# > Obicetrapib Targets All Atherogenic Lipoproteins Beyond LDL-C

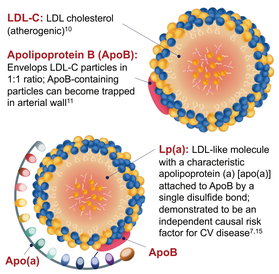
**Michael H. Davidson[1], Christie M. Ballantyne[2], Andrew Hsieh[1], Jeremy Smart[1], Marc Ditmarsch[1], Douglas Kling[1], Danielle Curcio[1], Mary R. Dicklin[3], John J.P. Kastelein[1]**

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

## Background

- Despite reductions in low-density lipoprotein cholesterol (LDL-C) with statin and non-statin lipid-lowering therapies (LLTs), most patients do not achieve LDL-C threshold attainment and have residual risk for cardiovascular (CV) events[1-3]
- An investigation of 8 large CV outcome trials demonstrated, on average, a relative risk reduction of 25% with statins, leaving the majority of risk unaddressed[4]
- In addition to LDL-C, atherogenic lipoproteins, including low-density lipoprotein particles (LDL-P), small dense LDL-C (sdLDL-C), and lipoprotein(a) [Lp(a)], contribute to residual risk for CV events[1,5-7]
- There is a significant need for novel treatments that reduce LDL-C, as well as other atherogenic lipoproteins, to lower the residual risk of CV events in patients with dyslipidemia[8]
- Obicetrapib is an oral cholesteryl ester transfer protein (CETP) inhibitor under investigation for reducing atherogenic lipoproteins and risk for CV events (**Figure 1**)[9]

**Figure 1. Atherogenic lipoproteins contributing to residual risk of CV events**




**Non–high-density lipoprotein cholesterol (non–HDL-C):** Includes all atherogenic lipoprotein particles (including LDL-C and very-low density lipoprotein cholesterol [VLDL-C])[12]

**LDL-P:** LDL particle concentration; believed to be robust predictor of CV risk[5]

**Small LDL-P:** More likely to become trapped in artery wall than larger LDL particles[13]

**sdLDL-C:** Small dense LDL-C, which is more atherogenic than larger LDL-C; lipolysis of triglyceride-rich LDL leads to sdLDL formation[6,14]

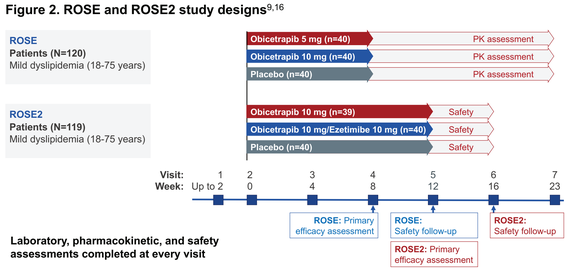
## Objective

- To examine the efficacy and safety of obicetrapib in lowering atherogenic lipoproteins across 3 phase 2 trials (Randomized Study of Obicetrapib as an Adjunct to High-Intensity Statin Therapy [ROSE], Study to Evaluate the Effect of Obicetrapib in Combination with Ezetimibe as an Adjunct to High-Intensity Statin Therapy [ROSE2], and Phase 2 Trial of Obicetrapib as an Adjunct to Stable Statin Therapy in Japanese Subjects [TA-8995-203])

## Methods

- All 3 studies were double-blind, randomized, placebo-controlled phase 2 trials[9,16,17]
  - ROSE (n=120) evaluated the effect of obicetrapib 5 mg or 10 mg as an adjunct to high-intensity statin (HIS) on LDL-C for 8 weeks and ROSE2 (n=119) evaluated the effect of obicetrapib 10 mg in combination with ezetimibe 10 mg as an adjunct to HIS on LDL-C for 12 weeks (**Figure 2**)[9,16]
  - TA-8995-203 (n=102) examined obicetrapib 2.5 mg, 5 mg, or 10 mg as an adjunct to atorvastatin 10 mg or 20 mg or rosuvastatin 5 mg or 10 mg for 8 weeks[17]
- In ROSE and ROSE2, participants included men and women aged 18 to 75 years with a fasting LDL-C >70 mg/dL and triglycerides (TG) <400 mg/dL receiving a stable dose of HIS therapy (atorvastatin 40-80 mg or rosuvastatin 20-40 mg) for at least 8 weeks prior to screening; patients were excluded if they were experiencing significant CV disease, hemoglobin A1c ≥10%, or uncontrolled hypertension at the time of screening[9,16]
- In TA-8995-203, participants included Japanese men and women aged 18 to 80 years with a fasting LDL-C >70 mg/dL or non-HDL-C >100 mg/dL and TG <400 mg/dL and were receiving atorvastatin 10 mg/day or 20 mg/day or rosuvastatin 5 mg/day or 10 mg/day at a stable dose for at least 8 weeks prior to screening; participants were excluded if they had current clinically active, or an acute episode of, atherosclerotic CV disease[17]
- A complete lipid profile and ApoB were measured in all 3 studies[9,16,17]
  - Additionally, Lp(a) was measured in ROSE and ROSE2[9,16]
- In ROSE2, sdLDL-C was assessed, and nuclear magnetic resonance was used to analyze lipoprotein subfractions (LDL-P)[9]

