Perspectives Session

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

July 30, 2024

Alzheimer's Association International Conference (AAIC) 2024
July 28 - August 1, 2024 / Philadelphia, PA, USA + Online

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
Does the Current Evidence for Lecanemab Mechanism Support a Rationale for Continued Lecanemab Dosing?	*Dennis Selkoe*
How Does the Latest Clinical Pharmacology Data & Modeling Support Continued Lecanemab Dosing?	*Larisa Reyderman*
Neuro-Dynamic Quantitative Systems Pharmacology (QSP) Model Supports Continued Lecanemab Treatment With Maintenance Dosing For Alzheimer's Disease	*Youfang Cao*
Is There 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*

Does the Current Evidence for the Lecanemab Mechanism Support a Rationale for Continued Lecanemab Dosing?

Dennis Selkoe

Brigham and Women's Hospital, Harvard Medical School, Boston, MA USA

Disclosures and Acknowledgments

Dennis Selkoe - Disclosures:

- Director and consultant to Prothena Biosciences
- Ad hoc consultant to Eisai

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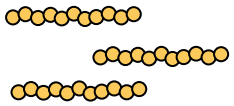
Generation of Amyloid β-Protein (Aβ) Occurs Throughout Life but can Lead to Aβ Aggregation with Age

Oligomers
2 to ~28 monomers

↕

"Protofibrils" (4-8 nm diffusible aggregates)
~~28 – >500 monomers



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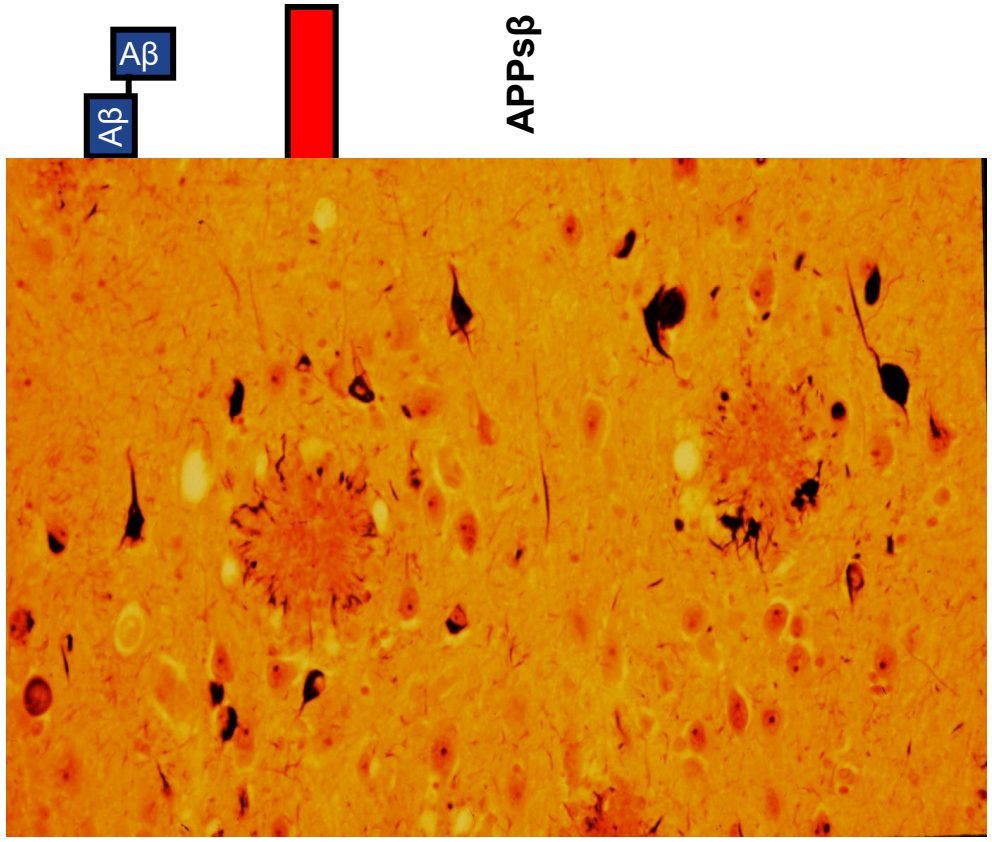
Amyloid plaques:
insoluble amyloid fibrils 8 nm wide and not readily diffusible



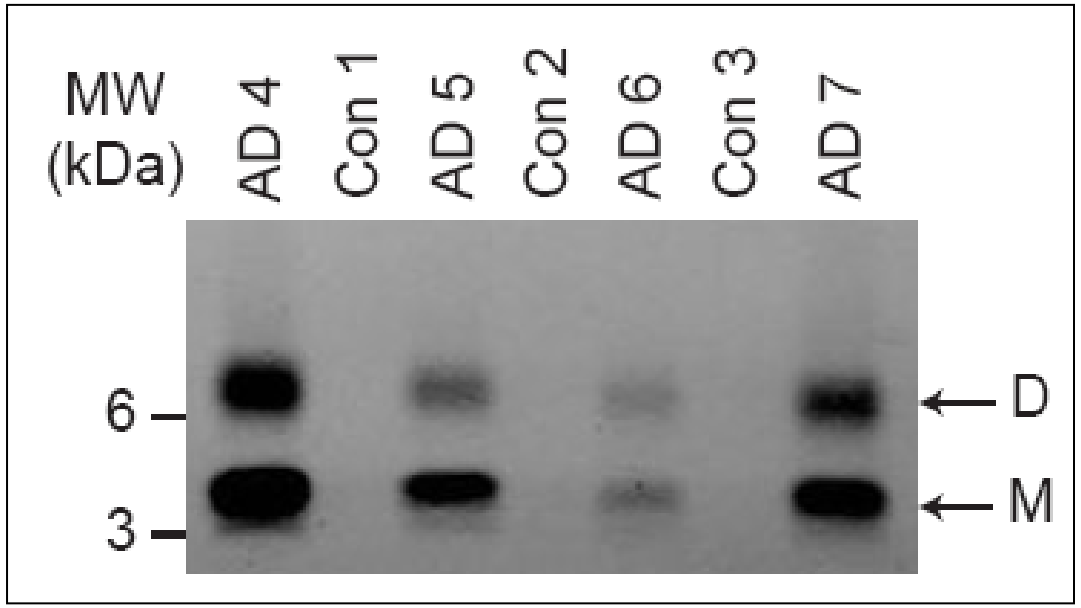
Aβ, amyloid beta. APPsβ, amyloid precursor protein sβ.

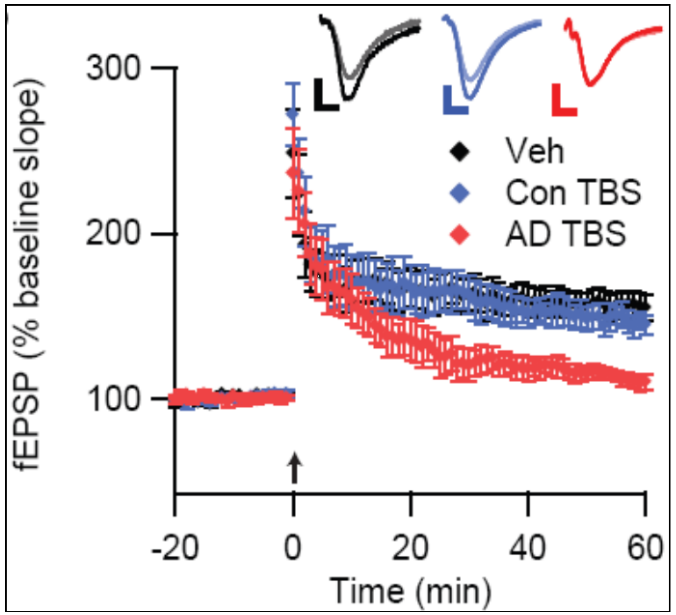
Haass, Schlossmacher et al. *Nature* 1992

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

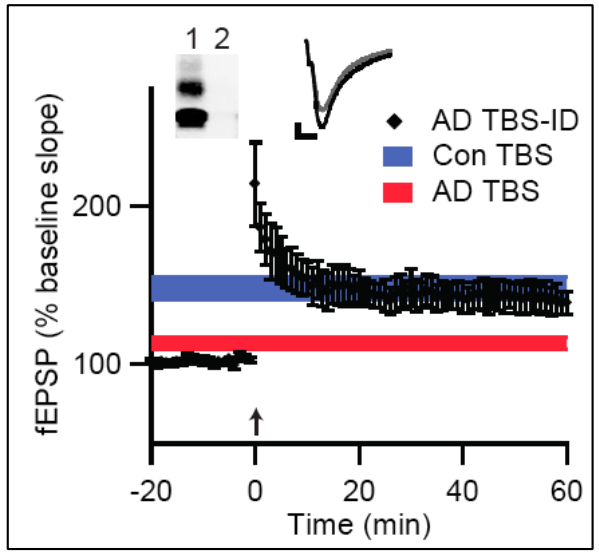
Aβ, amyloid beta. AD, Alzheimer's disease.

Diffusible Aβ Dimers/Oligomers Isolated from AD Brain Inhibit Long Term Potentiation (LTP) When Floated onto Normal Mouse Hippocampal Slices





LTP

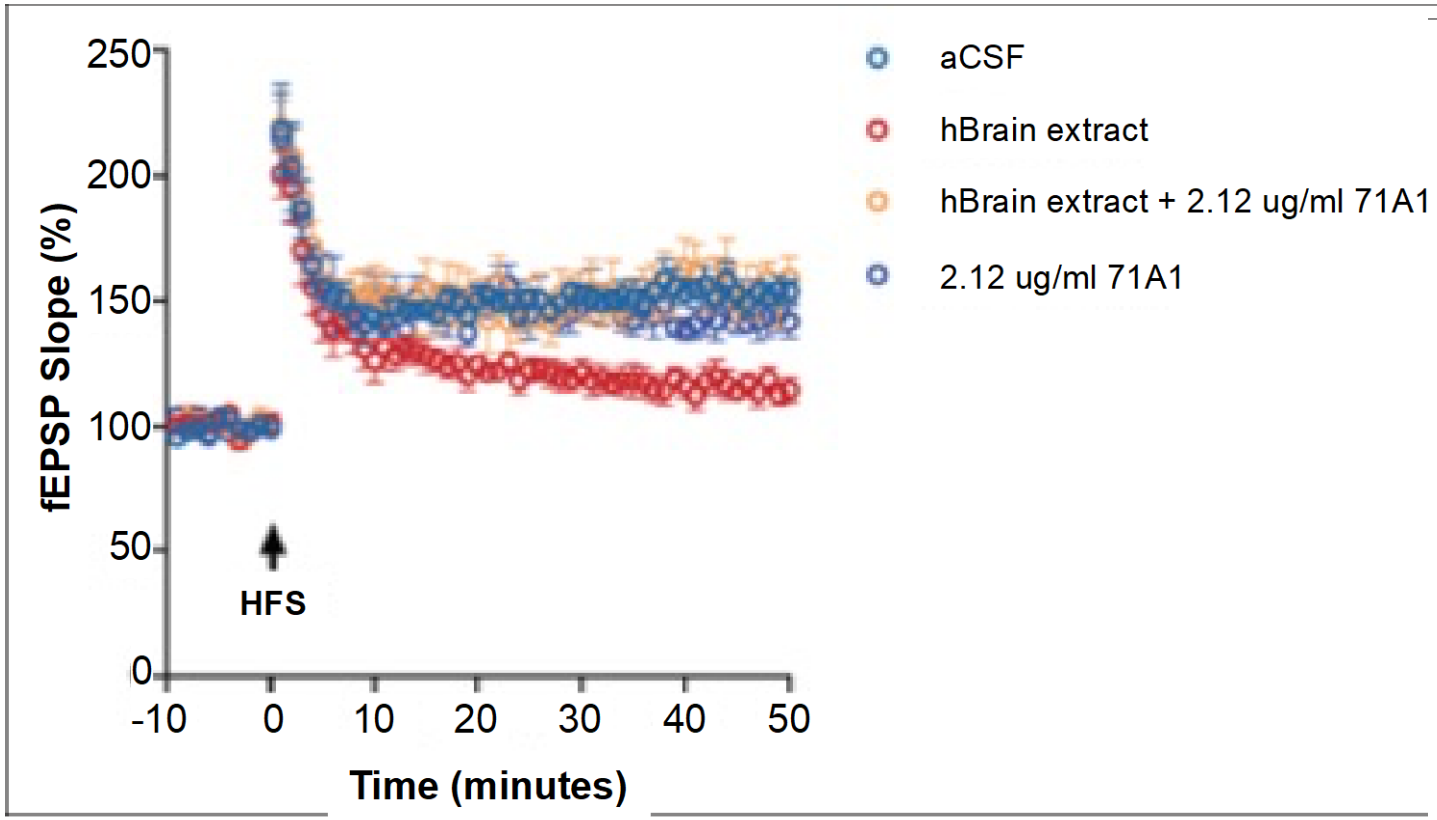


AD, Alzheimer's disease. Con, control. D, dimer. fEPSP, field excitatory postsynaptic potentials. LTP, long-term potentiation. M, monomer. Min, minutes. MW, molecular weight. TBS, tris-buggered saline. Veh, vehicle.

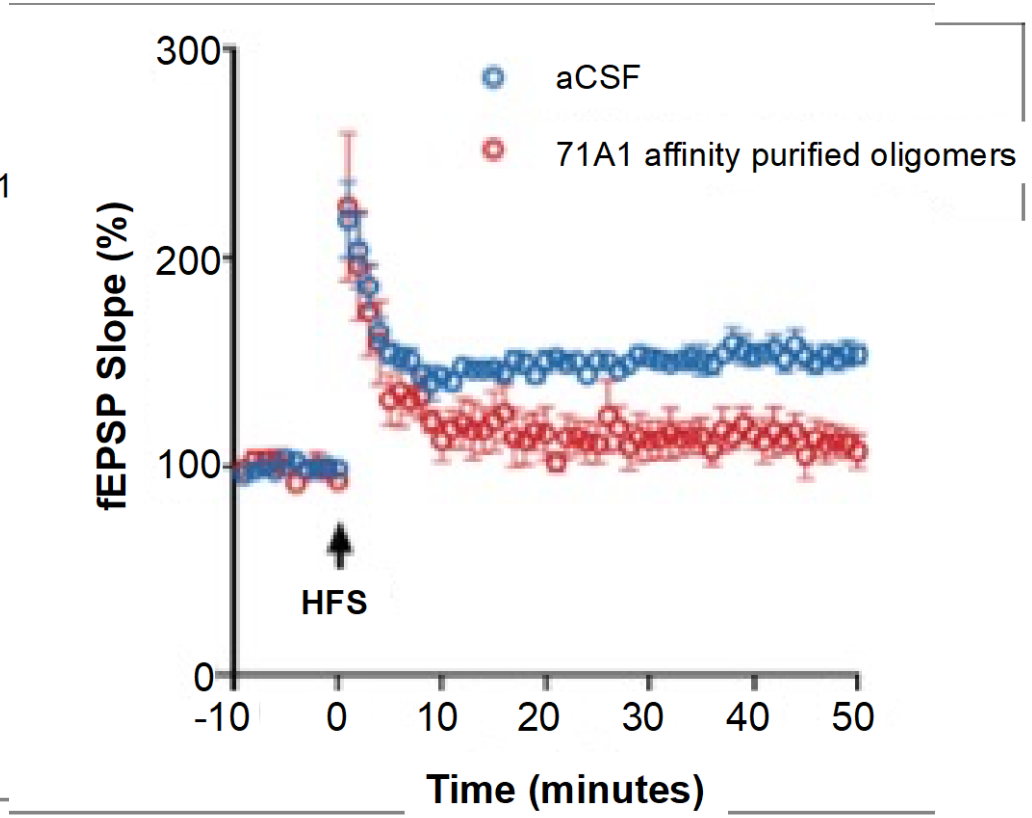
Shankar et al, *Nature Medicine* 2008

An Aβ Oligomer-Selective Antibody (71A1) Immuno-purifies Synaptotoxic Aβ Oligomers from AD Brain Soluble Extracts

71A1 Rescues LTP



71A1-purified Oligomers Directly Inhibit LTP

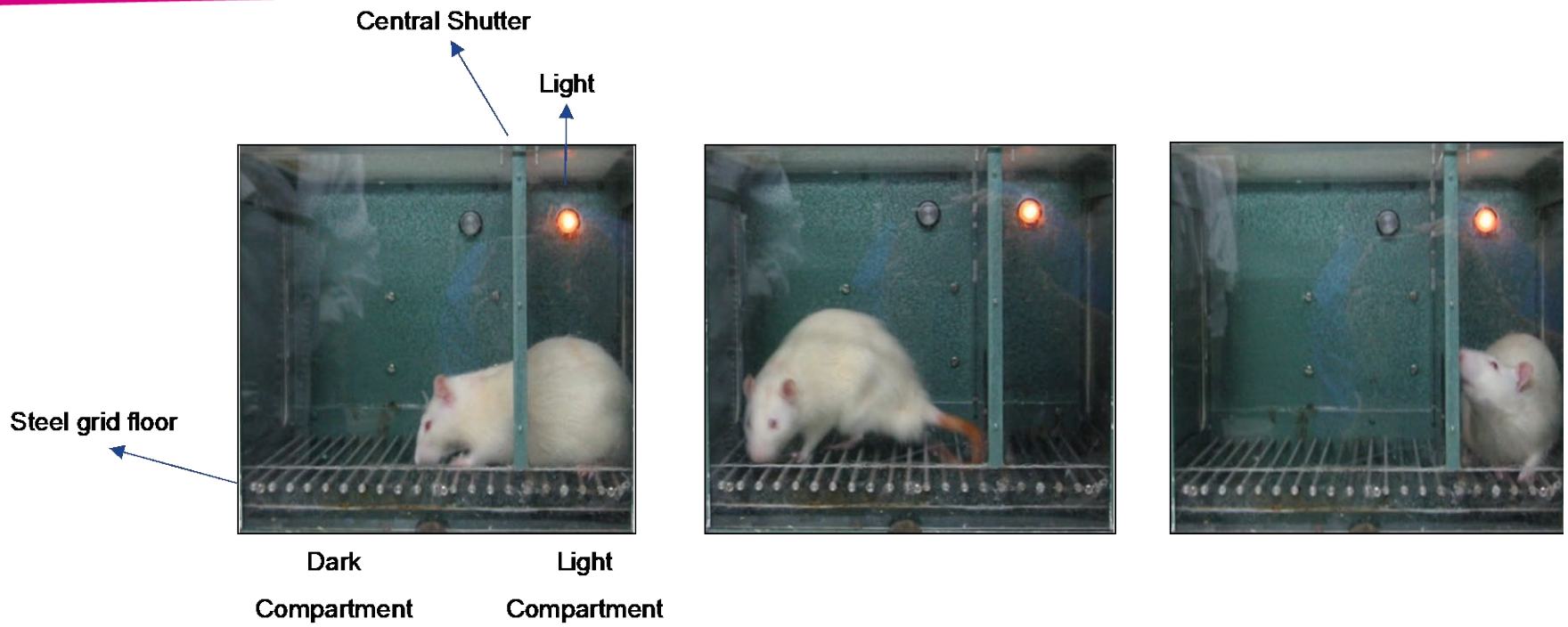


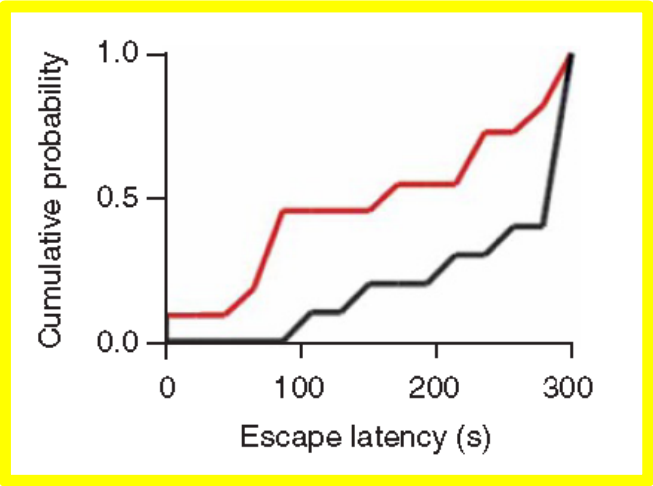
Aβ, amyloid beta. aCSF, artificial cerebrospinal fluid. AD, Alzheimer's disease. fEPSP, field excitatory postsynaptic potentials. hBrain, human brain. HFS, high-frequency stimulation. LTP, long-term potentiation.

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





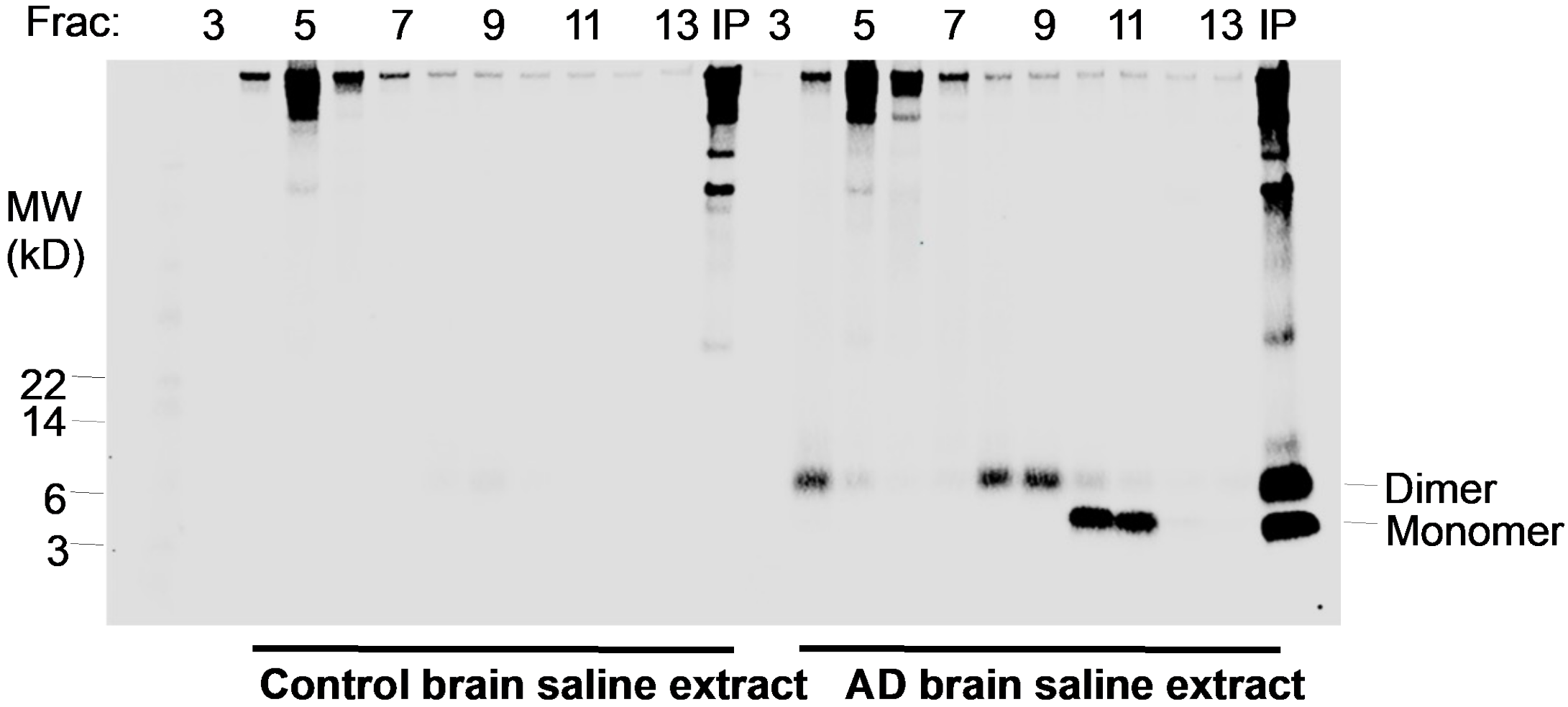
Rat forgets the earlier foot shock And reenters the dark chamber quickly

Shankar et al, *Nature Medicine* 2008

Aβ, amyloid beta.

Connecting Aβ Dimers/Oligomers with Tau

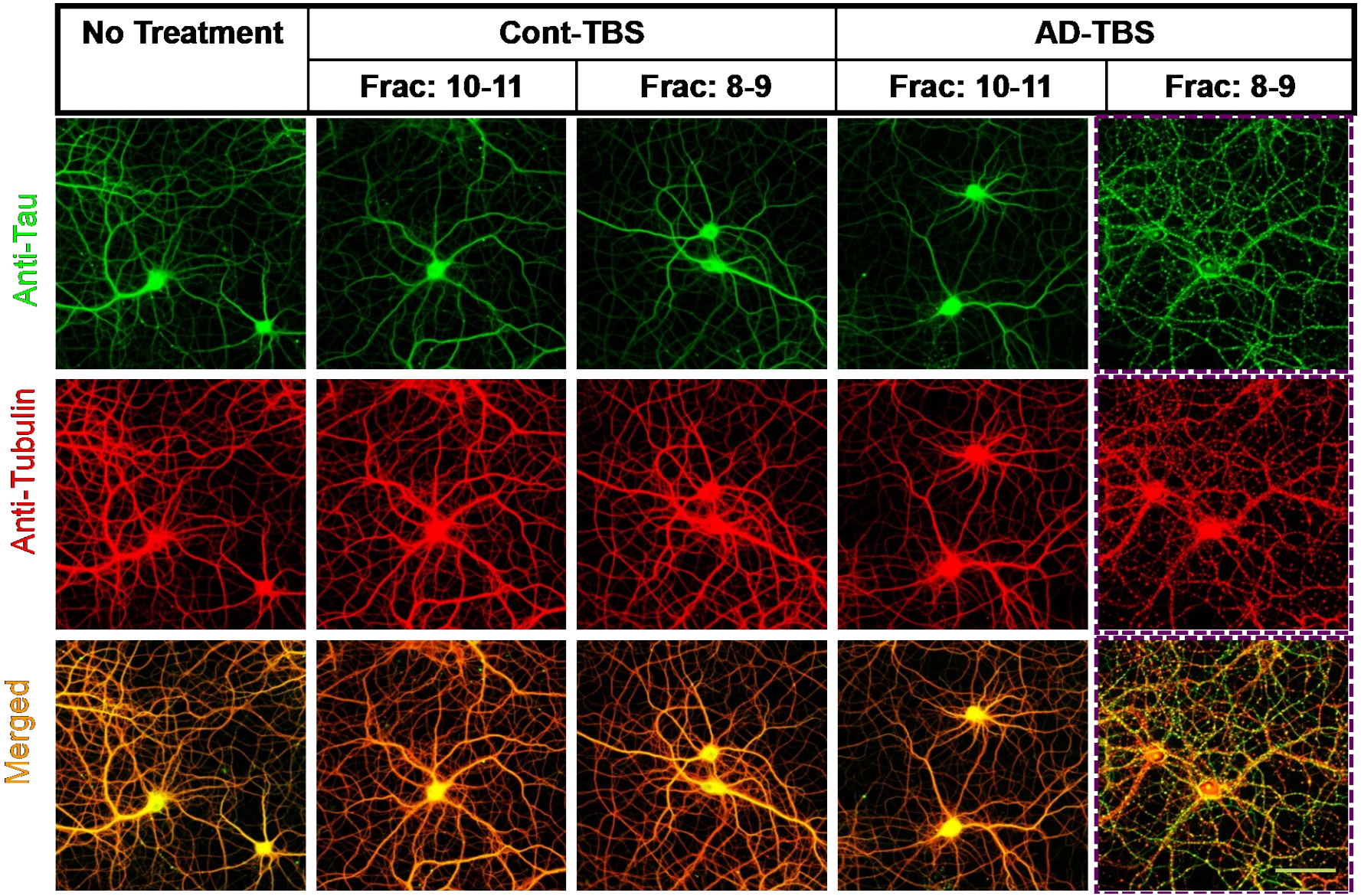
- Endogenous Aβ monomers and dimers/oligomers can be isolated by SEC from saline extracts of AD cortex



Aβ, amyloid beta. AD, Alzheimer's disease. IP, immunoprecipitate. MW, molecular weight. SEC, size exclusion chromatography.

