Baseline Characteristics for Clarity AD:

A Phase 3 Placebo-Controlled, Double-Blind, Parallel-Group, 18-Month Study Evaluating Lecanemab (BAN2401) in Early Alzheimer's Disease

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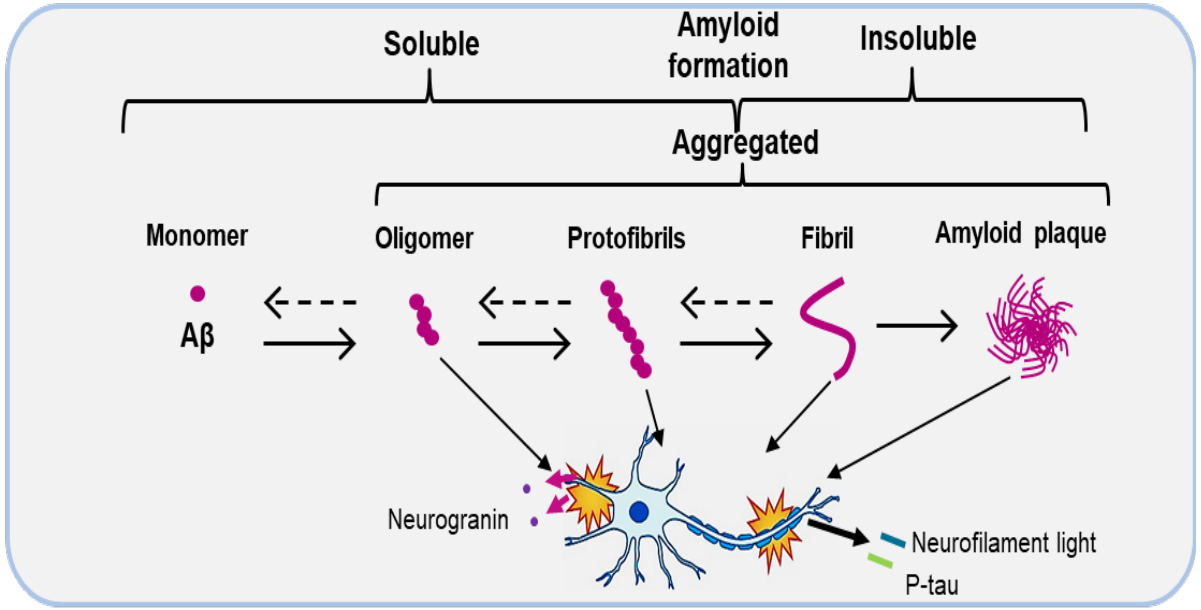
Disclosures

- Dr Swanson is an employee of Eisai Ltd.
- All authors are employees or former employees of Eisai Inc., Eisai Ltd, or Eisai Co Ltd.

Lecanemab Preferentially Binds Large Soluble Aβ Aggregates

- Humanized immunoglobulin G1 (IgG1) monoclonal antibody
- Selectively binds to soluble Aβ aggregate species
  - >1000-fold selectivity for protofibrils over Aβ monomers (low affinity for Aβ monomer[1])
  - Preferential activity for Aβ protofibrils over fibrils (>10x) [2-5]
- Placebo Controlled Randomized phase 2 study (N=856)[6]
  - Reduction in brain amyloid accompanied by a consistent reduction of clinical decline across several clinical and biomarker endpoints was demonstrated
  - Well-tolerated with 9.9% ARIA-E



ARIA-E = Amyloid related imaging abnormalities

1. Tucker S, et al. J Alzheimers Dis. 2015;43(2):575-88. 2. Lord A, et al. *Neurobiol Dis*. 2009;36:425–34. 3. Sehlin D, et al. *PLoS One*. 2012;7:e32014. 4. Sehlin D, et al. *Neurodegener Dis*. 2011;8:117–23. 5. Logovinsky V, et al. *Alzheimer's Research & Therapy*. 2016;8:14. 6. Swanson et al. Alzheimers Res Ther. 2021;13(1):80.

