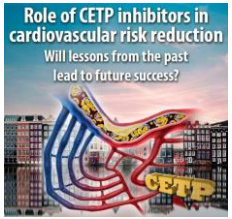
Exploring the role of novel CETP inhibitors in lipid management

Roxana Mehran, MD

New York, NY, USA

Role of CETP inhibitors in cardiovascular risk reduction - Will lessons from the past lead to future success?



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Disclosure of Financial Interest (for 36 months)

Affiliation/Financial Relationship	Company
Research Payments to Institution	Abbott, Abiomed, Alleviant, Amgen, AM-Pharma, Arena, AstraZeneca, AtriCure, Bayer, Biosensors, Biotronik, Boston Scientific, Bristol-Myers Squibb, CardiaWave, CeloNova, Chiesi, Concept Medical, CSL Behring, Cytosorbents, Daiichi Sankyo, Element Science, Faraday, Filterlex Medical, Humacyte, Idorsia, Janssen, Magenta, Mediasphere, Medtelligence, Medtronic, Novartis, OrbusNeich, Penumbra, PhaseBio, Philips, Pi-Cardia, PLx Pharma, Protembis, RenalPro, RM Global, Shockwave, Vivasure, Zoll.
Consulting	Cine-Med Research, Ionis Pharmaceuticals, Novartis, Novo Nordisk, Vectura, WebMD
Equity, <1%	Applied Therapeutics, Elixir Medical, Stel, ControlRad (spouse)
Scientific Advisory Boards/Committees	AMA, ACC (BOT member), SCAI

Background

- Despite treatment with high-intensity statin therapy (HIS), two thirds of patients do not reach their target LDL-C level.

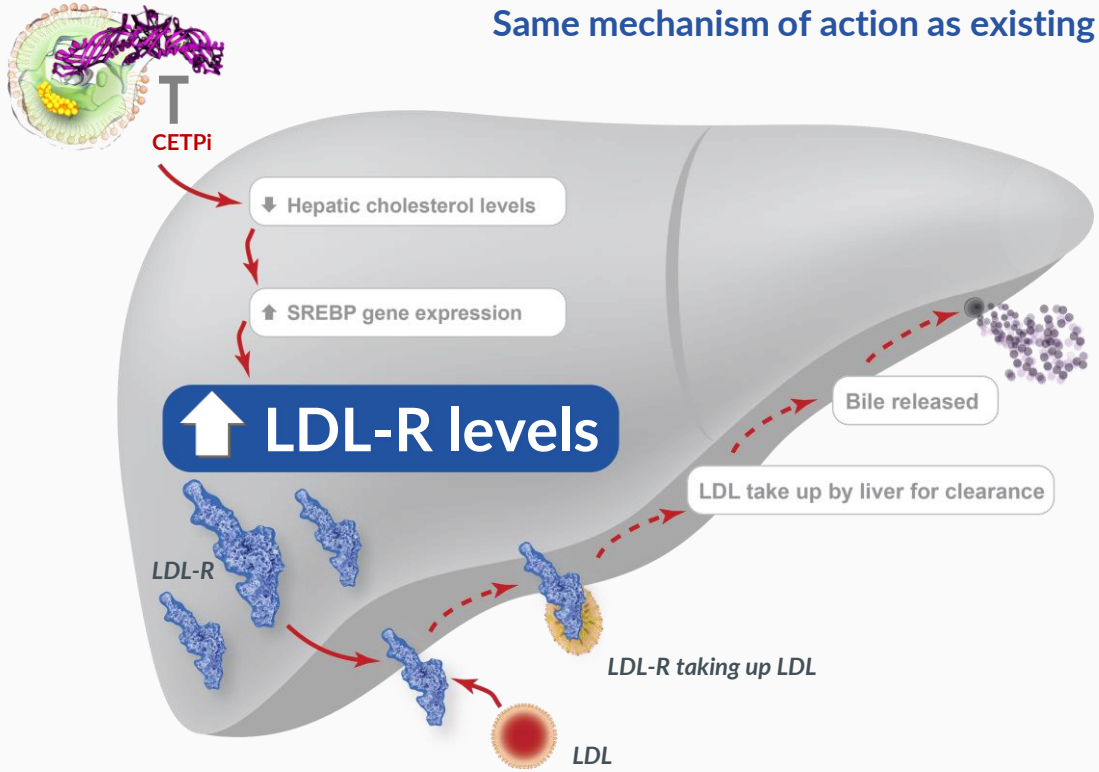
- Accordingly, there is a need for new therapies to produce effective reduction in LDL-C levels when used in combination with HIS therapy.

