Lecanemab

Peripheral and Central Nervous System Drugs Advisory Committee

June 9, 2023

Introductory Comments

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Lecanemab

- Lecanemab (Leqembi) was approved on January 6, 2023, 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 [see Clinical Studies (14)]. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.

Approval Pathways

- Traditional Approval
  - Substantial evidence of effectiveness demonstrated on a clinically meaningful endpoint (e.g., how a patient feels, functions, or survives) or validated surrogate
  - Drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling

Approval Pathways

- Accelerated Approval (21 CFR 314.500 - subpart H, accelerated approval regulations)
  - May be considered for serious or life-threatening diseases with an unmet need
  - Substantial evidence of effectiveness demonstrated on an endpoint that is not itself a direct measure of the clinical benefit of interest but is instead reasonably likely to predict that clinical benefit (e.g., surrogate or intermediate clinical endpoint) based on "epidemiologic, therapeutic, pathophysiologic, or other evidence"
  - FDA may require further adequate and well-controlled clinical trials to verify and describe clinical benefit for products approved under accelerated approval in order to obtain traditional approval

Lecanemab Accelerated Approval

- The accelerated approval of lecanemab took into consideration the following:
  - Alzheimer's disease is a serious or life-threatening diseases with an unmet need
  - Substantial evidence of effectiveness was demonstrated on a surrogate endpoint, reduction in amyloid plaque burden measured by positron emission tomography (PET) imaging, that was determined to be reasonably likely to predict clinical benefit
  - An ongoing/completed Phase 3 randomized, controlled clinical trial that could potentially verify the clinical benefit of lecanemab for the treatment of Alzheimer's disease (issued as post-marketing requirement (PMR) 4384-1)
- This submission contains results of Study 301 (CLARITY AD) that are intended to fulfill the PMR and verify the clinical benefit of lecanemab for the treatment of Alzheimer's disease

Study 301 (CLARITY AD)

- An 18-month (78-week) multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with mild cognitive impairment due to Alzheimer's disease (AD) or mild AD dementia
- Randomization to placebo (n=897) or lecanemab 10 mg/kg biweekly (n=898) in a 1:1 ratio
- Statistically significant treatment effects were demonstrated on the primary endpoint and secondary endpoints
  - Primary endpoint: change from baseline in the Clinical Dementia Rating - Sum of Boxes (CDR-SB) at 18 months of treatment
  - Secondary endpoints:
    - Brain amyloid plaque levels as measured by PET
    - Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog 14),
    - Alzheimer's Disease Composite Score (ADCOMS)
    - Alzheimer's Disease Cooperative Study – Activities of Daily Living – Mild Cognitive Impairment (ADCS-ADL-MCI)

Safety of Lecanemab

- Approved prescribing information (PI) for lecanemab includes warnings for:
  - Amyloid-related imaging abnormalities (ARIA)
    - Findings of edema (ARIA-E) or microhemorrhages and superficial siderosis (ARIA-H) on MRI
    - Usually asymptomatic but serious and life-threatening events can occur
  - Infusion-related reactions
- Safety in Study 301 appears to be generally consistent with current approved labeling for lecanemab

Questions for the Advisory Committee

- **Discussion:** Discuss the results from Study 301 (CLARITY AD) and whether they provide evidence of clinical benefit of lecanemab for the treatment of Alzheimer's disease (AD).
- **Vote:** Do the results of Study 301 (CLARITY AD) verify the clinical benefit of lecanemab for the treatment of AD?
- **Discussion:** Discuss the overall benefit/risk assessment of lecanemab for the treatment of AD. Additionally, consider the following subgroups in your assessment:
  - Apolipoprotein E (ApoE) ε4 homozygotes
  - Patients requiring concomitant treatment with anticoagulant agents
  - Patients with cerebral amyloid angiopathy

Clinical Overview of Efficacy

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Lecanemab

- Lecanemab is an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease
  - Received accelerated approval January 6, 2023
- Mechanism of Action:
  - Monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta
- Proposed Dosing Regimen
  - 10 mg/kg administered as an IV infusion once every two weeks

Anti-Amyloid Therapies Are Not a Distinct Class

- Previous failures of “anti-amyloid” therapies
  - Inclusion of individuals without evidence of brain amyloid pathology or at later stages of Alzheimer’s disease
  - Insufficient dosing
  - Unknown target engagement
  - Off-target effect
  - Lacking proof-of-concept prior to Phase 3 trials
  - ***Did not clear brain amyloid plaque***
- Newer generation of anti-amyloid therapies targeting aggregated amyloid has learned from previous failures

Accumulated evidence has established that robust reduction of brain amyloid plaque is associated with a reduction in clinical decline over 18 months

