Obicetrapib as an Adjunct to Stable Statin Therapy Significantly Lowers LDL-C, Non-HDL-C and Apolipoprotein B in Japanese Patients: Results from the Japan Phase 2 Study

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Rationale

- Obicetrapib is a highly selective and potent CETP inhibitor, which has been developed for the treatment of dyslipidemia and CV risk
- A Phase 2 study was conducted in Caucasian participants to evaluate the optimal dose of obicetrapib alone and in combination with medium-intensity statins in patients with mild dyslipidemia.
  - A daily dose of 10 mg obicetrapib in combination with medium-intensity statins resulted in an incremental LDL-C reduction of up to 45.3%
- Thus, there is a lack of clinical experience with obicetrapib when used in combination with moderate intensity stable statin therapy among individuals from the Asia-Pacific region
- The Japan Phase 2 trial was designed to fill the gap in clinical experience and characterize the safety, efficacy, and pharmacokinetics (PK) profile of obicetrapib within this population

Japan Phase 2 Trial

Objective: **The primary objective of this study is to evaluate the efficacy of obicetrapib, compared to placebo, in reducing serum low-density lipoprotein cholesterol (LDL-C) when taken as an adjunct to a pre-existing stable statin therapy regime**

Main Inclusion Criteria

- Stable statin (Atorvastatin: 10 mg or 20 mg, Rosuvastatin: 5 mg or 10 mg)
- Fasting LDL-C levels > 70 mg/dL; or Non-HDL-C > 100 mg/dL
- TG < 400 mg/dl

Main Exclusion Criteria

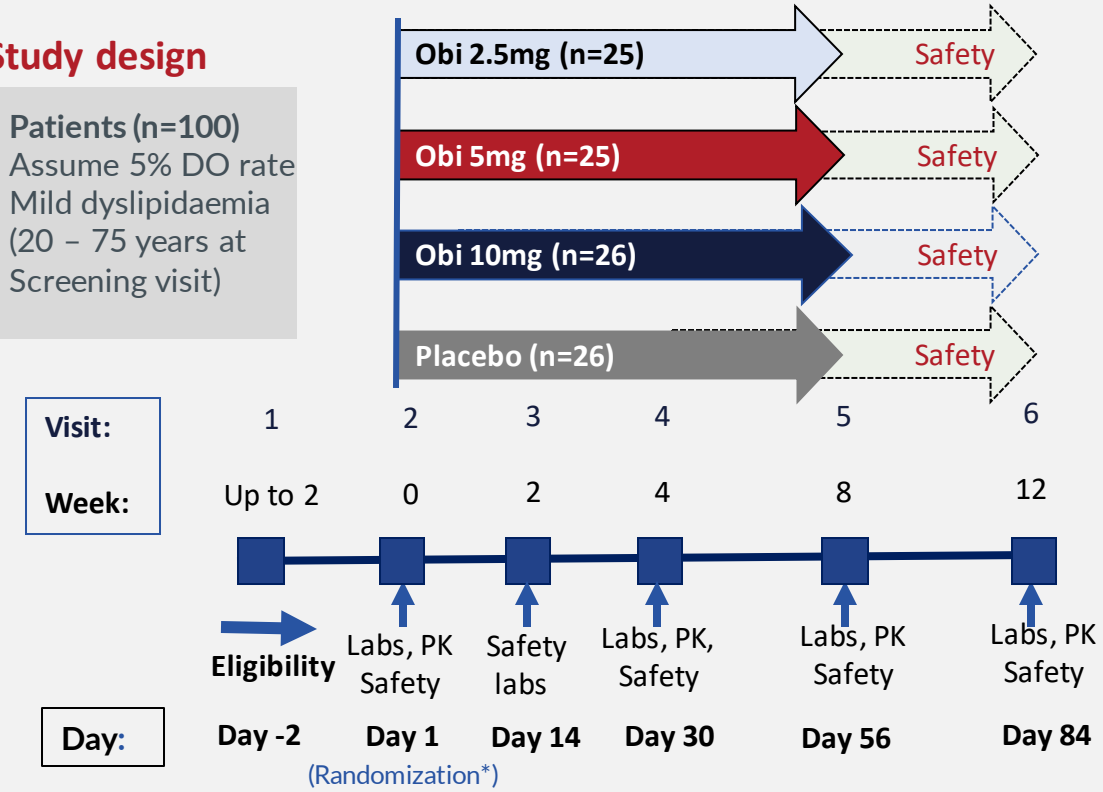
- Patients meeting JAS guidelines despite LDL-C levels > 70 mg/dL
- Current significant CV disease
- Uncontrolled hypertension (sitting SBP≥ 160 mmHg and/or sitting DBP ≥ 100 mmHg
- Glycosylated hemoglobin (HbA1c) ≥ 10%
- BMI criteria to ≥ 35 kg/m2

