Obicetrapib significantly increases plasma and high-density lipoprotein (HDL) levels of antioxidants

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Background

- Obicetrapib, a next-generation CETP inhibitor in phase 3 clinical development, dramatically increases HDL cholesterol, HDL particle concentration, and apoA1 (1, 2).
- Non-lipidated apoA1 (also known as pre-beta-1 HDL) captures cholesterol and lipophilic antioxidants (see Figure 1) via the ATP-binding cassette transporter A1 (3-6).
- The majority of lutein and zeaxanthin is transported by HDL (see Figure 2); this antioxidant transport is crucial to tissues such as the retina (implicated in age-related macular degeneration) and the brain (implicated in Alzheimer's disease) (7-9).
- Preliminary investigations demonstrated CETP inhibition with obicetrapib increased pre-beta-1 HDL and increased the uptake of lipophilic antioxidants (lutein, zeaxanthin, and α-tocopherol) in HDL particles (10).
- We hypothesized that raising HDL with obicetrapib would lead to an increase in the HDL levels of lipophilic antioxidants in a dose-ranging study in Japanese participants where obicetrapib at all doses significantly lowered LDL cholesterol, apoB, and non-HDL cholesterol, and raised HDL cholesterol (-45.8%, -29.7%, -37.0%, and +159%, respectively, with 10 mg) (2).

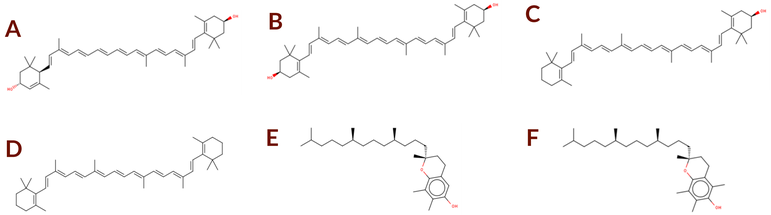

Figure 1. Chemical structures of (A) lutein, (B) zeaxanthin, (C) β-cryptoxanthin, (D) β-carotene, (E) γ-tocopherol, and (F) α-tocopherol.

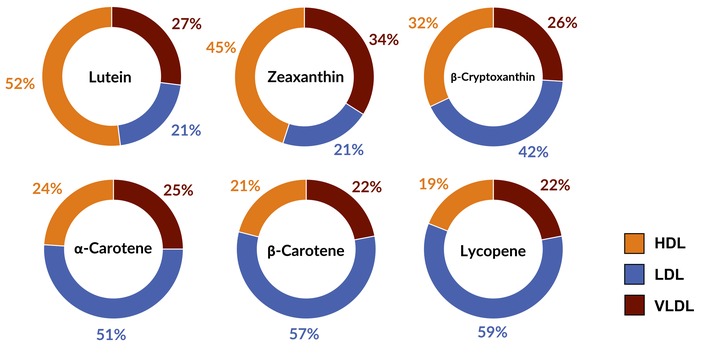

Figure 2. Approximate distribution of major carotenoids in plasma lipoproteins from a study that administered a high lutein-zeaxanthin diet to 12 subjects (9).

Objective

To evaluate the effect of obicetrapib on the amounts of lipophilic antioxidants transported by HDL in a dose-ranging study.

Methods

- Phase II clinical trial registered at ClinicalTrials.gov: NCT05421078.
- Participants: Japanese men and women (n=102) who had not achieved 2022 Japanese Atherosclerosis Society Guidelines for the Prevention of Atherosclerotic Cardiovascular Disease, with documented LDL cholesterol >70 mg/dL (or non-HDL cholesterol >100 mg/dL), while receiving stable statin therapy with either atorvastatin 10 or 20 mg/d or rosuvastatin 5 or 10 mg/d only for at least 8 weeks prior to screening.
- Participants received placebo or obicetrapib 2.5, 5, or 10 mg/d for 8 weeks.
- Plasma samples for this analysis were collected at clinic visits occurring at baseline (V2) and after 2 weeks (V3) and 8 weeks (V5) of treatment.
- Non-HDL in plasma was separated from HDL by beta-precipitation of apoB-containing particles.
- Lipophilic antioxidants including lutein, zexanthin, β-cryptoxanthin, γ-tocopherol and α-tocopherol, and β-carotene were quantifiedin the β-precipitation fractions (non-HDL and HDL) by liquid chromatography-tandem mass spectrometry (Waters Corporation) in electrospray ionization mode.
- OxLDL was determined by enzyme-linked immunosorbent assay (Mercodia).

Results

Table 1a. Percent changes (baseline/V2 to week 2/V3 and week 8/V5) in levels of carotenoid lipophilic antioxidants (lutein, zeaxanthin, β-cryptoxanthin, and β-carotene) in the HDL fraction.