Clinical Studies Relevant to Evaluation of Efficacy

- Study 201
  - Multicenter, randomized, double-blind, placebo-controlled study
  - Primary objectives: dose-regimen determination, safety, and tolerability
  - Observed reduction in brain amyloid plaque supported accelerated approval
- Study 301 (Clarity AD)
  - Multicenter, global, randomized, double-blind, placebo-controlled study
  - Primary objective: Efficacy and safety of lecanemab
  - In September 2021, FDA agreed that Study 301 may serve as a confirmatory clinical trial to verify the clinical benefit of lecanemab

Study 301: Trial Design

N=1795

Key eligibility criteria:
- MCI due to AD or mild AD dementia
- CDR global score of 0 or 1
- Positive amyloid pathology (PET or CSF)
- MMSE score ≥22

Core Phase (18 months)

Lecanemab (IV infusion) 10 mg/kg biweekly (n=898)

R 1:1

Placebo (IV infusion) biweekly (n=897)

Open-Label Extension (Up to 4 years)

Open-label lecanemab

Optional Longitudinal Studies:
- Amyloid PET; n=716
- Tau PET; n=257
- CSF biomarkers; n=281

Stratification factors:
- Clinical subgroup (MCI or mild AD dementia)
- ApoE ε4 status (carrier or non-carrier)
- Ongoing treatment with AD medications
- Geographic region

Primary Endpoint:
- CDR-SB at 18 months

Secondary Endpoints:
- Amyloid PET
- ADAS-Cog 14
- ADCOMS
- ADCS-ADL-MCI

Raters blinded to safety assessment

AD: Alzheimer's Disease, ADCOMS: Alzheimer's Disease Composite Score, CDR-SB: Clinical Dementia Rating-Sum of Boxes, MMSE: Mini-Mental State Examination, ADAS-Cog 14: Alzheimer's Disease Assessment Scale – Cognitive 14-Item Scale, ADCS-ADL-MCI: Alzheimer's Disease Cooperative Study Activities of Daily Living-Mild Cognitive Impairment, ApoE: apolipoprotein E, CSF: cerebrospinal fluid, PET: positron emission tomography

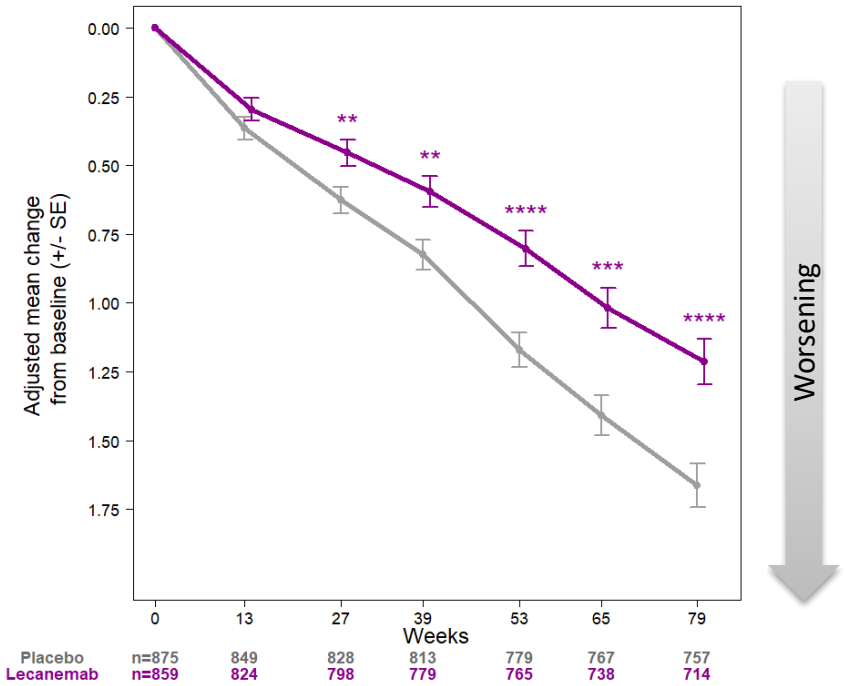
Efficacy Analysis Sets

- EMA/PMDA
  - Full Analysis Set+ (FAS+)
  - Randomized subjects who received at least one dose, have baseline assessment, and at least one post-dose primary efficacy measurement
- FDA/global
  - Full Analysis Set (FAS)
  - Excluded subjects randomized on or before the end date of dosing hold at sites which had dosing holds ≥6 weeks (i.e., 3 consecutive doses)
  - Excludes 68 subjects (42 placebo, 26 lecanemab) from 19 sites who missed ≥3 consecutive doses*

* Correction to FDA Briefing Document

EMA: European Medicines Agency, PMDA: Pharmaceuticals and Medical Devices Agency (Japan)

Study 301 Met Primary Endpoint (CDR-SB)



- Statistically significant reduction in decline (-0.45[-27%], p=0.00005)
- Similar observation in FAS population (-0.39[-25%], p=0.0004)
- Placebo decline of 1.66 over 18 months
- Robust to prespecified sensitivity analyses, including non-normality and potential of functional unblinding due to ARIA or infusion reactions