Primary Efficacy Endpoint

- Percent change from baseline in LDL-C at Day 56 compared to the placebo group

Study design

Patients (n=100)
Assume 5% DO rate
Mild dyslipidaemia
(20 – 75 years at Screening visit)



* Participants will be stratified according to their Screening Visit (0W) LDL-C levels (≥100 or <100 mg/dL)

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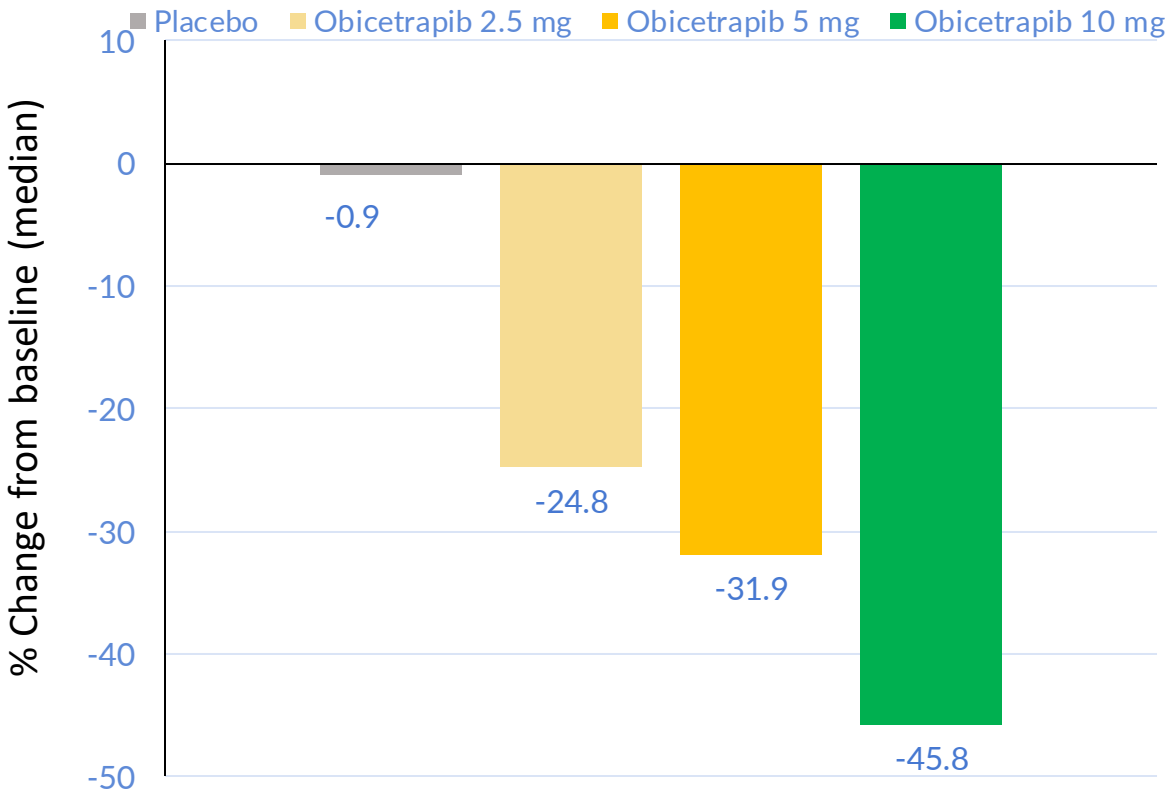
Baseline characteristics

		Placebo N=26	Obicetrapib 2.5 mg N=25	Obicetrapib 5mg N=25	Obicetrapib 10mg N=26
	Mean Age (yrs)	63.3	65.8	67.8	62.5
	Female %	23.1	40.0	24.0	28.4
	Mean BMI (kg/m^2)	25.5	25.15	25.84	26.05
Race %	Asian	100	100	100	100
Statin use (%)	Atorvastatin 10/20 mg	57.7	48.0	48.0	38.5
	Rosuvastatin 5/10 mg	42.3	52.0	52.0	61.5
Baseline level (Median)	LDL-C (mg/dL by PUC)	105.5	97	103.0	105.5
	Non-HDL-C (mg/dL)	132.0	124.0	132.0	132.0
	HDL-C (mg/dL)	55.5	52.0	57.0	53.0

