Does the Current Evidence Base Support Lecanemab Continued Dosing for Early Alzheimer's Disease?

October 30, 2024

Clinical Trials on Alzheimer's Disease Conference (CTAD) 2024
October 29 – November 1, 2024 / Madrid, Spain

Opening Remarks

- The pathophysiology of Alzheimer's disease (AD) involves abnormalities of amyloid beta (Aβ) and tau processing
  - Just as in other chronic progressive diseases, AD requires a long-term therapeutic strategy
  - Specific pathophysiological processes may need to be targeted for optimal long-term treatment at different stages of AD
- Lecanemab dual mechanism of action removes protofibrils that are thought to form and drive AD pathophysiology both before and after amyloid plaque is cleared
- In this symposium, we present the latest evidence supporting the need for lecanemab continued dosing in early symptomatic Alzheimer's disease
  - Current evidence for mechanism-based rationale
  - Latest clinical pharmacology data and modeling
  - Update on clinical and biomarker results from the Clarity AD study, including the latest efficacy and safety data out to 30-36 months

Does the Current Evidence Base Support Lecanemab Continued Dosing for Early Alzheimer's Disease?

Topic	Presenter
Mechanistic Rationale for Continued Lecanemab Dosing	***Akihiko Koyama***
Pharmacologic Support for a Maintenance Dosing Regimen with Lecanemab: An Update on the Latest Clinical Pharmacology Data and Modeling	***Larisa Reyderman***
Evidence for a Continued Benefit for Long-Term Lecanemab Treatment: A Benefit/Risk Update from Long-Term Efficacy, Safety and Biomarker Data	***Christopher van Dyck***
Panel Discussion / Q&A	***All***

Mechanistic Rationale for Continued Lecanemab Dosing

Akihiko Koyama

Eisai Inc.

Presented at the 2024 Clinical Trials on Alzheimer's Disease Annual Meeting (CTAD 2024), October 29 – November 1, 2024, Madrid, Spain.

Disclosures and Acknowledgments

Disclosures:

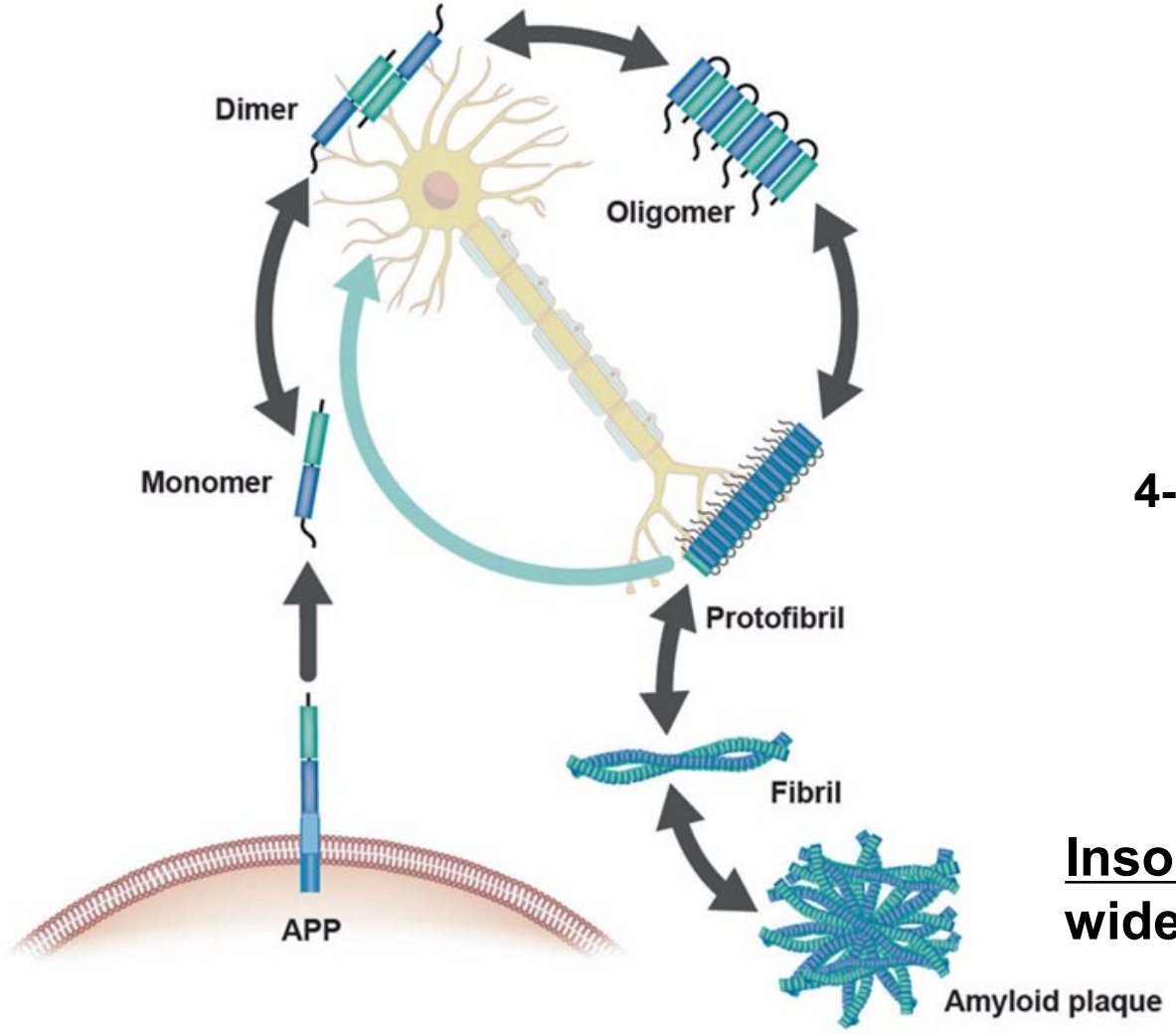
- Akihiko Koyama is a full-time employee of Eisai

Authors:

Michael Irizarry,[1] Akihiko Koyama,[1] Shobha Dhadda,[1] Lynn Kramer,[1] Dennis Selkoe,[2]

1. Eisai Inc. Nutley, NJ USA
2. Brigham and Women's Hospital, Harvard Medical School, Boston, MA USA

Generation of Amyloid β-Protein (Aβ) Occurs Throughout Life but can Lead to Aβ Aggregation with Age



Oligomers
2 to ~28 monomers

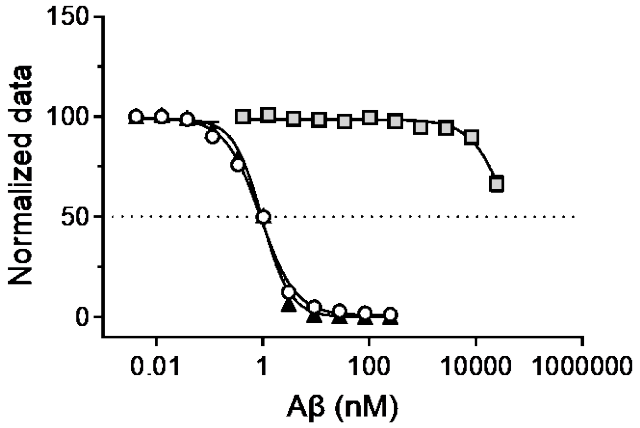
“Protofibrils”
4-8 nm diffusible aggregates
~~28 – >500 monomers

Amyloid plaques
Insoluble amyloid fibrils 8 nm wide and not readily diffusible

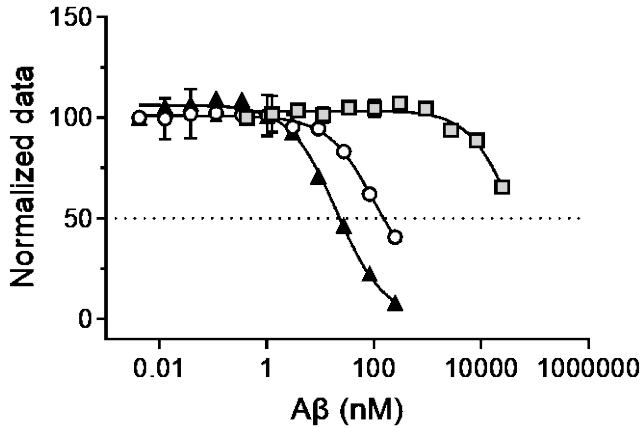
Hampel et al, *Mol Psychiatry* 2021.

Lecanemab Preferential Binding to Soluble Aβ Protofibrils

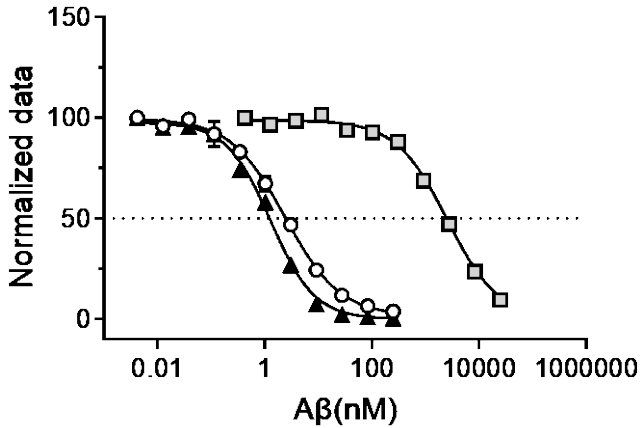
Lecanemab



Aducanumab



Gantenerumab



Monomers Protofibrils (small) Protofibrils (large)

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

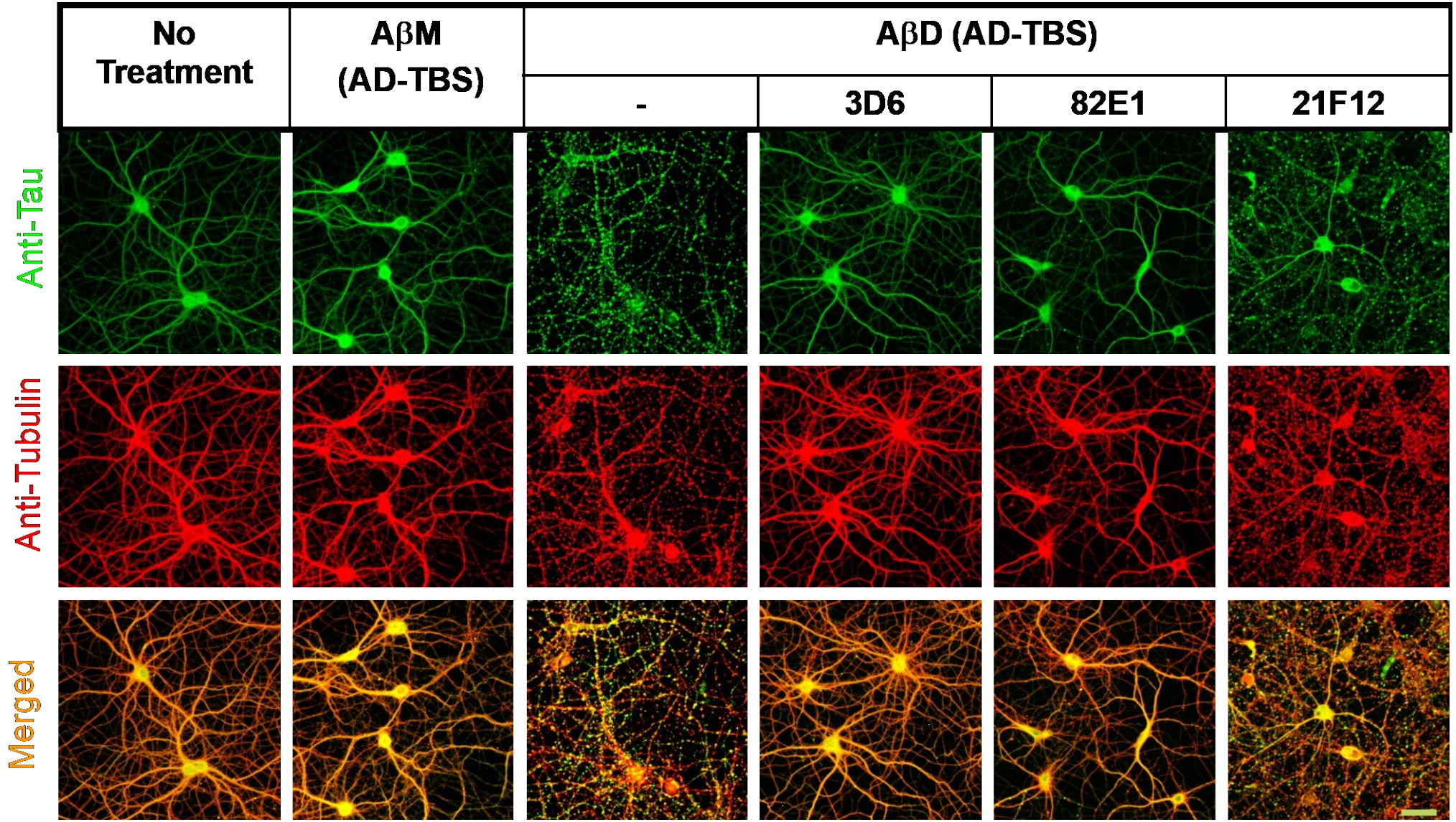
- **Lecanemab binds small protofibrils 100x and large protofibrils 25x stronger than aducanumab**
- **Gantenerumab is less selective and binds monomers with somewhat higher affinity compared to lecanemab and aducanumab**

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

Aqueously soluble oligomers/protofibrils are a minority of Aβ in AD brain but account for the major portion of the synaptic toxicity and are bound by lecanemab

Aβ, amyloid beta. AD, Alzheimer's disease.

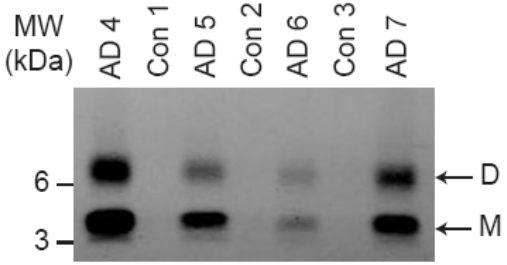
Aβ Dimers/Oligomers from AD Cortex Induce Neurite Dystrophy and Blocked by Anti-Aβ Antibodies

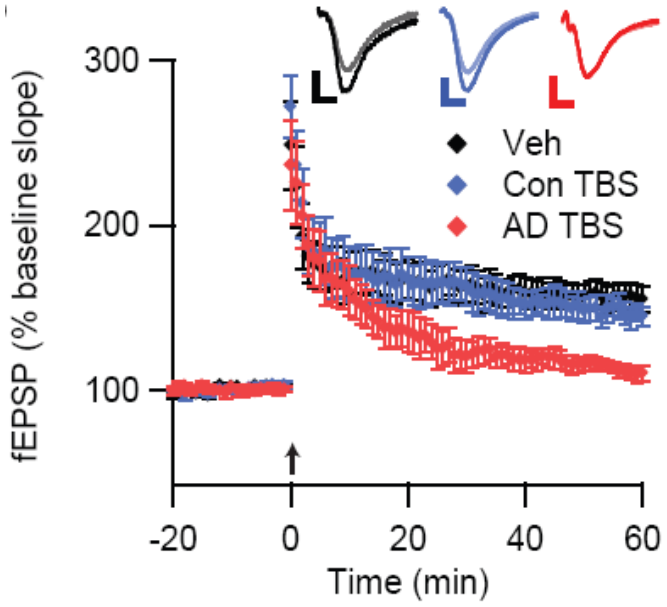


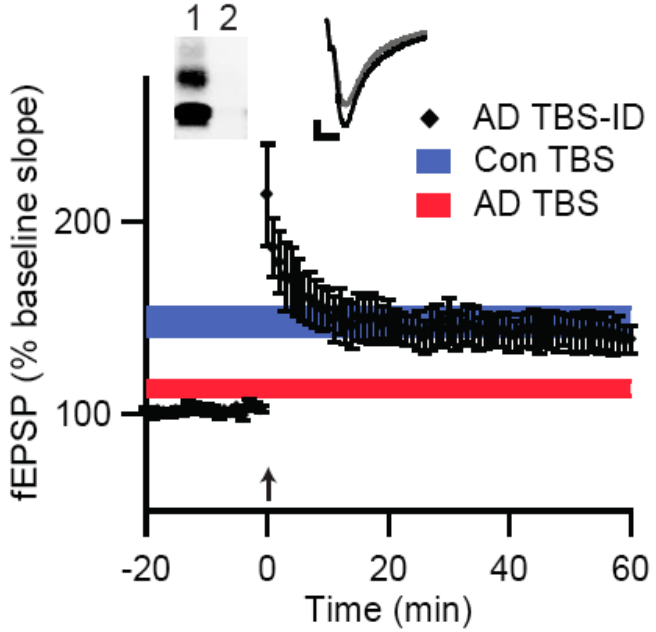
Aβ, amyloid beta.
AD, Alzheimer's disease.
Con, control. M, monomer.
TBS, tris-buffered saline.

