AHEAD 3-45 Study Design:

A Global Study to Evaluate Efficacy and Safety of Treatment with BAN2401 for 216 Weeks in Preclinical Alzheimer's Disease With Intermediate Amyloid (A3 Trial) and Elevated Amyloid (A45 Trial)

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AHEAD 3-45

- AHEAD 3-45 is a platform of two trials to test BAN2401 in preclinical AD populations with dosing regimens tailored to the baseline PET amyloid levels
  - A45 population: cognitively normal with elevated amyloid (> 40 centiloids)
  - A3 population: cognitively normal with intermediate amyloid (20-40 centiloids)

- AHEAD 3-45 will be conducted as a Public Private Partnership with the NIA Alzheimer's Clinical Trial Consortium (ACTC) and Eisai

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AHEAD 3-45: BACKGROUND

- Amyloid accumulation initiates and drives the initial spread of AD neuropathology
- Amyloid can be removed from brain with monoclonal antibodies against aggregated forms
  - eg, aducanumab, BAN2401, gantenerumab, donanemab
- Removal of amyloid from brain may be associated with cognitive/clinical benefit

- We hypothesize that removal of amyloid from brain at the earliest stage of amyloid accumulation, before substantial irreversible neurodegeneration, has great potential to slow disease progression

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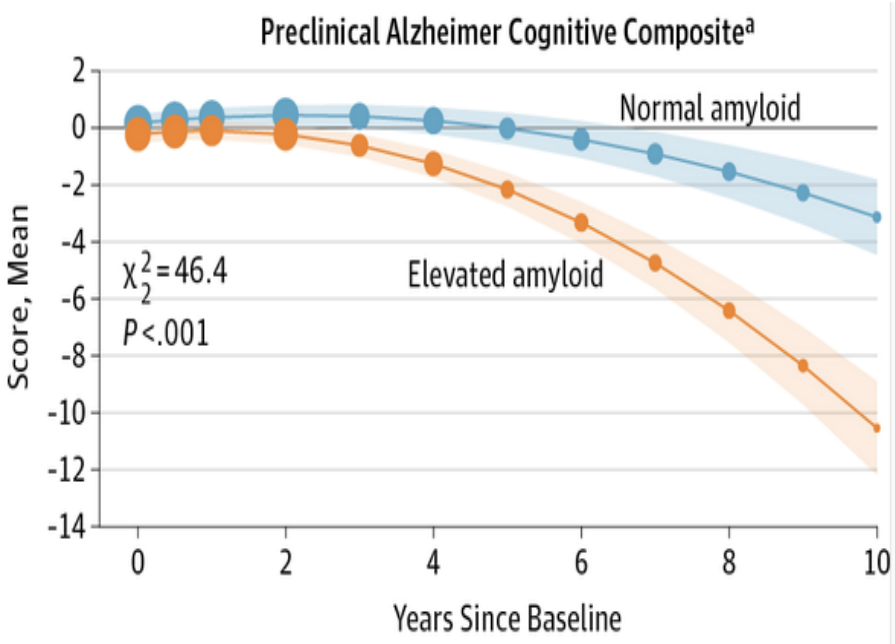
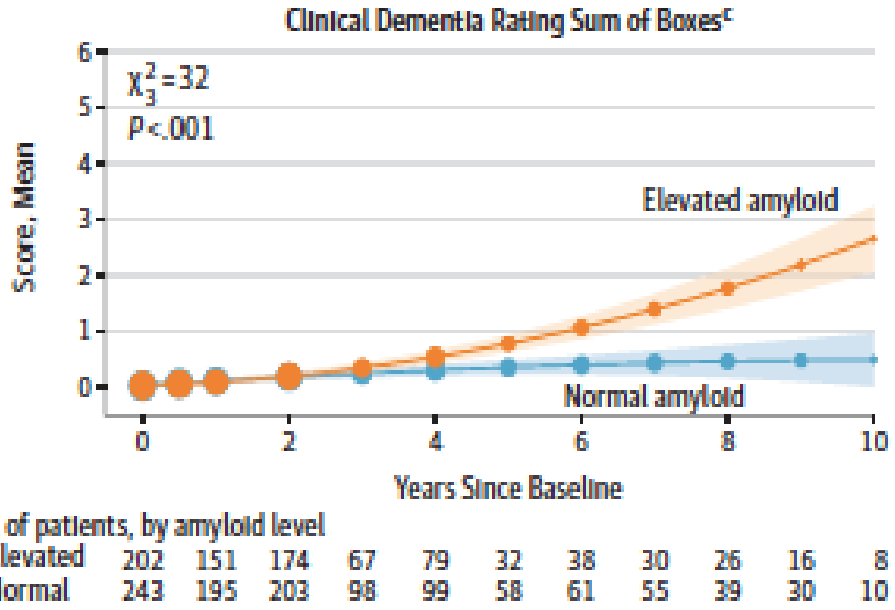
COGNITIVE DECLINE AND CLINICAL PROGRESSION IN PRECLINICAL (PRE-SYMPTOMATIC) AD - ADNI





