Sabirnetug overview and use of a pTau217 Assay as a Marker of Amyloid Burden for Screening Participants in an Ongoing Phase 2 Study, ALTITUDE-AD.

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Disclosure

- Dr. Siemers is an employee and shareholder at Acumen Pharmaceuticals

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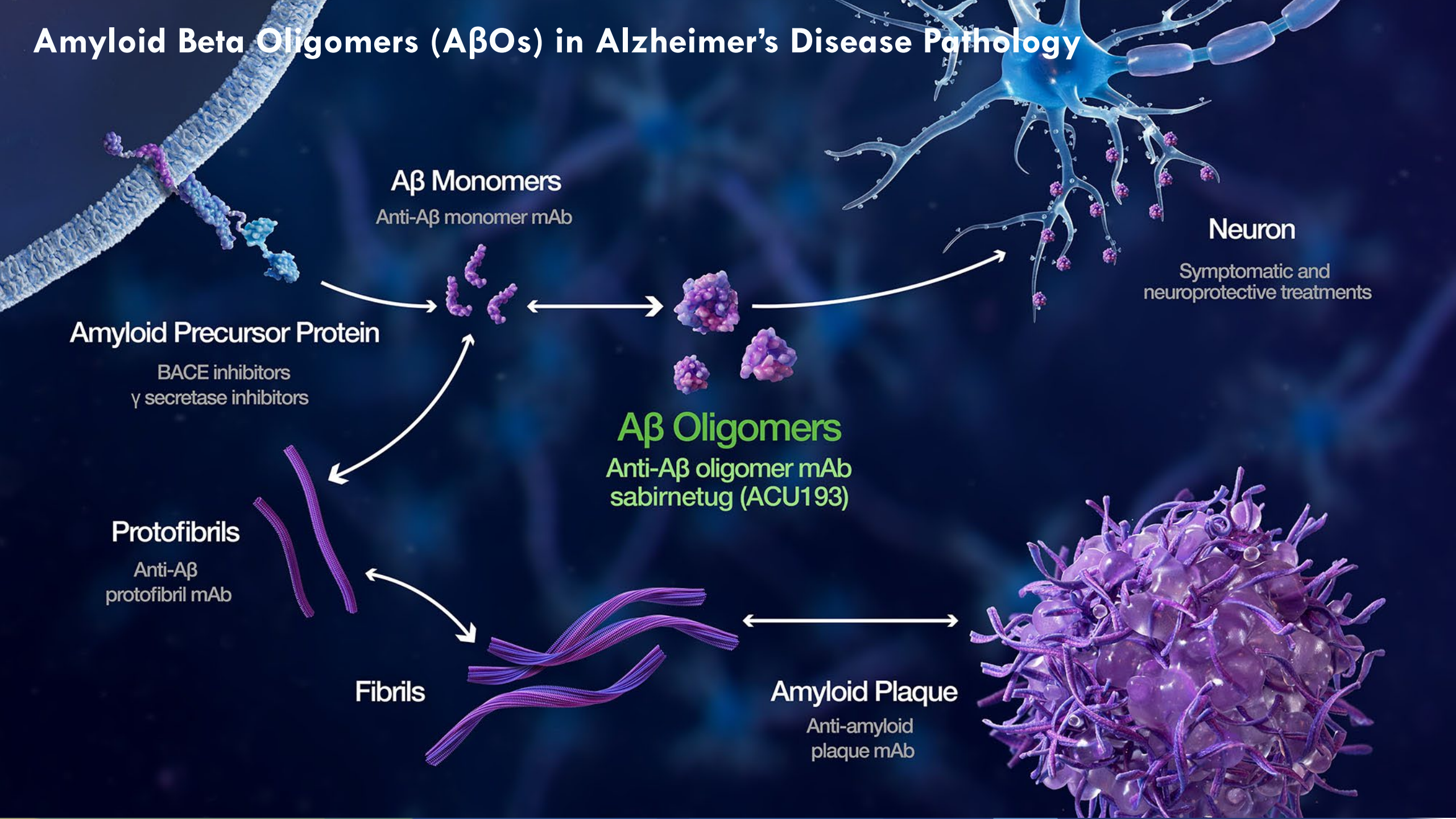
Amyloid Beta Oligomers (AβOs) in Alzheimer's Disease Pathology

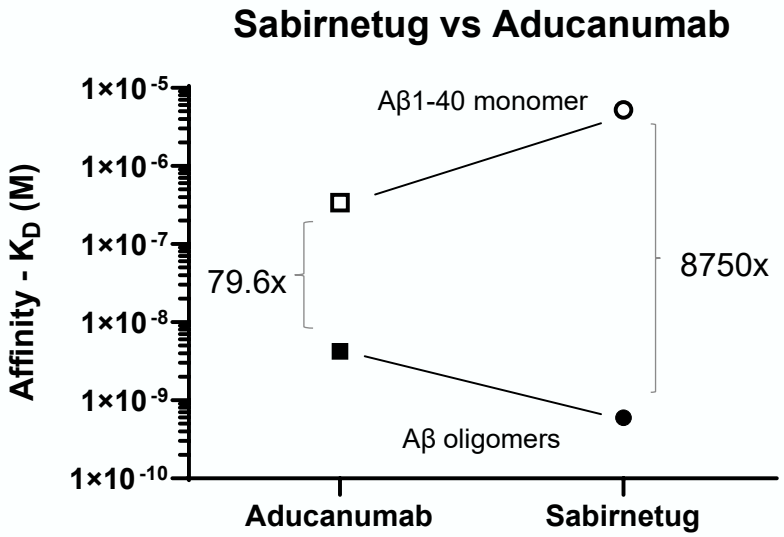


Sabirnetug is Highly Selective for Aβ Oligomers

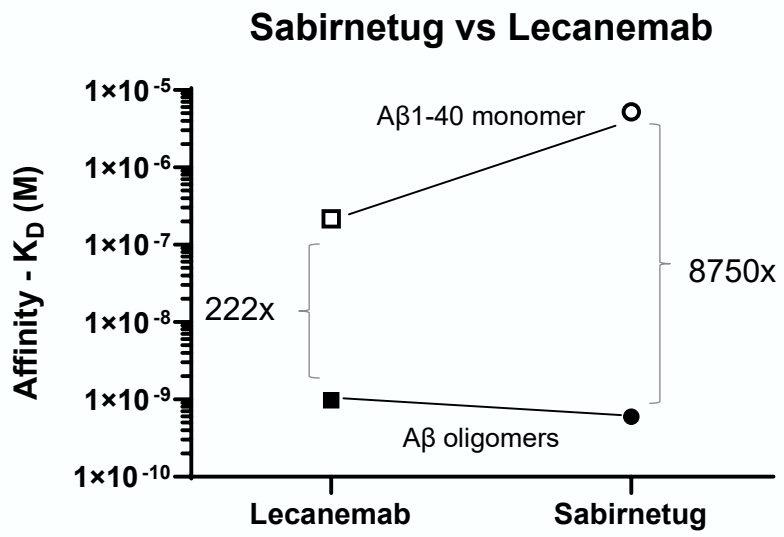
Relative selectivity for AβO versus monomeric Aβ measured with SPR

Higher binding affinity

Sabirnetug is more selective for AβOs than aducanumab

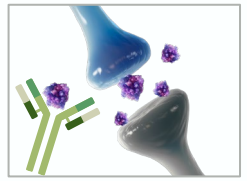


Sabirnetug is more selective for AβOs than lecanemab



Internal data, 2024

Targeting Soluble AβOs: An Early and Continuous Intervention in AD

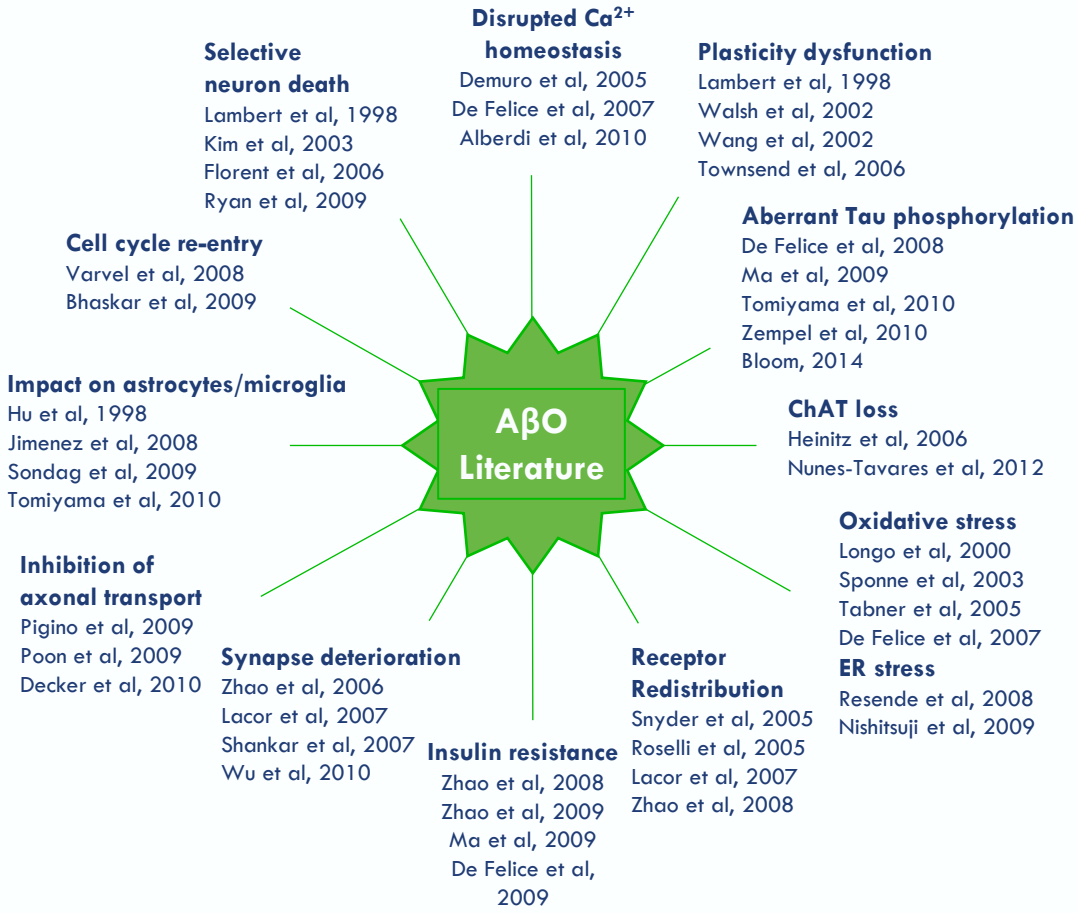


Why focus on soluble forms of Aβ?