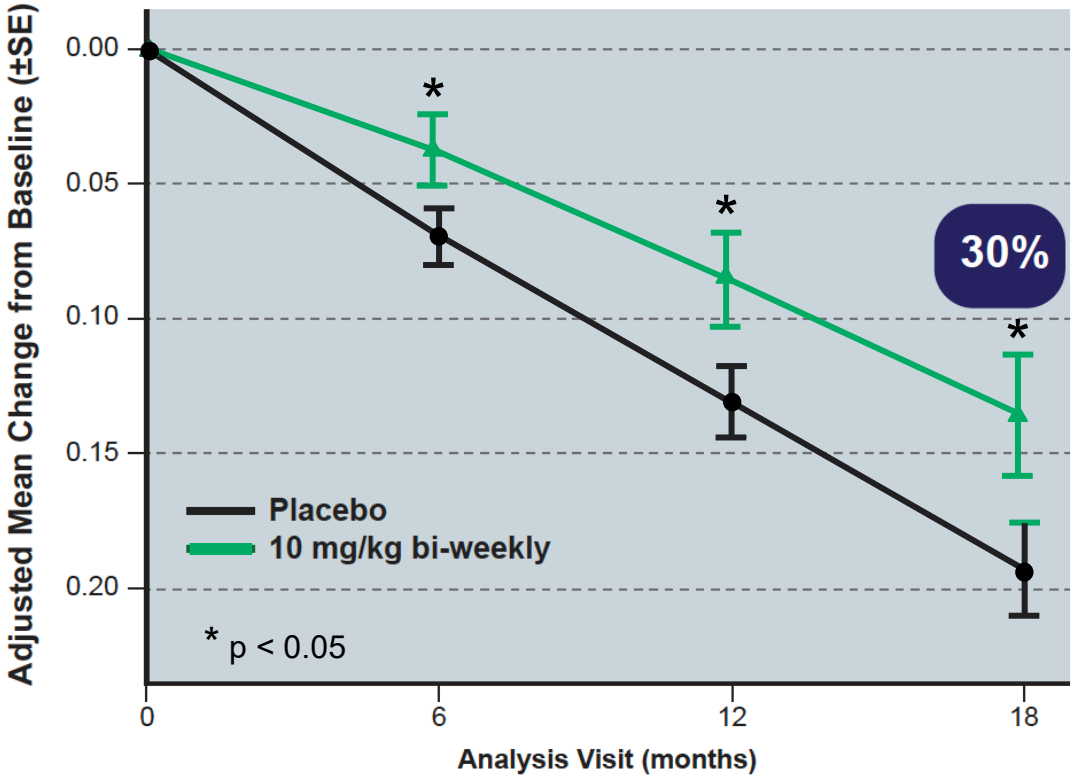
Lecanemab Phase 2 Core Study Results:

Early Clinical Effects: Amyloid Reduction Correlates with Reduction in Clinical Decline

- Clinical decline slowed as early as 6 months in assessments of cognition and function
- Core Phase 2 data suggest that clinical efficacy is correlated with amyloid reduction