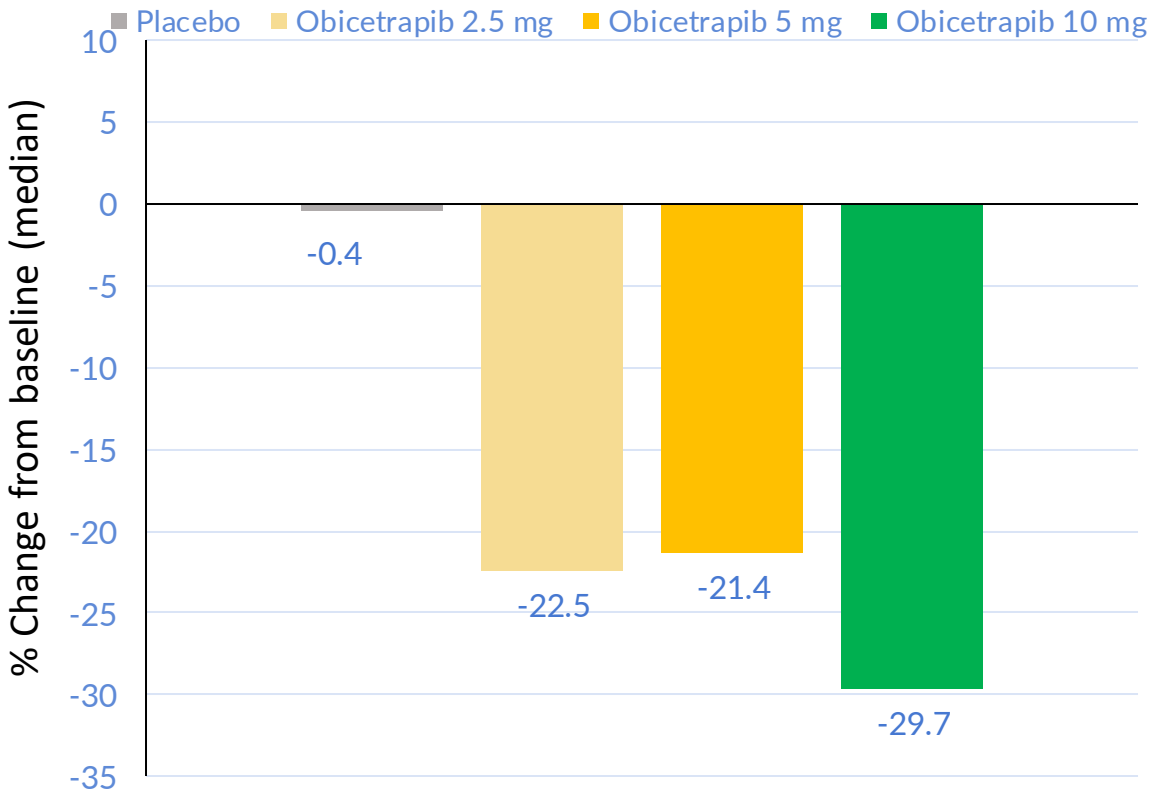
Obicetrapib significantly reduced LDL-C and ApoB