CDR-SB: Clinical Dementia Rating-Sum of Boxes, FAS: Full Analyses Set, ARIA: amyloid-related imaging abnormalities

Study 301 Met All Secondary Endpoints

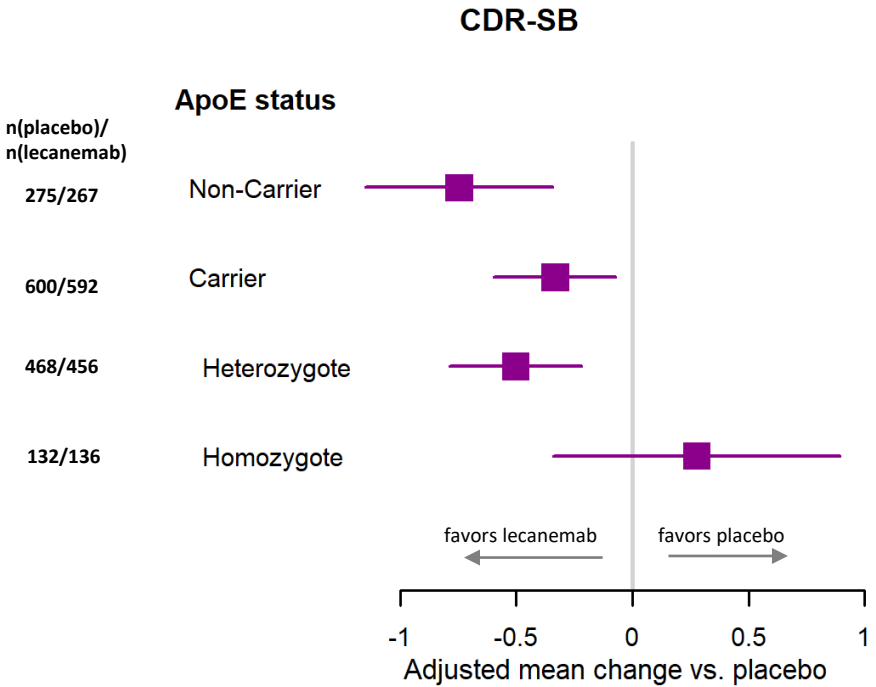
	Placebo Decline (N=875)		Lecanemab (N=859)			
Secondary Endpoint	**n**	**Adjusted Mean**	**n**	**Adjusted Mean**	**Difference vs. Placebo (%)**	**p-value**
ADAS-Cog 14	738	5.58	703	4.14	-1.44 (-26%)	p=0.00065
ADCS-ADL-MCI	707	-5.50	676	-3.48	2.02 (-37%)	p<0.00001
ADCOMS	749	0.21	708	0.16	-0.05 (-24%)	p=0.00002

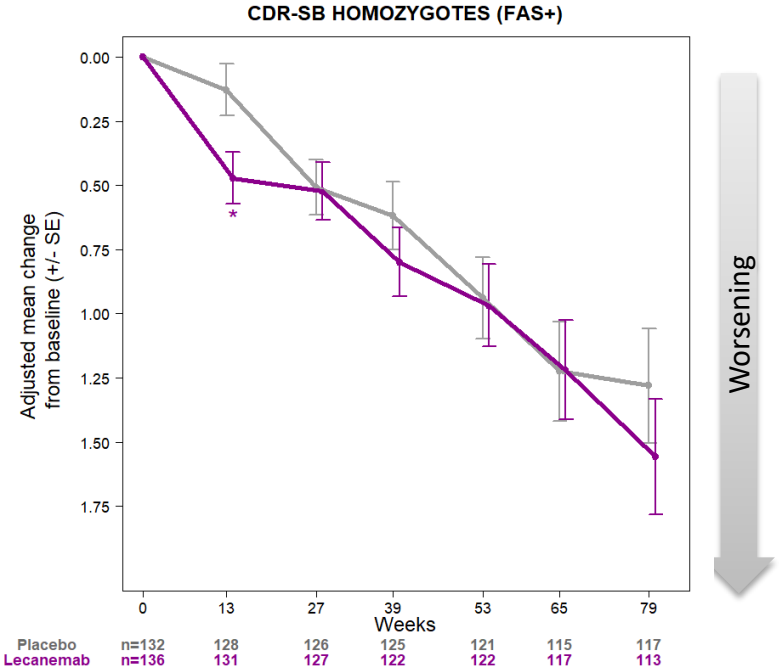
Source: Tables 14.2.2.2.2, 14.2.2.3.2, and 14.2.2.4.2 In Study 301 CSR
FAS+ Population

- **Statistically significant reduction in brain amyloid (-59.1 Centiloids, p<0.00001)**
- Similar results observed in FAS population

