Age, APOE Status, Renal Function, Glycemia, and Prior Ischemic Stroke Associate With Baseline Plasma p-tau217 in BROADWAY

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BACKGROUND

- Plasma phosphorylated tau 217 (p-tau217) is a validated biomarker of Alzheimer's disease (AD)-related pathology[1,2]
- In a recent multicohort study of patients with clinical atherosclerotic cardiovascular disease (ASCVD) who were asymptomatic for AD, higher baseline plasma p-tau217 levels were significantly associated with increased risk of progression to cognitive impairment over up to 13.5 years of follow-up[3]
- Furthermore, in BROADWAY (NCT05142722), a phase 3, randomized, double-blind, placebo-controlled trial that included patients with ASCVD and/or heterozygous familial hypercholesterolemia (HeFH), the cholesteryl ester transfer protein (CETP) inhibitor obicetrapib attenuated progression of plasma p-tau217, supporting further investigation of this therapeutic in the prevention of AD[2]

OBJECTIVE

To determine which baseline characteristics are associated with baseline plasma p-tau217 in the overall BROADWAY population of ASCVD and/or HeFH patients and whether these associations persist in a subgroup selected to include individuals most likely to harbor early AD pathology. A prespecified BROADWAY subgroup approximating eligibility for SPINOZA* (NCT07794670), an ongoing phase 2b trial of obicetrapib in preclinical AD, was examined to assess whether these associations were consistent in participants selected for likely early AD pathology.

METHODS

- **Population:** cross-sectional analysis of 1,861 participants (73.5% of randomized participants) with baseline p-tau217 measurements in BROADWAY including adults with ASCVD and/or HeFH receiving maximally tolerated lipid-lowering therapy (LLT)
- **Association Analyses:** each prespecified factor was tested in a separate ordinary least-squares model of log-transformed baseline p-tau217 using heteroskedasticity-consistent 3 (HC3) robust standard errors, adjusted for age, sex, apolipoprotein E (APOE) status, and estimated glomerular filtration rate (eGFR) (the focal factor was excluded from its own adjustment set)
  - Sixteen prespecified demographic, vascular, metabolic, renal, and lipid-related factors were tested with a false discovery (Benjamini-Hochberg [BH]) control; two analysis families were used: 16 prespecified factors with BH correction across all 16 (**Figure 1**), and additional vascular and renal/systemic factors evaluated in domain-level models with BH correction within domain (**Figure 2**)
- **Domain-level Evaluation:** the incremental contribution of AD biomarkers (phosphorylated tau 181 [p-tau181], glial fibrillary acidic protein [GFAP], neurofilament light [NfL], amyloid-β 42:40 ratio [Aβ42:40]), renal and systemic physiology (eGFR, serum albumin, hemoglobin, and urine albumin-to-creatinine ratio (UACR), which reflect both kidney function and general systemic illness), cardiometabolic status, and lipoprotein architecture was quantified using repeated cross-validation to identify factors most strongly associated with p-tau217 variability
- **SPINOZA-Enriched Sensitivity Analysis:** the SPINOZA trial includes APOE ε3/ε3, ε3/ε4, and ε4/ε4 participants; associated models were repeated in the prespecified BROADWAY subgroup (n=281) with eligibility applied genotype-specific age windows, plasma p-tau217 thresholds, and a plasma GFAP threshold in APOE ε3/ε4 and APOE ε3/ε3 participants
- This analysis evaluated cross-sectional associations with baseline p-tau217 only, with both randomized arms pooled before study drug administration; it did not evaluate change in p-tau217 over time, the effect of obicetrapib on p-tau217, or whether obicetrapib prevents AD