- Early studies with the CETP inhibitor obicetrapib demonstrated reductions of LDL-C levels by 45%.[1]

Hovingh et.al, Cholesterol ester transfer protein inhibition by TA-8995 in patients with mild dyslipidemia (TULIP): a randomised, double-blind, placebo-controlled phase 2 trial, The Lancet Journal, June 02, 2015DOI:https://doi.org/10.1016/S0140-6736(15)60158-1
NLA Scientific Session, Late Breaking Sessions, June 4, 2022

CETPi decreases hepatic cholesterol resulting in upregulation of LDL-R and improved LDL and ApoB clearance through the liver

Same mechanism of action as existing LDL-lowering drugs



Decrease in hepatic cholesterol

↓

Increase in hepatic LDL receptors

↓

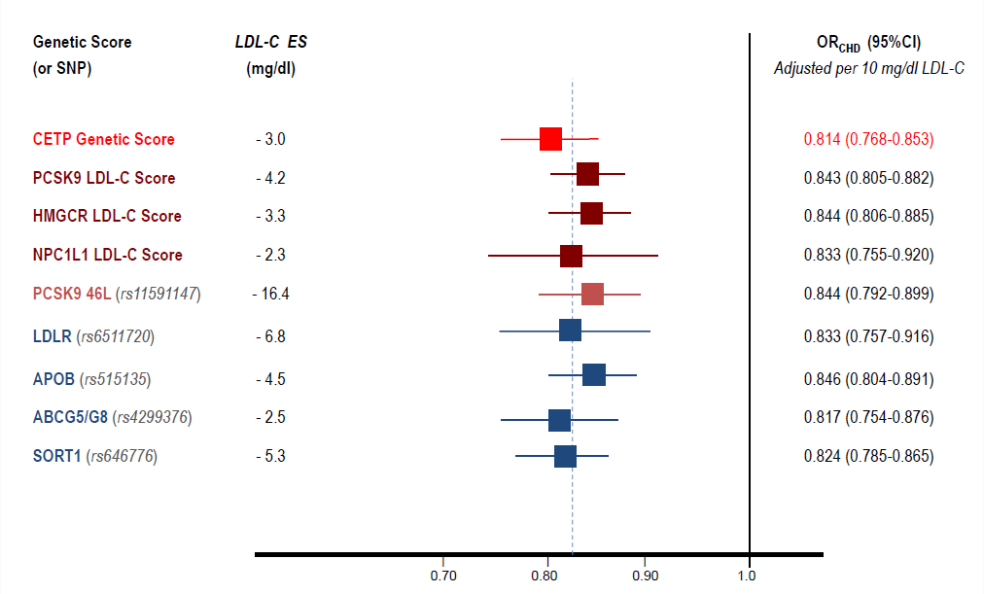
Decrease in plasma LDL levels

Adapted from:

Millar JS, et al. J Clin Invest. 2015;125:2510-22; van der Tuin SJ, et al. J Lipid Res. 2015;56:2085-93.

Association of CETP Score With Risk of Major Cardiovascular Events Is Dependent on ApoB-containing Lipoproteins

Mendelian randomization analyses indicate that the **impact of inhibiting CETP on the risk of cardiovascular events is likely depends on alterations in the levels of apoB-containing lipoproteins**, rather than changes in HDL-C. These results are consistent with findings for other modalities.



N=102,837 participants.

apoB and APOB, apolipoprotein B; CETP, cholesteryl ester transfer protein; HMGCR, HMG-CoA reductase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NPC1L1, Niemann-Pick C1-Like 1 intracellular cholesterol transporter 1; OR, odds ratio; PCSK9, proprotein convertase subtilisin/kexin type 9; SMD, standardized mean difference; SNP, single nucleotide polymorphisms.

Ference BA, et al. JAMA. 2017;318(10):947-956.

Chemistry

A Placebo-Controlled, Double-Blind, Randomized, Phase 2 Dose-Finding Study to Evaluate the Effect of Obicetrapib 5 and 10 mg as an Adjunct to High-Intensity Statin Therapy

Stephen J Nicholls, Marc Ditmarsch, John J Kastelein, Scott P Rigby, Douglas Kling, Danielle L Curcio, Nicholas J Alp, Michael H Davidson

ROSE

Obicetrapib and High Intensity Statin therapy (HIS)

Objective **To evaluate the effect of obicetrapib on top of HIS on LDL-C**

Inclusion criteria

- A stable dose of HIS (A 40 / 80; R 20 / 40) 8 weeks prior to screening
- Fasting LDL-C levels >1.8 mmol/L