LDL-C percent change from baseline



P<0.0001 for all dosages

ApoB percent change from baseline



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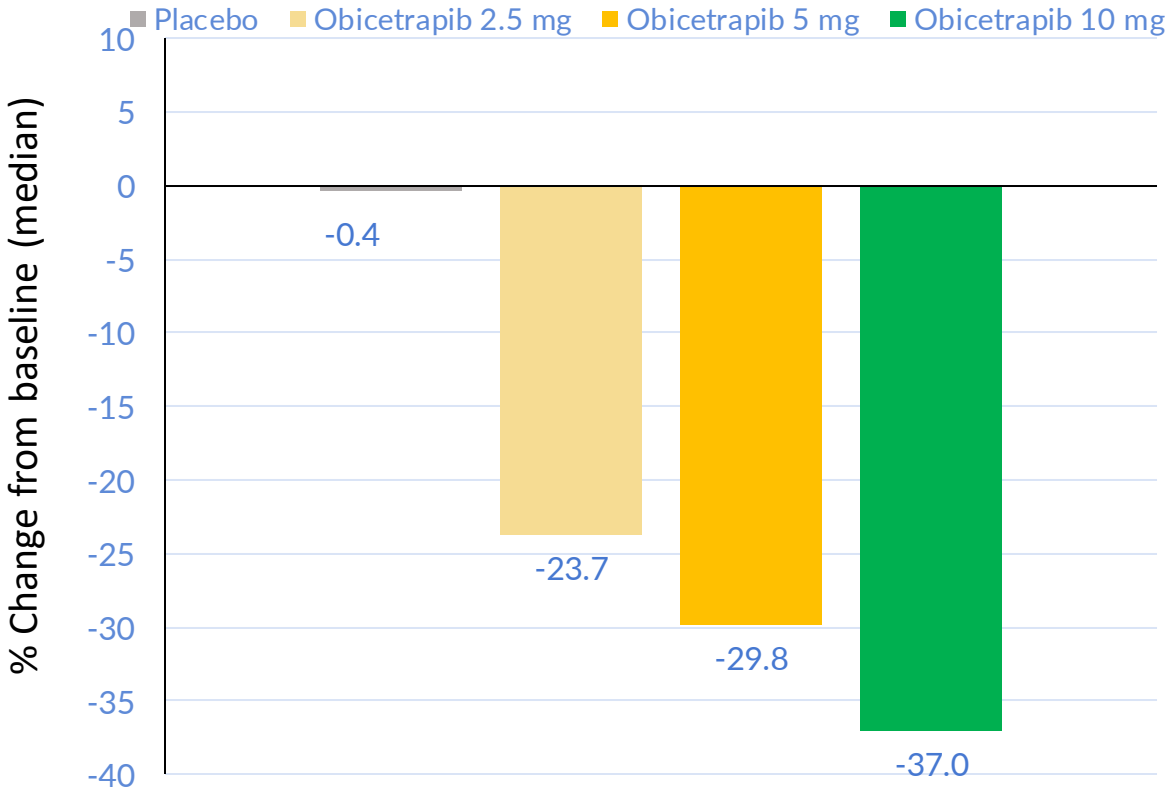
Obicetrapib significantly reduced non-HDL-C and increased HDL-C

Non-HDL-C percent change from baseline



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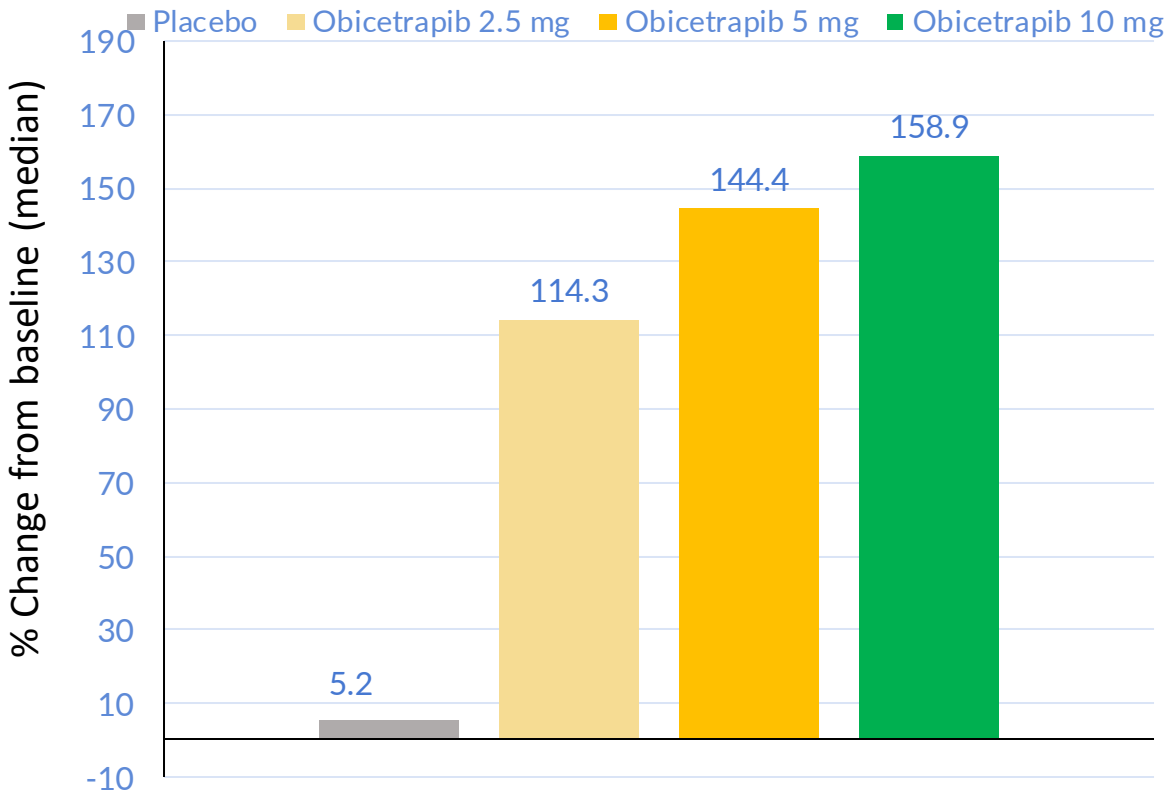
HDL-C percent change from baseline



