APOE4-Dependent Response to CETP Inhibition: A Responder Analysis Informing Alzheimer's Prevention Trial Enrichment Strategies

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BACKGROUND

- Alzheimer's disease (AD) prevention trials require enrichment strategies that identify individuals most likely to demonstrate treatment response[1]
- Apolipoprotein E4 *(APOE4)* is the strongest genetic risk factor for sporadic/late-onset AD, and up to 66% of patients with AD are *APOE4* carriers[2]
- Impaired lipid transport in *APOE4* carriers leads to a cycle of cholesterol buildup, oxidative stress and neuroinflammation, all contributing to AD pathology[3-7]
- Plasma phosphorylated tau at threonine 217 (p-tau217) is a strong predictor of AD pathology that increases exponentially in cognitively unimpaired *APOE4* carriers after age 65 years[8,9]
- The BROADWAY phase 3 substudy demonstrated that obicetrapib, an oral cholesteryl ester transfer protein (CETP) inhibitor that exerts comprehensive lipid modulation, significantly attenuated p-tau217 progression in atherosclerotic cardiovascular disease (ASCVD) patients, with effects most pronounced in *APOE4* carriers[1,10]

OBJECTIVE

To quantify treatment effects and define optimal populations for dedicated AD prevention trials with obicetrapib by conducting responder analyses among patients in the BROADWAY AD substudy

METHODS

- BROADWAY (NCT05142722) was a phase 3, randomized, double-blind, placebo-controlled trial (N=2530) evaluating the effect of obicetrapib 10 mg as an adjunct to maximally tolerated lipid-lowering therapy (LLT) in patients with ASCVD or heterozygous familial hypercholesterolemia (HeFH)
- Post hoc responder analyses were performed among BROADWAY AD substudy participants meeting genotype-specific evaluability criteria:
  - E4/E4 homozygotes: age >60 years, baseline p-tau217 ≥0.22 pg/mL
  - E3/E4 heterozygotes (age >60 years, baseline p-tau217 ≥0.372 pg/mL, baseline glial fibrillary acidic protein [GFAP] ≥100 pg/mL)
  - E3/E3 homozygotes (age >60 years, baseline p-tau217 ≥0.42 pg/mL, baseline GFAP ≥100 pg/mL)
- Treatment effects were assessed as median percent change from baseline and as responder rates defined as meaningful reduction >5% decrease in p-tau217

AD biomarker substudy population: 1535 patients, including 367 APOE4 carriers, with baseline p-tau217 above the lower limit of quantification and available end-of-study p-tau217 levels

Key Inclusion Criteria:
- ASCVD or HeFH
- Maximally tolerated LLT

Obicetrapib 10 mg (2:1 randomization) n=1017

Placebo n=518

Primary outcome: Change in p-tau217 from baseline to 12 months

Blood samples for AD biomarkers collected at baseline and at 12 months

RESULTS AND DISCUSSION

- Baseline demographics and clinical characteristics for the population included in this analysis are shown in **Table 1**
- In the post hoc responder analysis, treatment effects demonstrated a clear *APOE4*-dependent gradient, with significant reduction in p-tau217 levels vs placebo observed for E4/E4 homozygotes and E3/E/4 heterozygotes but not for E3/E3 individuals (**Figure 2**)
- Responder analyses reinforced this pattern, with 3.1 times more E4/E4 homozygotes achieving >5% reduction in p-tau217 levels with obicetrapib compared with placebo (**Figure 3**)
  - A similar pattern was observed for E3/E4 heterozygotes, with 2.1 times more responders among those receiving obicetrapib compared with placebo, but no treatment advantage was observed for E3/E3 individuals

Table 1. Demographics and Baseline Characteristics*

	E4/E4 (n=22)	E3/E4 (n=137)	E3/E3 (n=263)
Age, mean ± standard deviation	70.3 ± 5.0	72.4 ± 5.9	74.3 ± 6.1
Age, range (yr)	61-82	61-90	61-89
Female sex, n (%)	6 (27.3)	53 (38.7)	91 (34.6)
Race, n (%)			
White	18 (81.8)	112 (81.8)	222 (84.4)
Asian	2 (9.1)	13 (9.5)	27 (10.3)
Black	2 (9.1)	12 (8.8)	11 (4.2)
Other	0	0	3 (1.1)
Medical History, n (%)			
Diabetes	12 (54.5)	43 (31.4)	117 (44.5)
Hypertension	20 (90.9)	116 (84.7)	233 (88.6)
ASCVD only	19 (86.4)	118 (86.1)	238 (90.5)
HeFH	3 (13.6)	19 (13.9)	24 (9.1)

*Baseline AD biomarkers for the population included in the BROADWAY AD biomarker substudy can be found in Figure 1 of the poster titled *"Undiagnosed Alzheimer's Pathology in Cardiovascular Patients and its Implications for Prevention: BROADWAY Trial Dissected."*