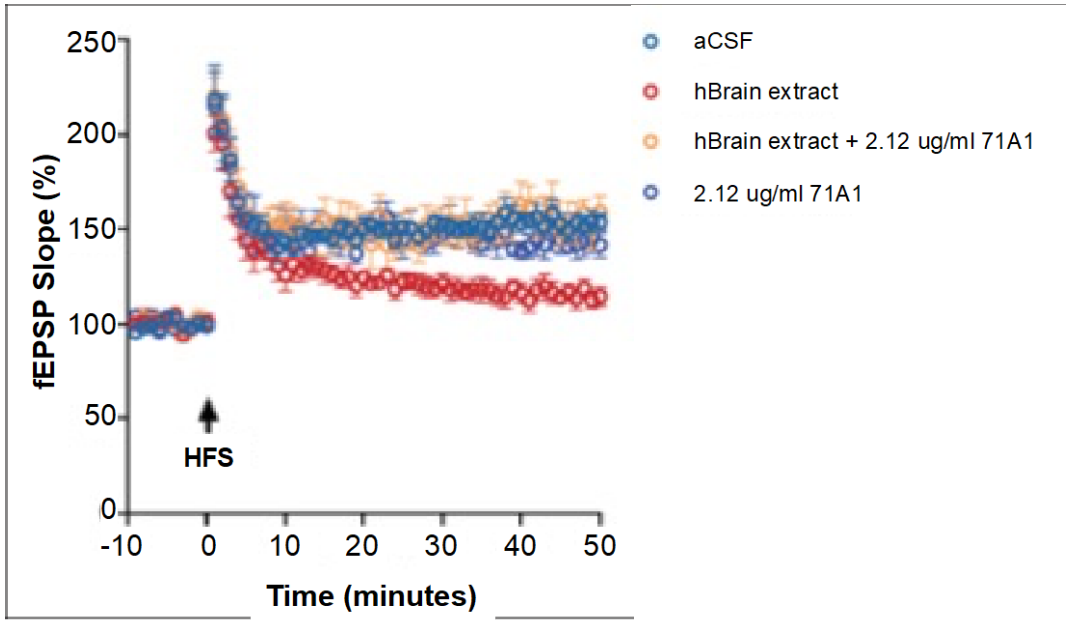
Jin et al, *PNAS* 2011

Diffusible Aβ Dimers/Oligomers Isolated from AD Brain Inhibit Long Term Potentiation (LTP) and Blocked by Anti-Aβ Antibodies







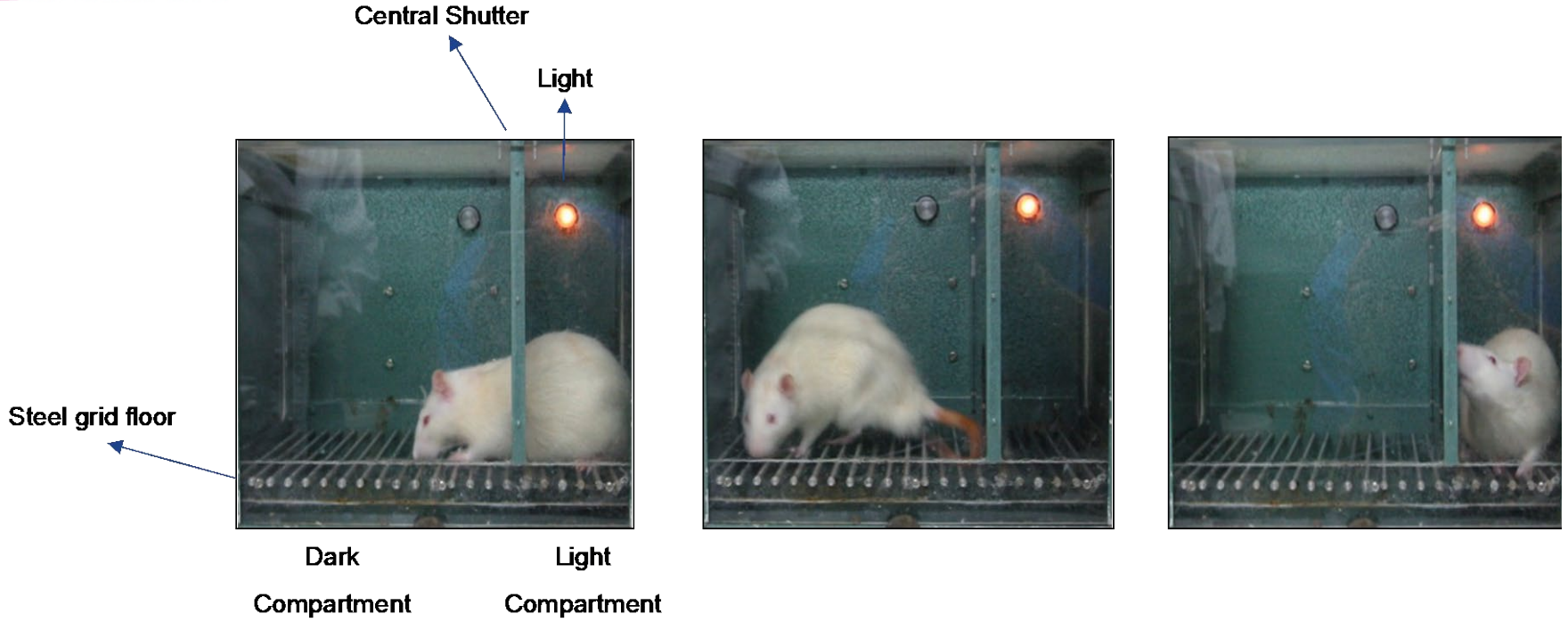


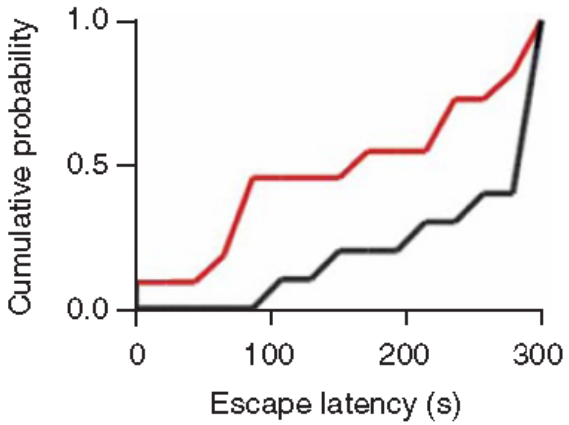
AD, Alzheimer's disease. Con, control. D, dimer. fEPSP, field excitatory postsynaptic potentials. LTP, long-term potentiation. M, monomer. Min, minutes. MW, molecular weight. TBS, tris-buggered saline. Veh, vehicle.

Shankar et al, *Nature Medicine* 2008, Liu et al, *Alzh Dem* 2021

Diffusible Aβ Oligomers from AD Cortex Impair Memory in Healthy Adult Rats

Human Aβ oligomers are infused into the cerebral ventricle of a normal rat



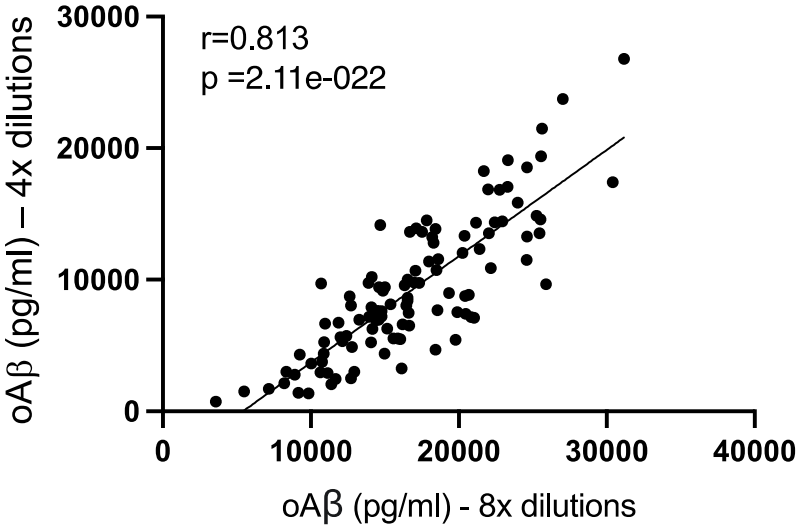


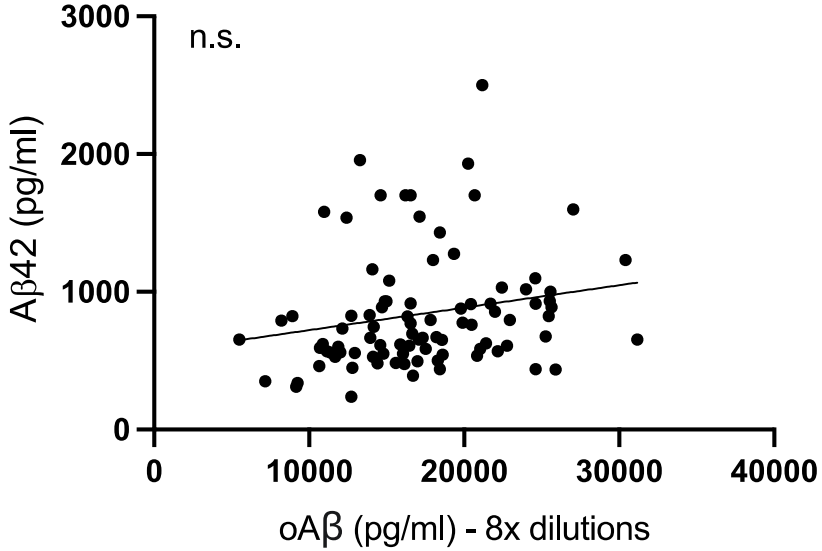
Rat forgets the earlier foot shock
And reenters the dark chamber quickly

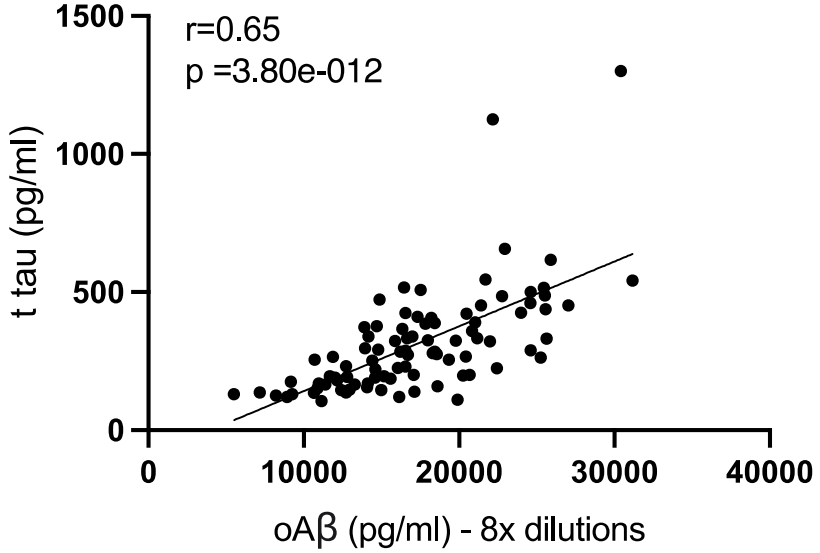
Aβ, amyloid beta.

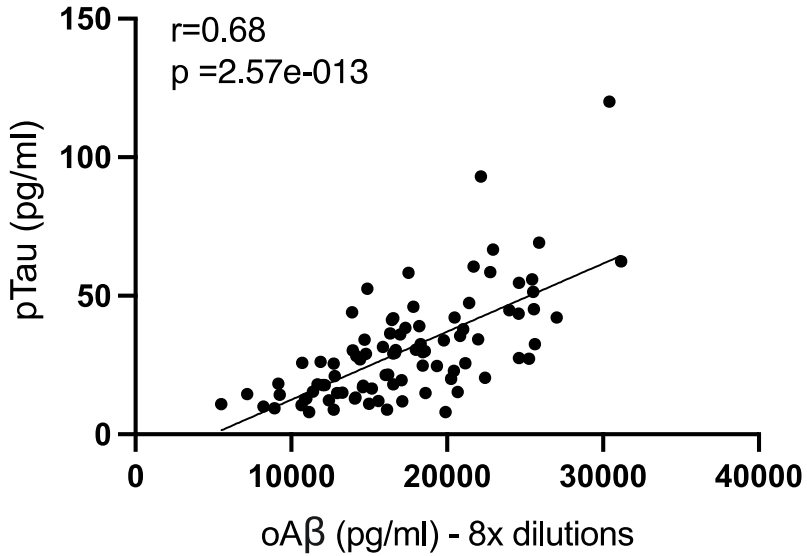
Shankar et al, *Nature Medicine* 2008

A New ELISA (71A1/3D6) Reveals CSF Levels of oAβ Correlate Directly with CSF Levels of Tau and pTau





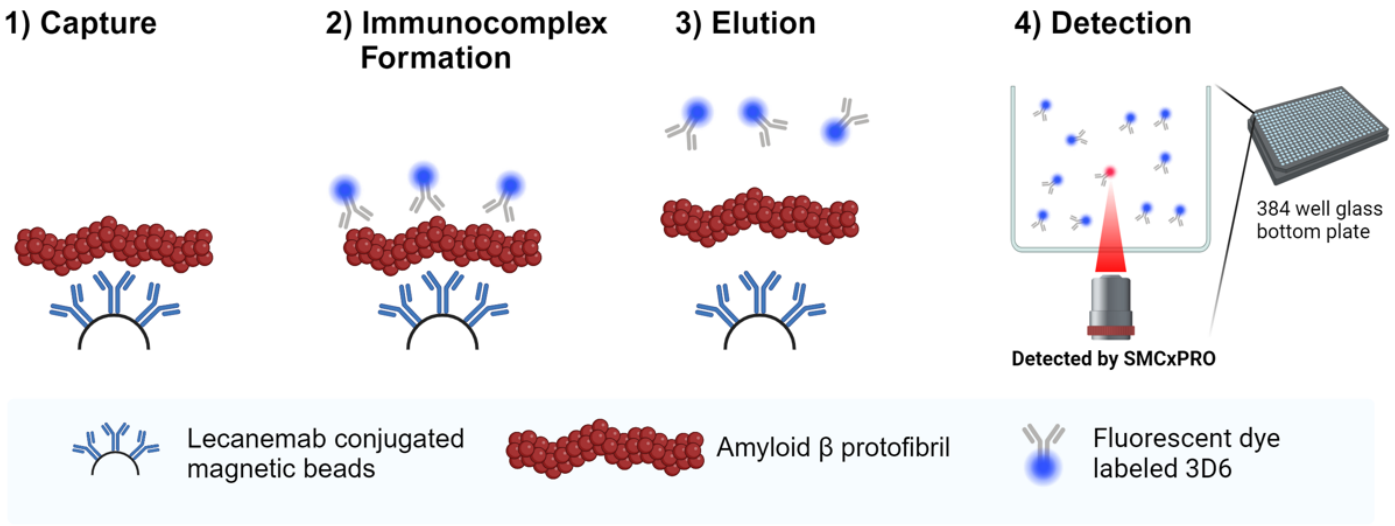


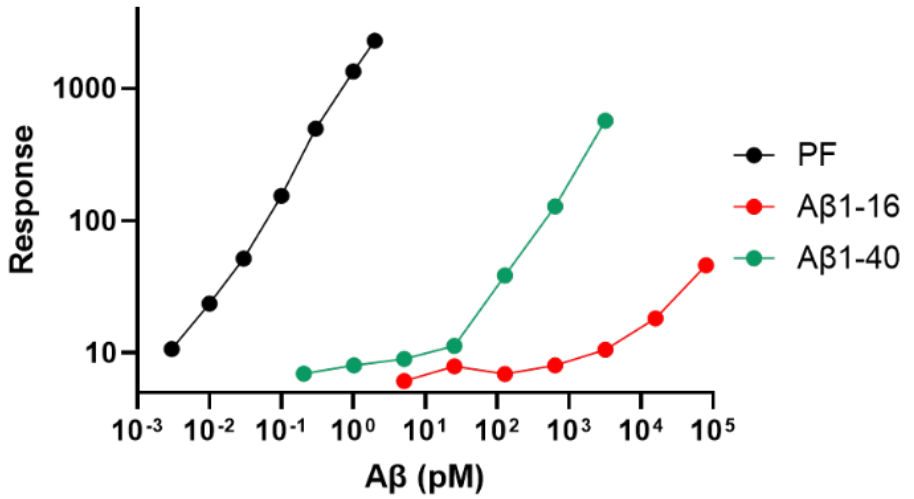


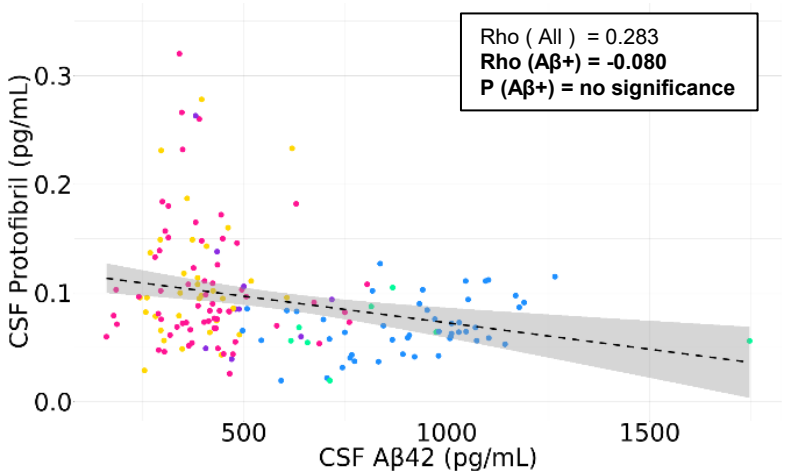
Aβ, amyloid beta.
CSF, cerebrospinal fluid.
ELISA, enzyme-linked immunosorbent assay.
oAβ, oligomers of Aβ.

