Biomarker Results from the Lecanemab Phase 2 Study: *Linking Disease Progression to Chronic Amyloid Treatment*

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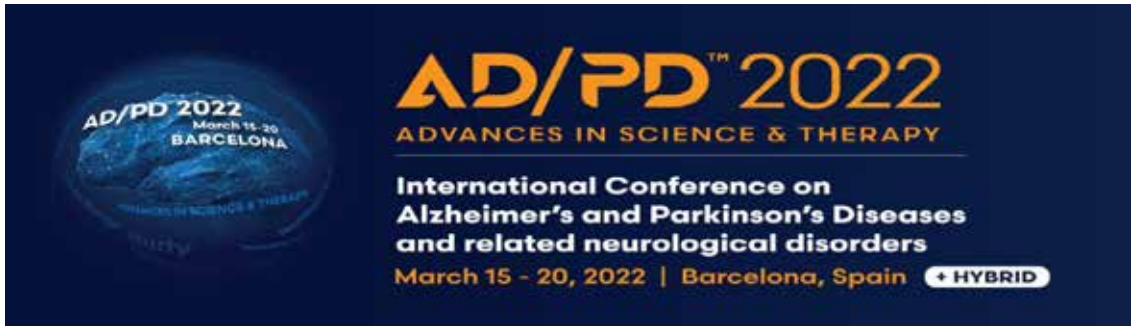
Presenter Disclosures: Eric McDade



	No, Nothing to disclose
X	Yes, please specify

Company / Name	Honoraria / Expense	Consulting / Advisory Board	Funded Research	Royalties / Patent	Stock Options	Ownership / Equity Position	Employee	Other (Please specify)
Eli Lilly		DSMB	X					
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Washington University-C2N				X				
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Hoffmann- La Roche			X					
Eisai			X					

Objectives

- Evaluate the association of amyloid plaque reduction by lecanemab with peripheral measures of AD biomarkers in the randomized Core phase of Study 201
- Evaluate the association of changes in peripheral measures of AD biomarkers with change in clinical outcomes during the randomized Core phase of Study 201
- Assess the relative change in amyloid plaque and peripheral measures of AD biomarkers after completion of treatment in the randomized core phase and prior to initiation of lecanemab in OLE (Gap phase)
  - Recapitulation of disease progression
  - As a method to guide chronic therapy in AD
- Review the implications of lecanemab for use in the DIAN-TU NexGen tau study

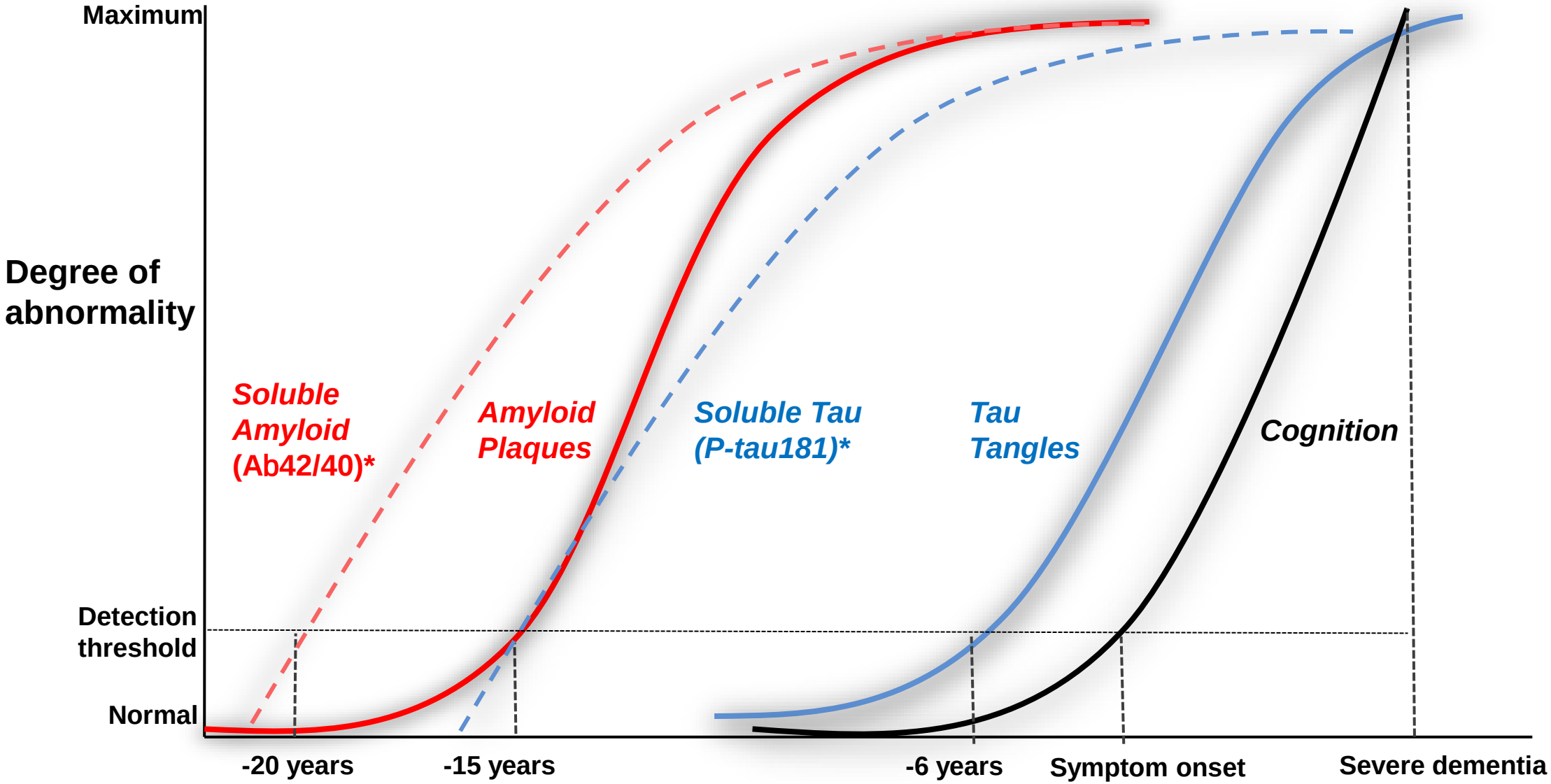
AD, Alzheimer's disease; DIAN-TU NexGen, Dominantly Inherited Alzheimer Network Trials Unit Tau Next Generation; OLE, open-label extension.

