CETP inhibition with obicetrapib remodels HDL2, and increases apoM, S1P, and monomeric-apoA-I resulting in significant increases in xanthophyll and carotenoid levels in plasma

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Background

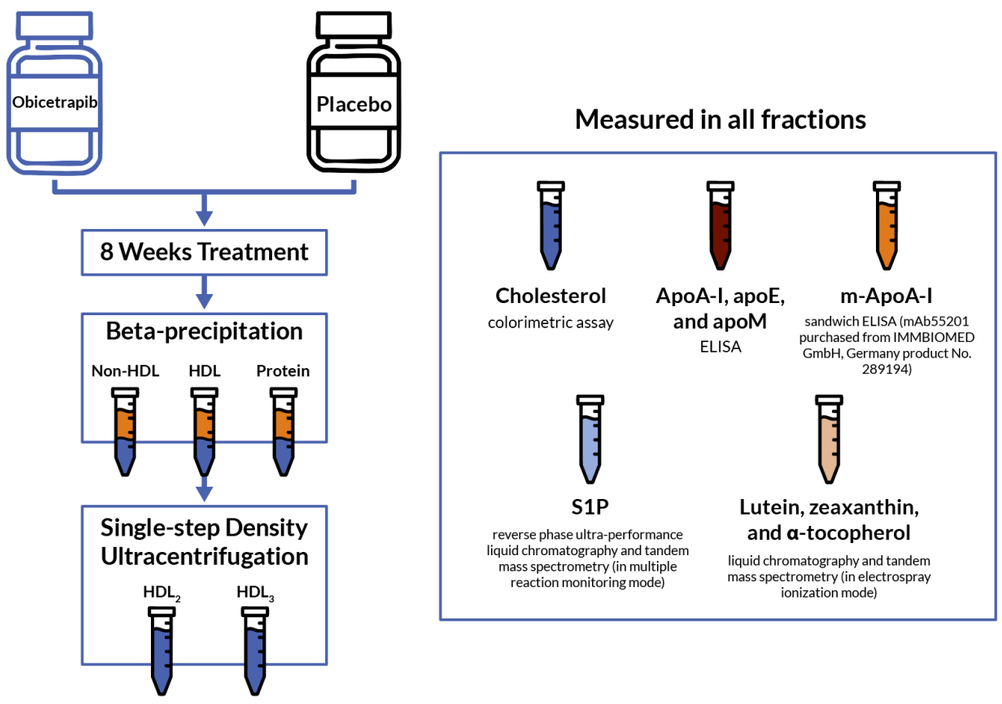
- Multiple studies have shown that low CETP activity and CETP inhibition potentially reduce the risk of dementia (1-3).
- The hypothesized mechanism of action centers on HDL associated compounds such as xanthophylls, lutein and zeaxanthin, and on the expression of apoM (S1P carrier) and S1P (signaling molecule with downstream effects on neovascularization and endothelial cell function), which are transported to the brain by HDL particles, particularly by non-lipidated apoA-I (pre-beta-1 HDL or m-apoA-I) (4-10).
- Obicetrapib, a next generation CETP inhibitor in phase 3 clinical development, dramatically increases HDL cholesterol, HDL particle concentration, and apoA-I (11,12).
- A preliminary investigation demonstrated that CETP inhibition with obicetrapib increased pre-beta-1 HDL and lipophilic antioxidants (lutein, zeaxanthin, and α-tocopherol) (13), and a sub-study analysis of the phase 3 BROADWAY trial indicated that obicetrapib slowed Alzheimer's disease biomarker progression in patients with ASCVD (14).
- However, the impact of obicetrapib on HDL remodeling (see Figure 2), including the concentrations of m-apoA-I, antioxidants, apoM, and S1P in the more lipid-rich HDL2 subfraction, were not assessed and were the focus of this investigation.

Objective

In order to understand the effect of potent CETP inhibition on HDL metabolism, and the consequential potential benefits for ASCVD and Alzheimer's disease, we aimed to evaluate the effect of low dose 2.5mg obicetrapib on the amount of lipophilic antioxidants transported by HDL and the concentrations of several plasma components known to bind to HDL, including apoA-I, m-apoA-I, apoE, apoM, and S1P.