ADAS-Cog 14: Alzheimer's Disease Assessment Scale – Cognitive 14-Item Scale, ADCS-ADL-MCI: Alzheimer's Disease Cooperative Study Activities of Daily Living-Mild Cognitive Impairment, ADCOMS: Alzheimer's Disease Composite Score, FAS+ - full analysis set

CDR-SB in Homozygous ApoE ε4 Carriers Was Only Subgroup for Which Treatment Contrast Did Not Favor Lecanemab

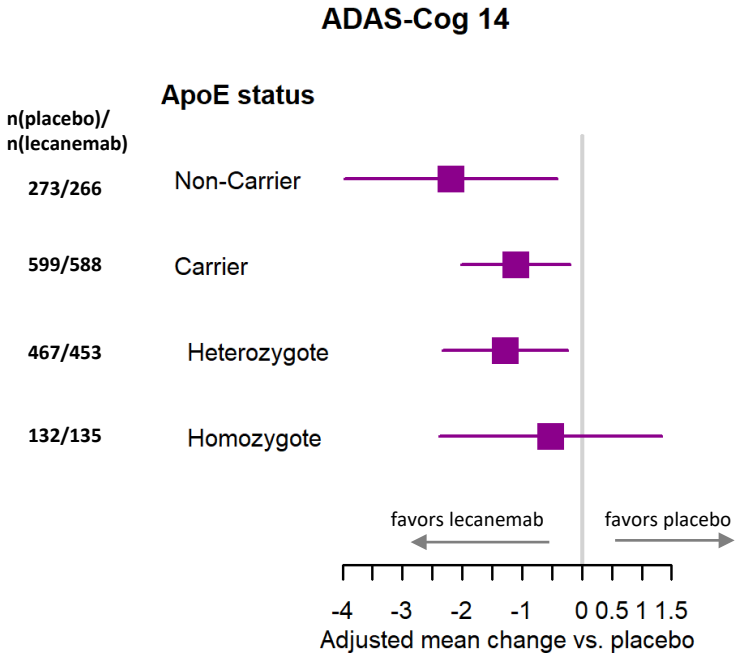


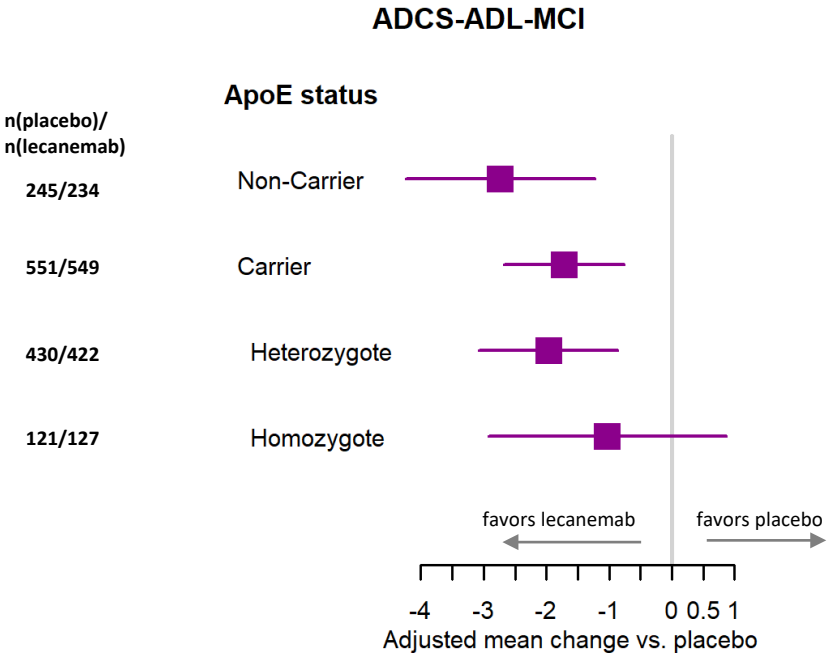


ApoE: apolipoprotein E, CDR-SB: Clinical Dementia Rating-Sum of Boxes, FAS+ - full analysis set

Longitudinal results for treatment and placebo groups largely overlap

Key Secondary Clinical Endpoints Favored Lecanemab in ApoE ε4 Homozygotes





Similar trends favoring lecanemab were observed for health outcome assessments and biomarkers

ADAS-Cog 14: Alzheimer's Disease Assessment Scale – Cognitive 14-Item Scale, ADCS-ADL-MCI: Alzheimer's Disease Cooperative Study Activities of Daily Living-Mild Cognitive Impairment, ApoE: apolipoprotein E