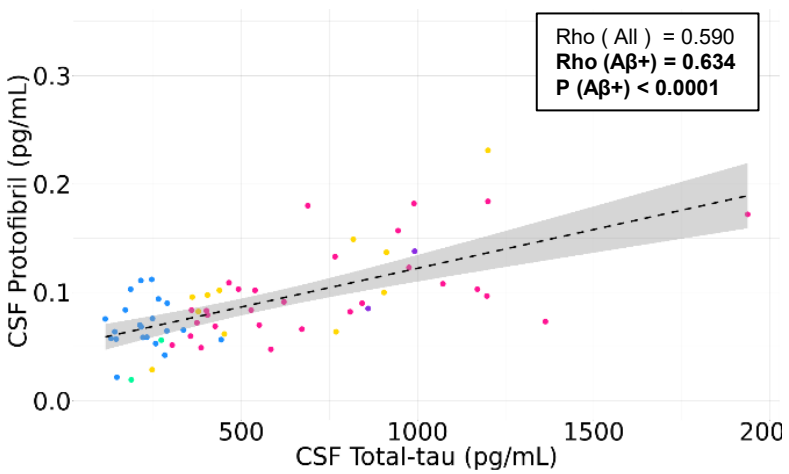
T. Yang, T. Xu, D Selkoe. unpublished data

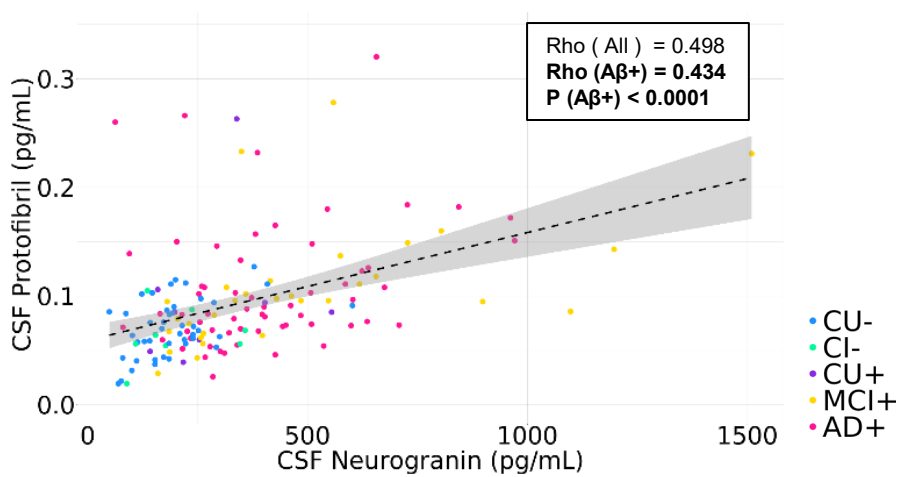
Lecanemab-bound Protofibril Assay Reveals CSF Protofibril Levels Correlate Directly with Neurodegeneration Biomarkers





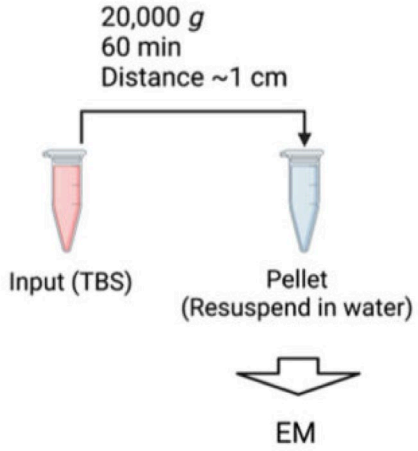


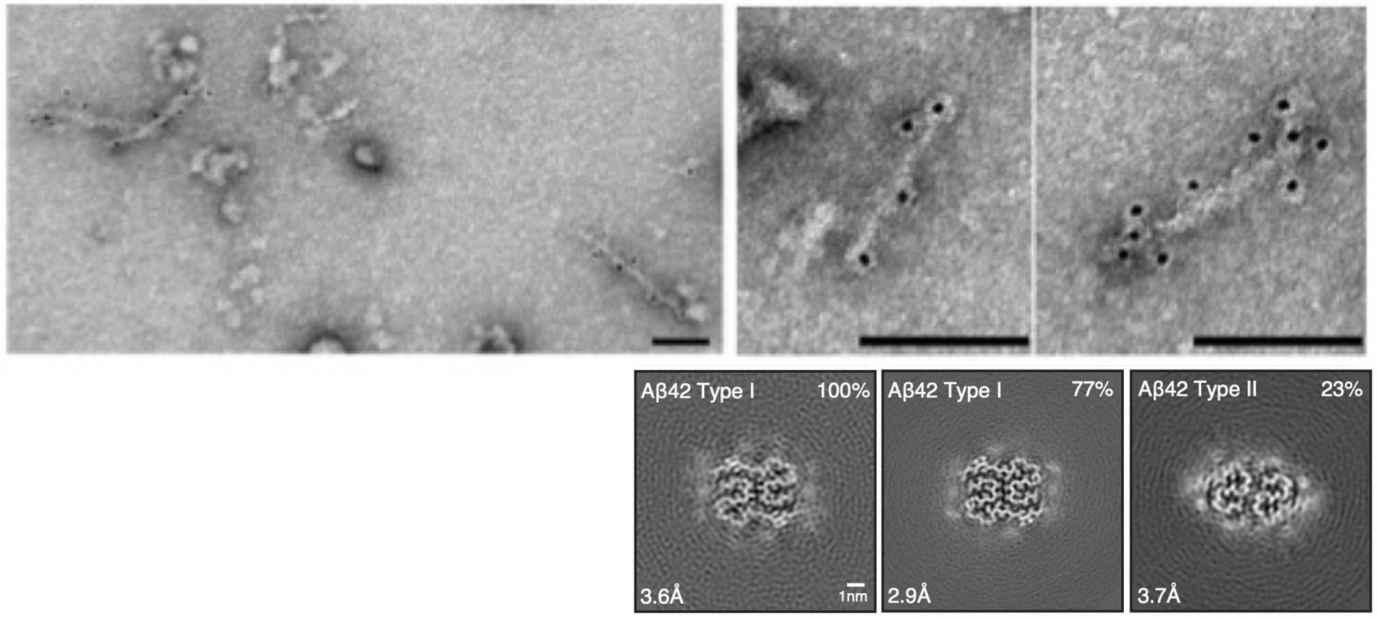




Kenjiro Ono, et al. AAIC 2024

Aqueous Soaking Extracts of AD Cortex Contain Diffusible Aβ Fibrils

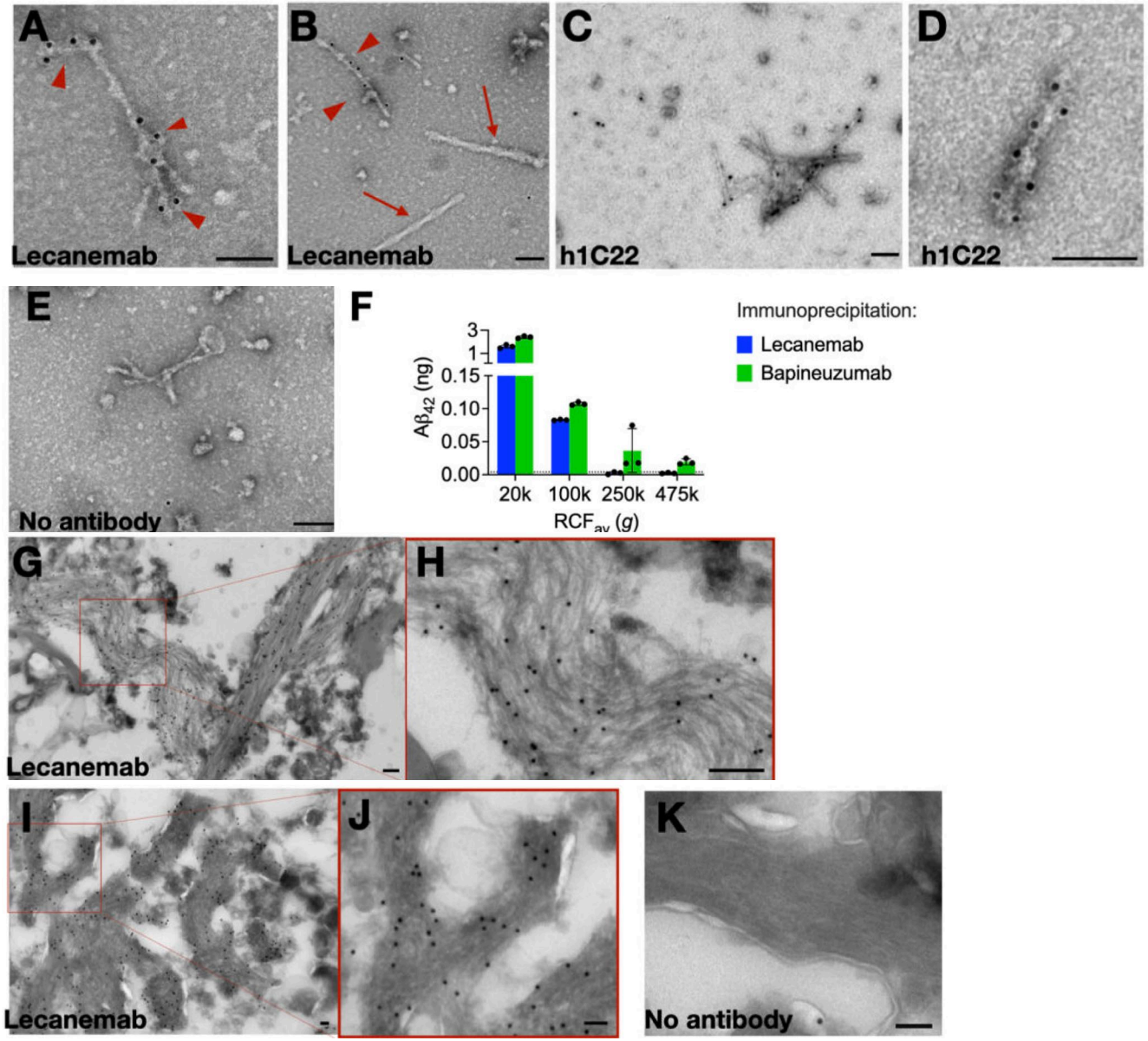




CryoEM of these diffusible fibrils reveals the same atomic structure as that of insoluble amyloid fibrils from plaque-rich cortex

Stern, A. et al, *Neuron* 2023
(Yang, Scheres, Goedert)

Lecanemab Binds Both Small Diffusible Fibrils in Aqueous Extracts and Amyloid Plaque Fibrils *in situ* of AD Cortex



Aβ, amyloid beta.
AD, Alzheimer's disease.
RCF_{av}, average relative centrifugal force.

Stern et al, *Neuron*, 2023

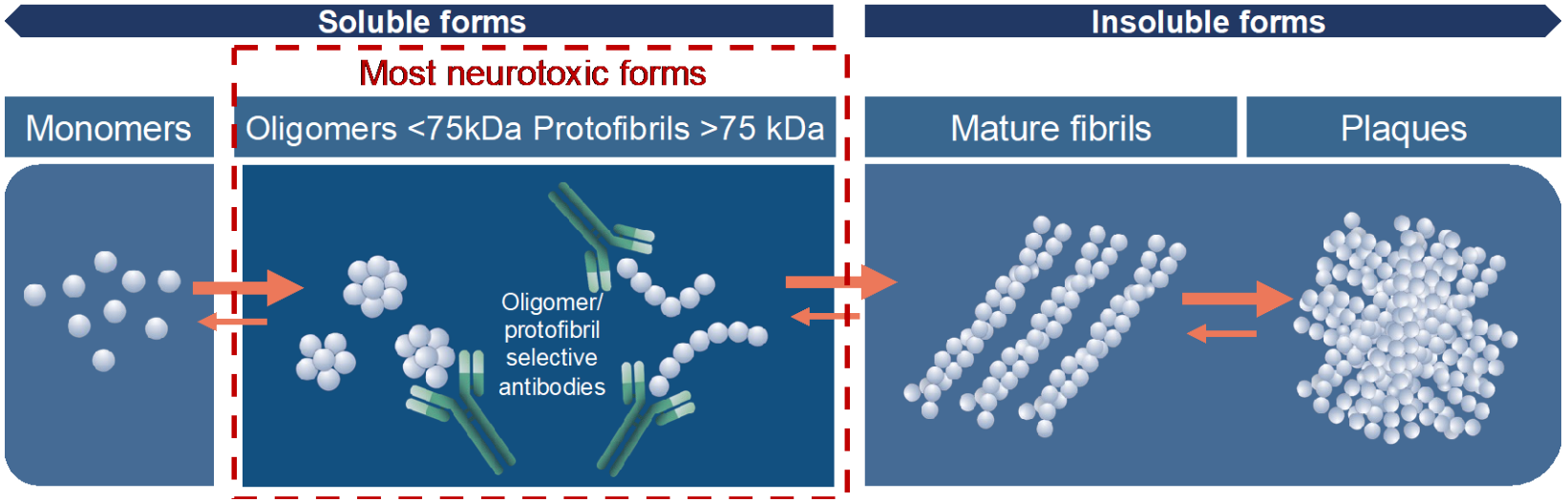
Lecanemab Unique Dual-Action Mechanism:

Targets Highly Toxic Protofibrils and Rapidly Clears Amyloid Plaques

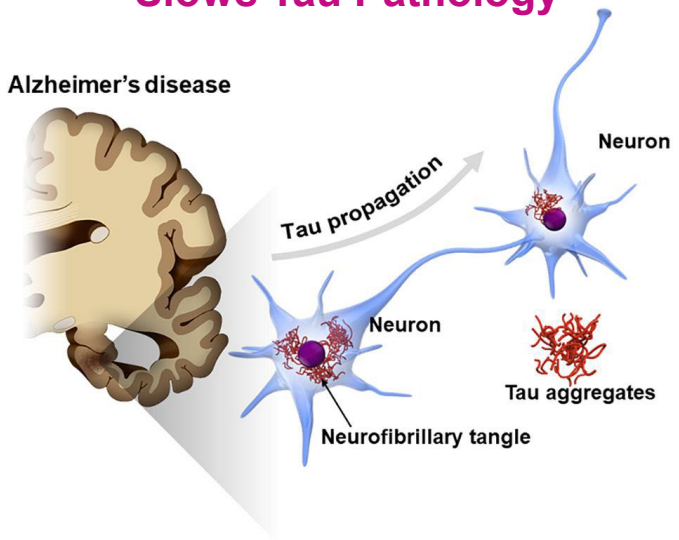
Lecanemab Dual Mechanism

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
- Lowering Aβ is a crucial step, but AD pathology may still include tau propagation from neuron to neuron

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, 2024. 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

Multiple Lines of Evidence Support an Ongoing Pathogenic Role for Soluble Aβ Oligomers and Diffusible Fibrils ('Protofibrils') in Neuronal Dysfunction

- Soluble and diffusible aggregated Aβ species, often called protofibrils, are abundant in AD brain
- These species are toxic and cause:
  - Synaptic dysfunction
  - Microglial activation
  - Tau phosphorylation and neuritic dystrophy
  - Impaired memory and learning (LTP and *in vivo* memory)
- Antibodies against these species from typical AD patients prevent neuronal dysfunction
- Lecanemab preferentially binds to soluble aggregated and diffusible species, that continue to be present and produced after clearance of plaques

The extensive evidence for a dual lecanemab mechanism supports the rationale for continued dosing as plaque reduction is achieved

Aβ, amyloid-beta; AD, Alzheimer's disease. LTP, long-term potentiation. PET, positron emission topography.

Pharmacologic Support for a Maintenance Dosing Regimen with Lecanemab: An Update on the Latest Clinical Pharmacology Data and Modeling

Larisa Reyderman

Eisai Inc. Nutley, NJ USA

Presented at the 2024 Clinical Trials on Alzheimer's Disease Annual Meeting (CTAD 2024), October 29 – November 1, 2024, Madrid, Spain.

Disclosures and Acknowledgements

Disclosures:

- LR is an employee of Eisai Inc.

Authors:

Larisa Reyderman, Brian Willis, Natasha Penner, Arnaud Charil, Shobha Dhadda, Steven Hersch, Michael Irizarry, Lynn Kramer

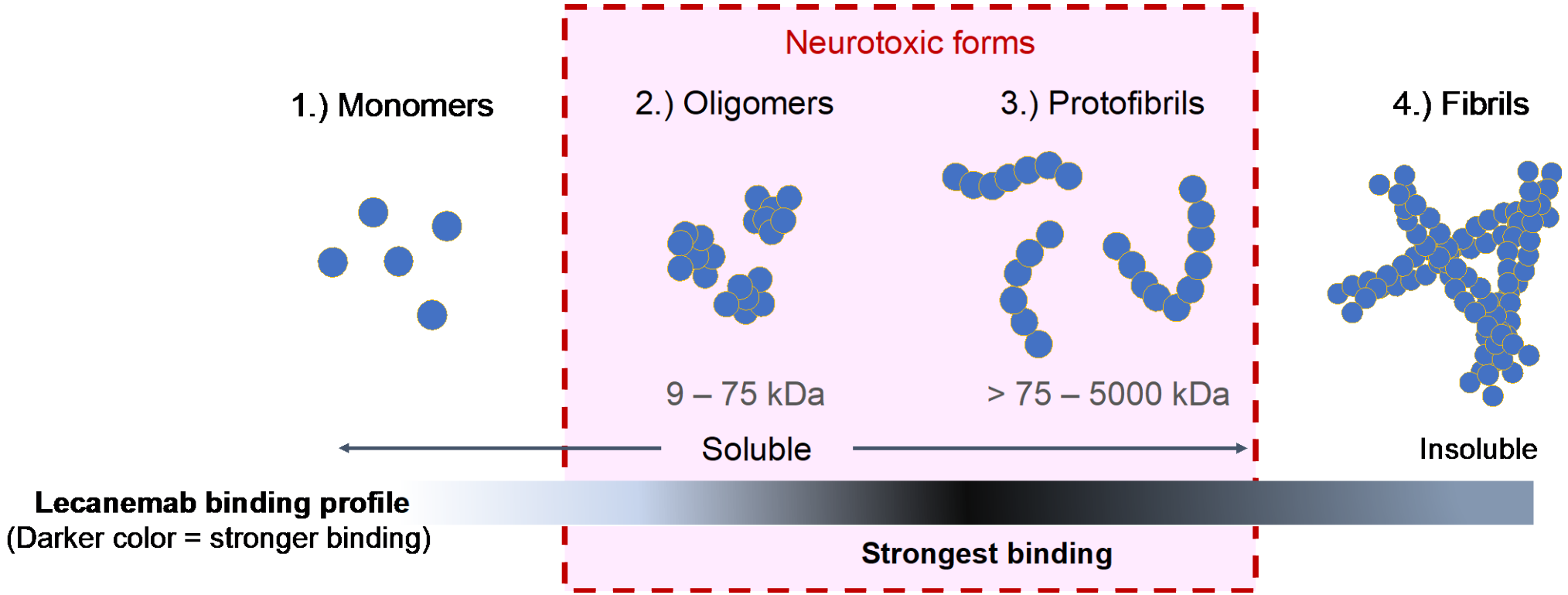
Eisai Inc. Nutley, NJ USA

Overview

- Alzheimer's disease (AD), like other chronic progressive diseases, requires a long-term therapeutic strategy
- Lecanemab dual mechanism of action removes protofibrils that continue to form and drive AD pathophysiology even after amyloid is cleared
- Discontinuation of treatment is associated with reaccumulation of biomarkers and reversion to placebo rate of clinical decline
- Modeling and simulation analyses allowed us to define less frequent dosing regimen to maintain biomarkers and further clinical benefit