Exclusion criteria

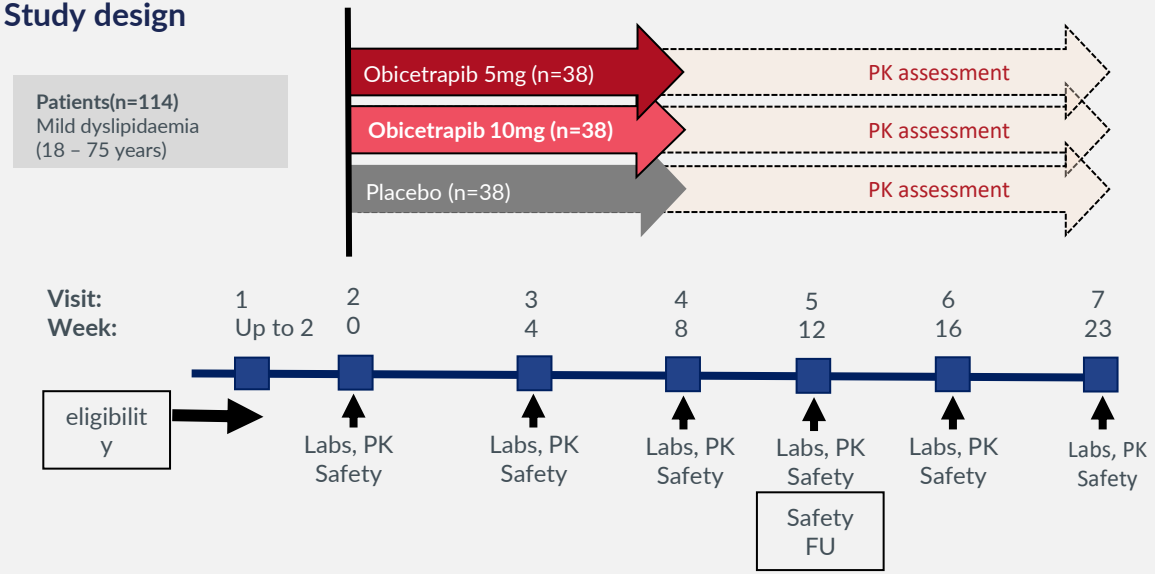
- Current significant CV disease
- Diagnosis of type 1 or type 2 diabetes mellitus;
- Uncontrolled hypertension

Primary efficacy endpoint

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

Prespecified assessment of LDL-C levels by preparative ultracentrifugation and Friedewald

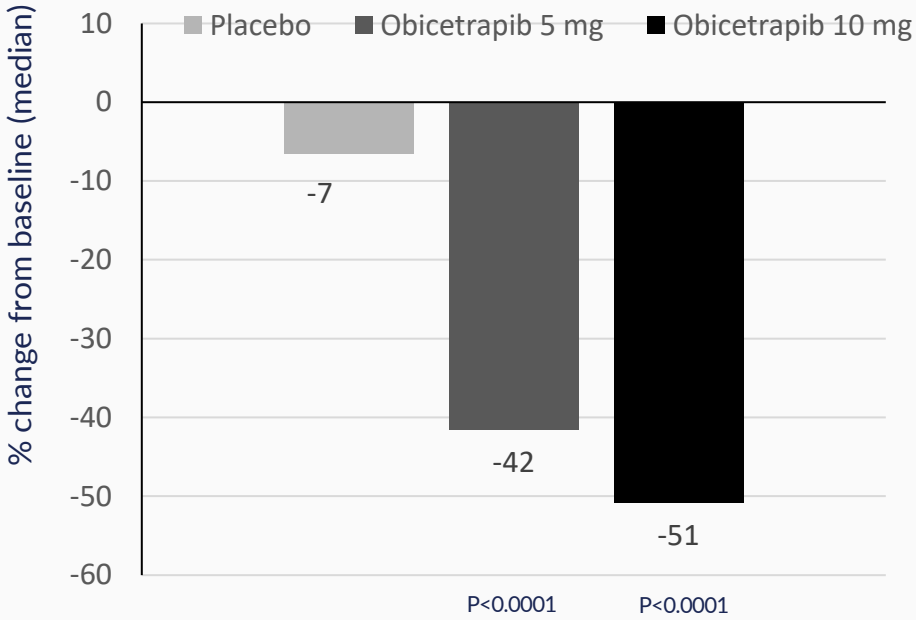
Study design



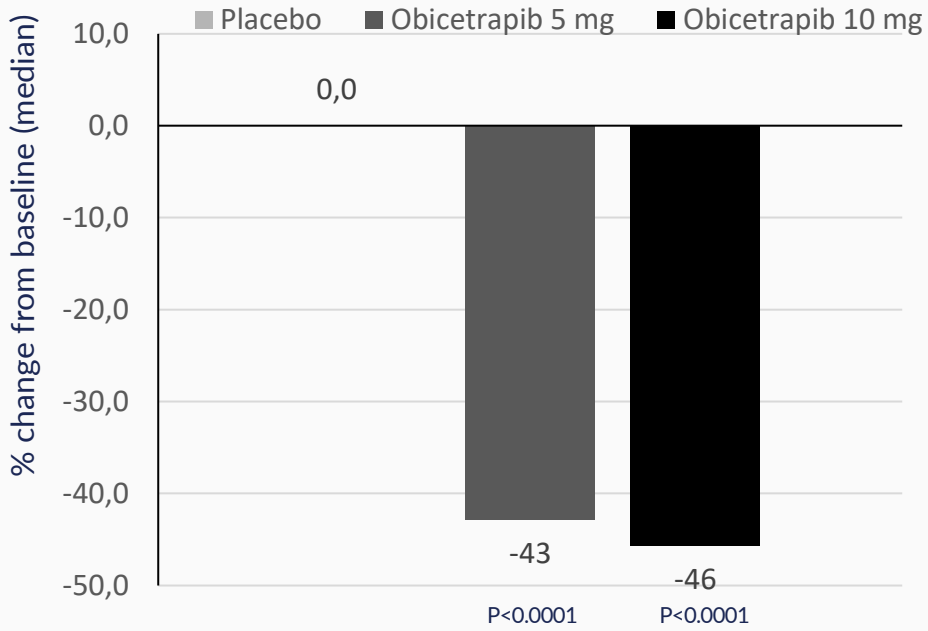
Nicholls SJ et al. *Nat Med* 2022;28:1672-1678.

