Lecanemab for Early Alzheimer's Disease: Long-Term Outcomes, Predictive Biomarkers and Novel Subcutaneous Administration

Clinical Trials on Alzheimer's Disease (CTAD)
Boston, MA, USA
October 24 – 27, 2023

Welcome and Introductions

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Lecanemab for Early Alzheimer's Disease: Long-Term Outcomes, Predictive Biomarkers and Novel Subcutaneous Administration

Topic	Presenter
Clarity AD: Review of the Mechanism-Based Rationale and Results of the Lecanemab Phase 3 Trial	***Christopher van Dyck***
Biomarker Assessments from Clarity AD: Downstream Implications of Targeting Protofibrils and Tau as a Predictive Biomarker	***Keith Johnson***
Lecanemab for the Treatment of Early Alzheimer's Disease: The Extension of Efficacy Results from Clarity AD	***Reisa Sperling***
Preliminary Update on Lecanemab Safety in Clarity AD Open-Label Extension, Including Subcutaneous Formulation	***Michael Irizarry***
Panel Discussion / Q&A	***Christopher van Dyck / All***

Clarity AD: Review of the Mechanism-Based Rationale and Results of the Lecanemab Phase 3 Trial

Christopher van Dyck

Yale University School of Medicine

Christopher van Dyck - Disclosures

Advisor/Consultant for:

Roche Pharmaceuticals
Eisai, Inc
Ono Pharmaceuticals
Cerevel

Yale University and Dr. van Dyck receive grant support from:

Eli Lilly
Biogen Idec
Roche Pharmaceuticals
Biohaven Pharmaceuticals
UCB

Janssen Pharmaceuticals
Eisai, Inc
Genentech, Inc
Cerevel Therapeutics

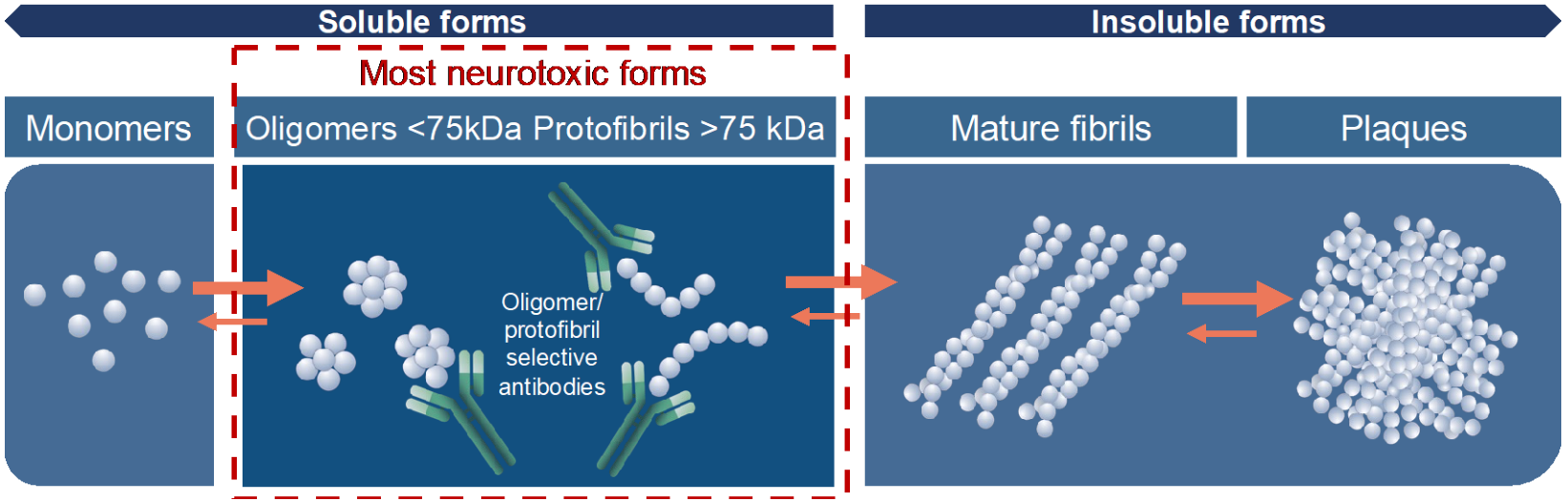
Lecanemab Unique Dual-Action Mechanism:

Targets Highly Toxic Protofibrils and Rapidly Clears Amyloid Plaques

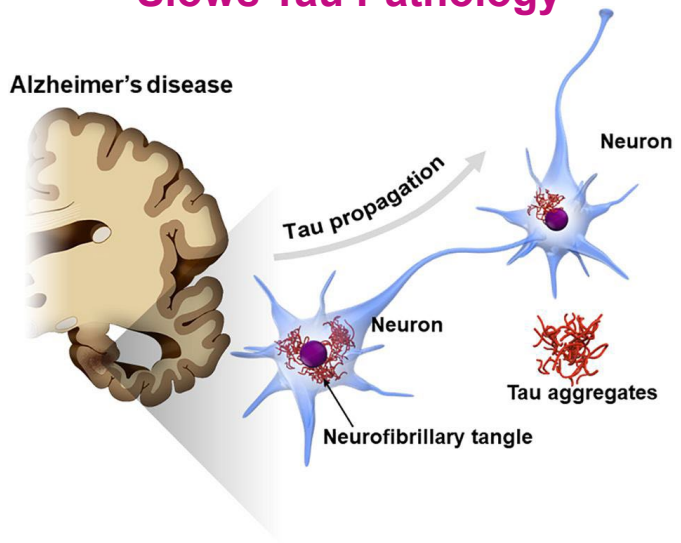
Lecanemab Dual Mechanism

Lecanemab Targets Protofibrils

Lecanemab Clears Plaques



Lecanemab Slows Tau Pathology



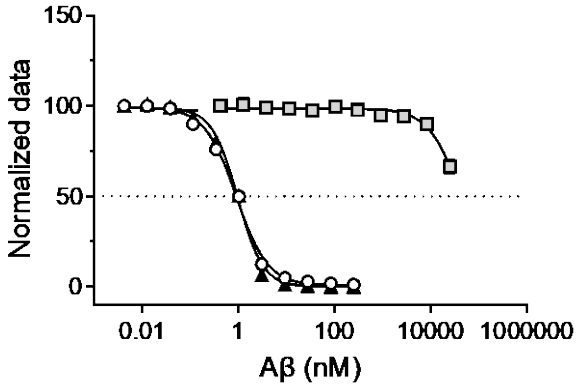
- The unique dual action of lecanemab rapidly clears amyloid plaque and highly toxic protofibrils[1-5]
  - Selectively binds to soluble Aβ aggregated species, with preferential activity for Aβ protofibrils over monomers (>1000x) and over fibrils (>10x)[1,6-10]
- Slows tau pathology in temporal lobe (early Braak regions) which is a hallmark of disease progression

Aβ, amyloid-beta; kDa, kilodaltons. Source: Presented at CTAD 2021. Note: Illustration is based on data from Biacore, inhibition ELISA and immunoprecipitation.

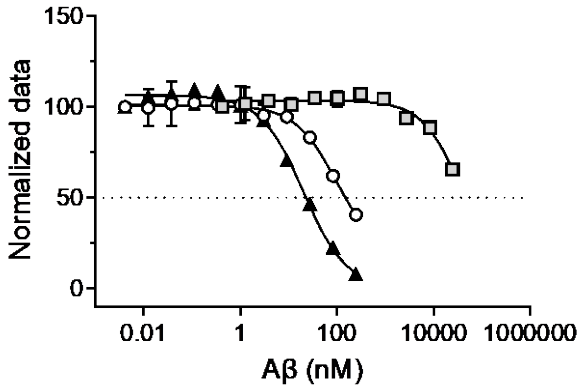
1. Söderberg L, et al. Neurotherapeutics. 2022 Oct 17. 2. van Dyck CH, et al. N Engl J Med. 2023 Jan 5;388(1):9-21. 3. Lecanemab prescribing information Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269s001lbl.pdf Accessed July 24, 2023. 4. Stern AM, et al. Neuron. 2023 Jul 5;111(13):2012-2020.e4. 5. Ono K, Hampel H. Int J Mol Sci. 2020 Jan 31;21(3):952. 6. Tucker S, et al. J Alzheimers Dis. 2015;43(2):575-88. 7. Lord A, et al. *Neurobiol Dis*. 2009;36:425–34. 8. Sehlin D, et al. *PLoS One*. 2012;7:e32014. 9. Sehlin D, et al. *Neurodegener Dis*. 2011;8:117–23. 10. Logovinsky V, et al. *Alzheimer's Research & Therapy*. 2016;8:14

Lecanemab Preferential Binding to Soluble Aβ Protofibrils

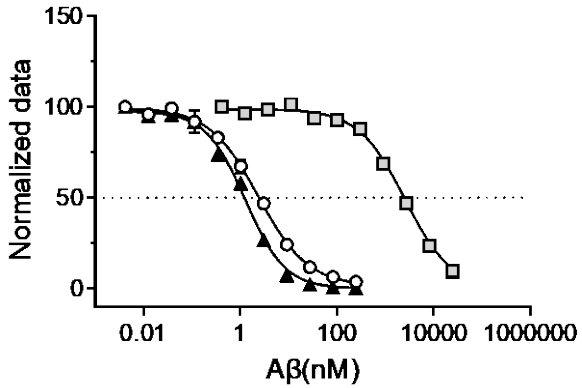
Lecanemab



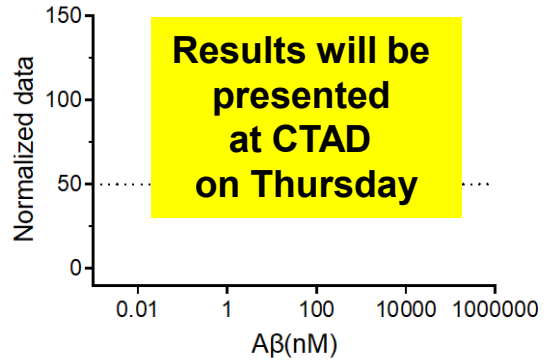
Aducanumab



Gantenerumab



Donanemab



Monomers Protofibrils (small) Protofibrils (large)

- Small protofibrils, approx. 75-300 kDa,
- Large protofibrils, approx. 300-5000 kDa

- Lecanemab binds small protofibrils 100x and large protofibrils 25x stronger than aducanumab
- Gantenerumab is less selective and binds monomers with somewhat higher affinity compared to lecanemab and aducanumab

Binding to Aβ Monomers and Large Protofibrils by Inhibition ELISA

Antibody	Monomers IC_{50} (nM)	Small Protofibril IC_{50} (nM)	Large Protofibril IC_{50} (nM)
Lecanemab	>25,000	0.80 ± 0.10	0.79 ± 0.20
Aducanumab	>25,000	>83	22.0 ± 2.0
Gantenerumab	2600 ± 130	2.5 ± 0.10	1.3 ± 0.10

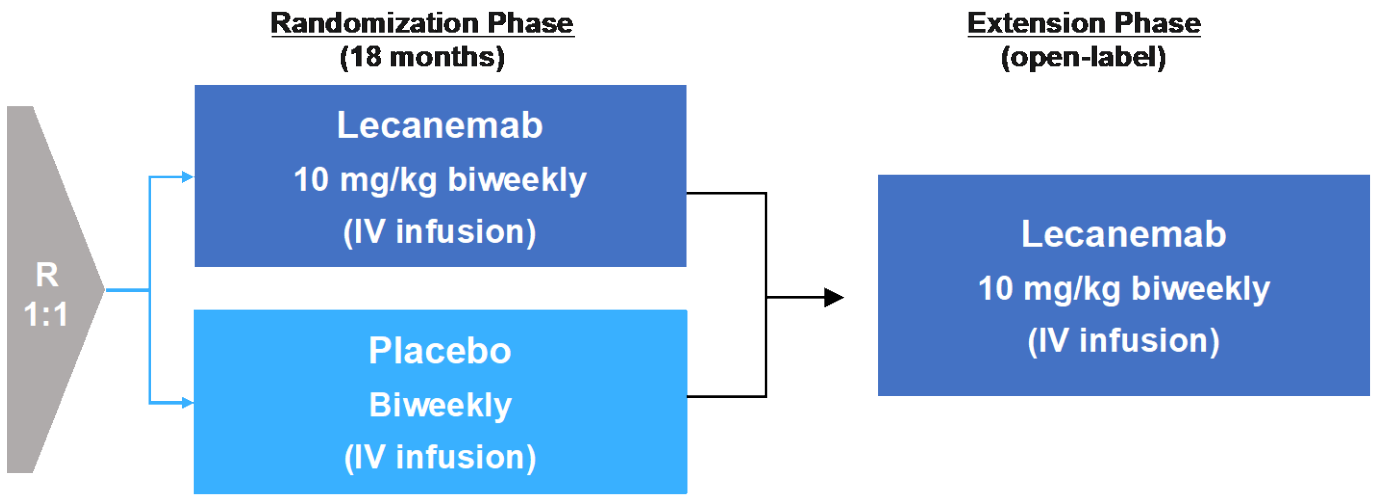
Aβ, amyloid-beta; kDa, kilodaltons. IC50, half-maximal inhibitory concentration. Söderberg L, et al. Neurotherapeutics. 2023 Jan;20(1):195-206.

Clarity AD Study Design

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

Study Population

- 1,795 participants 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:

CDR: Change from Baseline at 18 months

Key Secondary Outcome Measures:

Change from Baseline at 18 months:
Amyloid PET
ADAS-Cog14
ADCOMS
ADCS MCI-ADL

Extension Phase Primary Outcome Measures

Number of Participants with TEAEs
Change from Core Study Baseline in CDR-SB

Optional longitudinal sub-studies

- Amyloid burden (amyloid PET; n=716)
- Brain tau pathology (tau PET; n=342)
- CSF biomarkers of neurodegeneration (n=281)
- Subcutaneous formulation (OLE)

AD, Alzheimer's disease; ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCOMS, Alzheimer's Disease Composite Score; ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; ApoE4, apolipoprotein E4; CDR-SB, Clinical Dementia Rating-sum of boxes; CSF, cerebrospinal fluid; IV, intravenous; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam; OLE, open-label extension; PET, positron emission tomography; SD, standard deviation; TEAEs, treatment emergent adverse events; WMS-IV LMSII, Wechsler Memory Scale IV-Logical Memory (subscale) II.

Clarity AD and Tau PET Substudy

Tau PET Substudy Baseline Characteristics Similar to Overall Study Population

	All Participants		Tau PET Substudy[1]	
	Placebo (N=875)	Lecanemab 10 mg/kg biweekly (N=859)	Placebo (N=167)	Lecanemab 10 mg/kg biweekly (N=175)
Age, mean (standard deviation), years	71.0 (7.8)	71.4 (7.9)	72.4 (7.8)	71.8 (7.8)
Female, n (%)	464 (53.0)	443 (51.6)	92 (55.1)	84 (48.0)
CDR Global=0.5	706 (80.7)	694 (80.8)	132 (79.0)	127 (72.6)
MMSE, mean (SD)	25.6 (2.23)	25.5 (2.19)	25.6 (2.09)	25.6 (2.18)
AD Stage				
MCI	544 (62.2)	528 (61.5)	108 (64.7)	101 (57.7)
Mild dementia	331 (37.8)	331 (38.5)	59 (35.3)	74 (42.3)
ApoE4 Status				
Noncarrier	275 (31.4)	267 (31.1)	70 (41.9)	75 (42.9)
Heterozygous	468 (53.5)	456 (53.1)	84 (50.3)	77 (44.0)
Homozygous	132 (15.1)	136 (15.8)	13 (7.8)	23 (13.1)
CDR-SB, mean (SD)	3.22 (1.343)	3.17 (1.340)	3.31 (1.332)	3.40 (1.307)
Amyloid PET Centiloids, mean (SD)	75.28 (41.85)	77.94 (44.78)	73.84 (41.032)	70.65 (46.844)
ADAS-Cog14, mean (SD)	24.37 (7.561)	24.45 (7.082)	22.88 (6.959)	22.65 (6.723)
ADCS MCI-ADL	40.9 (6.89)	41.2 (6.61)	40.68 (6.669)	40.66 (6.919)

ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; ApoE4, apolipoprotein E4; CDR-SB, Clinical Dementia Rating-sum of boxes; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam; PET, positron emission tomography; SD, standard deviation.

[1]Subjects with a baseline tau PET

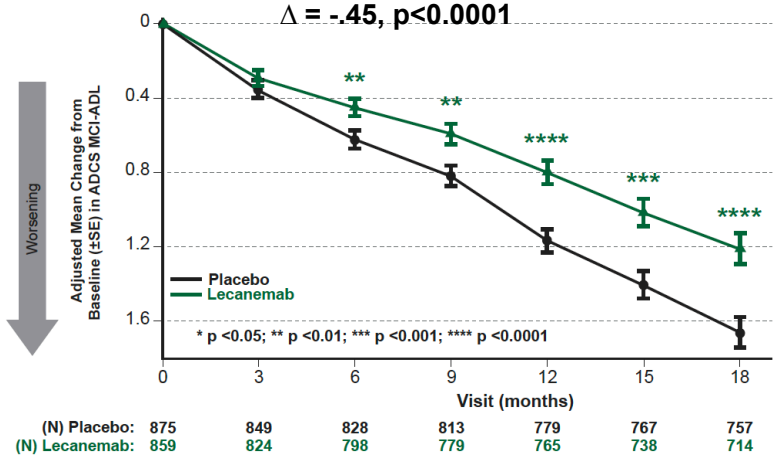
Clarity AD and Tau PET Substudy: Clinical Outcomes[1]

Efficacy Results Similar in Tau PET Substudy to Overall Study Population

Overall Clarity AD

CDR-SB

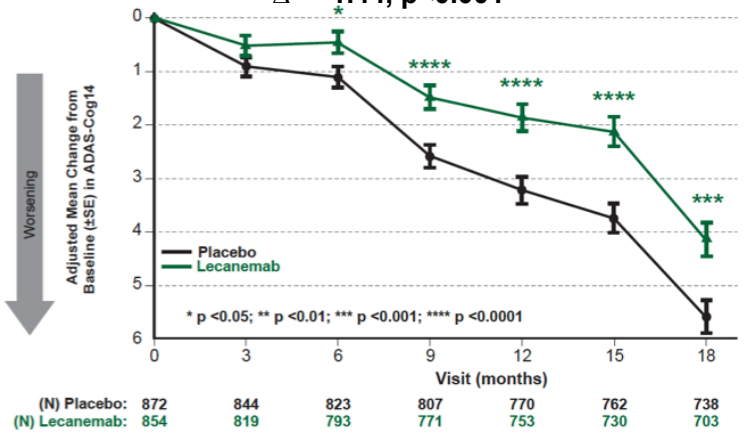
% Less decline = 27%
Δ = -.45, p<0.0001



(N) Placebo:	875	849	828	813	779	767	757
(N) Lecanemab:	859	824	798	779	765	738	714

ADAS-Cog14

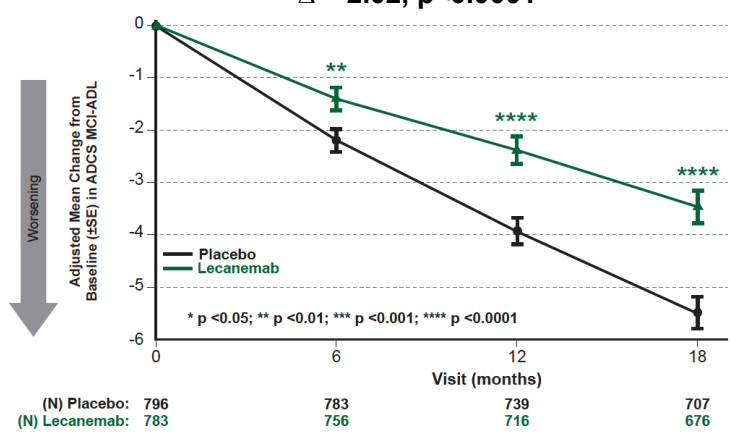
% Less decline = 26%
Δ = -1.44, p<0.001



(N) Placebo:	872	844	823	807	770	762	738
(N) Lecanemab:	854	819	793	771	753	730	703