- Soluble Aβ forms appear early in the course of disease pathophysiology
- Reduced neuronal toxicity and intervention at the synaptic level may prevent irreversible neuronal cell death
- Production of toxic soluble Aβ persists after plaque removal

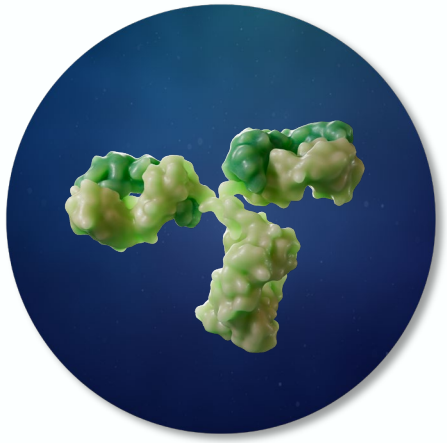
Consequences of soluble Aβ oligomer production:

- x Synapses dysfunction and loss
- x Tau hyperphosphorylation
- x Immune cell activation
- x Functional impairment



Adapted from Cline et al. 2018

Sabirnetug (ACU193) Overview



- **Sabirnetug**
  - Humanized monoclonal IgG2 antibody
  - Highly selective for globular amyloid beta oligomers (AβOs)
  - Clinical effect on synaptic biomarkers consistent with proposed mechanism of targeting AβOs[1]

- **INTERCEPT-AD Phase 1 clinical trial (NCT04931459, completed)[2,3]**
  - US-only study in early symptomatic AD (MCI or mild dementia with amyloid positivity based on PET)
  - SAD and MAD study design
  - Objectives: safety, pharmacokinetics, and target engagement

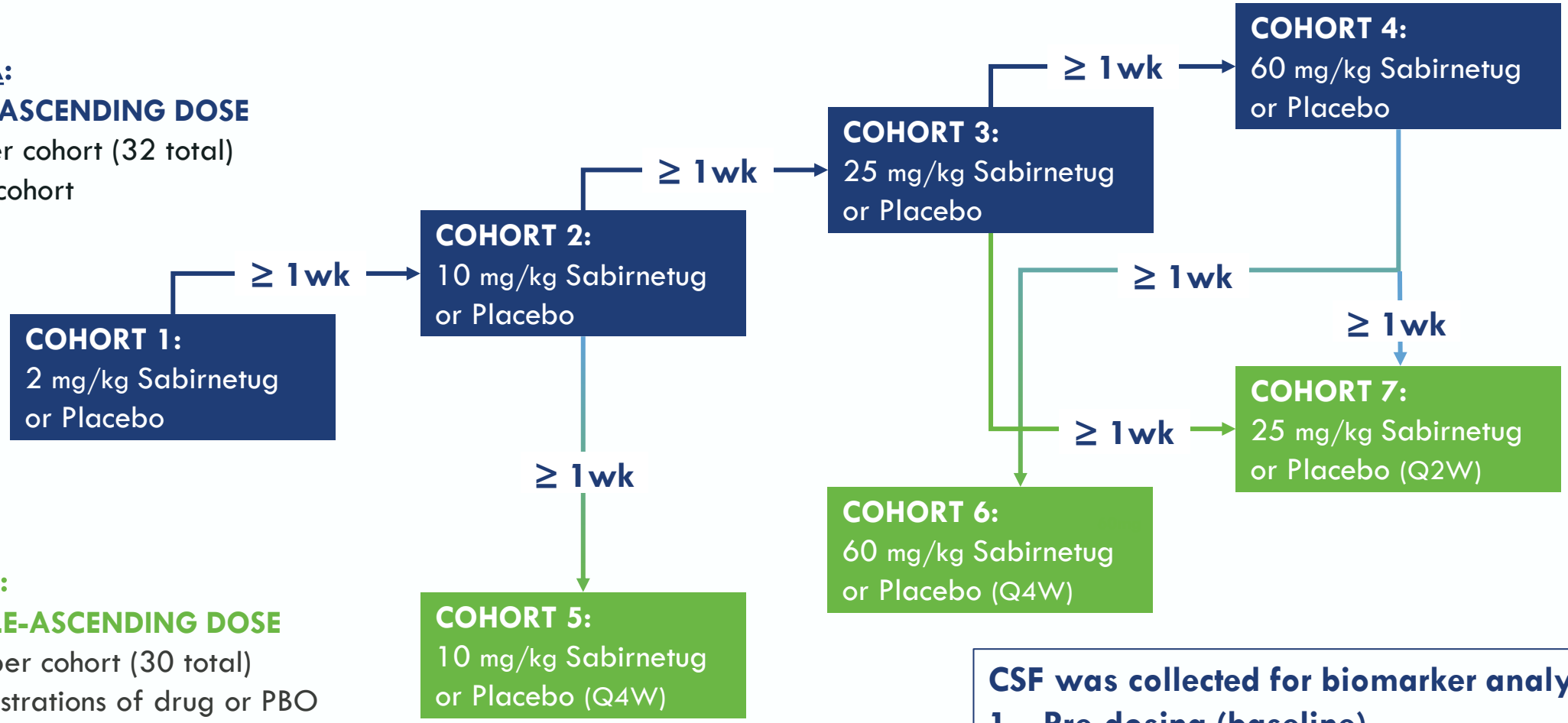
INTERCEPT-AD STUDY

- **ALTITUDE-AD Phase 2 clinical trial (NCT06335173, ongoing)**
  - Global study in MCI or mild AD participants
  - US, Canada, UK, Germany and Spain
  - MMSE: 22-30
  - CDR-GS: 0.5 or 1 and CDR Memory Box ≥0.5
  - Primary objective: evaluate efficacy in slowing cognitive and functional decline
  - iADRS change from baseline to Week 80

ALTITUDE-AD
CLINICAL RESEARCH STUDY

1. Cline et al. AAIC 2024
2. Siemers et al. JPAD 2025; 12:100005.
3. Cline et al. JPAD 2026; in press

INTERCEPT-AD: A Randomized Placebo Controlled Phase 1 Study in Early AD Patients



CSF was collected for biomarker analysis:

1. **Pre-dosing (baseline)**
2. **Post-dosing (7-21 days; endpoint)**

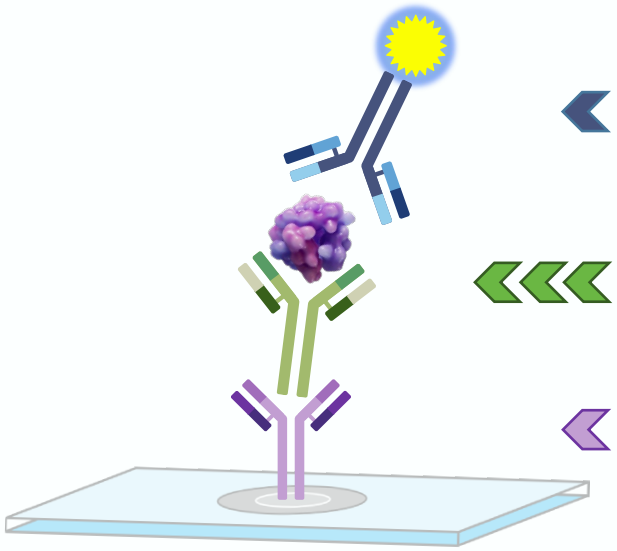
Q2W: Dosing every two weeks; Q4W: Dosing every four weeks.