Alzheimer's is a Chronic Disease Whose Pathophysiology Continues Even After Amyloid Plaque Removal

- Lecanemab has unique selectivity towards toxic soluble species of Aβ

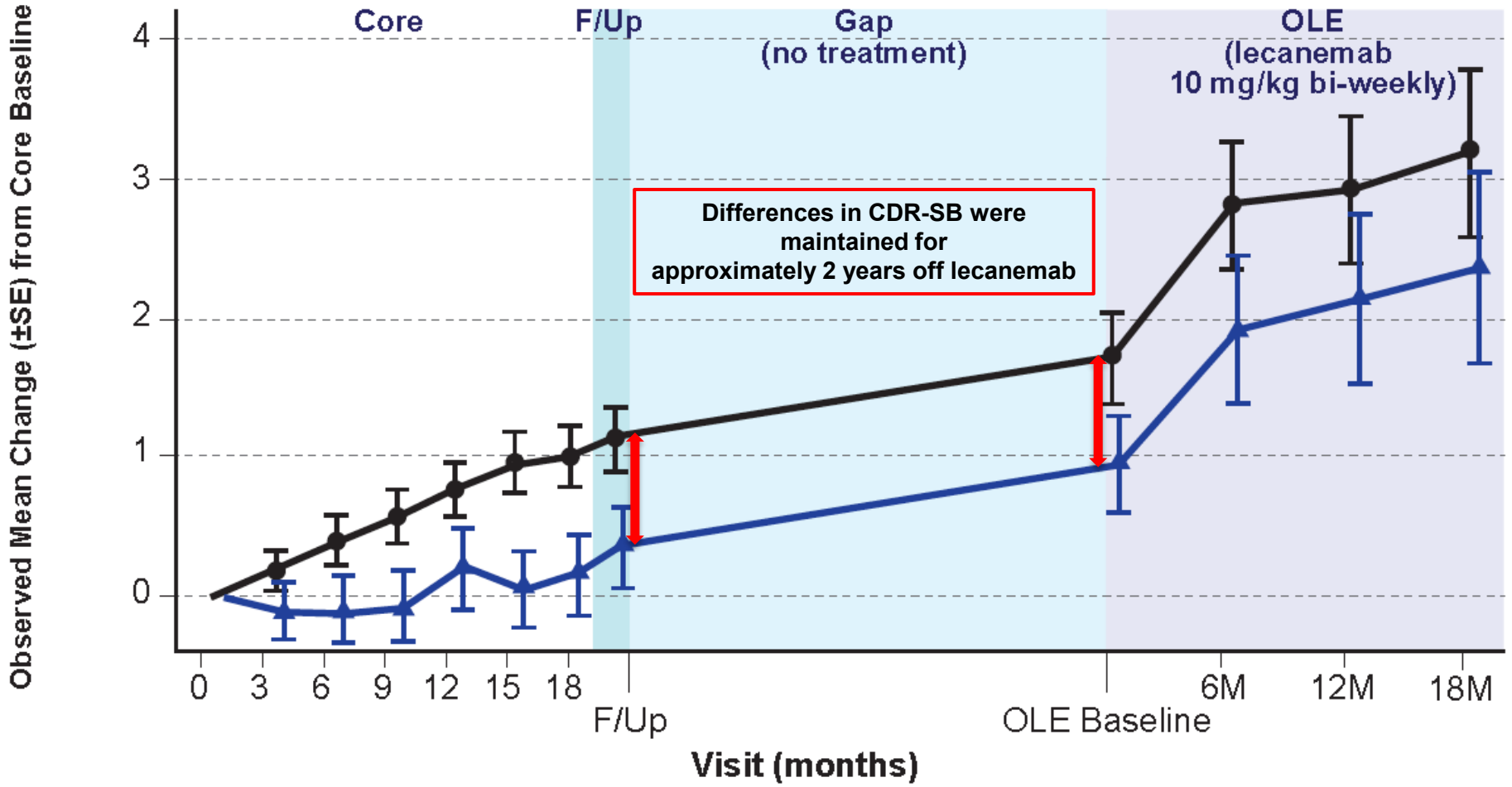


Protofibrils and oligomers continue to be produced even after plaques are cleared, providing mechanistic justification for ongoing treatment with lecanemab to maintain clinical and biomarker efficacy

Aβ, amyloid beta.

Clinical Effect is Maintained During Interruption of Lecanemab Treatment but Reverts to Placebo Rate of Decline (Study 201)

CDR-SB



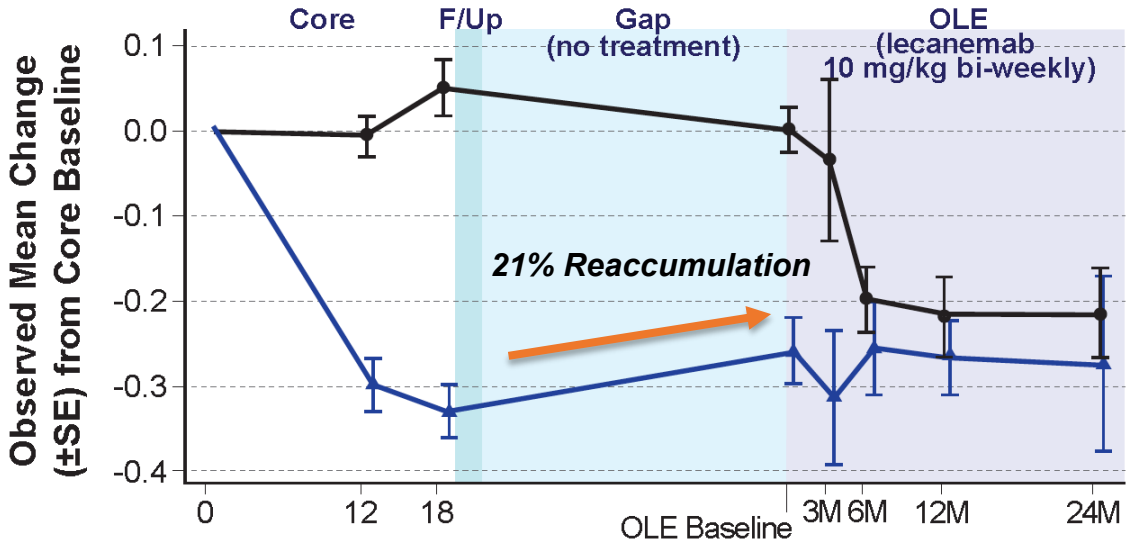
Core Treatment:												
Placebo:	40	40	39	39	39	35	35	35	40	37	33	29
10 bi-Weekly:	31	31	30	30	29	29	29	29	31	30	27	24

- **Initiating lecanemab treatment in OLE reduced clinical decline in subjects who received placebo and in subjects who were treated with lecanemab during Study 201 Core**

CDR-SB , Clinical Dementia Rating – Sum of Boxes. OLE, open-label extension. McDade et al. Alzheimers Res Ther. 2022;14:191.

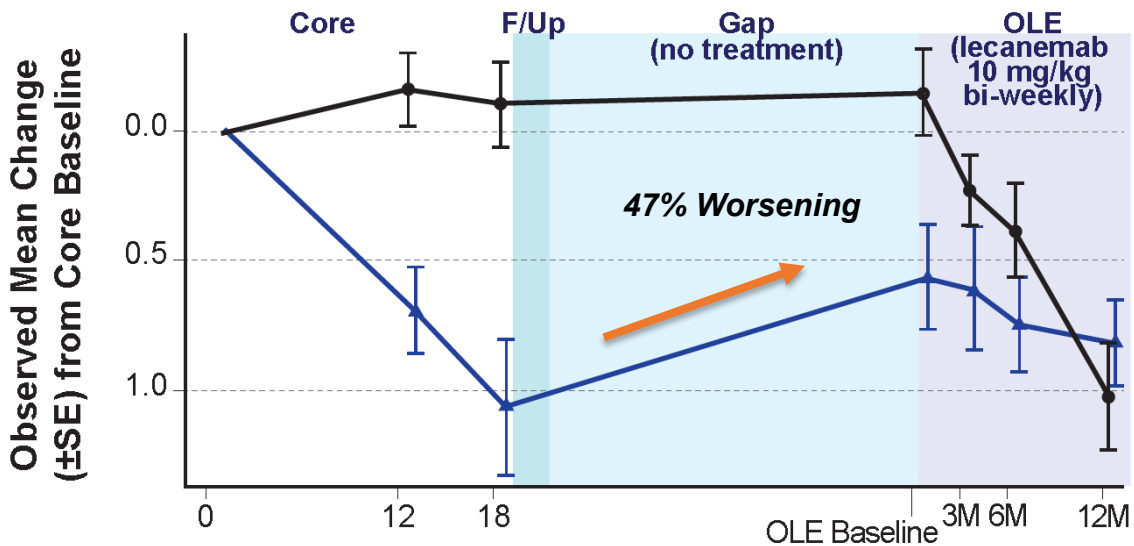
Interrupting Treatment is Associated with Variable Rates of Reaccumulation of AD Biomarkers: Amyloid PET & Aβ42/40 Ratio (Study 201)

Amyloid PET



Core Treatment:								
Placebo:	18	14	13	16	3	1	9	6
10 bi-Weekly:	17	13	12	12	9	1	12	3

Aβ42/40 Ratio



Core Treatment:							
Placebo:	32	32	30	32	31	31	31
10 bi-Weekly:	25	23	24	25	23	24	25

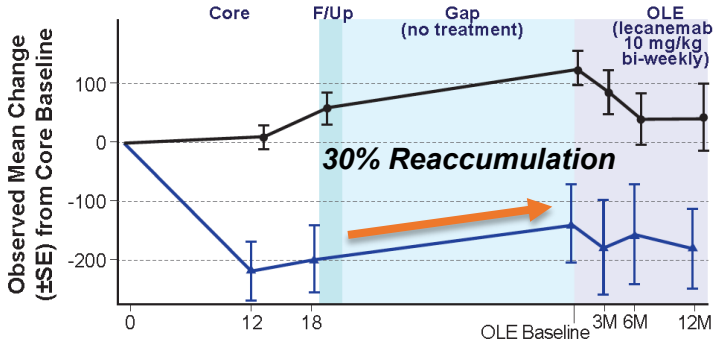
Long-term therapy continues to improve biomarkers further, and avoid the reaccumulation of biomarkers when anti-amyloid treatment is stopped

McDade et al. Alzheimers Res Ther. 2022;14:191.

Aβ42/40 = ratio of Aβ42 to Aβ40. OLE = open-label extension. PET= positron emission tomography.

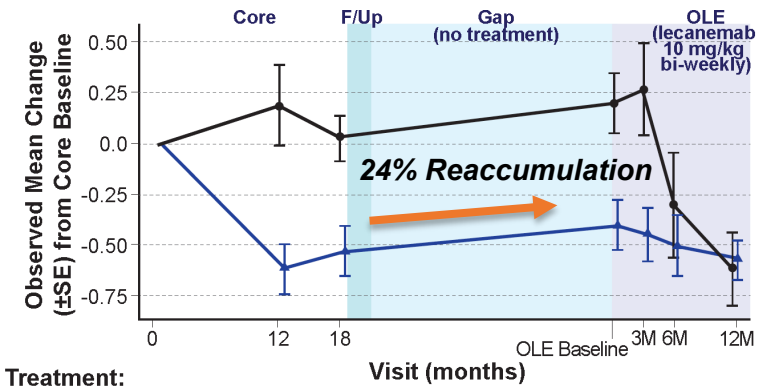
Interrupting Treatment is Associated with Reaccumulation of AD Pathology: GFAP, pTau181 & pTau217 (Study 201)

GFAP



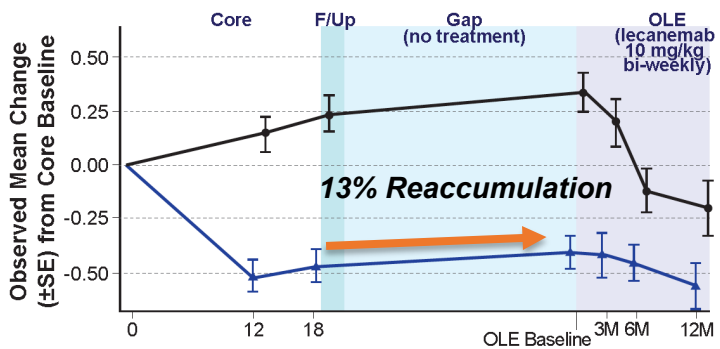
Core Treatment:							
Placebo:	22	22	21	22	22 20	15
10 bi-Weekly:	23	21	23	23	19 21	16

pTau181



Core Treatment:							
Placebo:	39	34	35	27	26 27	25
10 bi-Weekly:	30	26	30	20	18 20	20

pTau217



Core Treatment:							
Placebo:	22	22	20	22	22 20	13
10 bi-Weekly:	23	22	23	23	19 21	16

Long-term therapy continues to improve biomarkers further, and avoid the reaccumulation of biomarkers when anti-amyloid treatment is stopped

GFAP = glial fibrillary acidic protein. pTau181, phosphorylated tau 181. pTau217, phosphorylated tau 217.

McDade et al. Alzheimers Res Ther. 2022;14:191. Data on File. Eisai Inc.

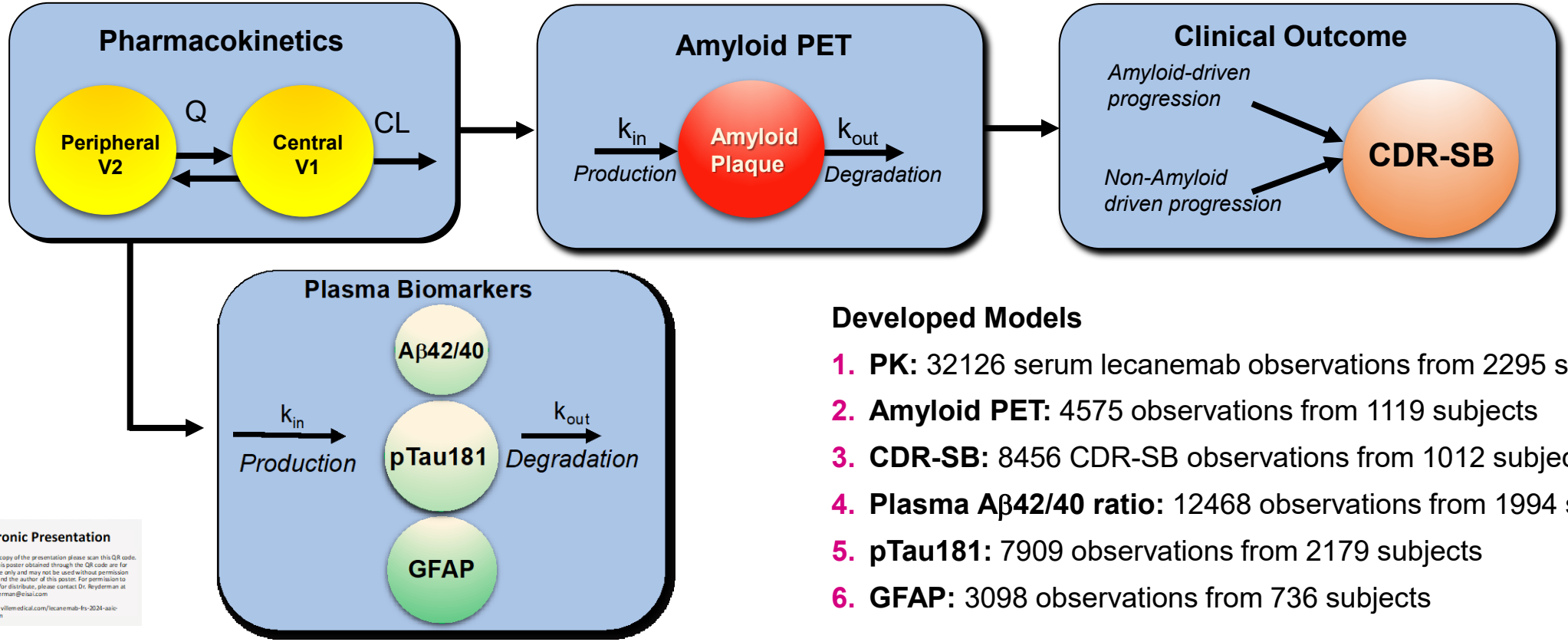
WHAT IS THE IDEAL MAINTENANCE DOSING REGIMEN WITH LECANEMAB AFTER AMYLOID CLEARANCE?

Defining Maintenance Dose for Longer-Term Clinical Benefit

- PK/PD models were used to select maintenance dosing regimen:
  - Can sustain clinical efficacy (CDR-SB)
  - Can sustain improvement in plasma biomarkers of amyloid and tau pathophysiology and neuroinflammation
- Simulation analyses were conducted to define optimal time to transition from bi-weekly to maintenance dosing
  - Initiating maintenance dosing at 18 or 24 months

CDR-SB = Clinical Dementia Rating – Sum of Boxes. PD, pharmacodynamic. PK, pharmacokinetics.

