Safety and Efficacy of Obicetrapib in Patients at High Cardiovascular Risk

Stephen J. Nicholls, Adam J. Nelson, Marc Ditmarsch, John J.P. Kastelein, Christie M. Ballantyne, Kausik K. Ray, Ann Marie Navar, Steven E. Nissen, Mariko Harada-Shiba, Danielle L. Curcio, Annie Neild, Douglas Kling, Andrew Hsieh, Julie Butters, Brian A. Ference, Ulrich Laufs, Maciej Banach, Roxana Mehran, Alberico L. Catapano, Yong Huo, Michael Szarek, Violeta Balinskaite, and Michael H. Davidson

Background

- Low-density lipoprotein cholesterol (LDL-C) lowering is a cornerstone of treatment of patients at high risk of cardiovascular events[1]
- Many high-risk patients fail to achieve LDL-C targets despite use of existing lipid-lowering therapies[2]
- Obicetrapib is a cholesteryl ester transfer protein (CETP) inhibitor that reduces atherogenic lipid parameters and raises high-density lipoprotein cholesterol (HDL-C) when added to statins[3-5]

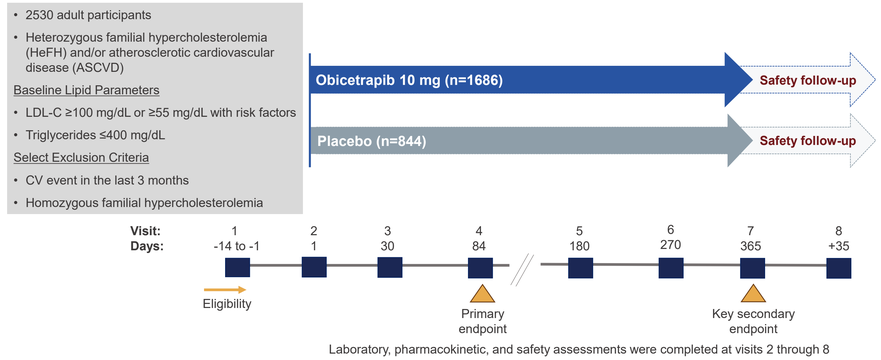
Objective

- To evaluate the efficacy, safety, and tolerability of obicetrapib, as an adjunct to maximally tolerated lipid-modifying therapies, in patients at high risk of cardiovascular (CV) events and suboptimal LDL-C control

Methods

- The study design for BROADWAY (NCT05142722) is summarized in **Figure 1**
- The primary endpoint was percent change in LDL-C from baseline to day 84
- Secondary endpoints included percent change in LDL-C from baseline to day 365, percent of patients achieving LDL-C targets, and changes in other lipid parameters

Figure 1. BROADWAY: a randomized, double-blind, placebo-controlled trial evaluating the effect of obicetrapib 10 mg as an adjunct to maximally tolerated lipid-lowering therapy (LLT)



Laboratory, pharmacokinetic, and safety assessments were completed at visits 2 through 8

