ALZHEIMER'S ASSOCIATION AAIC 26

CETP Inhibition for Alzheimer's Prevention: Obicetrapib's Multi-Pathway Effects on Lipid-Mediated Pathophysiology

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BACKGROUND

Dysregulated cholesterol transport and impaired apolipoprotein E (APOE)-mediated amyloid-β (Aβ) clearance are upstream drivers of Alzheimer's disease (AD).[1] This is particularly true for *APOE4* carriers, who exhibit deficient lipid efflux, glial cholesteryl ester accumulation, and early blood-brain barrier (BBB) dysfunction.[1,2] Cholesteryl ester transfer protein (CETP) inhibition may address these upstream foundational lipid imbalances through multiple convergent pathways.[2] Obicetrapib is a potent, oral CETP inhibitor that achieves comprehensive lipid modulation and has demonstrated significant reductions in AD-relevant plasma biomarkers.[3]

OBJECTIVE

To integrate clinical data with Mendelian randomization evidence and preclinical mechanistic literature to characterize how CETP inhibition engages pathways relevant to AD prevention.

METHODS

Data for this analysis were drawn from 3 sources:

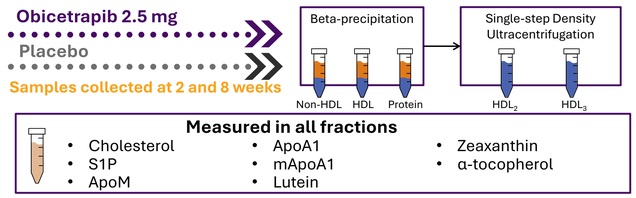
1 The BROADWAY AD Biomarker substudy[3]

Included 1535 participants with atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia.

Obicetrapib 10 mg (2:1 randomization)
Placebo
Blood samples for AD biomarkers collected at baseline and at 12 months

2 A phase 2 trial (NCT05421078)[4]

Included 12 Japanese participants with elevated cholesterol (LDL-C >70 mg/dL or non-HDL-C>100 mg/dL) while receiving statin therapy.



3 A Mendelian randomization (MR) analysis[5]

Used aggregate data from independent genome-wide association studies to evaluate the potential causal effects of lower CETP on biomarker concentrations.

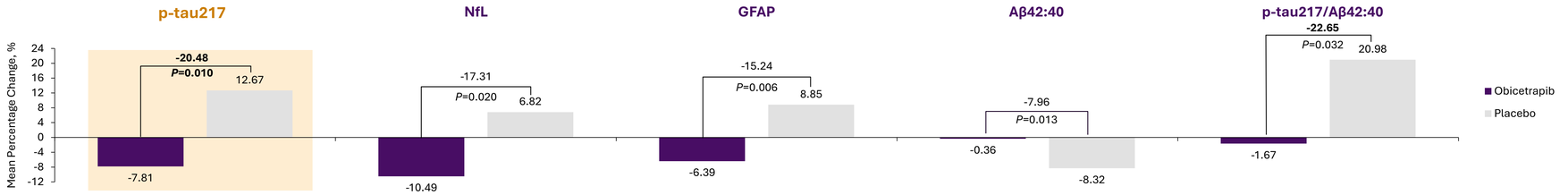
RESULTS

- Treatment with obicetrapib once daily for 12 months in BROADWAY significantly reduced plasma p-tau217 and other AD biomarkers compared with placebo, with the strongest effect in *APOE4/E4* homozygotes (**Figure 1**)
- Obicetrapib significantly modified lipid profiles after 12 months of treatment in BROADWAY **(Figure 2)**
- The concentrations of S1P, ApoM **(Figure 3)**, ApoA1, mApoA1 **(Figure 4),** and lipophilic antioxidants **(Figure 5)** were increased in the HDL2 fraction after treatment with obicetrapib 2.5 mg in the phase 2 study
- Complementary MR analyses demonstrate that genetically lower CETP activity associates with higher total brain volume and reduced dementia risk, with amplified protection in *APOE4* carriers[5]

CONCLUSIONS

- Obicetrapib demonstrates robust, APOE4-enriched reductions in p-tau217 and favorable changes across biomarkers, including tau phosphorylation, neurodegeneration, neuroinflammation, HDL-functionality, and amyloid processing
- Convergent evidence supports CETP inhibition as a multi-pathway upstream intervention that addresses the foundational lipid dysregulation driving AD pathogenesis, distinct from approaches targeting downstream inflammation or amyloid clearance alone
- These findings provide strong rationale for dedicated AD prevention trials in at-risk *APOE4* populations