Target Engagement Assessed by Measuring Sabirnetug-AβO Complex in CSF

- Novel assay configuration tailored to selectively detect sabirnetug-AβO complex in CSF as direct measure of target engagement
- Translated for clinical use from a preclinical assay developed by Merck that showed sabirnetug engages target AβOs in transgenic mouse brain (tg2576) in dose dependent manner

(please see slide 40 for more information)

MSD S-Plex (Turbo) Immunoassay



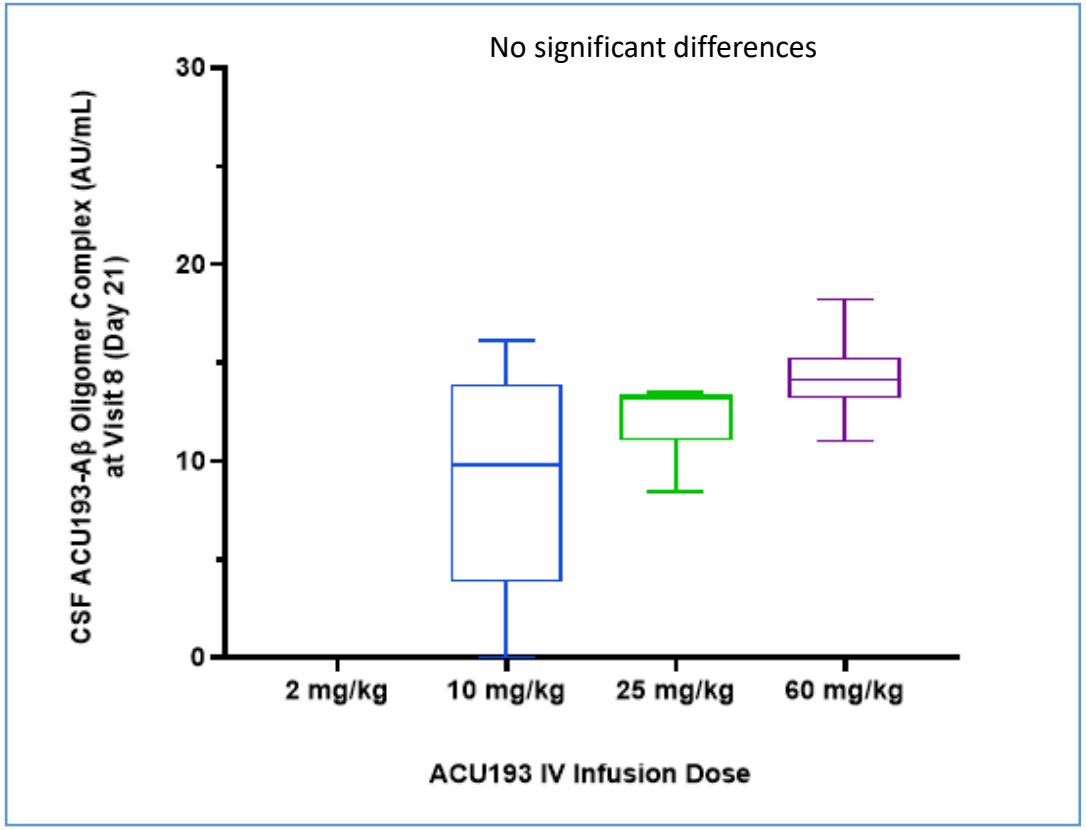
AβO selective detection
(anti-AβO mAb)

Only Sabirnetug-AβO complex is measurable

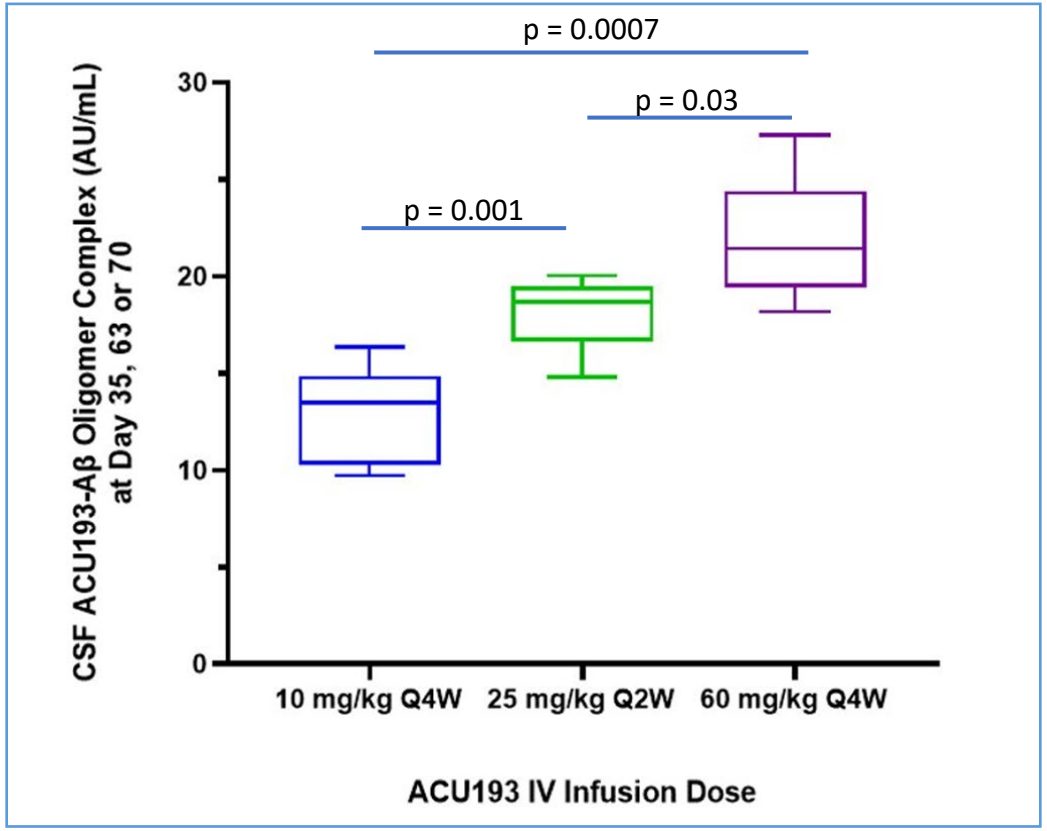
Sabirnetug drug specific capture
(anti-sabirnetug idiotype mAb)

Target Engagement of ACU193 with AβOs is Dose Proportional

Single Dose Cohorts



Multiple Dose Cohorts*

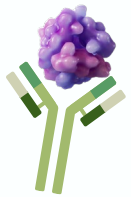


Dose-related target engagement

*One patient from Cohort 5 (10 mg/kg Q4W) excluded because only received one administration of drug (discontinued after lacunar infarct)

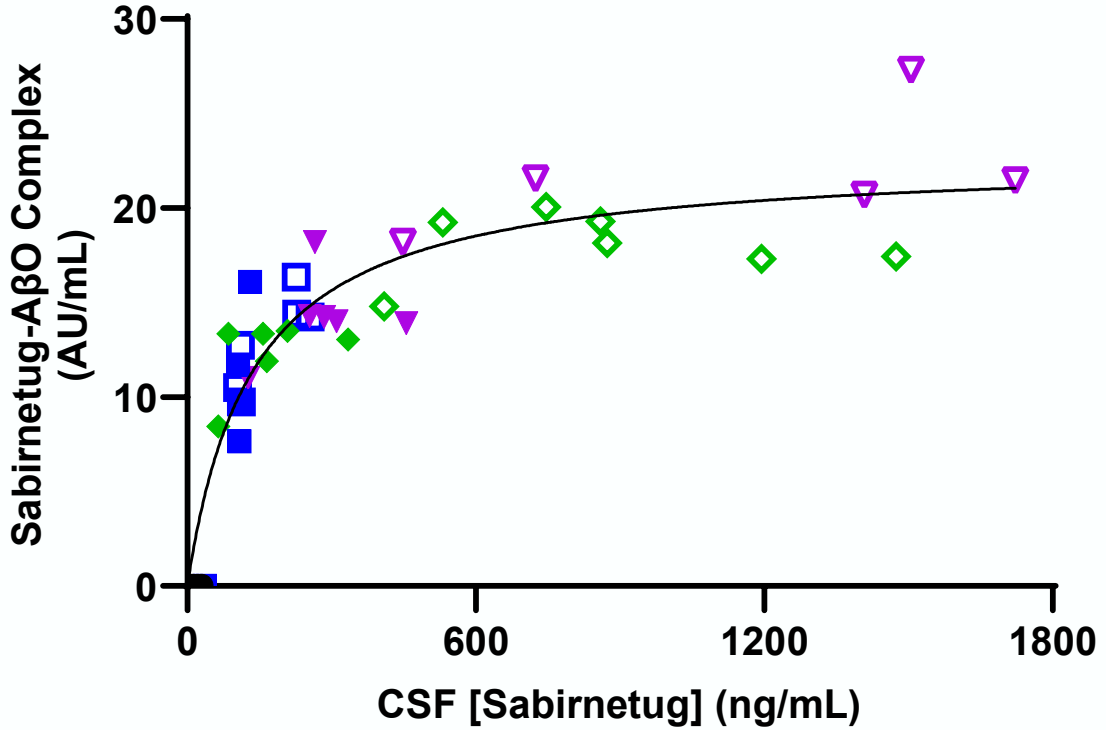
Central Target Engagement (Sabirnetug-AβO Complex) Approaches Maximum at Highest Sabirnetug Doses Administered in INTERCEPT-AD

Target Engagement



Sabirnetug-AβO Complex

Single & Multiple Dose Cohorts - Exposure Response Relationship (Emax Model)



- SAD 2 mg/kg
- SAD 10 mg/kg
- SAD 25 mg/kg
- SAD 60 mg/kg
- MAD 10 mg/kg Q4W
- MAD 25 mg/kg Q2W
- MAD 60 mg/kg Q4W