P<0.0001 for all dosages

Safety - AEs, SAEs and withdrawal overview

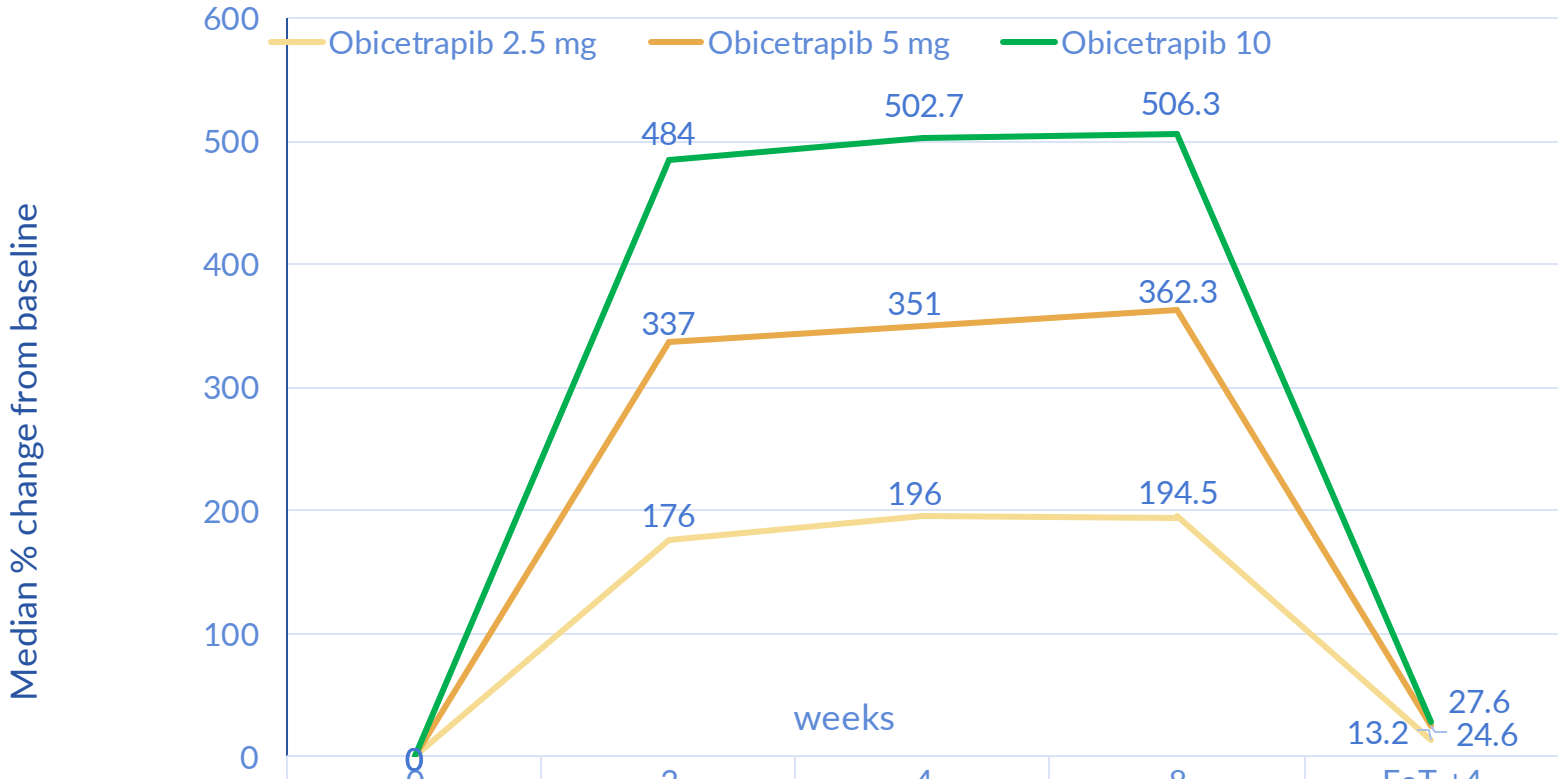
	Placebo	Obicetrapib 2.5 mg	Obicetrapib 5 mg	Obicetrapib 10 mg
TEAEs (%)				
TEAEs, total	16 (61.5)	11 (44.0)	9 (36.0)	15 (57.7)
TEAEs, related	0	0	0	0
TEAEs, severe	0	0	0	0
TESAEs				
TESAEs, total	0	0	1 (4.0)	0
TESAEs, related	0	0	0	0
Deaths	0	0	0	0
Withdrawal's study / medication				
TEAEs leading to discontiuation of study drug	0	0	0	0

