Synergistic Effect of Obicetrapib and Ezetimibe on Circulating LDL Particles

Michael H. Davidson, MD[1]; Christie M. Ballantyne, MD[2]; Andrew Hsieh, PharmD[1]; Marc Ditmarsch, MD[1]; Douglas Kling, BS, MBA[1]; Danielle Curcio, BS, MBA[1]; Mary R. Dicklin, PhD[3]; John J.P. Kastelein, MD, PhD[1]

[1]NewAmsterdam Pharma, Naarden, The Netherlands; [2]Baylor College of Medicine, Houston, TX, U.S.; [3]Midwest Biomedical Research, Addison, IL, U.S.

Background

- Updates to risk-based low-density lipoprotein cholesterol (LDL-C) goals inevitably mean that there will be a need to add LDL-C lowering therapy even for patients already on high intensity statin therapy.
- Current non-statin oral add-on lipid-lowering therapies reduce LDL-C individually by 20-25%, whereas potent injectable therapies have had limited uptake.
- As a result, there remains a high unmet need for effective, safe oral therapies to be used as an adjunct to high-intensity statins.
- The novel cholesteryl ester transfer protein (CETP) inhibitor obicetrapib is currently in phase III development for dyslipidemia in high-risk patients unable to achieve sufficient LDL-C lowering with other lipid-lowering medications (1-5).
- The Study to Evaluate the Effect of Obicetrapib in Combination with Ezetimibe as an Adjunct to High-intensity Statin Therapy (ROSE2) demonstrated robust LDL-C-lowering and excellent safety of obicetrapib 10 mg monotherapy and in combination with 10 mg ezetimibe (2).

Objective

The ROSE2 study further examined the effect of obicetrapib 10 mg monotherapy and in combination with 10 mg ezetimibe on lipoprotein particles [with nuclear magnetic resonance (NMR)] and small, dense (sd)LDL-C.

Participants

- **Inclusion criteria:** men and women 18-75 years of age with fasting LDL-C >70 mg/dL and triglycerides <400 mg/dL while receiving a stable dose of high-intensity statin (40-80 mg atorvastatin or 20-40 mg rosuvastatin) for at least the prior 8 weeks.
- **Major exclusion criteria:** current clinically manifest cardiovascular disease; uncontrolled hypertension; glycated hemoglobin ≥10%; active muscle disease or persistent creatine kinase >3 times the upper limit of normal; renal or hepatic dysfunction; significant anemia; and recent history of malignancy, alcohol, or drug abuse.
- **Excluded medications:** proprotein convertase subtilisin kexin type 9 therapies and bempedoic acid.

Methods

- Randomized, placebo-controlled, double-blind phase II trial (NCT05266586).
- Conducted from March 2022 to September 2022 in 18 clinical research sites in the U.S.
- Laboratory measurements were completed by Medpace Reference Laboratory (Cincinnati, OH, U.S.) using AU5800 analyzers (lipids) (Beckman Coulter, Brea, CA, U.S.) and the Antellica® NEPH 630 System BNII System/ ProSpec® system (ApoB) (Siemens Healthcare Diagnostics Products, Marburg, Germany).
- NMR spectra for LDL particles (LDL-P) and HDL particles (HDL-P) were assessed in serum samples on a Vantera® Clinical Analyzer (LabCorp, Morrisville, NC, U.S.).
  - Small LDL-P = 18-21.2 nm
  - Large HDL-P = 8.8-13 nm

Statistical Analyses

- Statistical analyses were conducted using SAS (version 9.4, SAS Institute, Cary, NC, U.S.). All tests of significance were performed at alpha = 0.05, two-sided.
- Primary endpoint: percent change from baseline to week 12 in LDL-C for the combination of obicetrapib plus ezetimibe compared with placebo.
- Exploratory endpoints: percent changes in NMR-assessed lipoprotein particles and sdLDL-C.
- Pre-specified primary analysis population: modified intent-to-treat population (mITT) which was defined as all participants who received at least 1 dose of study drug and had a baseline LDL-C value.
- Post-hoc primary analysis population: on-treatment population which excluded participants from the mITT population in the obicetrapib treatment groups with plasma obicetrapib <100 ng/mL at either or both week 4 and week 12.