Methods

Figure 1. Study design.



We analyzed these in samples from a Phase 2 clinical trial registered at ClinicalTrials.gov: NCT05421078. Participants included Japanese men and women with documented LDL cholesterol >70 mg/dL (or non-HDL cholesterol >100 mg/dL), while treated with stable atorvastatin 10 or 20 mg/d or rosuvastatin 5 or 10 mg/d. They received placebo or obicetrapib 2.5, 5, or 10 mg/d for 8 weeks.

Table 1. Baseline characteristics of the subset of participants in the placebo and obicetrapib 2.5 mg groups from the dose-ranging phase 2 clinical trial of 8 weeks obicetrapib (15).

	Placebo (n=7)	Obicetrapib 2.5 mg (n=13)
Age, y, mean (SD)	66 (7)	66 (10)
Female sex, n (%)	1 (14.3)	6 (46.2)
Body mass index, kg/m², mean (SD)	25.9 (3.7)	24.9 (3.6)
Statin therapy, n (%)		
Atorvastatin 10 mg or Rosuvastatin 5 mg	4 (57.1)	12 (92.3)
Atorvastatin 20mg or Rosuvastatin 10 mg	3 (42.9)	1 (7.7)

Results

- In patients treated with 2.5 mg/day obicetrapib, concentrations of ApoA-I, m-ApoA-I, ApoM, ApoE, S1P, cholesterol, lutein, zeaxanthin, and α-tocopherol were significantly increased in the HDL2-C fraction (Table 2).
- These concentration shifts were not observed in the placebo group, where no significant increases were detected.

Table 2. Obicetrapib 2.5 mg group: Baseline and changes from baseline in the levels of apoA-I, m-apoA-I, apoM, apoE, S1P, cholesterol, and lipophilic antioxidants in the HDL2 subfraction following 2 and 8 weeks of treatment (n=13).

	Baseline[a]	Week 2 change from baseline[a]	*P* value[b]	Week 8 change from baseline[a]	*P* value[b]
ApoA-I(mg/dL)	7.7 (4.4, 16.6)	28.0 (22.3, 32.8)	**0.0002**	39.6 (26.6, 43.9)	**0.0002**
m-ApoA-I(μg/mL)	15.6 (11.0, 26.0)	67.2 (59.6, 78.0)	**0.0002**	79.2 (52.1, 95.5)	**0.0002**
ApoM (μg/mL)	900 (660, 1530)	3220 (1820, 4370)	**0.0002**	5620 (3300, 7430)	**0.0002**
ApoE (μg/mL)	2.4 (1.8, 2.6)	2.0 (0.1, 2.6)	0.0823	3.9 (2.0, 5.1)	**0.0127**
S1P (nmol/L)	18.0 (13.2, 31.3)	51.7 (36.1, 100.8)	**0.0002**	114.0 (90.8, 142.5)	**0.0002**
Cholesterol (mg/dL)	10.1 (7.9, 11.0)	15.1 (14.3, 23.8)	**0.0002**	31.5 (24.8, 35.7)	**0.0002**
Lutein (ng/mL)	10.5 (9.9, 25.6)	25.8 (17.5, 43.0)	**0.0002**	48.6 (30.8, 58.1)	**0.0005**
Zeaxanthin (ng/mL)	2.8 (1.9, 4.9)	5.6 (3.2, 8.5)	**0.0002**	9.7 (7.2, 14.9)	**0.0002**
α-Tocopherol (ng/mL)	682 (483, 848)	1562 (1134, 2142)	**0.0002**	1660 (1152, 2176)	**0.0002**