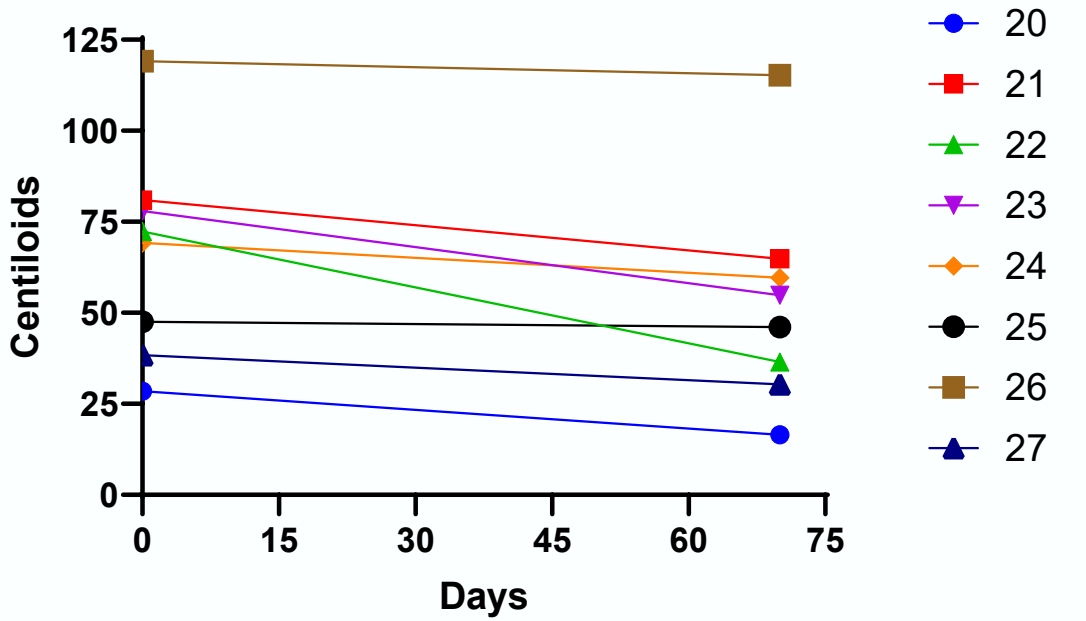
Emax: 22.7 AU/mL Complex
EC50: 136 ng/mL ACU193

*One patient from Cohort 5 (10 mg/kg Q4W) excluded because only received one administration of drug (study drug discontinued after lacunar infarct).

ACUMEN

Nearly All Sabirnetug-Treated Patients in High Dose MAD Cohorts Showed Reductions in Plaque Load After Three Doses at 63 or 70 days

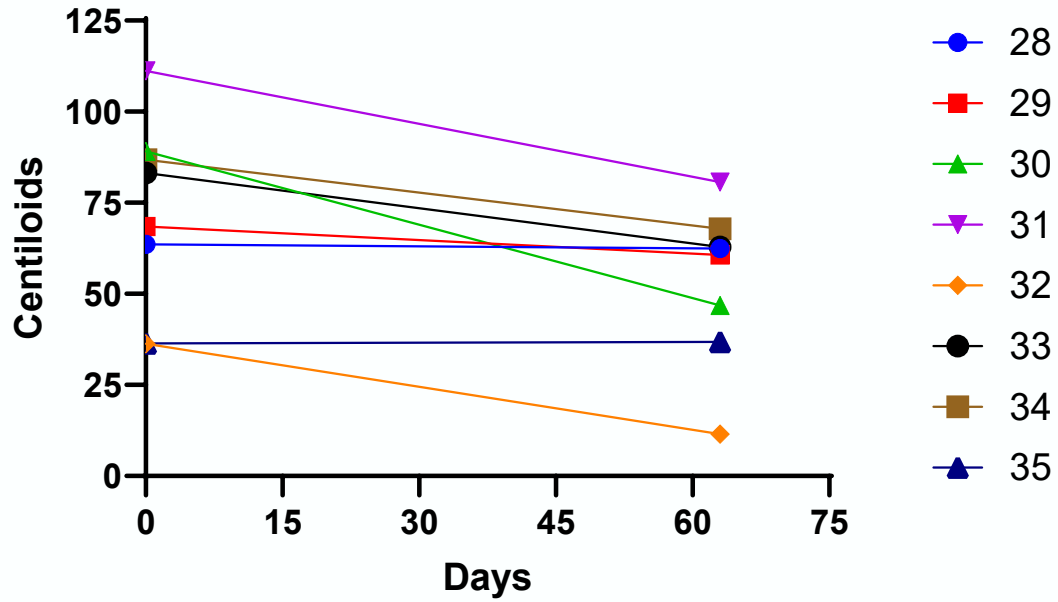
25 mg/kg Q2W MAD



Mean reduction in amyloid plaque

Δ (absolute value, centiloids)	13.7
Δ (%, centiloids)	20.6%

60 mg/kg Q4W MAD



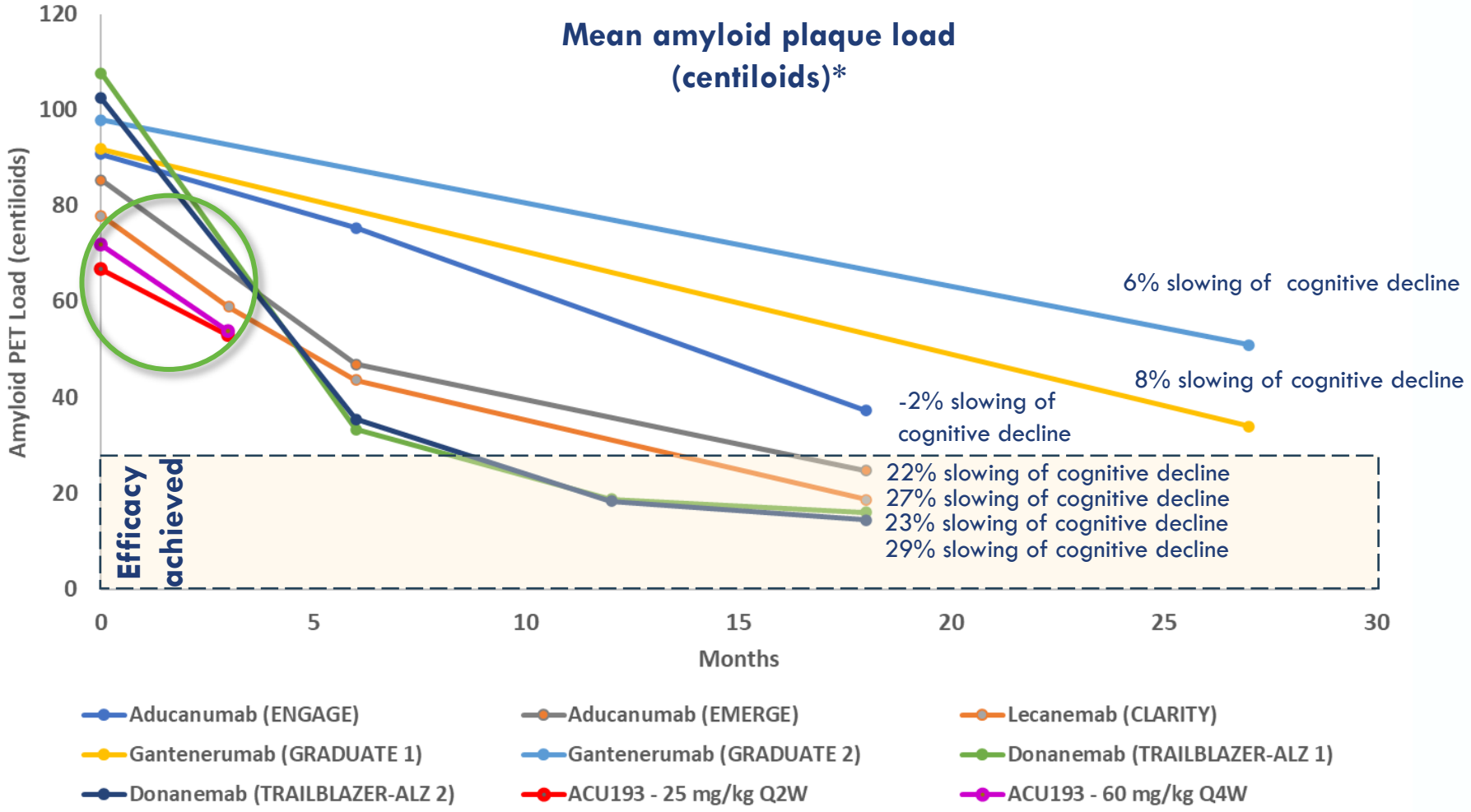
Mean reduction in amyloid plaque

Δ (absolute value, centiloids)	18.1
Δ (%, centiloids)	25.6%

Plaque load based on florbetapir PET

ACUMEN

Highest Doses of INTERCEPT-AD Reduced Amyloid Plaque at Similar Rate and Magnitude to Lecanemab at Comparable Timepoints



Acumen Pharmaceuticals, data on file; van Dyck (2023), NEJM (amyloid PET reduction estimated from graphs).

*There have been no head-to-head clinical trials between the product candidates listed above. Study designs and protocols for each product candidate were different, and as a result, results may not be comparable between product candidates.