Figure 1. Percentage Change in AD Biomarkers Among *E4/E4* Carriers at 12 Months in the Phase 3 BROADWAY Trial



Central Figure. The Effect of CETP Inhibition on Preventing *APOE4*-Associated AD

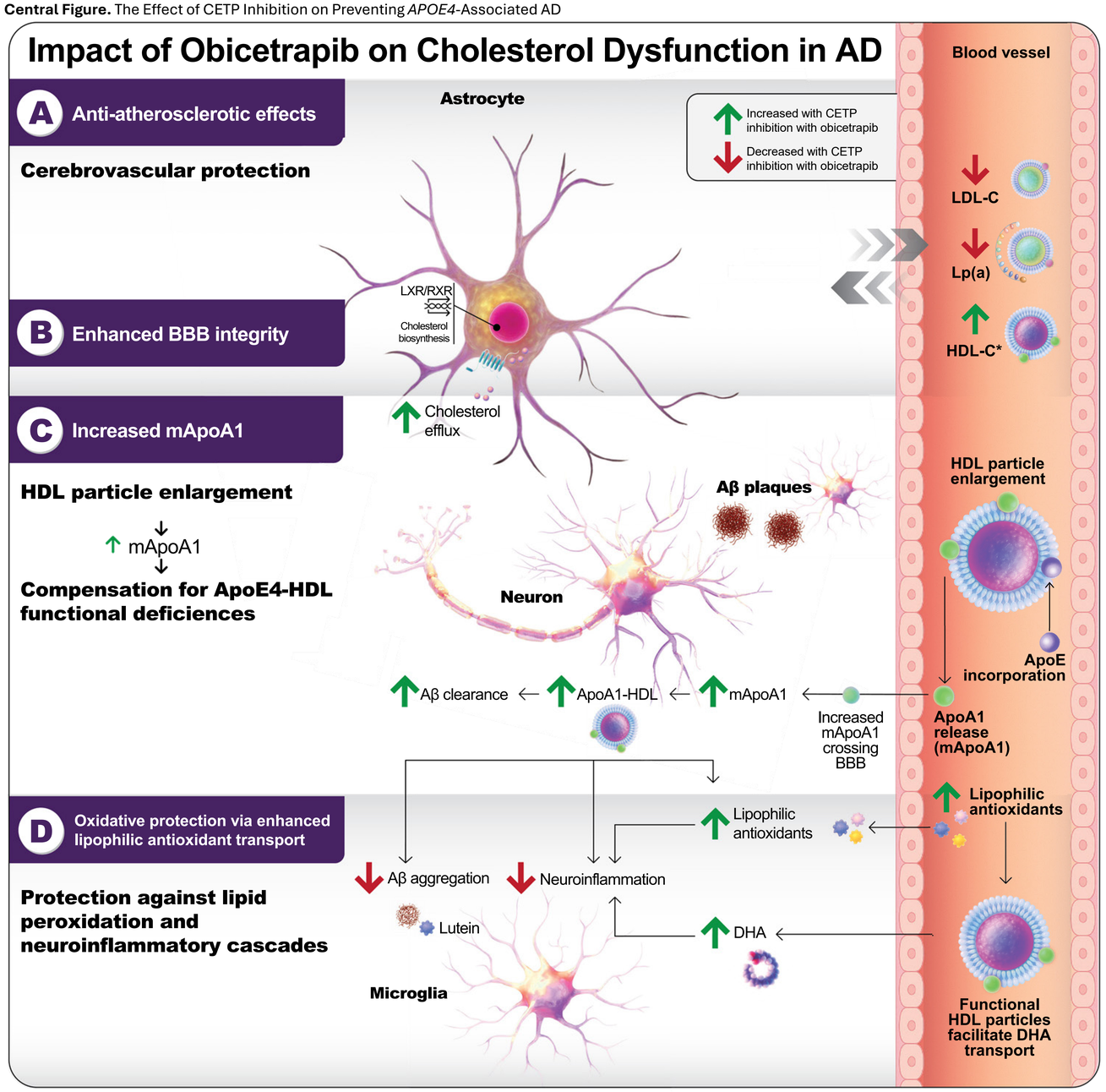
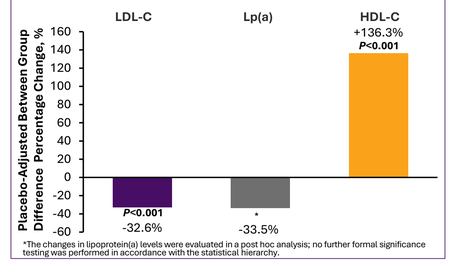