Obicetrapib	% change vs V2							
	Lutein		Zeaxanthin		β-cryptoxanthin		β-carotene	
	V3	V5	V3	V5	V3	V5	V3	V3
2.5 mg	31.77***	48.44*	49.61**	28.94	161.27*	271.27	55.61**	23.72
5 mg	25.02	100.66***	35.03*	68.97*	99.08*	185.53*	23.77	82.86**
10 mg	38.16***	123.98*	37.43***	78.95***	109.67*	280.92*	86.99**	366.50**

*p<0.05
**p<0.01
***p<0.001
****p<0.0001

Table 1b. Percent changes (baseline/V2 to week 2/V3 and week 8/V5) in levels of tocopherol lipophilic antioxidants (γ-tocopherol and α-tocopherol) in the HDL fraction.

Obicetrapib	% change vs V2			
	γ-tocopherol		α-tocopherol	
	V3	V5	V3	V5
2.5 mg	76.82***	16.04	89.26****	48.50**
5 mg	49.15*	16.44	47.98****	26.63**
10 mg	42.10***	-4.84	57.73****	33.82****

*p<0.05
**p<0.01
***p<0.001
****p<0.0001

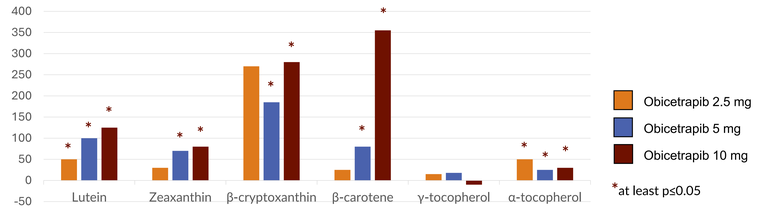

Figure 3. Percent changes (baseline/V2 to week 8/V5) in levels of carotenoid and tocopherol lipophilic antioxidants.

Table 2a. Percent changes (baseline/V2 to week 2/V3 and week 8/V5) in levels of carotenoid lipophilic antioxidants (lutein, zeaxanthin, β-cryptoxanthin, and β-carotene) in the non-HDL fraction.

Obicetrapib	% change vs V2							
	Lutein		Zeaxanthin		β-cryptoxanthin		β-carotene	
	V3	V5	V3	V5	V3	V5	V3	V3
2.5 mg	-16.88**	-54.79**	-22.25**	-64.92**	31.73	20.48	1.95	-4.72
5 mg	-22.93*	-27.14	-26.32	-41.46	18.07	-14.38	17.05*	132.17***
10 mg	-25.08***	-44.35***	-29.23***	-49.20***	1.86	12.67	4.30	298.54*

*p<0.05
**p<0.01
***p<0.001
****p<0.0001

Table 2b. Percent changes (baseline/V2 to week 2/V3 and week 8/V5) in levels of tocopherol lipophilic antioxidants (γ-tocopherol and α-tocopherol) in the non-HDL fraction.

Obicetrapib	% change vs V2			
	γ-tocopherol		α-tocopherol	
	V3	V5	V3	V5
2.5 mg	-7.22	-55.68**	-23.47****	-65.05****
5 mg	-15.27	-42.94**	-28.98***	-50.50****
10 mg	-26.44**	-65.63***	-32.86****	-50.57****

*p<0.05
**p<0.01
***p<0.001
****p<0.0001

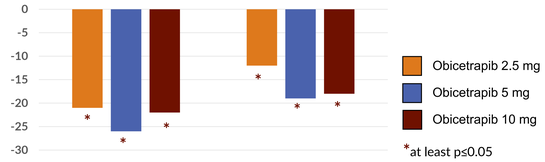

Figure 4. Percent change (baseline/V2 to week 8/V5) in oxLDL levels in plasma.

Conclusions

Lipophilic antioxidants are distributed according to their lipophilicity in various lipoproteins. Obicetrapib robustly increased all antioxidant levels in HDL and generally decreased antioxidant levels in non-HDL across dose levels (2.5 mg to 10 mg). Despite a decrease in lipophilic antioxidants in non-HDL, which was on par with the LDL cholesterol reduction, obicetrapib also decreased plasma levels of oxLDL. These data support the well-established evidence that HDL protects against LDL oxidation, likely because of the large amount of lipophilic antioxidants transported by HDL. These results also support the potential use of obicetrapib in diseases with high unmet medical need that are associated with low HDL and low levels of lipophilic antioxidants in plasma and tissues, such as age-related macular degeneration, neurodegenerative disorders, and sickle cell anemia.

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Abbreviations

apo, apolipoprotein; CETP, cholesteryl ester transfer protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; oxLDL, oxidized LDL; V, visit; VLDL, very low-density lipoprotein

Support

This study was funded by NewAmsterdam Pharma, Naarden, The Netherlands.

NewAmsterdam Pharma