Conclusions

- Obicetrapib 2.5, 5 and 10 mg on top of moderate intensity dose statin therapy was well tolerated in a Japanese population with a safety profile similar to placebo
- Obicetrapib 5 and 10 mg on top of moderate intensity dose statin therapy reduced median LDL-C levels with -32% and -46% from baseline respectively
- The exposure of obicetrapib across the dosages were at max 30% higher compared to concentration observed in the ROSE Ph2 study
- Both from an efficacy as well as a safety perspective obicetrapib appears to display the same characteristics in a Japanese population as a Caucasian population.
- Obicetrapib can be a valuable addition for high risk ASCVD patients who do not achieve their target LDL-C guideline goals despite the use of moderate dose statin therapy.

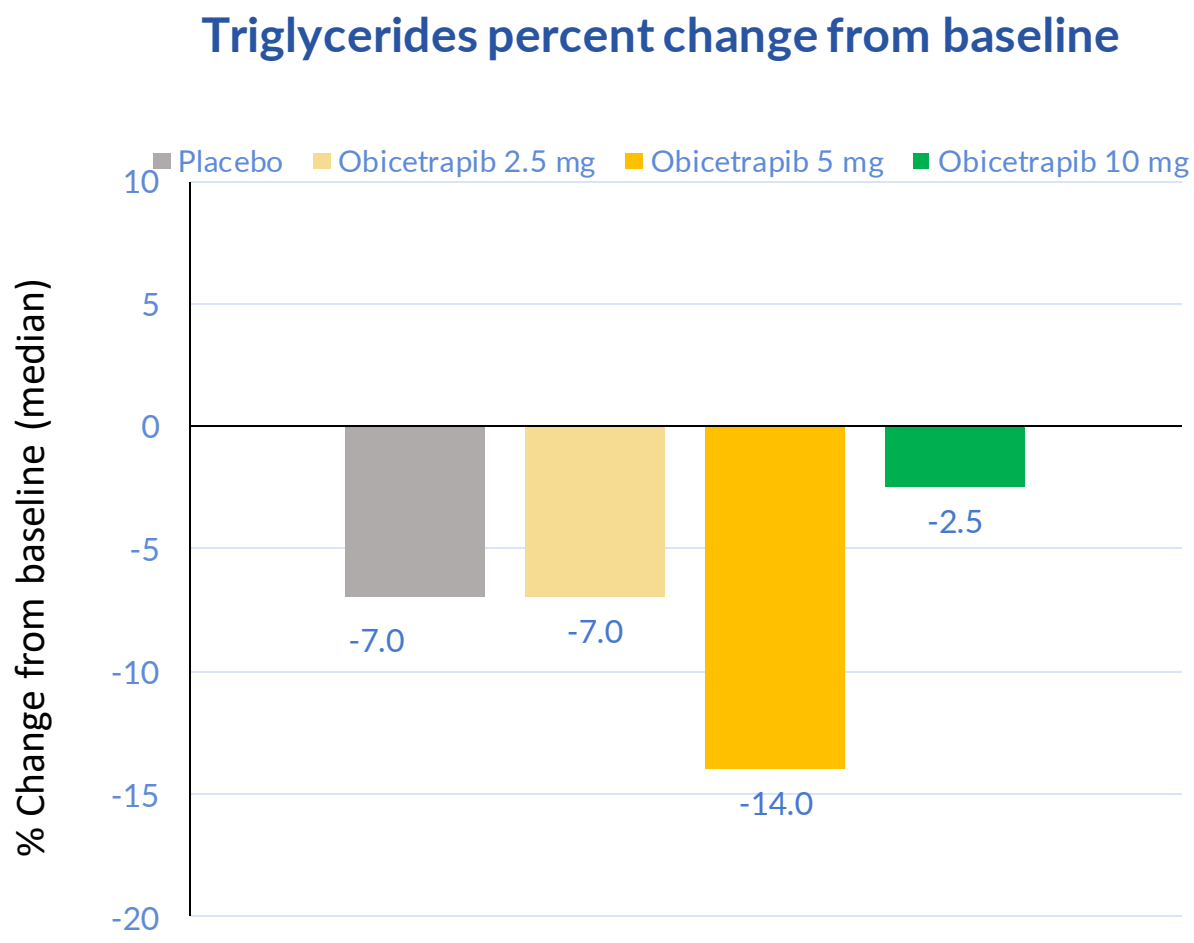
Back-up

Plasma levels of obicetrapib during and after end of therapy (EoT)