Jin et al, *PNAS* 2011

Aβ Dimers/Oligomers from AD Cortex Induce Neurite Dystrophy After Treatment of Normal Rat or Human Neurons

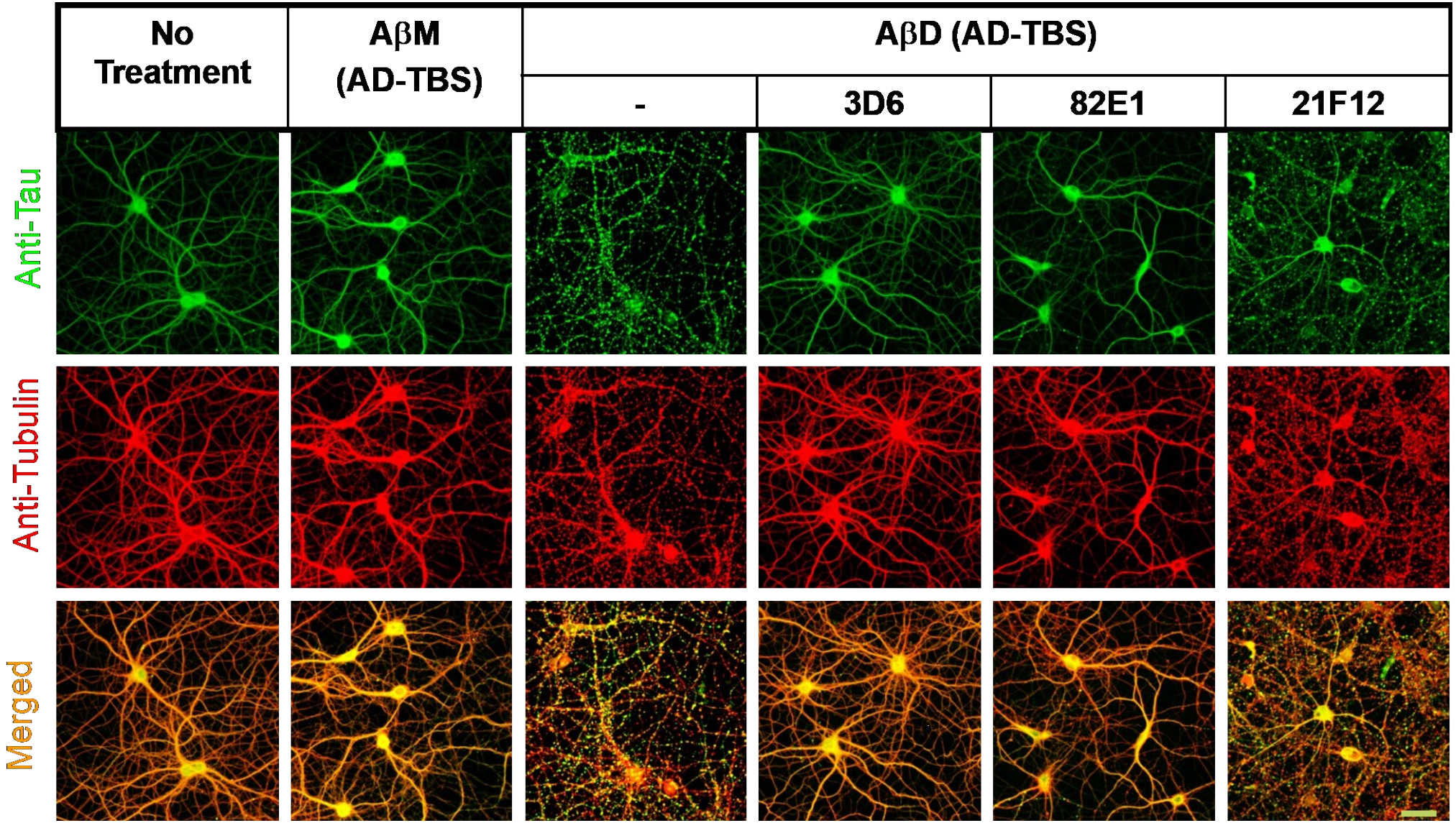


…and oAß increases pTau levels in neurons

Aβ, amyloid beta.
AD, Alzheimer's disease.
Con, control.
oAβ, oligomers of Aβ.
TBS, tris-buffered saline.

Jin et al, *PNAS* 2011

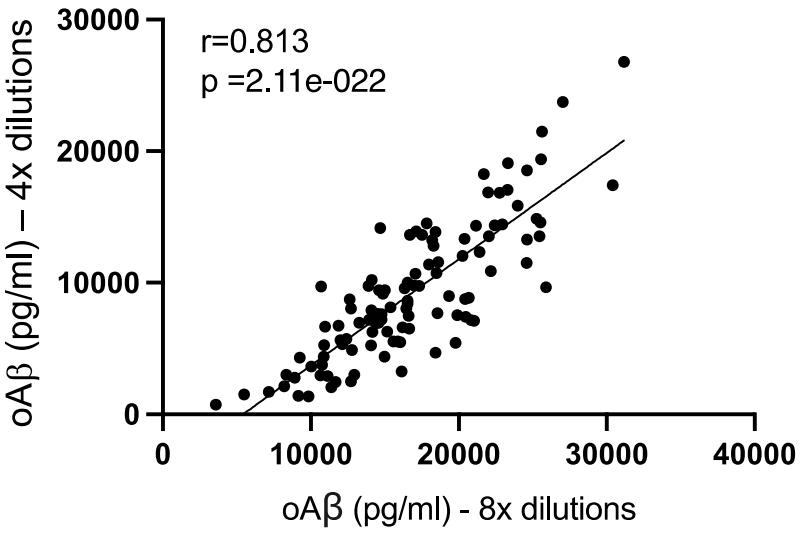
Antibodies to the N- but Not the C-terminus of Aβ Prevent Aβ Oligomer-Induced Neuritic Dystrophy

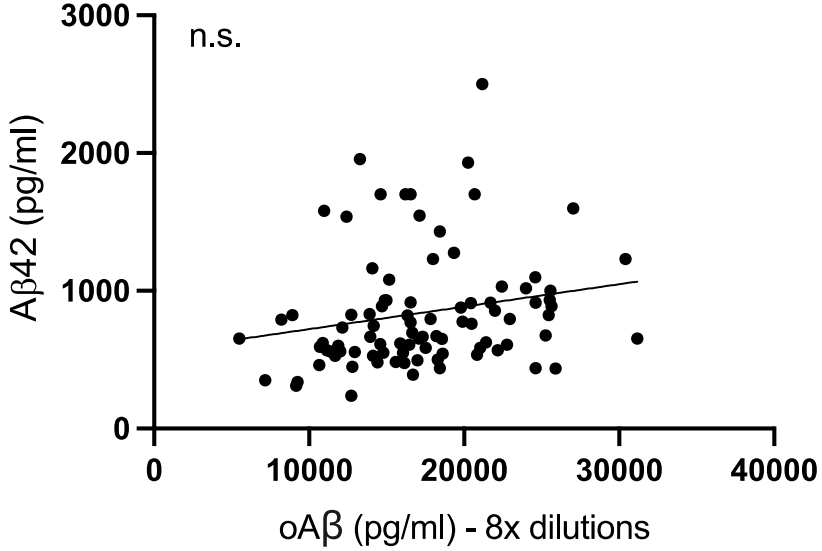


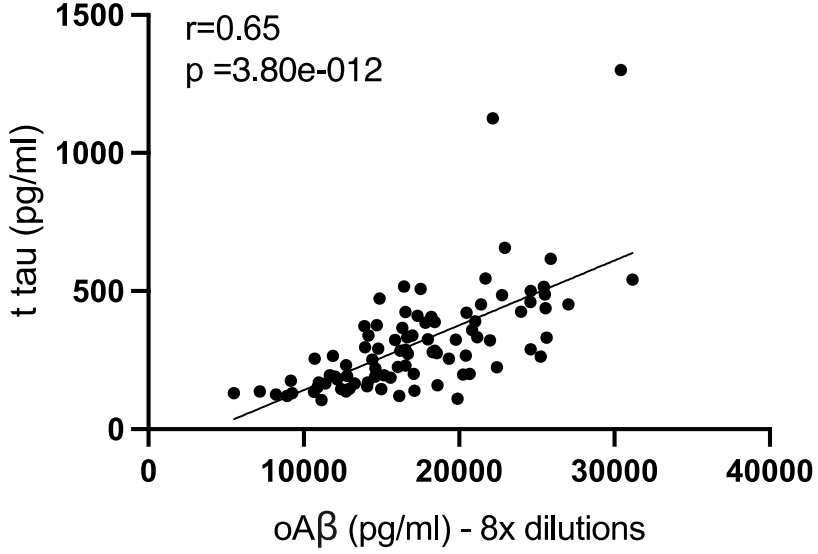
Aβ, amyloid beta.
AD, Alzheimer's disease.
Con, control. M, monomer.
TBS, tris-buffered saline.

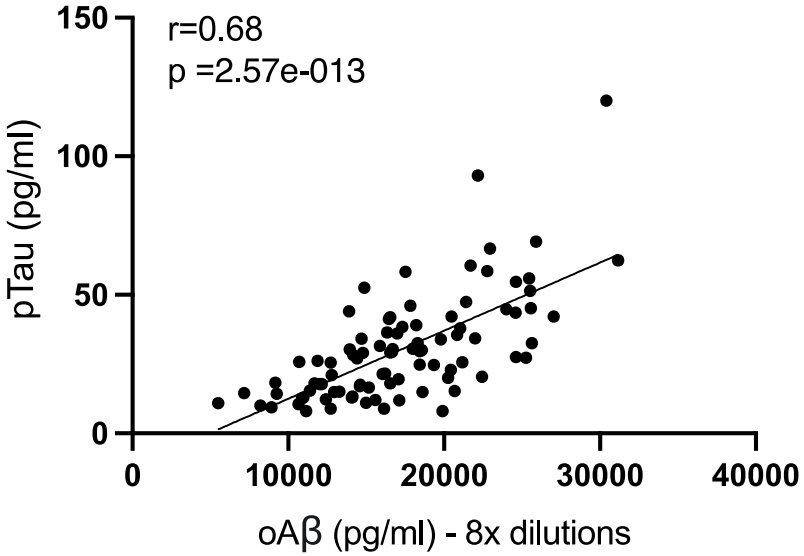
Jin et al, *PNAS* 2011

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





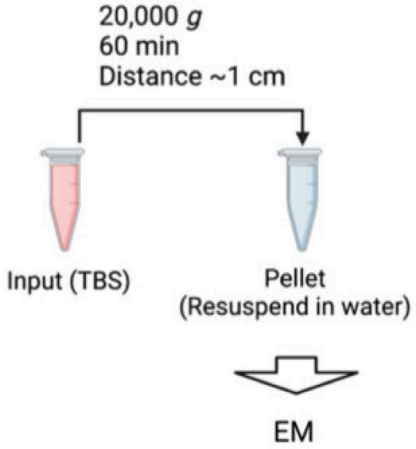


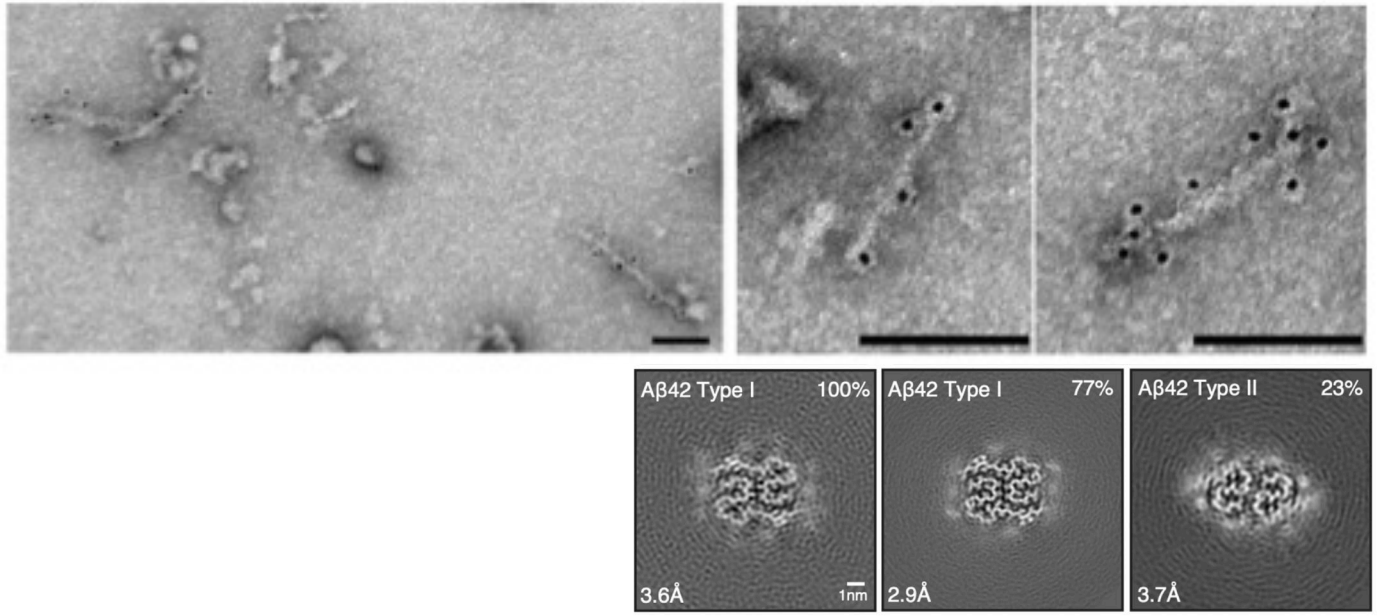


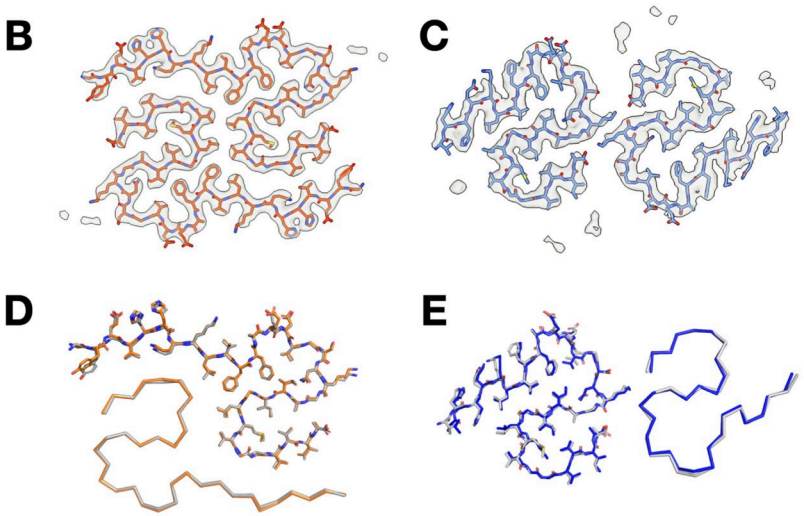
Aβ, amyloid beta.
CSF, cerebrospinal fluid.
ELISA, enzyme-linked immunosorbent assay.
oAβ, oligomers of Aβ.

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

Aqueous Soaking Extracts of AD Cortex Contain Diffusible Aβ Fibrils



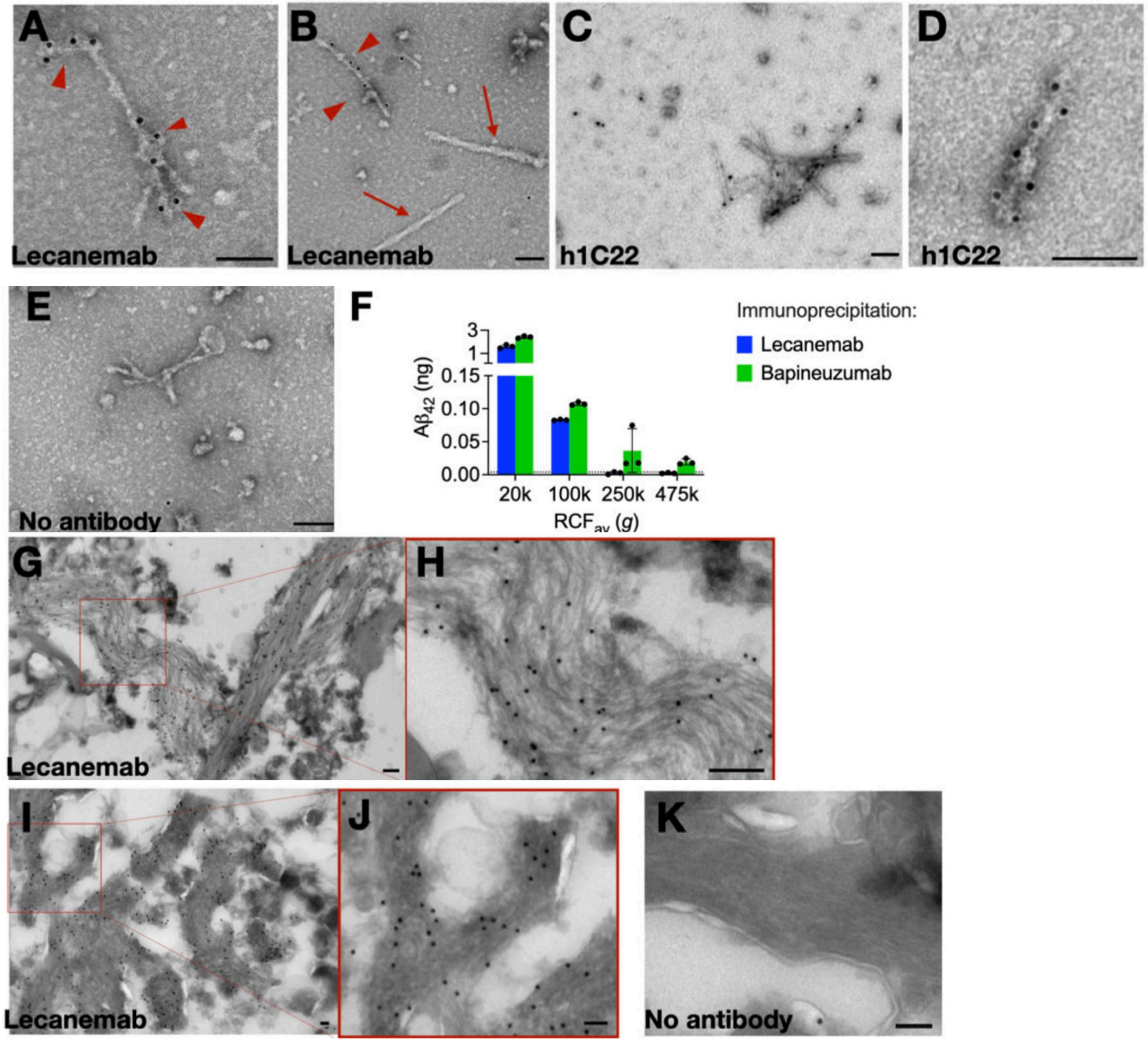




CryoEM of these diffusible fibrils reveals the same atomic structure as that of insoluble amyloid fibrils from plaque-rich cortex

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

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

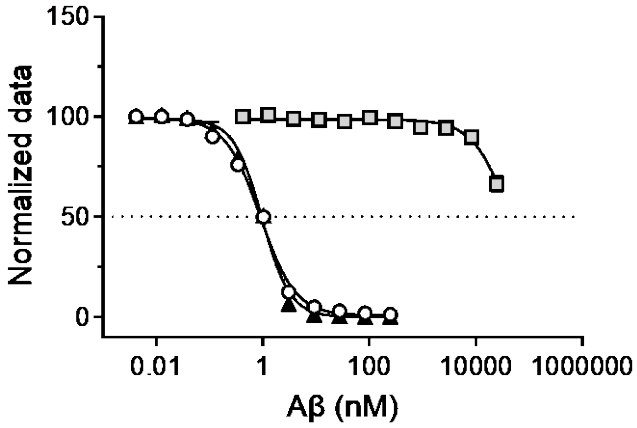


Aβ, amyloid beta.
AD, Alzheimer's disease.
RCF_{av}, average relative centrifugal force.

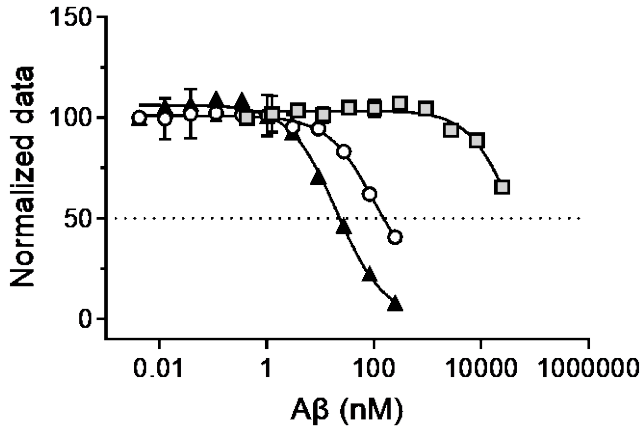
Stern et al, *Neuron*, 2023

Lecanemab Preferential Binding to Soluble Aβ Protofibrils

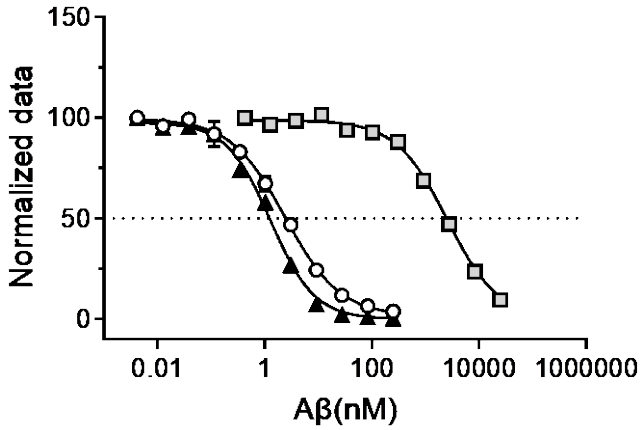
Lecanemab



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.

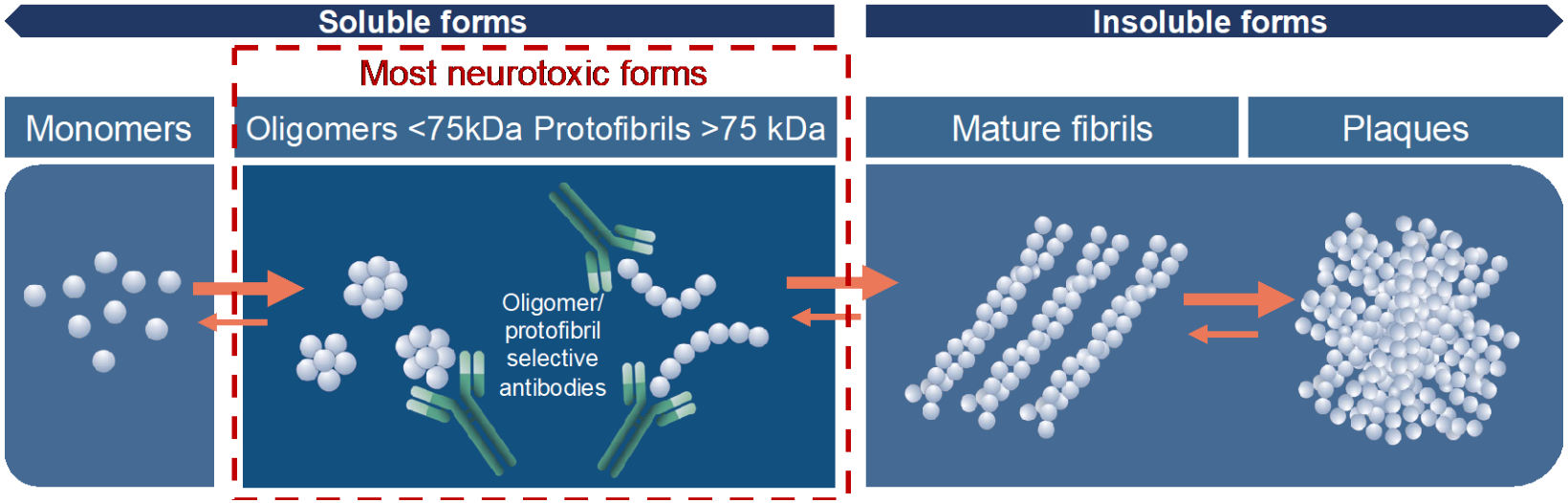
Lecanemab Unique Dual-Action Mechanism:

Targets Highly Toxic Protofibrils and Rapidly Clears Amyloid Plaques

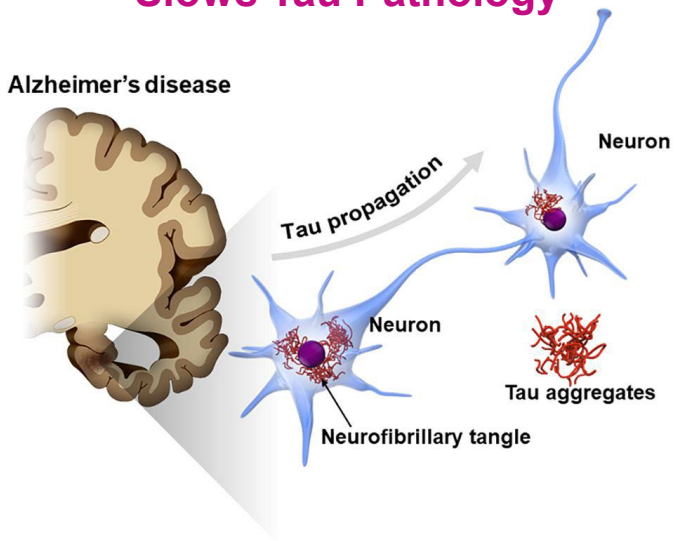
Lecanemab Dual Mechanism

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.

