Obicetrapib lowers LDL-cholesterol by substantially increasing LDL-ApoB clearance rates in humans

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Introduction

Obicetrapib is a novel cholesteryl ester transfer protein (CETP) inhibitor. In the BROADWAY study, a recent phase 3 clinical trial in over 2500 patients with familial hypercholesterolemia or atherosclerotic cardiovascular disease, obicetrapib resulted in a 32.6% reduction in LDL-cholesterol (LDL-C) compared to placebo (Nicholls SJ et al. *NEJM*. 2025). The mechanism underlying the LDL-C lowering by obicetrapib has not yet been described.

Objective

To determine the physiological mechanism underlying the reduction in LDL-C and ApoB in response to obicetrapib using a stable isotope tracer study.

Methods

Adults with LDL-C 100-190 mg/dL and triglycerides ≤ 400 mg/dL not on baseline lipid-lowering therapy were recruited. Enrolled participants were randomized 1:1 to obicetrapib 10mg daily or matching placebo. This study was approved by the Penn IRB.

Figure 1. Study flow diagram. After screening, enrolled participants completed a baseline kinetic study, followed by 8-12 weeks of treatment with obicetrapib or placebo, followed by a second on-treatment kinetic study.

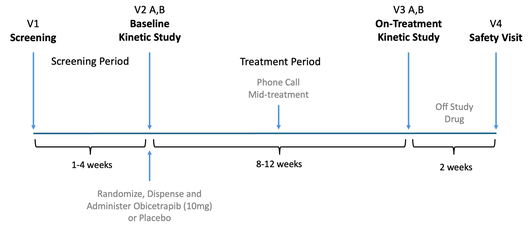
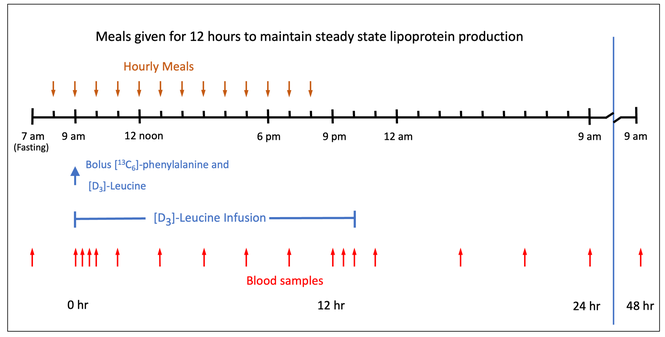


Figure 2. Inpatient lipoprotein kinetic study (Baseline and On-treatment).



Isolation of plasma VLDL, IDL, LDL, and HDL was completed using ultracentrifugation, and ApoB-100 was isolated from VLDL, IDL and LDL fractions using gel electrophoresis (SDS-PAGE).

Results

Of the 39 patients who screened for the study, 22 were eligible and were randomized.

Table 1. Baseline characteristics

	Placebo (n=11)	Obicetrapib (n=11)
Age, mean (SD)	30.7 (7.2)	35.5 (9.7)
Male, n (%)	9 (81.8)	5 (45.5)
White, n(%)	6 (54.5)	7 (63.6)
BMI, mean (SD)	25.1 (2.8)	24.8 (3.7)
Total cholesterol, mean (SD), mg/dL	193.4 (17.7)	190.2 (21.7)
Triglycerides, mean (SD), mg/dL	108.8 (59.5)	79.8 (29.8)
LDL-C, mean (SD), mg/dL	121.2 (18.7)	122.1 (16.7)
HDL-C, mean (SD), mg/dL	50.4 (10.5)	52.2 (9.4)
Apolipoprotein B, mean (SD), mg/dL	95.6 (8.4)	95.0 (12.9)

All 22 participants completed the study. Compared to placebo, obicetrapib resulted in a mean LDL-C reduction of 38% (p<0.0001), a mean apoB reduction of 22% (p<0.001), and a mean increase in HDL-C of 107% (p=0.002). **Obicetrapib significantly increased the fractional catabolic rate (FCR) of LDL-ApoB-100 from 0.362 pools/day to 0.531 pools/day (54% increase) compared to a negligible change in the placebo group (p=0.002)** (Fig. 3, Table 2)

Figure 3. FCR of LDL-ApoB-100 at baseline (Visit 2A) and on-treatment (Visit 3A) for placebo and obicetrapib groups.