Treatment Effect in Homozygous ApoE ε4 Carriers

- No *a priori* expectation for diminished treatment effect in ApoE ε4 carriers or for a different effect in homozygous and heterozygous carriers
- Inconsistent findings in ApoE ε4 carrier subgroups across other therapies in the class
- Stratification was based on ApoE ε4 carrier status (carrier/non-carrier) and not genotype (homozygous/heterozygous)
- Size of homozygous ApoE ε4 carrier subgroup is one of smallest tested in Study 301
- Results for secondary endpoints, health outcome measures, and biomarkers all support treatment effect in homozygous ApoE ε4 carriers

Confirmation of Clinical Benefit of Lecanemab

- Study 301 met primary endpoint, reducing change from baseline on CDR-SB (-0.45, p=0.00005), an integrated scale that meaningfully assesses function and cognition
- Statistically significant treatment effects on all multiplicity-controlled secondary endpoints (amyloid PET, ADAS-Cog 14, ADCOMS, ADCS-ADL-MCI)
- Supported by favorable results across prespecified subgroups
- Biomarkers reflecting target engagement (brain amyloid), downstream tau pathophysiology (tau PET), and neurodegeneration (t-tau) support observations on clinical outcome measures

U.S. FOOD & DRUG ADMINISTRATION

Statistical Overview

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Analysis Populations

- FAS+: all randomized patients who received at least one dose of study drug and had a baseline assessment and at least one post-baseline CDR-SB assessment
- FDA FAS: subset of FAS+ with prespecified exclusion of 68 patients at sites closed for 6 or more weeks during peak COVID period in 2020
- Sample size was to be increased by 200 patients to a total of approximately 1766 randomized patients in Dec 2020, due to concerns about missed doses related to the COVID-19 pandemic

Analysis Methods

- Primary analysis: CDR-SB analyzed by a mixed model for repeated measures (MMRM) in the FDA FAS population to compare the treatment group difference at Week 79
  - Covariates used in the MMRM model: baseline score, visit (categorical), baseline score by visit interaction, presence of concomitant AD medications, baseline disease severity (MCI/Mild AD), APOE4 status, region, treatment group, and treatment group-by-visit interactions
  - CDR-SB assessments collected after changes in concomitant AD medications are included
  - Handling of missing data was based on “missing at random” assumption

Subject Disposition

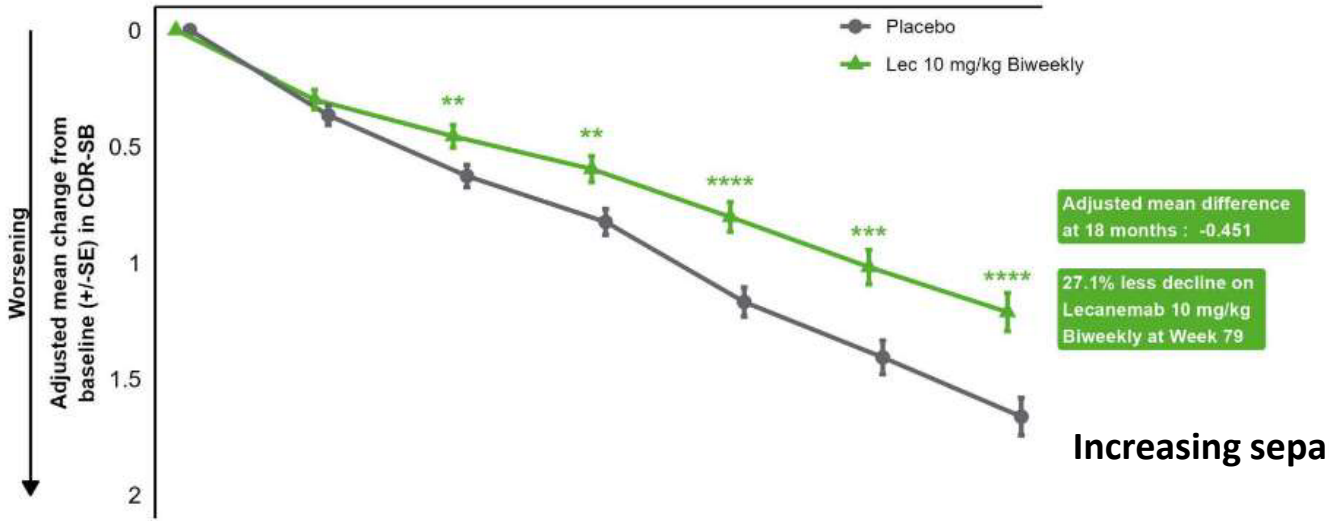
	Placebo	Lecanemab 10 mg/kg biweekly
Randomized	897	898
FAS+	875	859
FDA FAS	833	833
Symptomatic Alzheimer's medication changes	101 (11.2%)	96 (10.7%)
Deaths within 79 Weeks	8	7
Missing Week 79 CDR-SB assessment	140 (15.6%)	184 (20.5%)

Primary Results in FAS+

Endpoint	Treatment Group	N	Baseline Score	Week 79 LS Mean	PBO-LEC Difference (95% C.I.)	p-value
CDR-SB	Placebo	875	3.22	1.66	0.45 (0.23, 0.67)	<0.0001
	Lecanemab	859	3.17	1.21	--	

