SPINOZA: Rationale and Design of a Phase 2b Trial of Obicetrapib in APOE-Stratified Preclinical Alzheimer's Disease

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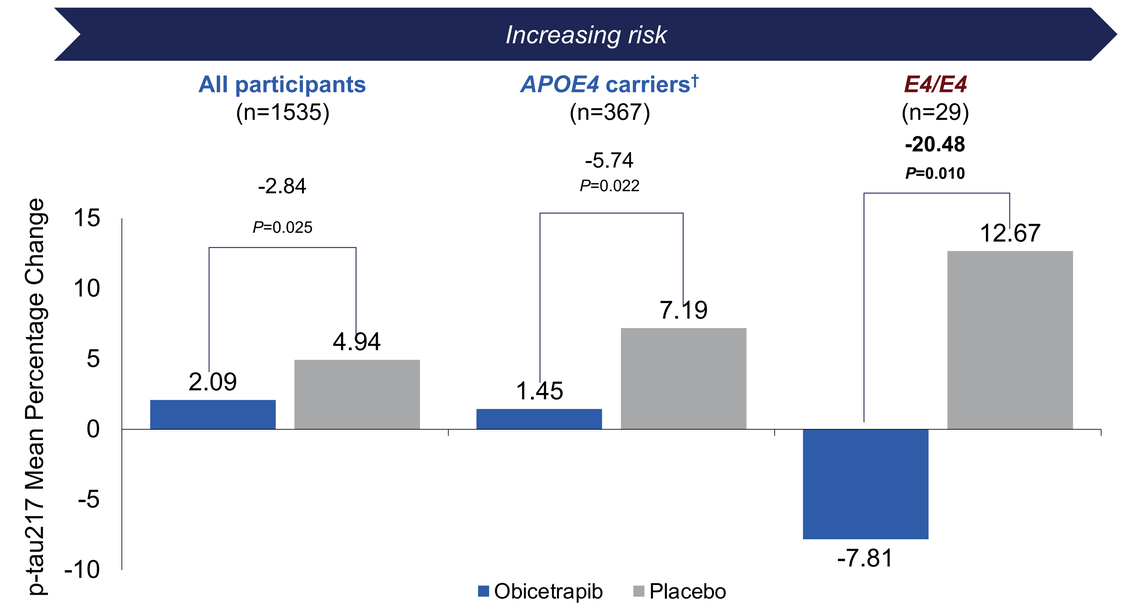
BACKGROUND

- Up to 66% of patients with Alzheimer's disease (AD) are apolipoprotein E4 (*APOE4*) carriers, the strongest genetic risk factor for sporadic/late-onset AD[1]
  - Impaired lipid transport in *APOE4* carriers leads to a cycle of oxidative stress and neuroinflammation, causing cholesterol buildup and contributing to AD pathology[2-6]
- Plasma phosphorylated tau at threonine 217 (p-tau217) is a reliable and strong predictor of AD pathology that has been shown to increase exponentially in cognitively unimpaired *APOE4* carriers after age 65 years[7,8]
- In a prespecified biomarker substudy (n=1535) of BROADWAY (N=2530), a Phase 3 trial in participants with atherosclerotic cardiovascular disease (ASCVD) and/or heterozygous familial hypercholesterolemia (HeFH), obicetrapib, a potent oral cholesteryl ester transfer protein (CETP) inhibitor, significantly attenuated increases in p-tau217 over 12 months (**Figure 1**)[9,10]
  - Effects followed an *APOE* genotype gradient and were greatest in *APOE4/E4* homozygotes, in whom the placebo-adjusted treatment difference was -20.5% (*P*=0.010)[9]
  - CETP inhibition may therefore address upstream lipid dysregulation implicated in the initiation of amyloid accumulation, tau pathology, astrocytic reactivity, neuroinflammation, and neurodegeneration, providing the rationale for the SPINOZA trial in preclinical AD[9,10]