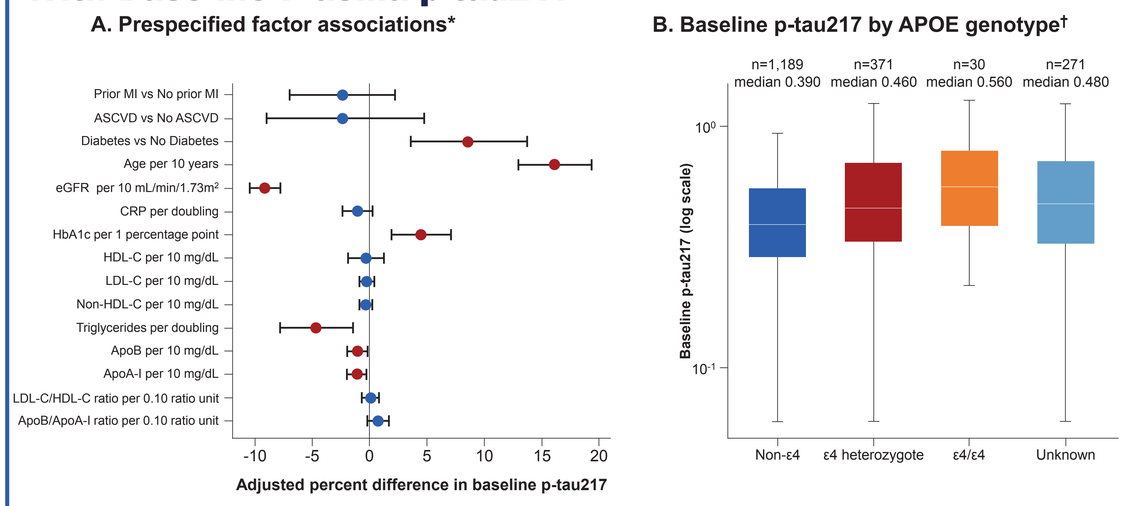
RESULTS

- All 16 prespecified factors were tested in the same framework, each in a separate model adjusted for age, sex, APOE status, and eGFR, with the focal factor omitted from its own adjustment set (**Figure 1**)
  - Eight factors remained associated with baseline p-tau217 after BH correction: older age (+16.1% per 10 years), lower eGFR (−9.1% per 10 mL/min/1.73 m²), APOE status (omnibus q<0.001; highest in ε4/ε4 and lowest in non-ε4 carriers), diabetes (+8.6%), higher HbA1c (+4.5% per percentage point), and small inverse associations with triglycerides (−4.7% per doubling), apolipoprotein B (ApoB) (−1.1% per 10 mg/dL), and apolipoprotein A-I (ApoA-I) (−1.1% per 10 mg/dL)
  - The APOE ε4 allele-dose gradient persisted after adjustment for eGFR: +23.7% in ε4 heterozygotes (95% CI: 16.6% to 31.2%) and +46.6% in ε4/ε4 (95% CI: 27.3% to 68.9%) versus non-ε4 carriers
  - Prior myocardial infarction (MI), established ASCVD, C-reactive protein (CRP), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), non-HDL-C, and both lipid ratios were not associated
  - The inverse triglyceride, ApoB, and ApoA-I associations may reflect background LLT rather than a biological effect
- When added to a model of age, sex, and APOE, companion AD biomarkers improved prediction of p-tau217 substantially (Δ cross-validated R^2 +0.503), renal and systemic physiology modestly (+0.079), and cardiometabolic status and lipoprotein architecture minimally (+0.016 and +0.005, respectively)
  - Most of the companion-biomarker gain came from p-tau181 alone (+0.476), a closely related p-tau measured in the same sample and therefore not independent evidence; GFAP, NfL, and Aβ42:40 together contributed +0.155, approximately twice the renal and systemic contribution
- In the separate vascular and renal/systemic domain models, prior ischemic stroke was associated with 15.9% higher p-tau217, but MI and established ASCVD were not (**Figure 2A**); lower serum albumin, lower eGFR, lower hemoglobin, and higher UACR all tracked with higher p-tau217, consistent with reduced renal clearance and systemic illness (**Figure 2B**)
- Results of the sensitivity analysis in the prespecified BROADWAY subgroup at risk for preclinical AD are shown in **Table 1**

CONCLUSIONS

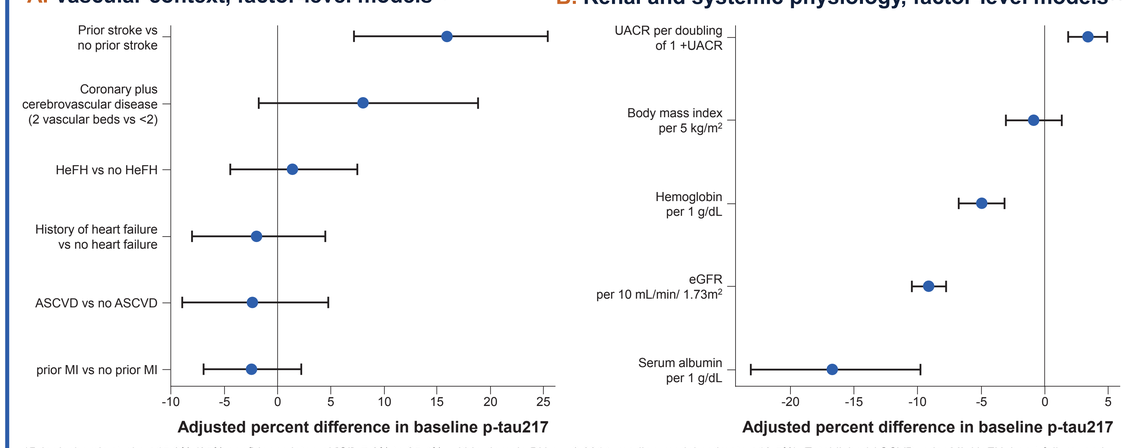
- Baseline p-tau217 in this ASCVD trial cohort associated with age, APOE status, renal function, prior ischemic stroke, and glycemic status more strongly than with conventional lipid measures or prior MI
- Conventional lipid measures were not a major correlate: triglycerides, ApoB, and ApoA-I showed small inverse associations that may reflect background LLT rather than a biological effect, and lipoprotein architecture added negligible out-of-sample explanatory information (Δ cross-validated R^2 +0.005)
- Lower serum albumin, lower eGFR, lower hemoglobin, and higher UACR all tracked with higher p-tau217, so baseline p-tau217 in a cardiovascular population reflects both AD-related pathology and renal clearance and systemic illness; a cross-sectional concentration cannot fully separate the two
- The APOE ε4 allele-dose gradient persisted after adjustment for eGFR, supporting an AD-related component that renal function and glycemic status do not explain
- In the prespecified BROADWAY subgroup approximating SPINOZA eligibility, the APOE and eGFR associations were directionally consistent with the full cohort, supporting the rationale for the SPINOZA clinical trial* evaluating obicetrapib in participants with preclinical AD