Donohue M, Sperling R et al. *JAMA* 2017

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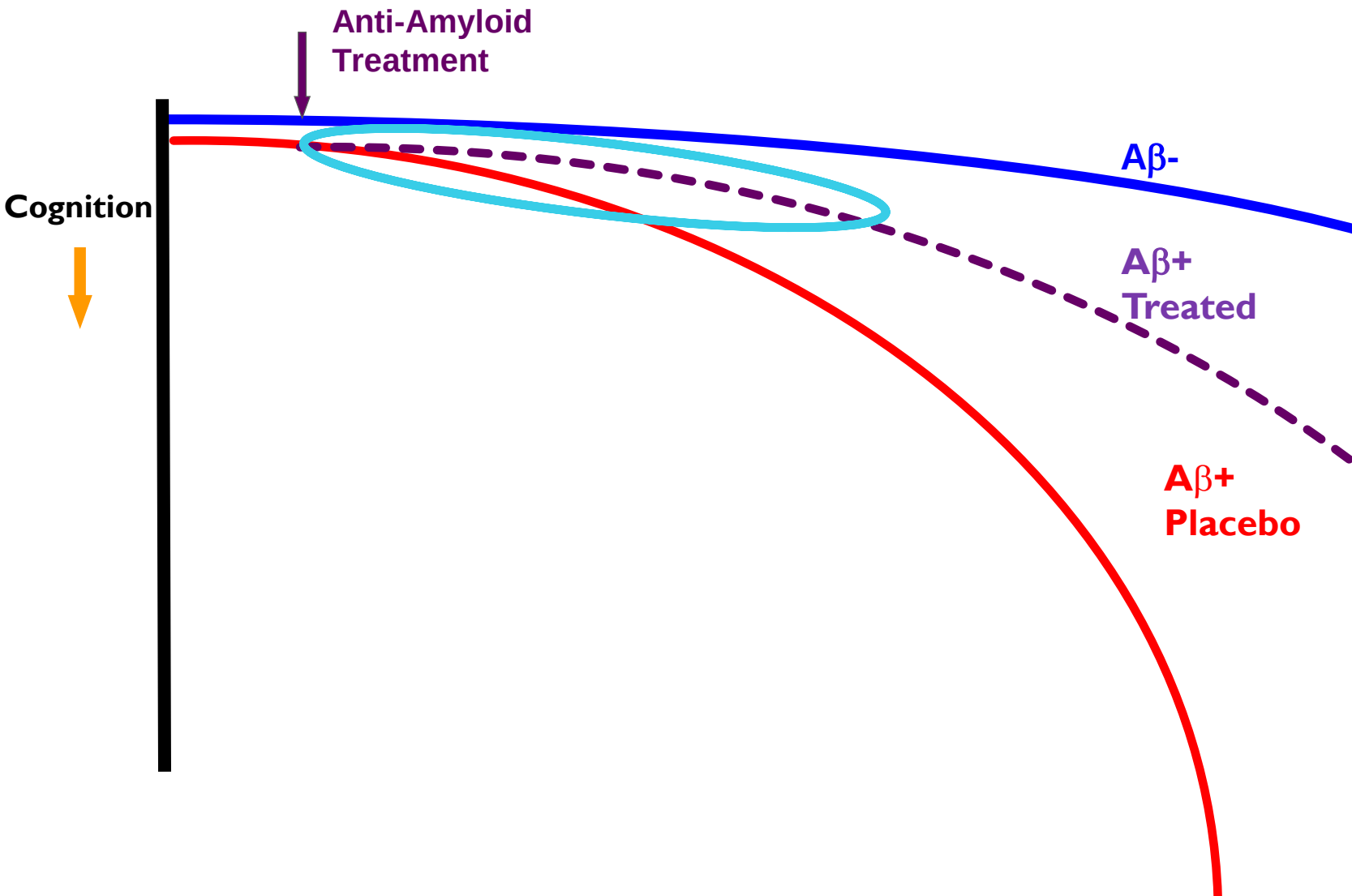
TARGETING AMYLOID AT THE PRECLINICAL (PRE-SYMPTOMATIC) STAGE OF AD