Note: FDA FAS (Covid pandemic related exclusions) and FAS+ population results are consistent

Change in CDR-SB Over Time in Controlled Phase (FAS+)



	Baseline	Week 13	Week 27	Week 39	Week 53	Week 65	Week 79
Placebo	875	849	828	813	779	767	757
Lec 10 mg/kg Biweekly	859	824	798	779	765	738	714

Increasing separation over time

Sensitivity Analyses

- Selected Sensitivity analyses:
  - Tipping point analysis to explore sensitivity to alternative missing not at random assumptions
  - Censoring assessments after initiation/dose adjustment of symptomatic AD drug or treatment discontinuation
  - Censoring assessments after ARIA adverse events
  - With imputation as if control patient for lecanemab arm after study discontinuation due to treatment-related adverse events
  - Full ITT population analysis

- The analyses show that the result of the primary analysis on CDR-SB is reasonably insensitive to the handlings of missing data and intercurrent events

Key Secondary Endpoint Results

Endpoint	Treatment Group	N	Baseline score	Week 79 LS Mean	PBO-LEC Difference (95% C.I.)	p-value
Amyloid PET (Centiloids)	Placebo	325	1.4	3.6	59.2 (55.6, 62.7)	<.0001
	Lecanemab	342	1.4	-55.5	--	
ADAS-COG-14	Placebo	872	24.4	5.6	1.4 (0.6, 2.3)	0.0007
	Lecanemab	854	24.4	4.2	--	
ADCOMS (x 100)	Placebo	833	39.9	20.9	4.5 (2.2, 6.9)	0.0002
	Lecanemab	831	39.7	16.3	--	
ADCS-ADL-MCI	Placebo	796	41.1	-5.5	-2.0 (-2.8, -1.2)	<.0001
	Lecanemab	783	41.3	-3.5	--	

Note: Study 301 satisfied Hierarchical Testing Plan to account for multiplicity

Summary

- Study 301 provides statistical evidence for lecanemab, based on the results of primary endpoint and key secondary endpoints
  - Week 79 CDR-SB difference 0.45 (95% C.I.= 0.23, 0.67)
    - Difference emerges by Week 27 and increases over time
  - Key secondaries:
    - ADAS-Cog-14 difference: 1.4 (95% C.I.= 0.6, 2.3)
    - ADCOMS difference: 0.05 (95% C.I.=0.02, 0.07)
    - ADCS-ADL-MCI difference: -2.0 (95% C.I. -2.8, -1.2)
- Dr. Erten-Lyons will present the safety data

Clinical Overview of Safety

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Key Safety Issues

- Infusion Related Reactions and Hypersensitivity
- Amyloid Related Imaging Abnormalities (ARIA)
- Cerebral Hemorrhage

Overview of Safety in Study 301

	Placebo N=898 n (%)	Lecanemab N=898 n (%)
Deaths*	7 (0.8)	6 (0.7)
Treatment Emergent Adverse Events	737 (82)	800 (89)

** Includes deaths for which the precipitating event occurred within 30 days of a dose of lecanemab*

Most Common Treatment Emergent Adverse Events in Study 301

Adverse Reaction	Placebo N= 897 n (%)	Lecanemab N =898 n (%)
Infusion related reaction	64 (7)	236 (26)
ARIA-E	15 (2)	113 (13)
ARIA-H microhemorrhage	69 (8)	126 (14)
Headache	73 (8)	101 (11)

Amyloid Related Imaging Abnormalities (ARIA)

- Monoclonal antibodies directed against aggregated forms of beta amyloid (Aβ), including lecanemab, can cause ARIA, observed on brain MRI.
- It is hypothesized that anti-Aβ antibodies accelerate breakdown and clearance of Aβ, which may disrupt vascular integrity and result in leakage into surrounding tissues with parenchymal or sulcal changes observed on MRI:
  - ARIA-E (edema): vasogenic edema or sulcal effusion.
  - ARIA-H (hemosiderin deposition): microhemorrhage and superficial siderosis.

ARIA

- ARIA can occur spontaneously in patients with Alzheimer's disease (AD) or cerebral amyloid angiopathy (CAA).
- ARIA-H and ARIA-E can occur together.
- ARIA is usually asymptomatic, although rarely serious and life-threatening events can occur. When present, reported symptoms associated with ARIA may include headache, confusion, visual changes, dizziness, nausea, gait difficulty, and focal neurologic deficits.