ADCS MCI-ADL

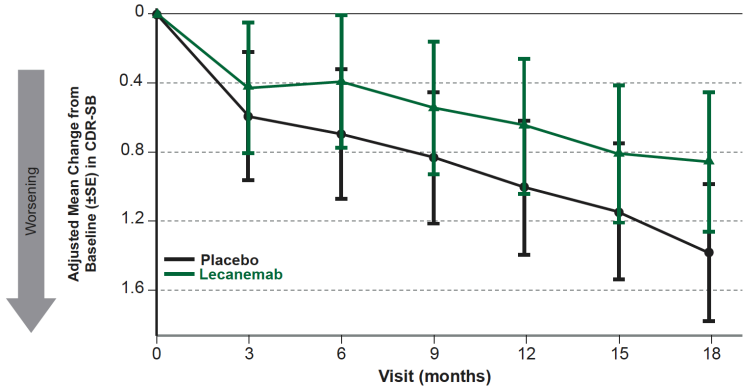
% Less decline = 37%
Δ = 2.02, p<0.0001



(N) Placebo:	796	783	739	707
(N) Lecanemab:	783	756	716	676

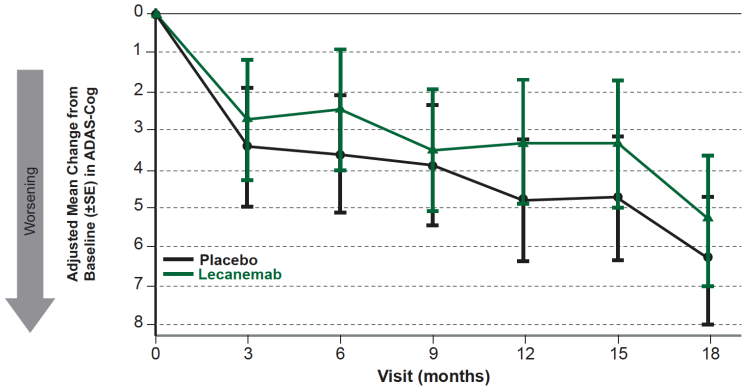
Tau PET Substudy

% Less decline = 37.9%
Δ = -.53, p = 0.033



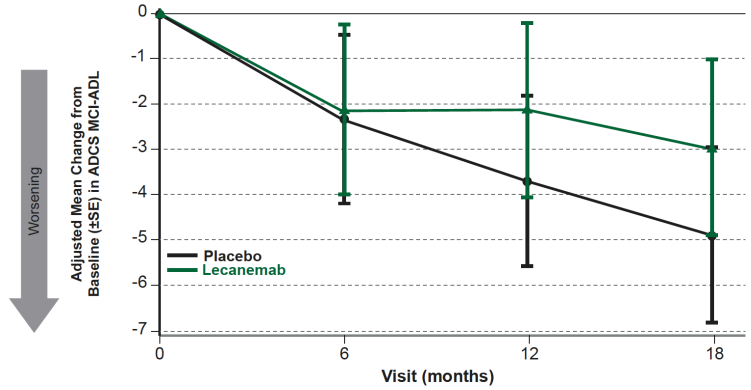
(N) Placebo:	167	165	154	148	138	130	131
(N) Lecanemab:	175	165	160	154	148	142	134

% Less decline = 16%
Δ = -1.01, p = 0.34



(N) Placebo:	166	164	153	146	137	130	130
(N) Lecanemab:	175	164	161	152	148	143	134

% Less decline = 39.2%
Δ = 1.92, p = 0.042



(N) Placebo:	151	147	129	125
(N) Lecanemab:	167	156	146	134

[1]Subjects with a baseline tau PET

Note: Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.
ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale; 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; SE, standard error.

Summary

- Lecanemab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody with a dual mechanism of action
  - Targets highly toxic protofibrils and rapidly clears amyloid plaques
  - Selectively binds to soluble Aβ aggregated species, with preferential activity for Aβ protofibrils over monomers (>1000x) and over fibrils (>10x)
- Clarity AD met all primary and secondary efficacy endpoints ($p<0.001$)
  - Consistency of results across scales of cognition and function (27-37% slowing)
- Tau PET substudy participants and efficacy results similar to overall population
  - Keith will next present Tau PET substudy results

PET, positron emission tomography.

Biomarker Assessments from Clarity AD: Downstream Implications of Targeting Protofibrils and Tau as a Predictive Biomarker

Keith Johnson

Massachusetts General Hospital
Brigham and Women's Hospital
Harvard Medical School

Keith Johnson - Disclosures

- Consultant: Novartis, Merck
- Spouse consultant to: Abbvie, AC Immune, Acumen, Alector, Bristol-Myers-Squibb, Genentech, Ionis, Janssen, Oligomerix, Prothena, Roche, Shionogi, Vaxxinity
- Research funding:
  - National Institute on Aging:

    P01AG036694; R01AG054029; U24AG057437; R01 AG03689;

    R01 Alzheimer's Tau Platform
  - Alzheimer's Association, Fidelity Biosciences
  - GHR Foundation
  - Gates Ventures
  - Eli Lilly
  - Eisai
  - Accelerating Medicines Partnership FNIH

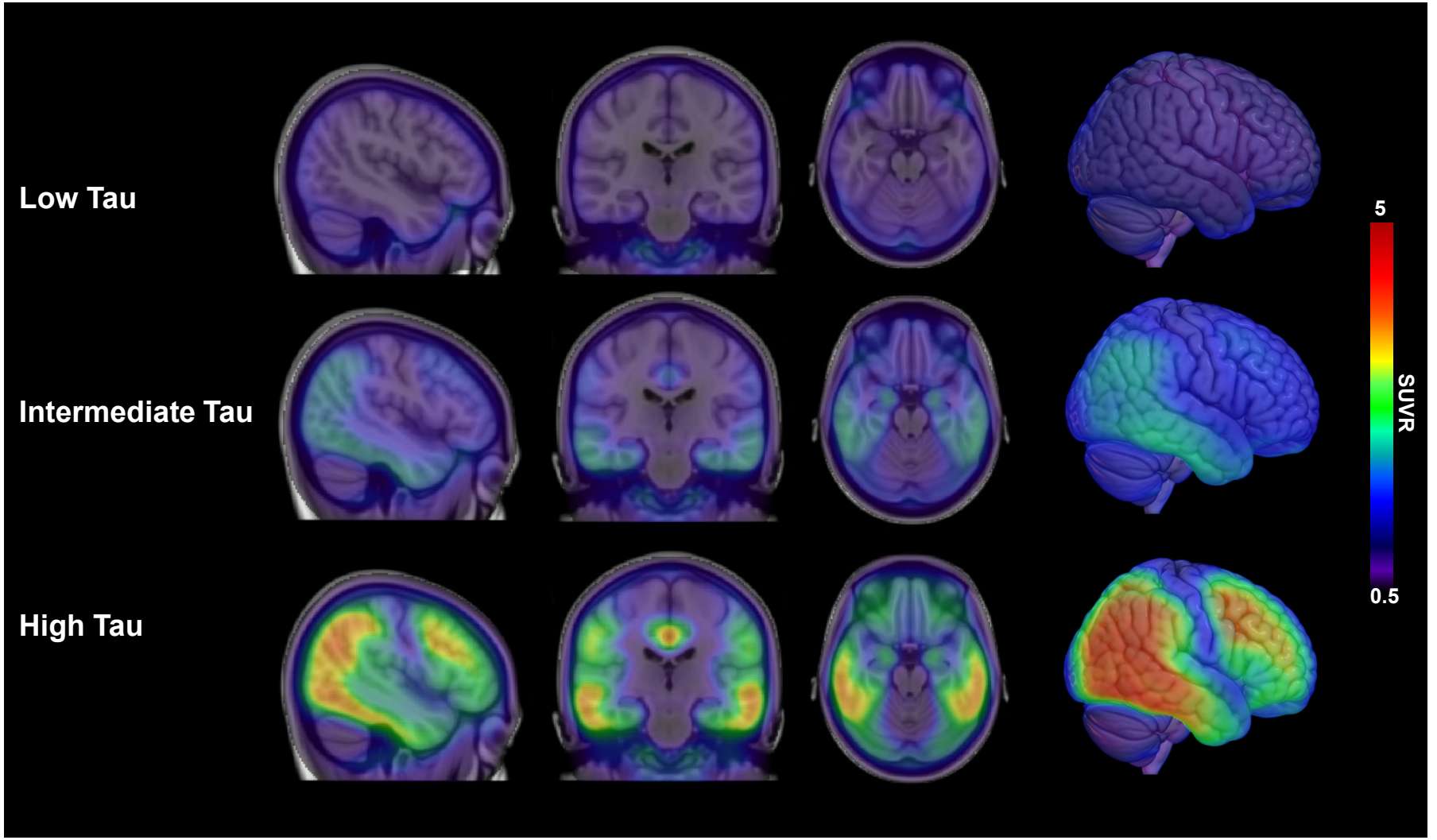
Tau PET Substudy

Lower Tau Indicative of Earlier Alzheimer's Disease

Baseline stratification

- MK6240 PET processed at Invicro (ref region: ventral cerebellum)
- Whole cortical gray matter Tau PET cutoffs derived from MK6240 scans in the Lantheus/Cerveau database [clinical AD, amyloid positive, mean MMSE (SD): 23.4 (3.5)]
  - **Low SUVr <1.06**
    - n=141 (41.2%)
  - **Intermediate SUVr 1.06-2.91**
    - n=191 (55.8%)
  - **High SUVr >2.91**
    - n=10 (2.9%)

Averaged Scans from the Tau PET Substudy (n=342)



AD, Alzheimer's disease; MMSE, Mini-Mental State Exam; PET, positron emission tomography; SD, standard deviation; SUVr, standardized uptake value ratio.

Unique Early Population Not Previously Studied or Analyzed and Reported

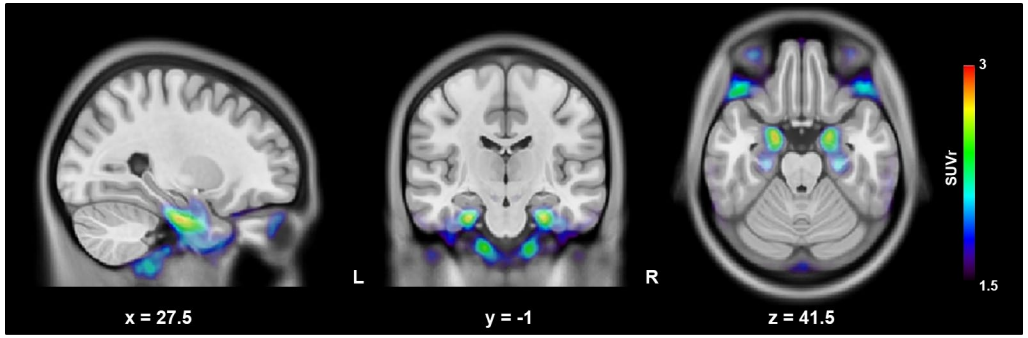
- Unlike other recently reported studies, there was no tau PET exclusion criteria in Clarity AD which allowed inclusion of early AD participants with low tau (grey matter PET SUVr <1.06) and confirmed cognitive/functional impairment due to AD
  - Included all early AD participants (MMSE 22-30, 60% clinically diagnosed with MCI, 80% global CDR 0.5)
  - Elevated amyloid levels confirmed by visual read (no exclusion based on CL level) or CSF
- 40% of Clarity AD tau PET substudy have low tau PET SUVr (<1.06)
- Elevated tau in the entorhinal cortex confirmed by MK6240 PET

AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating-sum of boxes; MMSE, Mini-Mental State Exam; PET, positron emission tomography; SD, standard deviation; SUVr, standardized uptake value ratio.

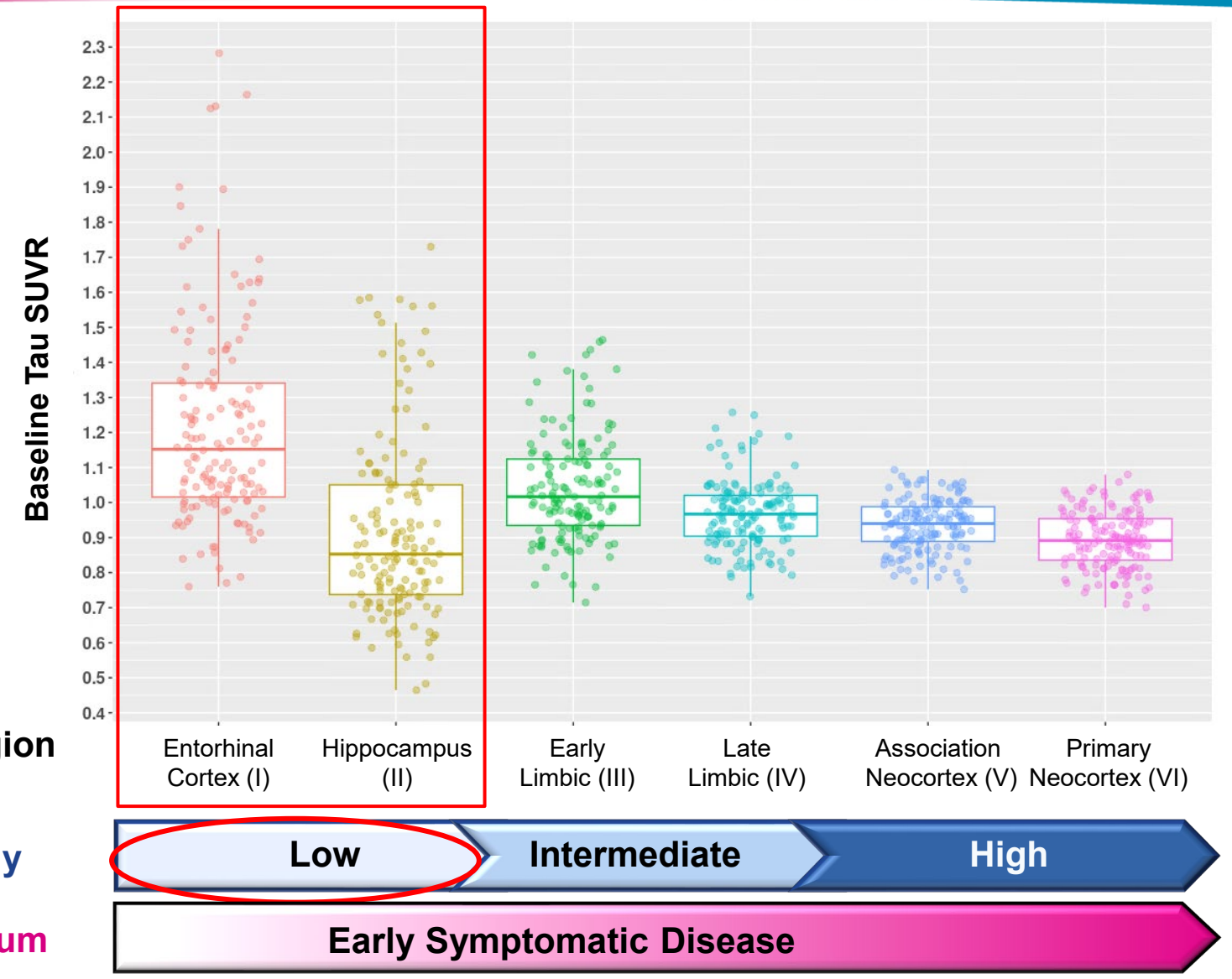
Anatomical Distribution of Tau PET Signal in Low Tau Subgroup

Characterized by Signal in Entorhinal Cortex

Average Image of 20 Low Tau Participants with Entorhinal Uptake



- Not previously analyzed and/or reported in previous anti-amyloid antibody clinical trials



PET, positron emission tomography; SUVr, standardized uptake value ratio.

Tau PET Substudy Baseline Characteristics

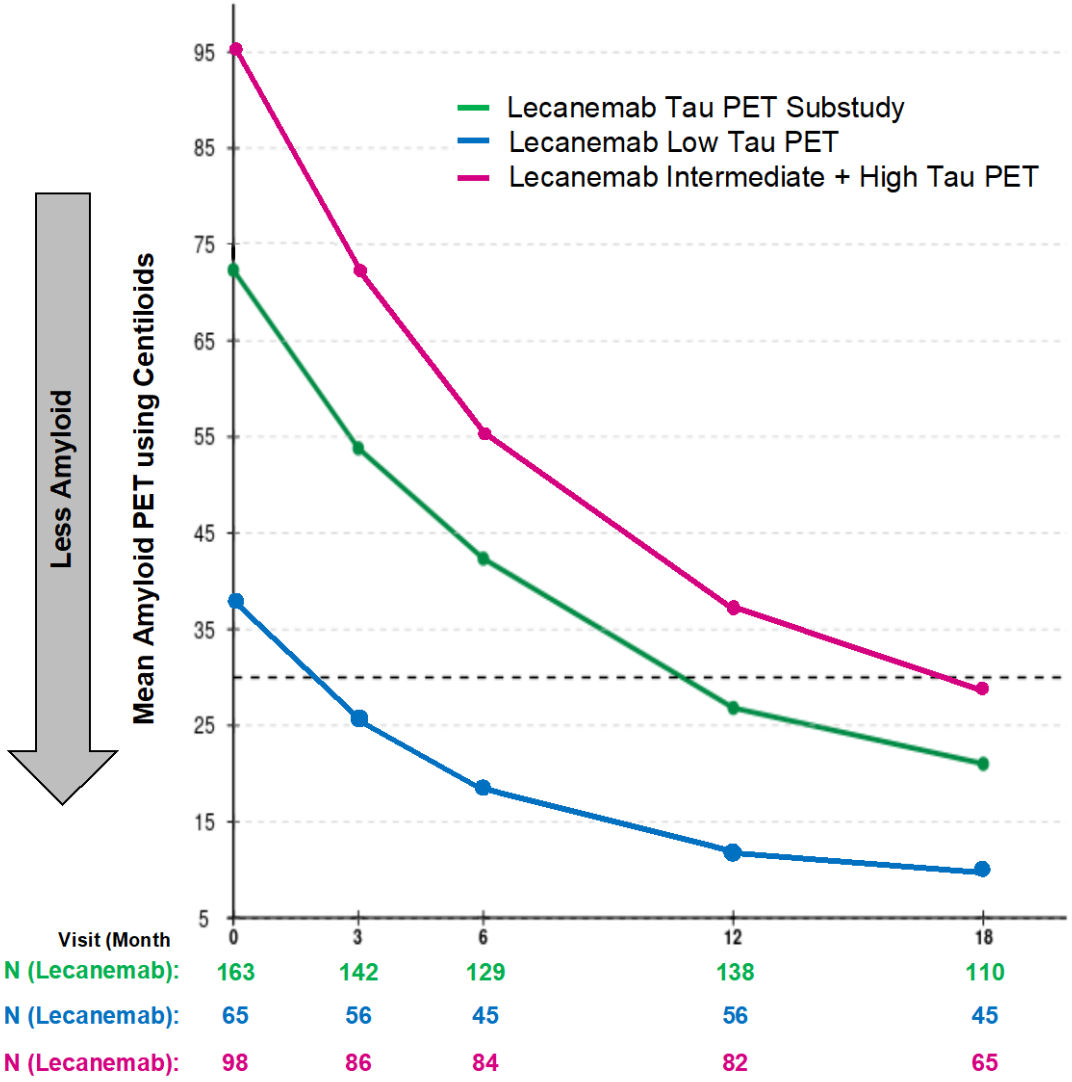
Generally Similar Across Tau Populations with Exception of Amyloid Load

	Tau PET Substudy		Low Tau		Intermediate/High Tau	
	Placebo (N=167)	Lecanemab (N=175)	Placebo (N=71)	Lecanemab (N=70)	Placebo (N=96)	Lecanemab (N=105)
Age, mean (SD), years	72.4 (7.8)	71.8 (7.8)	71.8 (8.6)	72.6 (7.6)	72.8 (7.1)	71.2 (7.9)
Female, n (%)	92 (55.1)	84 (48.0)	36 (50.7)	30 (42.9)	56 (58.3)	54 (51.4)
Caucasian	155 (92.8)	163 (93.1)	64 (90.1)	64 (91.4)	91 (94.8)	99 (94.3)
Years since diagnosis	1.47 (1.949)	1.47 (1.444)	1.48(1.907)	1.68 (1.482)	1.45 (1.990)	1.33 (1.409)
Years since onset of symptoms	4.21 (3.042)	4.32 (2.443)	3.81 (2.027)	4.77 (2.488)	4.51 (3.596)	4.01 (2.377)
CDR Global=0.5	132 (79.0)	127 (72.6)	56 (78.9)	47 (67.1)	76 (79.2)	80 (76.2)
Mild dementia due to AD	59 (35.3)	74 (42.3)	21 (29.6)	34 (48.6)	38 (39.6)	40 (38.1)
MCI	108 (64.7)	101 (57.7)	50 (70.4)	36 (51.5)	58 (60.4)	65 (61.9)
ApoE4 Status						
Noncarrier	70 (41.9)	75 (42.9)	36 (50.7)	42 (60.0)	34 (35.4)	33 (31.4)
Carrier	97 (58.1)	100 (57.1)	35 (49.3)	28 (40.0)	62 (64.6)	72 (68.6)
Heterozygous	84 (50.3)	77 (44.0)	34 (47.9)	24 (34.3)	50 (52.1)	53 (50.5)
Homozygous	13 (7.8)	23 (13.1)	1 (1.4)	4 (5.7)	12 (12.5)	19 (18.1)
On AChEIs and/or memantine	66 (39.5)	71 (40.6)	31 (43.7)	24 (34.3)	35 (36.5)	47 (44.8)
CDR-SB, mean (SD)	3.31 (1.332)	3.40 (1.307)	3.20 (1.369)	3.44 (1.424)	3.40 (1.304)	3.38 (1.230)
Amyloid PET Centiloids, mean (SD)	73.84 (41.032)	70.65 (46.844)	50.36 (37.637)	36.35 (35.790)	90.96 (34.536)	93.51 (38.753)
ADAS-Cog14, mean (SD)	22.88 (6.959)	22.65 (6.723)	20.56 (6.285)	21.39 (6.562)	24.59 (6.968)	23.49 (6.728)
ADCOMS, mean (SD)	0.40 (0.144)	0.41 (0.145)	0.37 (0.145)	0.39 (0.148)	0.42 (0.141)	0.41 (0.142)
ADCS MCI-ADL, mean (SD)	40.68 (6.669)	40.66 (6.919)	40.35 (6.832)	38.81 (6.927)	40.90 (6.581)	41.92 (6.657)
MMSE, mean (SD)	25.65 (2.094)	25.62 (2.178)	25.92 (2.136)	25.46 (2.012)	25.45 (2.051)	25.72 (2.285)

AChEIs, acetylcholinesterase inhibitors; ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCOMS, Alzheimer's Disease Composite Score; ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; ApoE4, apolipoprotein E4; CDR-SB, Clinical Dementia Rating-sum of boxes; MMSE, Mini-Mental State Exam; PET, positron emission tomography; SD, standard deviation.