AHEAD 3-45: TWO TRIALS CONDUCTED TOGETHER AT EACH SITE

- Therapeutic: BAN2401 (dose regimens tailored to initial amyloid load)
- Population: cognitively normal individuals accumulating amyloid
  - A3 (n=400): amyloid PET 20-40 centiloids (intermediate, early preclinical)
  - A45 (n=1000): amyloid PET > 40 centiloids (elevated, preclinical)
- Treatment period: 4 years
- Key outcomes tailored to population
  - A3: biomarkers: amyloid PET, tau PET (Phase 2)
  - A45: cognitive/PRO: PACC5, CFI (Phase 3)

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AHEAD 3-45: OUTCOMES

- Cognitive: PACC5, C3, International Shopping List, Trail Making Test
- Subjective concerns: CFI
- Clinical/functional: ADCS-ADL, CDR-SB
- Imaging: amyloid and tau PET, vMRI, rs-fMRI
- Cerebrospinal fluid (subset): Aβ[1-42], Aβ[1-40], t-tau, p-tau, neurogranin, and NFL
- Plasma: Aβ[1-42], Aβ[1-40], t-tau, p-tau, and NFL

- Principal outcomes:
  - A3: amyloid PET, tau PET
  - A45: PACC5, CFI

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AHEAD 3-45: STUDY DESIGN FEATURES

- Common recruitment for efficiency
  - Utilize TRC-PAD, APR, GeneMatch
- Amyloid PET disclosure processes (APOE disclosure optional)
- Titrated BAN2401 aims to reduce ARIA-E
- BAN2401 dosing designed to halt amyloid accumulation (A3) and reduce amyloid below threshold (A45) during the first 2 years
  - Requires q2week dosing in A45 for first 2 years
- Maintain normal amyloid levels for the duration (4 years) so that:
  - A3: effect on downstream biomarkers (eg, tau PET)
  - A45: effect on cognition (PACC5) and subjective concerns (CFI)