Figure 2. Median Percentage Change in P-tau217 by *APOE* Genotype

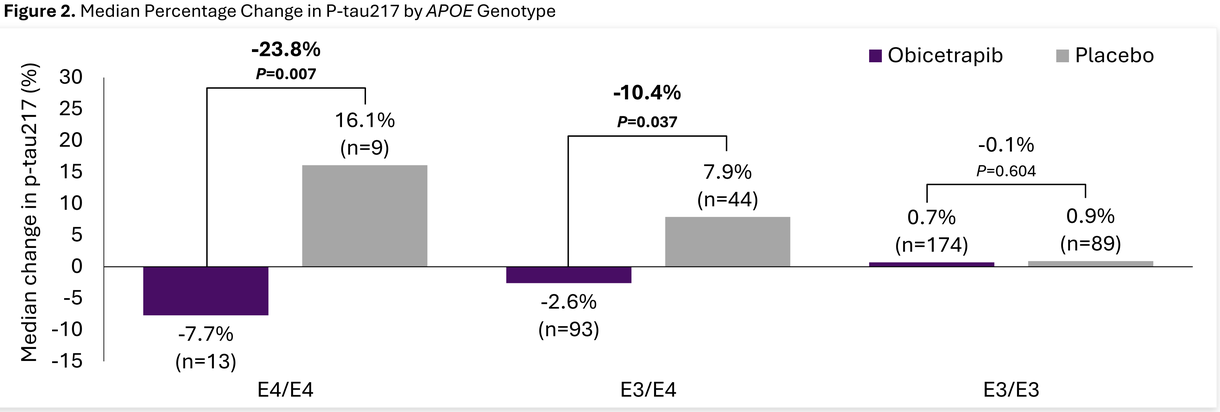
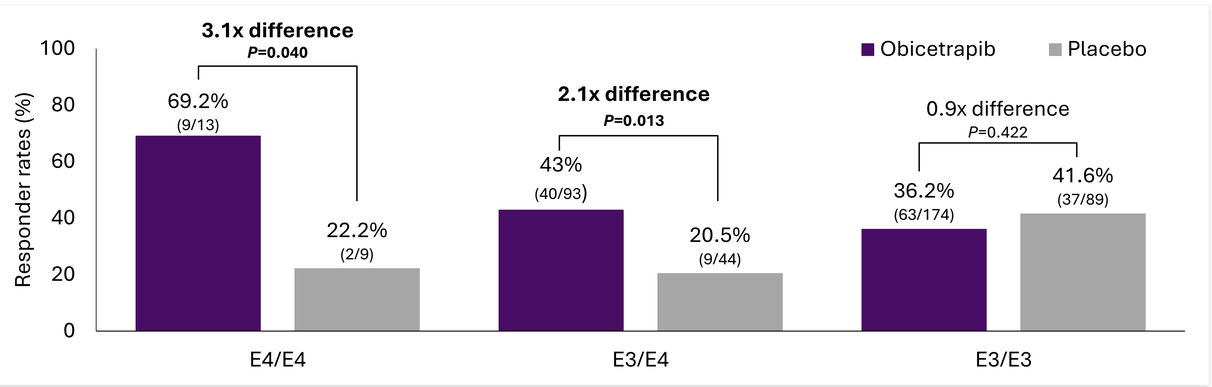


Figure 3. Rates of Responders With >5% Decrease in P-tau217



CONCLUSIONS

- CETP inhibition with obicetrapib produces *APOE4*-dependent biomarker improvements that scale with genetic risk burden, with the largest treatment effect seen for E4/E4 homozygotes and a smaller but significant effect seen for E3/E4 heterozygotes
  - The absence of effect in E3/E3 strengthens the mechanistic interpretation that obicetrapib compensates for *APOE4*-associated lipid transport dysfunction rather than providing nonspecific benefit
- These findings support an *APOE4*-enrichment strategy for AD prevention trials with obicetrapib, with E4/E4 homozygotes representing the highest yield population
- A planned phase 2b study will prospectively evaluate obicetrapib in *APOE4*-enriched populations using these genotype-specific criteria to optimize detection of clinically meaningful prevention effects

AFFILIATIONS AND DISCLOSURES

Andrew Hsieh, Michael H Davidson, Adam Johnson, Marc Ditmarsch, and John JP Kastelein are employees of NewAmsterdam Pharma and hold stock or options.

REFERENCES

1. Davidson MH et al. *Am J Prev Cardiol.* 2026;26:101442. **2.** Mattsson N et al. *Alzheimers Dement.* 2018;14(7):913-924. **3.** Hu X et al. *Biosci Trends.* 2024;18(2):195-197. **4.** Wei Y et al. *Immun Ageing.* 2022;19(1):19. **5.** Simpson DSA et al. *Antioxidants (Basel).* 2020;9(8):743. **6.** Wu Q et al. *Antioxidants (Basel).* 2022;11(11):2201. **7.** Mehta N et al. *Pharmacol Res.* 2023;197:106972. **8.** Martínez-Dubarbie F et al. *Alzheimers Res Ther.* 2024;16(1):268. **9.** Palmqvist S et al. *JAMA.* 2020;324(8):772-781. **10.** Davidson MH et al. *J Prev Alzheimers Dis.* 2026;13(1):100394.