INTERCEPT-AD: ARIA-E summary

SAD

2 mg/kg
Cohort 1

ApoE	D21	D140
3,4		
3,3	PBO	PBO
3,4		
2,3		
3,4	PBO	PBO
3,3		
3,3		
3,3		

10 mg/kg
Cohorts 2, 5

ApoE	D21	D140
3,4	PBO	PBO
3,3		
3,3		
3,4		
3,4	PBO	PBO
3,4		
3,4		
3,4		

25 mg/kg
Cohorts 3, 7

ApoE	D21	D140
3,3		
3,3	PBO	PBO
4,4		
3,3		
2,4		
3,3	PBO	PBO
3,4		
3,3		

60 mg/kg
Cohorts 4, 6

ApoE	D21	D140
4,4	PBO	PBO
3,4		
3,4	PBO	PBO
3,3		
3,3		
3,4		
2,4		
3,4		

MAD

ApoE	D28	D70	D196
2,3			
3,3			
3,3			
4,4			
3,3	PBO	PBO	PBO
3,4			
4,4			
3,4			
3,3			
3,4	PBO	PBO	PBO

ApoE	D28	D70	D98
3,3			
3,4			
3,4			
3,4			
3,4			
3,4	PBO	PBO	PBO
3,3			
3,4	PBO	PBO	PBO
4,4			
4,4			

ApoE	D28	D63	D126
3,4			
3,3			
3,3			
4,4			
4,4	PBO	PBO	PBO
3,3			
3,4			
3,4			
3,4	PBO	PBO	PBO
3,3			

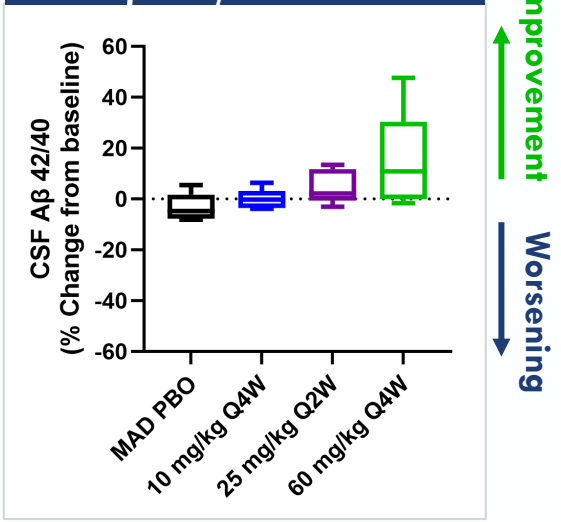
NO ARIA-E
Asymptomatic ARIA-E
Symptomatic ARIA-E
Discontinued

PBO: Patient on placebo

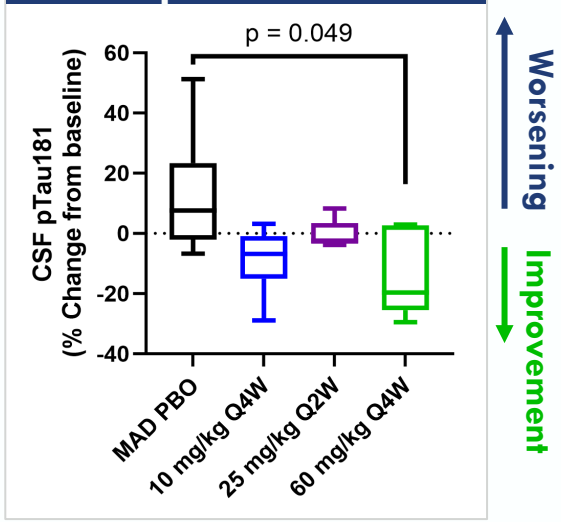
No ε4 homozygotes developed ARIA-E despite comprising 6 individuals (13%) in study; 4/5 ARIA-E cases are ε4 heterozygotes and 1/5 (at 60 mg/kg) was a non-carrier.

Sabirnetug-Associated Changes in CSF Biomarkers Indicate Downstream Pharmacology for Amyloid, pTau Species, and Synaptic Markers After 3 Administrations

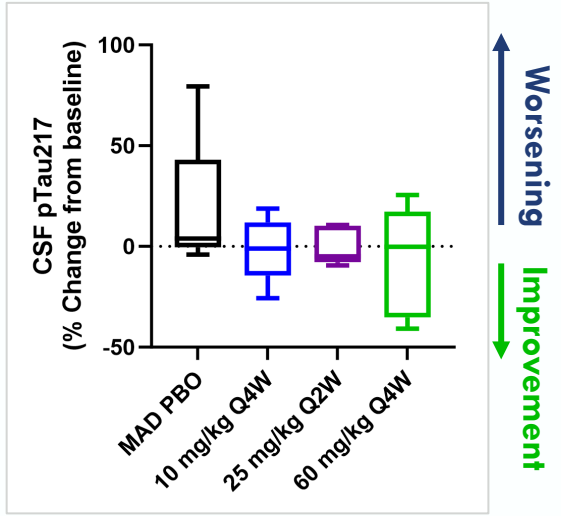
Aβ 42/40 Ratio



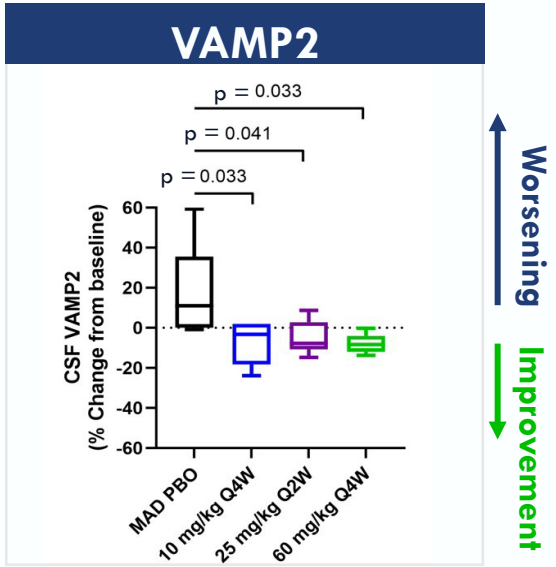
pTau181



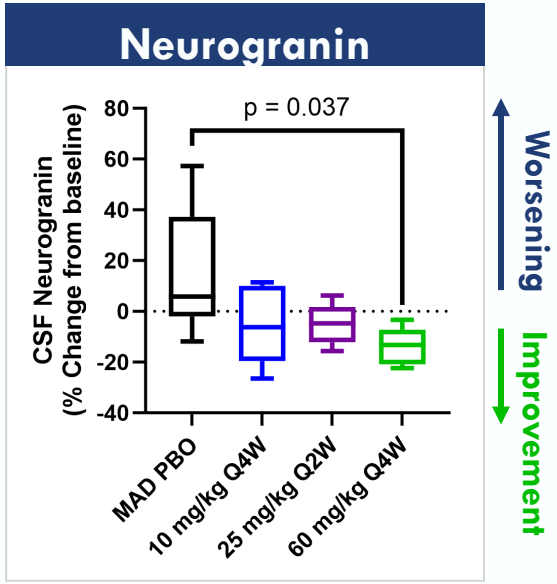
pTau217



VAMP2



Neurogranin

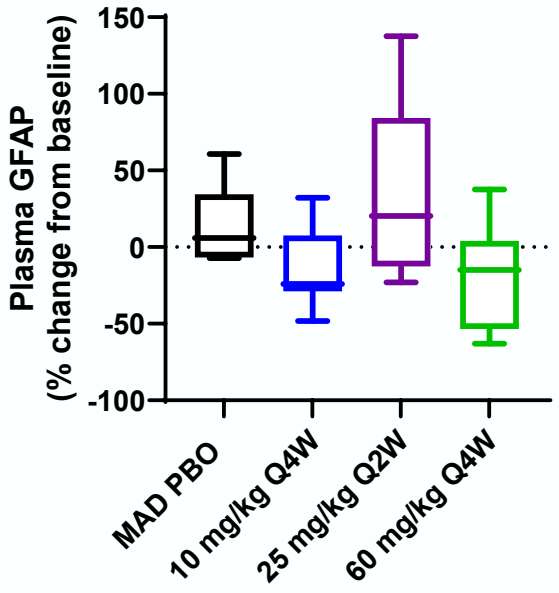


- *n = 8 subjects/treated group; 6 subjects in pooled placebo (PBO)*
- *p-values from unpaired, 2-sided Student's t test*

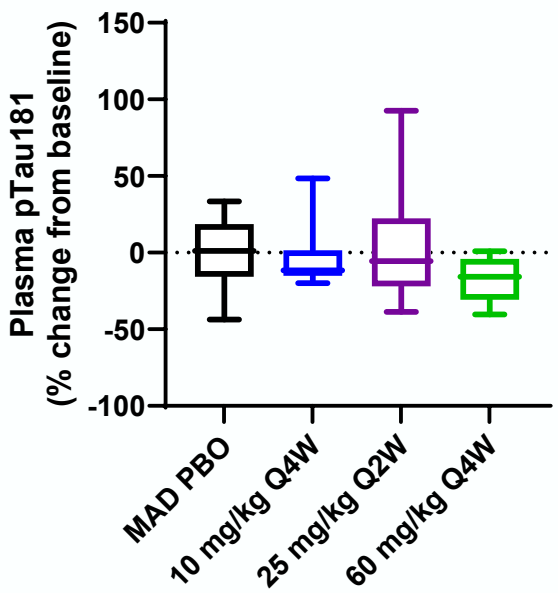
Trend Toward Normalizing Plasma Biomarkers with 10 mg/kg and 60 mg/kg Q4W