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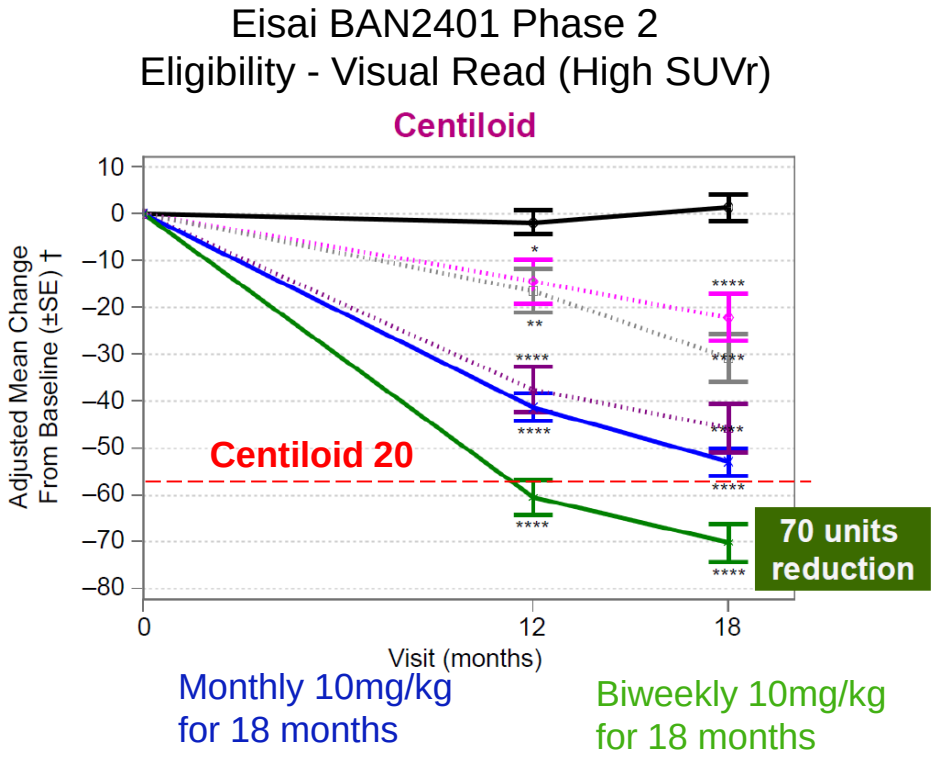
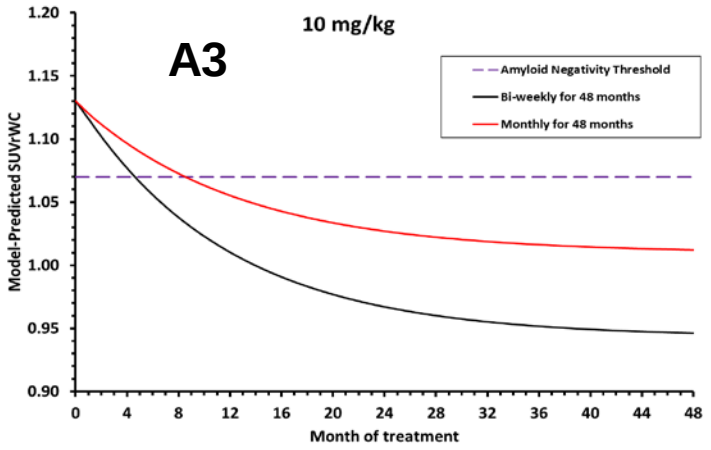
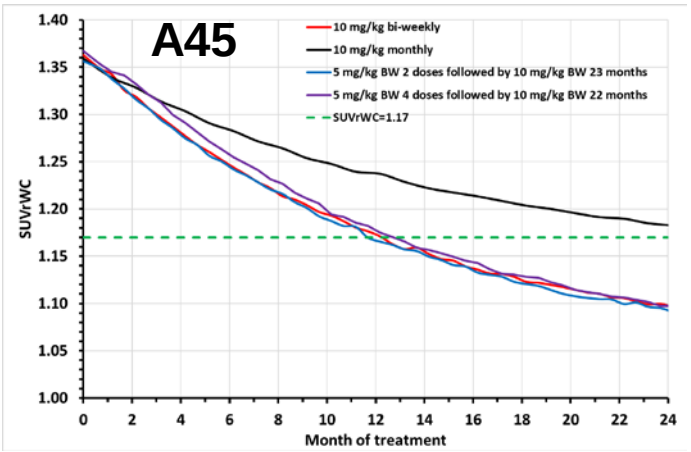
TARGETED DOSING TO REDUCE AMYLOID BURDEN