LDL-C percent change from baseline by different measurement approaches

Preparative Ultracentrifugation

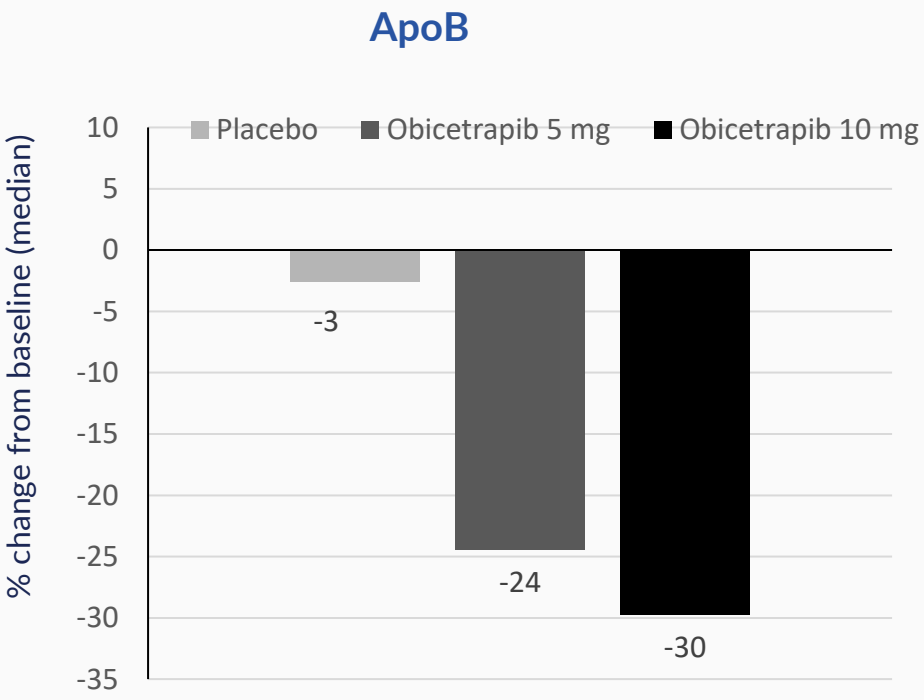


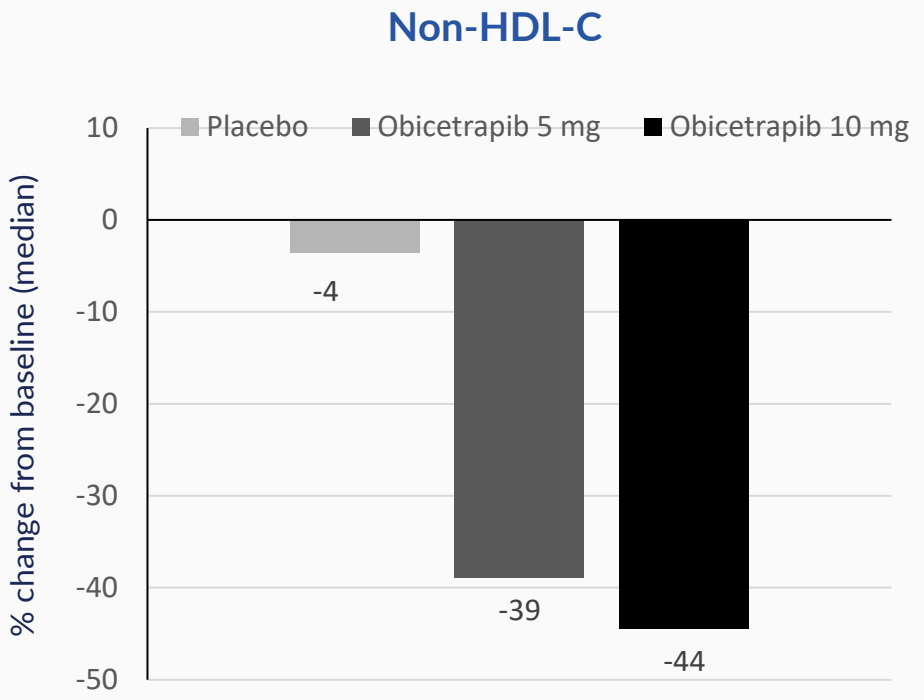
Friedewald



Nicholls SJ et al. *Nat Med* 2022;28:1672-1678.