How Does the Latest Clinical Pharmacology Data & Modeling Support Continued Lecanemab Dosing?

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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

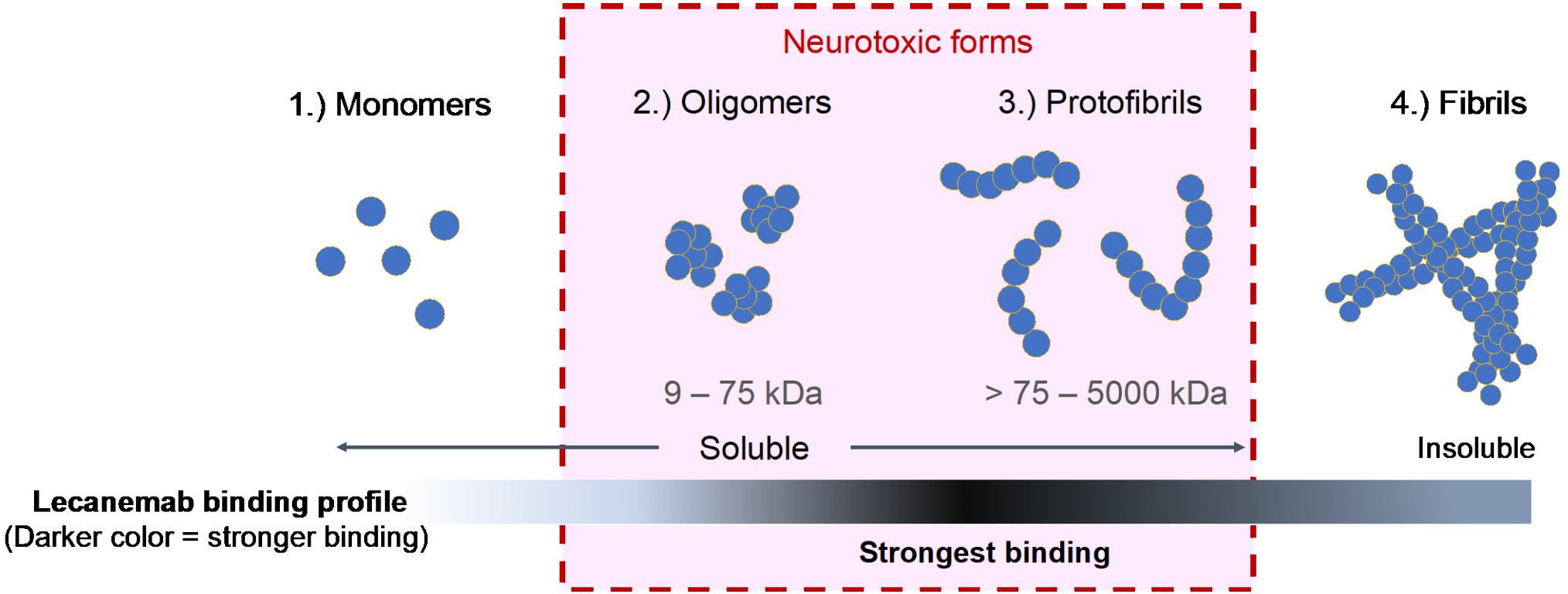
Eisai Inc. Nutley, NJ USA

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

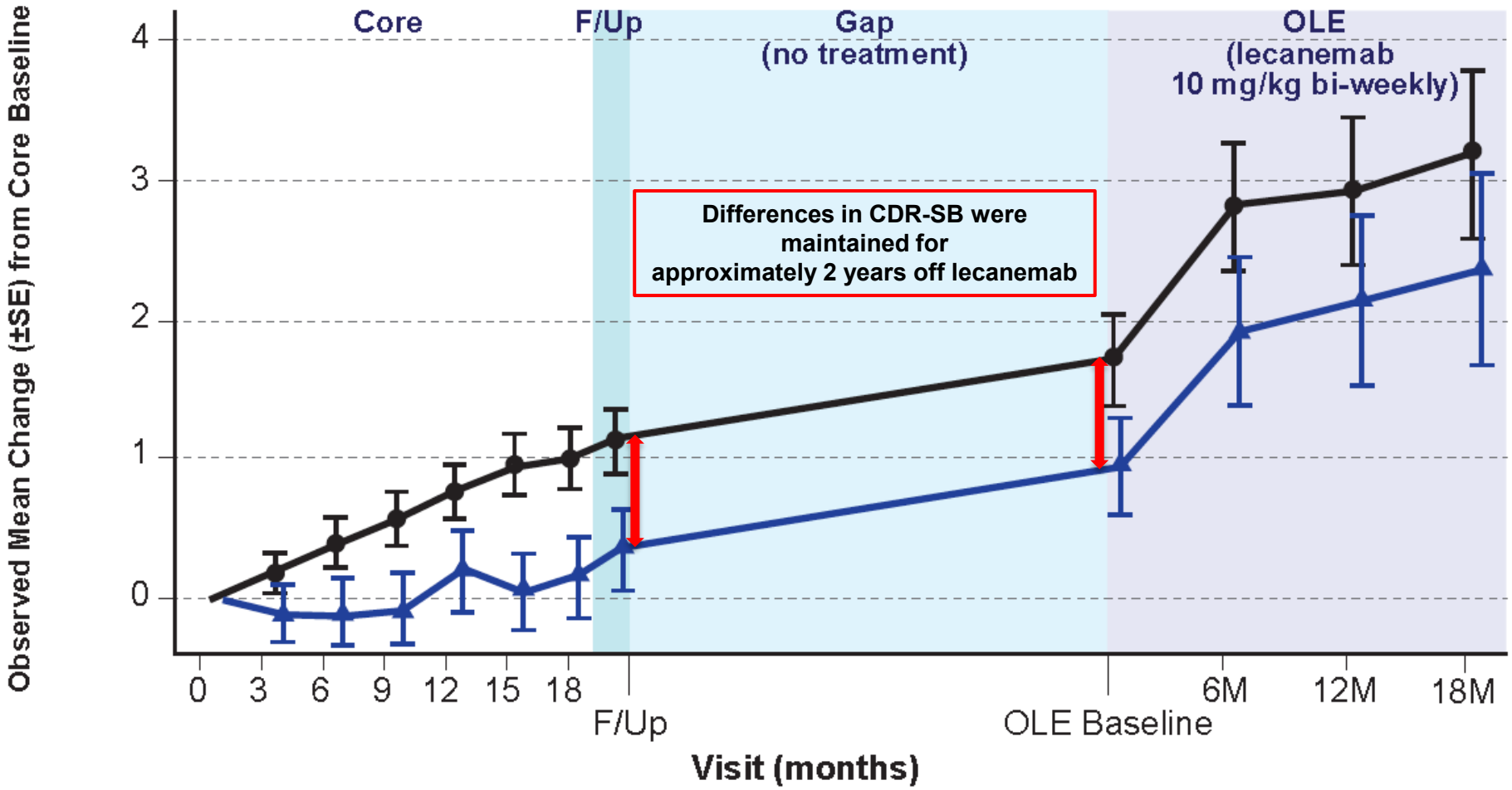


Protofibrils and oligomers continue to be produced even after plaques are cleared, providing mechanistic justification for ongoing treatment with lecanemab to maintain clinical and biomarker efficacy

Aβ, amyloid beta.

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

CDR-SB



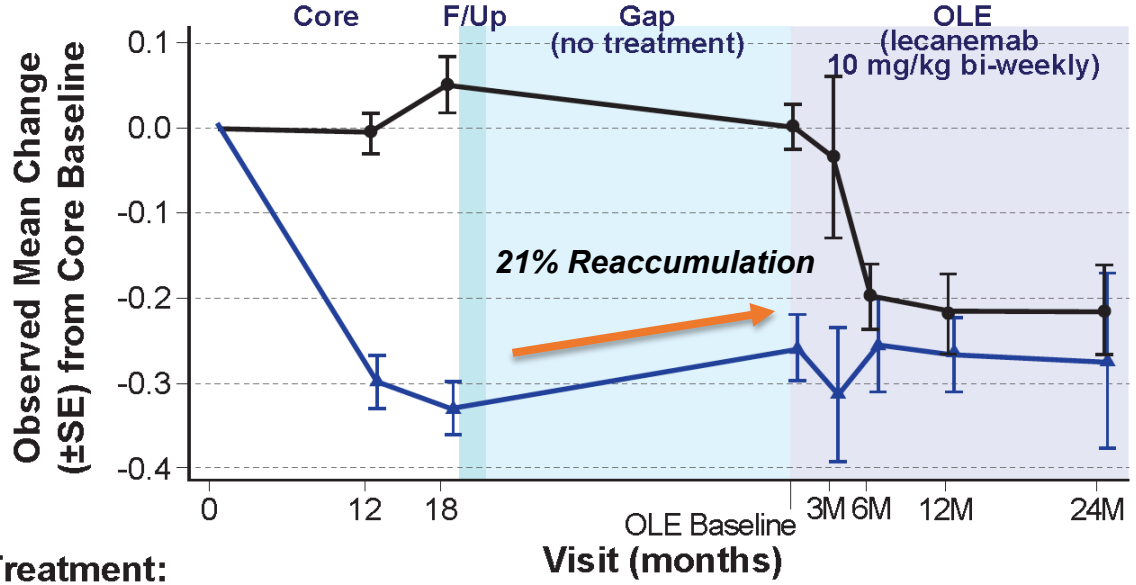
Core Treatment:												
Placebo:	40	40	39	39	39	35	35	35	40	37	33	29
10 bi-Weekly:	31	31	30	30	29	29	29	29	31	30	27	24

- **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.

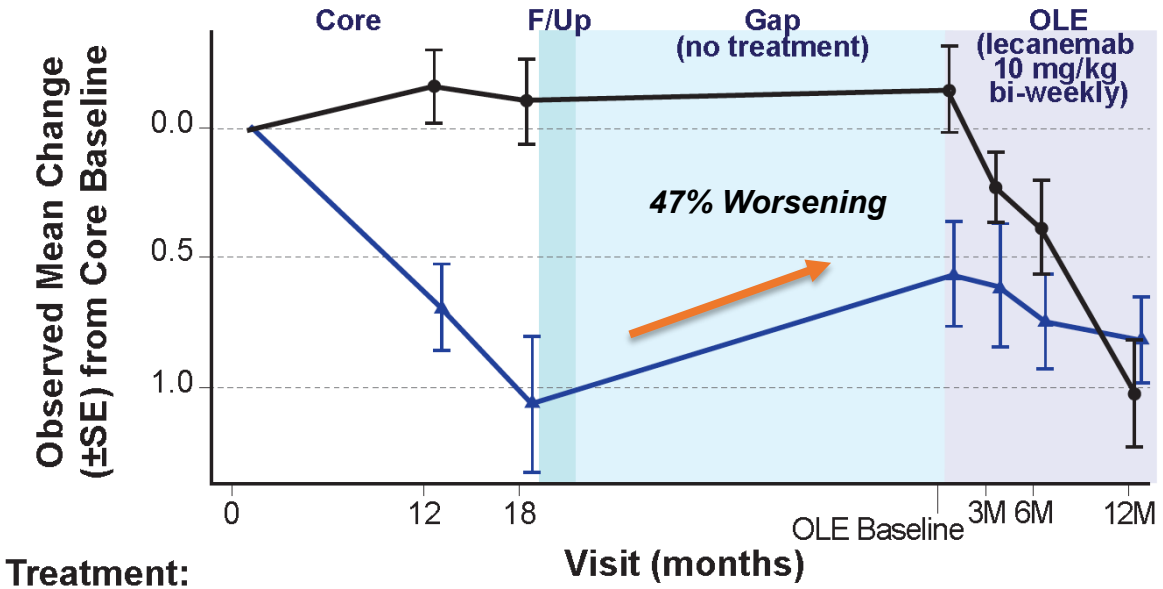
Interrupting Treatment is Associated with Variable Rates of Reaccumulation of AD Biomarkers: Amyloid PET & Aβ42/40 Ratio (Study 201)

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

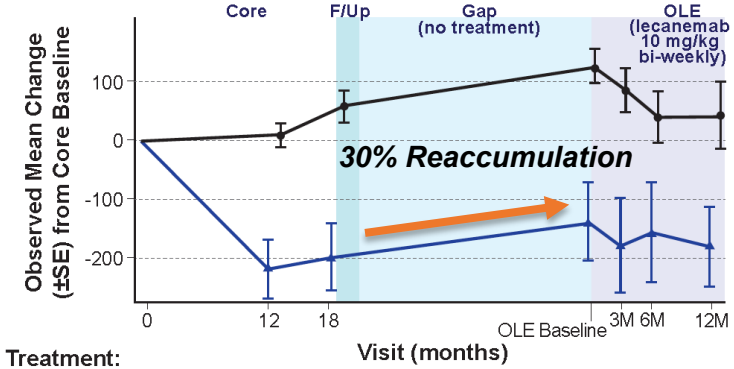
Long-term therapy continues to improve biomarkers further, and avoid the reaccumulation of biomarkers when anti-amyloid treatment is stopped

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

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

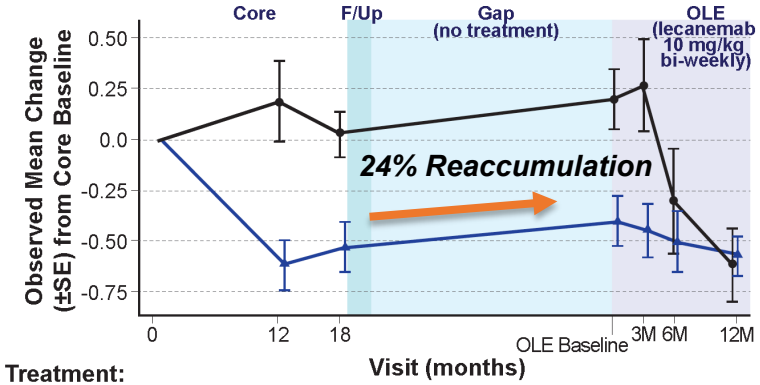
Interrupting Treatment is Associated with Reaccumulation of AD Pathology: GFAP, pTau181 & pTau217 (Study 201)

GFAP



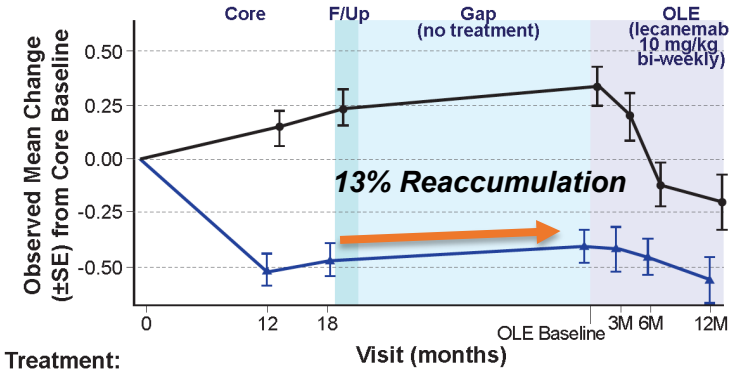
Core Treatment:							
Placebo:	22	22	21	22	22	20	15
10 bi-Weekly:	23	21	23	23	19	21	16

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.

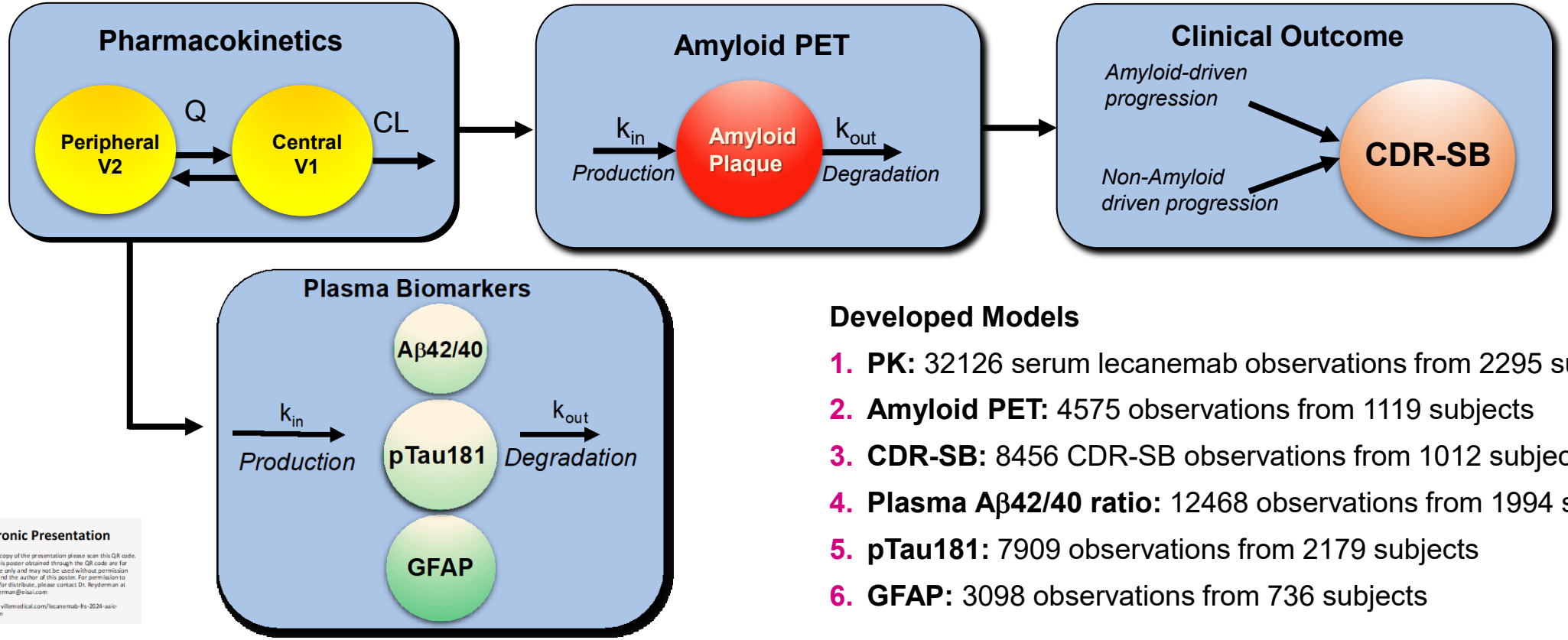
WHAT IS THE IDEAL MAINTENANCE DOSING REGIMEN WITH LECANEMAB AFTER AMYLOID CLEARANCE?

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



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

Electronic Presentation

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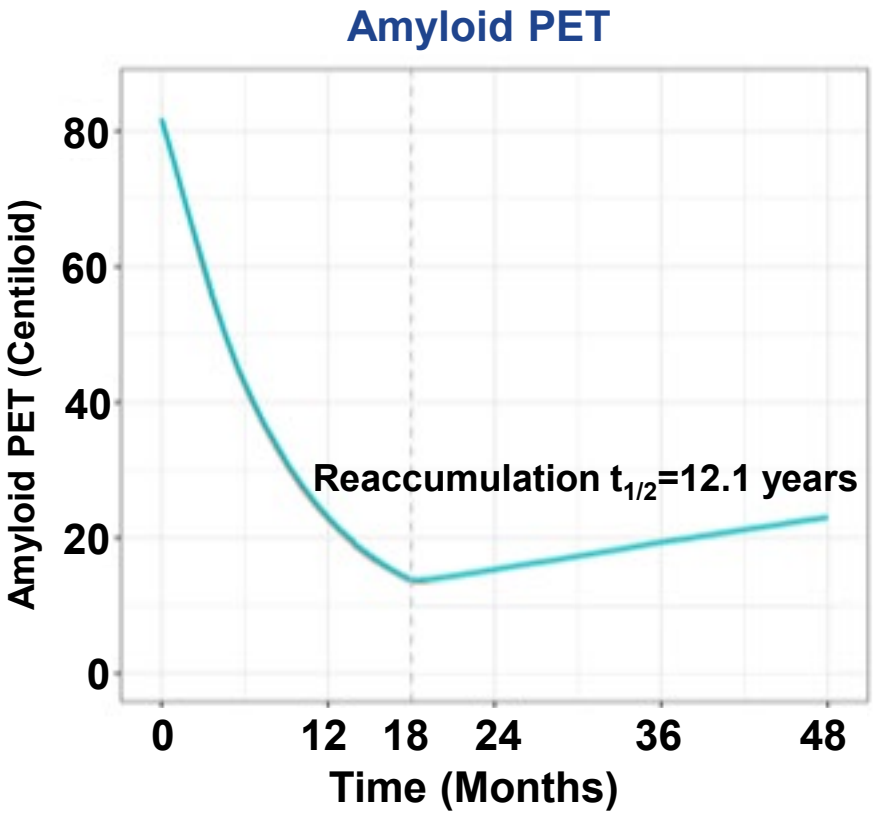
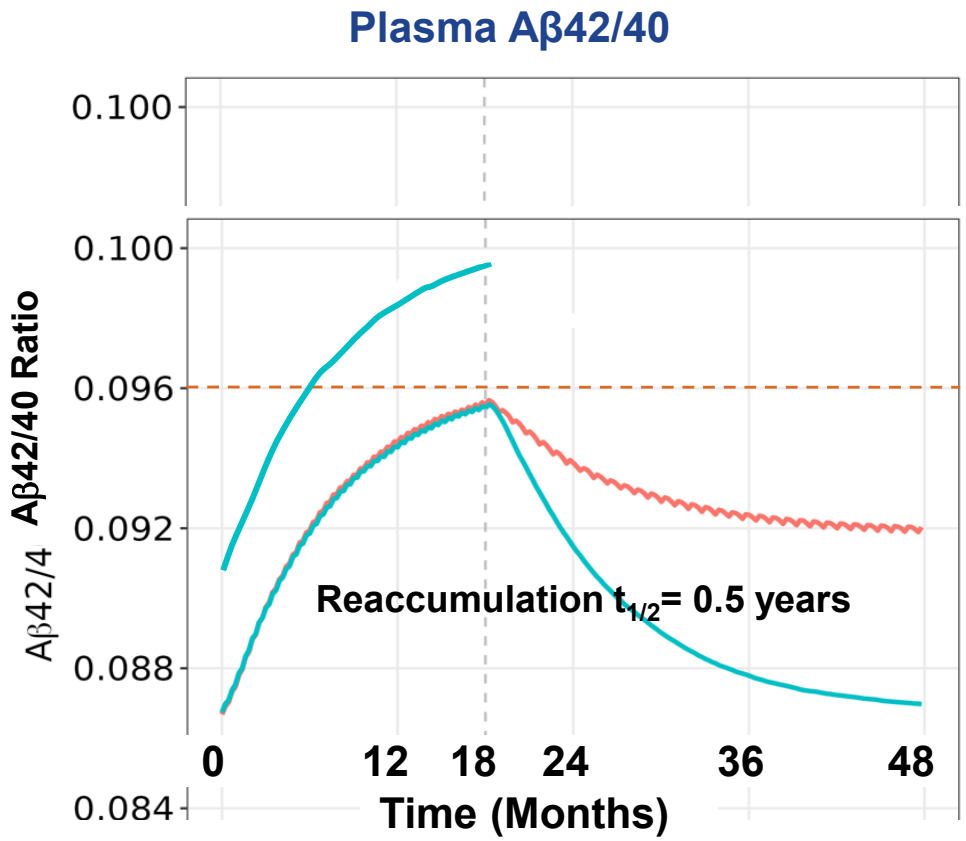
https://mayvillemedical.com/lecanemab-frs-2024-aaic-presentation