Incidence of ARIA and Cerebral Hemorrhage in Study 301

	Placebo N=897 n (%)	Lecanemab N=897 n (%)
ARIA	84 (9)	191 (21)
Symptomatic ARIA	2 (0.2)	29 (3)
ARIA-E	15 (2)	113 (13)
ARIA-H Isolated ARIA-H	80 (9) 69 (8)	152 (17) 78 (9)
ARIA-H microhemorrhage	68 (8)	126 (14)
ARIA-H superficial siderosis	21 (2)	50 (6)
Cerebral Hemorrhage*	0 (0)	6 (0.7)

**Cerebral hemorrhage >1cm occurring within 40 days of last dose included*

Incidence of ARIA and Cerebral Hemorrhage by ApoE ε4 Status in Study 301

	Non-Carriers		Heterozygote		Homozygote	
	Placebo n=286 n (%)	Lecanemab N=278 n (%)	Placebo N=478 n (%)	Lecanemab N=479 n (%)	Placebo N=133 n (%)	Lecanemab N=141 n (%)
ARIA	11 (4)	37* (13)	44 (9)	91* (19)	29 (22)	63 (45)
ARIA-E	1 (0.3)	15 (5)	9 (2)	52 (11)	5 (4)	46 (33)
ARIA-H	11 (4)	32 (12)	41 (9)	66 (14)	28 (21)	54 (38)
Cerebral Hemorrhage	0	1 (0.4)	0	3 (0.6)	0	2 (1)

** Correction to FDA Briefing Document.*
ARIA-H includes microhemorrhages and superficial siderosis, excludes cerebral hemorrhage.
Cerebral hemorrhage>1cm occurring within 40 days of last dose included.

Incidence of Cerebral Hemorrhage With Antithrombotics in Study 301

	Cerebral Hemorrhage	
	Placebo	**Lecanemab**
Not on antithrombotic	0/584	3/545 (0.6)
On antithrombotic	0/304	3/328 (0.9)
Aspirin ≤81 mg	0/144	0/162
Aspirin ≥81 mg, other antiplatelet or dual antiplatelet	0/107	1/116 (0.9)
Anticoagulation	0/72	2/79 (2.5)

Source: Extracted from Eisai Table sBLA IR9-1mod, submitted May 1, 2023, cerebral hemorrhage>1cm occurring within 40 days of last dose included

Deaths Associated With Cerebral Amyloid Angiopathy (CAA) and Inflammatory Vasculitis in Study 301

- A high burden of CAA and findings consistent with an inflammatory vasculitis were identified on autopsy in 2 deaths in ApoE ε4 homozygotes on lecanemab, both of whom complained of headaches shortly after exposure to lecanemab. An additional death with possible CAA occurred in an ApoE ε3 homozygote with cerebral hemorrhage in the setting of confounding factors including anticoagulant use.
- The inflammatory vasculitis in the 2 cases with a high burden of CAA resembled CAA related inflammation (CAA-ri), a spontaneous inflammatory response to the vascular amyloid deposits which presents with symptoms and imaging findings similar to ARIA-E and ARIA-H. [1,2]
- The risk of both severe CAA and CAA-ri is highest in ApoE ε4 homozygotes.[1, 3]
- Up to 90% of patients with AD are reported to have some degree of underlying CAA, but not all show characteristics MRI findings during life.[4, 5]
- Risk of lecanemab use in patients with CAA is not well characterized; the benefit-risk discussion needs to consider the uncertainties with this potential risk.

1. Souza et al. Inflammatory Cerebral Amyloid Angiopathy: A Broad Clinical Spectrum. J Clin Neurol 2023;19(3):230-241.
2. Sperling et al. Amyloid Related Imaging Abnormalities (ARIA) in Amyloid Modifying Therapeutic Trials: Recommendations from the Alzheimer's Association Research Roundtable Workgroup. Alzheimers Dement.2011 July; 7(4) 367-385.
3. Ringman JM et al. Cerebral Amyloid Angiopathy and influence of *APOE* Genotype in Persons with Pathologically Verified Alzheimer Disease. JAMA Neurol 2014; 71:878-883
4. Love S et al. Insights into the pathogenesis and pathogenicity of cerebral amyloid angiopathy. Frontiers in Bioscience 14, 4778-4792, January 1, 2009.
5. Jäkel L et al. Prevalence of cerebral amyloid angiopathy: A systematic review and meta-analysis. Alzheimers Dement. 2022 Jan;18(1):10-28

Safety Summary and Conclusions

- ARIA, cerebral hemorrhage, infusion-related reactions and hypersensitivity are the main safety signals associated with lecanemab.
- Risk of ARIA is higher in ApoE ε4 homozygotes compared to heterozygotes and noncarriers.
- Risk in the presence of CAA, or with antithrombotic use are not well characterized; the benefit-risk discussion needs to consider these uncertainties with the potential risks.
- Risks and uncertainties can be described in prescribing information.
- Prescriber and patient education regarding ARIA, and surveillance for any new or worsening neurological symptoms and follow up with unscheduled MRIs, particularly in ApoE ε4 homozygotes, may mitigate some risks of ARIA associated with lecanemab.