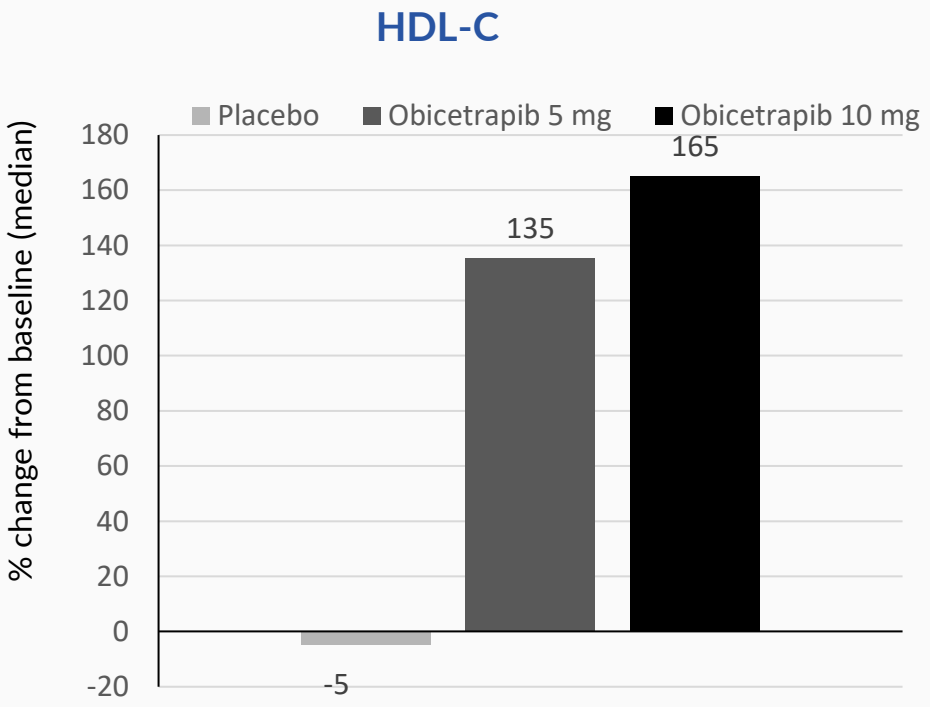
ApoB and non-HDL-C percent change from baseline

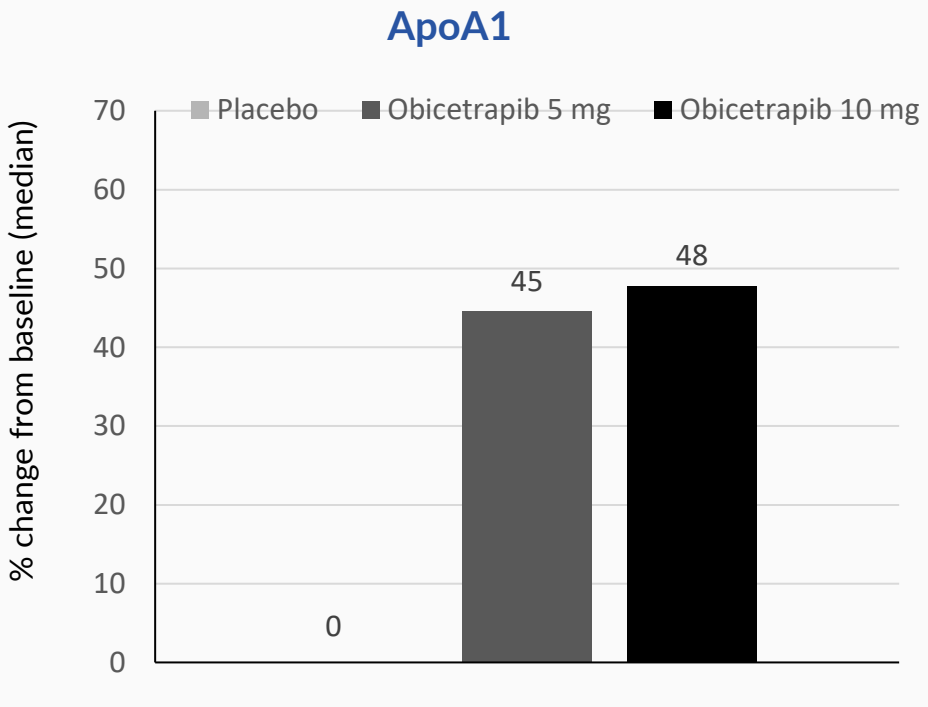




Nicholls SJ et al. *Nat Med* 2022;28:1672-1678.