OBJECTIVE

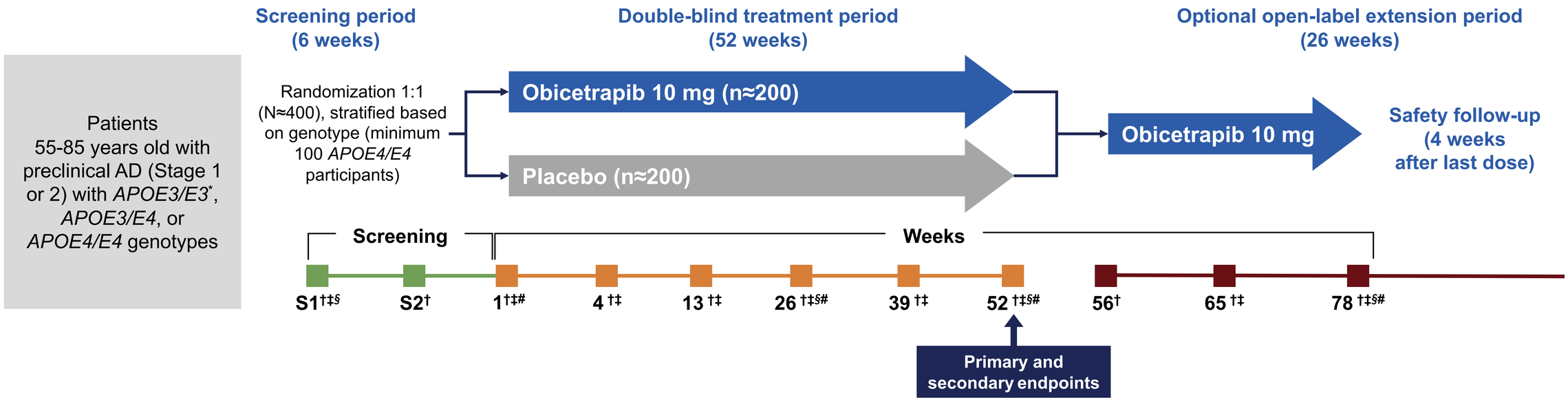
To investigate the efficacy and safety of CETP inhibition with obicetrapib in preclinical AD participants carrying *APOE3/E3*, *APOE3/E4*, or *APOE4/E4* genotypes by quantifying changes in plasma p-tau217 levels

Figure 1: Changes (%) in p-tau217 Progression by Subgroups With Increasing Risk of AD Pathology in BROADWAY Biomarker Substudy Population*



*The BROADWAY biomarker substudy analysis population included 1535 participants; the full BROADWAY trial randomized 2530 participants with ASCVD and/or HeFH.
†*APOE3/E4* or *E4/E4*.

Figure 2: SPINOZA Trial: a Phase 2b, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess the Efficacy and Safety of Obicetrapib in Participants With Preclinical AD



*Inclusion of *APOE3/E3* provides a prespecified specificity test: to explore whether treatment effect differs across *APOE4/E4, APOE3/E4,* and *APOE3/E3* genotypes.
†Vital signs and safety assessments completed at every visit.
‡Plasma sample for p-tau217 collected at S1 and Weeks 1, 4, 13, 26, 39, 52, 65, and 78.
§Cognitive assessments (PACC5) and functional assessments (Amsterdam IADL) complete at Weeks 1, 26, 52, and 78.
#Plasma sample for other biomarkers collected at Weeks 1, 26, 52, and 78.
S1, screening session 1; S2, screening session 2.

METHODS

- SPINOZA (NCT07794670) is a multicenter, randomized, double-blind, placebo-controlled Phase 2b trial designed to assess the efficacy, safety, and tolerability of obicetrapib in participants with preclinical AD (**Figure 2**)
  - Eligibility applied genotype-specific age windows, plasma p-tau217 thresholds, and a plasma glial fibrillary acidic protein (GFAP) threshold in *APOE3/E4* and *APOE3/E3* participants
- A prespecified interim analysis by an independent unblinded statistician (sponsor will remain blinded) will support sample size re-estimation and possible population enrichment
- Trial endpoints are summarized in **Figure 3**
  - Cognition is a secondary endpoint measured by PACC5 (Preclinical Alzheimer's Cognitive Composite 5), and daily functional performance is assessed as an exploratory endpoint via the Amsterdam IADL (instrumental activities of daily living)

Figure 3: Efficacy Endpoints and Safety for SPINOZA

Primary Efficacy Endpoint
- Change from baseline to Week 52 in plasma p-tau217

Secondary Efficacy Endpoints
- Change from baseline to Week 52 in plasma AD biomarkers
  - Aβ42/Aβ40
  - p-tau217/Aβ42
  - p-tau217/Aβ42/40
  - BD-tau
- Change from baseline to Week 52 in PACC5 score

Exploratory Efficacy Endpoints
- Blood-based biomarkers for
  - Astrocytic reactivity
  - Neurodegeneration
  - Neuroinflammation
  - Synaptic integrity
  - Functional performance
  - Lipid biology (LDL, HDL, non-HDL, and triglycerides)

Safety
- Incidence of TEAEs by frequency, severity, and seriousness
- Change from baseline in clinical laboratory tests and vital signs
- Incidence of clinically significant changes in physical examination

Aβ, amyloid beta; BD-tau, brain-derived tau; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- SPINOZA is a Phase 2b study evaluating obicetrapib, a potent CETP inhibitor as a novel therapeutic strategy in preclinical AD
- By integrating plasma p-tau217 as a primary endpoint with comprehensive biomarker and cognitive assessments, the trial seeks to determine whether targeting lipid biology may influence pathways associated with early AD progression
- Results from SPINOZA will inform the clinical development of CETP inhibition as a potential therapeutic strategy for individuals with preclinical AD

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DISCLOSURES:

MHD, MD, AH, AW, AJ, JJPK all are employees and shareholders of NewAmsterdam Pharma

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