Results

Figure 1. Study Design of ROSE2

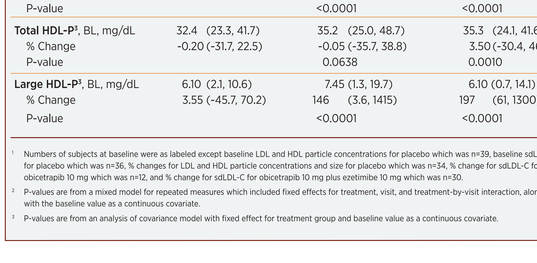


Table 1. Lipoprotein lipids and particle concentrations in ROSE2

Parameter	Placebo (n=40)[1]	Obi 10 mg (n=26)[1]	Obi 10 mg + Eze 10 mg (n=31)[1]
	Median (min, max)		
LDL-C[2], BL, mg/dL	95.5 (60, 211)	100 (35, 189)	87.0 (62, 152)
% Change	-6.35 (-36.4, 96.7)	-43.5 (-78.4, 22.6)	-63.4 (-83.7, -29.7)
P-value		<0.0001	<0.0001
Non-HDL-C[2], BL, mg/dL	126 (73, 227)	122 (57, 209)	116 (77, 189)
% Change	-5.55 (-34.9, 83.6)	-37.5 (-59.2, 20.0)	-55.6 (-76.2, -30.8)
P-value		<0.0001	<0.0001
ApoB[2], BL, mg/dL	89.0 (52, 146)	85.0 (33, 130)	85.0 (56, 130)
% Change	-2.05 (-30.9, 76.9)	-24.2 (-44.8, 27.1)	-34.4 (-54.3, -14.7)
P-value		<0.0001	<0.0001
Total LDL-P[3], BL, nmol/L	1083 (632, 1650)	1057 (275, 1588)	1048 (692, 1848)
% Change	-5.65 (-38.6, 35.9)	-54.8 (-82.4, 4.7)	-72.1 (-95.7, -12.9)
P-value		<0.0001	<0.0001
Small LDL-P[3], BL, nmol/L	717 (316, 1088)	702 (84, 1517)	763 (68, 1411)
% Change	-8.30 (-36.7, 86.2)	-92.7 (-98.3, 11.9)	-95.4 (-99.8, 1.5)
P-value		<0.0001	<0.0001
sdLDL-C[3], BL, mg/dL	35.2 (15.0, 85.8)	36.0 (18.4, 66.1)	41.2 (25.2, 67.3)
% Change	-3.7 (-48.0, 95.1)	-30.9 (-54.7, 16.7)	-44.4 (-68.0, -2.4)
P-value		<0.001	<0.001
HDL-C[2], BL, mg/dL	42.5 (31, 68)	47.0 (28, 111)	46.0 (28, 76)
% Change	0.75 (-33.3, 45.0)	142 (34.9, 311)	136 (46.5, 261)
P-value		<0.0001	<0.0001
Total HDL-P[3], BL, mg/dL	32.4 (23.3, 41.7)	35.2 (25.0, 48.7)	35.3 (24.1, 41.6)
% Change	-0.20 (-31.7, 22.5)	-0.05 (-35.7, 38.8)	3.50 (-30.4, 46.9)
P-value		0.0638	0.0010
Large HDL-P[3], BL, mg/dL	6.10 (2.1, 10.6)	7.45 (1.3, 19.7)	6.10 (0.7, 14.1)
% Change	3.55 (-45.7, 70.2)	146 (3.6, 1415)	197 (61, 1300)
P-value		<0.0001	<0.0001

[1] Numbers of subjects at baseline were as labeled except baseline LDL and HDL particle concentrations for placebo which was n=39, baseline sdLDL-C for placebo which was n=36, % changes for LDL and HDL particle concentrations and size for placebo which was n=34, % change for sdLDL-C for obicetrapib 10 mg which was n=12, and % change for sdLDL-C for obicetrapib 10 mg plus ezetimibe 10 mg which was n=30.