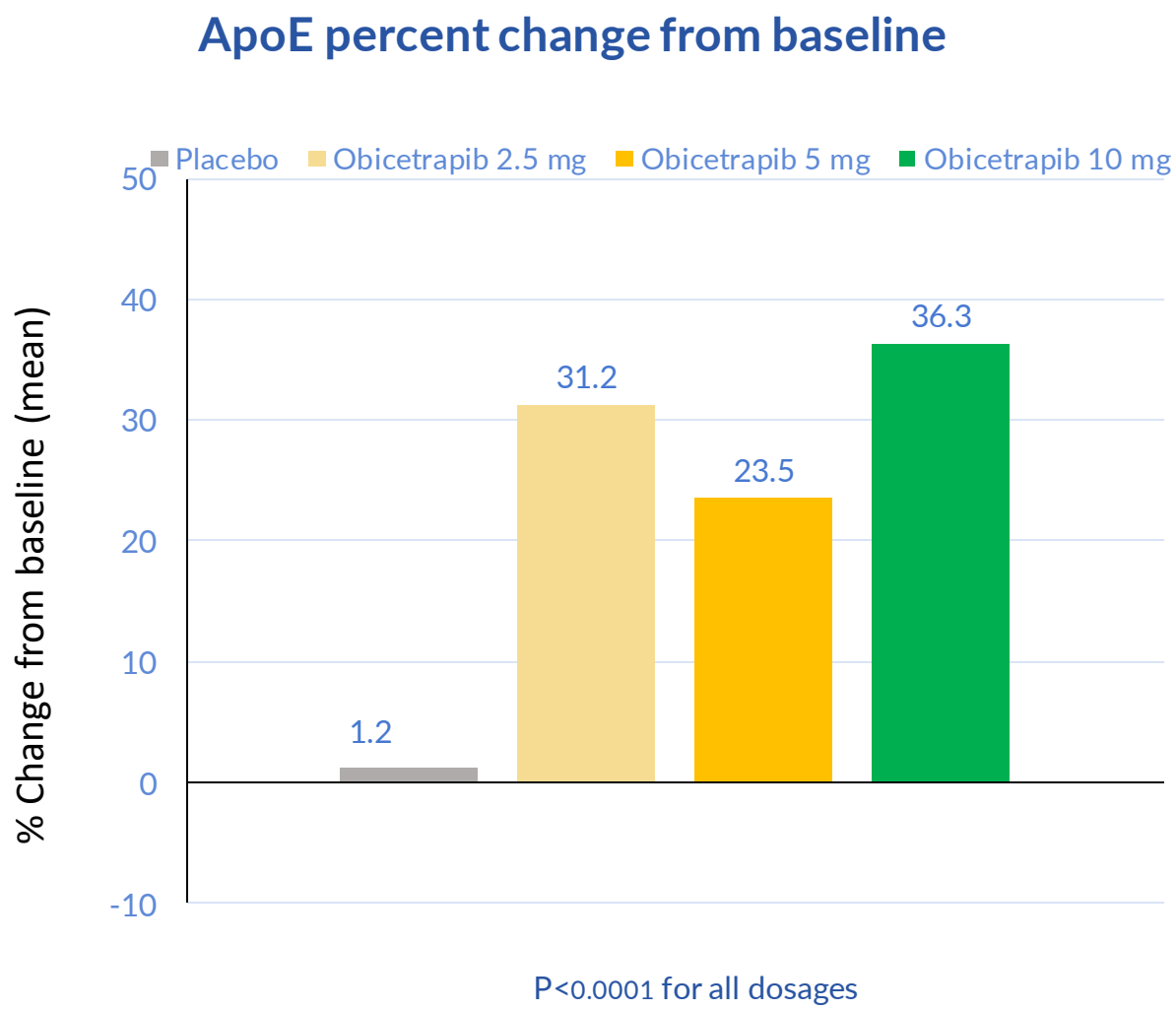


	0	2	4	8	EoT +4
Obicetrapib 2.5 mg	0	176	196	194.5	13.2
Obicetrapib 5 mg	0	337	351	362.3	24.6
Obicetrapib 10	0	484	502.7	506.3	27.6

Obicetrapib did not significantly reduce Triglycerides



Obicetrapib significantly increased ApoE



P<0.0001 for all dosages

LDL-C determination

LDL-C was determined using the following 2 approaches:

1. LDL-C was calculated using the Friedewald equation unless triglycerides (TG) ≥400 mg/dL or LDL-C ≥ 50 mg/dL. If TG ≥ 400 mg/dL or LDL-C ≥ 50 mg/dL, then LDL-C level was measured directly by preparative ultracentrifugation (PUC), also referred to as betaquantification; and
2. In addition, at baseline (Day 1 [Visit 2]) and at the end of the 8-week Treatment Period (Day 56 [Visit 5]), LDL-C was measured for all participants by PUC.

Statistical methods I

- The Intent-to-Treat (ITT) Population included all participants randomized into the study.
- The Modified ITT (mITT) Population included all participants in the ITT Population who received at least 1 dose of any study drug and had a baseline value for the LDL-C assessment.
- The Safety Population included all participants who received at least 1 dose of any study drug.
- The mITT Population was the primary population for the efficacy analyses.
- The primary efficacy analysis of the percent change in LDL-C was performed using a mixed model for repeated measures (MMRM) approach.
- In order to maintain the overall Type I error rate, the secondary efficacy endpoints were tested sequentially at the 0.05 significance level according to the pre-specified order of hierarchy.
- All safety endpoints were summarized descriptively. No statistical inference were applied to the safety endpoints.
- Plasma obicetrapib concentrations were summarized with descriptive statistics based on the PK Population.

Statistical methods II