Lecanemab Effect on Amyloid in Tau PET Substudy

Consistent Amyloid Reductions for Subgroups Across Clinical Assessments



Amyloid PET clearance (% <30 CL) in lecanemab	6m n (%)	12m n (%)	18m n (%)
Tau PET Substudy	48 (37.2)	83 (60.1)	79 (71.8)
Intermediate + High Tau PET	17 (20.2)	35 (42.7)	**37 (56.9)**
Low Tau PET	31 (68.9)	48 (85.7)	**42 (93.3)**

Observed data.
CL, clearance; m, month; PET, positron emission tomography.

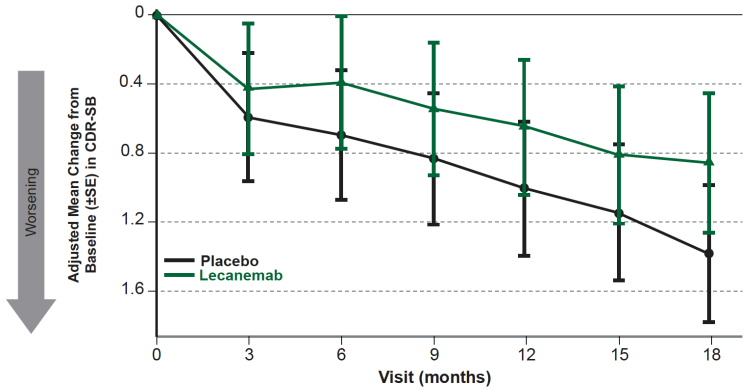
Tau PET Subgroups: Clinical Outcomes[1]

Stability or Improvement With Early-Stage Treatment

Tau PET Substudy

CDR-SB

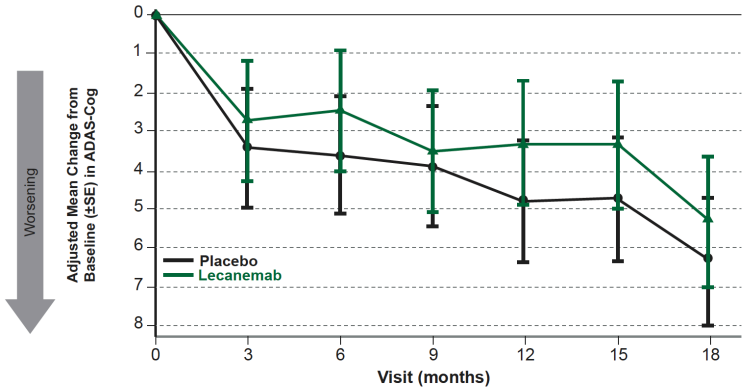
% Less decline = 37.9%
Δ = -.53, p = 0.033



(N) Placebo:	167	165	154	148	138	130	131
(N) Lecanemab:	175	165	160	154	148	142	134

ADAS-Cog14

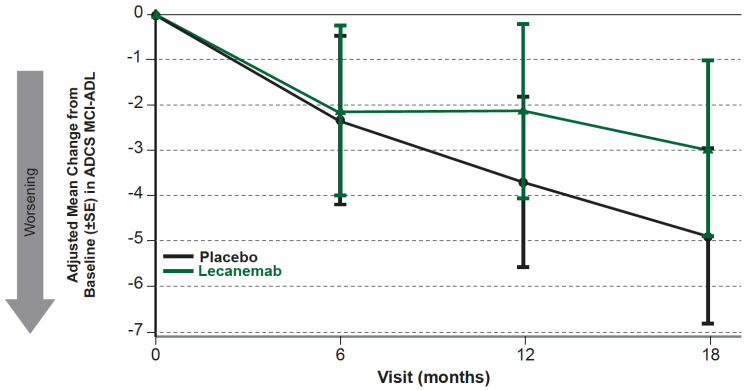
% Less decline = 16%
Δ = -1.01, p = 0.34



(N) Placebo:	166	164	153	146	137	130	130
(N) Lecanemab:	175	164	161	152	148	143	134

ADCS MCI-ADL

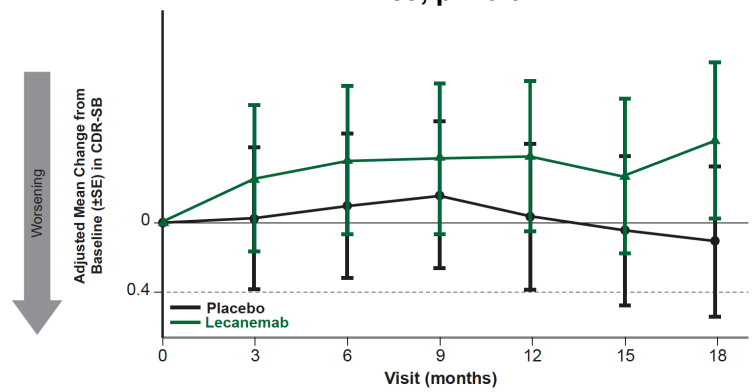
% Less decline = 39.2%
Δ = 1.92, p = 0.042



(N) Placebo:	151	147	129	125
(N) Lecanemab:	167	156	146	134

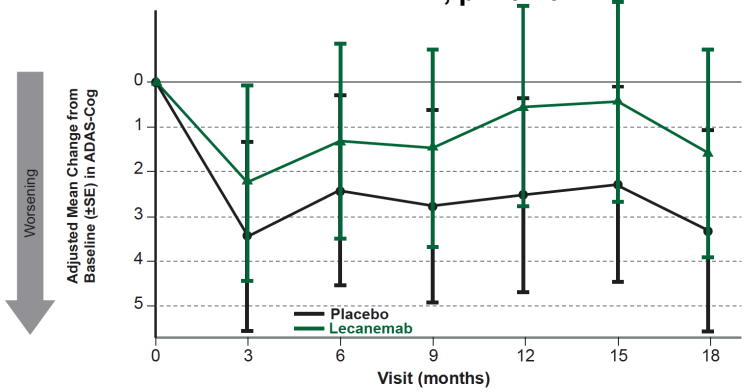
Low Baseline Tau

% Less decline = 549%
Δ = -.59, p = 0.022



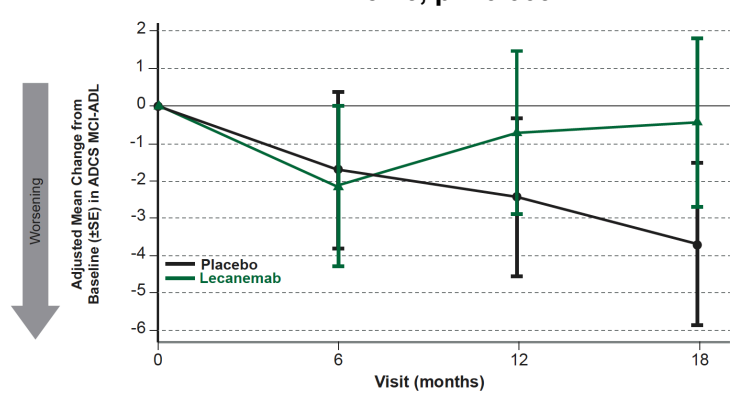
(N) Placebo:	71	71	67	66	62	58	58
(N) Lecanemab:	70	66	63	61	57	52	50

% Less decline = 52.4%
Δ = -1.74, p = 0.20



(N) Placebo:	71	71	67	66	62	58	57
(N) Lecanemab:	70	66	64	59	57	53	50

% Less decline = 88.2%
Δ = 3.26, p = 0.009



(N) Placebo:	63	61	55	54
(N) Lecanemab:	68	63	59	53

Note: Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.

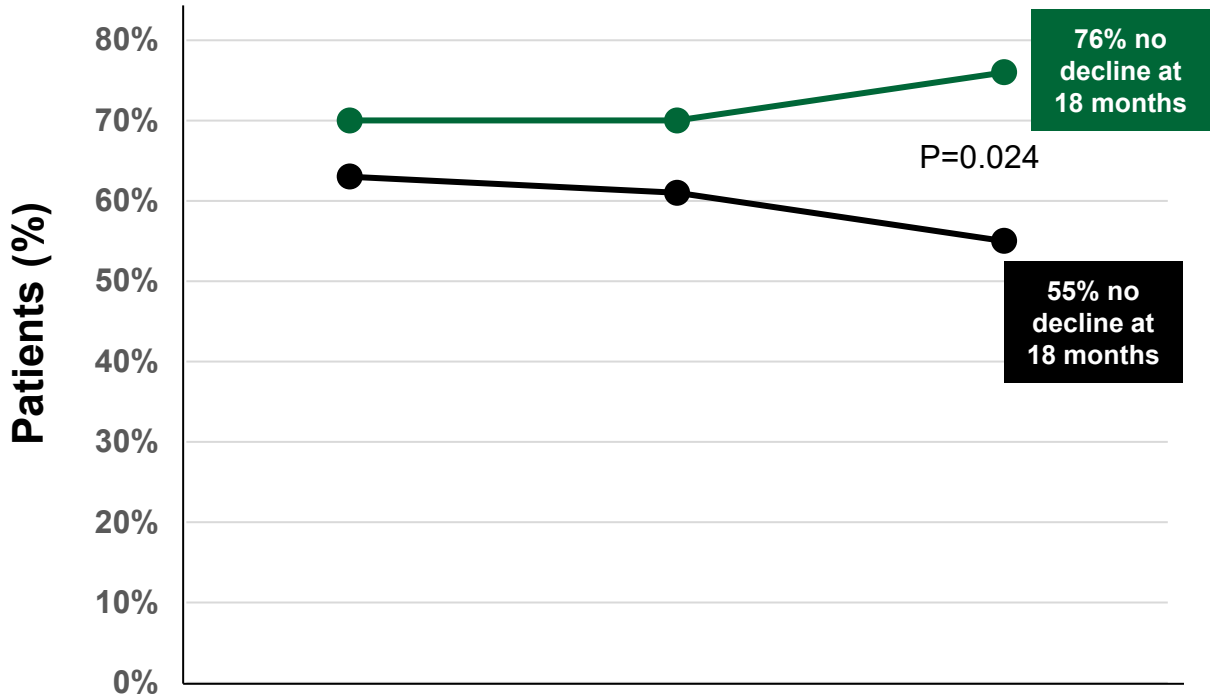
ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; CDR-SB, Clinical Dementia Rating-sum of boxes; SE, standard error.

[1]Subjects with a baseline tau PET

Observed Rates for ‘No Decline’ and ‘Improvement’

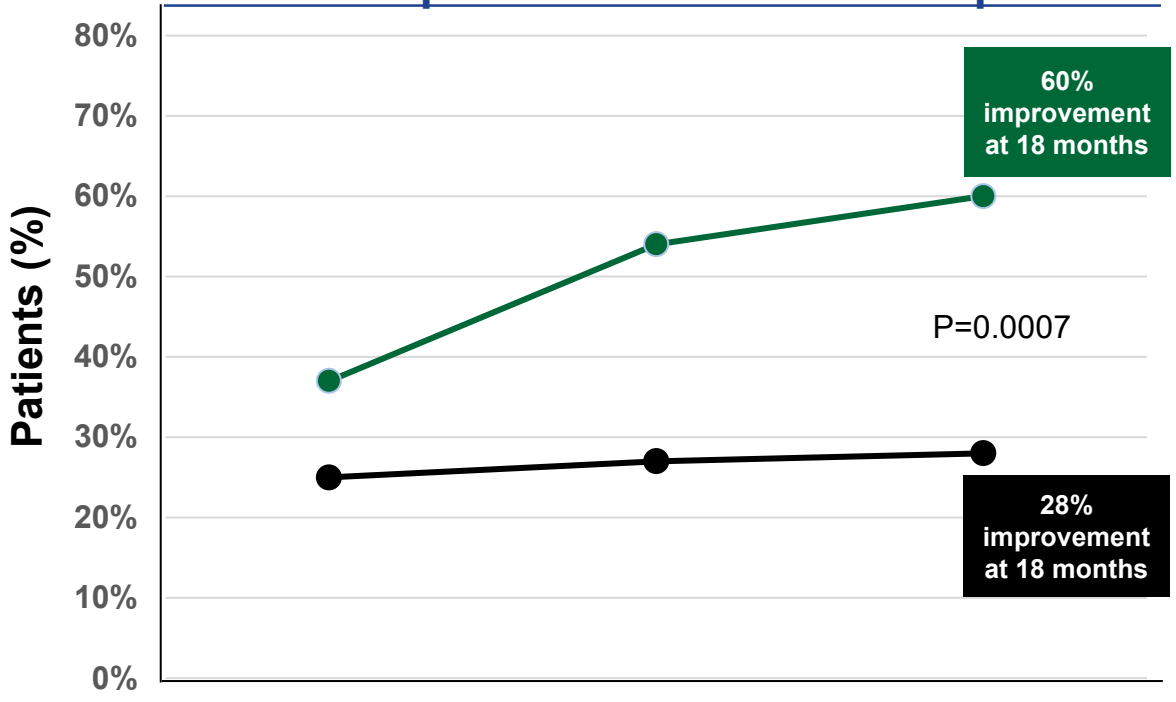
Improving and Stabilizing in Participants with Low/Baseline Tau

CDR-SB No Decline - Low Tau Population



Visit (Month)	0	6	12	18
(N) Placebo	71	67	62	58
(N) Lecanemab	70	63	57	50

CDR-SB Improvement - Low Tau Population



Visit (Month)	0	6	12	18
(N) Placebo	71	67	62	58
(N) Lecanemab	70	63	57	50

Observed rates for ‘No Decline’ and ‘Improvement’ at 18 months

- ADAS-Cog14: 74% and 68% for lecanemab vs 56% and 32% for placebo
- ADCS MCI-ADL: 75% and 70% for lecanemab vs 46% and 46% for placebo

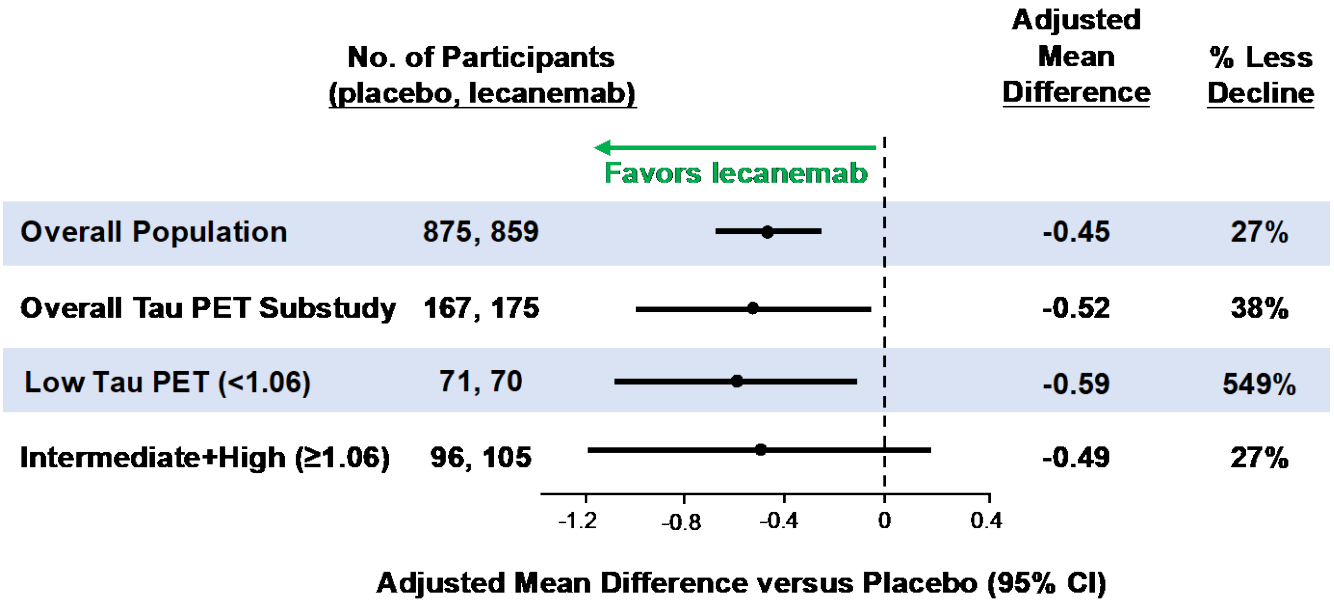
CDR-SB, Clinical Dementia Rating-sum of boxes; PET, positron emission tomography

*This was a post-hoc analysis with nominal p values and no adjustment for multiplicity