Figure 1: Adjusted (Age, Sex, APOE Status, and eGFR) Associations of 16 Prespecified Factors and APOE Genotype With Baseline Plasma p-tau217



*Red markers indicate BH q < 0.05. Age +16.1% per 10 years; eGFR −9.1% per 10 mL/min/1.73 m²; diabetes +8.6%; HbA1c +4.5% per percentage point; triglycerides −4.7% per doubling; ApoB −1.1% and ApoA-I −1.1% per 10 mg/dL. Prior MI, established ASCVD, CRP, HDL-C, LDL-C, non-HDL-C, and both ratios were null.
†Overall APOE omnibus test q<0.001 (adjusted for age, sex, eGFR). Adjusted differences versus non-ε4 were +23.7% for ε4 heterozygotes (95% CI: +16.6% to +31.2%) and +46.6% for ε4/ε4 participants (95% CI: +27.3% to +68.9%). APOE ε4 carriership by age was the only prespecified interaction surviving BH correction (+7.4%; q = 0.048).

Figure 2: Vascular History and Renal and Systemic Physiology as Correlates of Baseline Plasma p-tau217, Adjusted for Age, Sex, APOE Status, and eGFR



*Prior ischemic stroke +15.9% (95% confidence interval [CI], 7.2% to 25.4%; within-domain BH q = 0.0014; median-model estimate +18.5%). Established ASCVD, prior MI, HeFH, heart failure, and coronary plus cerebrovascular disease did not reach significance.
†Adjusted percent difference in baseline p-tau217 with 95% CI; core adjustment for age, sex, APOE status, and eGFR.
‡Serum albumin −16.7% per 1 g/dL; eGFR −9.1% per 10 mL/min/1.73 m²; hemoglobin −5.0% per 1 g/dL; UACR +3.4% per doubling. All within-domain BH q < 0.001.

Table 1. Sensitivity Analysis: Adjusted (Age, Sex, APOE Status, and eGFR) Associations With Baseline Plasma p-tau217 in the Prespecified BROADWAY Subgroup at Risk for Preclinical AD (n=281)*

Factor	Unit	Adjusted Value	q†
APOE status‡	Omnibus test	–	<0.001
eGFR	Per 10 mL/min/1.73 m²	−4.7%	0.003
Established ASCVD	Yes vs no	−17.4%	0.049
ApoB	Per 10 mg/dL	−2.4%	0.049
LDL-C/HDL-C ratio	Per 0.10 ratio unit	−0.7%	0.049
ApoB/ApoA-I ratio	Per 0.10 ratio unit	−3.2%	0.049

*Adjusted percent difference in baseline p-tau217; ordinary least squares with heteroskedasticity-consistent (HC3) standard errors, adjusted for age, sex, APOE status, and eGFR (focal factor omitted). The subgroup included APOE ε3/ε3, ε3/ε4, and ε4/ε4 participants, with eligibility defined by genotype-specific age windows, plasma p-tau217 thresholds, and a plasma GFAP threshold in ε3/ε4 and ε3/ε3 participants. Baseline and end-of-study p-tau217 availability was also required. This was a sensitivity subgroup defined using age, p-tau217, GFAP, and APOE, not an independent replication cohort. Only factors with q<0.05 are shown.
†BH across 16 primary tests.
‡APOE status was part of cohort selection, so its association is expected.

*The SPINOZA trial design can be found in Poster P005 titled "SPINOZA: Rationale and Design of a Phase 2b Trial of Obicetrapib in APOE-Stratified Preclinical Alzheimer's Disease"

DISCLOSURES
This analysis was funded by NewAmsterdam Pharma. Akash Patel reports no conflict of interest. Andrew Hsieh, Adam Johnson, Marc Ditmarsch, John JP Kastelein and Michael H Davidson are employees of NewAmsterdam Pharma and hold stocks or options. The authors declared no other competing interests.

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1. Palmqvist S et al. *JAMA.* 2020;324(8):772-781. **2.** Davidson MH et al. *J Prev Alzheimers Dis.* 2026;13(1):100394. **3.** Buckley RF et al. *JAMA.* 2026;336(11):950-959.

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