1-6 wk post-dosing

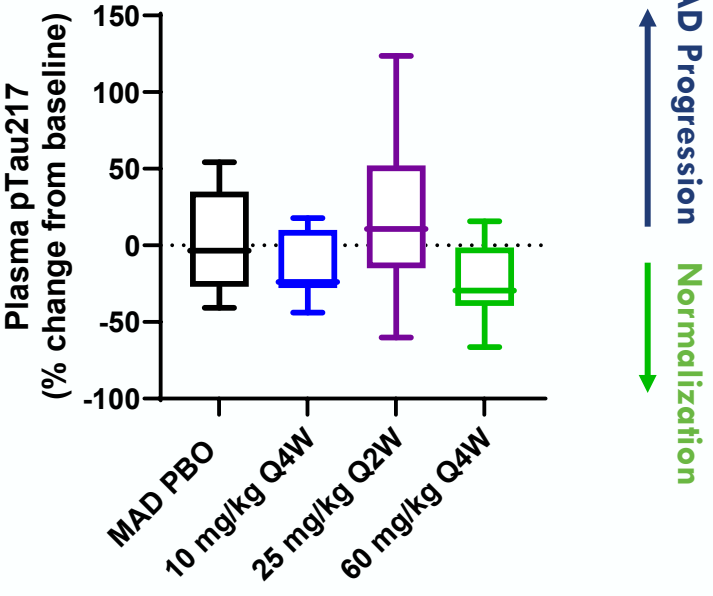
GFAP



pTau181



pTau217



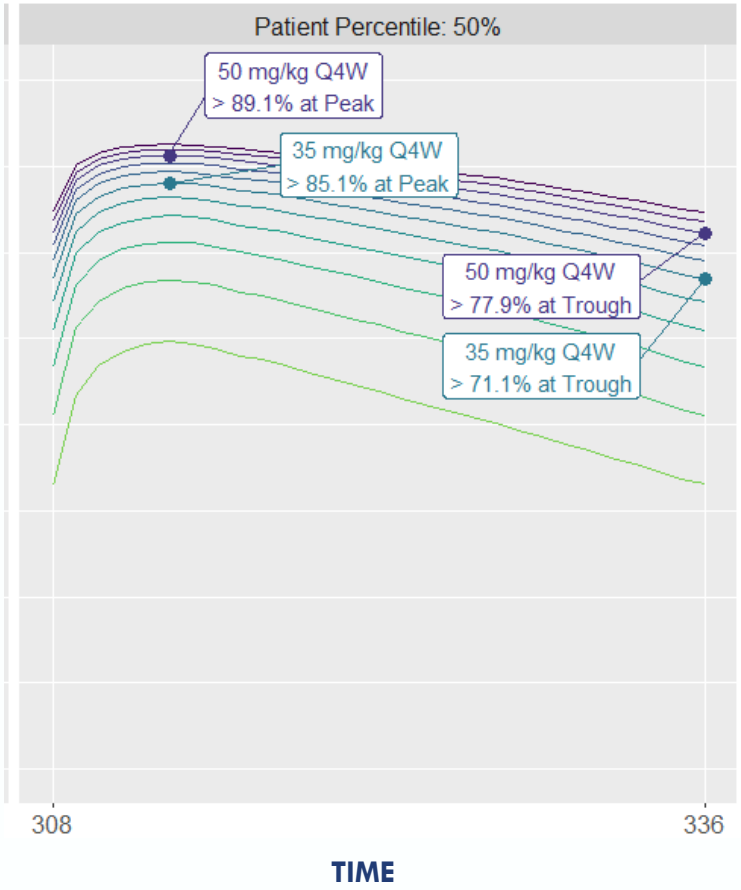
- Plasma levels of glial fibrillary acidic protein (GFAP), pTau181, and pTau217 in 10 mg/kg Q4W & 60 mg/kg Q4W cohorts trended toward a greater reduction from baseline levels than placebo
- More impact to fluid biomarkers was observed with longer dosing duration
  - The 25 mg/kg Q2W cohort differed in dose and sample timing, with drug on board for less time than the 10 mg/kg & 60 mg/kg Q4W cohorts

n = 8 subjects/treated group; 6 subjects in pooled placebo (PBO); p-values from unpaired, 2-sided Student's t test

ACUMEN

Simulated CSF Target Engagement at Steady-State

CSF target engagement was simulated at a candidate list of doses given Q4W at steady-state



Ph2 Dosing Strategy (ALTITUDE-AD)

lower dose: 35 mg/kg Q4W

upper dose: 50 mg/kg Q4W

- Notable **diminishing differentiation** as dose increases
- Doses were selected with **peak-trough** variation in mind: select doses based on trough (end of dosing interval) CSF engagement

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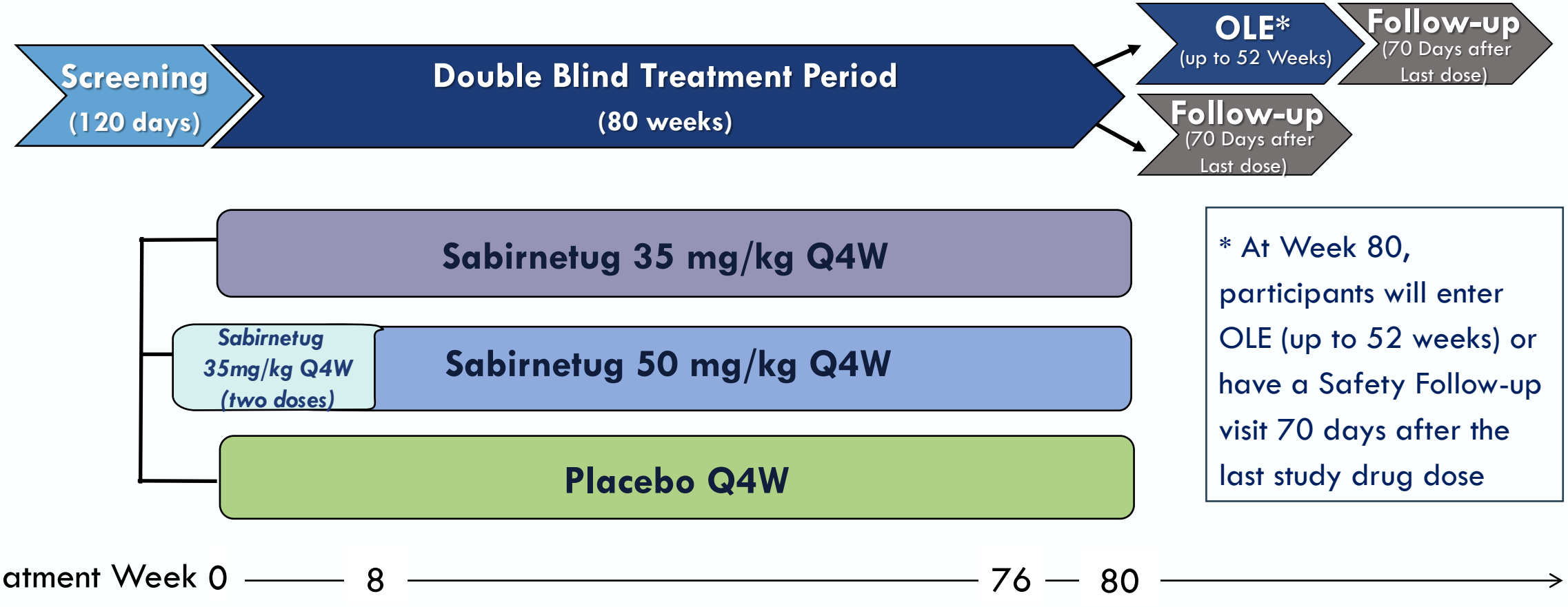
CERTARA

ALTITUDE-AD: Phase 2 Study Design of Sabirnetug for Early AD

540 participants randomized 1:1:1



* At Week 80, participants will enter OLE (up to 52 weeks) or have a Safety Follow-up visit 70 days after the last study drug dose