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

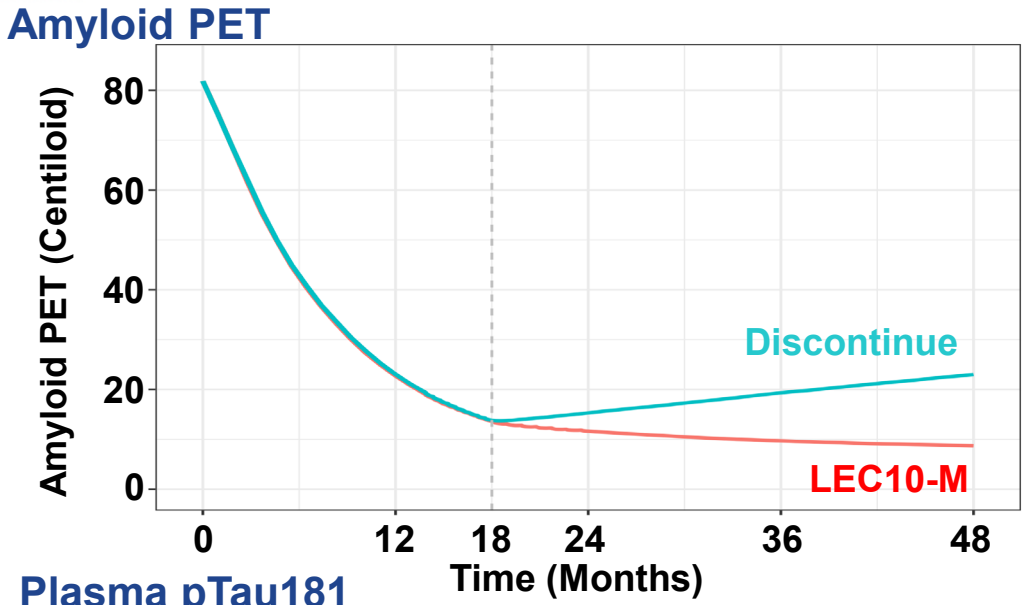


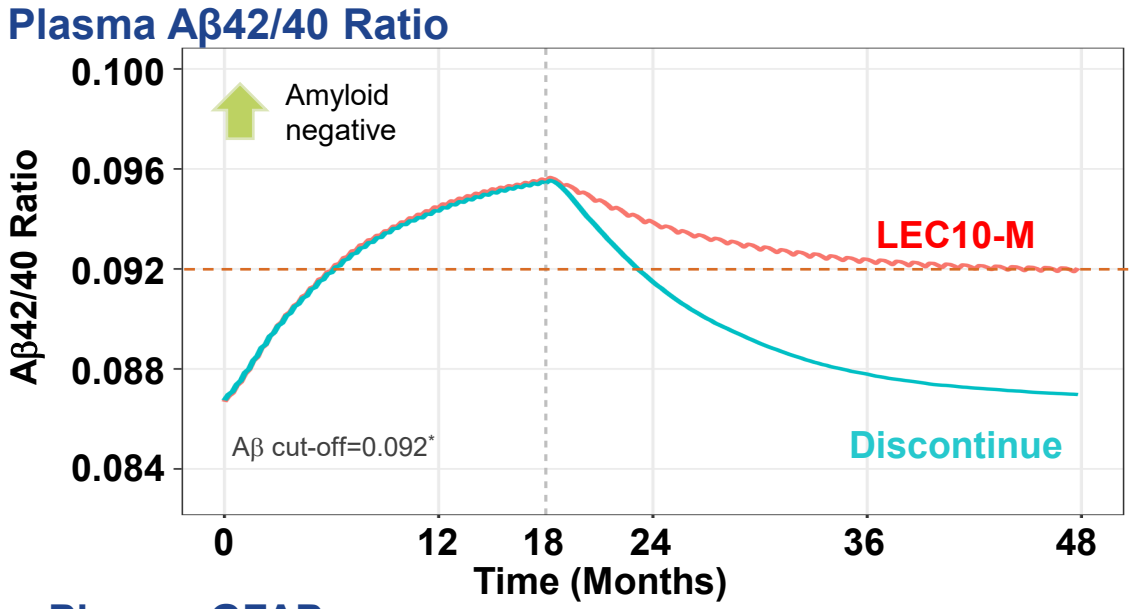


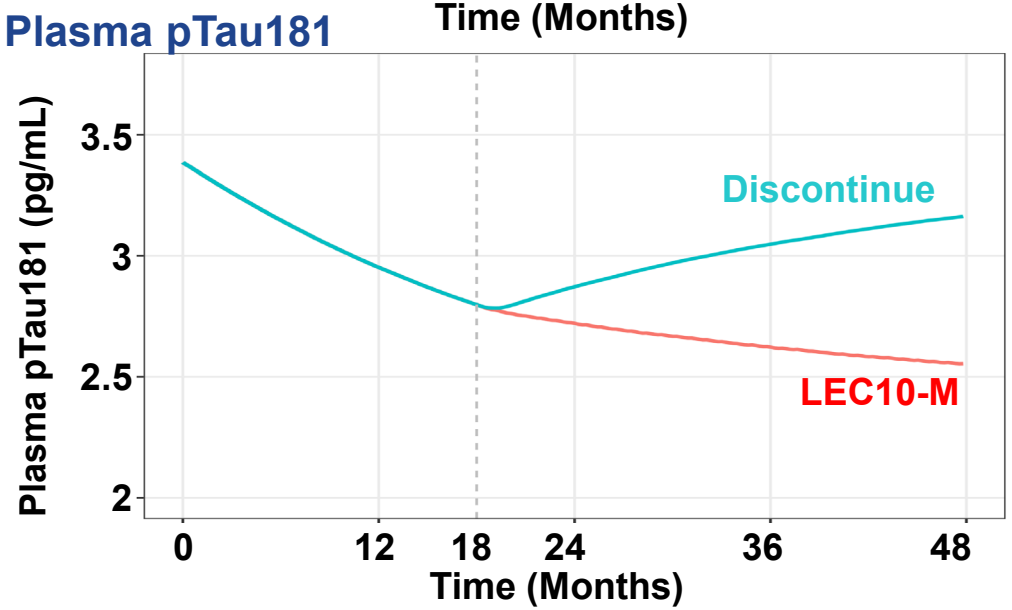
- Changes in fluid biomarkers on treatment discontinuation are more sensitive measures of disease progression
  - Half the treatment effect on Aβ42/40 ratio is lost within 6 months while half the treatment effect on amyloid PET is lost within 12.1 years
  - Similar loss of treatment effect observed for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

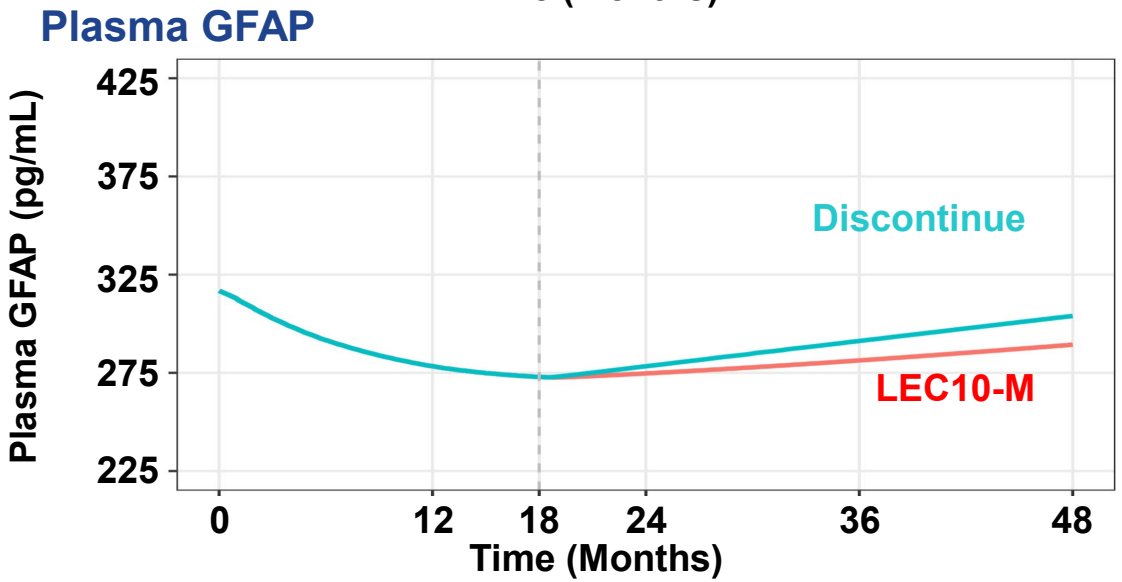
Aβ, amyloid beta. PET, positron emission tomography. pTau181, phosphorylated tau 181. pTau217, phosphorylated tau 217.

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



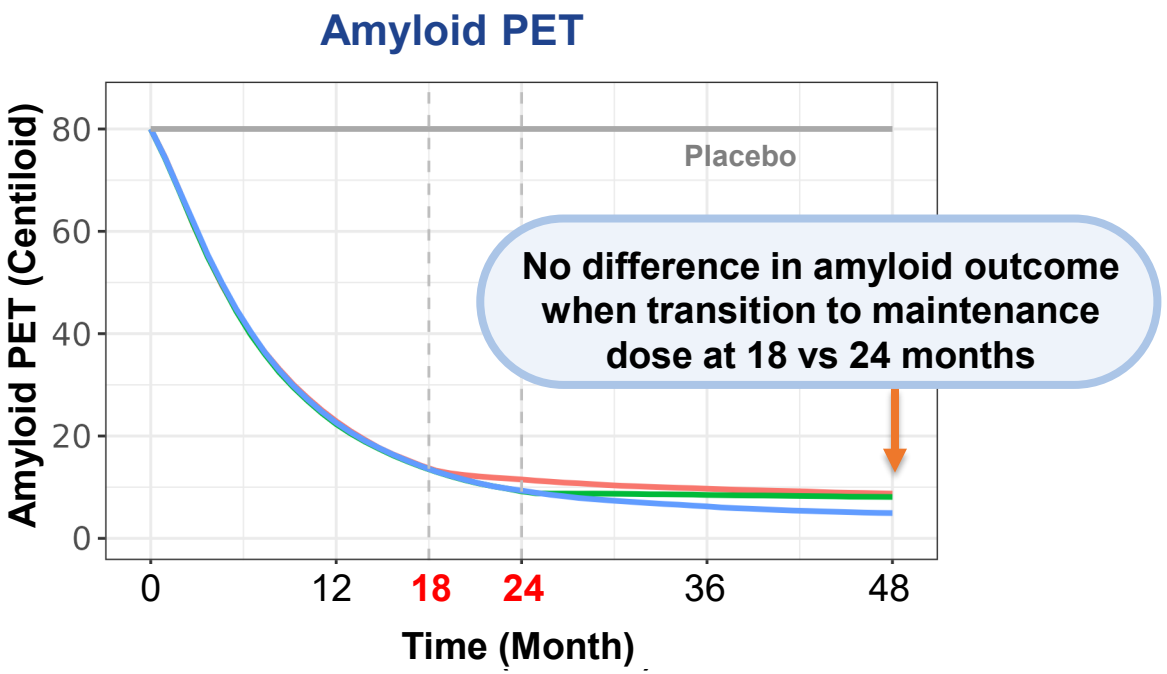


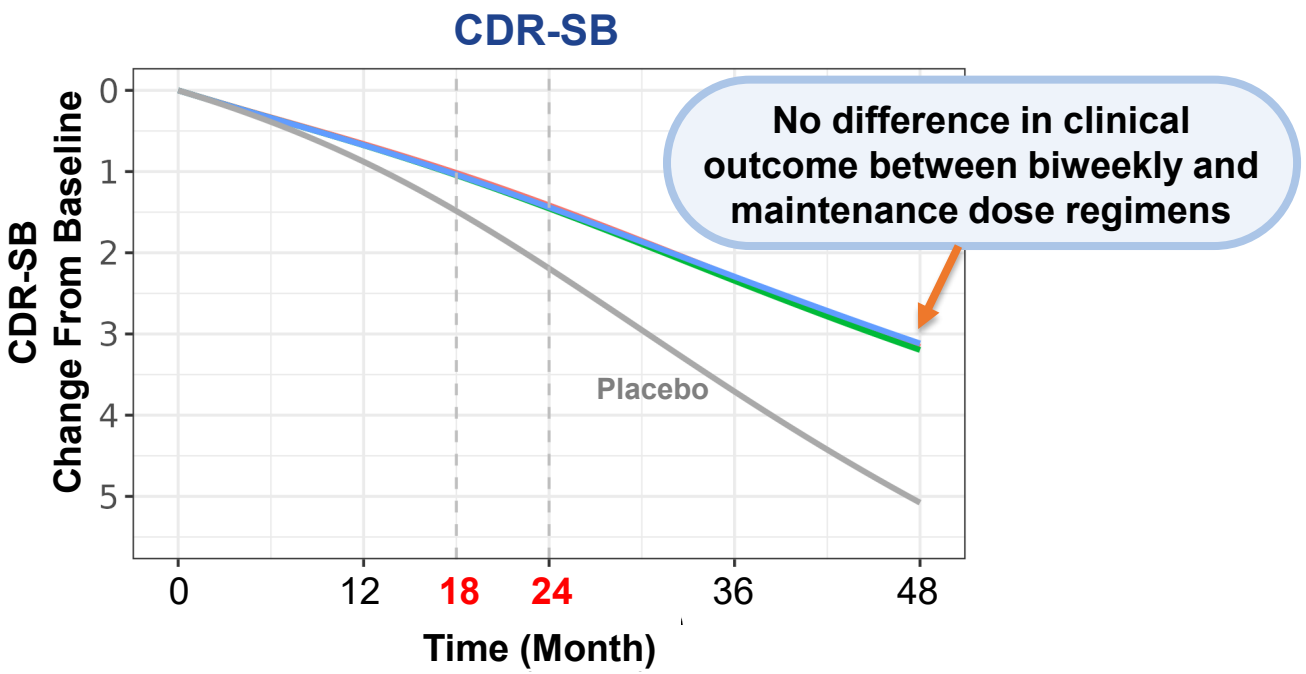




Aβ, amyloid beta. GFAP, glial fibrillary acidic protein. LEC10-M, lecaneamb 10 mg/kg monthly. PET, positron emission tomography. pTau181, phosphorylated tau 181. *Verbel et al. 14th Annual CTAD Conference. 2021. Boston, MA. USA.

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





Time of Maintenance Initiation

- 18 months LEC10-M
- 24 months LEC10-M
- Continuous LEC10-BW
- Placebo

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.

Neuro-Dynamic Quantitative Systems Pharmacology (QSP) Model Supports Continued Lecanemab Treatment With Maintenance Dosing For Alzheimer's Disease

July 30, 2024

Youfang Cao

Eisai Inc. Nutley, NJ. USA.

Disclosures and Acknowledgements

Disclosures:

- YC is an employee of Eisai

- KH is an Eisai-sponsored voluntary research associate professor at Washington University and has received salary from Eisai
- KH may receive income based on technology licensed by Washington University to C2N Diagnostics

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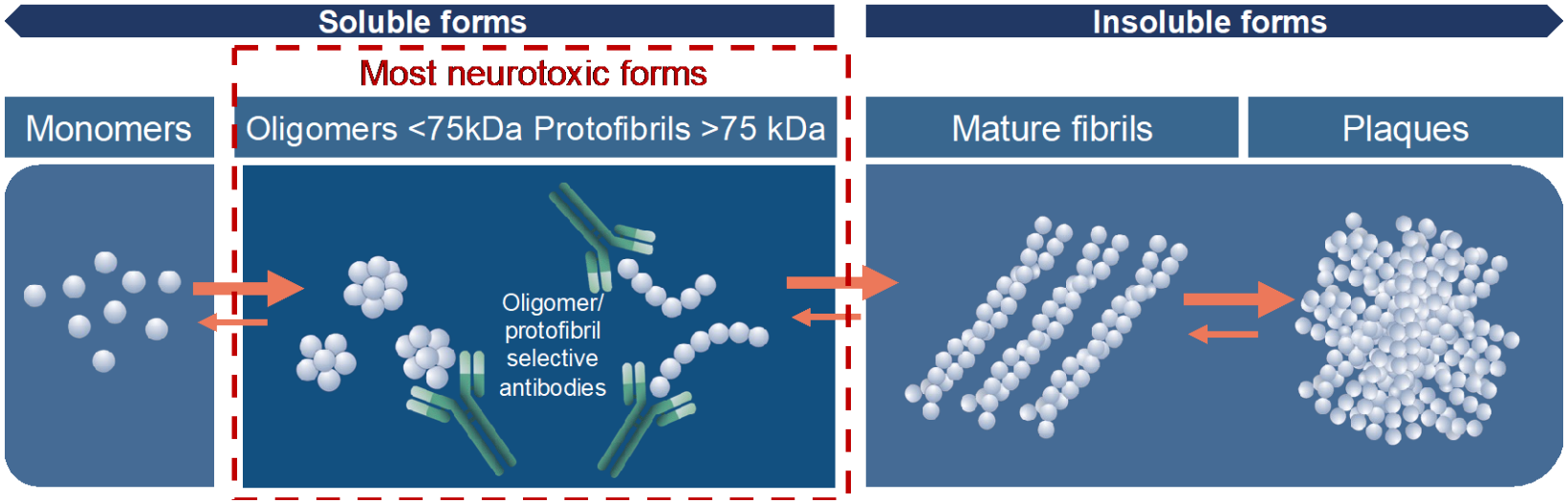
Lecanemab Unique Dual-Action Mechanism:

Targets Highly Toxic Protofibrils and Rapidly Clears Amyloid Plaques

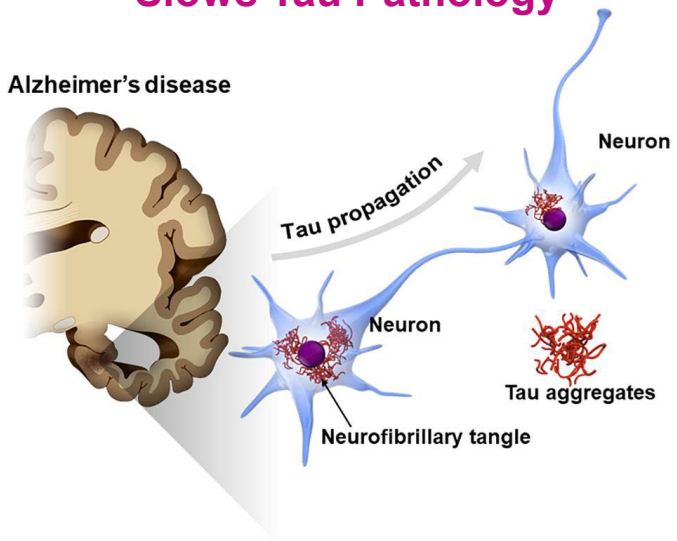
Lecanemab Dual Mechanism

Lecanemab Targets Protofibrils

Lecanemab Clears Plaques



Lecanemab Slows Tau Pathology



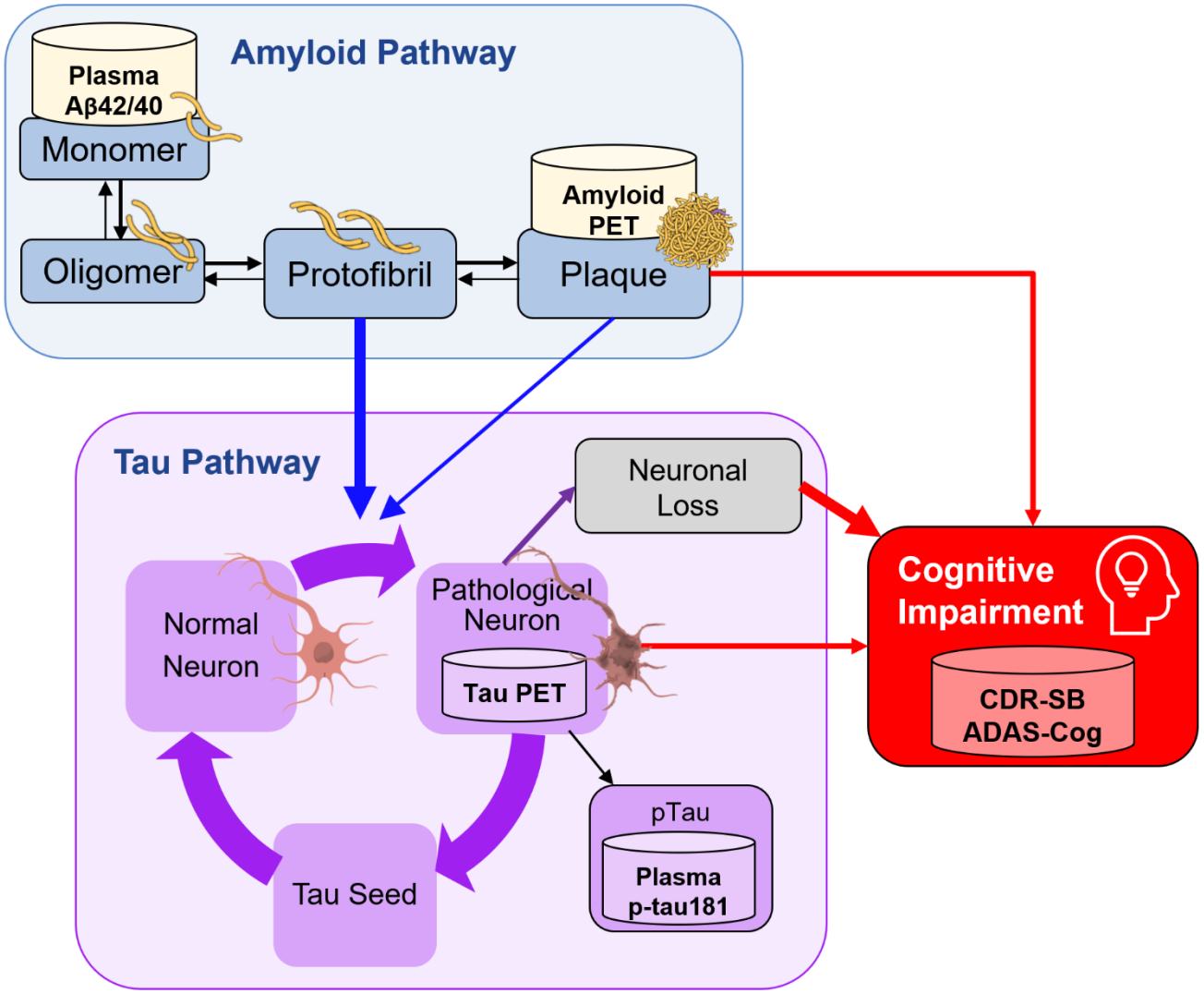
- The unique dual action of lecanemab rapidly clears amyloid plaque and highly toxic protofibrils[1-5]
  - Selectively binds to soluble Aβ aggregated species, with preferential activity for Aβ protofibrils over monomers (>1000x) and over fibrils (>10x)[1,6-10]
- Slows tau pathology in temporal lobe (early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

Neuro-Dynamic Quantitative Systems Pharmacology (QSP) Model

Incorporates Key Mechanisms of Alzheimer's Disease Pathophysiology

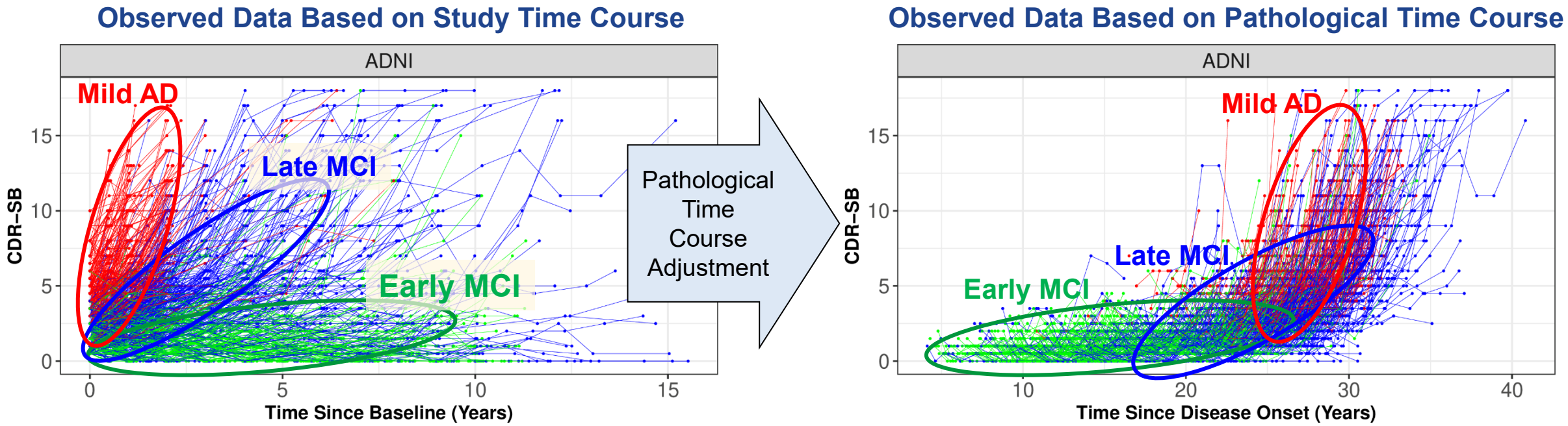


- **A mechanistic yet parsimonious model for AD pathophysiology:**
  - 11 equations and 74 parameters
- **Built the model on available literature evidence:**
  - Lecanemab binding affinities w/ protofibril vs plaque[1]
  - Amyloid monomer clearance rate[2]
  - Amyloid aggregation/deaggregation rates[3, 4]
  - Kinetics of tau isoforms in human neuron[5]
  - Tau pathology progression[6]
  - Effects of amyloid and tau in cognitive impairment[7]
- **Informed model parameters using a 6-dimensional dataset (N=4056):**
  - Clarity AD (Study 301)
  - Lecanemab Study 201
  - Alzheimer's Disease Neuroimaging Initiative (ADNI)

Aβ, amyloid beta. AD, Alzheimer's disease. ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale. CDR-SB, Clinical Dementia Rating-sum of boxes. PET, positron emission topography. QSP, Quantitative Systems Pharmacology.

1 Söderberg et al., Neurotherapeutics 2023. 2. May et al., J Neurosci 2015. 3. Michaels et al., Nature Chem 2020. 4. Dear et al., PNAS 2020. 5. Sato et al., Neuron. 2018. 6. Roberts et al. Acta Neuropathol Commun 2020. 7. Hanseeuw et al. JAMA Neurol 2019.

Aligning Individual Data on Pathological Time Course



The GRACE[1] approach was employed to adjust the relative AD pathological time for all the subjects in the QSP dataset.

Early MCI = Early Mild Cognitive Impairment: ADNI GO/2
Late MCI = Late Mild Cognitive Impairment: ADNI GO/2
Mild AD = Mild Alzheimer's disease dementia

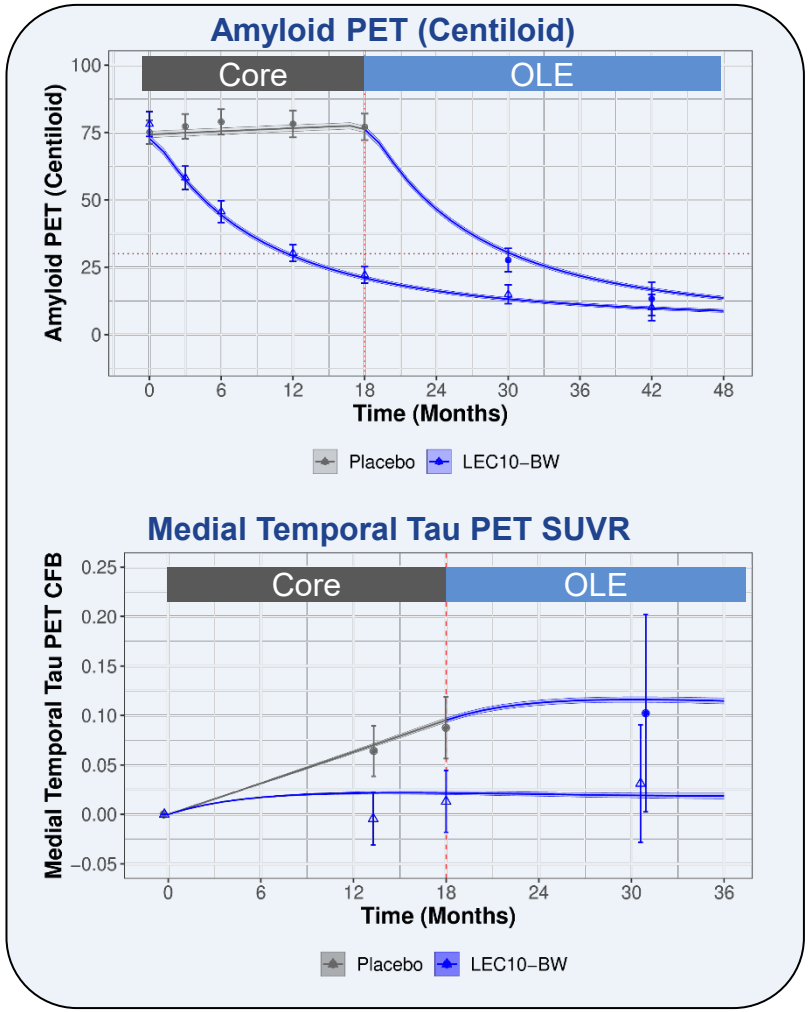
1. Donohue et al. 2014 Alzheimers Dement.