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NOVEL ASPECTS OF AHEAD 3-45 STUDY

Platform: 2 trials in adjacent populations with same assessment schedule, dose tailored to amyloid load

Age down to age 55 (additional risk algorithm in 55-64)

A3 is first trial in "early preclinical AD" in sporadic disease – the earliest feasible intervention (until we reach primary prevention)

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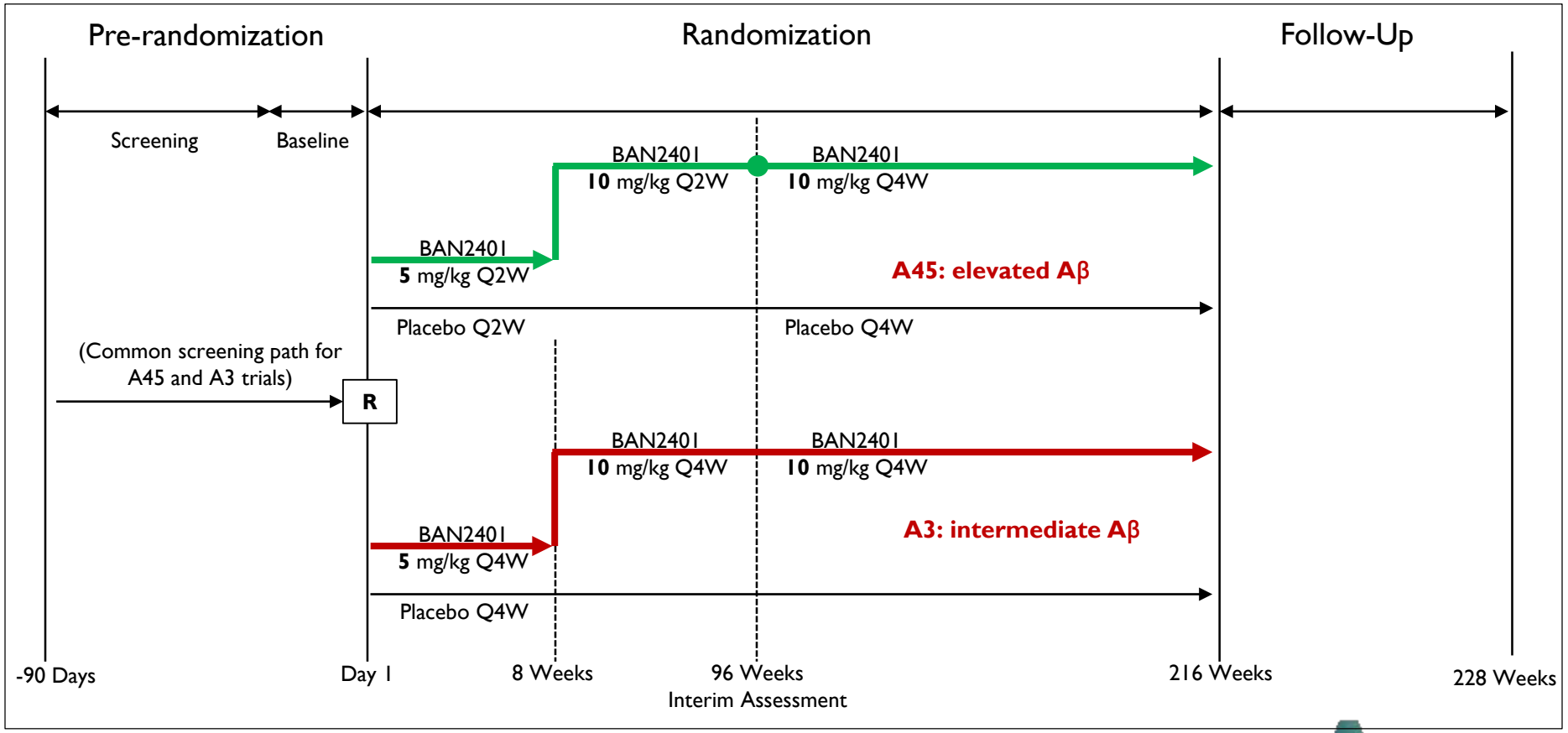
A45 AND A3 STUDY DIAGRAM