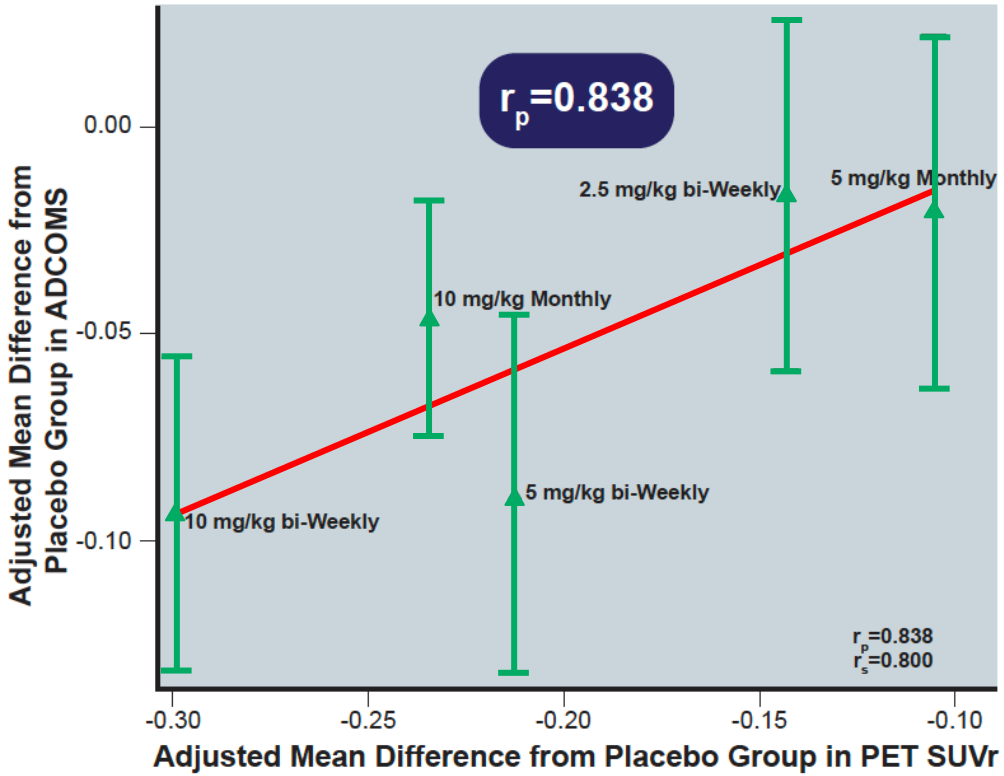
ADCOMS

Similar results for CDR-SB and ADAS-cog



ADCOMS / PET*

Similar results for CDR-SB and ADAS-cog



CDR-SB: Clinical Dementia Rating, sum of boxes. ADCOMS: Alzheimer's Disease Composite Score. ADAS-cog: Alzheimer's Disease Assessment Scale–cognitive subscale. PET SUVr: positron emission topography standardized uptake value ratio. ç
Adjusted mean was based on a protocol-specified mixed model for repeated measures (MMRM). The MMRM included baseline as a covariate, with treatment group, visit, region, randomization stratification variables (clinical stage, concurrent AD medication, APOE4 status), and treatment group-by-visit interaction as fixed effects. Analysis population: FAS. Data shown in right figure are for subjects enrolled in the PET sub-study with PET SUVr and clinical data at 12 or 18 months. *: r_p is Pearsons' correlation coefficient and r_s is Spearman's correlation coefficient.

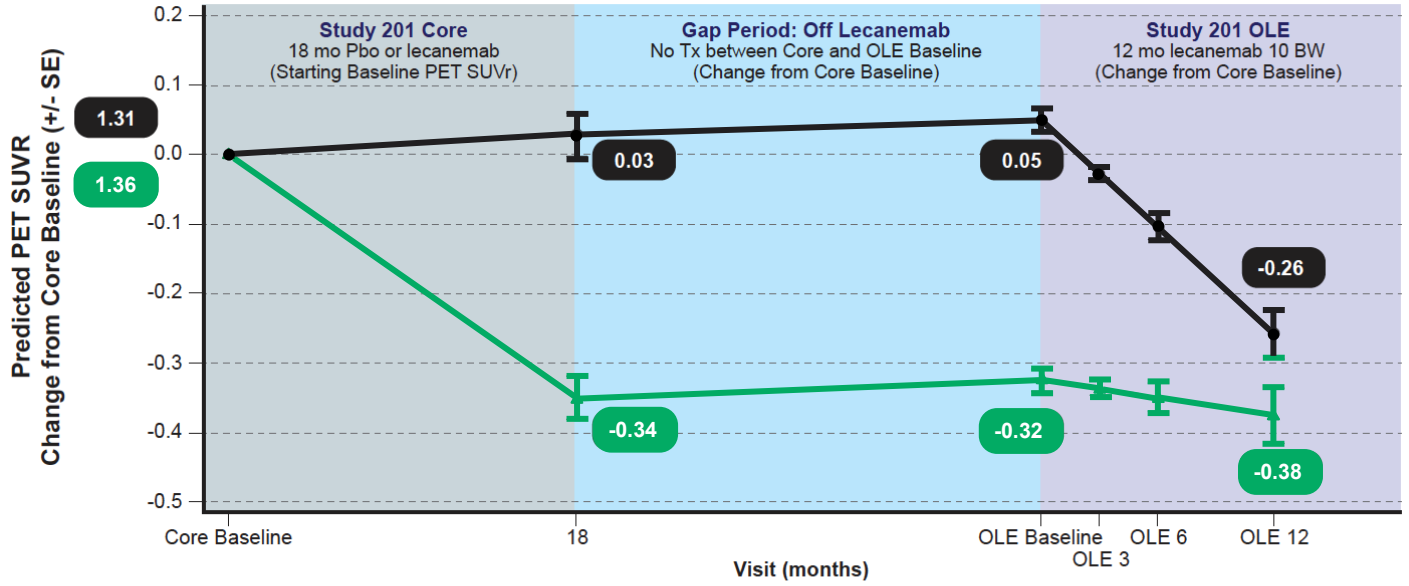
Adapted from Swanson et. al, 11th Clinical Trials on Alzheimer's Disease (CTAD) Conference October 24-27, 2018 and Swanson et al. Alzheimers Res Ther. 2021;13(1):80.