Does the sequence of AD biomarker progression anticipate response to amyloid plaque targeting therapies?

SOLUBLE AND AGGREGATED AMYLOID AND TAU IN AD PROGRESSION

Amyloid and Tau Biomarkers Trajectories in AD:

Sequential Changes in Disease Progression



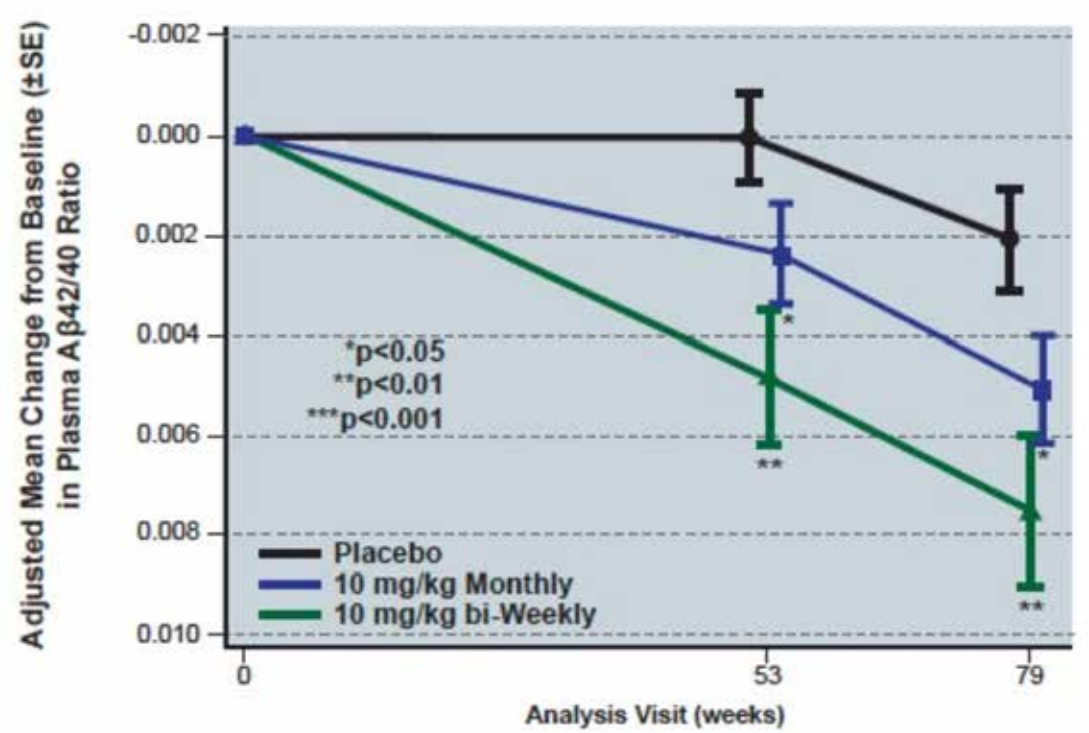
Aβ, amyloid-beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; P-tau, phosphorylated tau.

*plasma or CSF

Lecanemab Effect on Plasma Biomarkers of Amyloid and Tau Pathology:

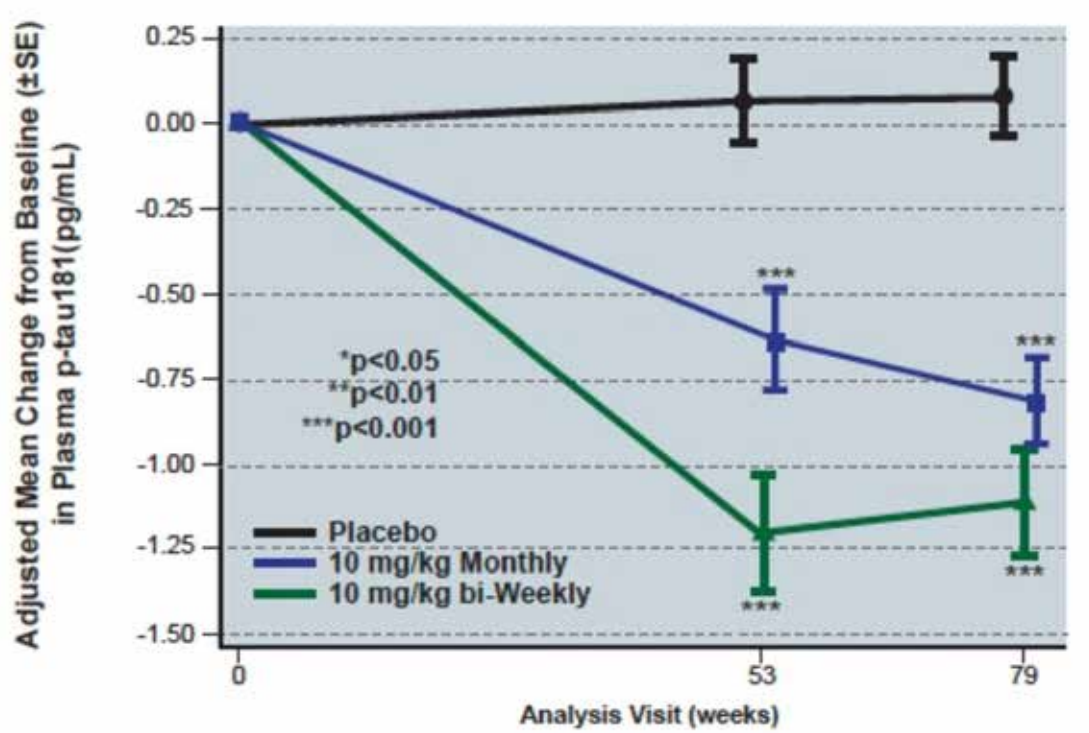
How Amyloid Plaque Reduction is Related to Soluble Amyloid and P-tau