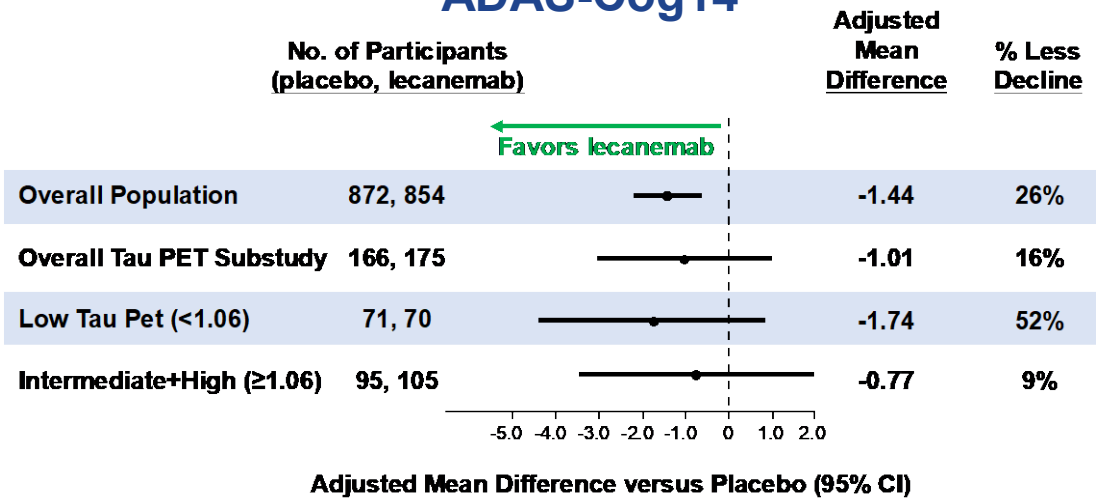
Tau PET Substudy

Consistent Outcomes for Subgroups Across Clinical Assessments

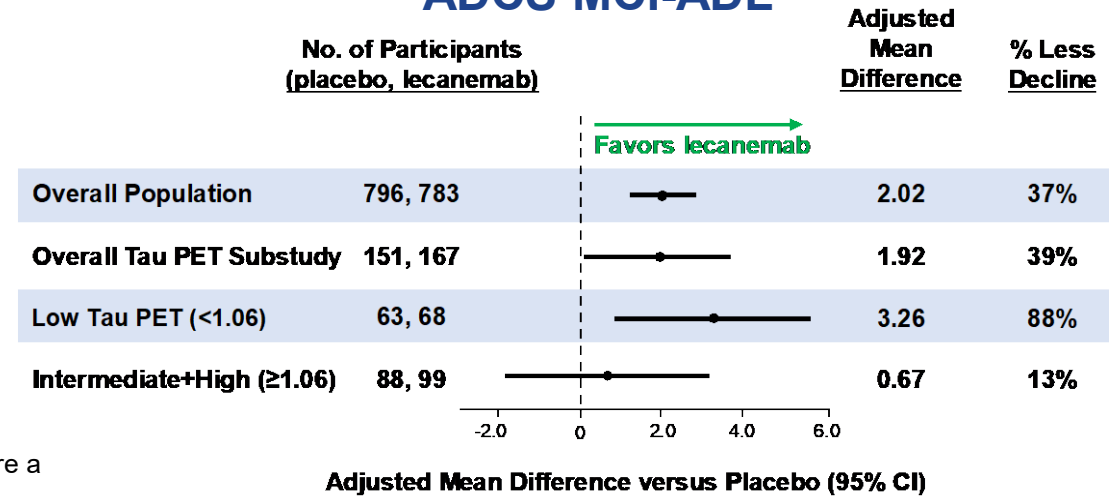
CDR-SB



ADAS-Cog14



ADCS MCI-ADL



*The longitudinal tau PET substudy was predefined. The subgroups (low and intermediate+high tau PET) were a post-hoc analysis with nominal p values and no adjustment for multiplicity

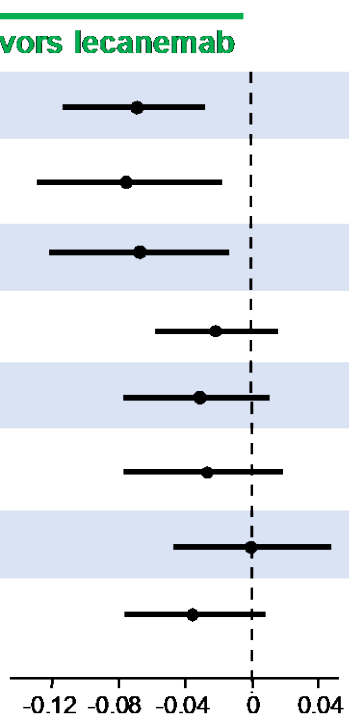
ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; CDR-SB, Clinical Dementia Rating-sum of boxes; CI, confidence interval; PET, positron emission tomography.

Tau PET Substudy

*Lecanemab Slows Tau Spread Especially in Temporal Lobe (Early Braak Regions)[1]**

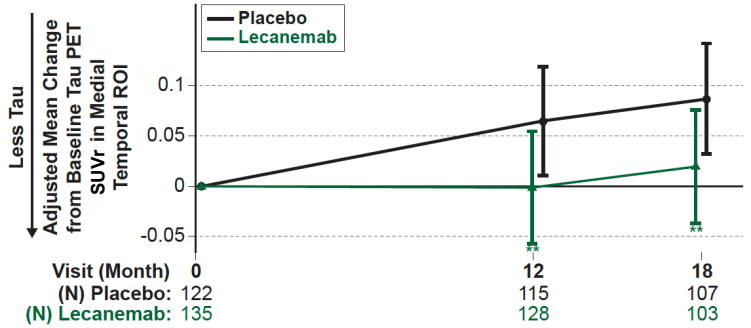
Tau PET SUVr

	No. of Participants (placebo, lecanemab)	Adjusted Mean Difference	P Value
Medial temporal	122, 135	-0.068	0.0024
Meta temporal	122, 135	-0.071	0.012
Temporal	122, 135	-0.065	0.016
Frontal	122, 135	-0.023	0.22
Cingulate	122, 135	-0.034	0.13
Parietal	122, 135	-0.029	0.25
Occipital	122, 135	-0.003	0.91
Whole cortical gray matter	122, 135	-0.035	0.10

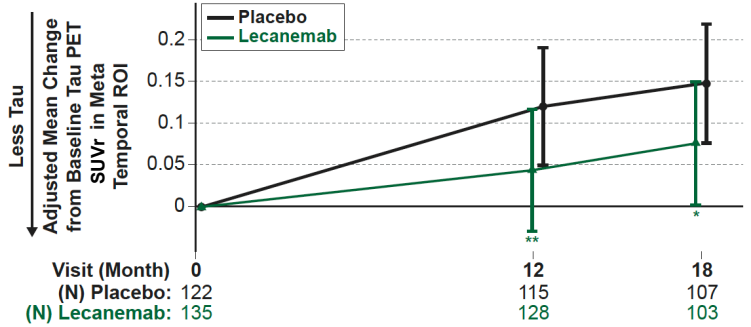


Adjusted Mean Difference versus Placebo (95% CI)

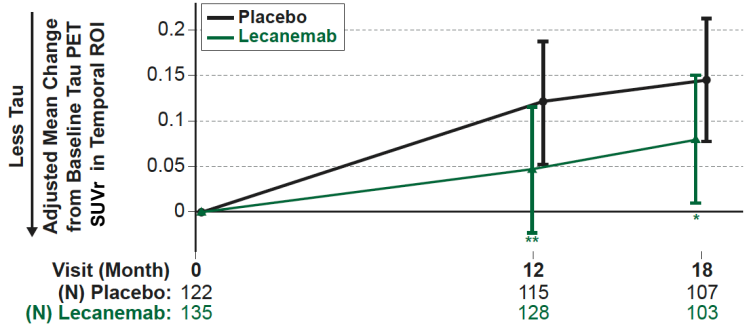
Medial Temporal



Meta Temporal



Temporal



[1]Baseline and at least one post-baseline tau PET

*Other regions favored lecanemab but were p > 0.05

Note: Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.

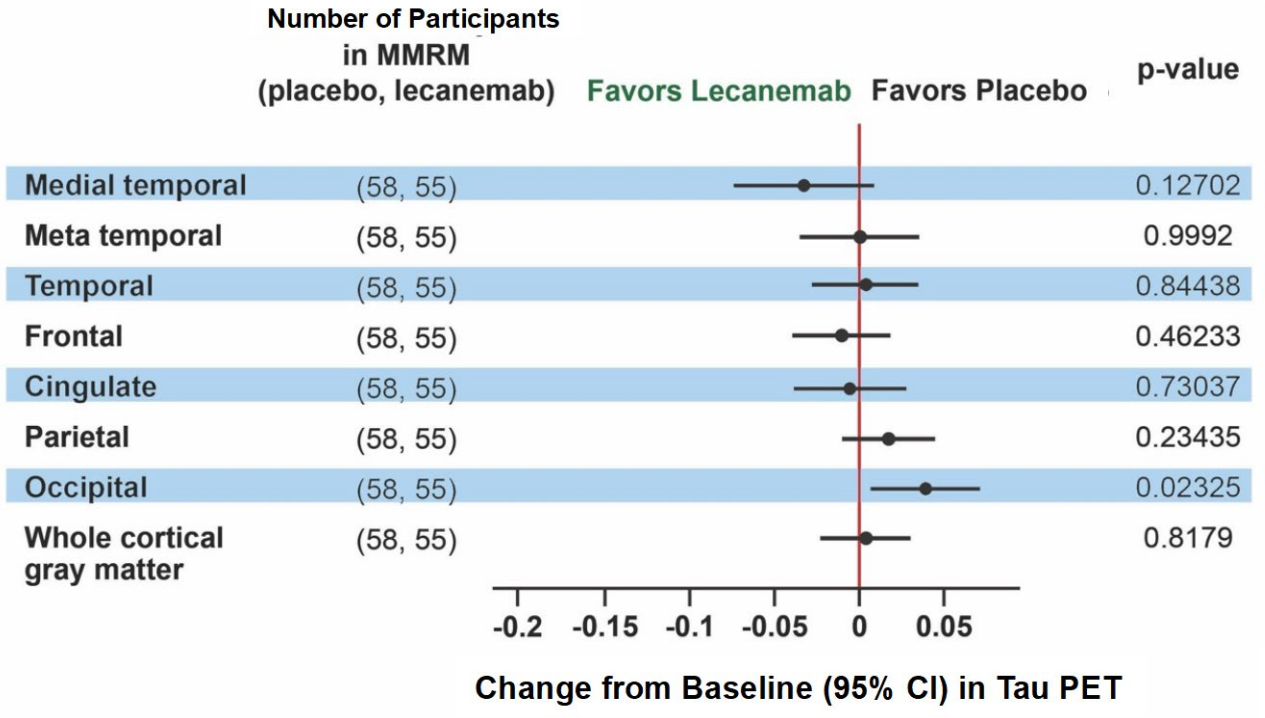
CI, confidence interval; PET, positron emission tomography; ROI, regions of interest; SUVr, standardized uptake value ratio.

Comparing Low Tau and Intermediate+High Tau PET Groups*

Lecanemab Slows Tau Spread in Earlier and Later Tau Brain Regions

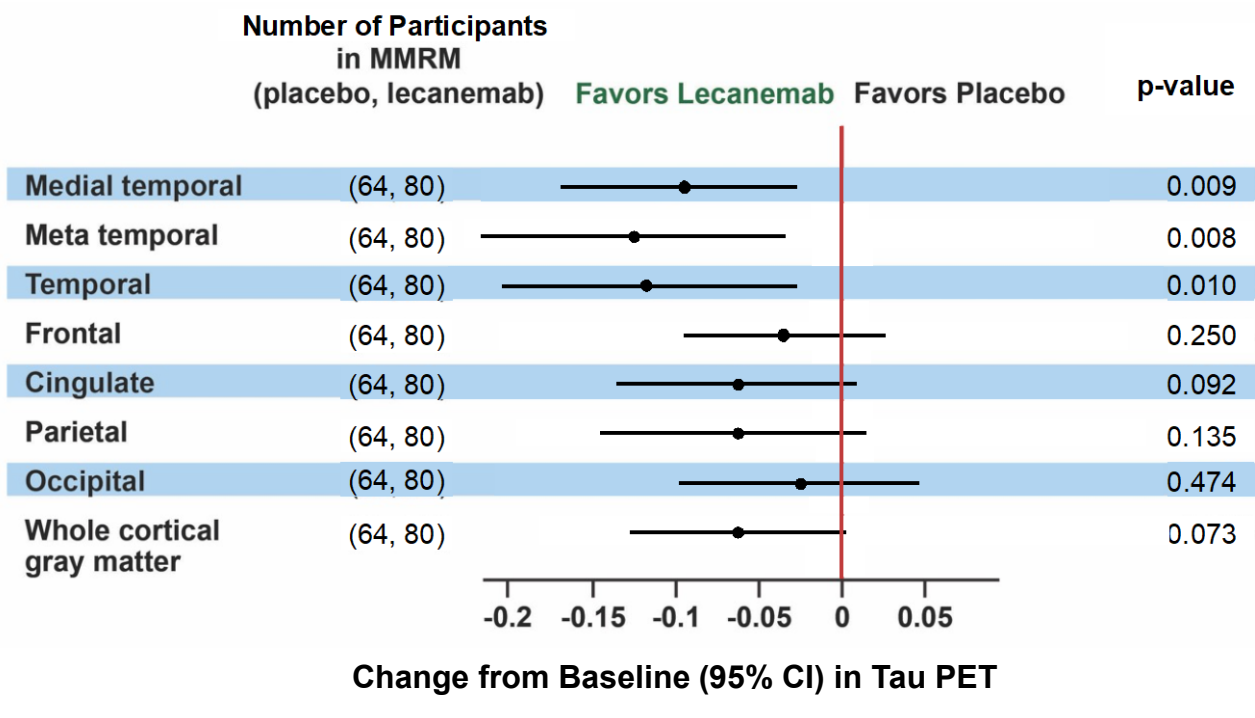
Low: Whole Cortical GM Tau <1.06

- **Lecanemab impacts medial temporal, earliest tau region**



Intermediate+High: Whole Cortical GM Tau ≥1.06

- **Lecanemab impacts progression more broadly**



*This was a post-hoc analysis with nominal p values and no adjustment for multiplicity

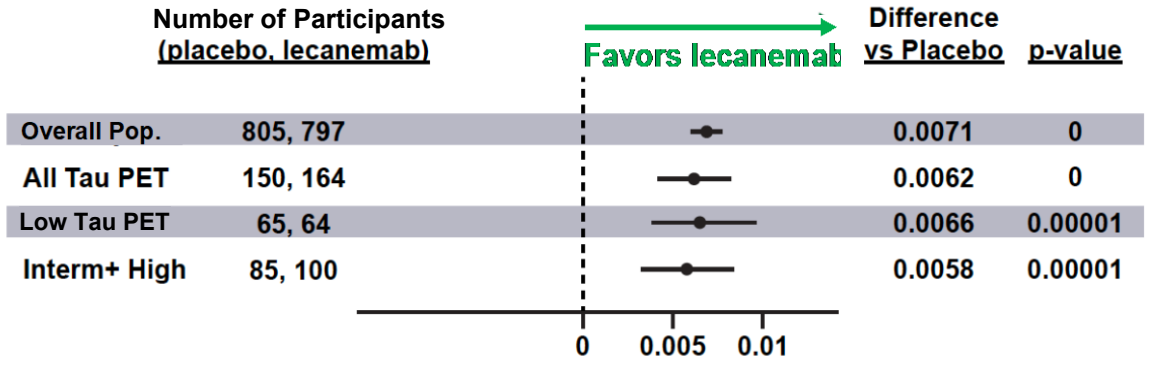
Note: Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.

CI, confidence interval; GM, gray matter; MMRM, mixed models for repeated measures; PET, positron emission tomography; ROI, regions of interest.

Fluid Biomarkers At 18 Months

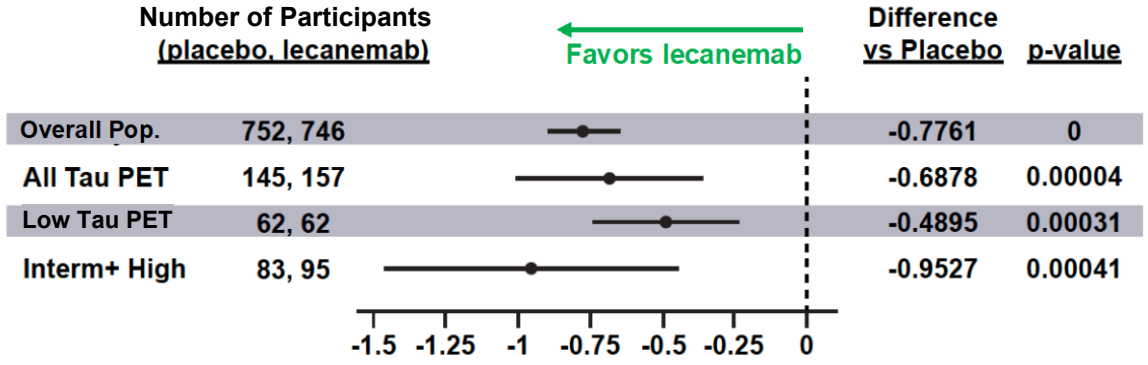
Improvement in Amyloid, Tau and Inflammation in Early and Late Tau Stages

Aβ42/40



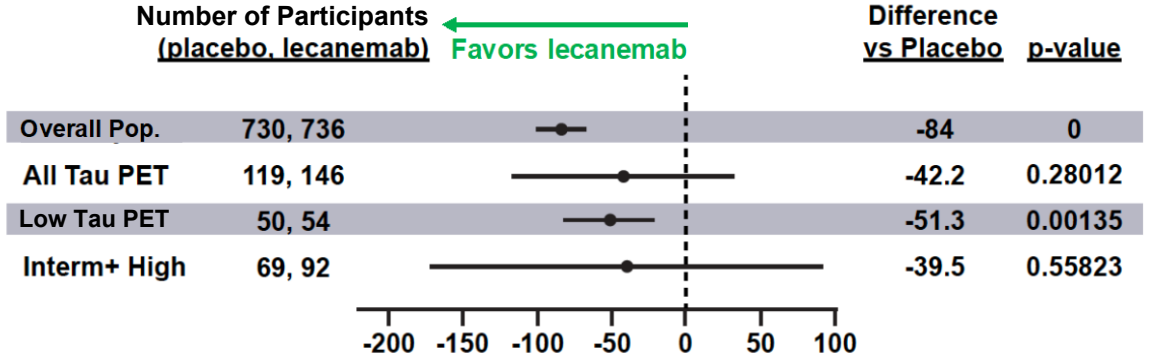
Adjusted Mean Difference vs Placebo (95% CI for difference) in Plasma Aβ42/40

pTau181



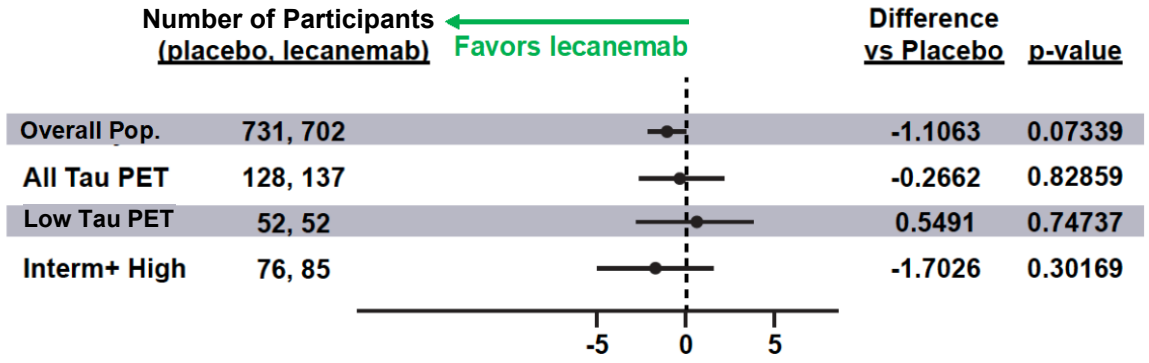
Adjusted Mean Difference vs Placebo (95% CI for difference) in Plasma pTau181

GFAP



Adjusted Mean Difference vs Placebo (95% CI for difference) in Plasma GFAP

NfL



Adjusted Mean Difference vs Placebo (95% CI for difference) in Plasma NfL

The longitudinal tau PET substudy was predefined. The subgroups (low and intermediate+high tau PET) were a post-hoc analysis with nominal p values and no adjustment for multiplicity

Note: Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.

Aβ, amyloid beta; CHG, change; GFAP, glial fibrillary acidic protein; interim, intermediate; MMRM, mixed models for repeated measures; NfL, neurofilament light chain protein; PET, positron emission tomography; ptau181, phosphorylated tau-181; pop, population.