Multiple Semi-Mechanistic PK/PD Models Developed Correlating Lecanemab Exposure With Amyloid PET, Plasma Biomarkers and Clinical Outcome



Electronic Presentation

To obtain a copy of the presentation please scan this QR code. Copies of this poster obtained through the QR code are for personal use only and may not be used without permission from AAIC and the author of this poster. For permission to reprint and/or distribute, please contact Dr. Reyderman at larisa_reyderman@eisai.com

https://mayvillemedical.com/lecanemab-frs-2024-aaic-presentation

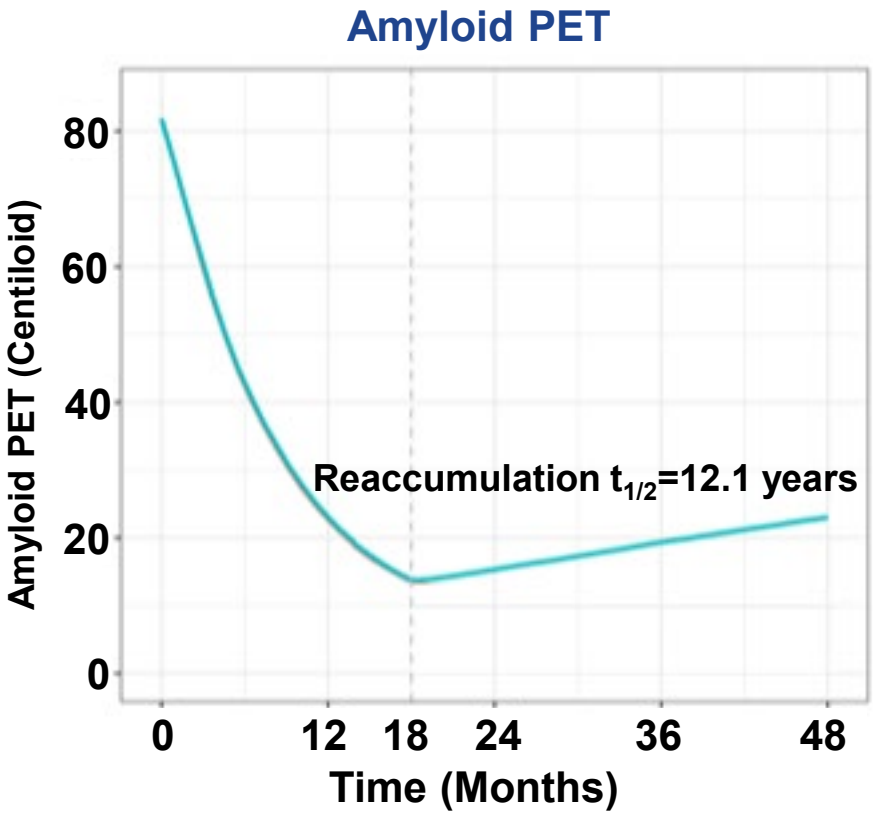
Developed Models

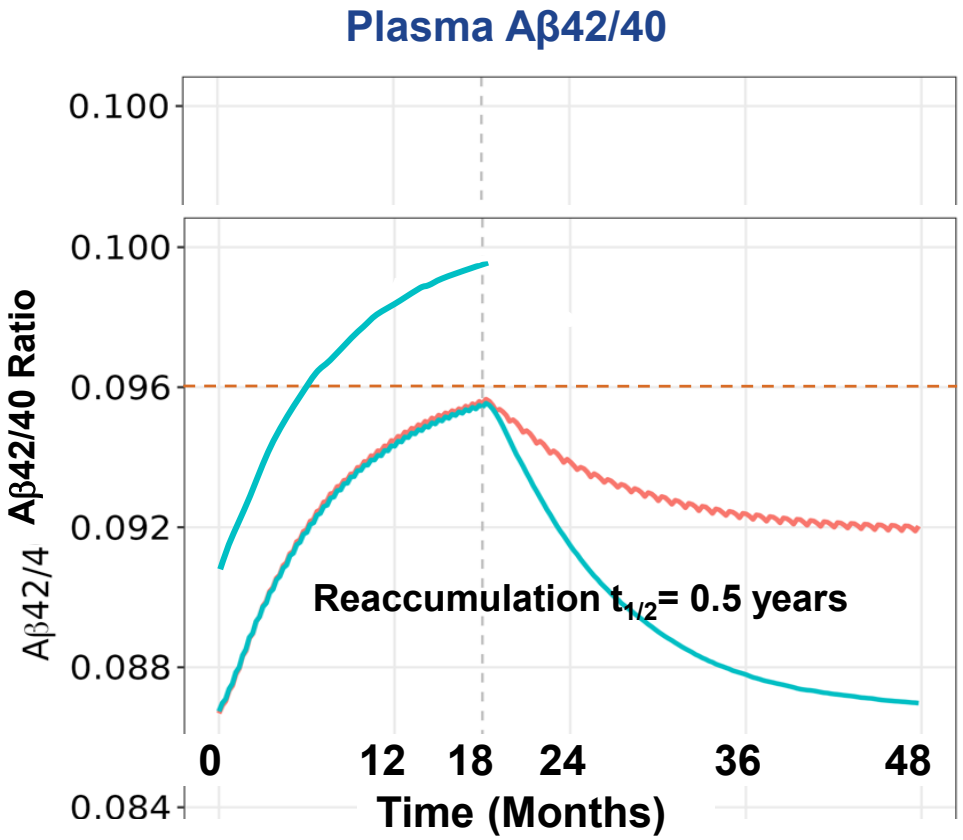
1. **PK:** 32126 serum lecanemab observations from 2295 subjects
2. **Amyloid PET:** 4575 observations from 1119 subjects
3. **CDR-SB:** 8456 CDR-SB observations from 1012 subjects
4. **Plasma Aβ42/40 ratio:** 12468 observations from 1994 subjects
5. **pTau181:** 7909 observations from 2179 subjects
6. **GFAP:** 3098 observations from 736 subjects

Models included data for up to 110 months in Study 201 Core and OLE and up to 54 months of continuous lecanemab biweekly dosing in Clarity AD Core and OLE

CL=clearance. k_{in}=zero-order rate for production of amyloid plaque. k_{out}=first-order rate of degradation of amyloid plaque. PET=positron emission tomography. PK=pharmacokinetics. PD=pharmacodynamics. Q=intercompartmental clearance. pTau181, phosphorylated tau 181. V1=central volume of distribution. V2=peripheral volume of distribution.

PK/PD Models Estimated That Fluid Biomarkers Reaccumulate at a Faster Rate Than Amyloid PET When Treatment is Discontinued After 18 Months



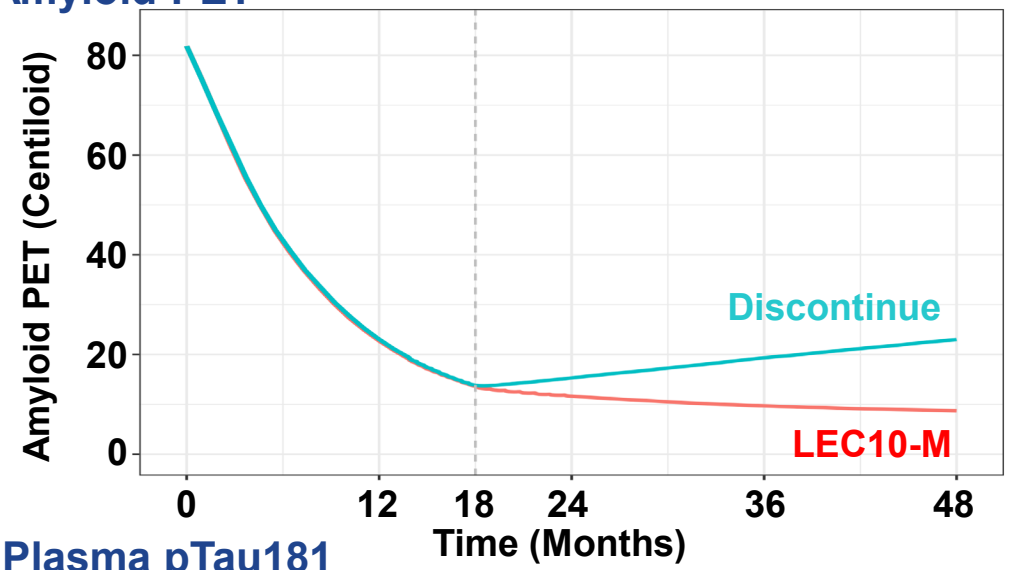


- Changes in fluid biomarkers on treatment discontinuation are more sensitive measures of disease progression
  - Half the treatment effect on Aβ42/40 ratio is lost within 6 months while half the treatment effect on amyloid PET is lost within 12.1 years
  - Similar loss of treatment effect observed for pTau181 ($t_{1/2}$=1.6 years) and GFAP ($t_{1/2}$=1.7 years)

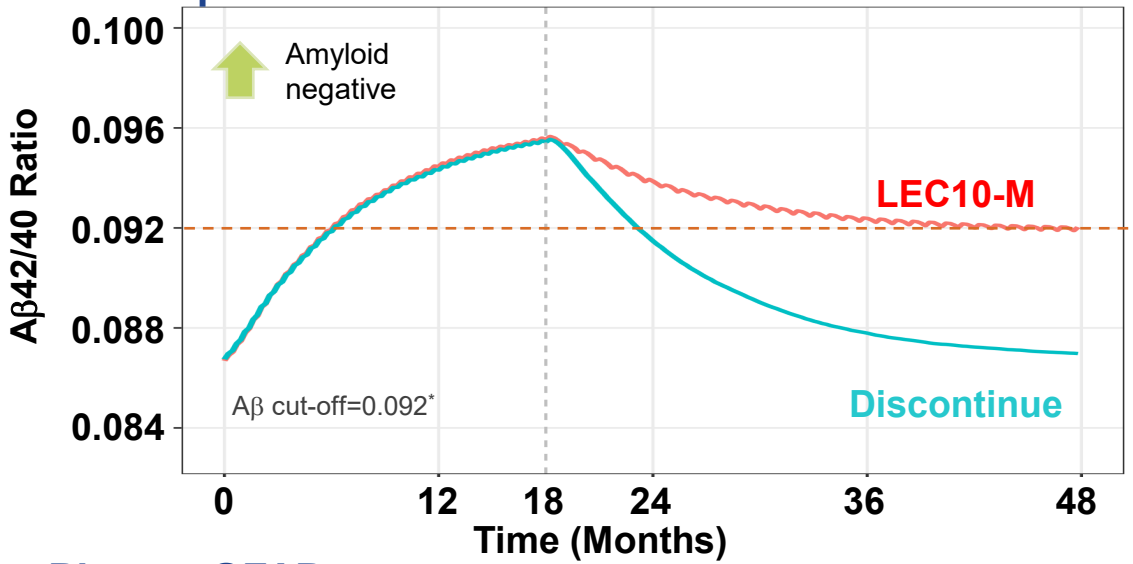
Aβ, amyloid beta. PET, positron emission tomography. pTau181, phosphorylated tau 181. pTau217, phosphorylated tau 217.

Monthly Maintenance Dose Prevents Reaccumulation of Brain Amyloid and Worsening of Plasma Biomarkers

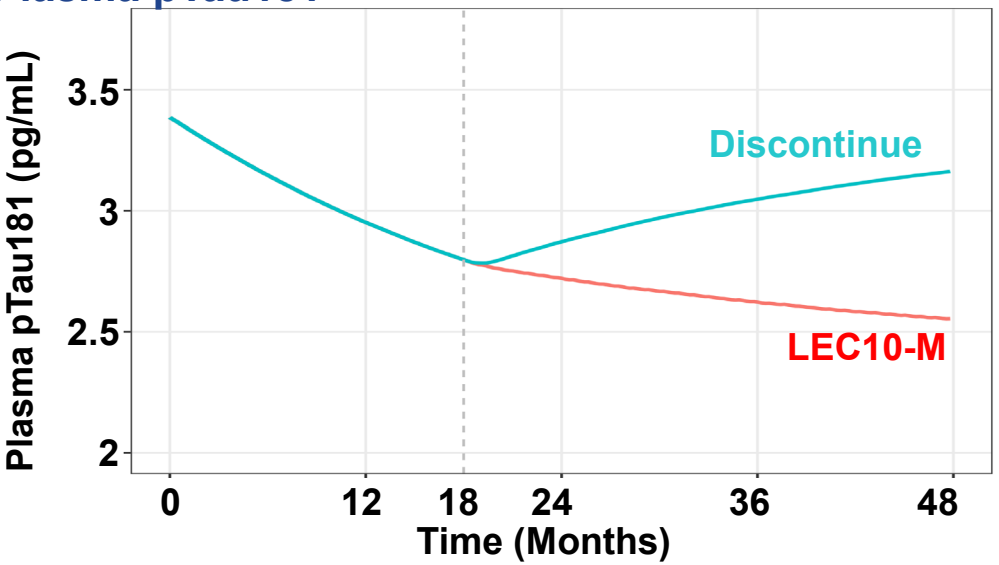
Amyloid PET



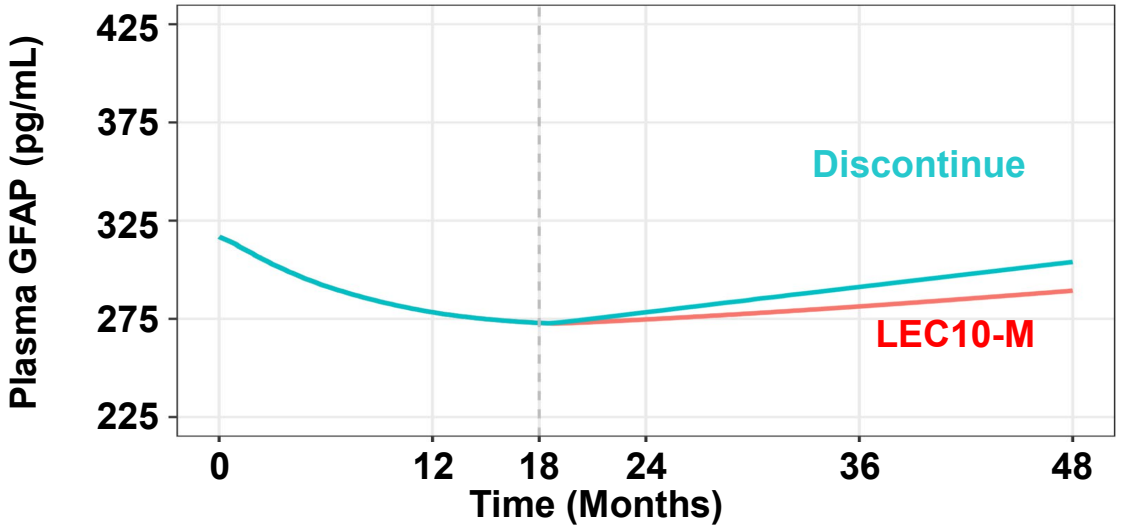
Plasma Aβ42/40 Ratio



Plasma pTau181

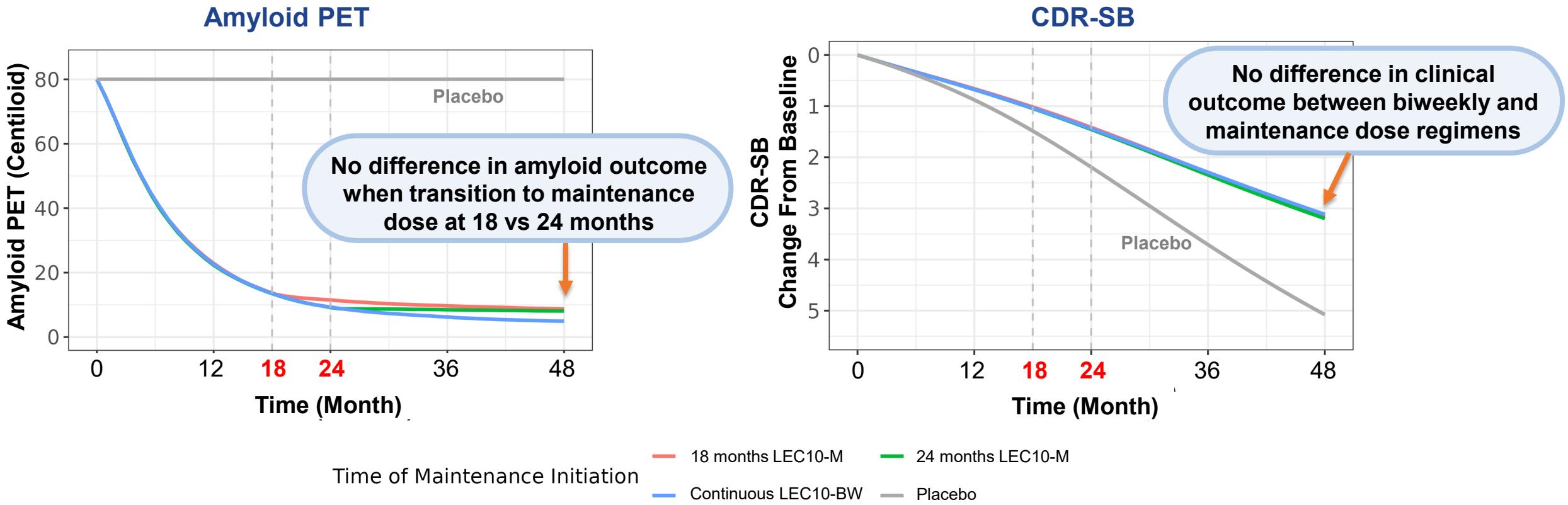


Plasma GFAP



Aβ, amyloid beta. GFAP, glial fibrillary acidic protein. LEC10-M, lecaneamb 10 mg/kg monthly. PET, positron emission tomography. pTau181, phosphorylated tau 181. *Verbel et al. 14th Annual CTAD Conference. 2021. Boston, MA. USA.

Initiating Monthly Maintenance Dosing at 18 or 24 Months Results in Similar Effect on CDR-SB & Amyloid PET Compared to Biweekly Dosing for 4 years



Similar effects when initiating monthly maintenance dosing at either 18 or 24 months

CDR-SB = Clinical Dementia Rating scale Sum of Boxes. LEC10-BW = lecanemab 10 mg/kg biweekly. LEC10-M = lecanemab 10 mg/kg monthly. PET = positron emission tomography.

Conclusions

- Alzheimer's disease, like other chronic progressive diseases, requires a long-term therapeutic strategy
- Lecanemab mechanism of action supports long-term therapy that continues to improve biomarkers further and avoid the reaccumulation of biomarkers when anti-amyloid treatment is stopped
- Phase 2 and OLE shows detrimental effect of stopping treatment, with reaccumulation of biomarkers and resumption of placebo rate of decline
- Modeling of extensive dose-ranging, placebo-controlled, and OLE data indicate that monthly maintenance dosing after 18 or 24 months of biweekly dosing can sustain efficacy and biomarker benefit of lecanemab

OLE = open-label extension.

Continued Benefit of Long-Term Lecanemab Treatment:

A Benefit/Risk Update from Long-Term Efficacy, Safety, and Biomarker Data

Christopher van Dyck

Yale University School of Medicine, New Haven, CT USA

Presented at the 2024 Clinical Trials on Alzheimer's Disease Annual Meeting (CTAD 2024), October 29 – November 1, 2024, Madrid, Spain.