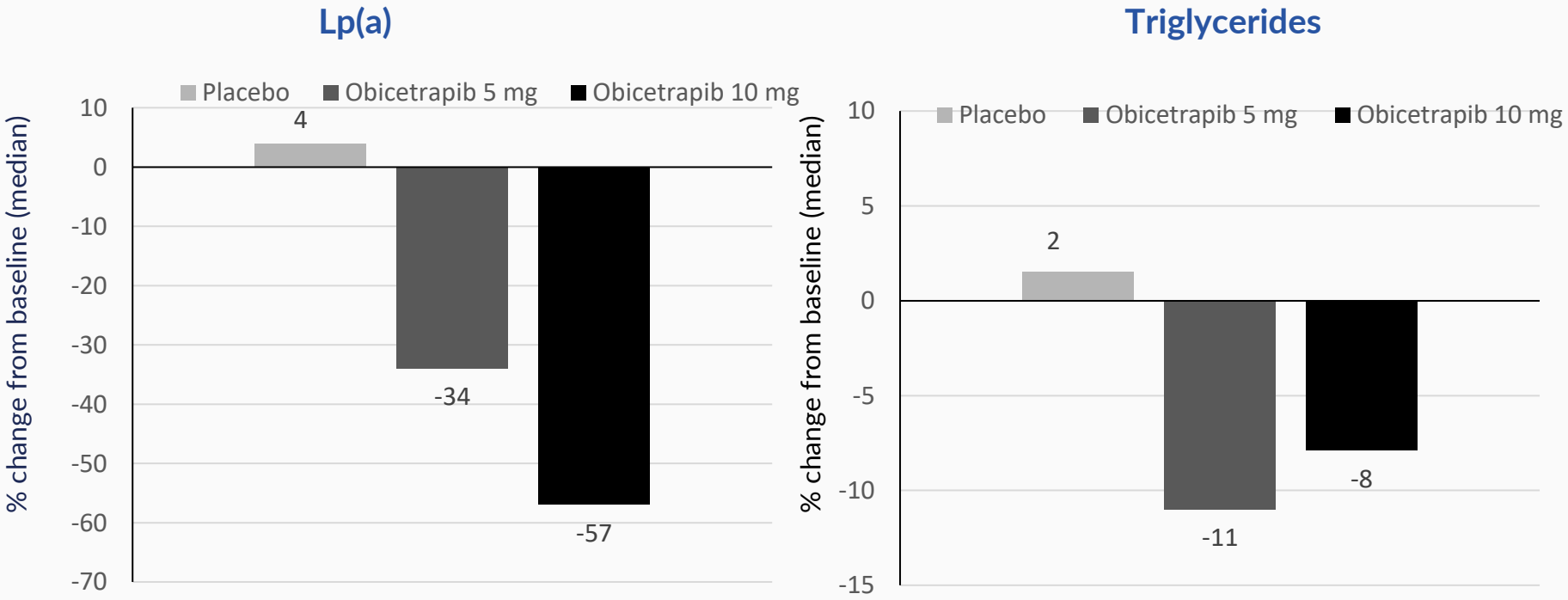
HDL-C and ApoA1 percent change from baseline





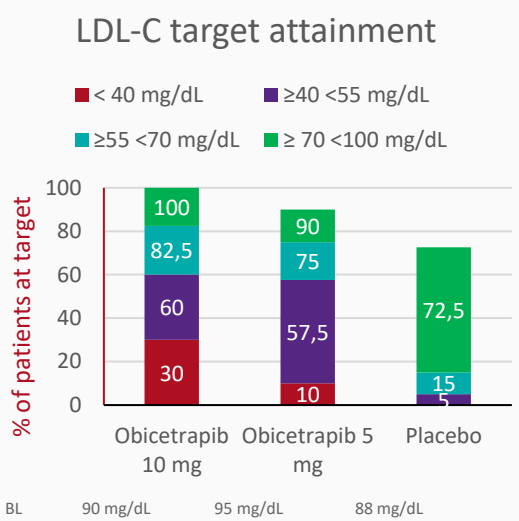
Nicholls SJ et al. *Nat Med* 2022;28:1672-1678.

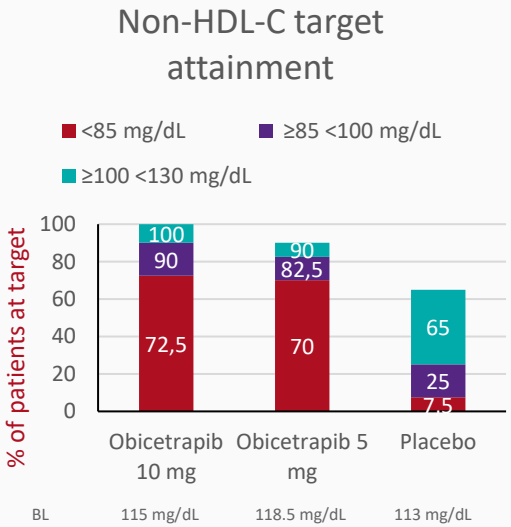
Lp(a) and triglycerides percent change from baseline