Increase in plasma Aβ42/40 ratio reflect changes in the dynamics of amyloid aggregation or normalization of amyloid levels related to brain amyloid clearance



Placebo:	88	82	66
10 mg/kg Monthly:	95	86	80
10 mg/kg bi-Weekly:	43	39	33

Lecanemab-mediated effects on P-tau181 demonstrate that targeting amyloid influence the downstream tau-related processes



Placebo:	179	164	162
10 mg/kg Monthly:	155	146	142
10 mg/kg bi-Weekly:	84	75	74

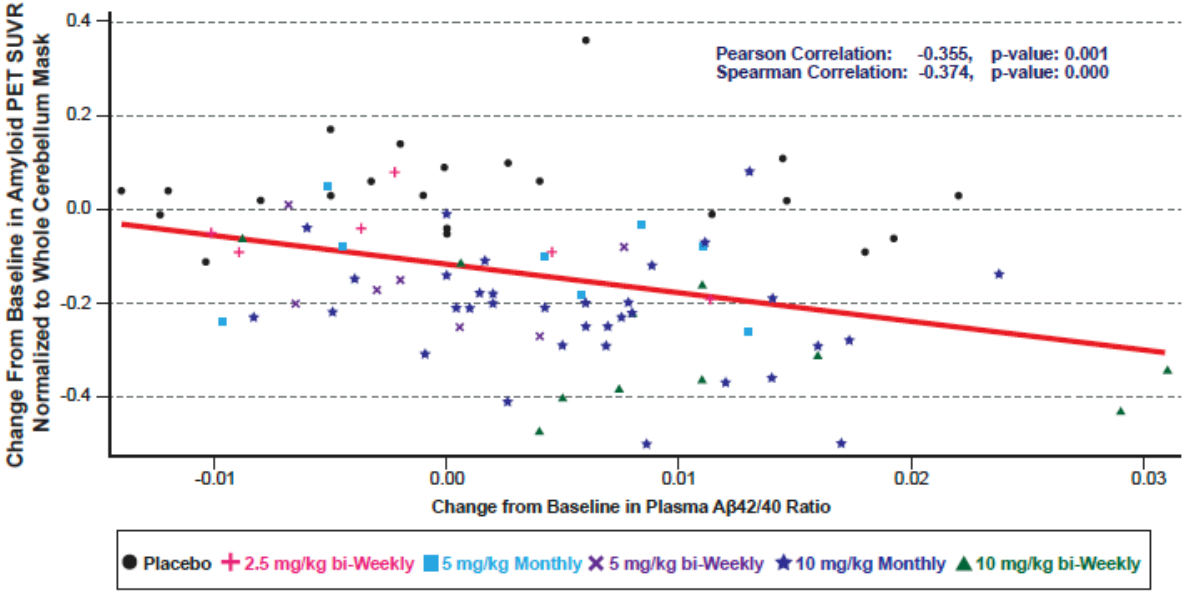
Y-axis was inverted for plasma **Aβ42/40 Ratio. Increase in** plasma **Aβ42/40 Ratio reflects decrease in brain amyloid levels for this inverted figure.**

Aβ, amyloid-beta; P-tau, phosphorylated tau.