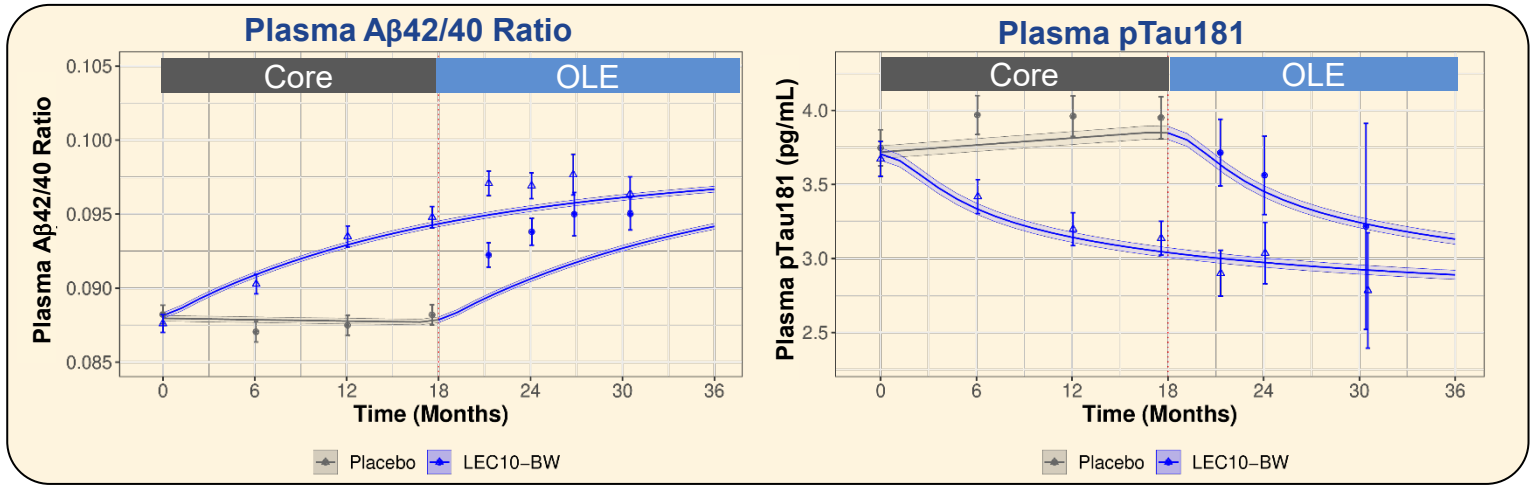
GRACE: Growth Models via Alternating Conditional Expectations.

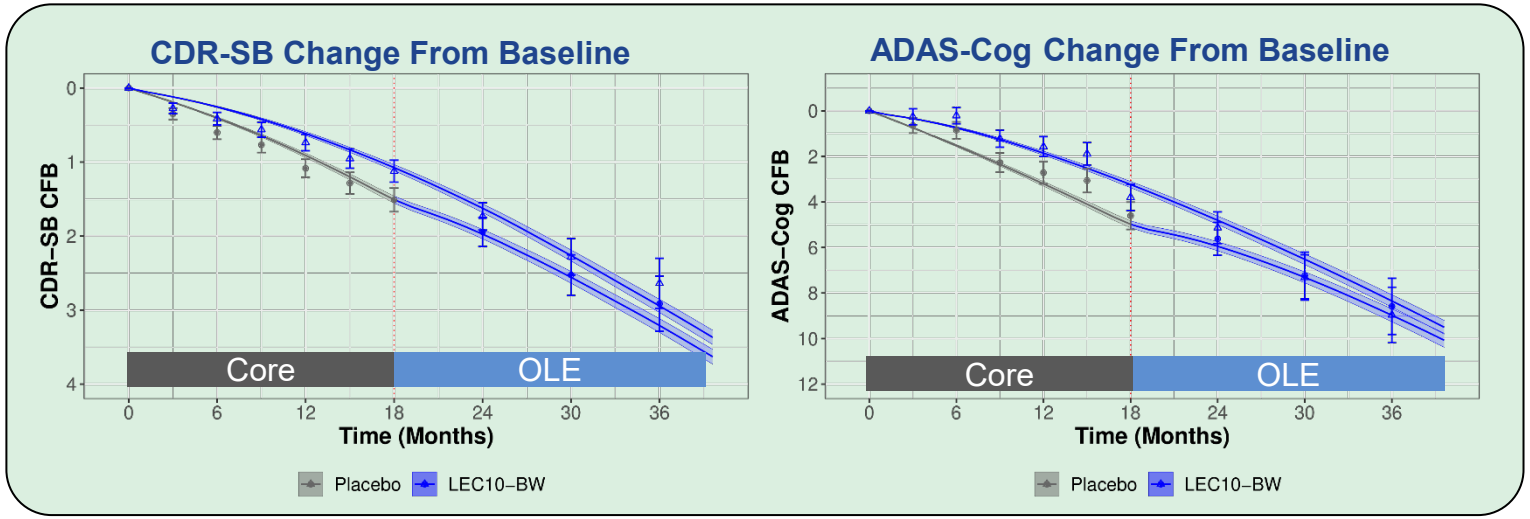
AD, Alzheimer's disease. ADNI, Alzheimer's Disease Neuroimaging Initiative. CDR-SB, Clinical Dementia Rating-sum of boxes. MCI, mild cognitive impairment.

QSP Model

Accurately Describes Six Key Outcomes From Clarity AD







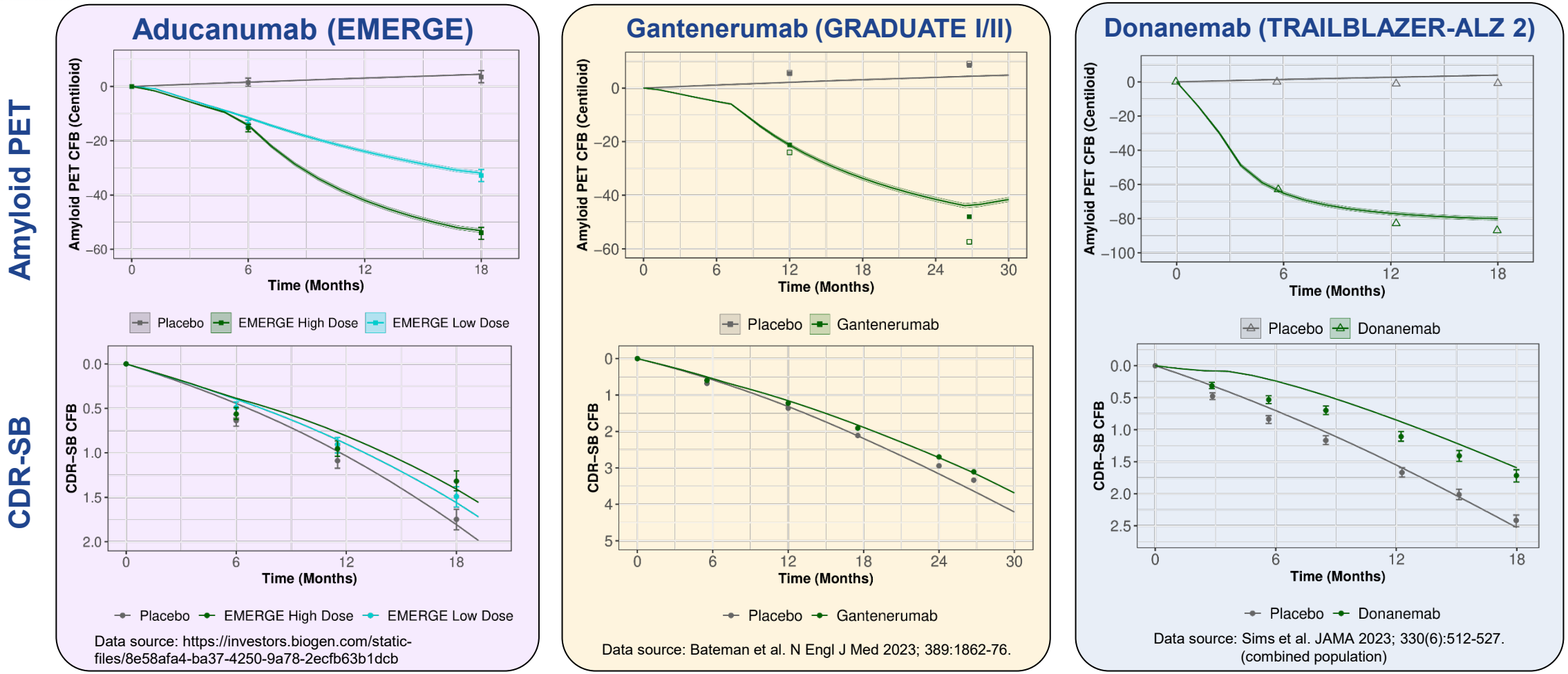
Simulations conducted using a virtual patient population of N=5000 created from the QSP model with matched baseline characteristics of Clarity AD population.

Note: Solid lines and dots represent the mean from simulations and data, respectively. Error bars and shaded areas are 95%ile CI.

Aβ, amyloid beta. AD, Alzheimer's disease. ADNI, Alzheimer's Disease Neuroimaging Initiative. ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale. CDR-SB, Clinical Dementia Rating-sum of boxes. CFB, change from baseline. LEC10-BW, lecanemab 10 mg/kg biweekly. PET, positron emission topography. ptau181, phosphorylated tau-181. QSP, Quantitative Systems Pharmacology. SUVR, standardized uptake value ratio.

QSP Model

Predicts Clinical Outcomes of Anti-Amyloid Treatments



Note: Solid lines and shaded areas represent the mean dynamics and 95% confidence intervals from QSP simulations. Dots and error bars represent the mean and 95% confidence intervals from data.

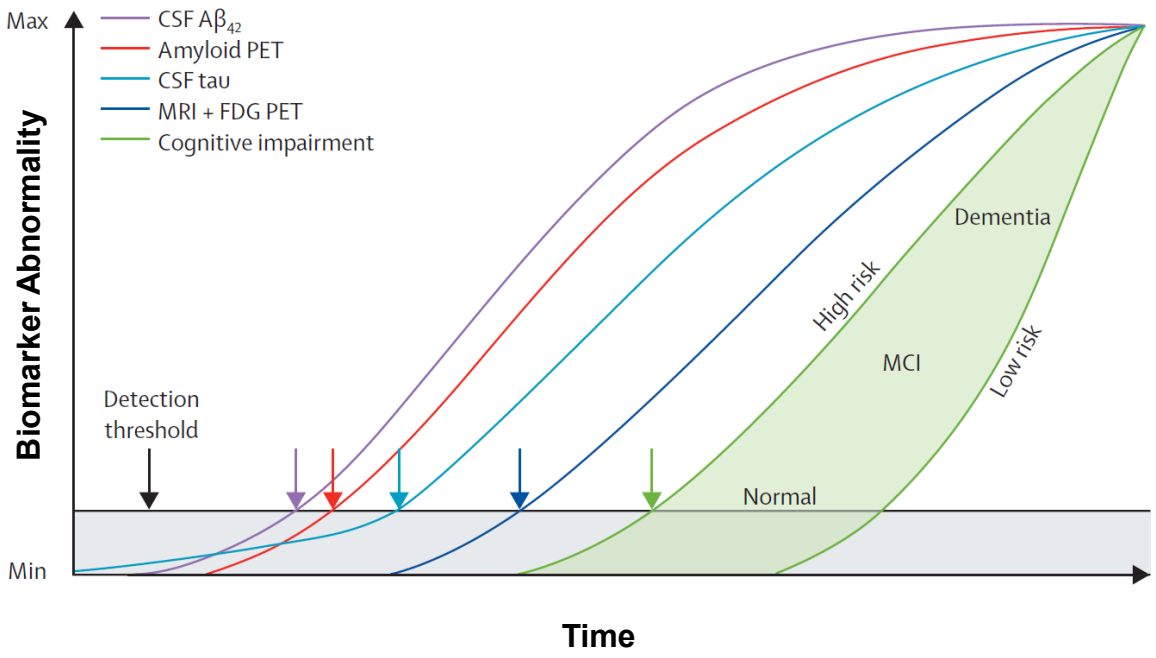
- Drug effect parameters were tuned to capture amyloid PET data for each mAb. Literature binding affinities were used when available
- QSP parameters of AD pathophysiology remained unchanged across drugs
- Simulations were performed using virtual patient populations mimicking the baseline age, amyloid PET, and CDR-SB of corresponding clinical trials
- ApoE4 genotype was used to titrate the dose for aducanumab according to the study design. Simulations followed the dose titration study design of these trials

CDR-SB, Clinical Dementia Rating-sum of boxes. CFB, change from baseline. PET, positron emission topography. QSP, Quantitative Systems Pharmacology.

QSP Model

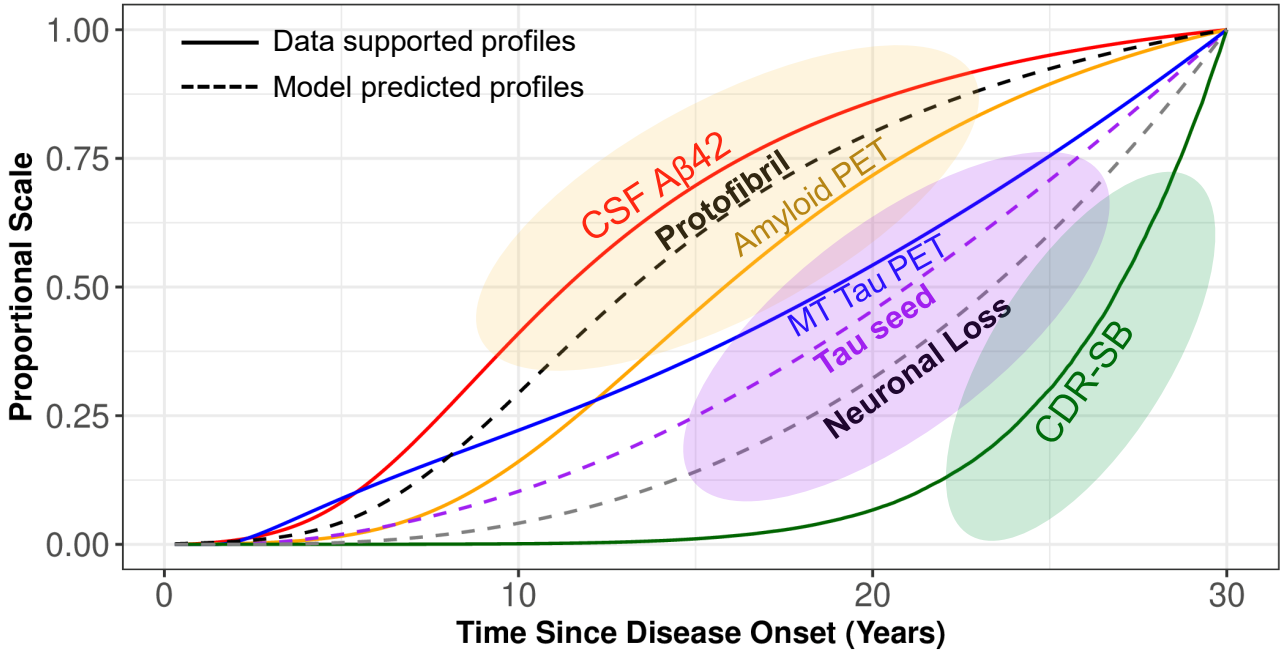
Describes AD Progression and Links Pathophysiology to Clinical Outcomes

AD Pathological Cascade



Jack et al. Lancet Neurol. 2013

QSP Simulated Pathological Cascade

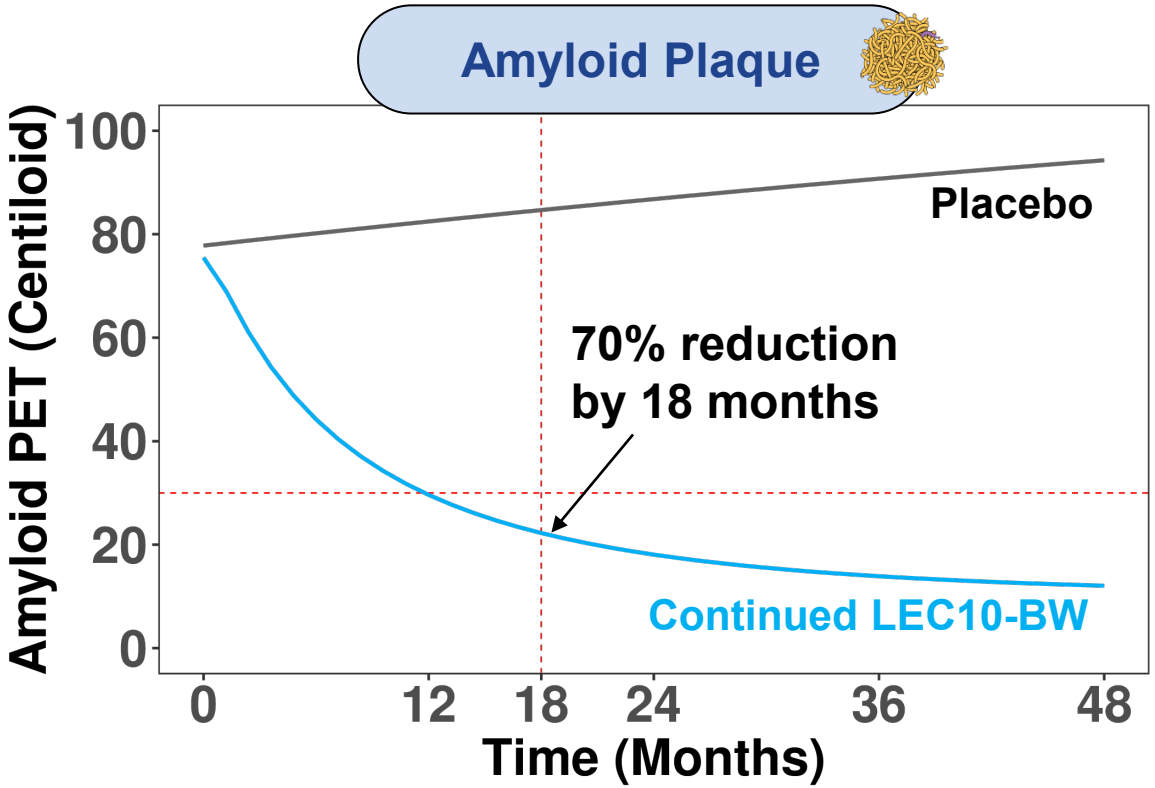


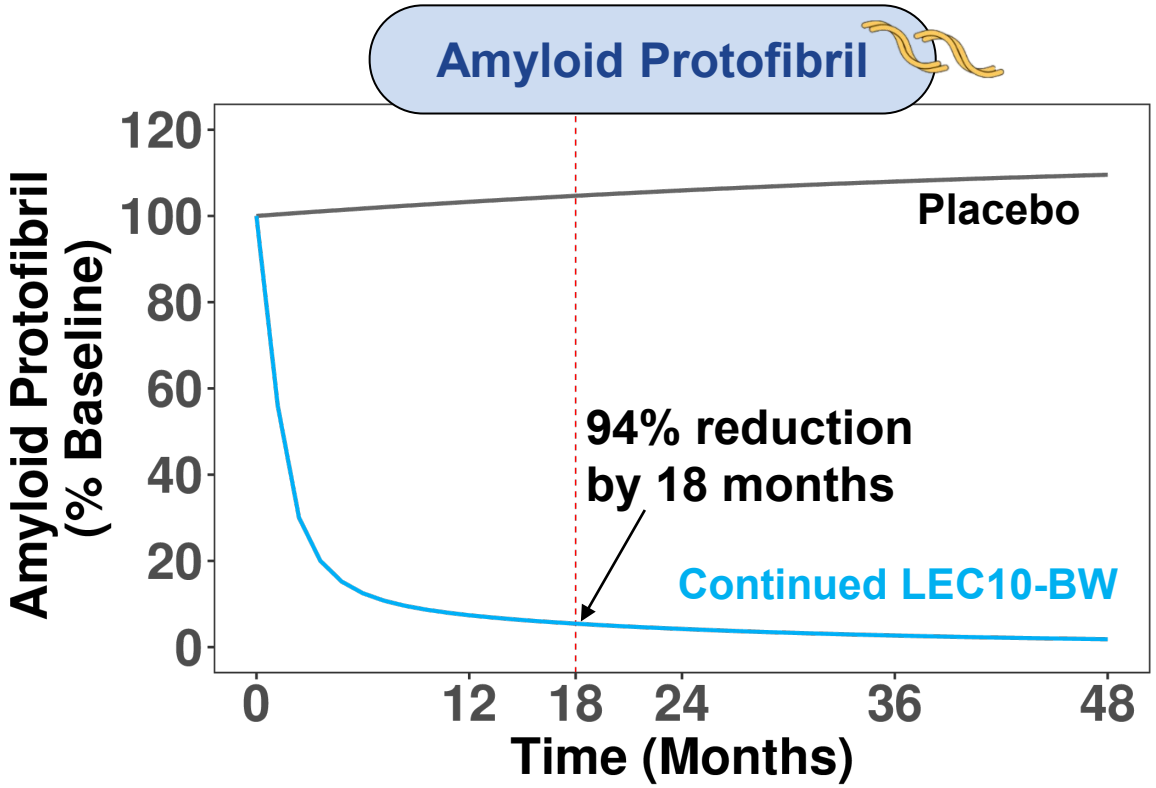
All simulated biomarkers are proportionally scaled between 0 and 1 to show their relative dynamics.

- Data informed biomarker profiles and clinical outcome simulated from mechanistic QSP model match literature expectations
- Model predicts biomarkers that are not measured clinically: protofibril, tau seed, and neuronal loss

Aβ, amyloid beta. AD, Alzheimer's disease. CDR-SB, Clinical Dementia Rating-sum of boxes. CSF, cerebrospinal fluid. FDG, 18F-fluoro-deoxy-glucose. MRI, magnetic resonance imaging. MCI, mild cognitive impairment. MT, medial temporal region of the brain. PET, positron emission topography. QSP, Quantitative Systems Pharmacology.

QSP Model Predicts Rapid Clearance of Neurotoxic Amyloid Protofibrils by Lecanemab



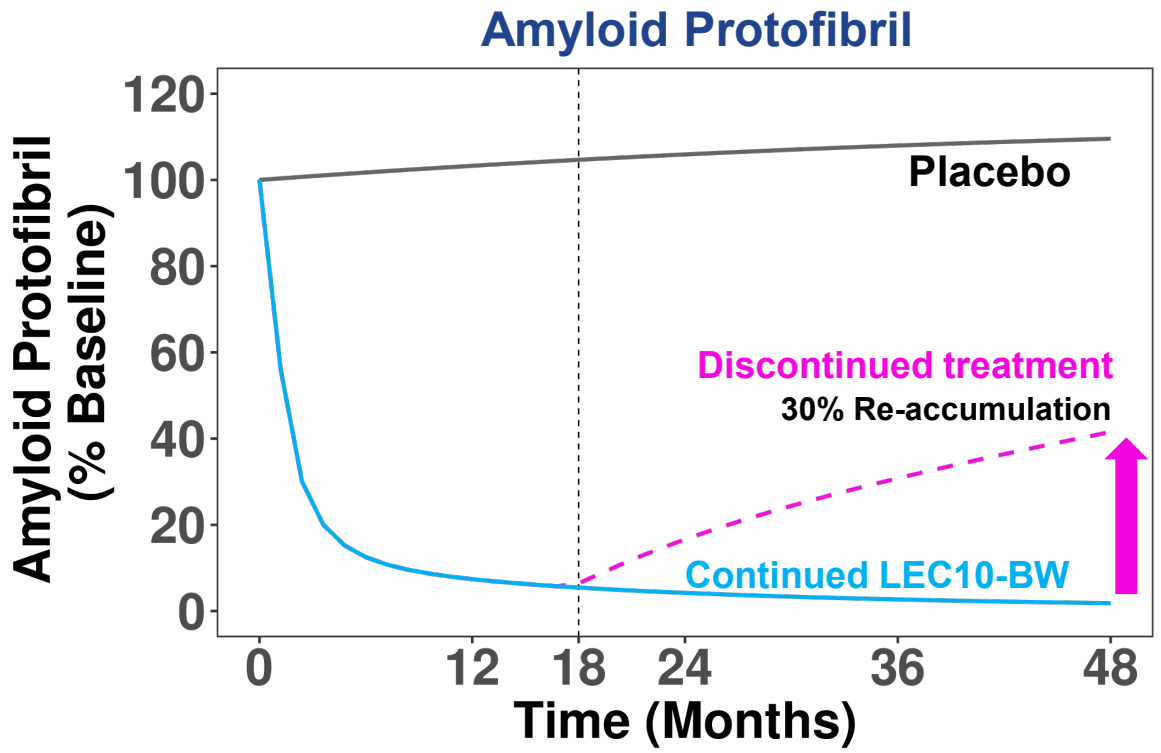


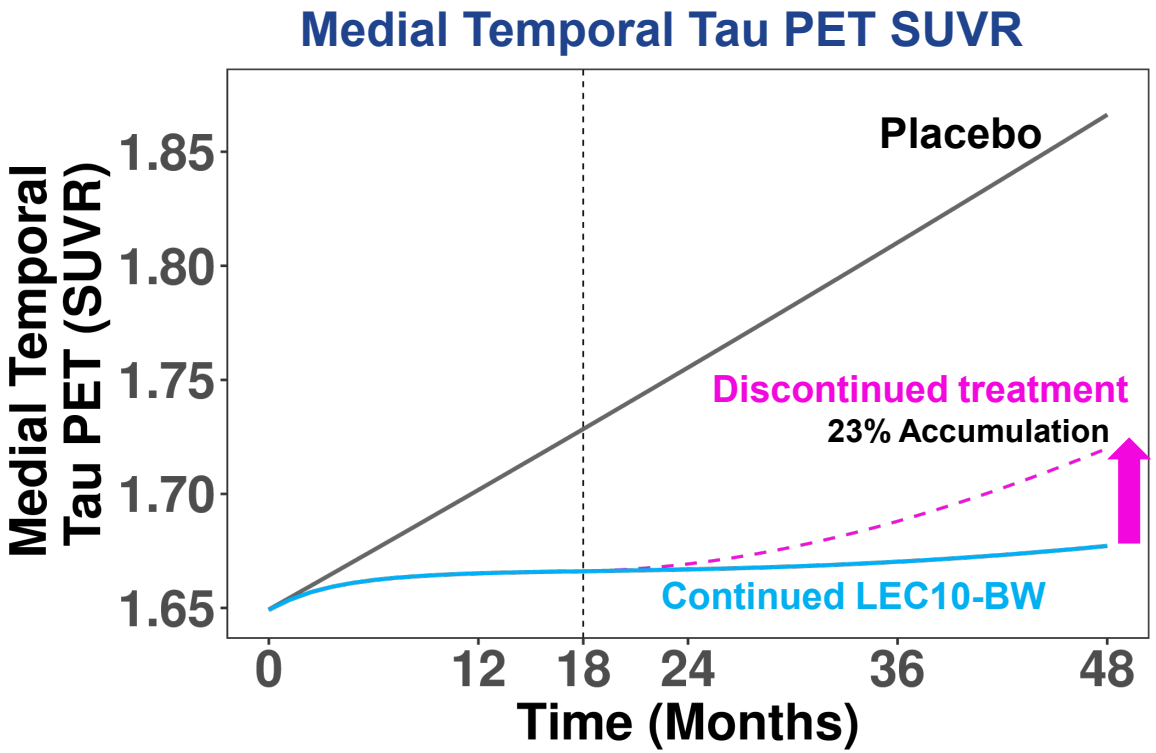
- **Model agrees with observed amyloid PET outcome**

- **Predicted impact on protofibrils.**
  To be confirmed by protofibril assay

LEC10-BW, Lecanemab 10 mg/kg biweekly. QSP, Quantitative Systems Pharmacology. PET, positron emission topography.