**Figure 2. ROSE and ROSE2 study designs[9,16]**




## Results

- Across ROSE, ROSE2, and TA-8995-203, obicetrapib 10 mg as an adjunct to HIS therapy with or without ezetimibe decreased LDL-C by -36.6% to -59.2% and led to reductions in non–HDL-C (-30.3% to -54.0%) and ApoB (-26.3% to -35.0%) (**Table 1**)[9,16,17]

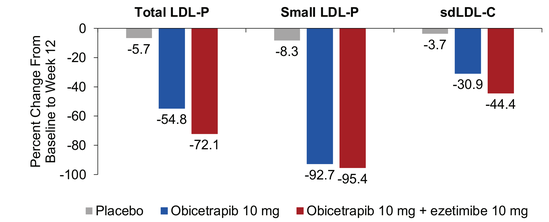
**Table 1.** LS mean changes from baseline in atherogenic lipoproteins in ROSE, ROSE2, and TA-8995-203[9,16,17]

| Lipoprotein | Obicetrapib 10 mg | Obicetrapib 10 mg + ezetimibe 10 mg |
|---|---|---|
| **LDL-C** | -36.6% to -44.2%[a] | -59.2%[b] |
| **Non–HDL-C** | -30.3% to -39.9%[a] | -54.0%[b] |
| **ApoB** | -26.3% to -28.1%[a] | -35.0%[b] |

[a]Combined results for obicetrapib monotherapy as an adjunct to HIS from ROSE, ROSE2, and TA-8995-203.
[b]Results are from ROSE2 only.

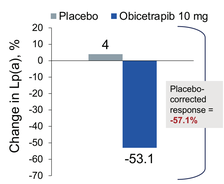
- In ROSE2, obicetrapib 10 mg with or without ezetimibe significantly decreased total LDL-P, small LDL-P, and sdLDL-C by -54.8% to -72.1%, -92.7% to -95.4%, and -30.9% to -44.4%, respectively (**Figure 3**)[10]

**Figure 3.** Median percent changes from baseline in atherogenic lipoproteins contributing to residual risk in ROSE2[10]




- A pooled analysis of Lp(a) data from ROSE and ROSE2 demonstrated a placebo-corrected reduction of -57.1% (**Figure 4**)[9,16,18]

**Figure 4.** Obicetrapib 10 mg as an adjunct to HIS therapy significantly lowered Lp(a) levels vs placebo in a pooled analysis of data from ROSE and ROSE2[9,16,18]




| Pooled | Placebo (n=63) | Obicetrapib 10 mg (n=64) |
|---|---|---|
| **Lp(a)** | | |
| **Baseline, nmol/L** | | |
| Median (min, max) | 44.8 (0.9, 410) | 31.1 (0.8, 435) |
| **End of treatment change, %** | | |
| Median (min, max) | 4.00 (-67.9, 145) | -53.1 (-97.5, 215) |
| *P* value vs placebo | | <0.001 |
| Median placebo-corrected response | | **-57.1** |

- Obicetrapib has a favorable safety and tolerability profile, with adverse events similar to placebo in frequency and severity (**Table 2**), and was nearly completely eliminated from circulation within 4 weeks after dosing[9,10,16,19,20]
  - The most common treatment-emergent adverse events (TEAEs), occurring in ≥2% of patients, were nasopharyngitis, headache, back pain, diarrhea, arthralgia, influenza, myalgia, and upper abdominal pain; hypertension and type 2 diabetes mellitus also occurred following treatment with placebo, but not with obicetrapib

**Table 2.** Rates of adverse events observed across phase 1 and 2 studies[9,10,16,19,20,a]

| | Placebo (N=283) | Pooled Obicetrapib (5 mg and 10 mg)[b] (N=386) |
|---|---|---|
| **TEAEs, n (%)** | | |
| TEAEs, total | 159 (56.2) | 194 (50.3) |
| TEAEs, related | 43 (15.2) | 46 (11.9) |
| TEAEs, severe | 7 (2.5) | 8 (2.1) |
| **TESAEs, n (%)** | | |
| TESAEs, total[b] | 7 (2.5) | 6 (1.6) |
| TESAEs, related | 0 | 0 |
| Deaths | 0 | 0 |
| **Withdrawals from study/medication, n (%)** | | |
| TEAEs leading to discontinuation of study drug | 13 (4.6) | 12 (3.1) |

TESAE, treatment-emergent serious adverse event.
[a]Pooled analysis of TULIP, OCEAN, ROSE, ROSE2, and TA-8995-203. [b]The pooled obicetrapib group includes patients treated with obicetrapib as a monotherapy and in combination with atorvastatin, rosuvastatin, and ezetimibe.

## Conclusions

- **Obicetrapib 10 mg as an adjunct to HIS therapy with or without ezetimibe 10 mg was well tolerated and demonstrated meaningful reductions in LDL-C, non–HDL-C, and ApoB**
- **Obicetrapib also led to reductions in LDL-P, sdLDL-C, and Lp(a), which are lipid components known to contribute to residual risk, thus providing support for its anti-atherogenic potential**
- **By reducing atherogenic lipoproteins in addition to LDL-C, obicetrapib as adjunct to statins and in combination with ezetimibe represents a promising therapy that may address residual risk for CV disease**

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