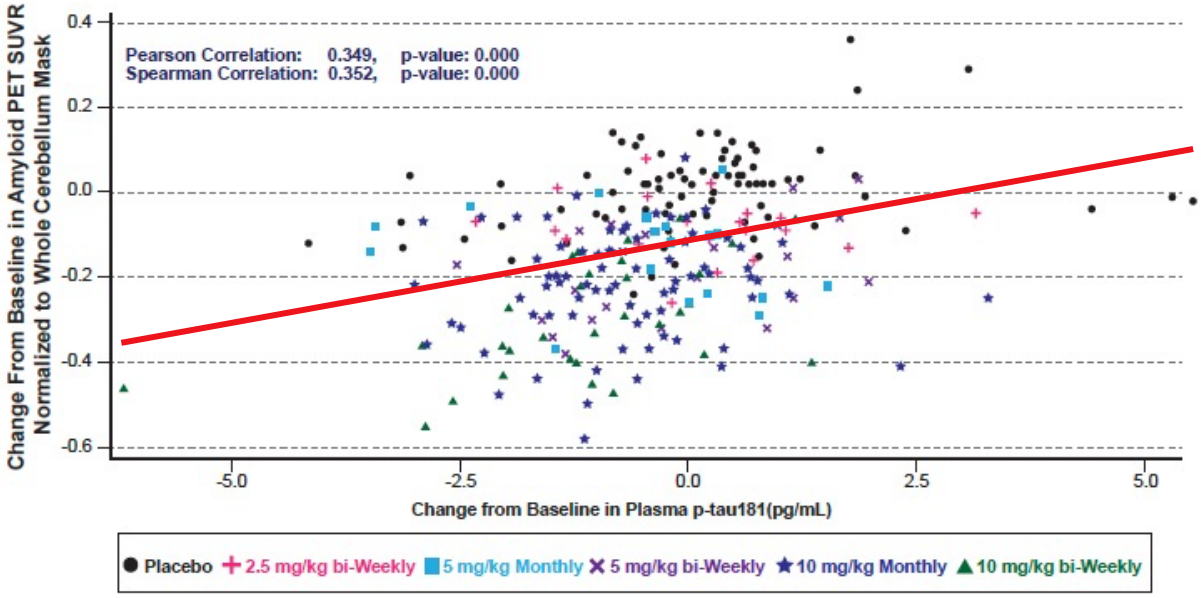
Peripheral Measures of Amyloid Reduction Provide Greater Opportunities for Implementation in Clinical Use:

Correlation with Amyloid PET

Change From Baseline in Amyloid PET SUVr and Plasma Aβ42/40 Ratio at 18 Months – Study 201 Core



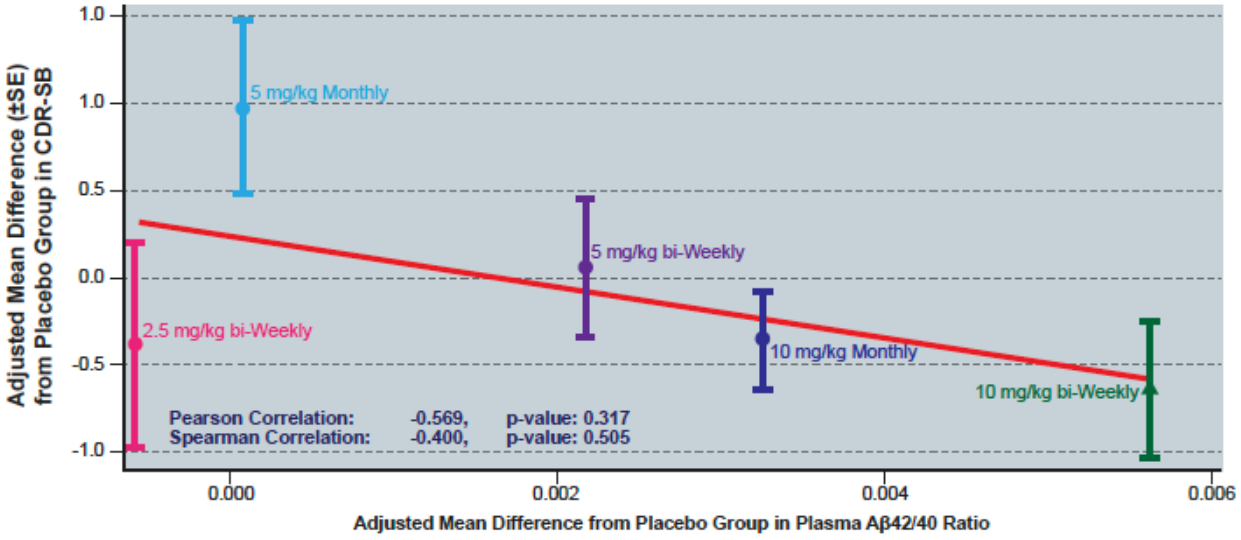
Change From Baseline in Amyloid PET SUVr and Plasma p-tau181 at 18 Months – Study 201 Core



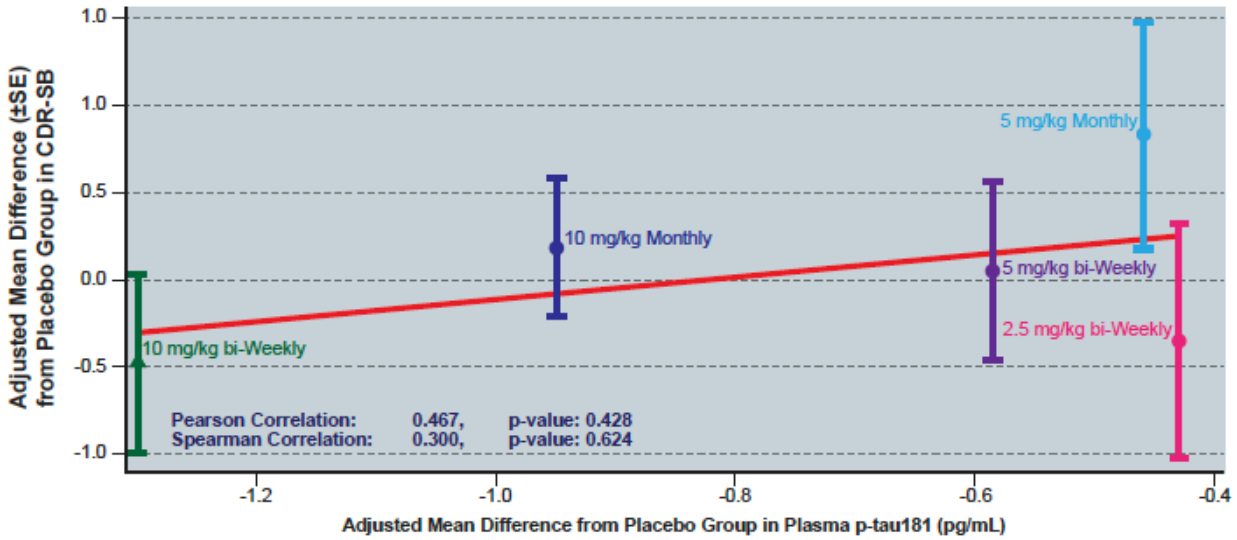
Aβ, amyloid-beta; PET, positron emission tomography; p-tau, phosphorylated tau; SUVr, standardized uptake value ratio.