Continued Protofibril Suppression Inhibits Tau PET Accumulation





- **Discontinuation: projected 30% protofibril re-accumulation by 48 months vs continued treatment**

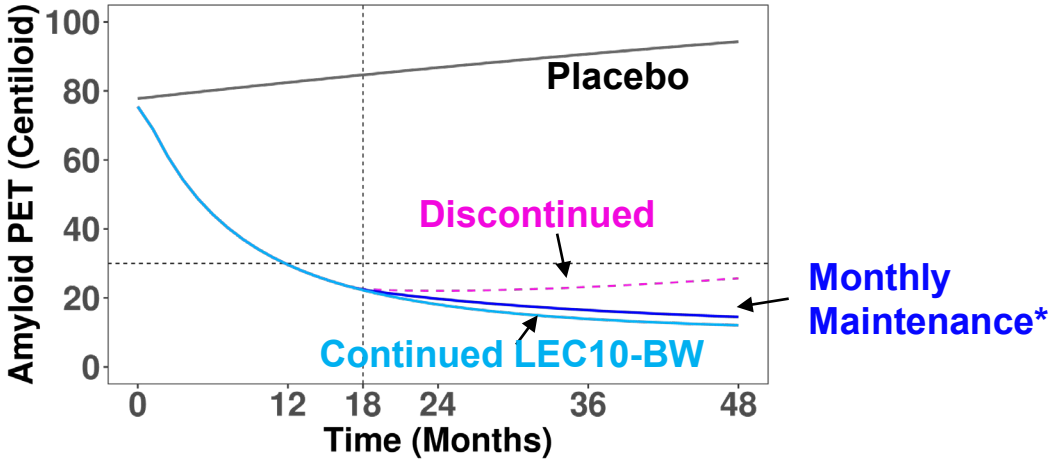
- **LEC10-BW stabilizes tau PET over 18 months**
- **Discontinuation: projected 23% tau accumulation in medial temporal region by 48 months vs continued treatment**

LEC10-BW, Lecanemab 10 mg/kg biweekly. CDR-SB, Clinical Dementia Rating-sum of boxes. CFB, change from baseline. LEC10-BW, lecanemab 10 mg/kg biweekly. PET, positron emission topography. SUVR, standardized uptake value ratio..

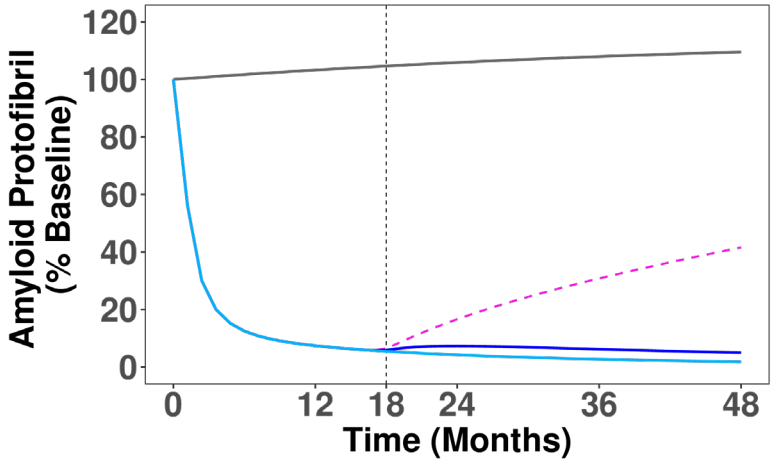
QSP Model

Supports Lecanemab Monthly Maintenance Dosing

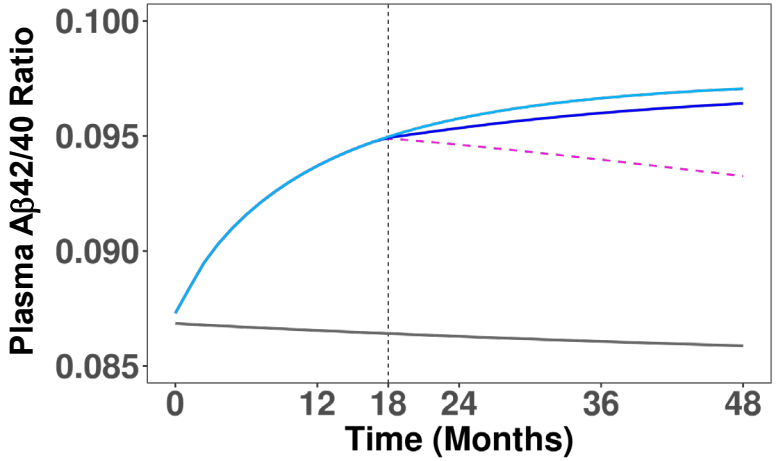
Amyloid PET (Centiloid)



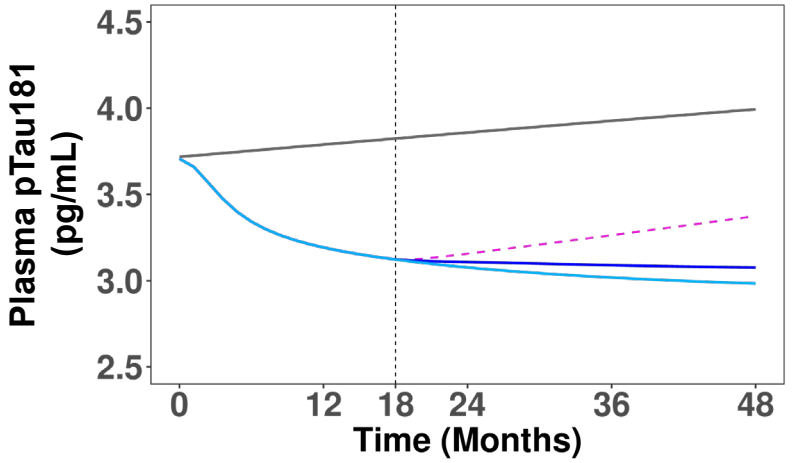
Amyloid Protofibril (% Baseline)



Plasma Aβ42/40 Ratio



Plasma pTau181



*Monthly Maintenance: lecanemab 10 mg/kg monthly dosing following 18 months of biweekly initial treatment

LEC10-BW, Lecanemab 10 mg/kg biweekly. Aβ, amyloid beta. CFB, change from baseline. PET, positron emission topography. ptau181, phosphorylated tau-181. QSP, Quantitative Systems Pharmacology.

Conclusions

- The neuro-dynamic QSP model was developed to mechanistically describe AD pathophysiology
- Model predicts that lecanemab aggressively clears the toxic amyloid protofibrils, which slows down tau pathology and disease progression
- Simulations showed that discontinued lecanemab treatment may result in rapid re-accumulation of amyloid protofibrils and rebound of tau pathology measured by tau PET
- Simulations support long-term benefit of monthly maintenance dosing of lecanemab treatment beyond 18 months

AD, Alzheimer's disease. QSP, Quantitative Systems Pharmacology. PET, positron emission topography.

Is There 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

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Disclosures and Acknowledgements

Christopher van Dyck – Disclosures:

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Eisai, Inc
Ono Pharmaceuticals
Cerevel

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Biohaven Pharmaceuticals
UCB
Janssen Pharmaceuticals
Eisai, Inc
Genentech, Inc
Cerevel Therapeutics

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

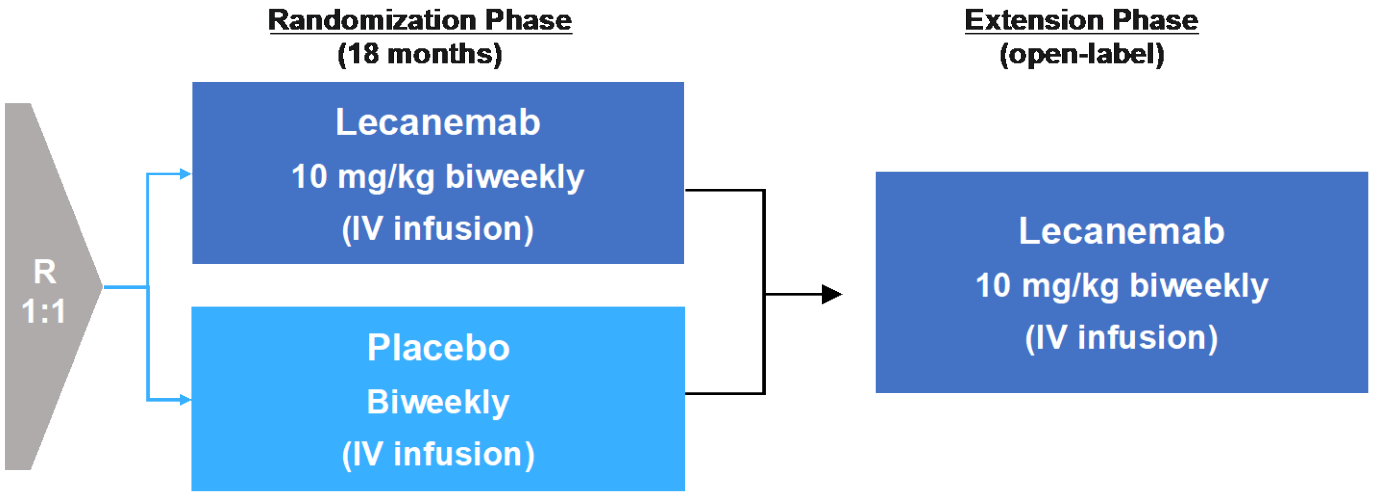
Clarity AD Study Design

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

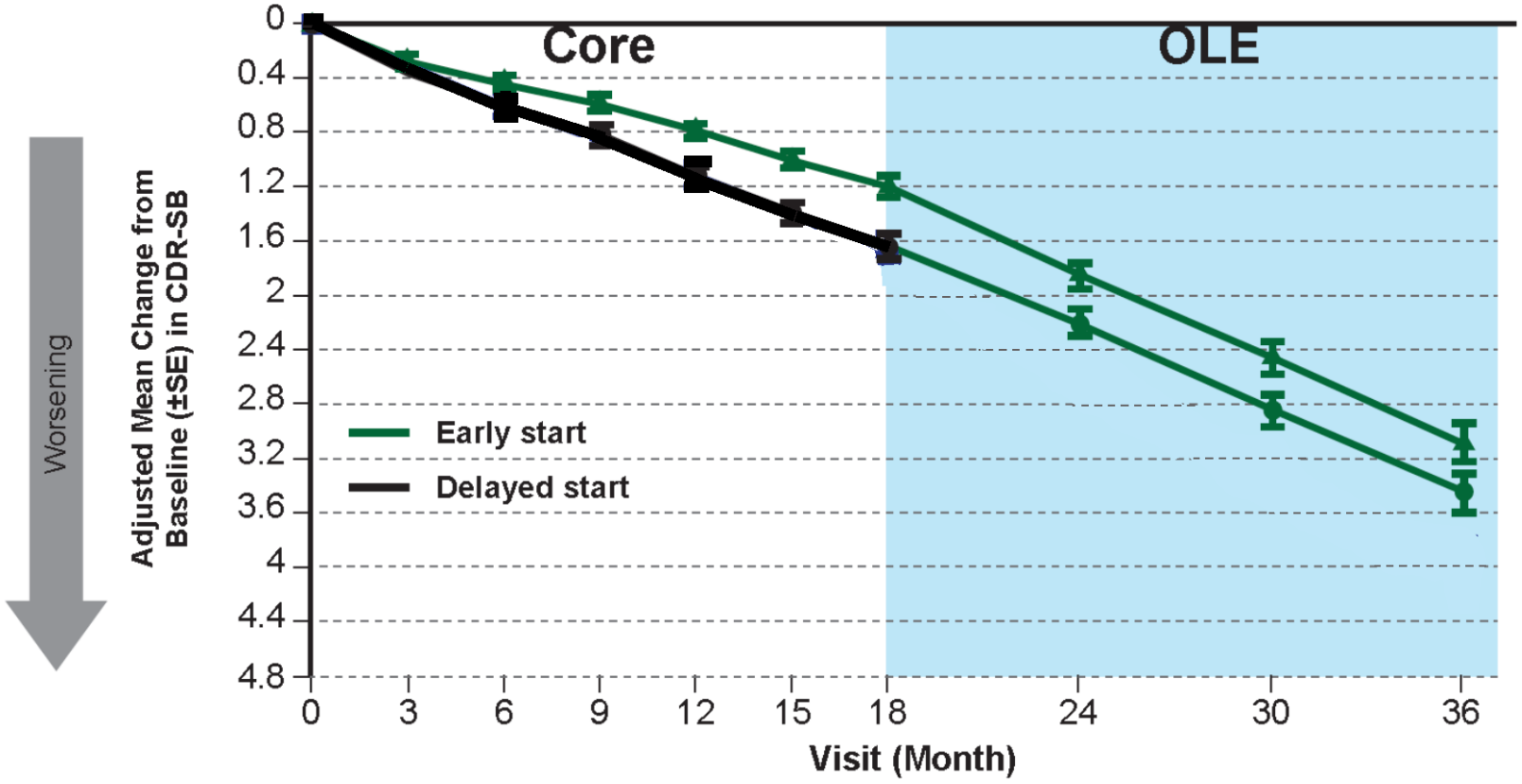
- Amyloid burden (amyloid PET; n=716)
- Brain tau pathology (tau PET; n=342)
- CSF biomarkers of neurodegeneration (n=281)
- Subcutaneous formulation (OLE)

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



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

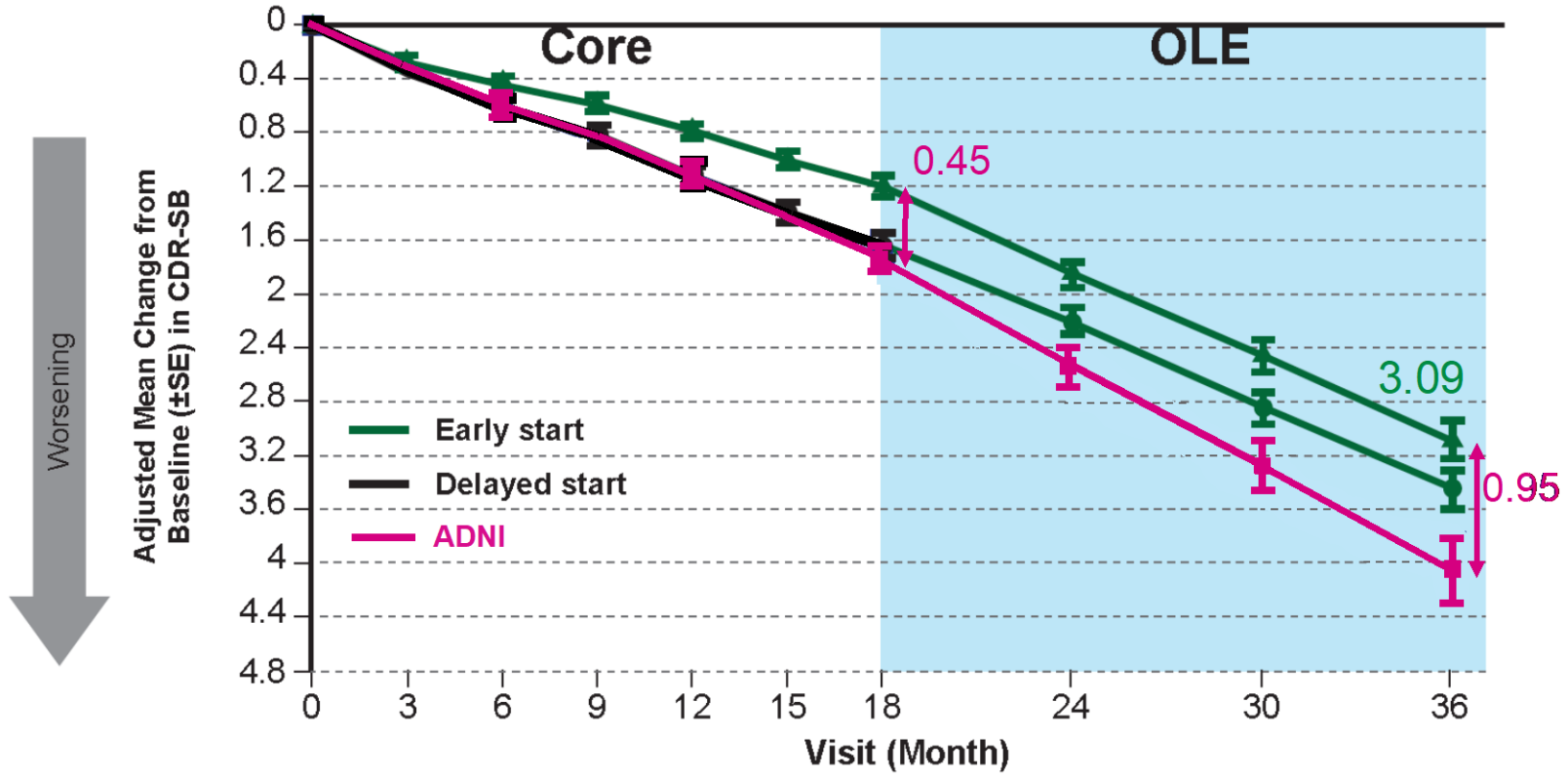
Note: Early start lecanemab 10 mg/kg biweekly group are those subjects on lecanemab 10 mg/kg biweekly in the Core. Delayed start LEC10-BW group (those subjects that initiate lecanemab 10 mg/kg biweekly in the OLE). OLE includes those participants on subcutaneous and intravenous formulations. Based on 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 represents exact population of those in Clarity AD study
- Matched ADNI participants show similar degree of decline to placebo group out to 18 months

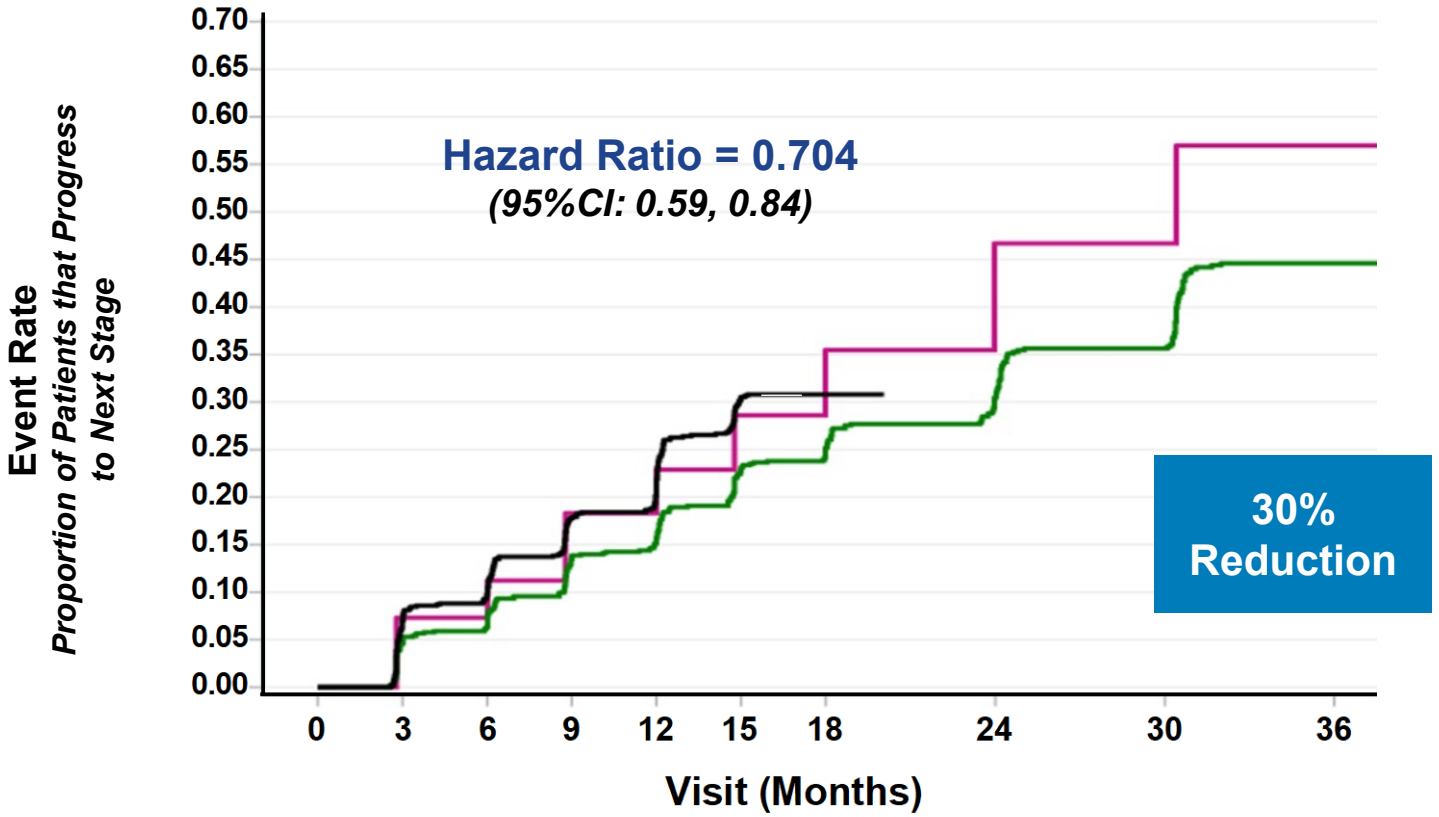
Note: Early start lecanemab 10 mg/kg biweekly group are those subjects on lecanemab 10 mg/kg biweekly in the Core. Delayed start LEC10-BW group (those subjects that initiate lecanemab 10 mg/kg biweekly in the OLE). OLE includes those participants on subcutaneous and intravenous formulations.
Based on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



N (Placebo):	875	793	759	660	615	530	268			
N (Lecanemab):	859	800	769	681	645	565	521	412	348	257
N (ADNI):	437	405	405	357	337	312	282	233	233	188

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"

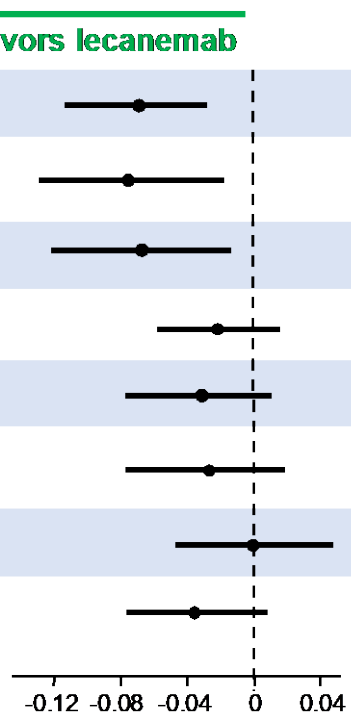
AD, Alzheimer's disease. ADNI, Alzheimer's Disease Neuroimaging Initiative. CDR-SB, Clinical Dementia Rating-sum of boxes. CI, confidence interval. MCI, mild cognitive impairment.

Tau PET Substudy

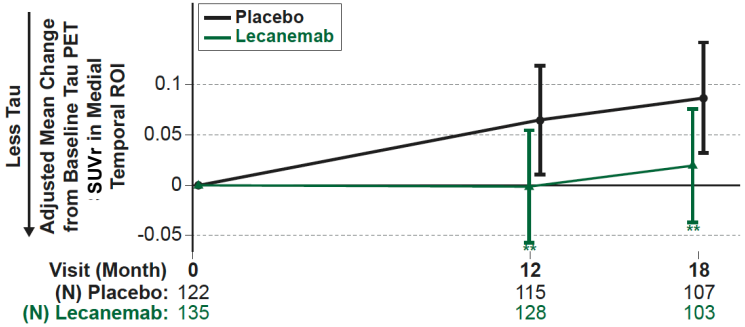
*Lecanemab Slows Tau Spread Especially in Temporal Lobe (Early Braak Regions)[1]**

Tau PET SUVr

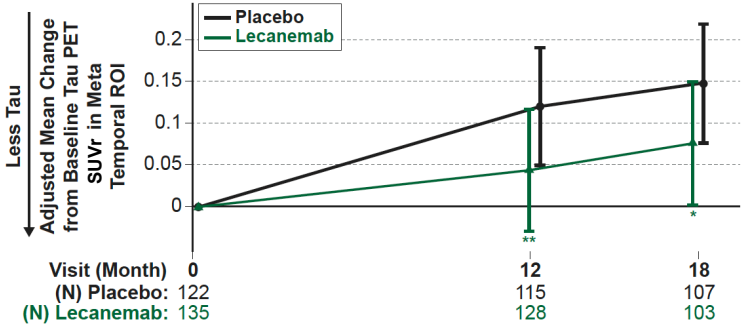
	No. of Participants (placebo, lecanemab)	Adjusted Mean Difference	P Value
Medial temporal	122, 135	-0.068	0.0024
Meta temporal	122, 135	-0.071	0.012
Temporal	122, 135	-0.065	0.016
Frontal	122, 135	-0.023	0.22
Cingulate	122, 135	-0.034	0.13
Parietal	122, 135	-0.029	0.25
Occipital	122, 135	-0.003	0.91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



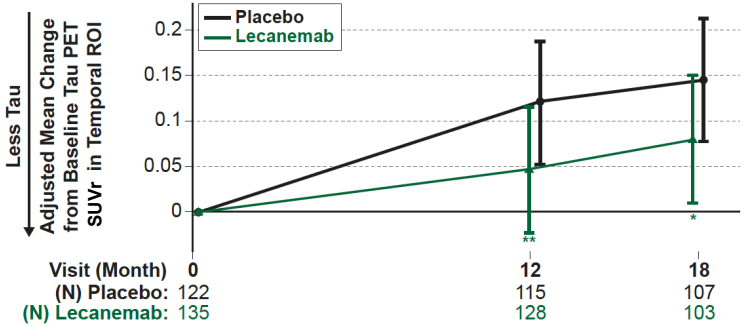
Medial Temporal



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.