Figure 2. Change From Baseline in Lipid Profiles at Day 84 in the Phase 3 BROADWAY Trial



*The changes in lipoprotein(a) levels were evaluated in a post hoc analysis; no further formal significance testing was performed in accordance with the statistical hierarchy.

Figure 3. Change From Baseline in S1P and ApoM in the HDL2 Fraction at 2 and 8 Weeks in the Phase 2 Trial

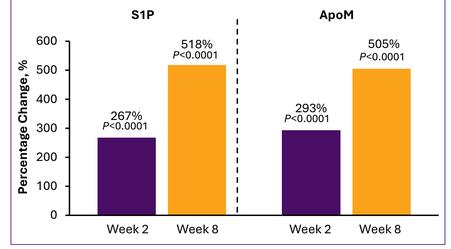


Figure 4. Change From Baseline in ApoA1 and mApoA1 in the HDL2 Fraction at 2 and 8 Weeks in the Phase 2 Trial

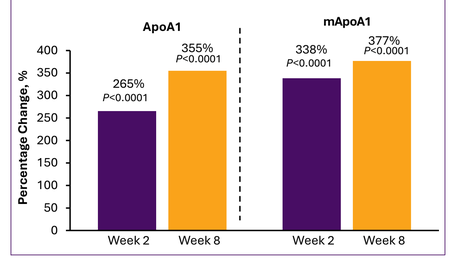
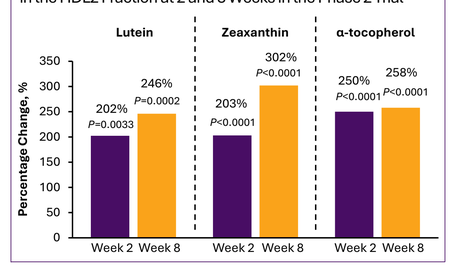


Figure 5. Change From Baseline in Lipophilic Antioxidants in the HDL2 Fraction at 2 and 8 Weeks in the Phase 2 Trial



AFFILIATIONS AND DISCLOSURES

MHD, AH, MD, AJ, NO, DLW, DC, DK, and JJPK are employees of NewAmsterdam Pharma and receive stocks or options. PS is a full-time employee of EQT LifeSciences, emeritus prof at Amsterdam University Medical Center, and consultant to New Amsterdam Pharma. MS reports receiving salary support from CPC, a nonprofit academic research organization affiliated with the University of Colorado. MS also reports serving as a consultant or research support (or both) from Amarin, Lexicon, NewAmsterdam Pharma, Novartis, Regeneron, Sanofi, Silence, and Tourmaline. EV received consultancy fees (paid to the university) for New Amsterdam Pharma, Treeway, ReMynd, Vivoryon, Biogen,Vigil Neuroscience, ImmunoBrain Checkpoint, Muna Therapeutics, Esai,Eli Lilly, CogRX, Therini, UCB and Roche. Within his university affiliation he is PI of studies of DIAN, AC immune, Alnylam, CogRX therapeutics, New Amsterdam Pharma, Janssen, UCB, Roche, Vivoryon, ImmunoBrain, GSK, MSD, Biogen, Alector, Eli Lilly, AriBio Fuij FilmToyama, GemVax. Co-founder van het CANDIDATE Center AmsterdamUMC. Scientific projects with the Dutch Soccer Association (KNVB).

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1. Gamba P et al. *Front Aging Neurosci*. 2015;7:119. **2.** Davidson MH et al. *Am J Prev Cardiol*. 2026;26:101442. **3.** Davidson MH et al. *J Prev Alzheimers Dis*. 2026;13(1):100394. **4.** Niesor E et al. Cholesteryl Ester Transfer Protein Inhibition and High-Density Lipoprotein Particle Composition: Consequences for Atherogenesis and Neurodegeneration, 12 January 2026, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.3.rs-8252502/v1]. **5.** Schmidt AF et al. *Alzheimers Res Ther*. 2024;16(1):228.