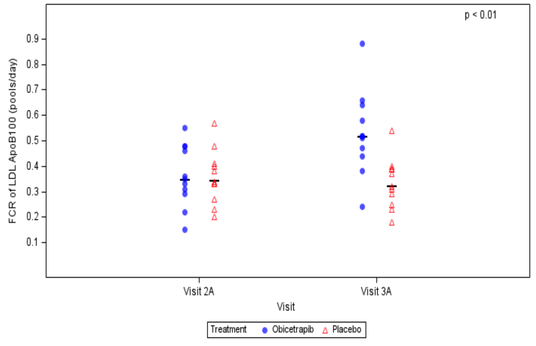
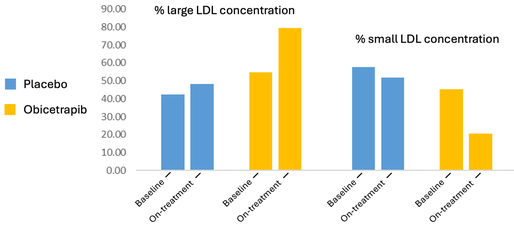


Table 2. Baseline and on-treatment ApoB kinetic parameters for obicetrapib compared to placebo using ANCOVA. Mean levels (with standard deviations) shown for baseline and on-treatment values. Change represents the adjusted least squares mean change (with 95% confidence intervals) from baseline using the baseline measure as a covariate. FCR = fractional catabolic rate, PR = production rate.

	Placebo (n=11)			Obicetrapib (n=11)			p-value
	Baseline	Treatment	Change	Baseline	Treatment	Change	
FCR of LDL-ApoB-100 (pools/day)	0.358 (0.108)	0.334 (0.099)	-0.026 (-0.109-0.057)	0.362 (0.121)	0.531 (0.165)	0.170 (0.087-0.253)	0.002
PR of LDL-ApoB-100 (mg/kg/day)	13.983 (3.892)	12.802 (3.940)	-1.119 (-3.110-0.871)	13.709 (4.832)	14.771 (3.867)	1.000 (-0.990-2.991)	0.13
FCR of Total ApoB-100 (pools/day)	1.012 (0.665)	0.919 (0.691)	-0.086 (-0.582-0.410)	0.923 (0.637)	1.439 (1.144)	0.510 (0.014-1.006)	0.09
% conversion VLDL-ApoB-100 to LDL-ApoB-100 (%)	74.00 (15.25)	71.86 (24.85)	-3.40 (-17.37-10.57)	80.12 (16.45)	78.96 (21.64)	0.11 (-13.86-14.08)	0.72

Exploratory analyses of particle size and composition showed a mean 16.5% reduction in LDL percent cholesteryl ester in the obicetrapib group compared to no change in the placebo arm. Obicetrapib treatment also resulted in a mean 66% reduction in the concentration of small LDL particles compared to a mean 14% reduction with placebo (Fig. 4).

Figure 4. Change in concentration of large and small LDL particles between baseline and on-treatment visits



Conclusions

Obicetrapib reduced LDL-ApoB levels by substantially increasing the rate of LDL-ApoB clearance from circulation and reducing the proportion of small LDL particles. These data complement the evidence from Mendelian randomization, preclinical and clinical outcome studies and conclusively support the mechanism of action of obicetrapib for LDL-C lowering as promoting the removal of circulating LDL particles.

Disclosures: AB receives research funding support from Amgen, Ionis, Kaneka, New Amsterdam Pharma, Novartis, and Regeneron; MD, JJPK, EW, DK, MHD are employees of NewAmsterdam Pharma, DR is on the scientific advisory board for Alnylam, Novartis, and Verve.