In ALTITUDE-AD, We Aim to Reduce PET/LP Burden by Screening for pTau217

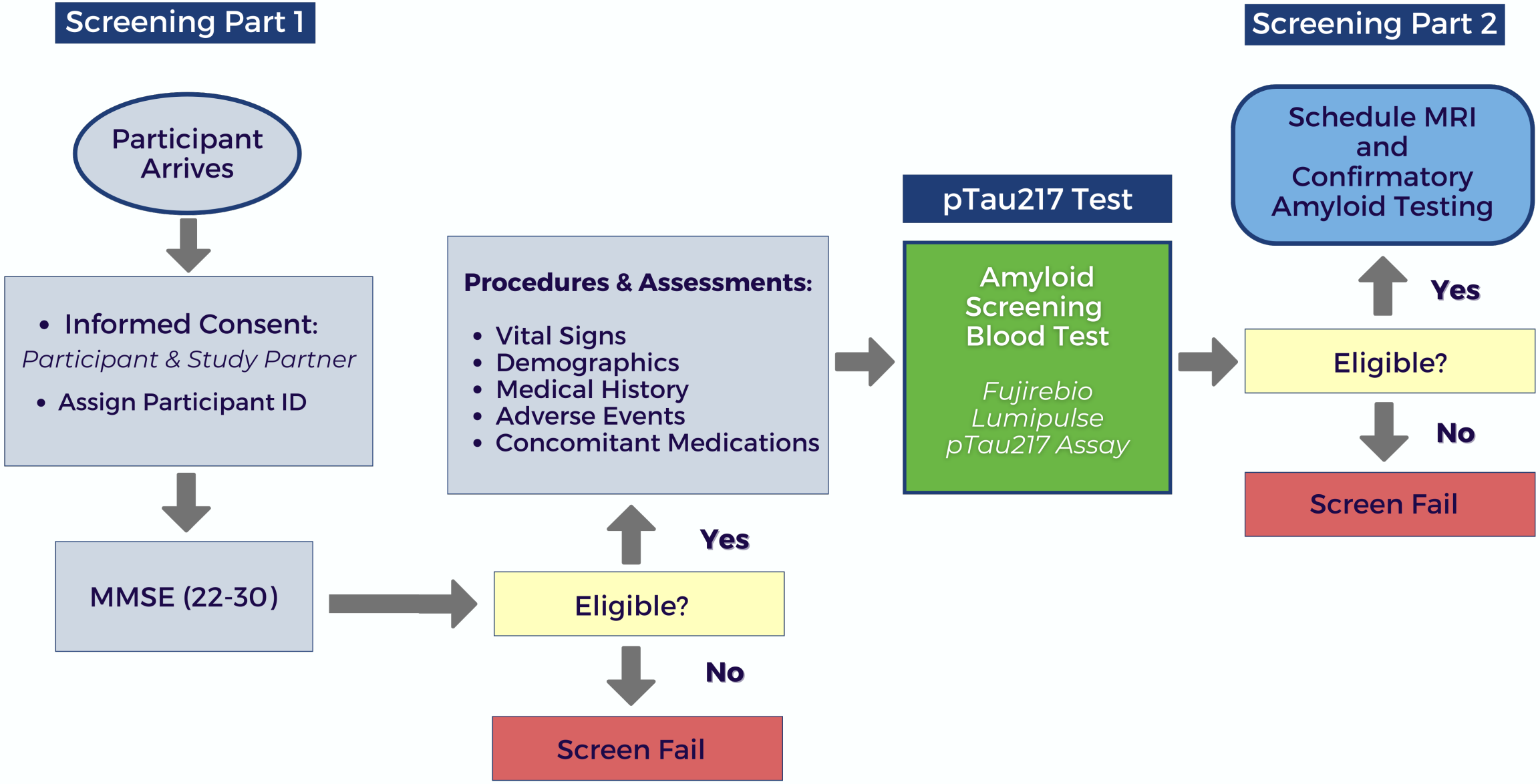
- Plasma concentrations of pTau217 are highly predictive for AD[1]
  - pTau217 is being used as an enrichment strategy to help identify potential participants with a high likelihood of meeting amyloid inclusion criteria on PET or CSF
  - The assay is not being used as a diagnostic

- The Fujirebio plasma pTau217 assay is a Lumipulse platform-based research use only assay that has been analytically and clinically validated as a Lab-Developed Test consistent with CLIA regulations

- For screening, we selected the pTau217 cut-point of 0.15 pg/mL because of its the high sensitivity (0.992) in this assay

[1]Ashton NJ, et al. *JAMA Neurol*. 2024;81(3):255–263.