Lecanemab Phase 2 Core and OLE Results in Imaging Subgroups:

Early and Significant Amyloid Clearance

- Time-dependent and statistically significant reduction in brain amyloid
  - Conversion to amyloid negative in 90% by 18 months in **Core** for those who participated in both Core and OLE imaging subgroups
    - 81% in Core for overall Core imaging subgroup
  - Conversion to amyloid negative of 50% by 3 to 6 months & 86% by 12 months in **OLE**

Amyloid PET SUVr



(N) And Percent Negative Based on PET SUVr

Placebo (10)	(10) 10%	(10) 10%	(3)	(7)	(8) 88%
10 Biweekly (10)	(10) 90%	(10) 80%	(4)	(6)	(7) 86%

OLE Baseline at 24m off drug; amyloid negative defined as SUVr < 1.17 using florbetapir as imaging tracer

Full Core Study Published Dataset:
Swanson et al. Alzheimers Res Ther. 2021;13(1):80.

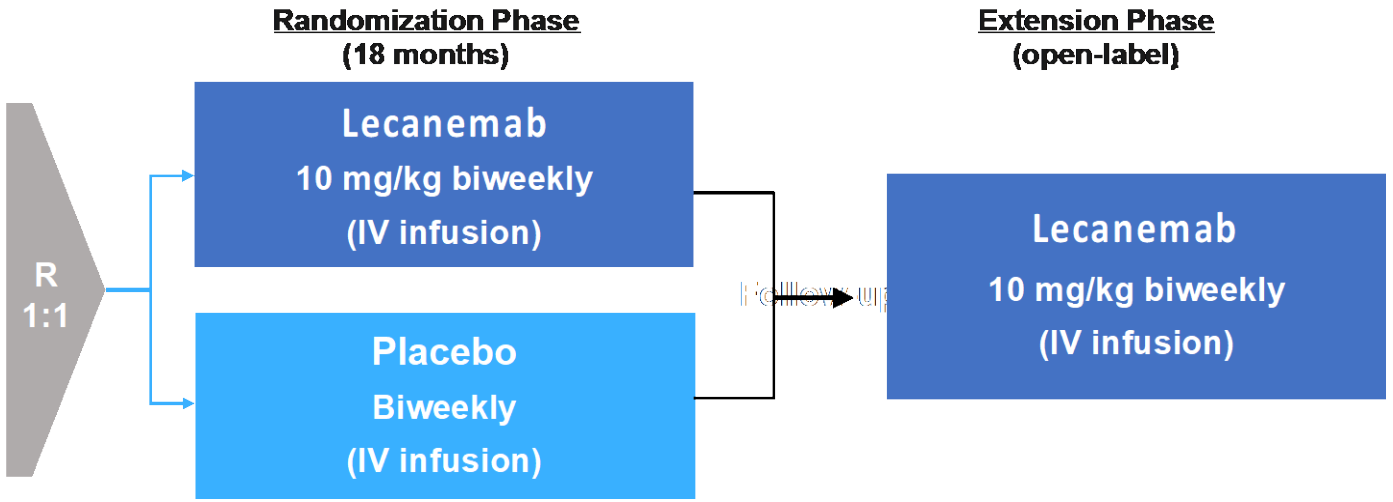
Amyloid negative threshold level= 1.17; PET SUVr: positron emission topography standardized uptake value ratio.
Swanson et al. AD / PD 2021 Annual Meeting.
Data represent the sub population that participated in the PET imaging subgroup in both the Core and OLE
Predicted PET SUVR change from Core baseline was based on piecewise regression for the subjects with baseline and postbaseline in PET sub study in Core Study and OLE phase.