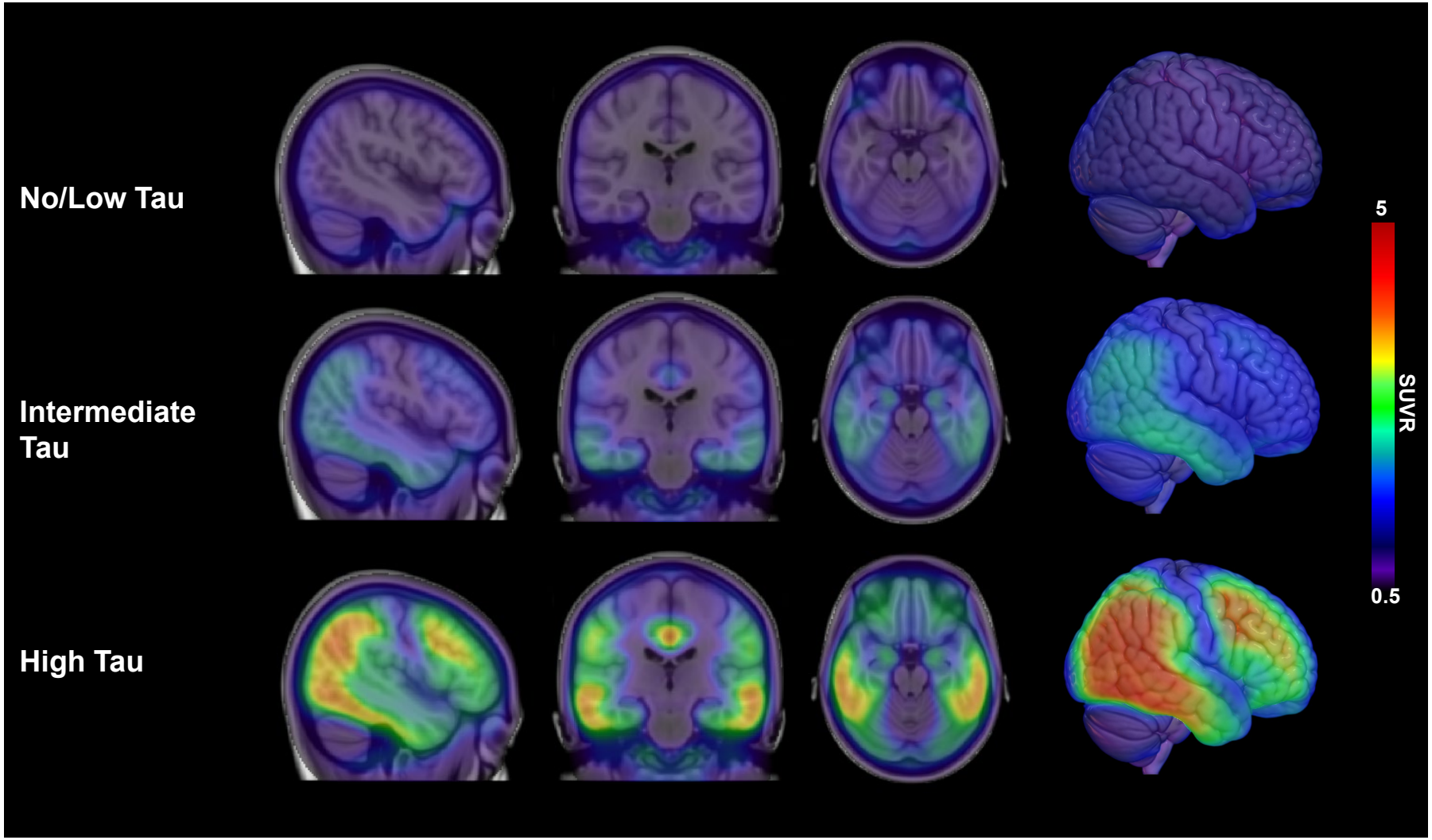
Tau PET Substudy

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)]
  - **No/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)

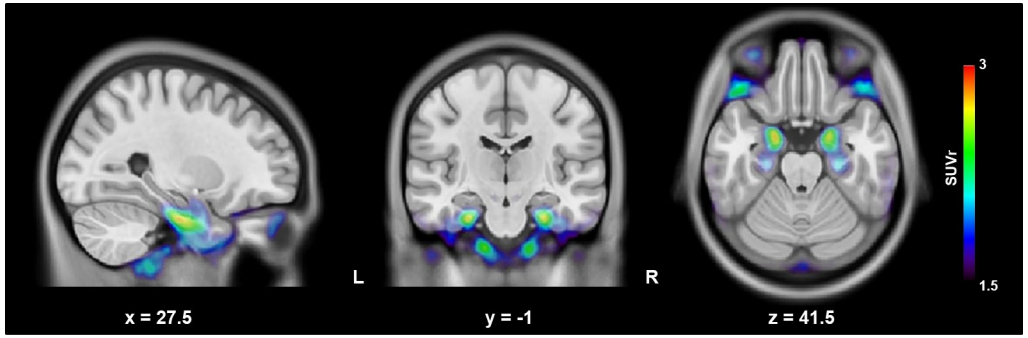


Tau terminology based on latest FDA definitions.
AD, Alzheimer's disease. MMSE, Mini-Mental State Exam. PET, positron emission tomography. SD, standard deviation. SUVR, standardized uptake value ratio.

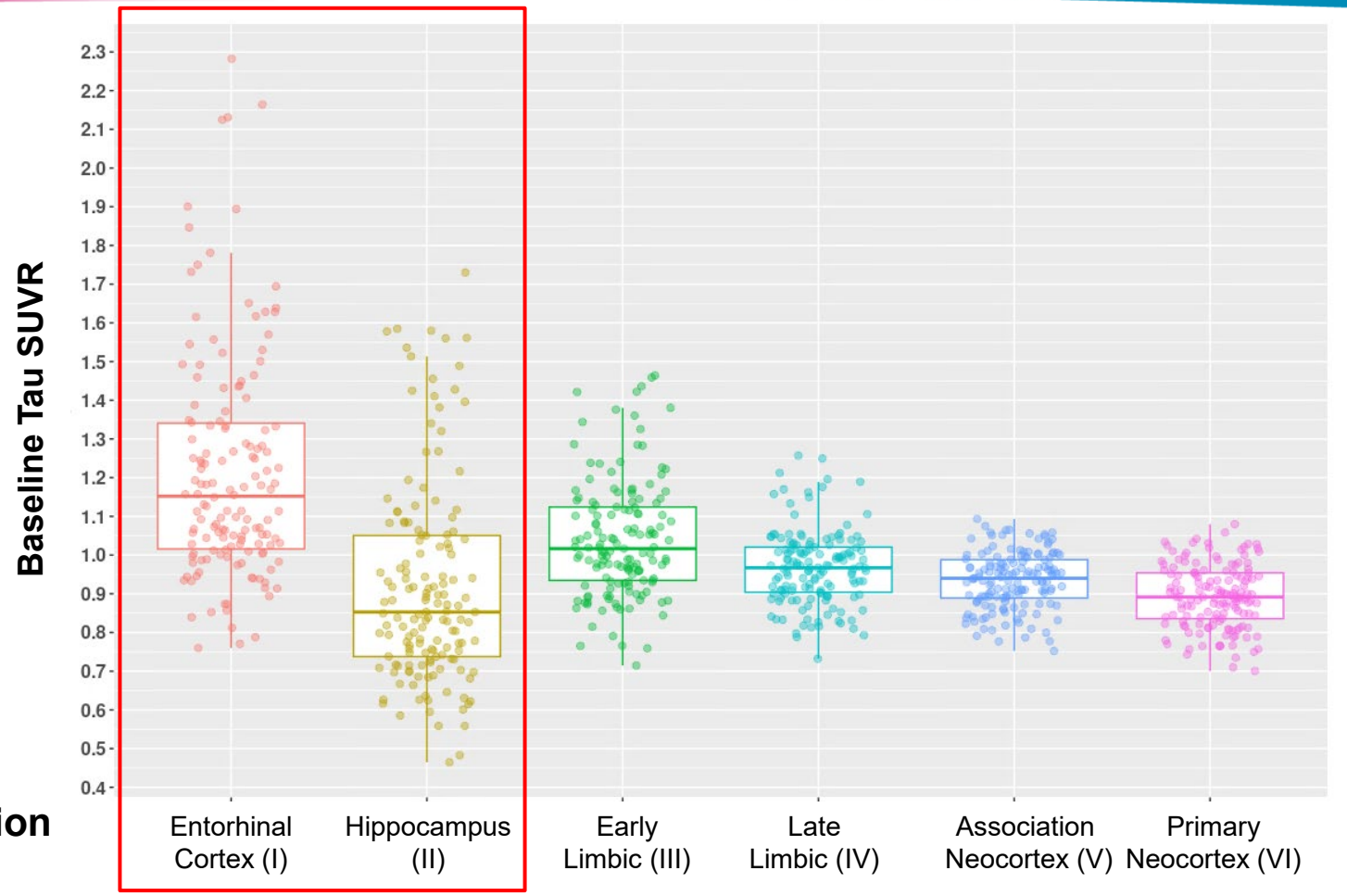
Anatomical Distribution of Tau PET Signal in No/Low Tau Subgroup

Characterized by Signal in Entorhinal Cortex

Average Image of 20 No/Low Tau Participants with Entorhinal Uptake



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



Neuroanatomical Region (Braak Stage)

Tau Pathology

Clinical Continuum

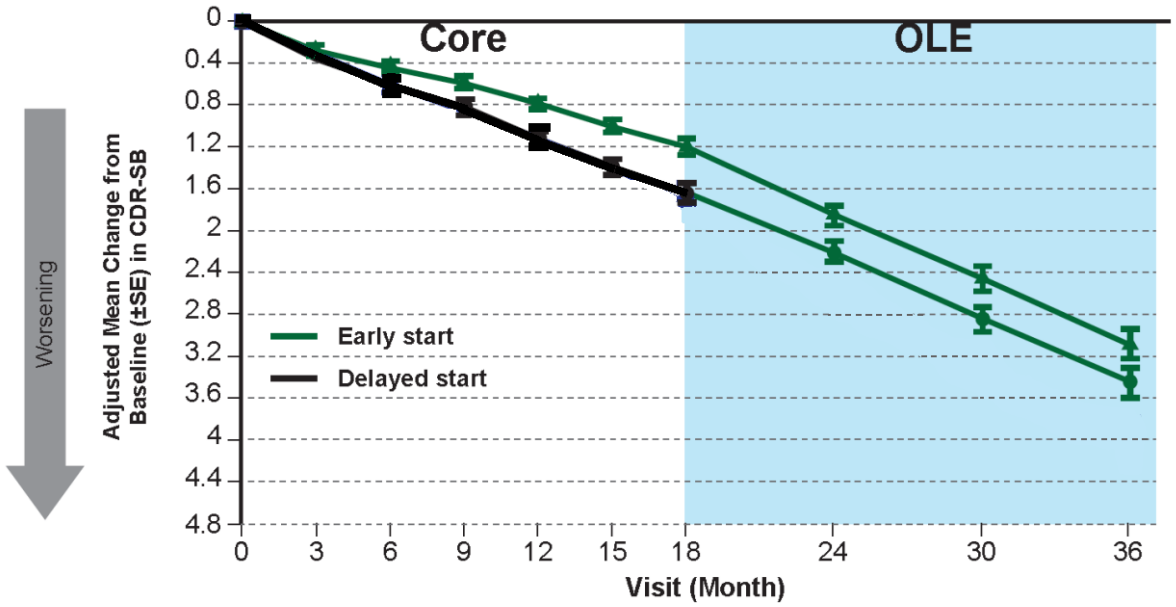
Slide Courtesy of Keith Johnson

Tau terminology based on latest FDA definitions.
PET, positron emission tomography;
SUVr, standardized uptake value ratio.

Clinical Outcomes Through 36 Months

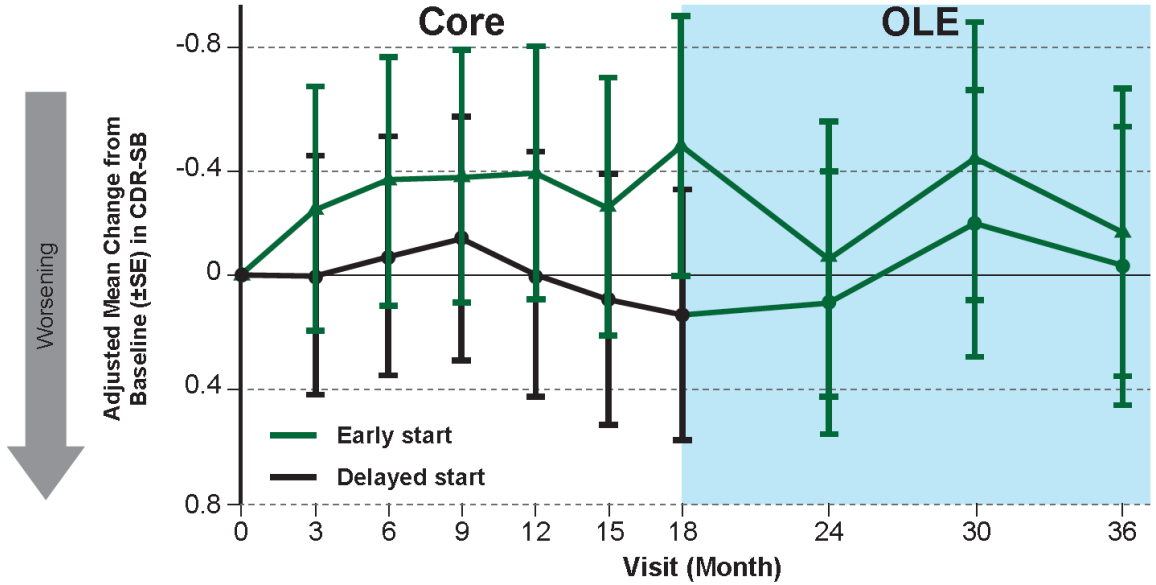
Subjects with No/Low Tau Continued to Benefit Through 36 Months

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

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

- The no/low tau subgroup represents 40% of the overall study population
- Similar results were observed for ADAS-Cog14 and ADCS MCI-ADL

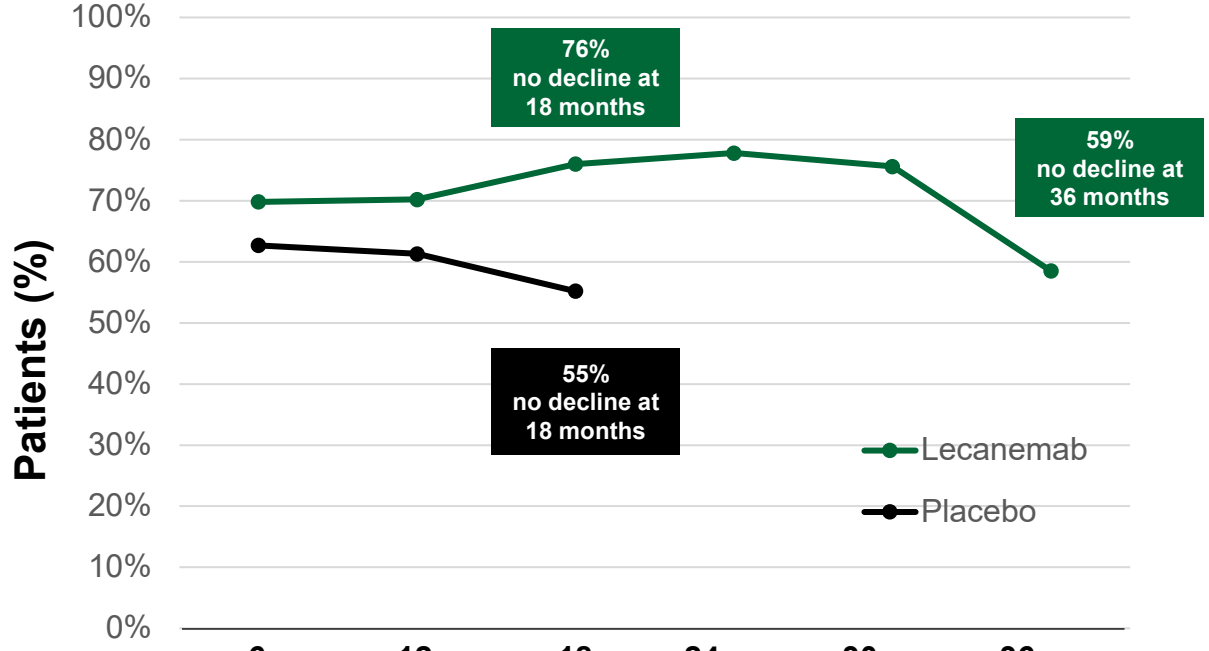
Tau terminology based on latest FDA definitions
OLE includes those participants on subcutaneous and intravenous formulations.

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

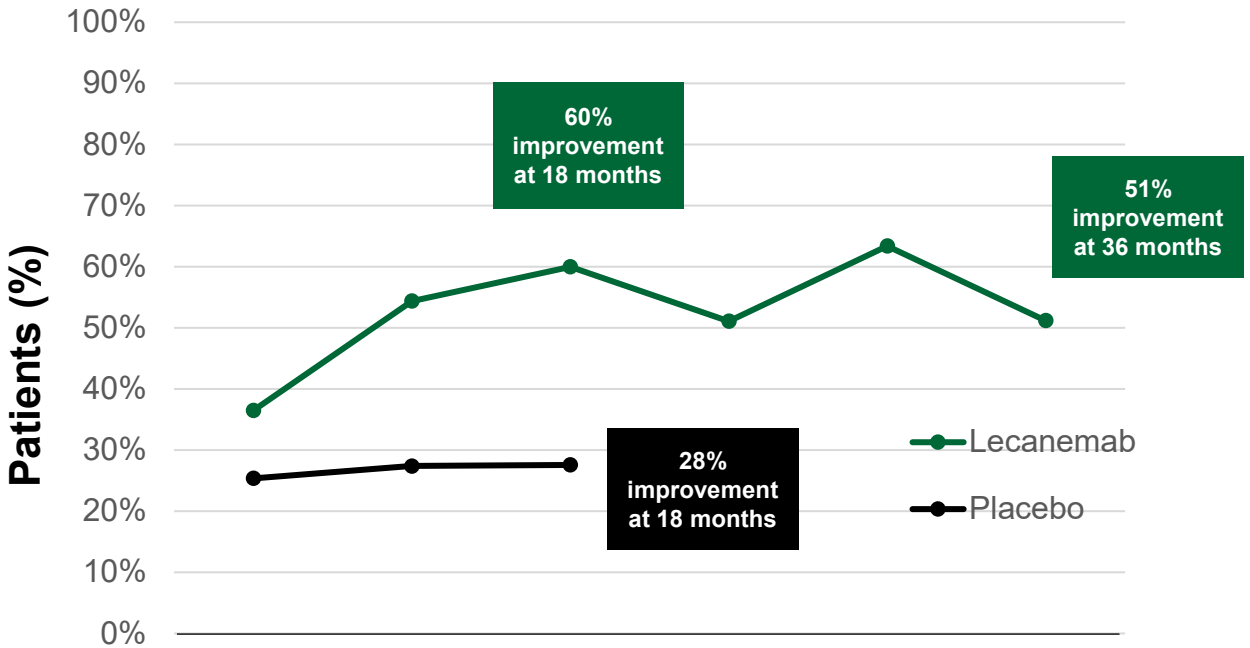
59% Had No Decline and 51% Had Improvement at 36 Months

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**

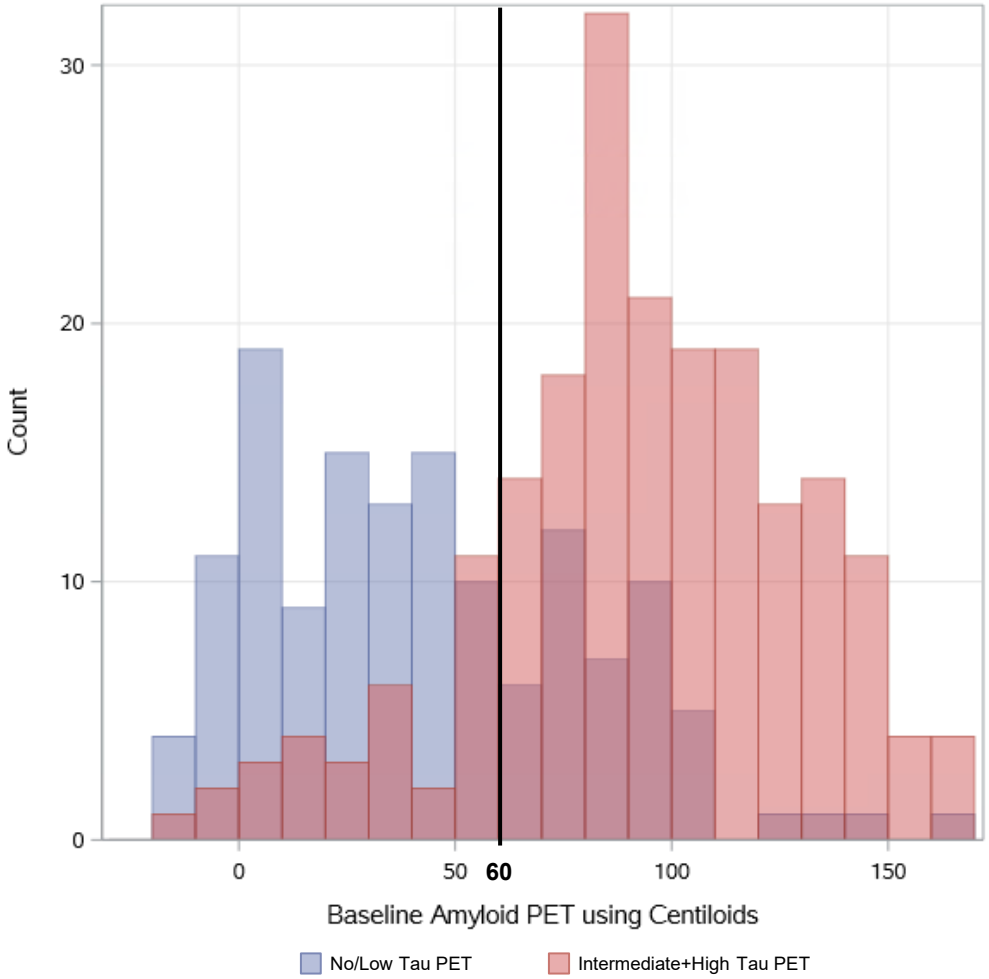
Tau terminology based on latest FDA definitions. Cutoffs for MK Tau PET: No/Low SUVR <1.06; Intermediate SUVR 1.06-2.91; High SUVR >2.91.
ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale. ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment. CDR-SB, Clinical Dementia Rating-sum of boxes. PET, positron emission topography.

No/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 pathological 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

Histogram of Amyloid PET (Tau PET Substudy)

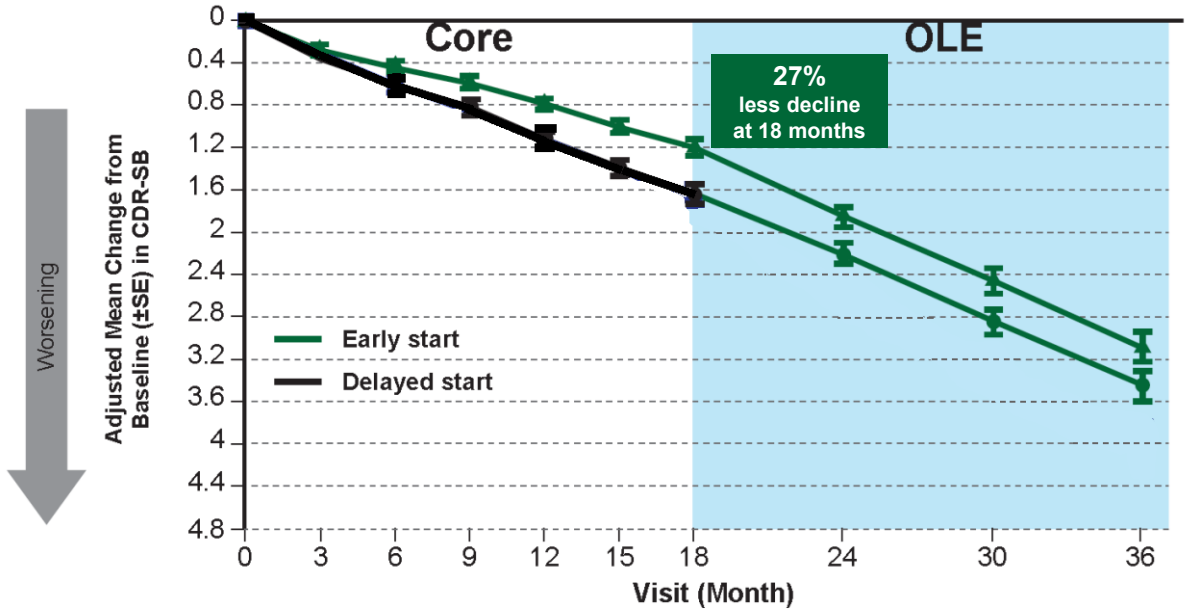


Tau terminology based on latest FDA definitions.
Observed data
CL, Centiloid. GM, gray matter. PET, positron emission tomography.