Summary

- Findings suggest that targeting protofibrils and clearing plaque leads to clinical efficacy, slowing of tau progression and improvement in pathophysiological biomarkers
  - Effects are observed in both early and late tau stages of disease
- Results in early stages (ie, low tau) support clinical stability or improvement with early initiation of lecanemab
  - At 18 months:
    - 76% no decline; 60% improved on CDR-SB
    - 74% no decline; 68% improved on ADAS-Cog14
    - 75% no decline; 70% improved on ADCS MCI-ADL
- Lecanemab slows tau spread in different brain regions in low tau and intermediate+high tau PET groups
- Data is supportive of further testing lecanemab in preclinical AD in AHEAD3-45 study

AD, Alzheimer's disease; ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale; 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 PET, positron emission tomography.

Lecanemab for the Treatment of Early Alzheimer's Disease: The Extension of Efficacy Results from Clarity AD

Reisa Sperling

Brigham and Women's Hospital
Massachusetts General Hospital
Harvard Medical School

Reisa Sperling - Disclosures

- RAS Consultant to: AbbVie, AC Immune, Acumen, Alector, Bristol-Myers Squibb, Genentech, Ionis, Janssen, Oligomerix, Prothena, Roche, Shionogi
- KAJ (Spouse) Consultant to: Merck, Novartis
- Research Funding:
  - National Institute on Aging:

    P01AG036694; R01AG054029; R01AG061848

    U24AG057437; R01 AG03689
  - Alzheimer's Association, GHR Foundation
  - Eli Lilly, Eisai – Public-Private Partnership Trial Funding
  - Accelerating Medicines Partnership FNIH

Clarity AD OLE Study Design

Clarity AD OLE is a global, open-label, single-arm study

Study Population

- 1,795 participants 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
- Completed the Core Study (except de novo participants)

Extension Phase
(open-label)

Lecanemab

10 mg/kg biweekly

(IV infusion)

Extension Phase

Primary Outcome Measures

Change from Core Study Baseline in CDR-SB out to 24 months

Additional Outcome Measures:

Change from Baseline at 24 months:
ADAS-Cog14
ADCS MCI-ADL

Biomarkers

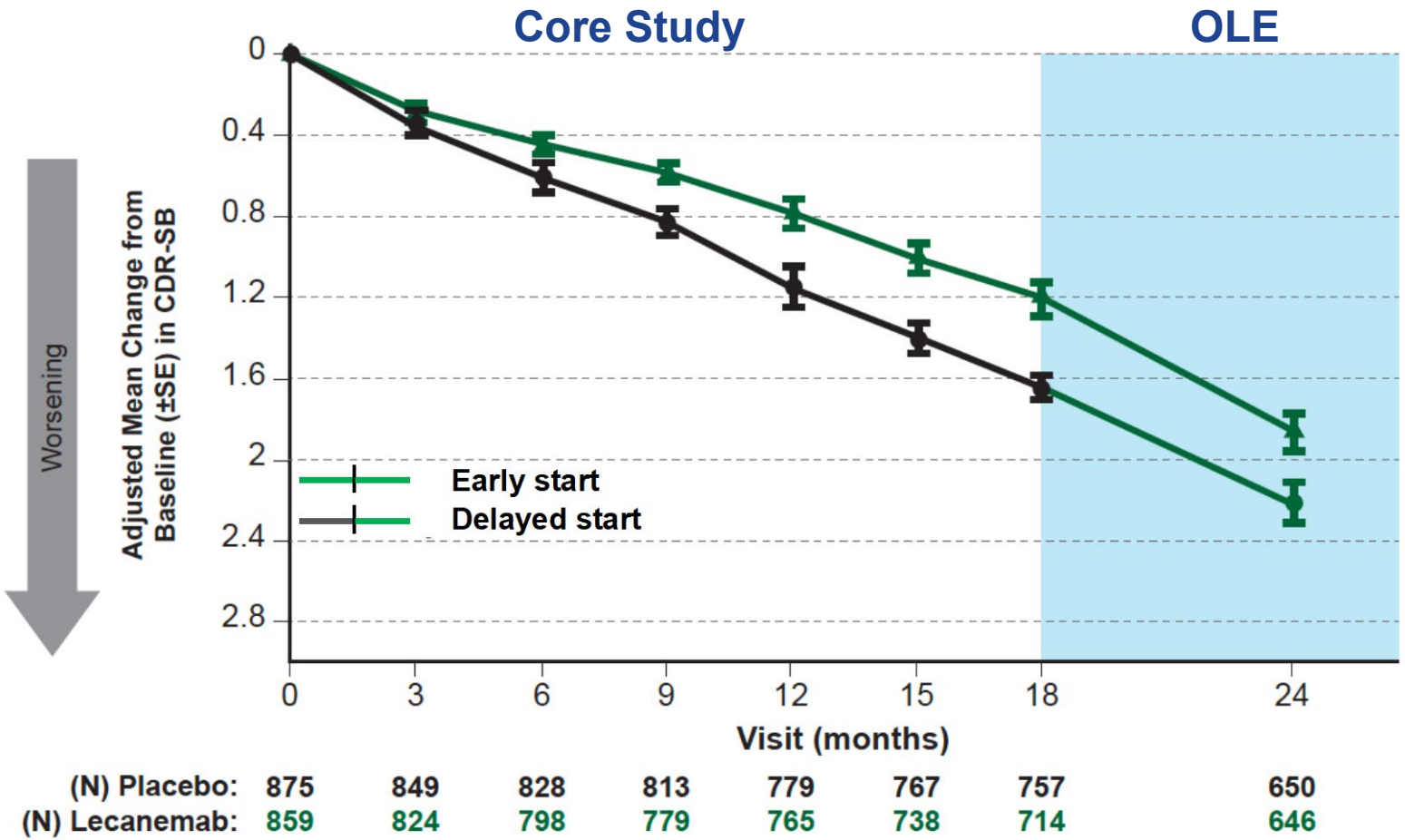
Exploratory analyses with earliest stage patients based on imaging estimates of AD pathology

AD, Alzheimer's disease; ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCOMS, Alzheimer's Disease Composite Score; ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; ApoE4, apolipoprotein E4; CDR-SB, Clinical Dementia Rating-sum of boxes; CSF, cerebrospinal fluid; IV, intravenous; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam; OLE, open-label extension; PET, positron emission tomography; SD, standard deviation; TEAEs, treatment emergent adverse events; WMS-IV LMSII, Wechsler Memory Scale IV-Logical Memory (subscale) II.

Clarity AD OLE: CDR-SB Through 24 Months

Lecanemab-Treated Participants Continued to Benefit Through 24 Months

- Separation between early and delayed start maintained between 18 & 24 months when all participants are on lecanemab ($p<0.05$[1])
- Similar disease trajectory for the early start and delayed start between 18 to 24 months



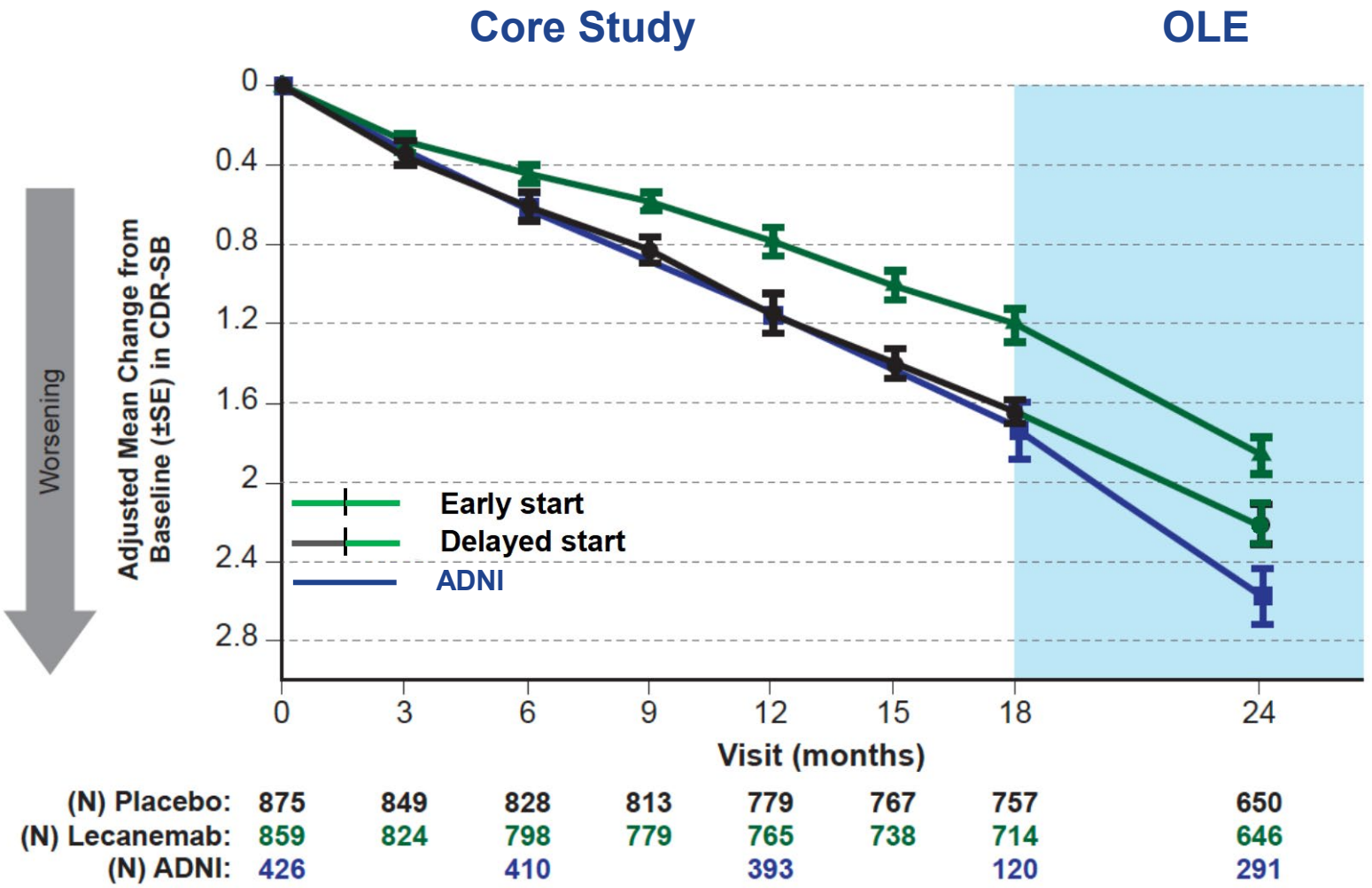
Note: Early start lecanemab 10 mg/kg biweekly group are those subjects on lecanemab 10 mg/kg biweekly in the Core. Delayed start LEC10-BW group (those subjects that initiate lecanemab 10 mg/kg biweekly in the OLE).

1. Based on testing the hypothesis that early start arm maintains at least half of the treatment effect seen at the end of 18 months. Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.

ADNI, Alzheimer's Disease Neuroimaging Initiative; CDR-SB, Clinical Dementia Rating-sum of boxes; OLE, open-label extension; SE, standard error.

Clarity AD CDR-SB: OLE in Context of Observational Cohort

Lecanemab-Treated Participants Continued to Benefit Through 24 Months



- These ADNI participants selected to match with Clarity AD population
  - Baseline demographics and clinical characteristics including randomization strata
- Matched ADNI participants show similar degree of decline to placebo group out to 18 months
- Caveats
  - ADNI is an observational cohort;
  - Delayed start is Open-label; all participants know they are receiving lecanemab

Note: Early start lecanemab 10 mg/kg biweekly group are those subjects on lecanemab 10 mg/kg biweekly in the Core. Delayed start LEC10-BW group (those subjects that initiate lecanemab 10 mg/kg biweekly in the OLE).

Based on testing the hypothesis that early start arm maintains at least half of the treatment effect seen at the end of 18 months. Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.

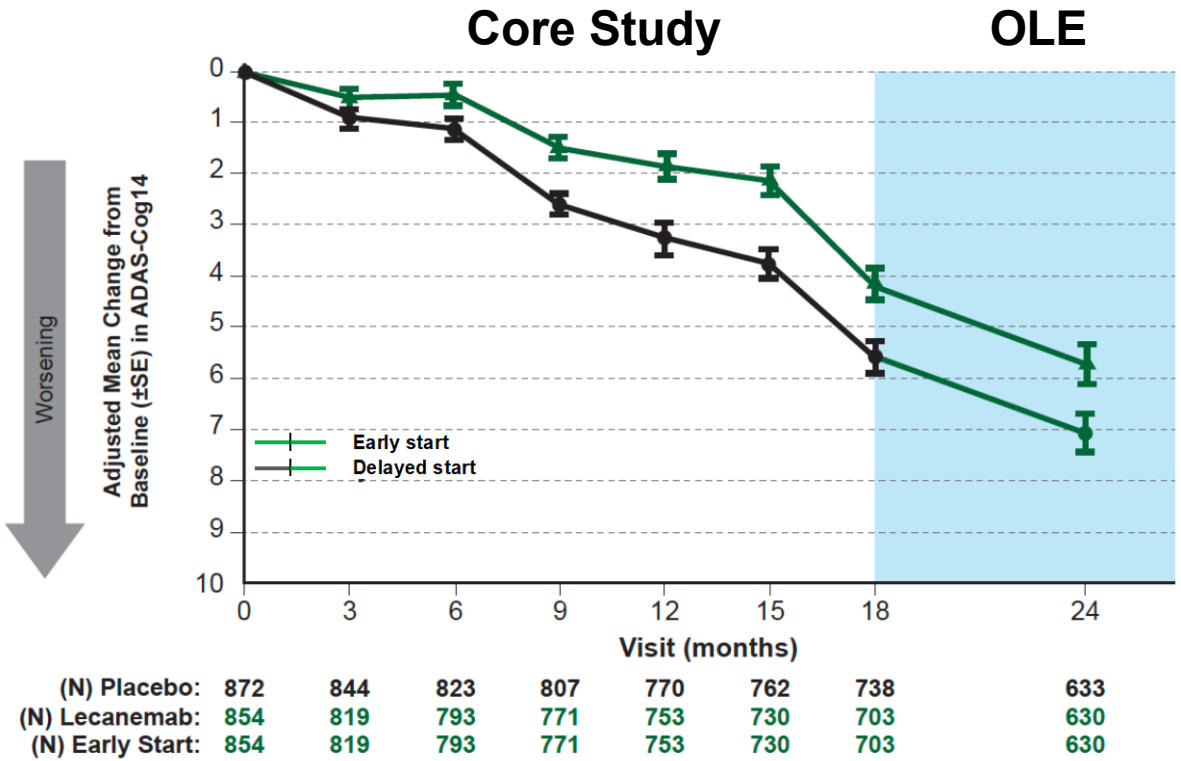
ADNI, Alzheimer's Disease Neuroimaging Initiative; CDR-SB, Clinical Dementia Rating-sum of boxes; OLE, open-label extension; SE, standard error.

ADAS-Cog14 and ADCS MCI-ADL Through 24 Months

Lecanemab-Treated Participants Continued to Show Benefit

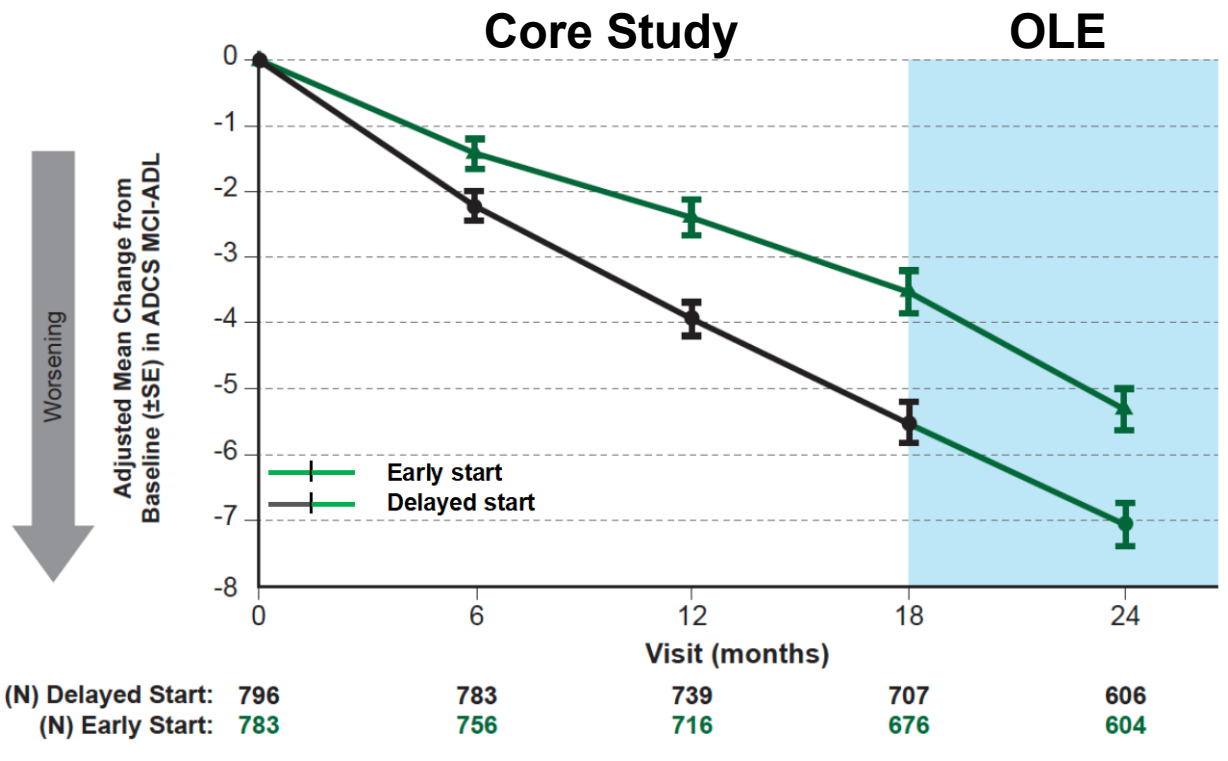
ADAS-Cog14

- Separation between the early start and delayed start maintained between 18 & 24 months when all participants are on lecanemab ($p<0.05$[1])
- Parallel disease trajectory for the early start and delayed start between 18 to 24 months



ADCS MCI-ADL

- Separation between the early start and delayed start maintained between 18 & 24 months when all participants are on lecanemab ($p<0.05$[1])
- Parallel disease trajectory for the early start and delayed start between 18 to 24 months



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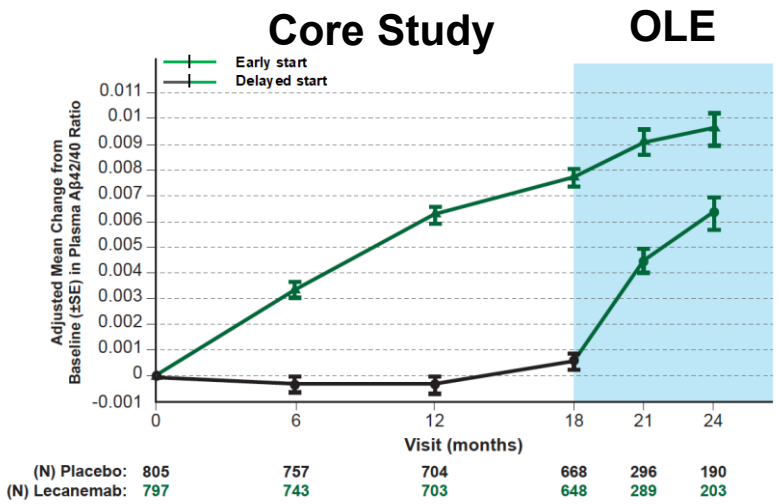
Based on testing the hypothesis that early start arm maintains at least half of the treatment effect seen at the end of 18 months. Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.

ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; OLE, open-label extension; SE, standard error.