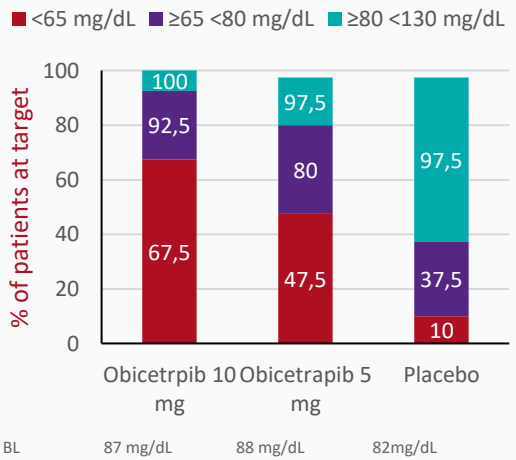


Nicholls SJ et al. *Nat Med* 2022;28:1672-1678.

LDL-C, non-HDL-C, ApoB target attainment







Nicholls SJ, et.al., Lipid lowering effects of the CETP inhibitor obicetrapib in combination with high-intensity statins: a randomized phase 2 trial. Nat Med. 2022 Aug;28(8):1672-1678. doi: 10.1038/s41591-022-01936-7. Epub 2022 Aug 11. PMID: 35953719

Conclusions

- Obicetrapib 5 and 10 mg on top of HIS therapy was well tolerated
- Obicetrapib 5 and 10 mg on top of HIS therapy reduced median LDL-C levels by -42% and -51% from baseline, respectively
- Obicetrapib LDL-C lowering comparable at all baseline LDL-C levels
- Obicetrapib LDL-C lowering is not mitigated in combination with HIS
- Obicetrapib LDL-C lowering is similar with both LDL-C quantitation methods
- 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 HIS therapy.

The combination of obicetrapib and ezetimibe lowers LDL-C in patients on high-intensity statins: results from the ROSE2 Trial (NCT05266586)

Christie M Ballantyne, Stephen J Nicholls, Marc Ditmarsch, John J Kastelein, Douglas Kling, Danielle L Curcio, Michael H Davidson

Objective

The primary objective of ROSE2 was to evaluate the lipid-lowering efficacy, safety, and tolerability of obicetrapib 10mg in combination with ezetimibe 10mg in patients treated with high-intensity statin therapy compared with placebo.

ROSE2 Trial: obicetrapib and high-intensity statin therapy

Objective To evaluate the effect of obicetrapib 10mg in combination with ezetimibe 10mg on top of HIS on LDL-C

Inclusion criteria

- Stable dose of high-intensity statins (A 40/80, R 20/40) 8 weeks before screening
- Fasting LDL-C levels >70 mg/dL (1.8 mmol/L)