[2] P-values are from a mixed model for repeated measures which included fixed effects for treatment, visit, and treatment-by-visit interaction, along with the baseline value as a continuous covariate.

[3] P-values are from an analysis of covariance model with fixed effect for treatment group and baseline value as a continuous covariate.

Figure 2. Median percent change from baseline in atherogenic lipoprotein particles and low-density lipoprotein cholesterol in ROSE2

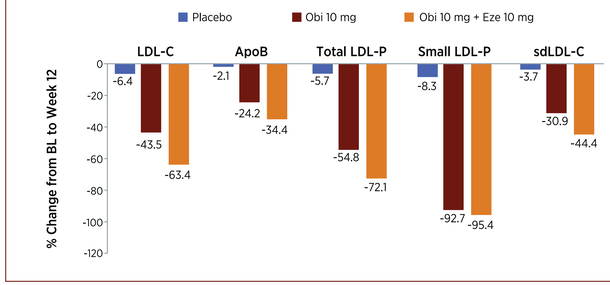
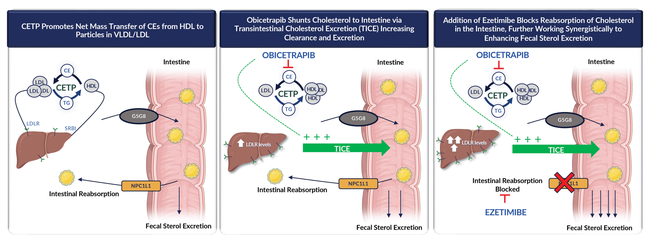


Table 2. Relative risk ranges for cardiovascular disease according to lipoprotein particles measured by NMR lipoprotein fractionation compared to ROSE 2 results

	Relative Risk Range			ROSE2	
Lipoprotein Fractions	**Low**	**Moderate**	**High**	**Placebo**	**Obi/Obi+Eze**
LDL-P, nmol/L	<935	935-1816	>1816	947	435/286
Small LDL-P, nmol/L	<467	467-820	>820	717.5	73.4/47.5
LDL size, nm	>20.5	—	≤20.5	20.26	21.0/21.0
HDL-P, nmol/L	>32.8	29.2-32.8	<29.2	30.8	34/35.3
Large HDL-P, nmol/L	>7.2	5.3-7.2	<5.3	6.3	145.8/197.4
HDL size, nm	>9.0	8.7-9.0	<8.7	9.3	11.2/11.0

https://www.clevelandheartlab.com/tests/lipoprotein-fractionation-nmr-with-lipids/

Figure 3. Synergistic mechanism of action of CETP inhibition with obicetrapib and NPC1L1 protein inhibition with ezetimibe result in increased net sterol clearance and excretion



Conclusions

Obicetrapib, an oral, once-daily low-dose CETP inhibitor, robustly reduces atherogenic lipoprotein particles and cholesterol concentrations when added to high-intensity statin therapy and in combination with ezetimibe on top of high-intensity statins thus normalizing the lipoprotein profile of these patients to reflect a physiological profile. These findings are consistent with a synergism among the different mechanisms of actions of these agents.

References

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Abbreviations

BL, baseline; CE, cholesterol ester; CETP, cholesteryl ester transfer protein; Eze, ezetimibe; FU, follow-up; G5G8, ATP-binding cassette transporter sub-family G member 5/member 8; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HDL-P, high-density lipoprotein particle concentration; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LDL-P, low-density lipoprotein particle concentration; LDLR, low-density lipoprotein receptor; mITT, modified intent-to-treat; NMR, nuclear magnetic resonance; NPC1L1, Niemann Pick C-1 Like-1; Obi, obicetrapib; PK, pharmacokinetic; sd, small, dense; SRB1, scavenger receptor class B, type 1; TG, triglyceride; TICE, transintestinal cholesterol excretion

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NewAmsterdam Pharma

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