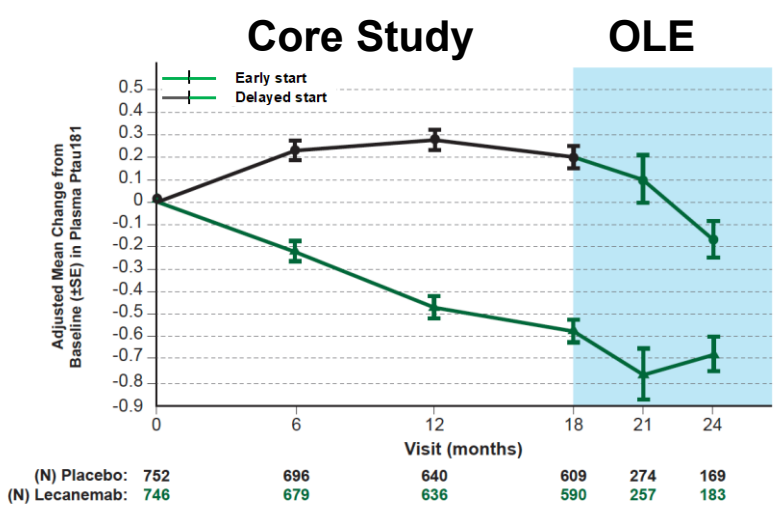
Clarity AD OLE: Biomarker Results Out to 24 Months

Preliminary Subset of Participants

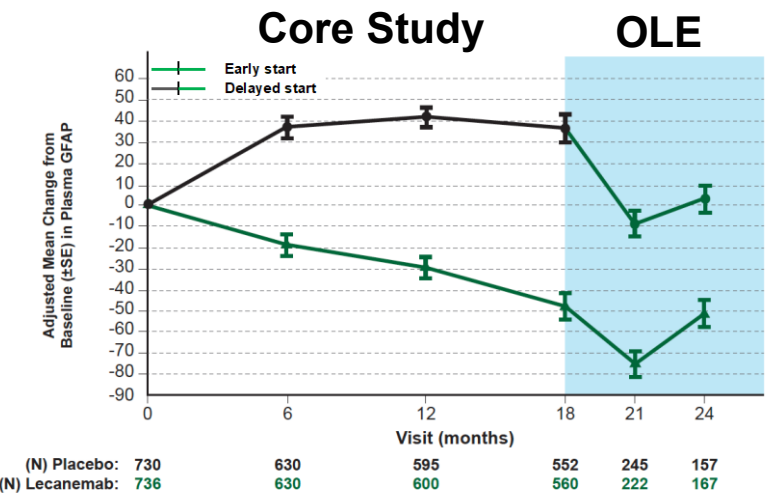
Plasma Aβ42/40 Ratio



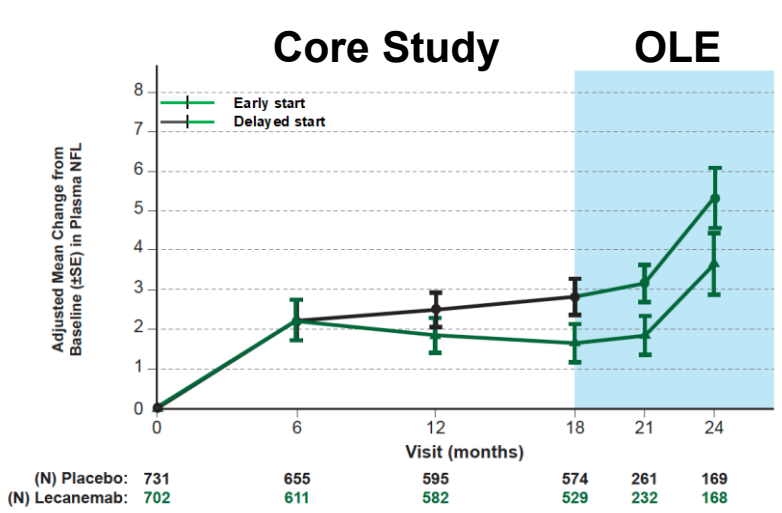
Plasma pTau181



Plasma GFAP



Plasma NFL



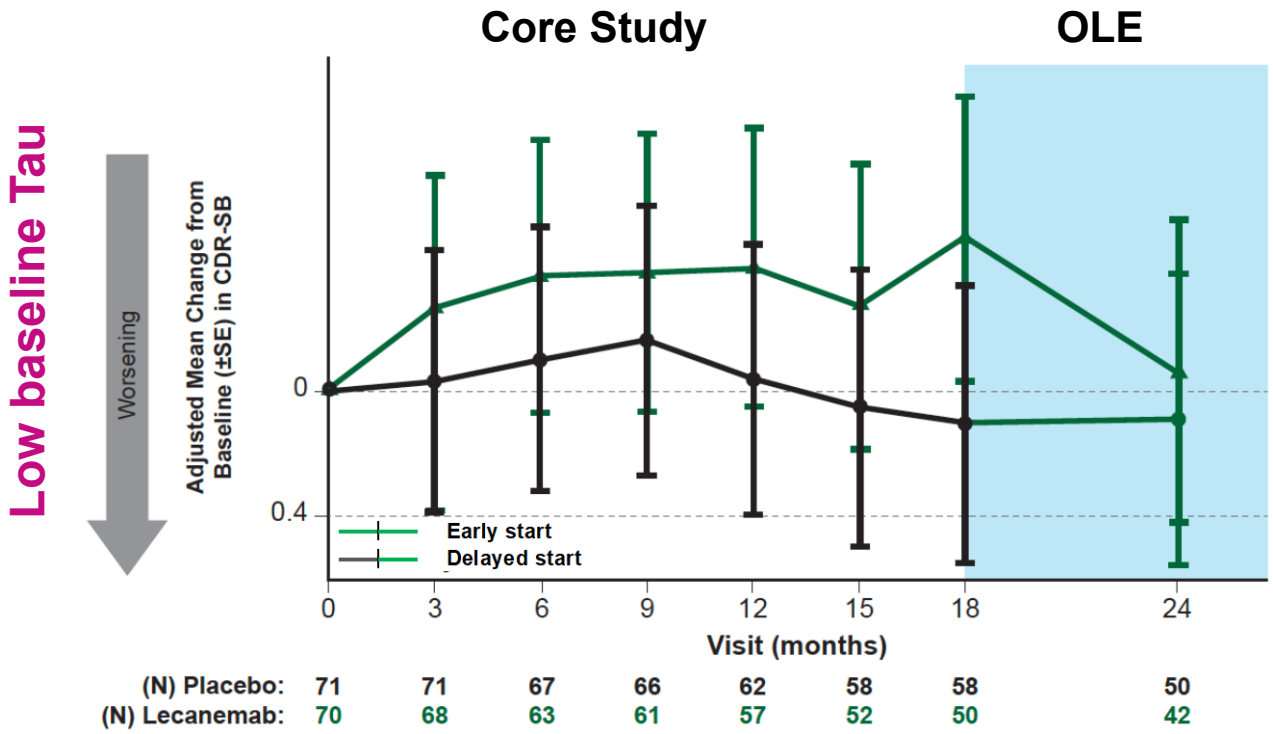
- Participants with continuous treatment continue to show improvement in biomarkers in Aβ42/40 and pTau181
- Participants on placebo who started lecanemab at 18 months show improvement in biomarkers within 3 months of treatment

Aβ, amyloid beta; CHG, change; GFAP, glial fibrillary acidic protein; MMRM, mixed models for repeated measures; NfL, neurofilament light chain protein; PET, positron emission tomography; ptau181, phosphorylated tau-181.

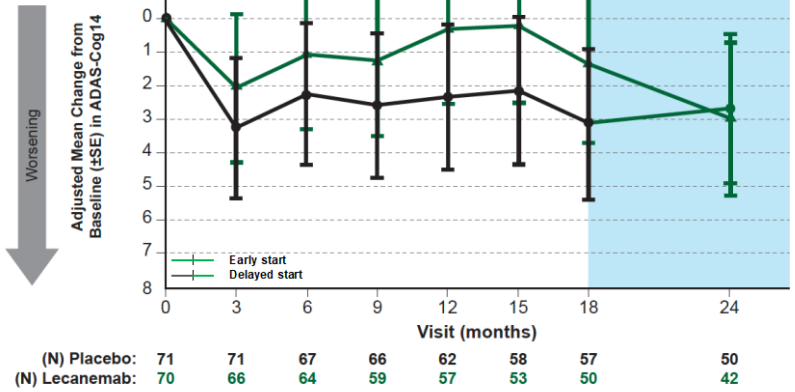
Clinical Outcomes Through 24 Months Low Tau Subgroup*

Lecanemab-Treated Low Tau Participants Maintain Cognitive Function Through 24 Months

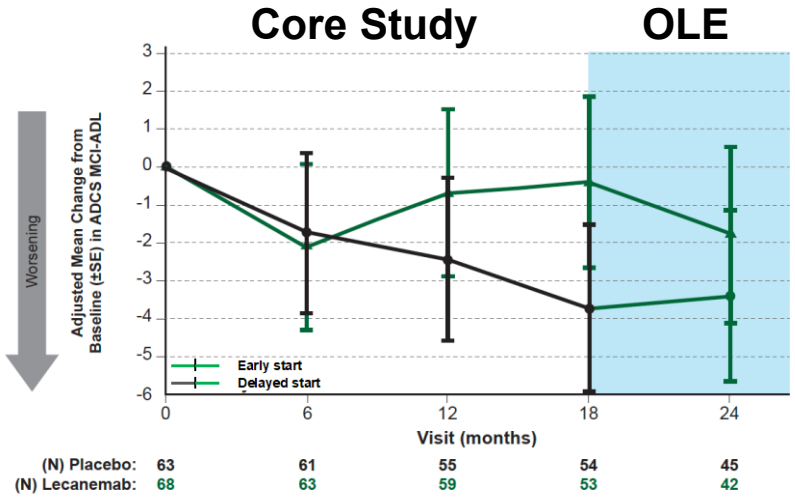
CDR-SB



ADAS-Cog14



ADCS MCI-ADL



Note: Early start lecanemab 10 mg/kg biweekly group are those subjects on lecanemab 10 mg/kg biweekly in the Core. Delayed start LEC10-BW group (those subjects that initiate lecanemab 10 mg/kg biweekly in the OLE).

Based on testing the hypothesis that early start arm maintains at least half of the treatment effect seen at the end of 18 months. Based on modified intention-to-treat analysis population. Adjusted mean change from baseline, SE and p-value are derived using mixed model repeat measures (MMRM) with treatment group, visit, treatment group by visit interaction, clinical subgroup, use of Alzheimer's disease symptomatic medication at baseline, ApoE4 carrier status, region, baseline value by visit interaction as fixed effects, and baseline value as covariate.

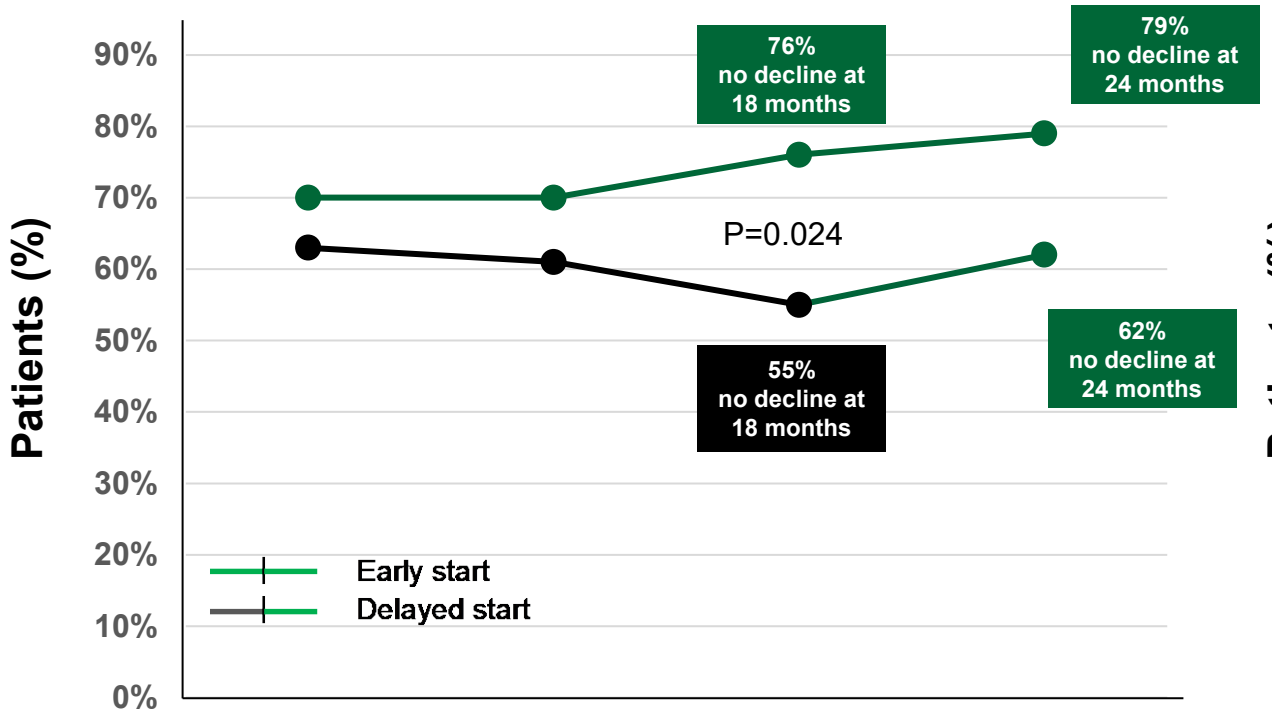
*This was a post-hoc analysis with nominal p values and no adjustment for multiplicity

ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale; 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; OLE, open-label extension; SE, standard error.

Observed ‘No Decline’ and ‘Improvement’ Rates in Low Tau

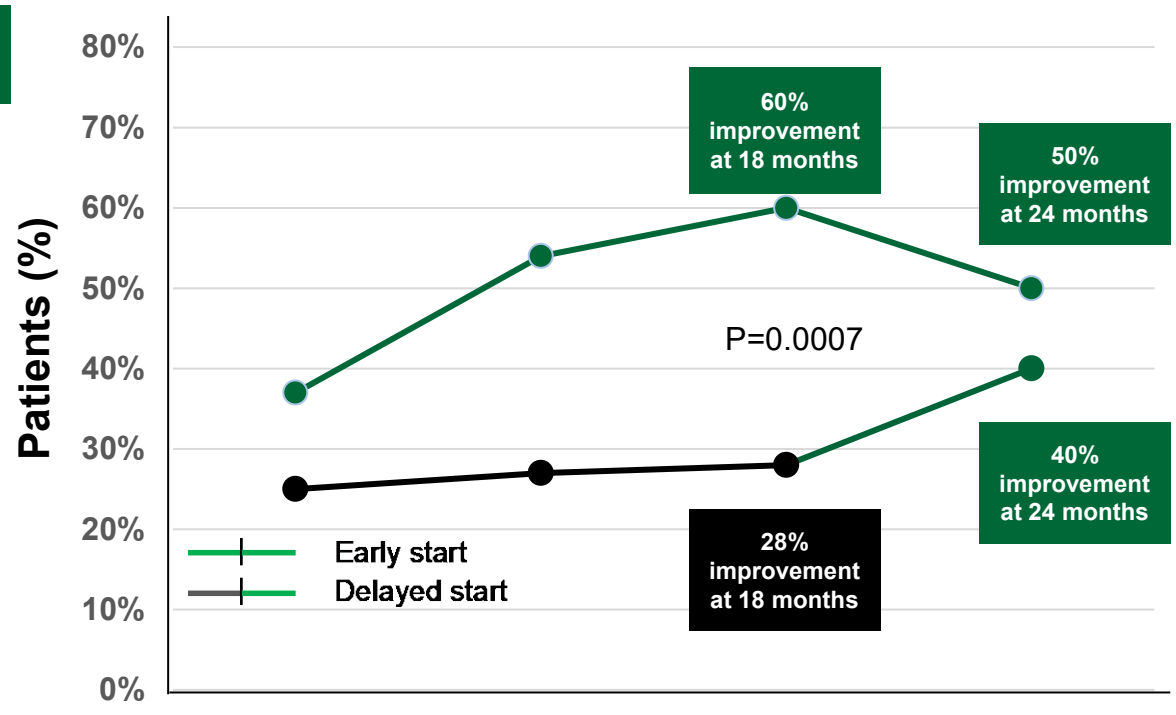
Early-Stage Participants Continue to Benefit from Lecanemab Through 24 Months

CDR-SB No Decline - Low Tau Population



Visit (Month)	0	6	12	18	24
(N) Placebo	71	67	62	58	
(N) Lecanemab	70	63	57	50	42

CDR-SB Improvement - Low Tau Population



Visit (Month)	0	6	12	18	24
(N) Placebo	71	67	62	58	
(N) Lecanemab	70	63	57	50	42

Observed rates for ‘No Decline’ and ‘Improvement’ at 24 months

- ADAS-Cog14: 67% and 62% for lecanemab
- ADCS MCI-ADL: 67% and 62% for lecanemab

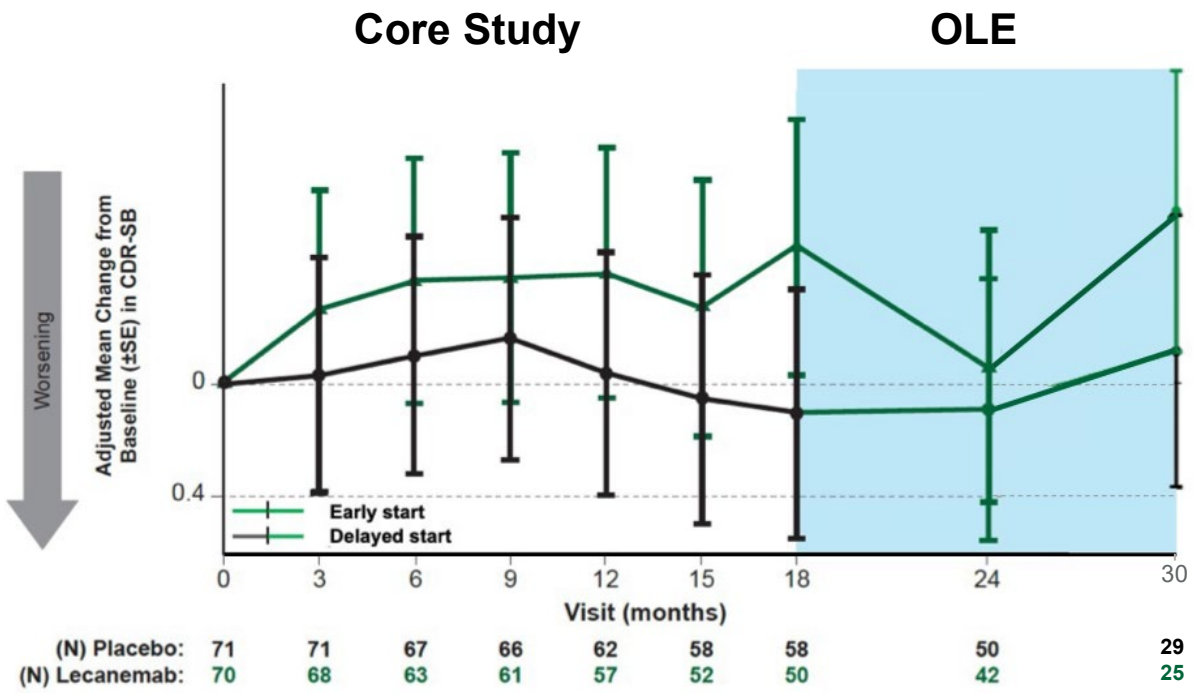
*This was a post-hoc analysis with nominal p values and no adjustment for multiplicity

CDR-SB, Clinical Dementia Rating-sum of boxes; PET, positron emission tomography

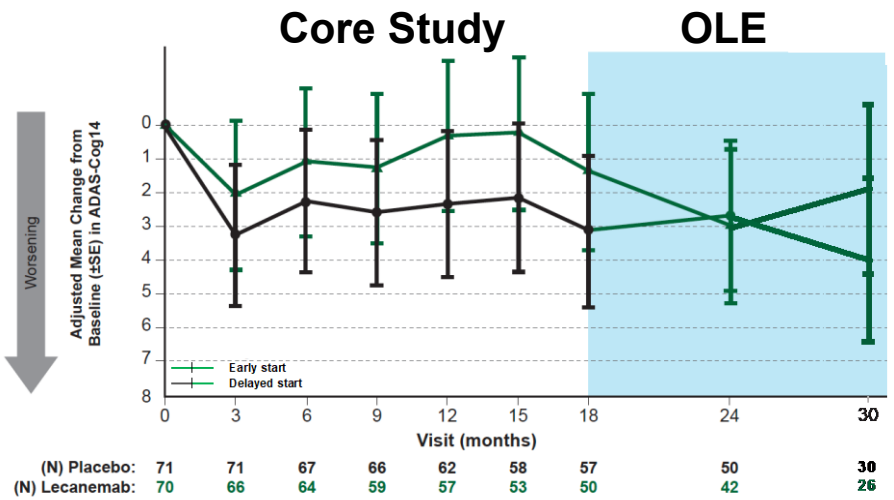
Clinical Outcomes in Low Tau Subgroup Through 30 Months (Preliminary)