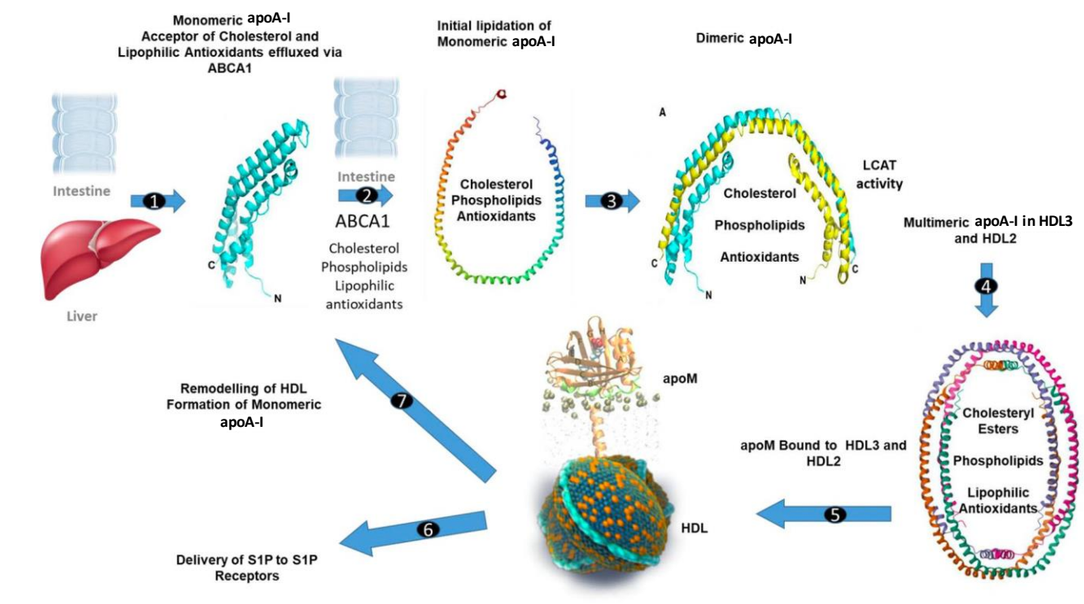
[a]Values are median (Q1, Q3).

[b]*P* values are from signed rank test

Conclusions

- CETP inhibition through obicetrapib increases HDL cholesterol, and remodels HDL particles, ultimately driving generation of m-apoA-I and enhancing antioxidant cargo.
- With obicetrapib 2.5 mg, HDL cholesterol rose, with the largest effect in the HDL2 fraction, without a decrease in the other fractions. The rise in HDL2 was accompanied by marked increases in apoA-I and m-apoA-I. As a result, both apoM and S1P significantly increased at 8 weeks. This coincided with significant enrichment of lutein and zeaxanthin in HDL2.
- This mechanism provides a plausible pathway for increased m-apoA-I as well as for xanthophyll delivery to the brain, with implications for prevention of neurodegenerative disease.

Figure 2. Cycle of HDL structure remodeling.



1. ApoA-I is secreted mainly by the intestine and liver as m-apoA-I. The amino acid sequence L^{137} Q^{138} E^{139} K^{140} L^{141} S^{142} P^{143} L^{144} is recognized by mAb55201 as a beta-sheet.
2. Upon lipidation via ABCA1, m-apoA-I acquires cholesterol, phospholipids, and lipophilic antioxidants.
3. Lipidation leads to the formation of helix 5 including amino acid sequence L Q E K L S P L not recognized by mAb55201.
4. Dimerization of apoA-I induces the formation of the LCAT binding site and enlargement of HDL as HDL3 and HDL2 particles.
5. ApoM moves from the protein (albumin) fraction to HDL2 and HDL3.
6. ApoM-bound HDL delivers S1P to S1P receptor expressing cells.
7. ApoM-bound HDL remodels HDL and generates m-apoA-I.

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Author Disclosures

EJN, Principal and Employee, Swiss Nutrition and Health Foundation,
MD, MACdK, JJPK, Employees and Shareholders of NewAmsterdam Pharma, SR, PJ, AH, Employees of Hartis Pharma.

Abbreviations

ABCA1, ATP-binding cassette transporter A1; apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CETP, cholesteryl ester transfer protein; ELISA, enzyme-linked immunosorbent assay; HDL, high-density lipoprotein; LCAT, lecithin cholesterol acyltransferase; LDL, low-density lipoprotein; m-apoA-I, monomeric apolipoprotein A1; mAb, monoclonal antibody; S1P, sphingosine-1-phosphate.

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