Can Plasma Biomarkers Help with Measuring Clinical Changes?

Correlation between Change From Baseline in Plasma Aβ42/40 Ratio and CDR-SB at 18 Months – Study 201 Core



Correlation between Change From Baseline in P-tau181 and CDR-SB at 18 Months – Study 201 Core



Aβ, amyloid-beta; CDR-SB, Clinical Dementia Rating Scale-sum of boxes; P-tau, phosphorylated tau.

BIOMARKER CHANGES FOLLOWING CESSATION OF THERAPY

Amyloid PET SUVr & Plasma Aβ42/40, P-tau181 Ratio After Discontinuation of Treatment:
Recapitulation of Disease Progression

Treatment discontinuation results in return towards pre-treatment in plasma Aβ42/40 Ratio (47%), P-tau181 (24%) and amyloid PET SUVr (21%), recapitulating the progression of the amyloid cascade

Plasma Aβ42/40 Ratio is reflective of continuous production of amyloid species and is an early indicator of brain plaque accumulation (redevelopment)

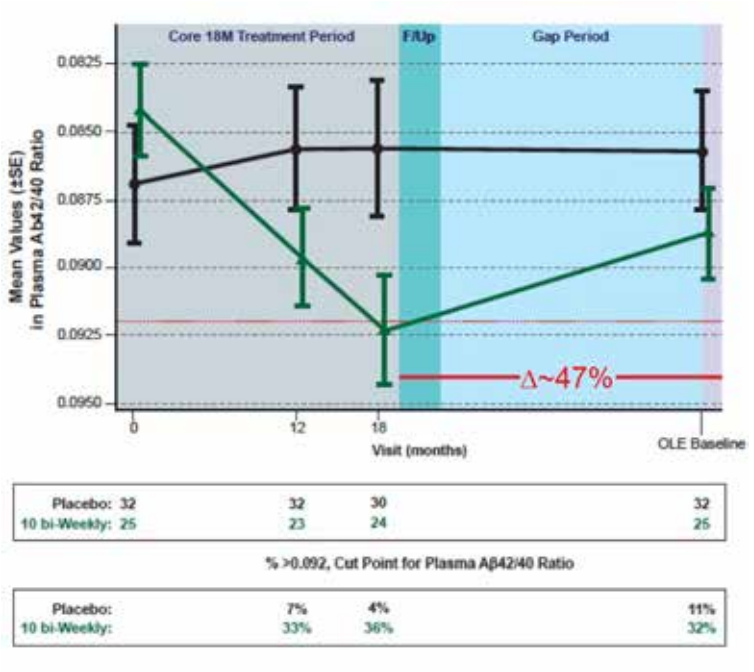
→

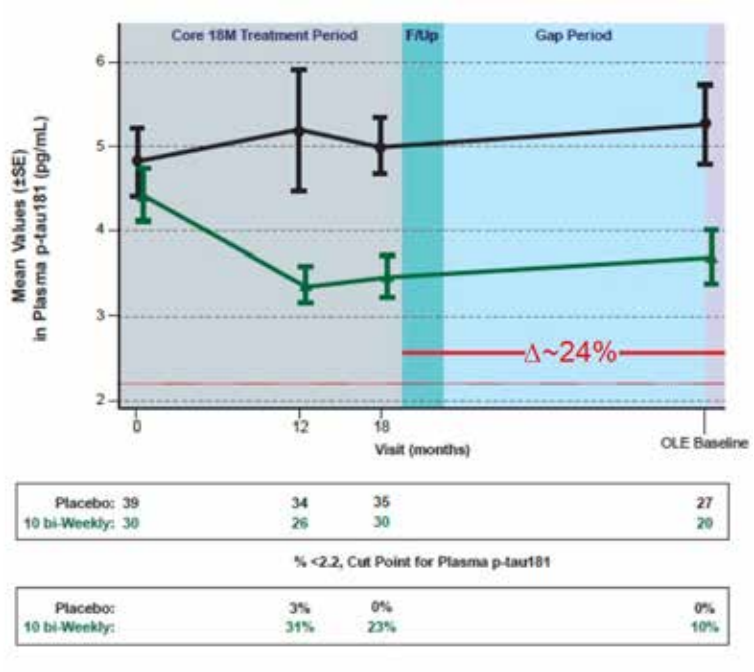
Increase in plasma p-tau181 is associated with clinical decline