Lecanemab-Treated Low Tau Participants

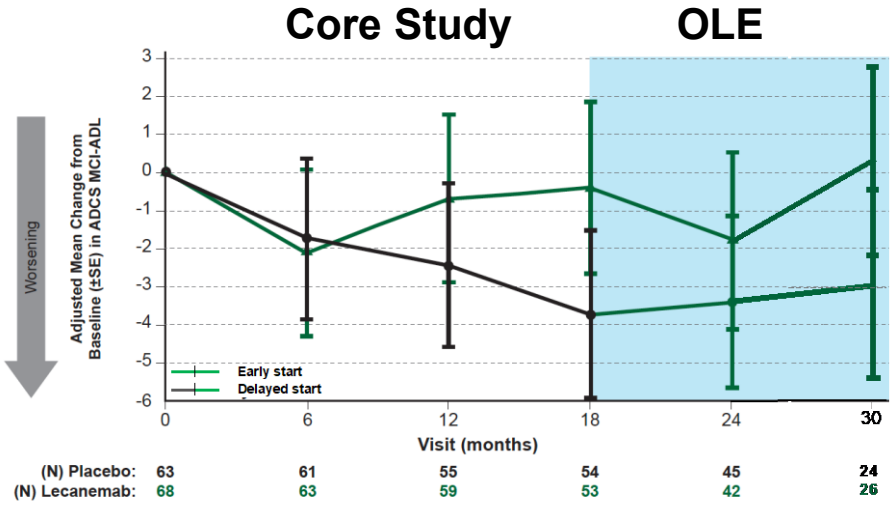
CDR-SB



ADAS-Cog14



ADCS MCI-ADL

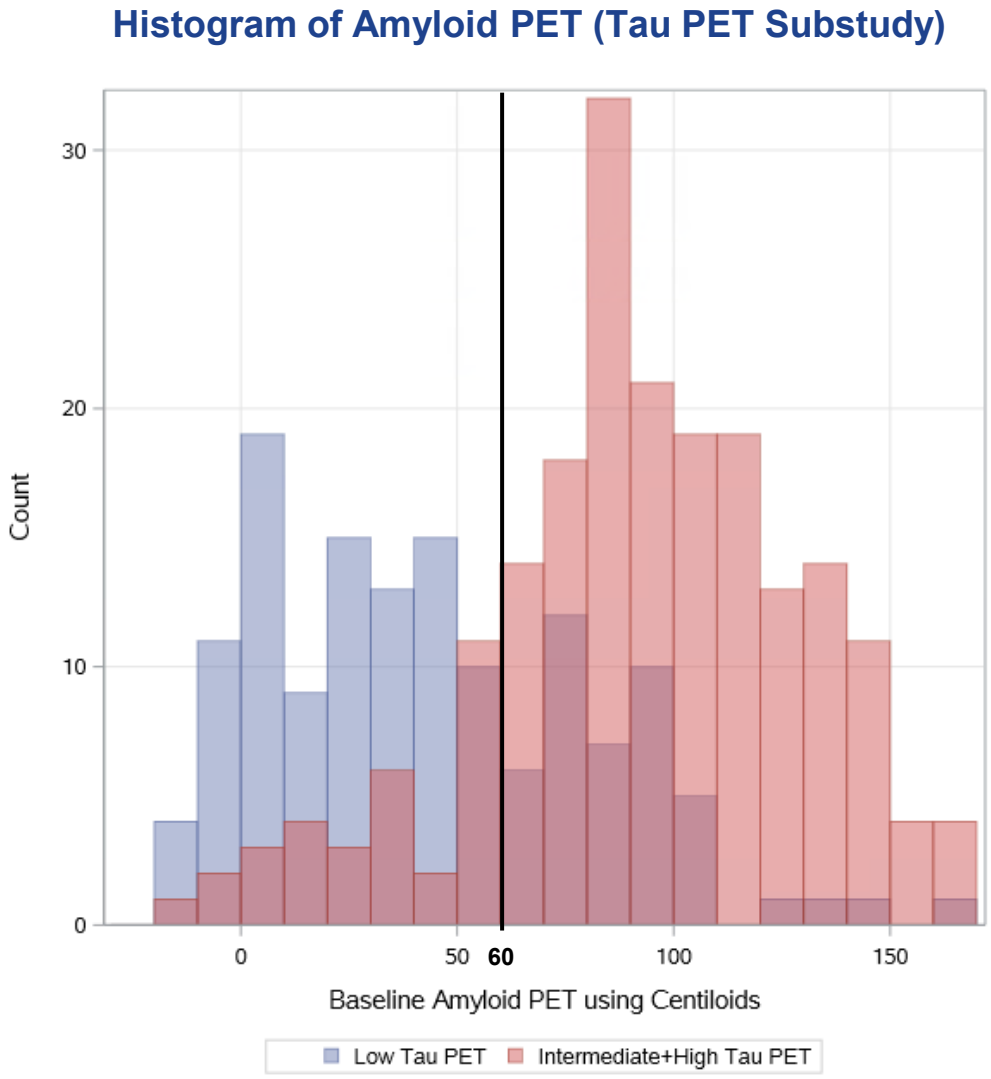


ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; CDR-SB, Clinical Dementia Rating-sum of boxes; OLE, open-label extension; PET, positron emission tomography

Low Tau Associated with Lower Levels of Amyloid

Early-Stage Participants Can Also be Identified by Amyloid PET <60 CL

- Due to relatively small sample size in tau PET substudy, we estimated a similar early stage of disease based on amyloid PET to apply to overall Clarity AD population
- Amyloid PET threshold <60 CL used to enrich for low tau population



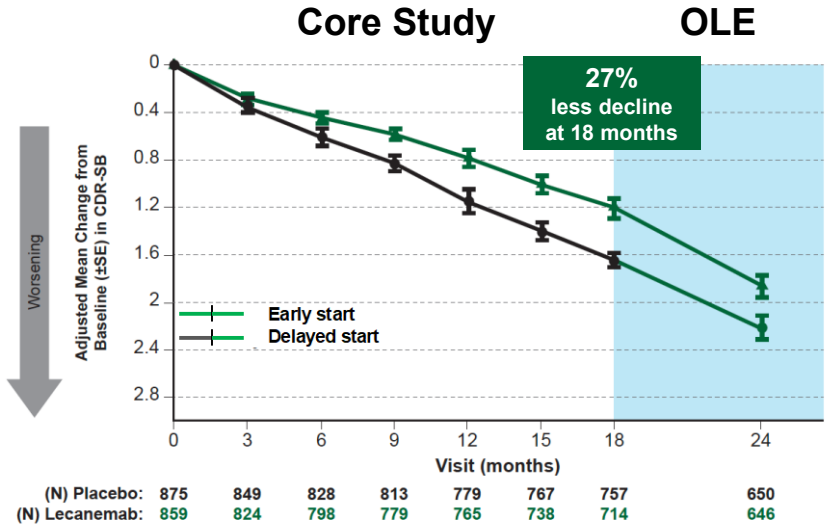
Observed data
ApoE4, apolipoprotein E4; CDR-SB, Clinical Dementia Rating-sum of boxes; GM, gray matter; PET, positron emission tomography.

Clinical Outcomes Through 24 Months (Overall and Baseline <60 CL)

Early-Stage Participants Continue to Benefit from Lecanemab Through 24 Months

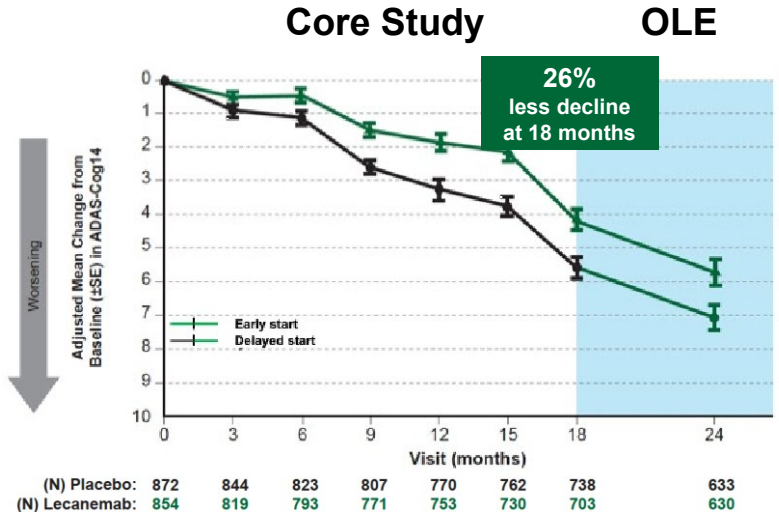
Overall Population

CDR-SB



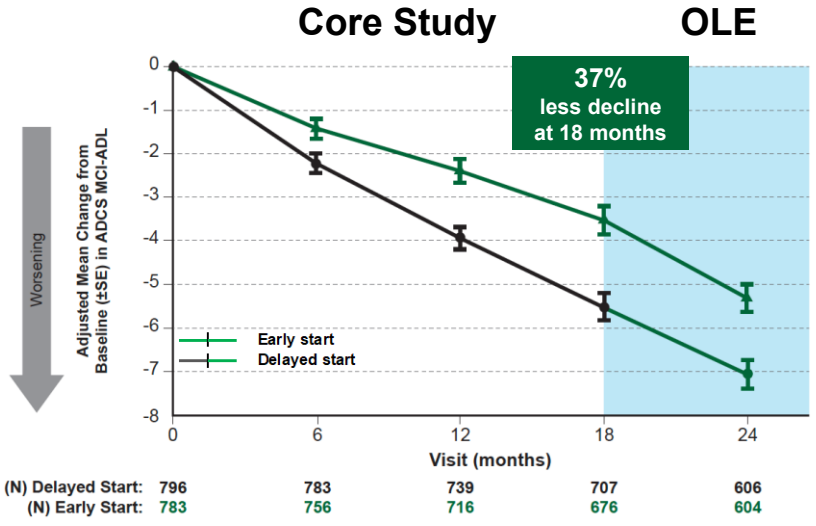
(N) Placebo:	875	849	828	813	779	767	757	650
(N) Lecanemab:	859	824	798	779	765	738	714	646

ADAS-Cog14



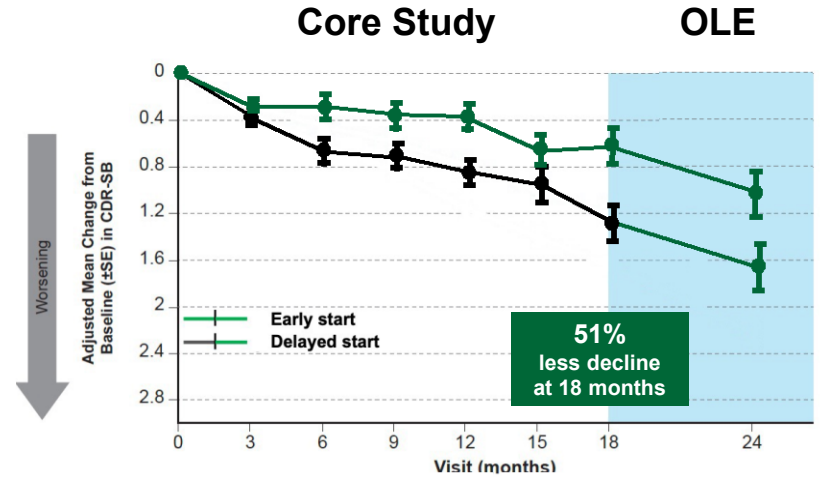
(N) Placebo:	872	844	823	807	770	762	738	633
(N) Lecanemab:	854	819	793	771	753	730	703	630

ADCS MCI-ADL

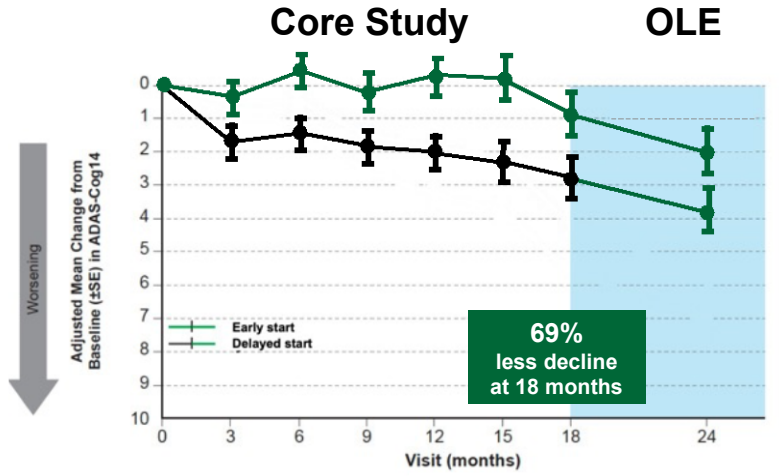


(N) Delayed Start:	796	783	739	707	606
(N) Early Start:	783	756	716	676	604

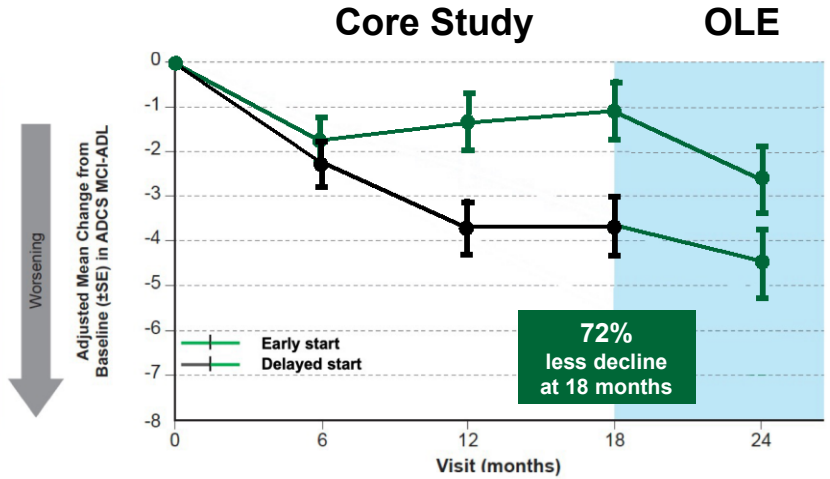
Baseline < 60 CL



N (Placebo):	191	186	178	175	164	160	161	132
N (Lecanemab):	185	173	176	164	157	150	146	126



N (Placebo):	189	184	176	172	162	157	154	132
N (Lecanemab):	185	174	177	164	156	149	145	126



N (Placebo):	168	164	152	144	119
N (Lecanemab):	166	161	144	135	113

60 CL is optimal cutoff to define low tau PET

Summary

- Maintenance of treatment difference with ongoing lecanemab treatment through 24 months, relative to the newly treated lecanemab participants, is consistent with a disease-modifying effect
- Pathological biomarkers improved at 3 months in newly treated participants and maintained at 24 months with continuous treatment
- Delayed start and lower pathology group results support early initiation of treatment with lecanemab
- These results support testing of lecanemab in an even earlier population as in the AHEAD3-45 Study

Preliminary Update on Lecanemab Safety in Clarity AD Open-Label Extension, Including Subcutaneous Formulation

Michael Irizarry
Eisai Inc.

Disclosure

- Dr. Irizarry is an employee of Eisai Inc.

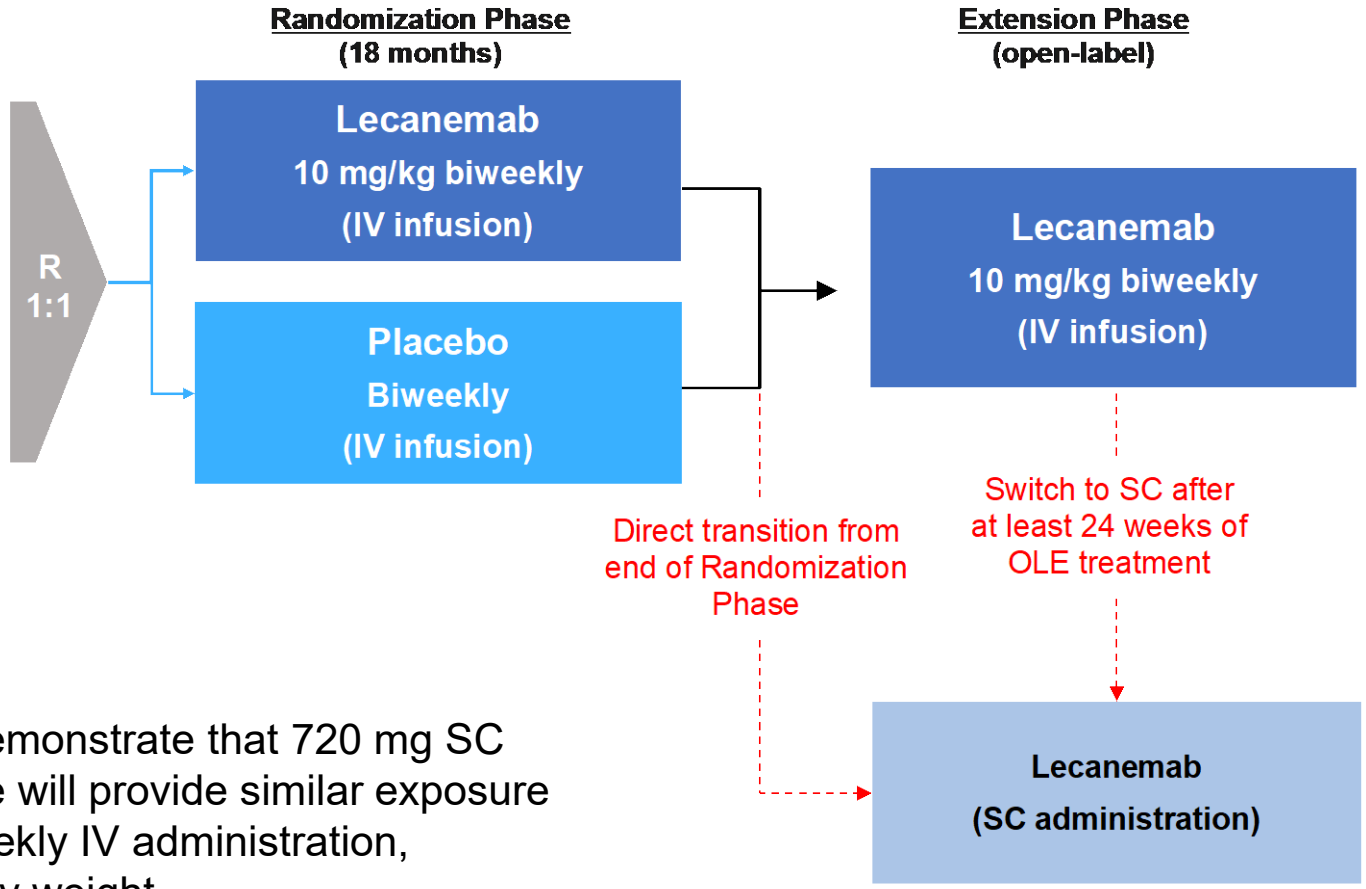
Clarity AD Study Design

SC Substudy

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

Study Population

- 1,795 participants 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)

