, or steroids.

The most common side effects of LEQEMBI include:

- infusion-related reactions
- headache
  swelling in areas of the brain, with or without small spots of bleeding in or on the surface of the brain (ARIA)

These are not all the possible side effects of LEQEMBI. For more information, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of LEQEMBI.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about LEQEMBI that is written for healthcare professionals.

There is a registry that collects information on treatments for Alzheimer's disease. The registry is named ALZ-NET (Alzheimer's Network for Treatment and Diagnostics). Your healthcare provider can help you become enrolled in this registry.

What are the ingredients in LEQEMBI?
Active ingredient: lecanemab-irmb.

Inactive ingredients: arginine hydrochloride, histidine, histidine hydrochloride monohydrate, polysorbate 80, and water for injection.

Manufactured by:
Eisai Inc.
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