Disclosures and Acknowledgements

Christopher van Dyck – Disclosures:

Advisor/Consultant for:

Roche Pharmaceuticals	Eisai, Inc
Ono Pharmaceuticals	Cerevel
Bristol Myers Squibb	UCB

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

Eli Lilly	Janssen Pharmaceuticals
Biogen Idec	Eisai, Inc
Roche Pharmaceuticals	Genentech, Inc
Cerevel Therapeutics	UCB

Authors:

Christopher van Dyck,[1] Reisa Sperling,[2] Shobha Dhadda,[3] David Li,[3]
Steven Hersch,[3] Michael Irizarry,[3] Lynn Kramer[3]

1. Yale University School of Medicine, New Haven, CT USA
2. Brigham and Women's Hospital, Massachusetts General Hospital, Harvard Medical School, Boston MA, USA
3. Eisai Inc. Nutley, NJ USA

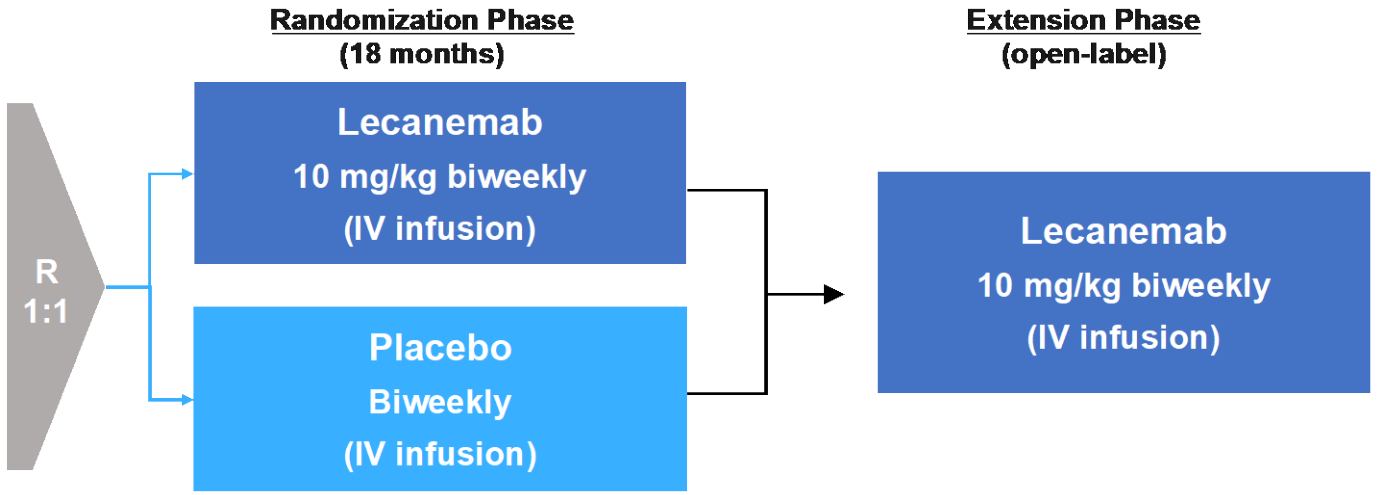
Clarity AD Study Design

Clarity AD Core and Open-Label Extension (OLE) Includes >3 Years of Lecanemab Treatment

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 Adverse Events
Change from Core Study Baseline in CDR-SB

Additional Outcome Measures:

Change from Baseline for:
ADAS-Cog14
ADCS MCI-ADL

Biomarkers

Optional longitudinal sub-studies

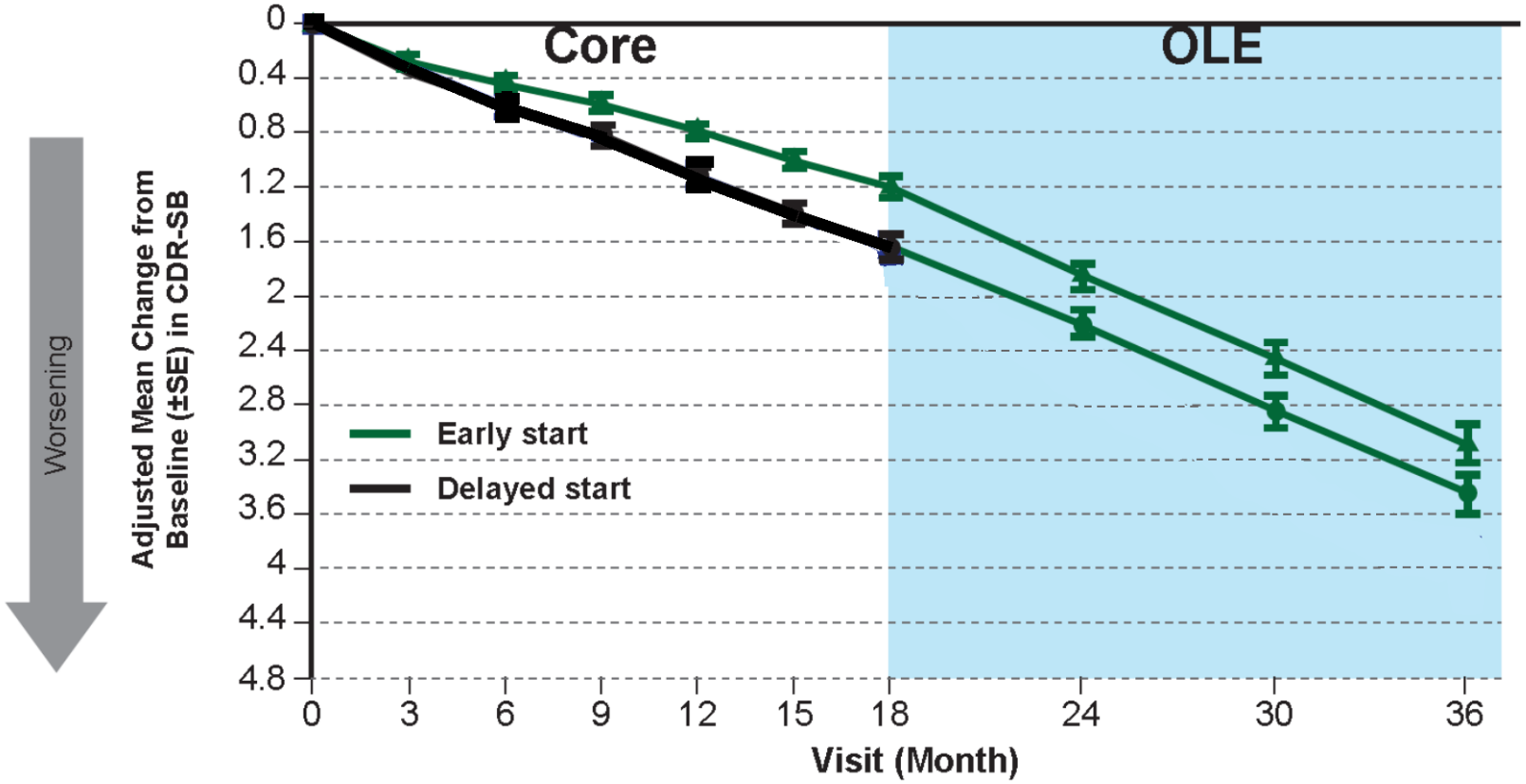
- Amyloid burden (amyloid PET; n=716)
- Brain tau pathology (tau PET; n=342)
- CSF biomarkers of neurodegeneration (n=281)
- Subcutaneous formulation (OLE)

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. van Dyck CH, et al., N Engl J Med. 2023;388:9-21.

Clarity AD OLE: CDR-SB Efficacy Through 36 Months

Lecanemab-Treated Patients Continue to Accrue Benefit Through 36 Months

- Delayed start group does not catch up to early start group, reflecting importance of early treatment initiation
- ADAS-Cog14 and ADCS MCI-ADL had similar results as CDR-SB



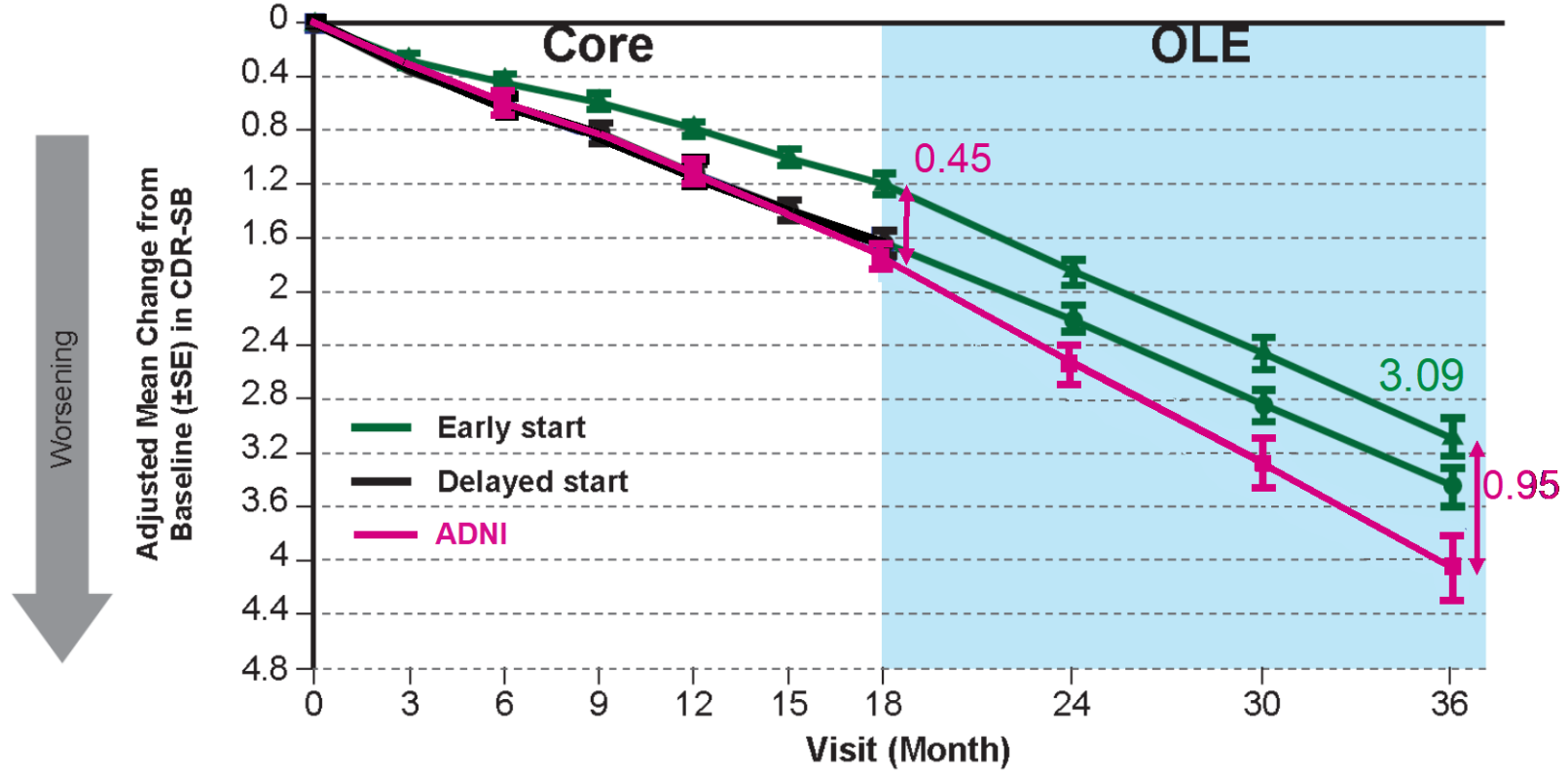
Note: Early start lecanemab 10 mg/kg biweekly group are those subjects on lecanemab 10 mg/kg biweekly in the Core. Delayed start LEC10-BW group (those subjects that initiate lecanemab 10 mg/kg biweekly in the OLE). OLE includes those participants on subcutaneous and intravenous formulations. Based on 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 OLE: CDR-SB Efficacy Through 36 Months

Lecanemab-Treated Patients Continue to Accrue Benefit Through 36 Months

- Treatment effect between lecanemab and ADNI cohort continues to expand from 18 through 36 months
- Delayed start group also shows benefit in OLE relative to ADNI cohort



N (Delayed start):	875	849	828	813	779	767	757	662	602	549
N (Early start):	859	824	798	779	765	738	714	659	613	569
N (ADNI):	436		410		401		121	301	173	173

- ADNI observational cohort was pre-specified and used during design of Clarity AD; represents exact population of those in Clarity AD study
- Matched ADNI participants for inclusion and exclusion criteria show similar degree of decline to placebo group out to 18 months

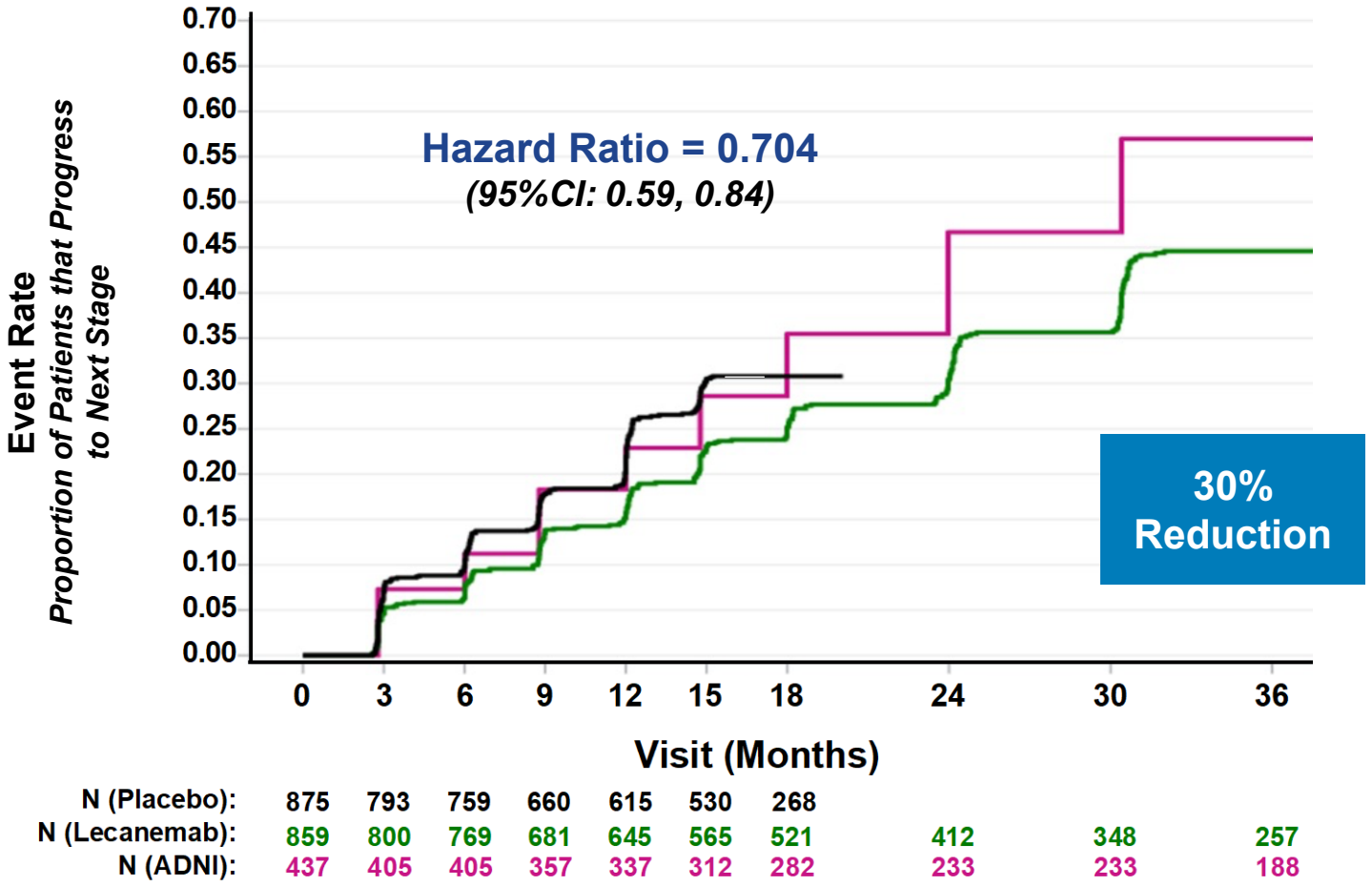
Note: Early start lecanemab 10 mg/kg biweekly group are those subjects on lecanemab 10 mg/kg biweekly in the Core. Delayed start LEC10-BW group (those subjects that initiate lecanemab 10 mg/kg biweekly in the OLE). OLE includes those participants on subcutaneous and intravenous formulations.
Based on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

Lecanemab Meaningfully Delayed Progression to Next AD Stage Through 36 Months (*Responder Analysis*)

Time to Worsening on CDR-SB

(Shift from MCI to dementia or from mild AD to moderate/severe AD)



CDR-SB Range	Staging Category
0	Normal
0.5 – 4.0	Questionable Cognitive Impairment
0.5 – 2.5	Questionable Impairment
3.0 – 4.0	Very Mild Dementia
4.5 – 9.0	Mild Dementia
9.5 – 15.5	Moderate Dementia
16.0 – 18.0	Severe Dementia

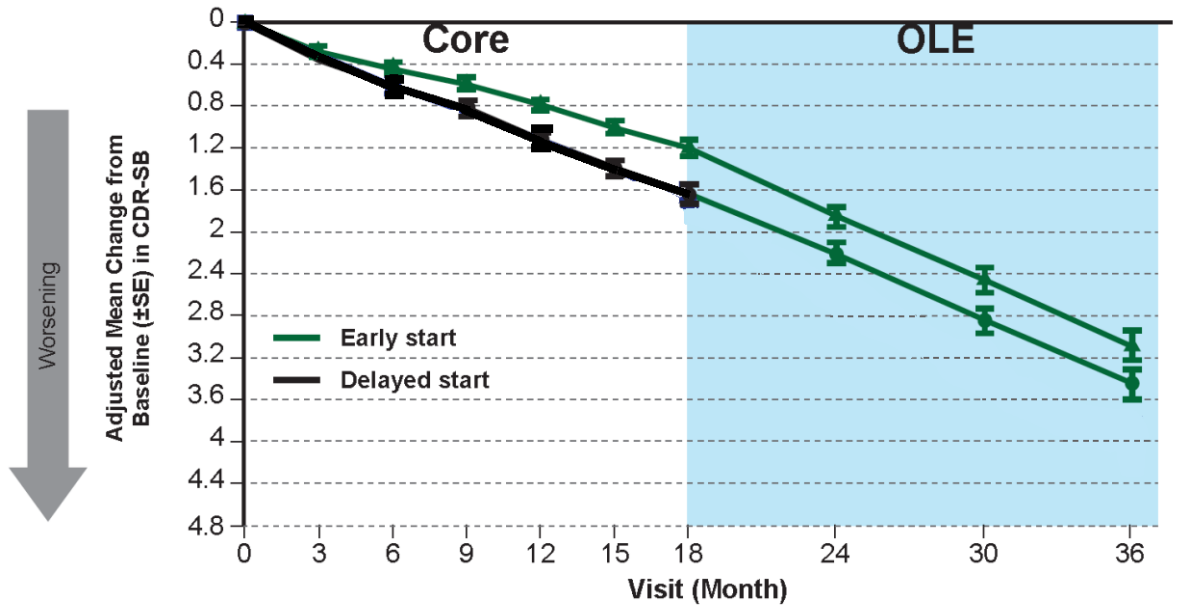
- Progression was defined as CDR-SB Score progressing from MCI (0.5-4) to mild AD dementia(4.5-9) or mild dementia to moderate dementia (9.5-15.1) based on dementia staging on CDR-SB (O'Bryant et al., Arch Neurol 2008)
- Given less frequent assessment, "Since controlled-based imputation was used for missing data in this analysis, CDR-SB (which has greater range) was used rather than global CDR for disease staging"

AD, Alzheimer's disease. ADNI, Alzheimer's Disease Neuroimaging Initiative. CDR-SB, Clinical Dementia Rating-sum of boxes. CI, confidence interval. MCI, mild cognitive impairment.