Results

Figure 2. Percent change in LDL-C with obicetrapib

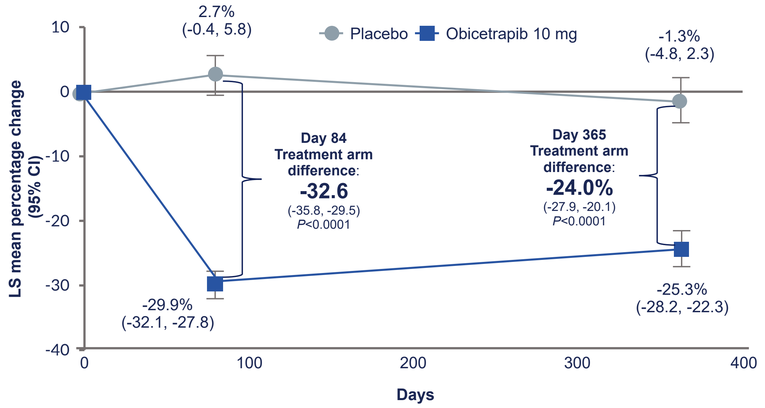


Figure 3. Percentage of patients achieving LDL-C goals at day 84

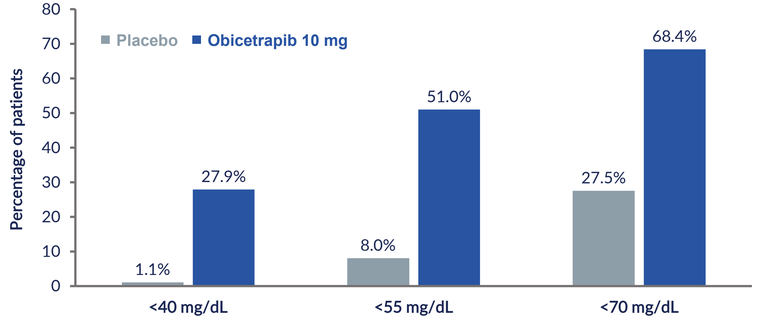


Table 1. Baseline demographics, medication use, and lipid parameters

	Placebo (n=844)	Obicetrapib (n=1686)
Baseline Demographics		
Age (y)	65.3	65.4
Female (%)	33.2	34.0
White (%)	76.7	73.6
Body mass index (kg/m²)	29.7	29.4
Diabetes (%)	39.8	37.0
ASCVD (%)	88.4	89.3
HeFH (%)	16.9	16.8
Baseline Medication Use		
Statin use (%)	92.7	90.9
High-intensity statin use (%)	70.1	70.1
Ezetimibe use (%)	26.1	26.9
PCSK9 inhibitor use (%)	3.9	3.7
Baseline Lipid Parameters		
LDL-C (mg/dL)	98.4	98.1
Non–HDL-C (mg/dL)	125.6	124.7
Apolipoprotein B (ApoB) (mg/dL)	91.9	91.6
HDL-C (mg/dL)	49.7	49.5
Triglycerides (mg/dL)	127.0	122.0
Lipoprotein (a) [Lp(a)] (nmol/L)	40.7	39.2

Table 2. Placebo-adjusted percent changes in other lipoproteins at day 84 and day 365

	LS mean percent change	
	Day 84	Day 365
non–HDL-C	-29.4	-23.0
ApoB	-18.9	-13.8
HDL-C	136.3	122.0
Apolipoprotein A1	43.2	-
Triglycerides	-7.8	-5.7
Lp(a)	-33.5	-

Table 3. Adverse event profile (%)

	Placebo (n=844)	Obicetrapib (n=1686)
Any adverse event that emerged during treatment period	60.8	59.7
Adverse event related to obicetrapib or placebo that emerged during treatment period	4.6	4.5
Mild	3.0	3.0
Moderate	1.7	1.4
Severe	0	0.1
Adverse event leading to discontinuation of obicetrapib or placebo that emerged during treatment period	5.1	4.0
Serious adverse event that emerged during treatment period	13.9	12.5
Death from any cause	1.4	1.1

- Baseline demographics, medication use, and lipid parameters are shown in **Table 1**
- At day 84, the least squares (LS) mean percent change from baseline in LDL-C with obicetrapib was -29.9%, with a placebo-adjusted percent change of 32.6% (**Figure 2**)
  - The placebo-adjusted percent change in LDL-C at day 365 was -24.0%
- A greater percentage of patients achieved LDL-C goals at day 84 with obicetrapib compared with placebo (**Figure 3**)
- Placebo-adjusted percent change in other lipoproteins are shown in **Table 2**
- Adverse events with obicetrapib were comparable to placebo (**Table 3**)
  - There were no obvious differences in events of special interest related to liver and kidney function, new diabetes or worsening glycemic control, macular degeneration, or CV events

Conclusions

- **Placebo-adjusted reduction in LDL-C with obicetrapib was 32.6% at day 84 and 24.0% at day 365 with 51% of patients achieving an LDL-C <55 mg/dL**
- **Obicetrapib resulted in placebo-adjusted reductions in Lp(a) by 33.5%, independent of lowering atherogenic lipid parameters and raising HDL-C**
- **Obicetrapib was well tolerated with no safety concerns**
- **The longer-term effect of obicetrapib on CV outcomes is currently being evaluated in the PREVAIL trial (NCT05202509)**
- **The findings suggest that obicetrapib has considerable promise as an approach to more effective lipid control in high CV risk patients**

1. Nurmohamed NS, Ditmarsch M, Kastelein JJP. Cholesteryl ester transfer protein inhibitors: from high-density lipoprotein cholesterol to low-density lipoprotein cholesterol lowering agents? *Cardiovasc Res.* 2022;118(14):2919-2931. doi:10.1093/cvr/cvab350 **2.** Gao Y, Shah LM, Ding J, Martin SS. US trends in cholesterol screening, lipid levels, and lipid-lowering medication use in US adults, 1999 to 2018. *J Am Heart Assoc.* 2023;12(3):e028205. doi:10.1161/JAHA.122.028205 **3.** Nicholls SJ, Ditmarsch M, Kastelein JJ, et al. Lipid lowering effects of the CETP inhibitor obicetrapib in combination with high-intensity statins: a randomized phase 2 trial. *Nat Med.* 2022;28(8):1672-1678. doi:10.1038/s41591-022-01936-7 **4.** Hovingh GK, Kastelein JJ, van Deventer SJH, et al. Cholesterol ester transfer protein inhibition by TA-8995 in patients with mild dyslipidaemia (TULIP): a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet.* 2015;386(9992):452-460. doi:10.1016/S0140-6736(15)60158-1 **5.** Ballantyne CM, Ditmarsch M, Kastelein JJ, et al. Obicetrapib plus ezetimibe as an adjunct to high-intensity statin therapy: a randomized phase 2 trial. *J Clin Lipidol.* 2023;17(4):491-503. doi:10.1016/j.jacl.2023.05.098