Clinical Outcomes Through 36 Months

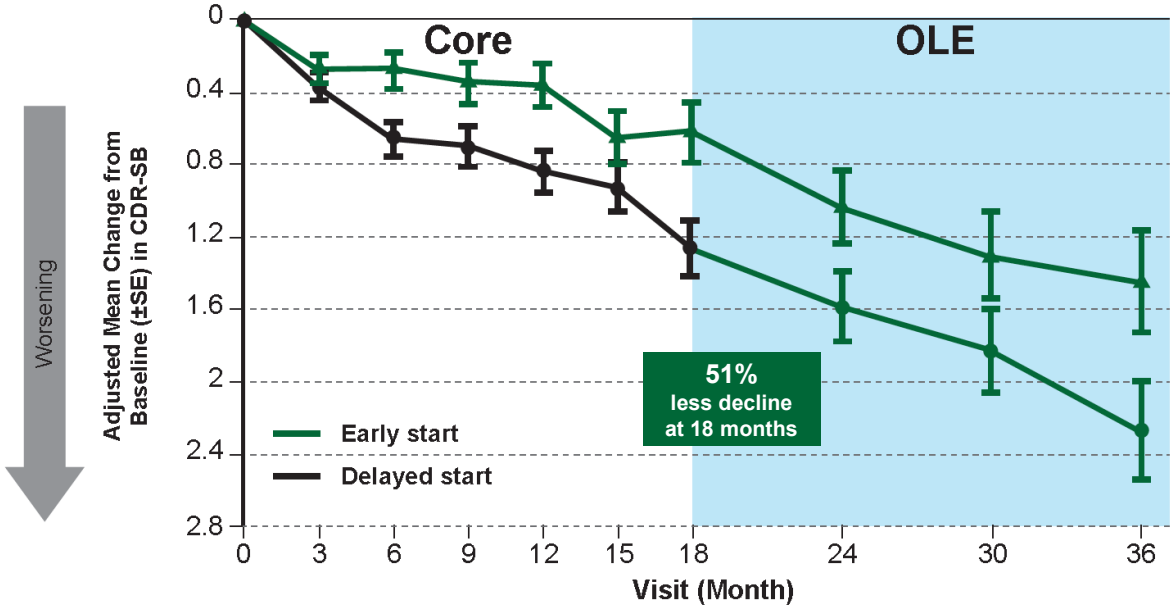
Subjects with Low Amyloid Continued to Benefit Through 36 Months

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

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

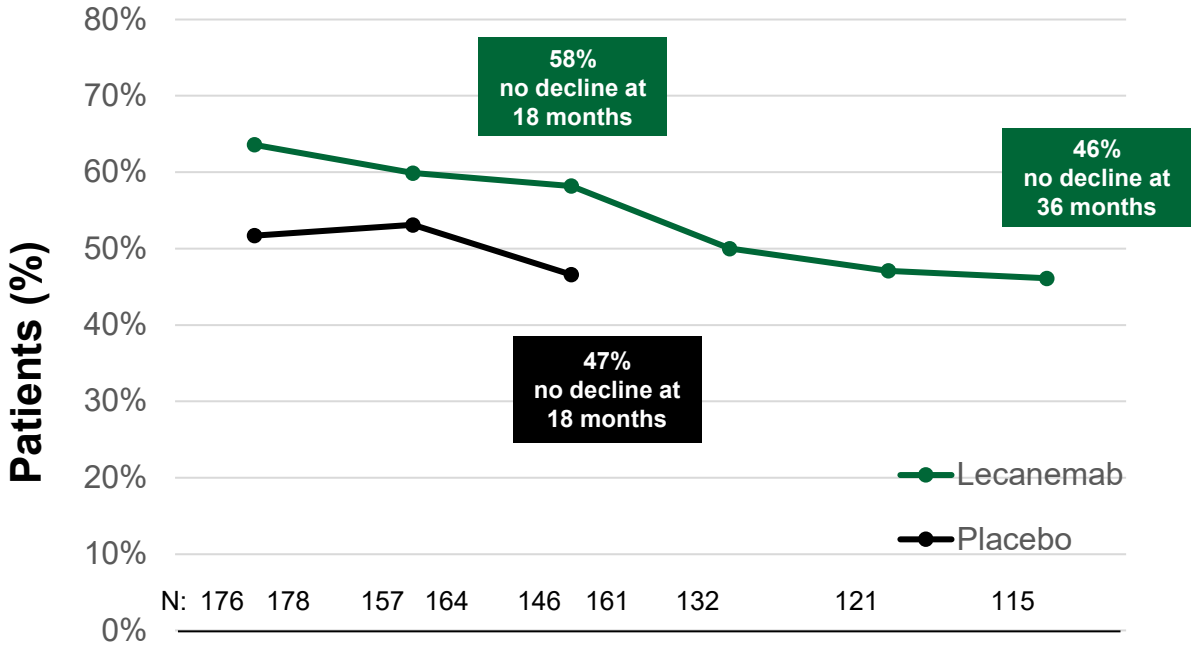
- The low amyloid subgroup (<60 Centiloids) represents 54% of the overall amyloid PET substudy population
- Similar results were observed for ADAS-Cog14 and ADCS MCI-ADL

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 Low Amyloid PET (<60CL): Response Rate

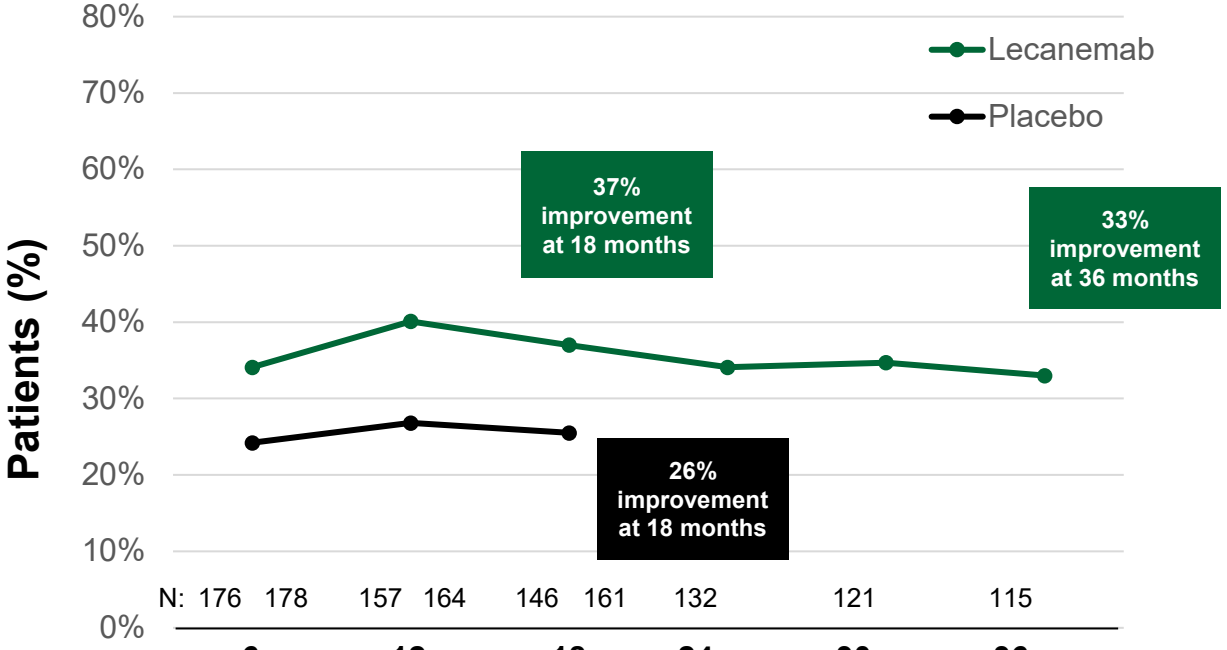
46% Had No Decline and 33% Had Improvement at 36 Months

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**

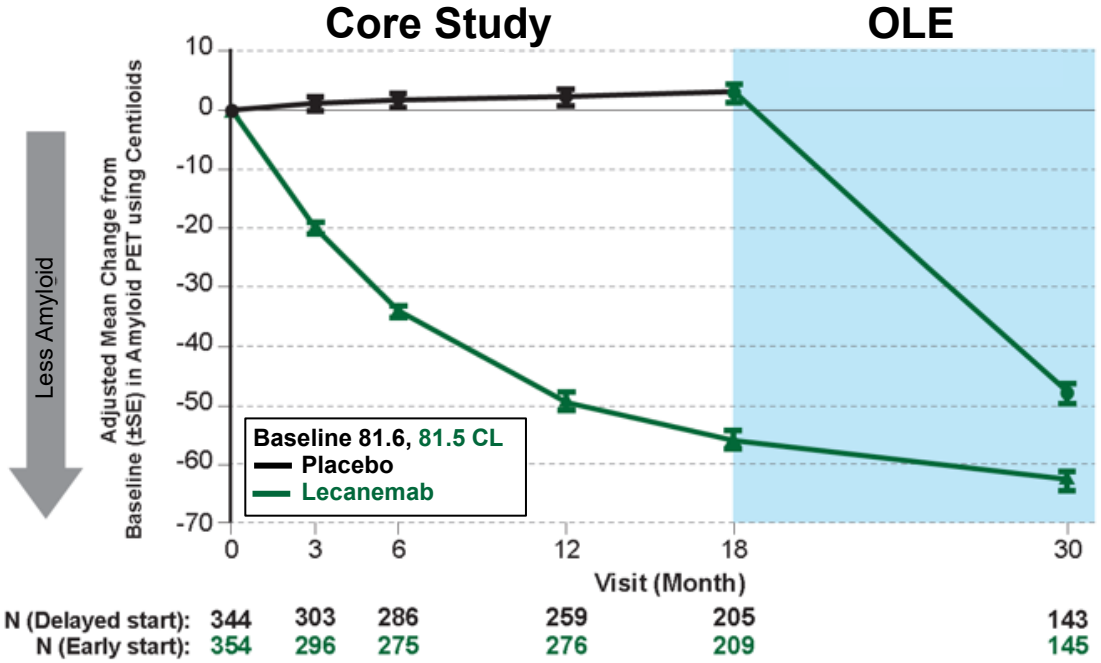
ADAS-Cog14, Alzheimer's Disease Assessment Scale-Cognitive Subscale. ADCS MCI-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment. CDR-SB, Clinical Dementia Rating-sum of boxes. CL, Centiloid. PET, positron emission topography.

Clarity AD OLE: Biomarker Results

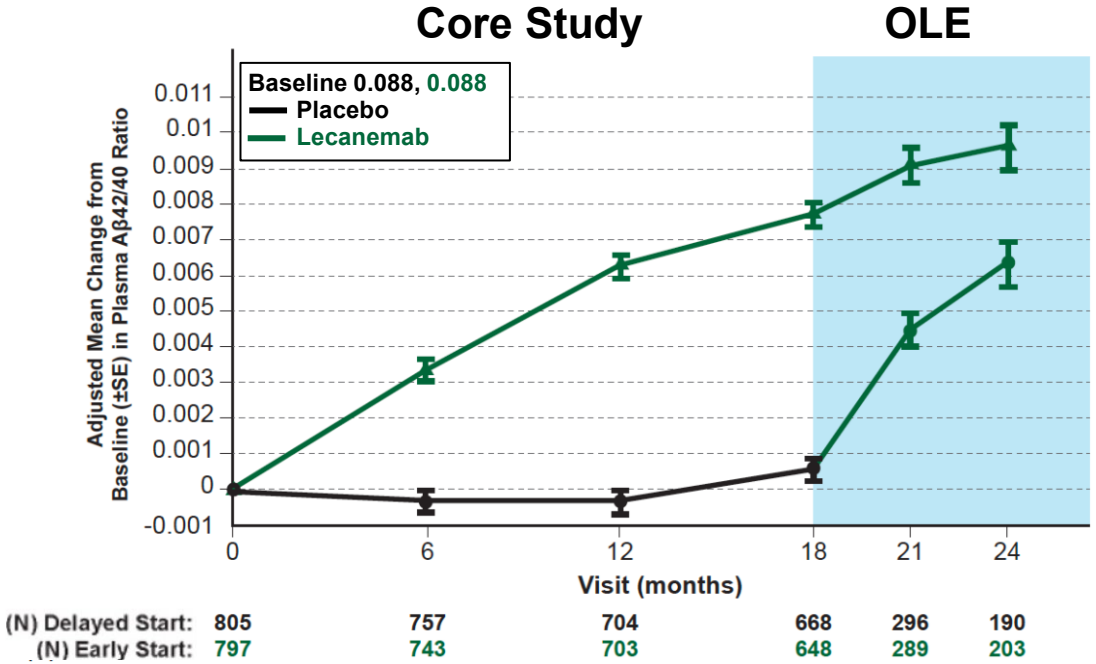
Continuous Treatment Results in Minimal Change in Plaque But Greater Aβ42/40 Change

- Participants on placebo who started lecanemab at 18 months show improvement in biomarkers within 3 months of treatment
- Approximately 70% of subjects were amyloid negative (<30 CL) at the OLE baseline; therefore, ongoing dosing provides benefit irrespective of OLE amyloid level

Amyloid PET



Plasma Aβ42/40 Ratio



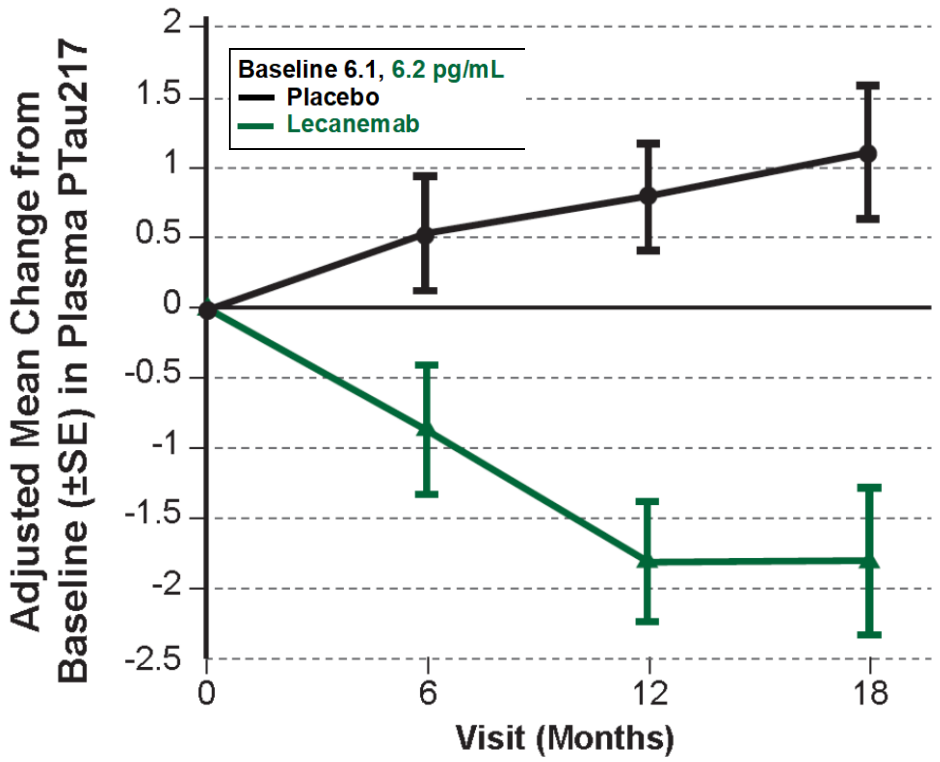
Amyloid PET only done every 12 months in OLE (ie, no 36 month). OLE includes those participants on subcutaneous and intravenous formulations.

Aβ, amyloid beta. CL, Centiloid. OLE, open-label extension. PET, positron emission tomography. SE, standard error.

Based on pharmacodynamic analysis population (amyloid PET substudy population). Adjusted mean change from baseline, standard error (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

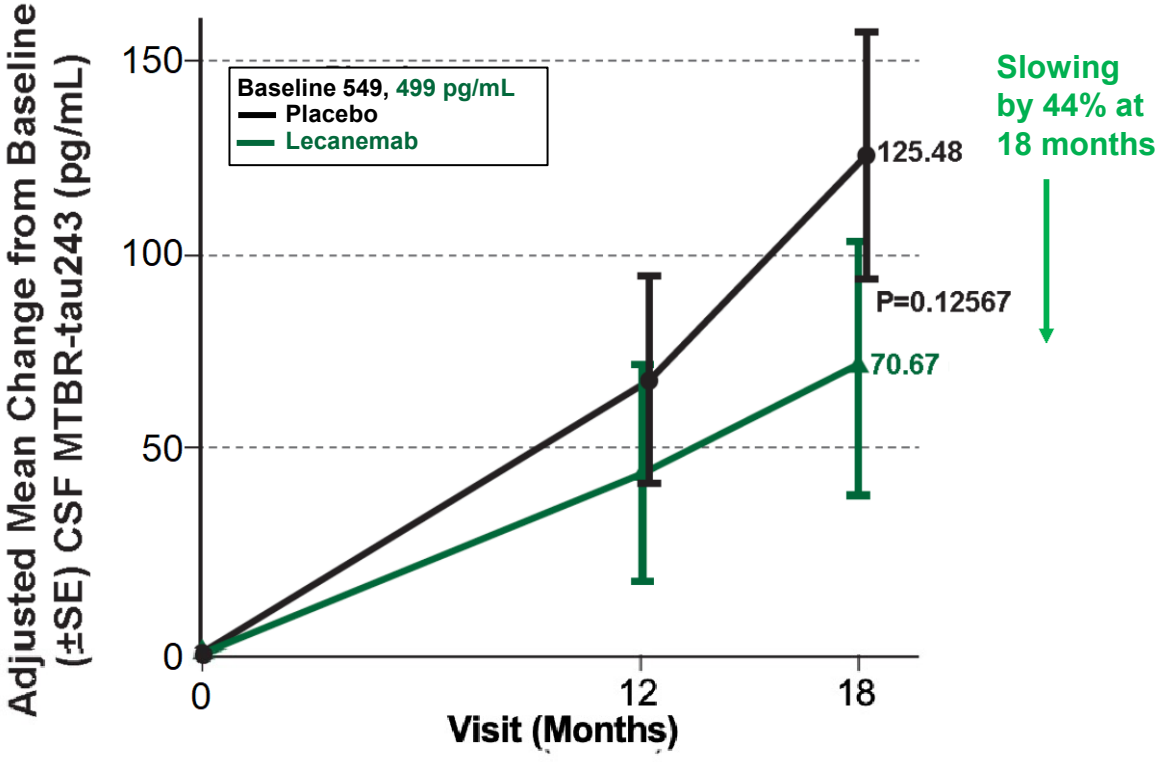
Lecanemab Reduces and Slows the Rate of Tau Pathology Biomarkers Plasma pTau217 and CSF MTBRtau243

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.

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https://mayvillemedical.com/wildsmith-2024-aaic-presentation

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

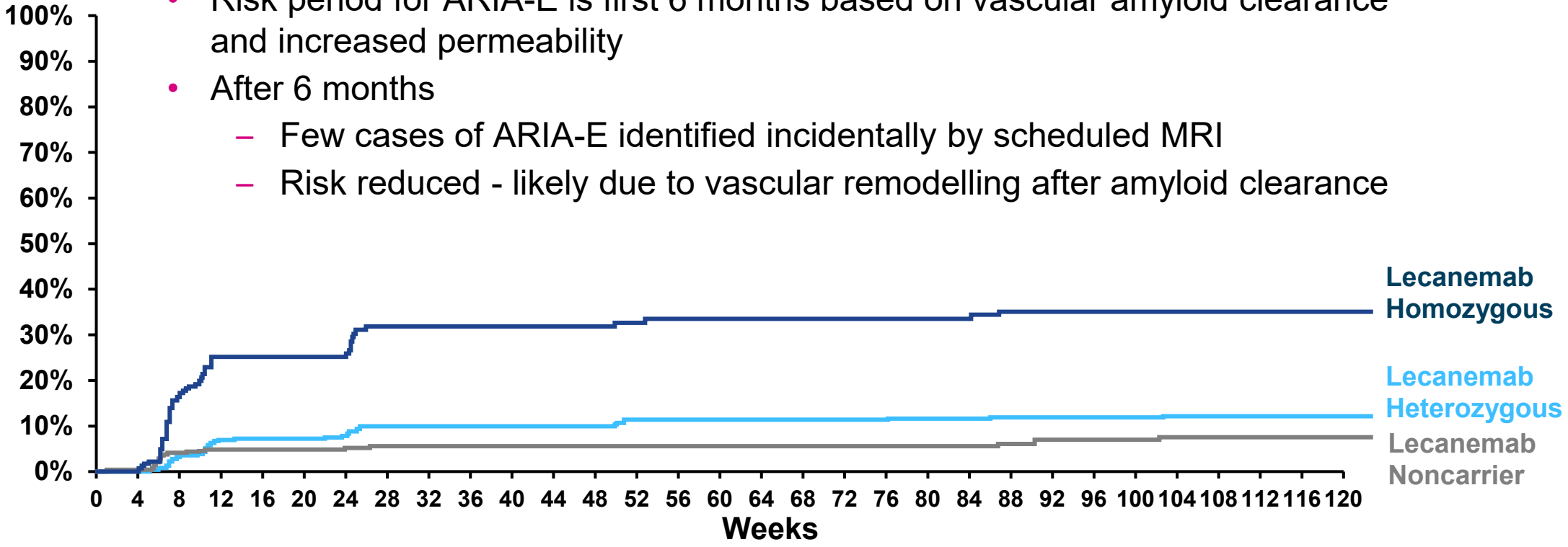
- No increase of known adverse events over time

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).

Long-Term Safety for Core Lecanemab Patients: ARIA-E

- Risk period for ARIA-E is first 6 months based on vascular amyloid clearance and increased permeability
- After 6 months
  - Few cases of ARIA-E identified incidentally by scheduled MRI
  - Risk reduced - likely due to vascular remodelling after amyloid clearance



MRI evaluations: ↑ ↑ ↑ ↑ ↑ ↑ * ↑ * ↑ *

LEC Homozygous (N)	141	141	116	101	101	100	100	91	89	89	89	89	89	88	86	86	86	85	85	85	81	76	74	73	73	73	73	69	67	66	66
LEC Heterozygous (N)	479	479	446	423	415	410	404	395	390	387	386	381	381	374	369	367	365	362	360	358	348	335	332	331	329	327	320	303	298	287	282
LEC Noncarrier (N)	278	277	259	255	250	247	245	239	235	231	225	221	220	216	214	211	208	205	205	204	203	195	192	190	188	188	184	173	170	169	168

* MRI schedule for placebo patients who transitioned to lecanemab in the OLE to capture ARIA (same MRI schedule as was done in beginning of trial).

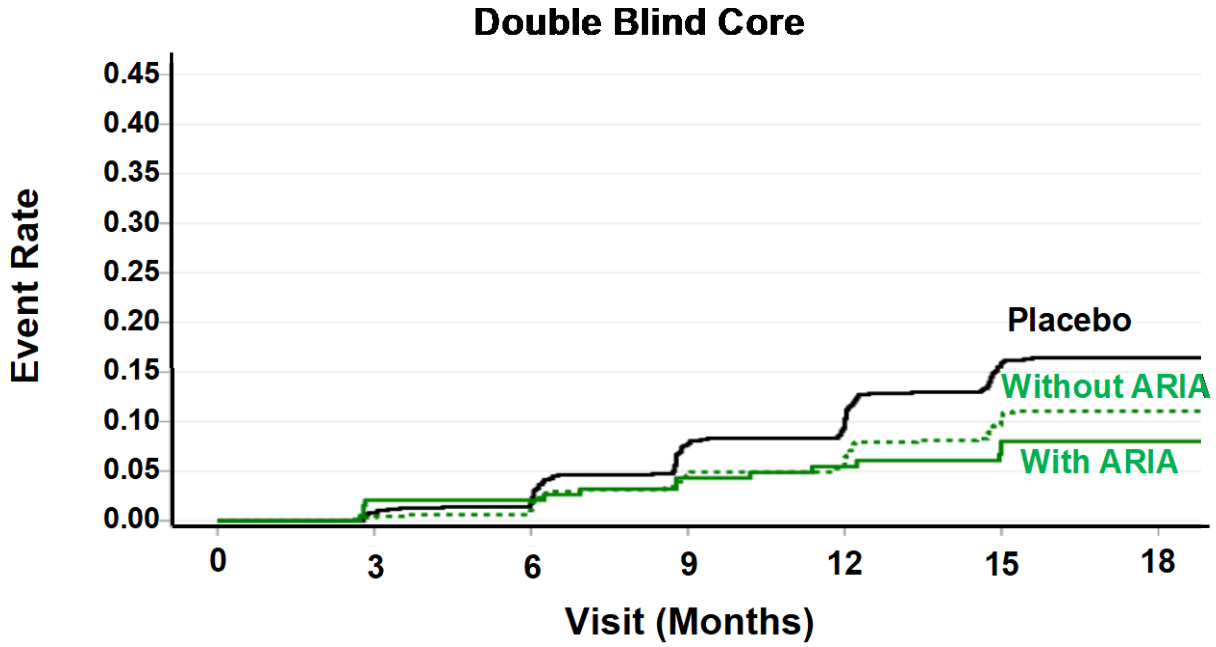
OLE data as of 30 Nov 2023; based on intravenous dataset.

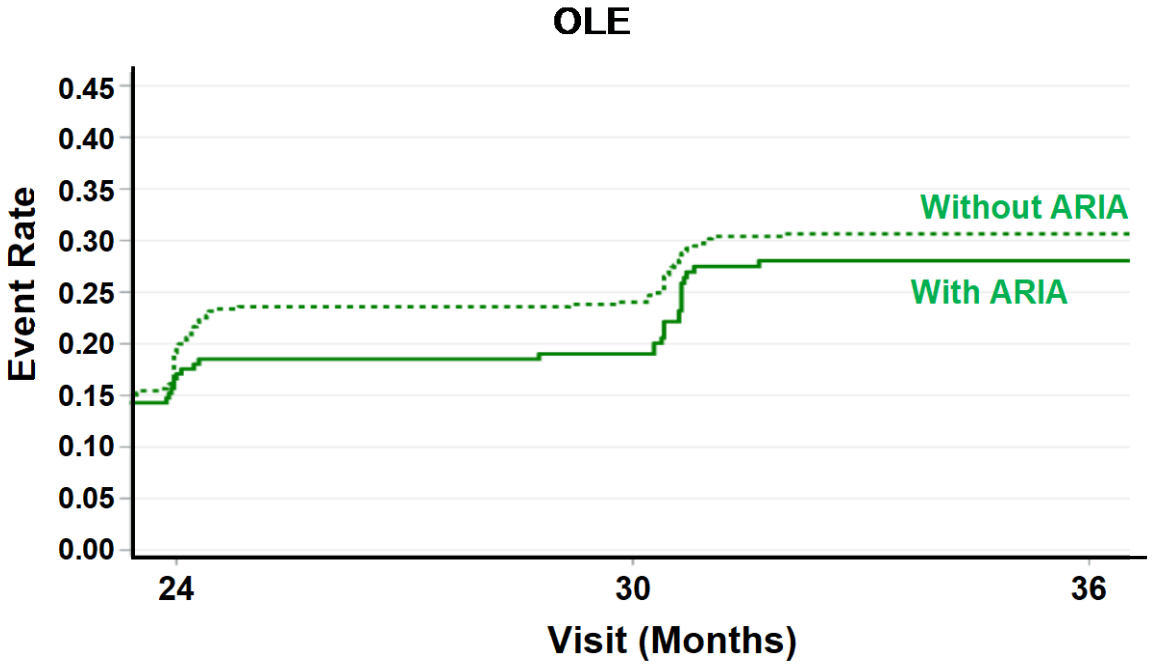
ARIA-E, amyloid related imaging abnormalities - edema; MRI, magnetic resonance imaging.

ARIA is Not Associated with Accelerated Long-Term Progression

- 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

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
- Amyloid pathway biomarkers improved at 3 months in newly treated participants and maintained/improved with continuous treatment
- 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
- After first six months, ARIA rates are low and similar to ARIA rates on placebo
- 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

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Panel Discussion and Q&A

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

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