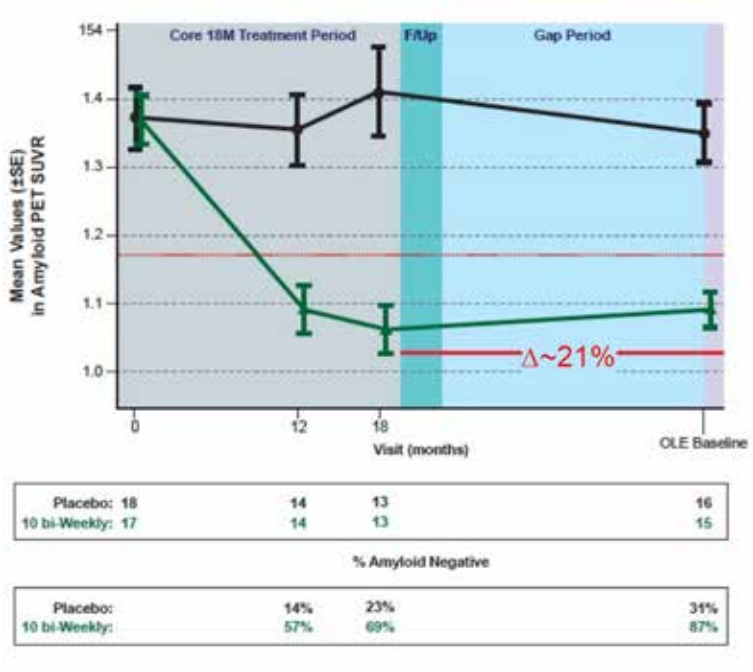
→

Increase in amyloid PET SUVr is reflective of slow rate of amyloid accumulation

Less Amyloid







Note: Y-axis was inverted for plasma **Aβ42/40 Ratio. Increase in** plasma **Aβ42/40 Ratio reflects decrease in brain amyloid levels for this inverted figure.**

Aβ, amyloid-beta; PET, positron emission tomography; p-tau, phosphorylated tau; SUVr, standardized uptake value ratio.

Dosing Regimen After Reaching PET Amyloid Negativity:

Model Predicted PET SUVr, Plasma Aβ42/40 Ratio, and Plasma P-tau181 Following Various Dosing Regimens After 18 Months Treatment at 10 mg/kg Biweekly

Aβ42/40:

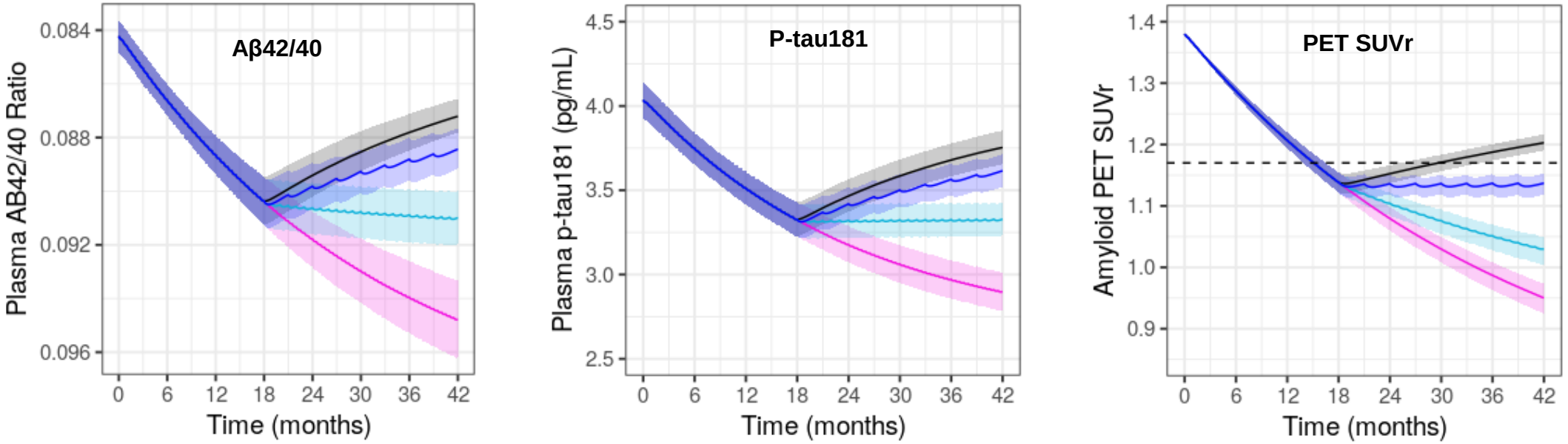
- A maintenance dose of 10 mg/kg monthly is predicted to maintain plasma Aβ42/40 ratio at a level achieved following 18 months of treatment

P-tau181:

- A maintenance dose of 10 mg/kg monthly is predicted to maintain plasma P-tau181 at a level achieved following 18 months of treatment

Amyloid PET SUVr:

- A maintenance dose of 10 mg/kg every 3 months is predicted to maintain SUVr constant and below amyloid PET SUVr threshold of 1.17 following 18 months of treatment



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The DIAN-TU Tau NexGen Trials