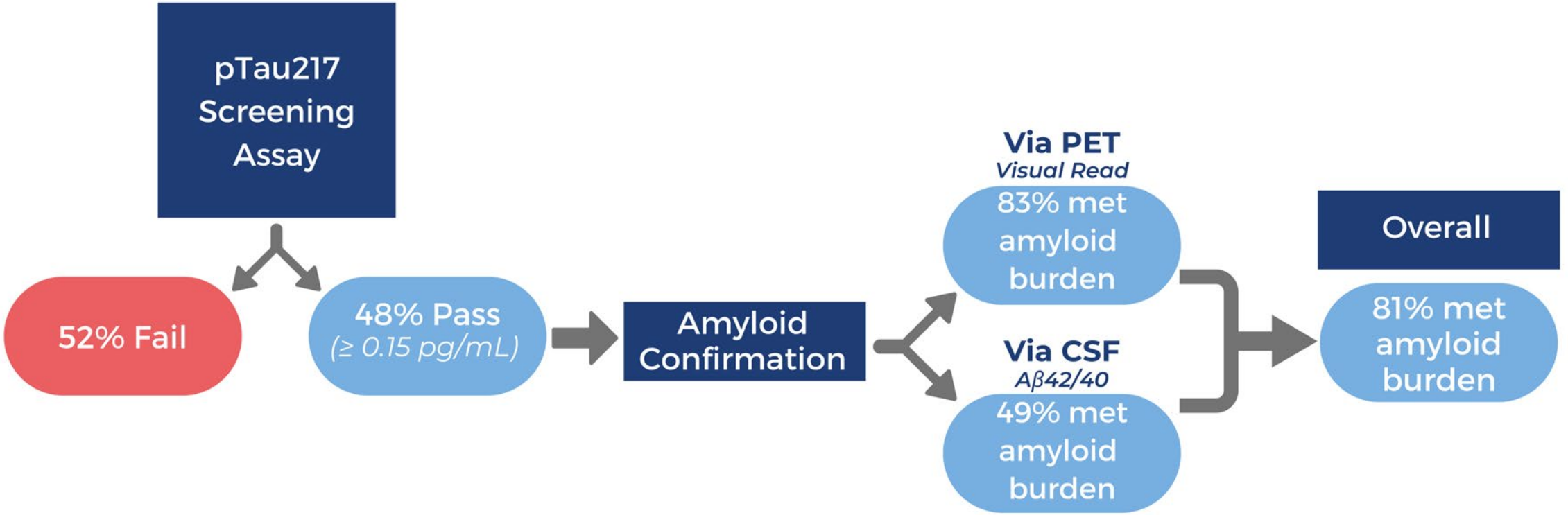
ALTITUDE-AD: Two-Part Screening Process



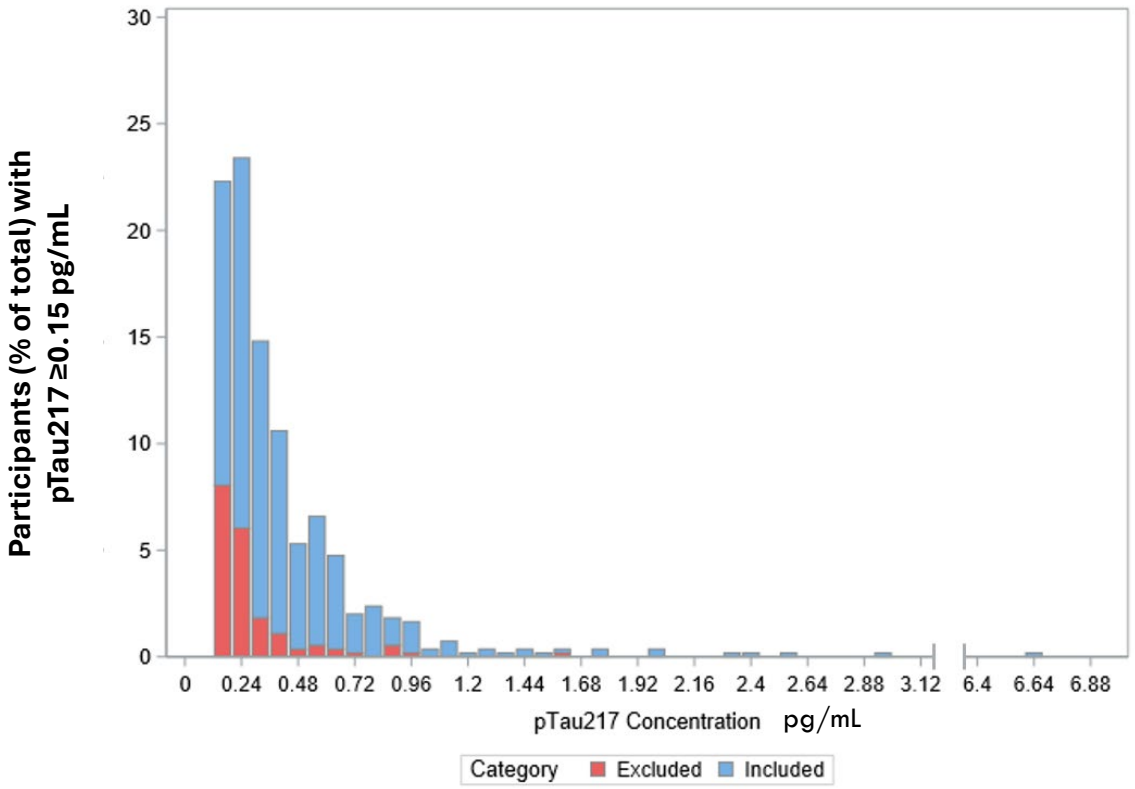
pTau217 Screening Results

North America (US and Canada) Study Data

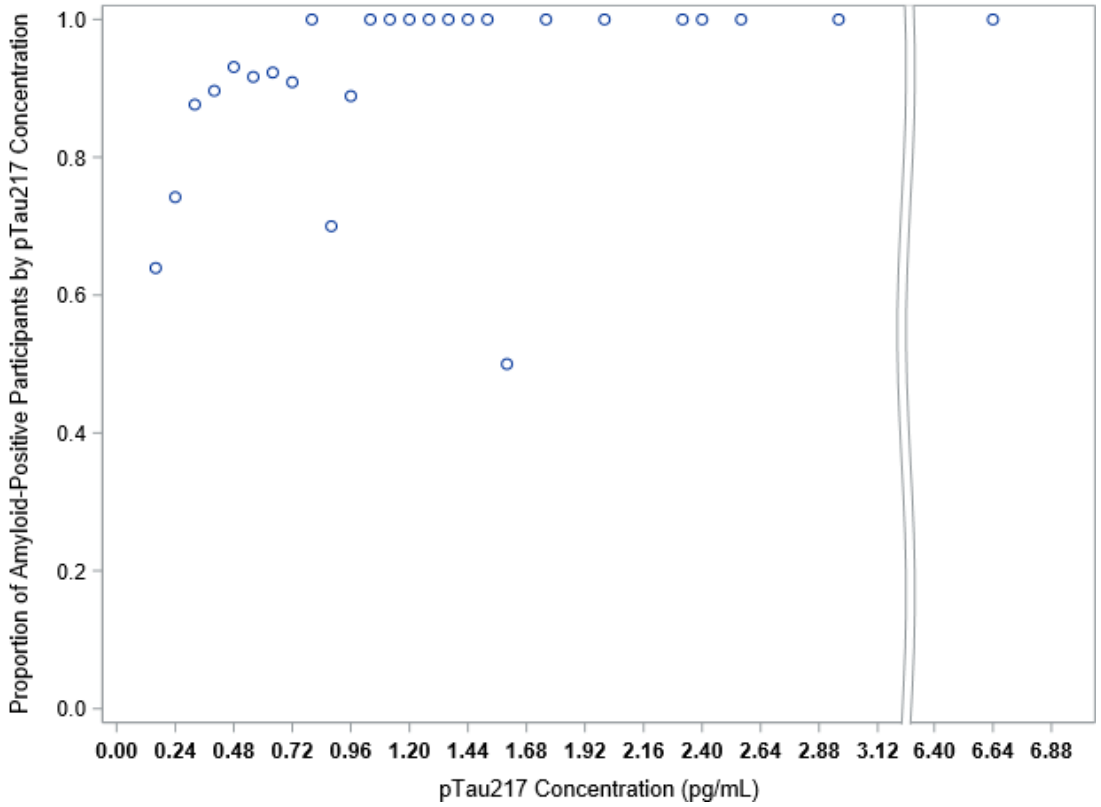
- UK and EU sites are not using pTau217 as a screening enrichment strategy (not CE marked)



Amyloid status for participants with plasma pTau217 ≥ 0.15 pg/mL

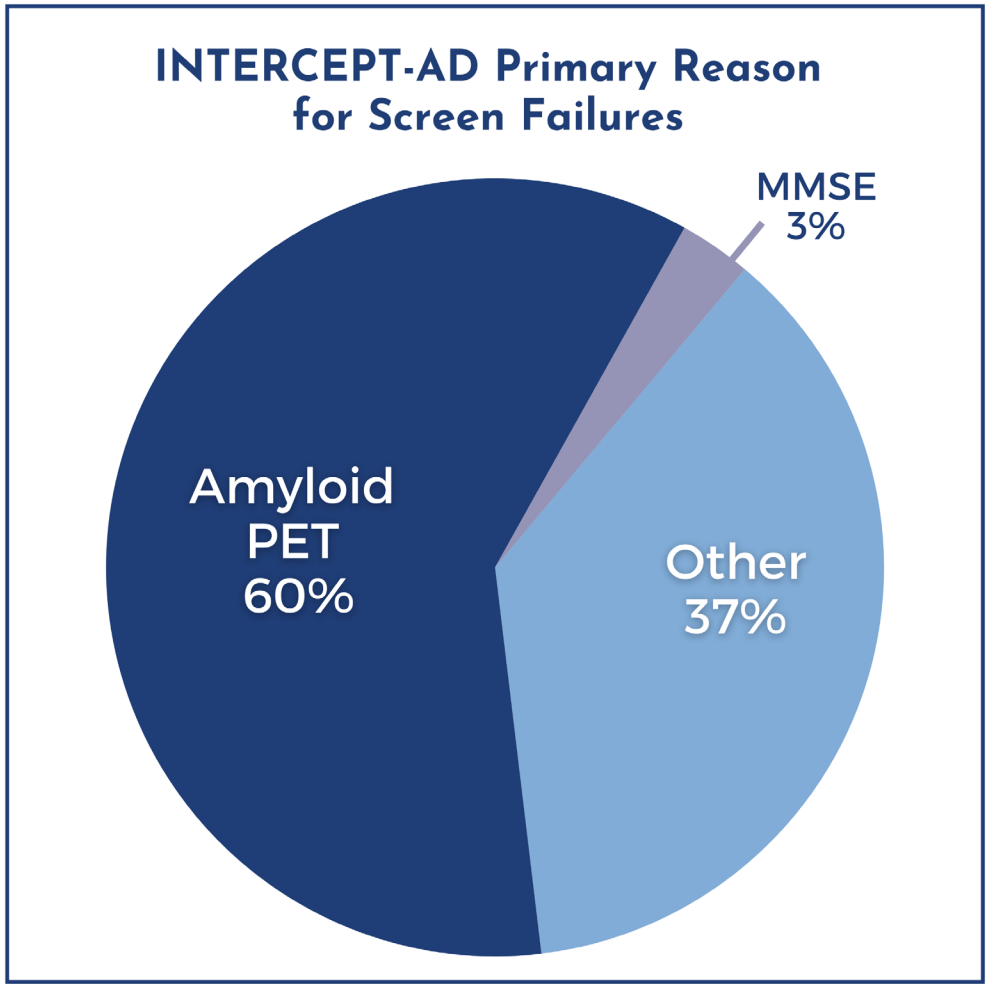


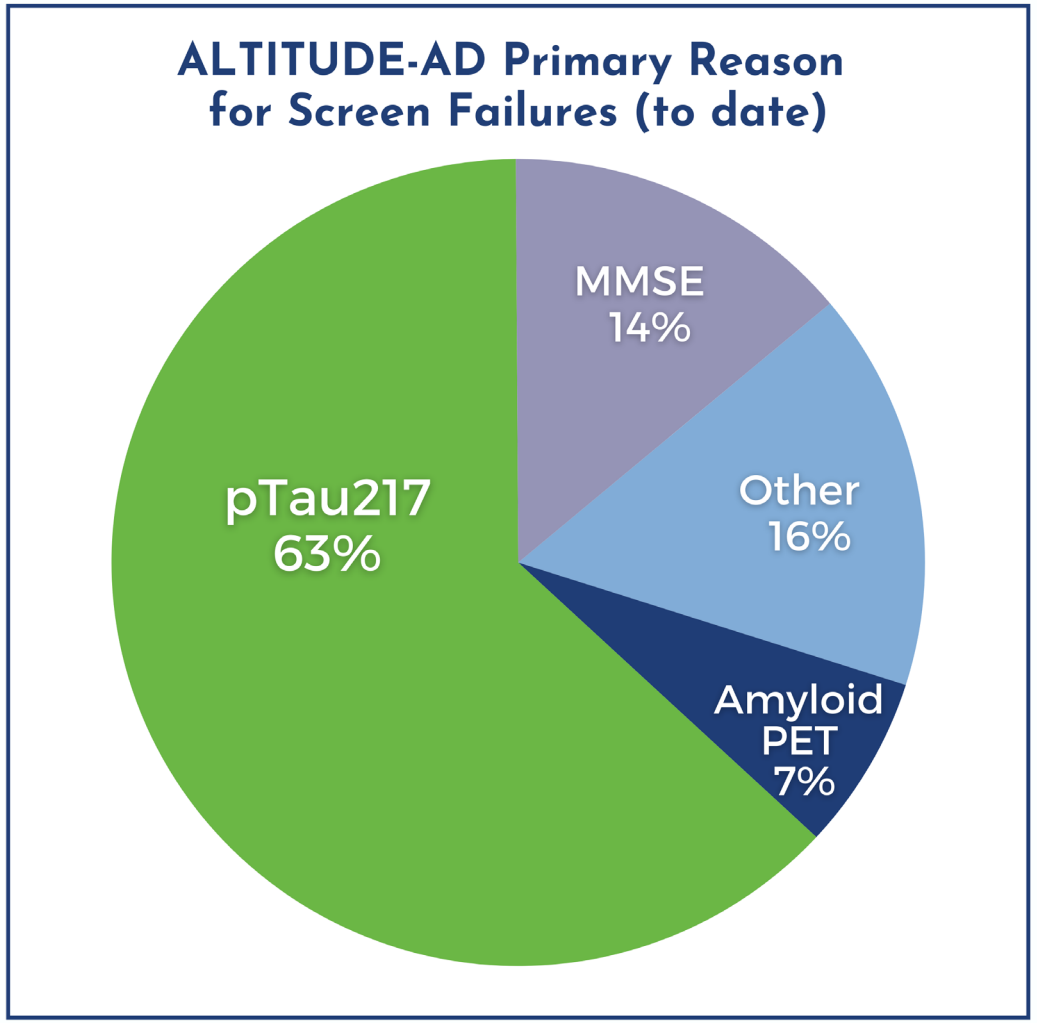
- Graph shows the percentage of participants included or excluded from the study based on amyloid status after a positive pTau217 result
- Bin width represents a pTau217 range of 0.08 pg/mL



- Graph shows the proportion of participants with positive PET or CSF after a positive pTau217 result
- Bin width represents a pTau217 range of 0.08 pg/mL

AD Trials Often Have High Percentages of Negative PET During Screening





Summary

The pTau217 enrichment strategy is performing as intended

- Improving amyloid positive screen rates
  - 78% of the participants who proceed to PET or CSF are enriched for meeting amyloid-based inclusion criteria
  - Significant improvement from INTERCEPT-AD where 40% of participants were amyloid positive via PET

- Reducing burden and fostering sustainability
  - More than half of potential study participants excluded because of a plasma pTau217 test result <0.15 pg/mL
    - Reduced burden for patients, clinical trial investigators/staff, and sponsor
    - Participants were spared LP and unnecessary radiation exposure with an amyloid PET
    - Savings in time and resources

Acknowledgments

- The authors are grateful to the study participants and their study partners, as well as the study investigators and staff, all of whom make the ALTITUDE-AD clinical trial possible

Thank you!