Clarity AD Study Design

Clarity AD is a global, placebo-controlled, double-blind, parallel-group, randomized study

Patient Population

- 1,766 patients with Early AD
- MCI due to AD or mild Alzheimer's dementia
- Amyloid pathology confirmed
- MMSE score between 22 and 30 at screening and baseline
- WMS-IV LMSII ≥1 SD below age-adjusted mean at screening



Randomization Phase
Primary Outcome Measure:
Change from Baseline in the CDR-SB
(Time Frame: 18 months)

Extension Phase
Primary Outcome Measures
Number of Participants with TEAEs
(Time Frame: up to Month 45)
Change from Core Study Baseline in CDR-SB
(Time Frame: up to Month 45)

Randomization will be stratified according to
- Clinical subgroup (MCI due to AD or mild AD dementia)
- Presence or absence of ongoing approved AD treatment (eg, acetylcholinesterase inhibitors, memantine, or both)
- ApoE4 status (ie, carriers or non-carriers)
- Geographical region

3 optional longitudinal sub-studies
- Amyloid PET
- Tau PET
- CSF biomarkers of neurodegeneration

MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE, Mini-Mental State Exam; WMS-IV LMSII, Wechsler Memory Scale IV-Logical Memory (subscale) II; SD, standard deviation, CDR-SB, Clinical Dementia Rating, sum of boxes; TEAEs, treatment emergent adverse events; PET, positron emission topography; CSF, cerebrospinal fluid.

Clarity AD Core Study Endpoints

Primary Endpoint

- The primary efficacy endpoint in the core study is change in CDR-SB from baseline at 18 months

Secondary & Other Endpoints

Key secondary endpoints include change from baseline at 18 months in:

- Amyloid PET SUVr
- ADCOMS
- ADAS-Cog14

Other objectives include change from baseline at 18 months in:

- ADCS-ADL-MCI
- MMSE, CDR-Global
- Biomarkers*

Safety

- Adverse Events
- Laboratory Abnormalities
- Vital Signs
- Monitored throughout the study by the sponsor and by an independent data safety monitoring committee

CDR-SB: Clinical Dementia Rating, sum of boxes. ADCOMS: Alzheimer's Disease Composite Score. ADAS-cog: Alzheimer's Disease Assessment Scale–cognitive subscale. PET SUVr: positron emission topography standardized uptake value ratio. MMSE, Mini-Mental State Exam. ADAS-ADL-MCI: Alzheimer's Disease Cooperative Study/Activities of Daily Living scale adapted for mild cognitive impairment (MCI) subjects. * Amyloid PET positive to negative conversion; Tau PET; Blood and CSF biomarkers, including: Aβ[1-42], neurogranin, NFL, t-tau, and p-tau; Morphometric measures in the brain as measured by vMRI; Changes in brain tau pathology (tau PET)

Key Inclusion Criteria

Diagnosis:

MCI due to AD - intermediate likelihood:

- **Meet the NIA-AA core clinical criteria for MCI due to AD- intermediate likelihood**
- **Global CDR score of 0.5 and CDR Memory Box score of ≥0.5 at screening and baseline**

Mild AD dementia:

- **Meet the NIA-AA core clinical criteria for probable Alzheimer's disease dementia**
- **Global CDR score of 0.5 - 1.0 and a CDR Memory Box score of ≥0.5 at screening and baseline**

Key Inclusion Criteria that must be met by all participants:

- Objective impairment in episodic memory (≥ 1 standard deviation below age-adjusted mean in WMS-IV LMII)
- Positive biomarker of amyloid burden
- Male or female participants 50-90 years of age
- MMSE score ≥22 at screening and baseline and ≤30 at screening and baseline
- Body mass index >17 and <35 at Screening
- Stable dose of concomitant AD treatment for ≥12 weeks prior to baseline
- Treatment-naive subjects are eligible

MCI, mild cognitive impairment; AD, Alzheimer's disease; MMSE, Mini-Mental State Exam; WMS-IV LMSII, Wechsler Memory Scale IV-Logical Memory (subscale) II; CDR-SB, Clinical Dementia Rating; NIA-AA, National Institute on Aging and Alzheimer's Association.

Key Exclusion Criteria
(*Core Study*)

- Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the participant's AD
- History of TIA, stroke, or seizures within 12 months of screening
- Any psychiatric diagnosis or symptoms or other medical conditions that could interfere with study procedures
- Geriatric Depression Scale score ≥ 8 at screening
- Contraindications to magnetic resonance imaging (MRI) scanning
- Evidence of other clinically significant lesions on brain MRI at screening that could indicate a dementia diagnosis other than AD
- Participants who have any known prior exposure to lecanemab or any anti-amyloid therapies

TIA, transient ischemic attack.

Key Inclusion/Exclusion Criteria

(*Open-Label Extension Study*)

- **Inclusion Criteria:** Participants who have completed Visit 42 (Week 79) of the Core Study
- **Exclusion Criteria:** Participants who discontinued early from the Core or who develop medical conditions during the Core Study that would interfere with the safety of the subject during the Extension Phase

Baseline Subject Characteristics

Characteristic	Combined Total N=1795
Age, median (range), years	72 (50, 90)
Age Group, n (%)	
<65 years	353 (19.7)
≥65 to <80	1203 (67.0)
≥80	239 (13.3)
Female , n (%)	938 (52.3)
Race, n (%)	
Asian	303 (16.9)
Black	47 (2.6)
Caucasian	1381 (76.9)
Native American	2 (<1)
Native Hawaiian or Other Pacific Islander	1 (<1)
Other	33 (1.8)
Missing	28 (1.6)
Ethnicity, n (%)	
Hispanic or Latino	232 (12.9)
Not Hispanic or Latino	1527 (85.1)
Missing	36 (2.0)
Region, n (%)	
North America	1072 (59.7)
Europe	429 (23.9)
Asia-Pacific	294 (16.4)

data cutoff of May 3, 2021

Comparison of Clarity AD and Phase 2 Populations

	Clarity AD Total N=1795	Lecanemab Phase 2 Study Total N=854
Patient Characteristic		
Age, median (range), years	72 (50, 90)	72 (50, 90)
Age ≥65, %	80	80
Female, %	52	50
Caucasian, %	77	90
MCI due to AD, %	62	64
ApoE4 carriers,* %	69	71
Clinical Endpoints		
CDR-SB, mean (SD)	3.2 (1.3)	3.0 (1.4)
ADCOMS, mean (SD)	0.4 (0.1)	0.4 (0.2)
ADAS-Cog, mean (SD)	25.3 (7.3)	22.2 (7.4)
MMSE, mean (SD)	25.6 (2.2)	25.6 (2.4)
Global CDR, mean (SD)	0.6 (0.2)	0.6 (0.2)

*by laboratory.
data cutoff of May 3, 2021

CDR-SB: Clinical Dementia Rating, sum of boxes. ADCOMS: Alzheimer's Disease Composite Score. ADAS-cog: Alzheimer's Disease Assessment Scale–cognitive subscale; MMSE, Mini-Mental State Exam.

Conclusions

- Clarity AD study builds on encouraging findings from the lecanemab phase 2 study
- Clarity AD study is designed to confirm clinical efficacy, safety, and pharmacodynamic properties of lecanemab 10 mg/kg biweekly versus placebo in subjects with early AD
- Baseline characteristics in 1795 subjects are consistent with previous studies and representative of an early AD population
- Clarity AD was initiated in March 2019 and enrollment is complete (except in China)

Acknowledgments

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