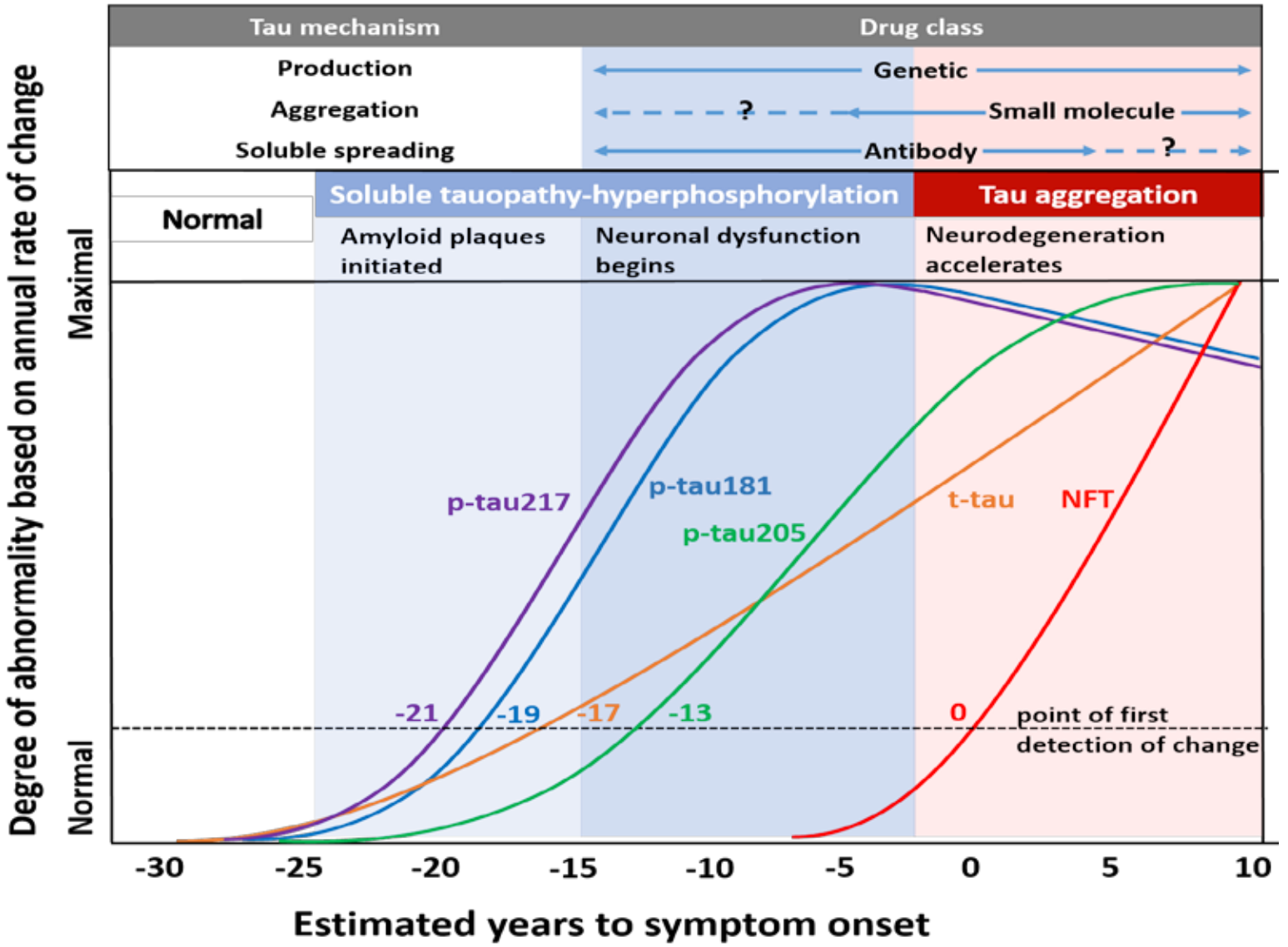
MAXIMIZING AMYLOID TARGETING IN TAU TRIALS

DIAN-TU Tau NexGen Trials

(Randall J Bateman PI)

Stages of Tau Pathology & Potential Mechanisms to Target Tau.

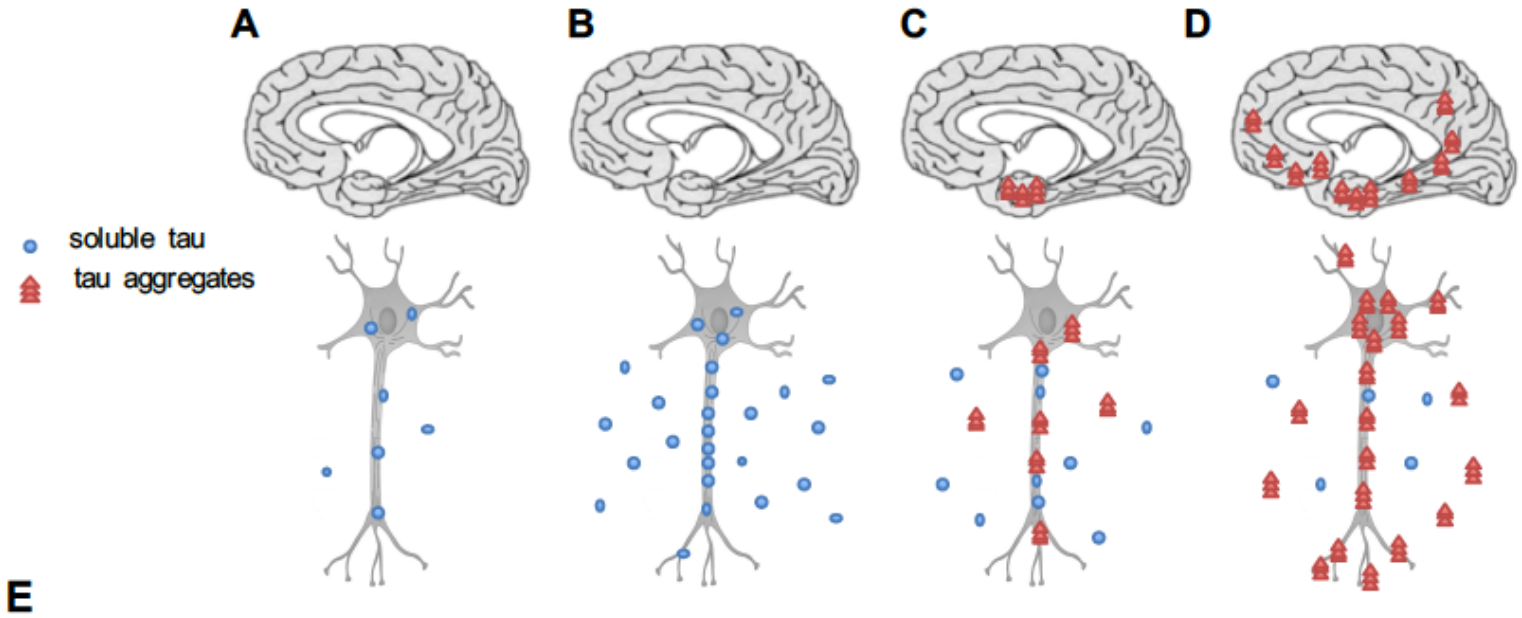
- Increasingly strong evidence highlights the role of amyloid plaques in triggering tau dysregulation
- Optimize tau therapeutics by removing a key driver of tau dyshomeostasis (amyloid)