SC Substudy Primary Outcome Measures

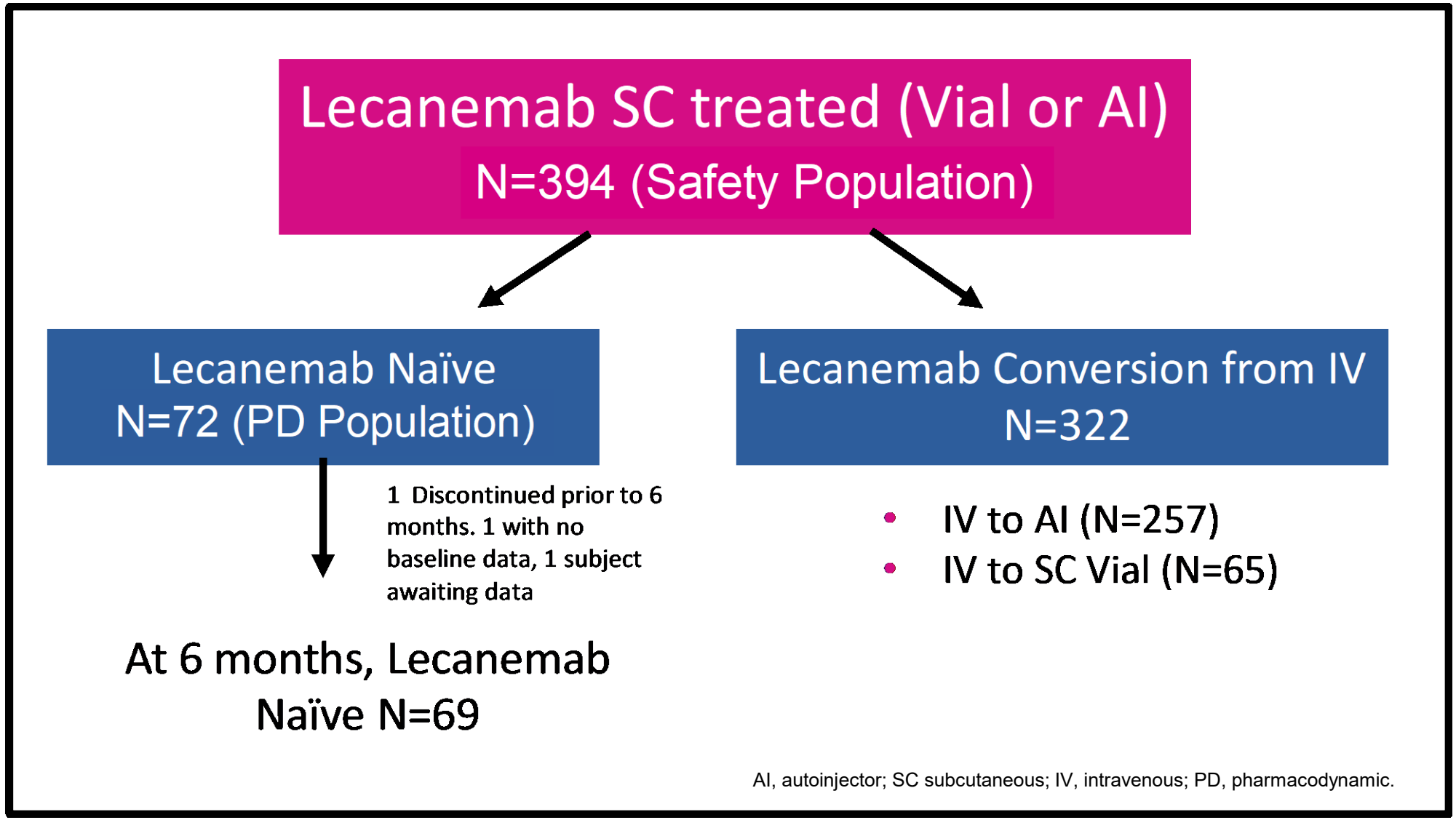
Safety (N=394)

Pharmacokinetics/Pharmacodynamics

- PK/PD models demonstrate that 720 mg SC fixed weekly dose will provide similar exposure to 10 mg/kg biweekly IV administration, regardless of body weight

AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating-sum of boxes; CSF, cerebrospinal fluid; IV, intravenous; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam; OLE, open-label extension; PD, pharmacodynamic; PK, pharmacokinetic; SC, subcutaneous; SD, standard deviation; TEAEs, treatment emergent adverse events; WMS-IV LMSII, Wechsler Memory Scale IV-Logical Memory (subscale) II.

Lecanemab Subcutaneous Formulation: Patient Disposition



AI, autoinjector; SC subcutaneous; IV, intravenous; PD, pharmacodynamic.

SC Substudy

Baseline Characteristics Generally Similar

	SC (N=394) n(%)	SC Lecanemab Naïve (N=72) n(%)
Age, mean (SD), years	70.9 (7.80)	73.3 (7.74)
Female, n (%)	209 (53.0)	37 (51.4)
CDR Global=0.5	332 (84.5)	61 (85.9)
MMSE, mean (SD)	25.90 (2.185)	26.52 (2.235)
Mild dementia due to AD	114 (28.9)	15 (20.8)
ApoE4 Status		
Noncarrier	132 (33.5)	26 (36.1)
Heterozygous	210 (53.3)	35 (48.6)
Homozygous	47 (11.9)	6 (8.3)
CDR-SB, mean (SD)	3.04 (1.246)	2.98 (1.359)
Amyloid PET Centiloids, mean (SD)	76.58 (42.243)	77.42 (38.792)
ADAS-Cog14, mean (SD)	21.77 (6.658)	19.18 (7.343)
ADCS MCI-ADL, mean (SD)	41.95 (6.399)	42.80 (5.886)

Pharmacokinetics of SC are Comparable to IV

- 90% CI for SC vs IV is within BE (Bioequivalence) limits of 80 to 125%, with lower limit much higher than 80%

Parameter	Units	Geometric mean ratio of SC/IV for AUC(0-2 weeks)	90% CI for geometric mean ratio
$AUC_{(ss,2weeks)}$	h*ug/mL	111%	(99%, 124%)

Model: ANOVA with covariate= treatment

- Note: AUC is 11% higher on SC vs IV

AUC, area under the curve; CI, confidence intervals; CL clearance; IV, intravenous; PK, pharmacokinetic; SC, subcutaneous; SS, steady state.

Pharmacodynamic Comparability (Amyloid PET Centiloids)

SC Administration Results in 14% Greater Amyloid Removal

- 90% CI for SC vs IV meets PD comparability with lower bound much higher than 80%
  - In addition, PD comparability was confirmed by population PK/PD modeling
- Results of the preliminary PD comparability analysis suggest that SC administration is similar in removing amyloid compared to IV administration at 6 months of treatment

	IV (N=354)		SC denovo (N=71)		Ratio (SC/IV)	Lower Bound of 90% CI for ratio (SC/IV)
	Mean	SE	Mean	SE		
All subjects	-35.4	1.14	-40.3	2.27	114%	102%
All subjects, baseline amyloid PET ≥ 30 CL	-41.4	1.35	-45.8	2.68	111%	99%

Model: ANCOVA with covariates= treatment, baseline Centiloids, age

Note:

- Only significant covariates (baseline amyloid and age) included in the model
- At 6 months, n=275 for IV and n=69 for SC

AUC, area under the curve; CI, confidence intervals; CL clearance; IV, intravenous; PET, positron emission tomography; PD, pharmacodynamic; SC, subcutaneous; SE, standard error.

Safety of Subcutaneous Lecanemab

Very Low Incidence of Systemic Injection-Related Reactions

	SC (N=394) n(%)	SC Lecanemab Naïve (N=72) n(%)
Injection-Related reactions	33 (8.4)	11 (15.3)
Local injection site reactions	32 (8.1)	11 (15.3)
Systemic injection reactions	2 (0.5)	0
Skin rash	0	0
Other hypersensitivity	0	0

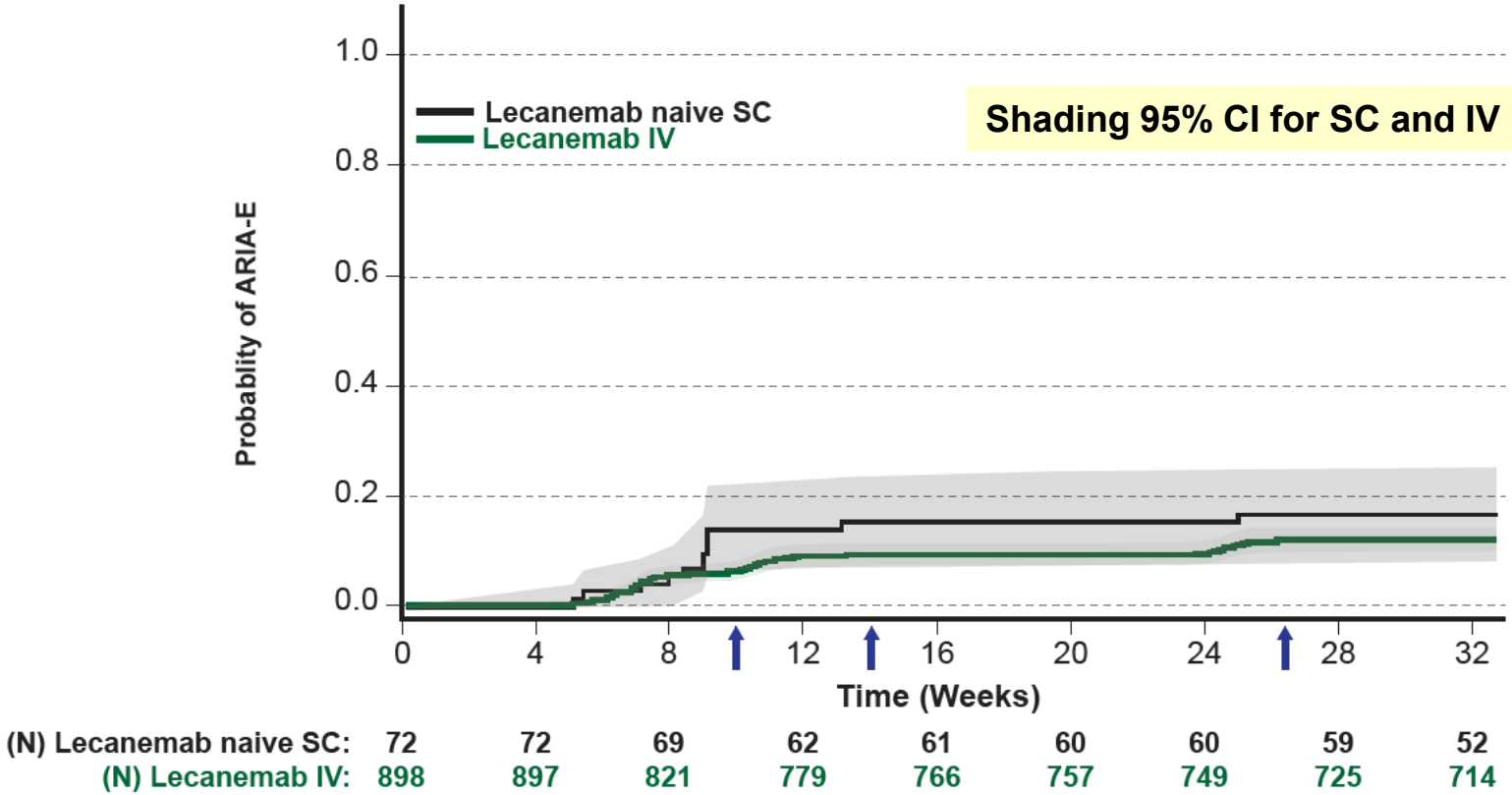
- Systemic injection/infusion reactions are uncommon with SC administration
- There was a low rate of local injection site reactions
  - Most mild and moderate in severity consisting of redness, irritation, or swelling
  - No skin rash or other hypersensitivity reactions reported

SC, subcutaneous.

Timing, Frequency and Severity (Clinical and Radiographic) of ARIA Similar SC to IV

- Confidence intervals for ARIA-E in the SC group are broad due to the sample size and low event rate

Rate of ARIA-E on Lecanemab Naïve SC vs IV



Note: PET scan is prior to injection/infusion indicated by the blue arrows

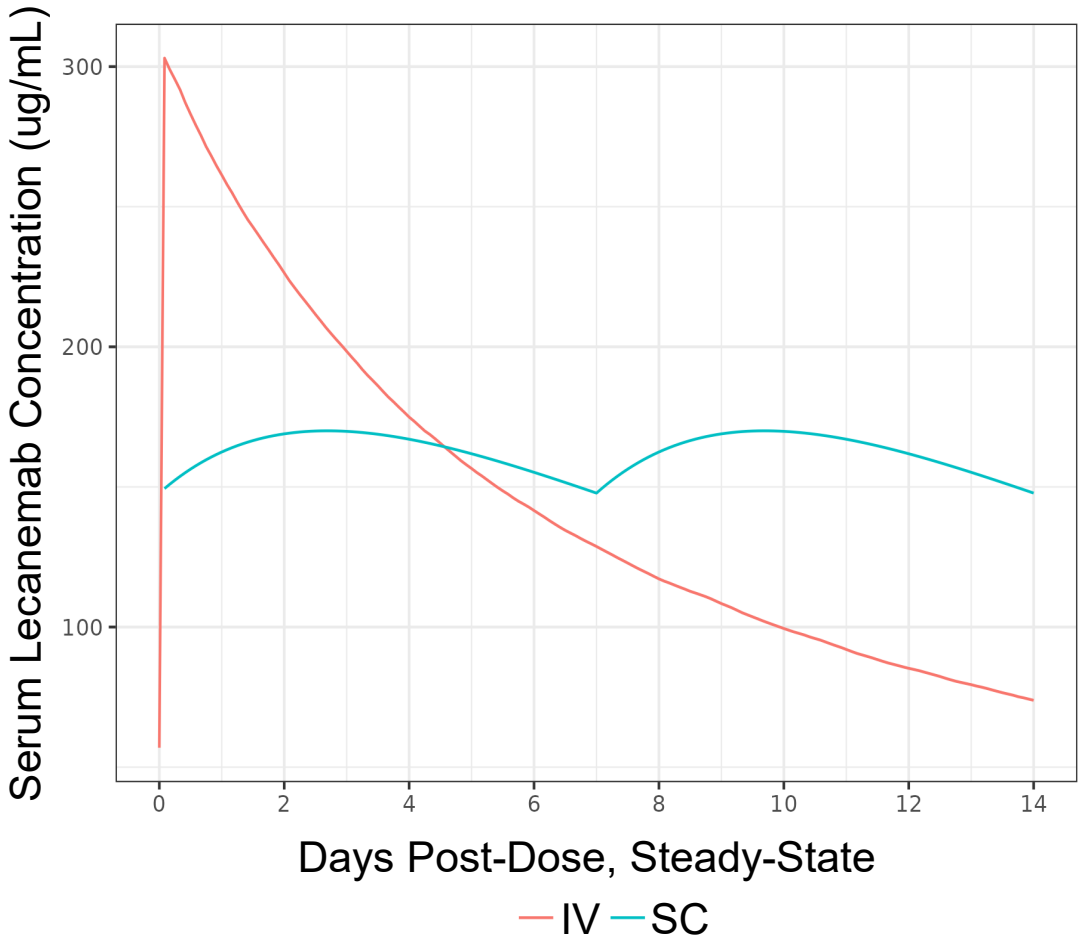
	Lecanemab Naïve SC N (%)	Lecanemab IV N (%)
ARIA-E	12 (16.7%)	113 (12.6%)
ARIA-H	16 (22.2%)	155 (17.3%)
Isolated ARIA-H	6 (8.3%)	80 (8.9%)

- There was no intracerebral hemorrhage on SC

ARIA-E, amyloid related imaging abnormalities - edema; IV, intravenous; PET, positron emission tomography; SC, subcutaneous.

Effect of PK Profile on Incidence of ARIA-E

- AUC strongly predicted amyloid lowering
- Exposure-safety analyses based on IV in our Phase 2 and 3 trials (red line) found that lecanemab exposure (as $C_{max,ss}$, AUC_{ss}, $C_{min,ss}$) was correlated with ARIA-E
- **Of these predictors, $C_{max,ss}$ was strongest predictor of ARIA-E incidence following IV administration**
- SC lecanemab results in minimal fluctuations between $C_{max,ss}$ and $C_{min,ss,}$ which is further influenced by more frequent dosing (weekly) compared to IV (biweekly)
- **Thus, following SC administration, AUC_{ss}, a more representative exposure parameter of a flat PK profile, may be a better predictor of incidence of ARIA-E**



Based on PK modeling

ARIA-E, amyloid related imaging abnormalities - edema; AUC_{ss}, area under the curve at steady state; Cmax,ss, maximum concentration at steady state; Cmin,ss, minimum concentration at steady state; IV, intravenous; PET, positron emission tomography; SC, subcutaneous.

Overall Adverse Event Summary

Safety in Open-Label Extension (OLE) Consistent with Core Study

	Placebo (n=897) n (%)	Lecanemab (n=898) n (%)	Lecanemab (Core+OLE) (n=1612) n (%)
Deaths*	8 (0.9)	7 (0.8)	16 (1.0)
Serious adverse event (SAE)	101 (11.3)	126 (14.0)	241 (15.0)
SAE with ARIA-E	0 (0)	7 (0.8)	18 (1.1)
SAE with ARIA-H	1 (0.1)	2 (0.2)	10 (0.6)
SAE with infusion-related reactions	0 (0)	11 (1.2)	20 (1.2)
SAE without ARIA or infusion-related reactions	101 (11.3)	111 (12.4)	205 (12.7)
Treatment-emergent AE (TEAE)**			
ARIA-E	15 (1.7)	113 (12.6)	219 (13.6)
ARIA-H	80 (8.9)	152 (16.9)	298 (18.5)
ICH	1 (0.1)	5 (0.6)	8 (0.5)
Infusion-related reactions	66 (7.4)	237 (26.4)	398 (24.7)

*Cause of deaths in placebo group: death, acute respiratory failure, myocardial infarction, metastases to bone, hemorrhage intracranial, COVID-19, pancreatic cancer, cardio-respiratory arrest.
Cause of death in lecanemab group: death, cerebrovascular accident, myocardial infarction, respiratory failure, metastases to meninges, COVID-19, diabetic ketoacidosis. No participants died with or from ARIA in Core study.
Cause of death in lecanemab in OLE: myocardial infarction, COVID-19, COVID-19 pneumonia, cerebral hemorrhage (2 subjects), cerebrovascular accident & seizure (1 subject), cerebrovascular accident, road traffic accident, cardiac failure acute
**AE rates are similar between placebo and lecanemab when ARIA and infusion-related reactions are excluded.
AE, adverse event; ARIA-E, amyloid related imaging abnormalities - edema; ARIA-H, ARIA with hemosiderin deposits; ICH, intracerebral hemorrhage.

Data cutoff: 01 Dec 2022

Summary

- Lecanemab SC may provide substantial benefit for greater patient access, improved compliance and convenience with overall lower costs to healthcare system
- PD comparability by amyloid plaque reduction has been confirmed at 6 months
  - SC administration resulted in 14% greater amyloid removal
- Rates of systemic adverse reactions are significantly lower with SC versus IV
  - Local injection or infusion site reactions were similar
- Timing, frequency and severity of ARIA-E, both clinical and radiographic, are similar for SC and IV
- Safety and immunogenicity in OLE were otherwise consistent with Clarity AD

ARIA-E, amyloid-related imaging abnormality-edema; IV, intravenous; OLE, open-label extension; PD, pharmacodynamic; PK, pharmacokinetic; SC, subcutaneous.

Overall Summary

- Targeting protofibrils and clearing plaque leads to clinical efficacy, slowing of tau progression and improvement in pathophysiological biomarkers
- Maintenance of treatment effect at 24 months and CDR-SB improvement in the low tau PET subgroup support early initiation of treatment with lecanemab
- The SC formulation has comparable PK and amyloid clearance to IV, providing a convenient dosing option
- These will be further studied in the ongoing Clarity AD OLE and AHEAD3-45 Study in preclinical AD

AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating Scale-Sum of Boxes; IV, intravenous; OLE, open-label extension; PET, positron emission tomography; PK, pharmacokinetics; SC, subcutaneous.

Thank you

Clarity AD

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Acknowledgements

Participants & Their Support

We acknowledge with thanks the individuals who enrolled in lecanemab Clarity AD Trial as well as their family, caregivers, and friends who supported them.

We also acknowledge the DSMB members, Site Investigators, Study Coordinators, Raters, contract research organization (CRO), and other personnel whose dedication and hard work in collecting data and providing care were essential to the completion of this trial.

Panel Discussion and Q&A

Clarity AD