Clinical Outcomes Through 36 Months

Subjects with No/Low Tau & Low Amyloid Continued to Benefit Through 36 Months

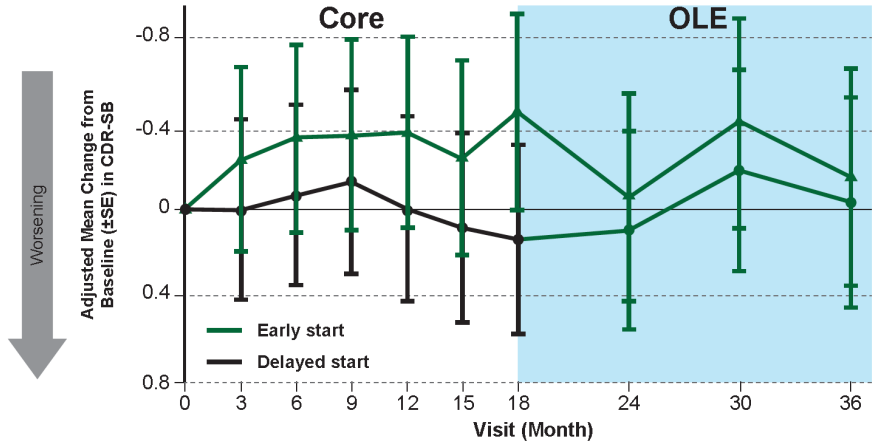
CDR-SB – Overall Population



N (Delayed start):	875	849	828	813	779	767	757	662	602	549
N (Early start):	859	824	798	779	765	738	714	659	613	569

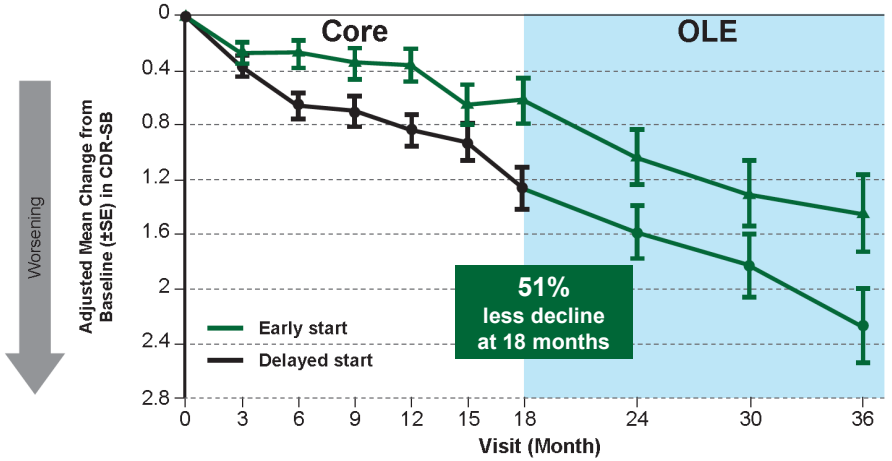
- **The no/low tau subgroup represents 40% of the overall study population**
- **The low amyloid subgroup (<60 Centiloids) represents 54% of the overall amyloid PET substudy population**
- **Majority improved or maintained out to 36 Months**
- **Similar results were observed for ADAS-Cog14 and ADCS MCI-ADL**

CDR-SB – No/Low-Tau Population



N (Delayed start):	71	71	67	66	62	58	58	55	49	44
N (Early start):	70	66	63	61	57	52	50	45	41	41

CDR-SB – Baseline < 60 CL



N (Delayed start):	191	186	178	175	164	160	151	138	124	118
N (Early start):	185	173	176	164	157	150	146	132	121	115

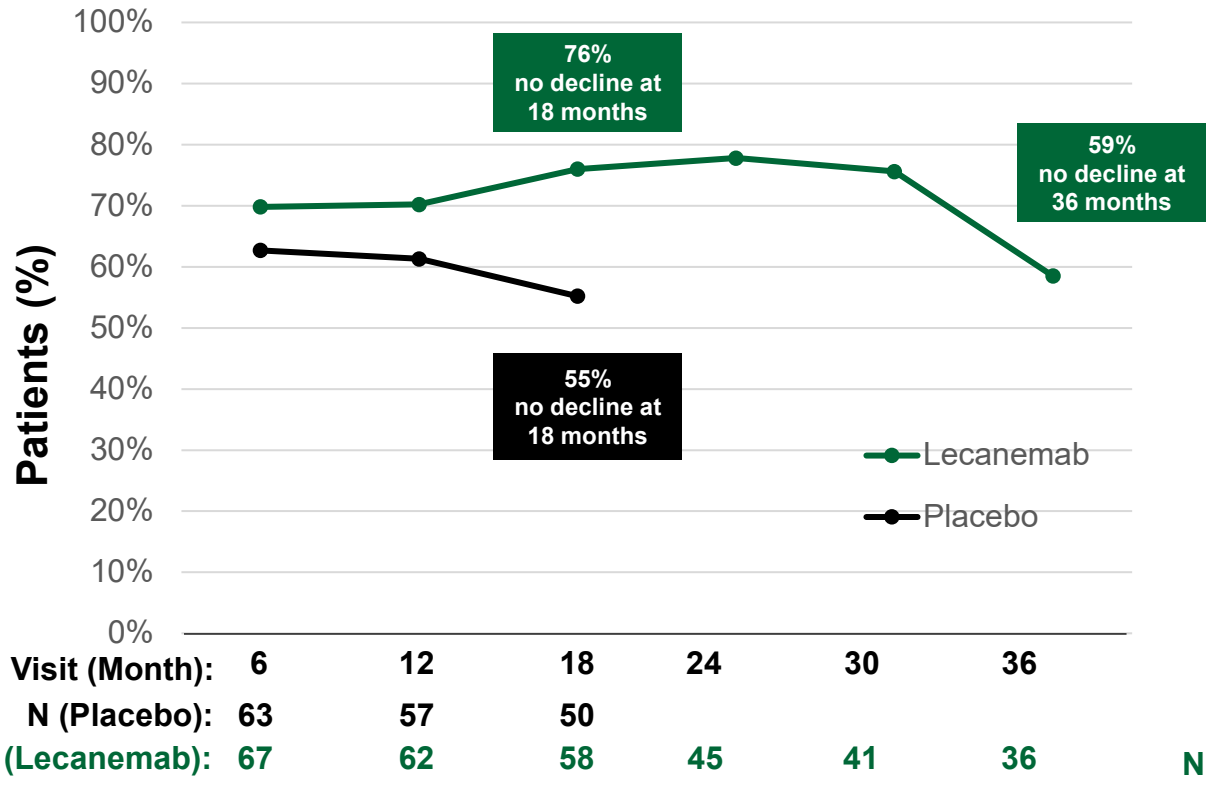
Tau terminology based on latest FDA definitions. OLE includes those participants on subcutaneous and intravenous formulations.

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

Subjects with No/Low Tau PET: Response Rate

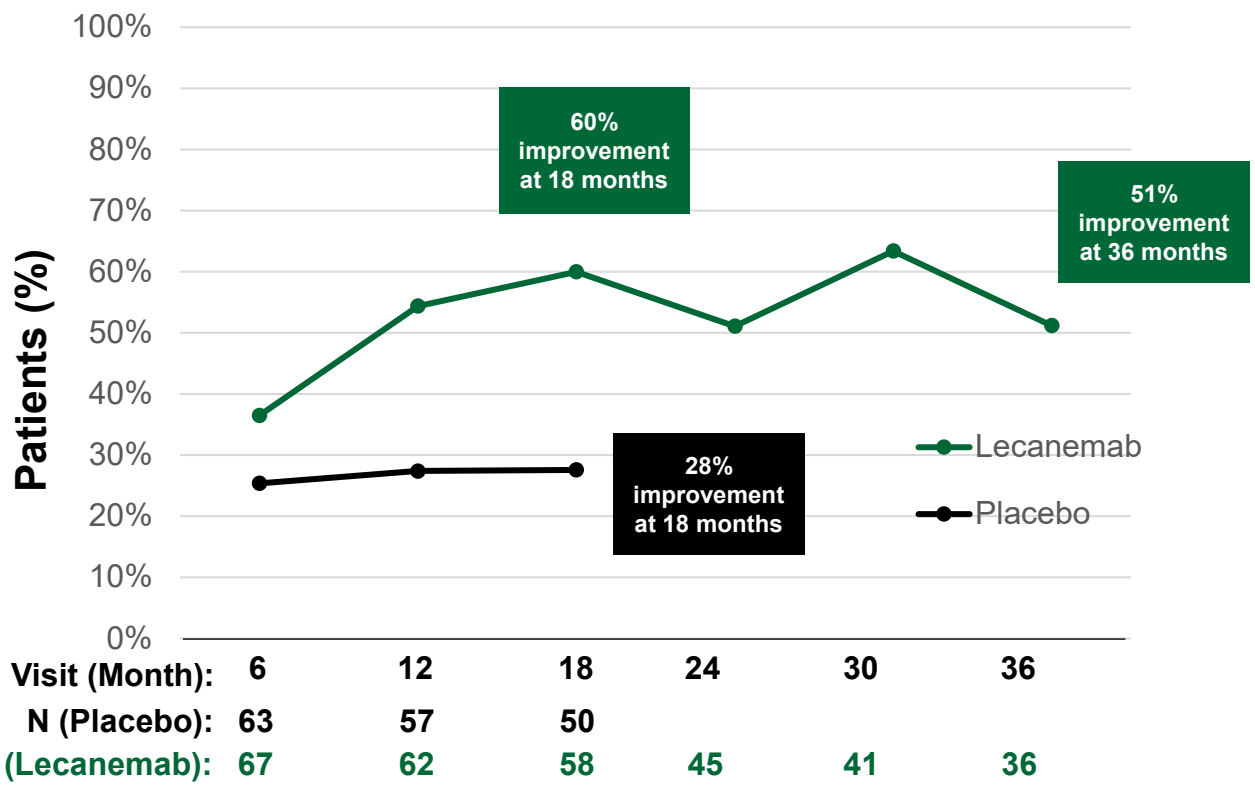
59% Had No Decline and 51% Had Improvement at 36 Months

CDR-SB No Decline – No/Low Tau Population



Visit (Month):	6	12	18	24	30	36
N (Placebo):	63	57	50			
N (Lecanemab):	67	62	58	45	41	36

CDR-SB Improvement – No/Low Tau Population



Visit (Month):	6	12	18	24	30	36
N (Placebo):	63	57	50			
N (Lecanemab):	67	62	58	45	41	36

Observed rates for 'No Decline' and 'Improvement' at 36 months

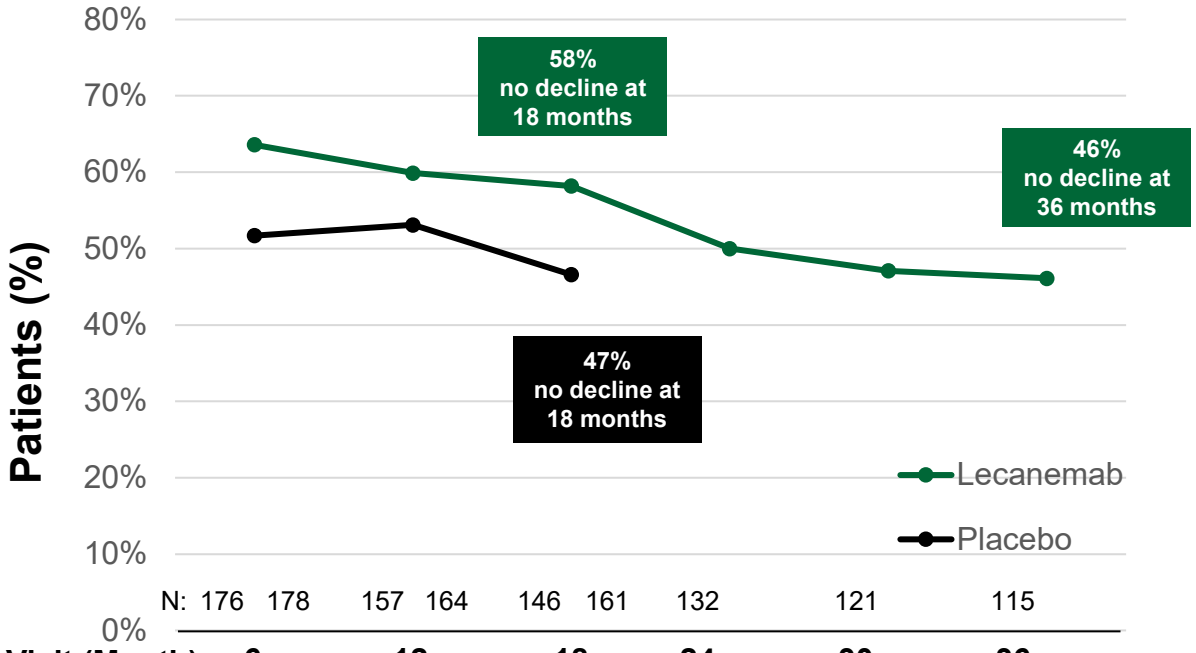
- **ADAS-Cog14: 63% and 61% for lecanemab**
- **ADCS MCI-ADL: 63% and 59% for lecanemab**

Tau terminology based on latest FDA definitions. Cutoffs for MK Tau PET: No/Low SUVR <1.06; Intermediate SUVR 1.06-2.91; High SUVR >2.91.
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 topography.

Subjects with Low Amyloid PET (<60CL): Response Rate

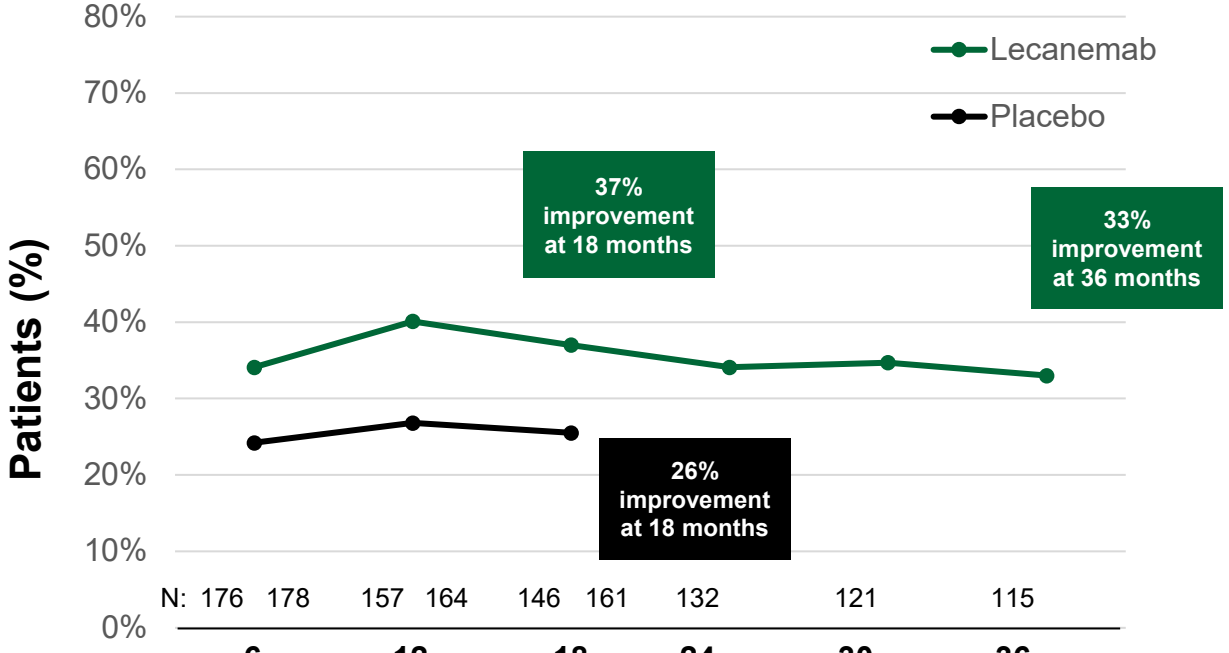
46% Had No Decline and 33% Had Improvement at 36 Months

CDR-SB No Decline – Low Amyloid Population



Visit (Month):	6	12	18	24	30	36
N (Placebo):	176	157	146			
N (Lecanemab):	178	164	161	132	121	115

CDR-SB Improvement - Low-Amyloid Population



Visit (Month):	6	12	18	24	30	36
N (Placebo):	176	157	146			
N (Lecanemab):	178	164	161	132	121	115

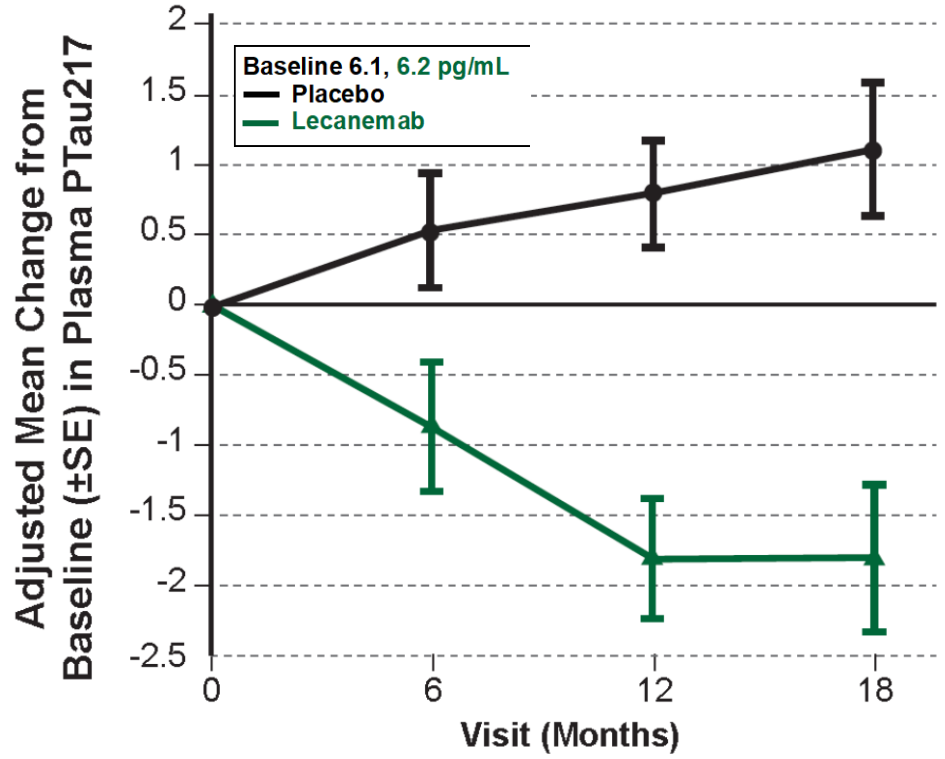
Observed rates for 'No Decline' and 'Improvement' at 36 months

- **ADAS-Cog14: 46% and 43% for lecanemab**
- **ADCS MCI-ADL: 51% and 48% for lecanemab**

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. CL, Centiloid. PET, positron emission topography.