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BAN2401 AHEAD 3-45: SINGLE PROTOCOL WITH COMMON SCREENING FOR BOTH STUDIES

	A45: Elevated Amyloid	A3: Intermediate Amyloid
Population	• Intact cognition (MMSE ≥ 27 after education adjustment; global CDR = 0) • Age: 55-80y (55-64y must have additional risk: 1) Known APOE e4 carrier, 2) positive family history for AD, or 3) prior amyloid positive scan)	
	• Elevated amyloid: amyloid PET >40 CL	• Intermediate amyloid: amyloid PET 20-40 CL
Treatment	• BAN2401 IV x 216 weeks (~4 years): o Titration: 5 mg/kg q2w, weeks 0-6 o Induction: 10 mg/kg q2w, weeks 8-94 o Maintenance: 10 mg/kg q4w, weeks 96-216 • Placebo	• BAN2401 IV x 216 weeks (~4 years): o Titration: 5 mg/kg q4w, weeks 0-4 o Treatment: 10 mg/kg q4w, weeks 8-216 • Placebo
	• Home infusions and SC administration may be implemented during the study to reduce participant burden	
Primary outcomes	• Clinical outcome for full approval: Preclinical AD Cognitive Composite 5 (PACC5) at week 216 • Biomarker outcomes used for accelerated approval (Interim Analysis): Amyloid PET SUVr; Tau PET; CSF/plasma Aβ/p-tau/protofibrils; panel (week 96)	• Amyloid PET SUVr at week 216 • Biomarker outcomes used for accelerated approval (Interim Analysis): Amyloid PET SUVr; Tau PET; CSF/plasma Ab/p-tau/protofibrils; panel (week 96)
Secondary Outcomes	• Clinical: Cognitive Function Index • Biomarkers: Amyloid PET, Tau PET	• Tau PET
Exploratory Outcomes	• Clinical: ADCS ADL-prevention; Computerized Cognitive Composite; ISLT; Trails; CDR-SB; time to CDR 0.5 • Biomarkers: vMRI, rs-MRI, CSF Aβ/tau/ptau/NG/NfL/protofibrils, plasma Nf-L/ptau181/ptau217	• Biomarkers: CSF Aβ/tau/ptau/NG/NfL (substudy), vMRI, rs-MRI, plasma Nf-L/ptau181/ptau217 • Clinical: PACC5, exploratory cognitive outcomes
Sample sizes	Clinical outcome (PACC5): approx. 1000 (500/arm) – 80% power for 38% slowing from baseline to week 216	Biomarker outcome: 300-400 (150-200/arm) – 90% power to detect treatment difference of equivalent of 0.04 FBP SUVr between treatment and placebo
Study site	100 sites (US, Canada, Japan, Australia, Singapore, EU)	

Aβ = amyloid beta, ADCS ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living, CDR-SB = Clinical Dementia Rating Scale-Sum of Boxes, CL = centiloid, CSF = cerebrospinal fluid, FBP = florbetapir, IA = interim analysis, IV = intravenously, MCI = mild cognitive impairment, NfL = neurofilament light chain, NG = neurogranin, PET = positron emission tomography, vMRI = volumetric magnetic resonance imaging

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