Concluding Remarks

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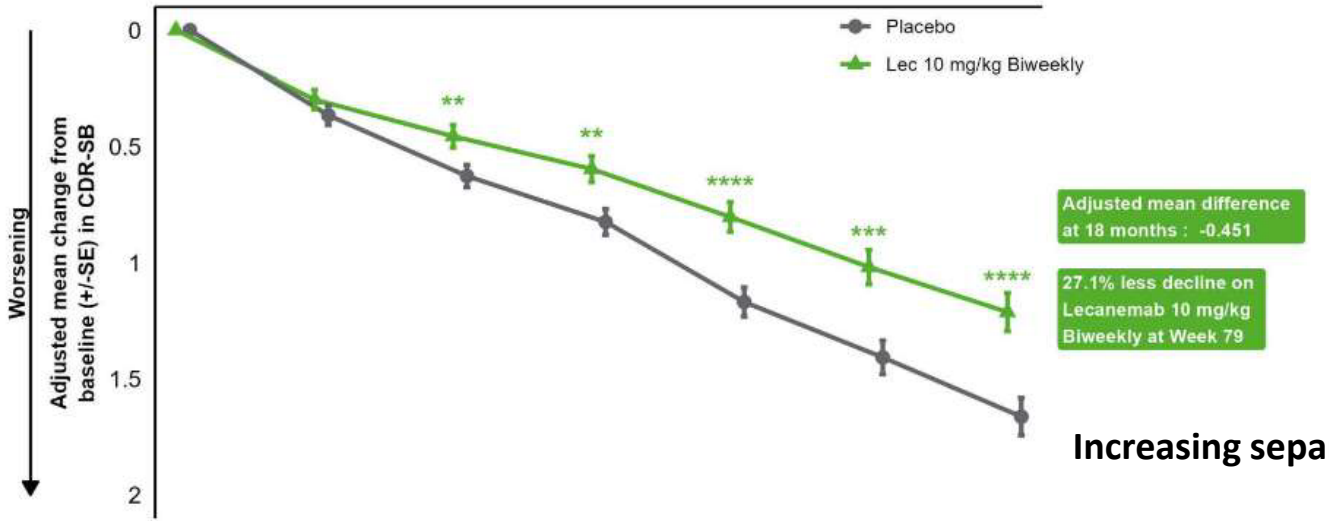
Clinical Dementia Rating Scale-sum of boxes

Scored as decline from previous usual level due to cognitive loss, not impairment due to other factors.

	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Source: https://knightadrc.wustl.edu/wp-content/uploads/2021/06/CDR-Table.pdf

Change in CDR-SB Over Time in Controlled Phase (FAS+)



	Baseline	Week 13	Week 27	Week 39	Week 53	Week 65	Week 79
Placebo	875	849	828	813	779	767	757
Lec 10 mg/kg Biweekly	859	824	798	779	765	738	714

Increasing separation over time

Lecanemab safety

- Identified risks of ARIA and infusion-related reactions are currently described as Warnings in the lecanemab prescribing information (PI) based on the Phase 2 study
- PI will be updated to incorporate safety information from Study 301

5 WARNINGS AND PRECAUTIONS

5.1 Amyloid Related Imaging Abnormalities

5.2 Infusion-Related Reactions

Apolipoprotein E (ApoE) ε4 homozygotes

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.

Concomitant Antithrombotic Medications

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.

Cerebral Amyloid Angiopathy

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.

Questions for the Advisory Committee

- **Discussion:** Discuss the results from Study 301 (CLARITY AD) and whether they provide evidence of clinical benefit of lecanemab for the treatment of Alzheimer's disease (AD).
- **Vote:** Do the results of Study 301 (CLARITY AD) verify the clinical benefit of lecanemab for the treatment of AD?
- **Discussion:** Discuss the overall benefit/risk assessment of lecanemab for the treatment of AD. Additionally, consider the following subgroups in your assessment:
  - Apolipoprotein E (ApoE) ε4 homozygotes
  - Patients requiring concomitant treatment with anticoagulant agents
  - Patients with cerebral amyloid angiopathy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Backup Slides Shown

Current pharmacovigilance measures for lecanemab

- Expedited reporting of any deaths in ongoing studies and of deaths resulting from cerebral hemorrhage greater than 1 centimeter in size in the postmarketing setting.
- Postmarketing pharmacovigilance to characterize the risk of ARIA and the monitoring for ARIA associated with the use of Leqembi, with biannual reports of ARIA-E and ARIA-H (specifying microhemorrhage or superficial siderosis), along with any incident cerebral hemorrhage greater than 1 centimeter in size.
- Postmarketing pharmacovigilance with biannual reports to identify and analyze cases of vasculitis that occur after use of Leqembi.
- Postmarketing pharmacovigilance to characterize the risk of infusion reactions associated with the use of Leqembi.