Adapted from Barthelèmy et al, 2020

DIAN-TU Tau NexGen, Dominantly Inherited Alzheimer Network Trials Unit Tau Next Generation; NFT, neurofibrillary tangle; P-tau, phosphorylated tau; t-tau, total tau.

Rationale for Tau-Based Drug Studies



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Clinical Stages:		Cognitively normal (CDR=0)	Very mild AD (CDR=0.5)		Mild AD (CDR=1)
Pathophysiology stage:		A	B	C	D
Aggregated Brain Amyloid	Amyloid PET	Normal	↑	↑↑	↑↑↑
Aggregated brain tau	Tau PET	Normal	Normal	Braak I/II	Braak III/IV
soluble CSF tau concentration	Tau ELISA / MS	Normal	Very high	High	High
Production rate	Tau SILK	Normal	↑↑	↑↑	↑↑
Aggregation/ Irreversible loss (FTR)		Normal	Normal	↑	↑↑↑

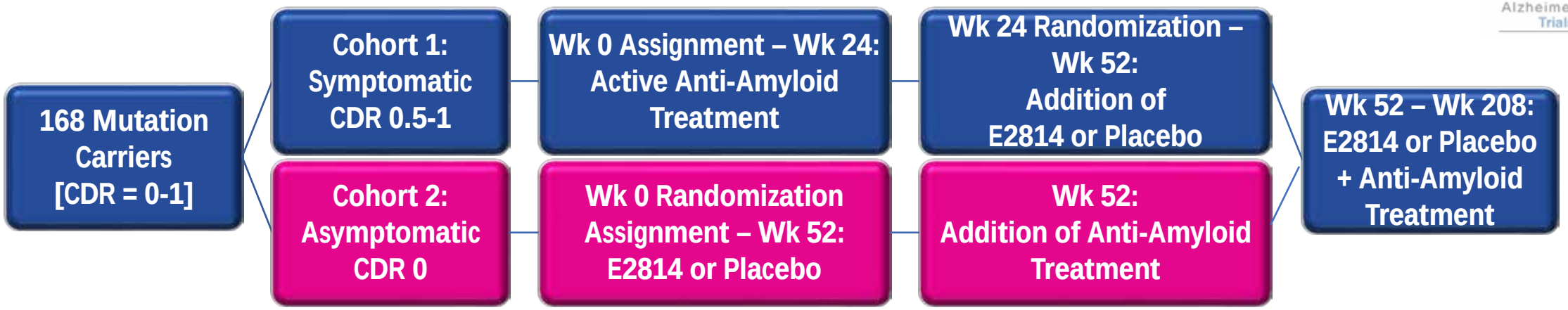
Amyloid plaques as a key driver of soluble tau production

Adapted from Sato, Barthelemy et al, Neuron 2018

AD, Alzheimer's disease; CDR, clinical dementia rating; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; FTR, fractional turnover rate; MS, mass spectrometry; PET, positron emission tomography; SILK, stable isotope labelling kinetics.

E2814 NexGen Design:

Amyloid and Tau Across the AD Clinical-Pathological Spectrum



- **Symptomatic: anti-amyloid drug first (6 mo), then add anti-tau drug**
- **Asymptomatic: anti-tau drug first (12 mo), then add anti-amyloid drug**
- **1:1 randomization**

AD, Alzheimer's disease; CDR, clinical dementia rating; DIAN-TU NexGen, Dominantly Inherited Alzheimer Network Trials Unit Tau Next Generation.

Conclusions

- Lecanemab treatment results in a dose-dependent change of central and peripheral amyloid and P-tau biomarkers
- Changes in peripheral amyloid and P-tau biomarkers begin to return towards pre-treatment levels following discontinuation of dosing, prior to amyloid PET (recapitulating normal biomarker cascades)
- Peripheral biomarkers are likely to provide critical information on initial response to lecanemab (response vs non-response) and guiding decisions on long-term use
- Ongoing studies with sustained periods of maximal amyloid suppression are key to further understanding the association of peripheral amyloid and P-tau biomarkers with clinical outcomes and the role of these biomarkers in monitoring tau-specific therapies in combination with lecanemab
  - Phase 3 data will help address limitations of current data set, including relatively small data set; underrepresentation of APOE4 carriers in 10 mg/kg biweekly and overrepresentation in 10 mg/kg monthly in Core; possible biased population for Core to OLE (Gap period); and uncertainty regarding level of biomarker effect required for optimal clinical efficacy

APOE4, apolipoprotein-E4; OLE, open-label extension; PET, positron emission tomography; p-tau, phosphorylated tau.