- The primary efficacy analysis of the percent change from Day 1 to Day 56 in LDL-C was performed using a mixed model for repeated measures (MMRM) approach. The analysis included fixed effects for treatment, visit, and treatment-by-visit interaction, along with a covariate of the baseline value as a continuous covariate. Randomization was stratified by categories of LDL-C value (≥100 or <100 mg/dL) only to ensure similar distribution of LDL-C values across all treatments. The LS means for the pairwise comparison and its SE were used for the hypothesis testing. The null hypothesis of no treatment effect was rejected if the p-value, the probability of obtaining the observed or more extreme value of t statistic under the null hypothesis, was less than or equal to 0.05.
- In order to maintain the overall alpha level on the primary endpoint, the hypothesis testing was performed sequentially at the 2-sided alpha=0.05 significance level. The first comparison was the 10 mg obicetrapib group versus placebo; if significant, comparison of the 5 mg obicetrapib group versus placebo was performed, followed by the 2.5 mg obicetrapib group versus placebo. Hypothesis testing proceeded in this hierarchical step-down fashion until a comparison was not significant. At that point, all remaining sequential tests were deemed not significant.
- The MMRM approach included all available assessments of percent change in LDL-C from baseline to Day 14, Day 28, and Day 56. The model assumed the data were missing at random. If any data were missing, the model used all information from the other time points as well as baseline covariate values to estimate the mean treatment difference at the given time point. No imputation of missing data was performed for the primary efficacy endpoint analysis.
- Three sensitivity analyses were performed for the primary efficacy endpoint:
    1. MMRM with imputation;
    2. Analysis of covariance (ANCOVA); and
    3. ANCOVA using LDL-C by PUC.

    All sensitivity analyses were conducted on the mITT Population.