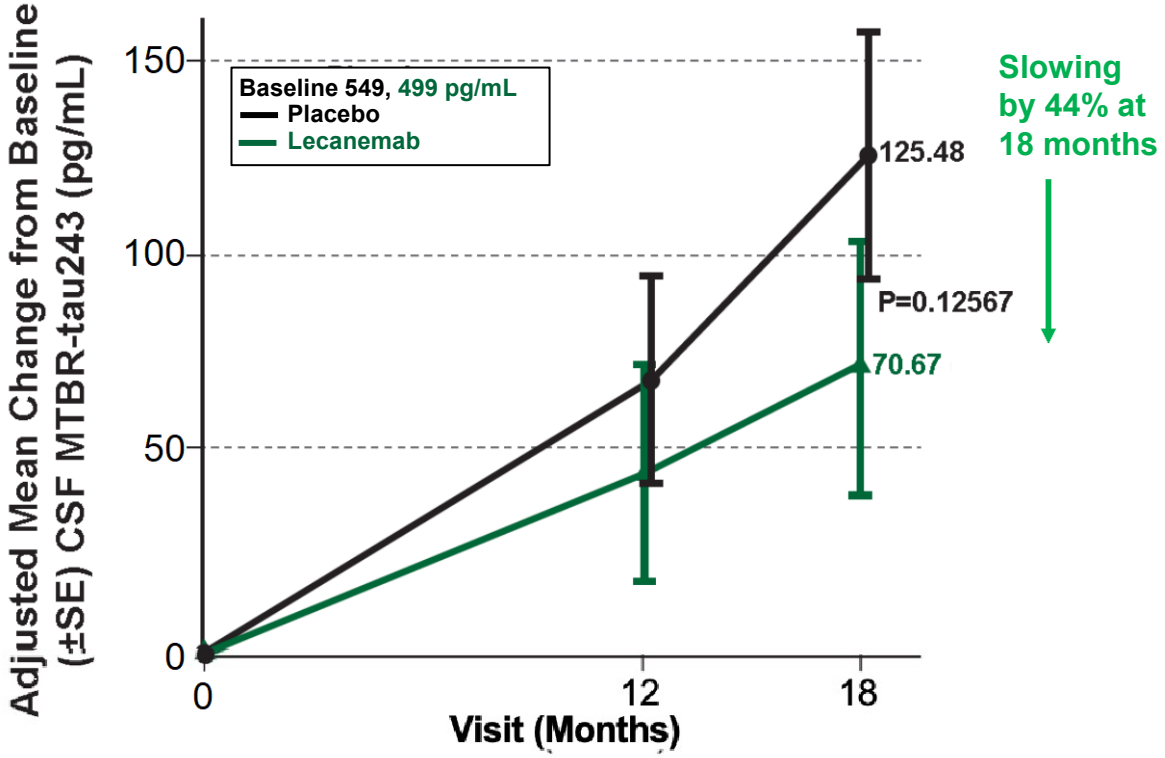
Lecanemab Reduces and Slows the Rate of Tau Pathology Biomarkers Plasma pTau217 and CSF MTBR-tau243

Plasma pTau217



(N) Placebo	157	125	108	118
(N) Lecanemab	145	111	108	107

CSF MTBR-tau243*



(N) Placebo	83	76	58
(N) Lecanemab	84	77	56

*167 subjects (PBO:N=83,LEC:N=84) are included in the MMRM CSFMTBR-tau243; Statistical significance not reached due to limited sample size; Data generated with C2N MTBR-tau (Product Code P0001)

CSF, cerebrospinal fluid. MMRM, mixed models for repeated measures. MTBR-tau243, microtubule-binding region (MTBR) of tau containing the residue 243. SE, standard error.

Summary of TEAE and ARIA (Exposure Adjusted)

Approx Core+OLE Exposure: 3480 Person-Years; Mean 2.2 yrs; >450 With 3 Years

	Placebo N = 897			Lecanemab N = 898			Lecanemab (Double-Blind + OLE) N = 1616		
	n	%	Exposure Adjusted*	n	%	Exposure Adjusted*	n	%	Exposure Adjusted*
Adverse Event (AE)	735	**81.9%**	59.6	798	**88.9%**	67.8	1480	**91.6%**	42.5
Serious Adverse Event (SAE)	101	**11.3%**	8.2	126	**14.0%**	10.7	332	**20.5%**	9.5
Death[a]	8	**0.9%**	0.7	7	**0.8%**	0.6	24	**1.5%**	0.7
Deaths with concurrent ARIA or ICH irrespective of ARIA being cause of death	1	**0.1%**	0.1	0	**0%**	0	3	**0.2%**	0.1
AEs Leading to Study Drug Withdrawal	28	**3.1%**	2.3	64	**7.1%**	5.4	160	**9.9%**	4.6
ARIA-E	15	**1.7%**	1.2	113	**12.6%**	9.6	238	**14.7%**	6.8
ARIA-H	80	**8.9%**	6.5	152	**16.9%**	12.9	385	**23.8%**	11.1
Isolated ARIA-H	69	**7.7%**	5.6	78	**8.7%**	6.6	211	**13.1%**	6.1
ICH[a]	2	**0.2%**	0.2	6	**0.7%**	0.5	11	**0.7%**	0.3

n, %, exposure-adjusted rate (per subject-year) are presented. OLE is based on IV datasets (as of 31 Mar 2024).
a: Includes all post-treatment events. Approx, approximate. yrs, years.
ARIA-E, amyloid related imaging abnormalities – edema. ARIA-H, ARIA with hemosiderin deposits. ICH, intracerebral hemorrhage.

***Exposure adjusted rate (per 100 persons per year)**

No New Clinically Significant Safety Events Identified with Long-Term Treatment

- No increase of known adverse events over time

MedDRA PT	Lecanemab (Double-Blind + OLE) N = 1616 <12 months		Lecanemab (Double-Blind + OLE) N = 1286 12 - <24 months		Lecanemab (Double-Blind + OLE) N = 872 24 - <36 months	
Cough	31	**1.9%**	27	**2.1%**	18	**2.1%**
Headache	131	**8.1%**	49	**3.8%**	17	**1.9%**
Diarrhea	58	**3.6%**	30	**2.3%**	12	**1.4%**
Infusion related reaction	369	**22.8%**	26	**2.0%**	11	**1.3%**
Nausea/Vomiting	62	**3.8%**	28	**2.2%**	12	**1.4%**
Rash	49	**3.0%**	33	**2.6%**	14	**1.6%**

MedDRA PT, Medical Dictionary for Regulatory Activities preferred term. OLE, open-label extension. OLE is based on IV datasets (as of 31 Mar 2024).

ARIA by APOE Genotype through Clarity AD Core + OLE

ARIA-E Occurs Early in Treatment and Isolated ARIA-H Continues at Rate Similar to Placebo

		Placebo N=897		Lecanemab Early Start Patients Only			
				<18 months (Core) N=898		≥18, <36 months (OLE) N=672	
ARIA-E	**Total**	**15**	**1.7%**	**113**	**12.6%**	**10**	**1.5%**
	APOE4-	1/286	0.3%	15/278	5.4%	4/205	2.0%
	APOE4+ heterozygote	9/478	1.9%	52/479	10.9%	4/373	1.1%
	APOE4+ homozygote	5/133	3.8%	46/141	32.6%	2/94	2.1%
ARIA-H	**Total**	**80**	**8.9%**	**152**	**16.9%**	**52**	**7.7%**
	APOE4-	11/286	3.8%	32/278	11.5%	15/205	7.3%
	APOE4+ heterozygote	41/478	8.6%	66/479	13.8%	26/373	7.0%
	APOE4+ homozygote	28/133	21.1%	54/141	38.3%	11/94	11.7%
Isolated ARIA-H	**Total**	**69**	**7.7%**	**78**	**8.7%**	**42**	**6.3%**
	APOE4-	10/286	3.5%	22/278	7.9%	14/205	6.8%
	APOE4+ heterozygote	35/478	7.3%	39/479	8.1%	20/373	5.4%
	APOE4+ homozygote	24/133	18%	17/141	12.1%	8/94	8.5%

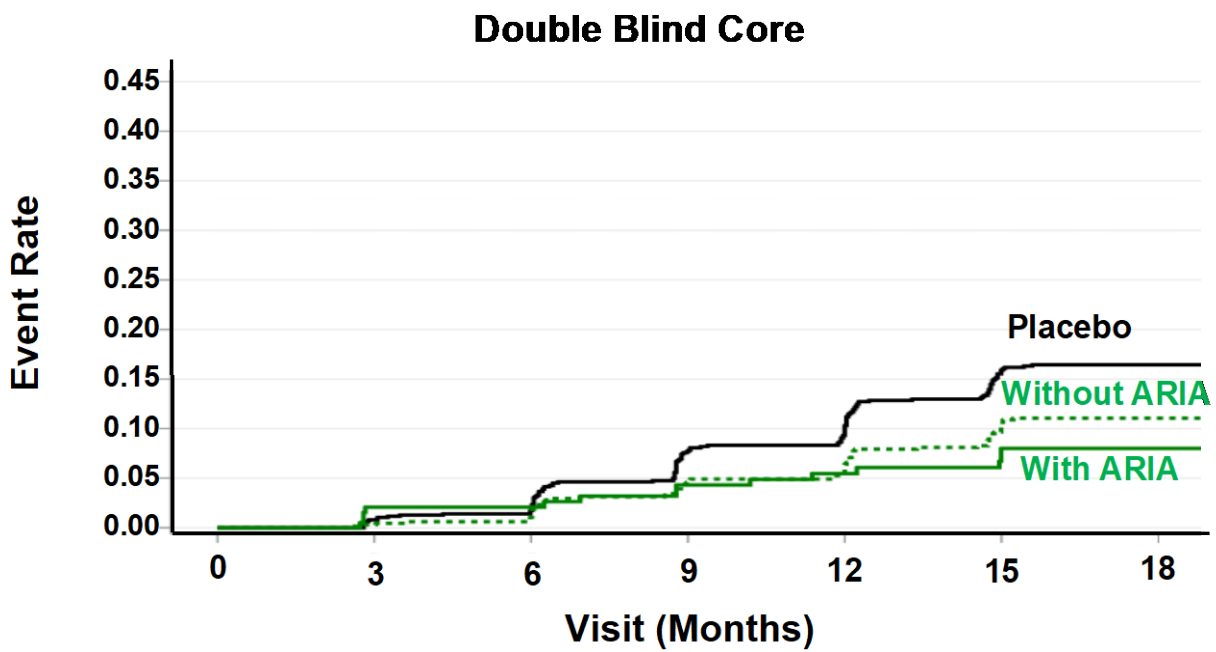
31 Mar 2024 cutoff dataset (IV only). Summarized based on the first occurrence.

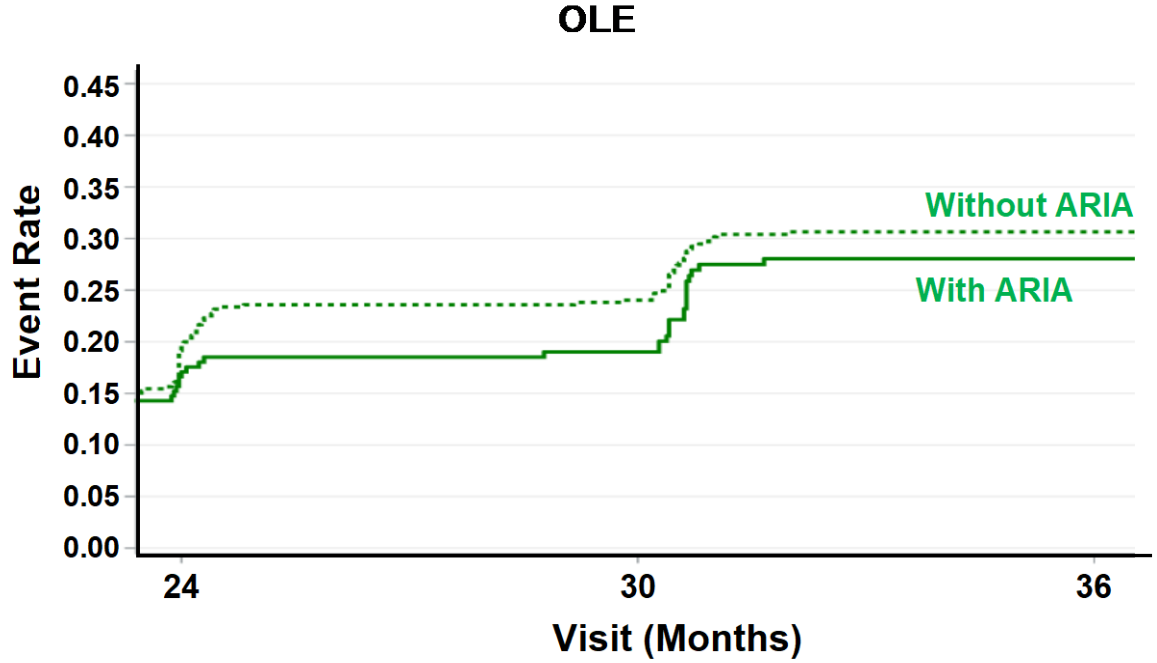
APOE4, apolipoprotein E4. ARIA-E, amyloid related imaging abnormalities – edema. ARIA-H, ARIA with hemosiderin deposits. OLE, open-label extension.

ARIA is Not Associated with Accelerated Long-Term Progression

- Risk period for ARIA-E is first 6 months based on vascular amyloid clearance and increased permeability
- Most patients who had ARIA had CDR-SB assessments *after* event
- Sensitivity analyses assessing impact on cognition or function showed no impact from ARIA
  - Multiple imputation (plausible and worst-case scenarios)
  - ARIA as covariate (fixed and time-varying)
  - No accelerated long-term progression for ARIA versus without ARIA irrespective of threshold

Time to Worsening of CDR-SB by 3.0 points*





Based on intravenous dataset. ARIA, amyloid related imaging abnormalities. CDR-SB, Clinical Dementia Rating-sum of boxes. OLE, open-label extension. Difference in starting KM rate in the OLE is due to not all core Lecanemab subjects from core entering OLE and core placebo converted to Lecanemab in OLE

*Was assessed at multiple points (eg, 1.5, etc)

Summary

- OLE results support disease-modifying effect and the importance of continued long-term lecanemab treatment
- Lecanemab-treated participants continued to accrue benefit through 36 months
- Early-stage patients (no/low tau or low amyloid) show stability or improvement over 18-36 months, supporting early initiation of treatment with lecanemab
- Lecanemab slows rate of increase in plasma pTau217 & CSF MTBR-tau243 in Clarity AD, a clear demonstration of drug effect on amyloid and tau pathology cascade
- No new safety signals are observed with continued lecanemab treatment
- ARIA is not associated with accelerated long-term progression

AD, Alzheimer's disease. ARIA, amyloid related imaging abnormalities. CSF, cerebrospinal fluid. MTBR-tau243, microtubule-binding region (MTBR) of tau containing the residue 243. OLE, open-label extension. pTau217, phosphorylated tau-217.

Thank you

Clarity AD

Electronic Presentation

To obtain a copy of the presentation please scan this QR code. Copies of this poster obtained through the QR code are for personal use only and may not be used without permission from CTAD and the author of this poster. For permission to reprint and/or distribute, please contact Dr. Irizarry at michael_irizarry@eisai.com

https://mayvillemedical.com/lecanemab-2024-CTAD-presentation

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.

Editorial support, funded by Eisai Inc, was provided by Mayville Medical Communications.
Funding for the studies and analyses was provided by Eisai Inc. and Biogen Inc.