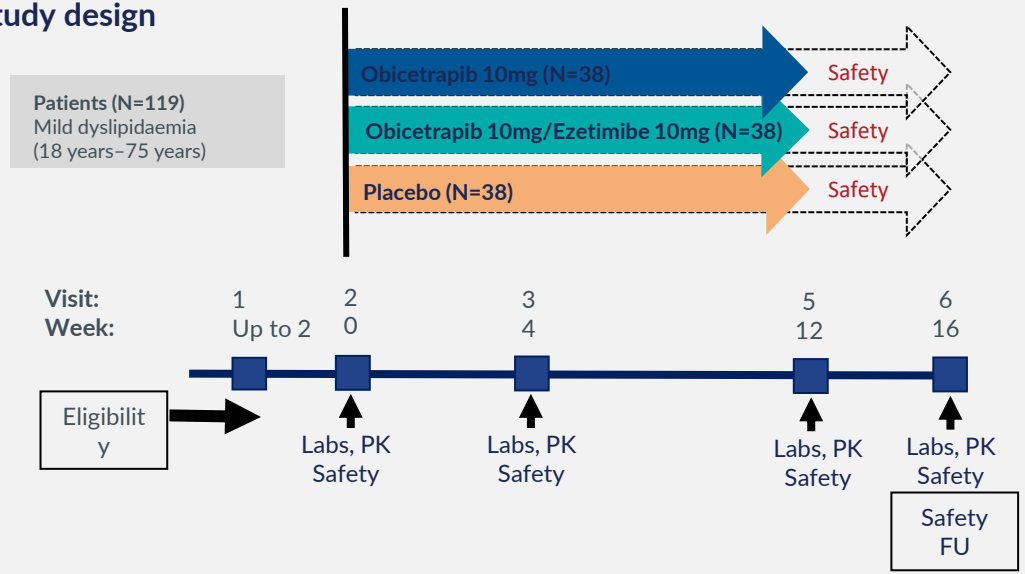
Exclusion criteria

- Current significant CV disease
- HbA1c ≥10%
- Uncontrolled hypertension

Primary efficacy endpoint

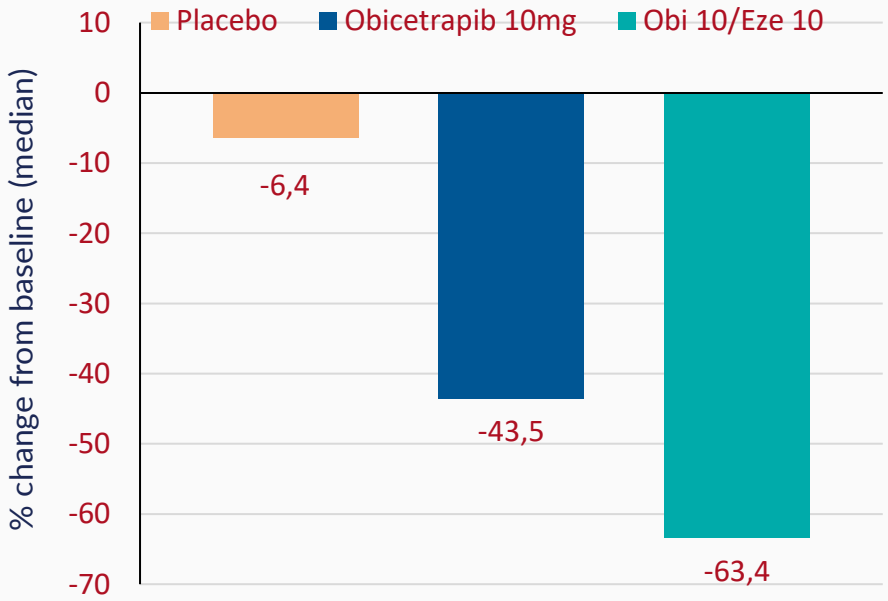
- Percent change from baseline in LDL-C compared with the placebo group

Study design



Ballantyne CM et al. J Clin Lipidol. In press.

LDL-C in mg/dL and percent change from baseline

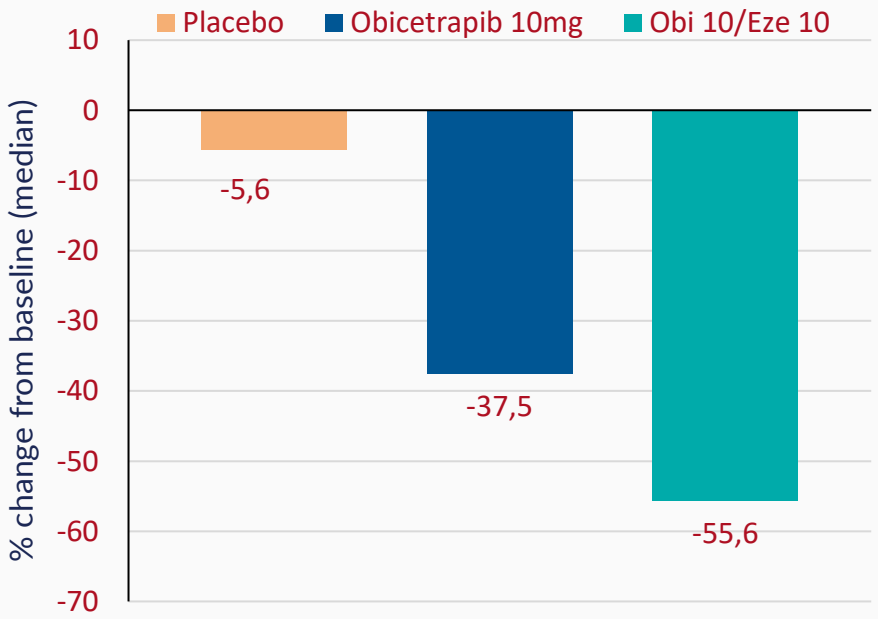


Median (min, max) LDL-C levels (mg/dL) at baseline and EoT

Time	Placebo	Obicetrapib 10mg	Obi 10/Eze 10
Baseline Median	95.5 (60, 211) (N=40)	100.0 (35, 189) (N=26)	87.0 (62, 152) (N=31)
EoT Median	88.0 (55, 188) (N=36)	55.5 (21, 148) (N=26)	39.0 (15, 96) (N=31)
% Change from Baseline (median)	-6.4 (-36.4, 96.7) (N=36)	-43.5 (-78.4, 22.6) (N=26)	-63.4 (-83.7, -29.7) (N=31)
% change from baseline LS mean (95% CI)	-0.85 (-7.75, 6.05)	-39.20 (-47.41, -30.99)	-59.23 (-66.75, -51.71)
P-value	-	<0.0001	<0.0001

Ballantyne CM et al. J Clin Lipidol. In press.

Non-HDL-C in mg/dL and percent change from baseline

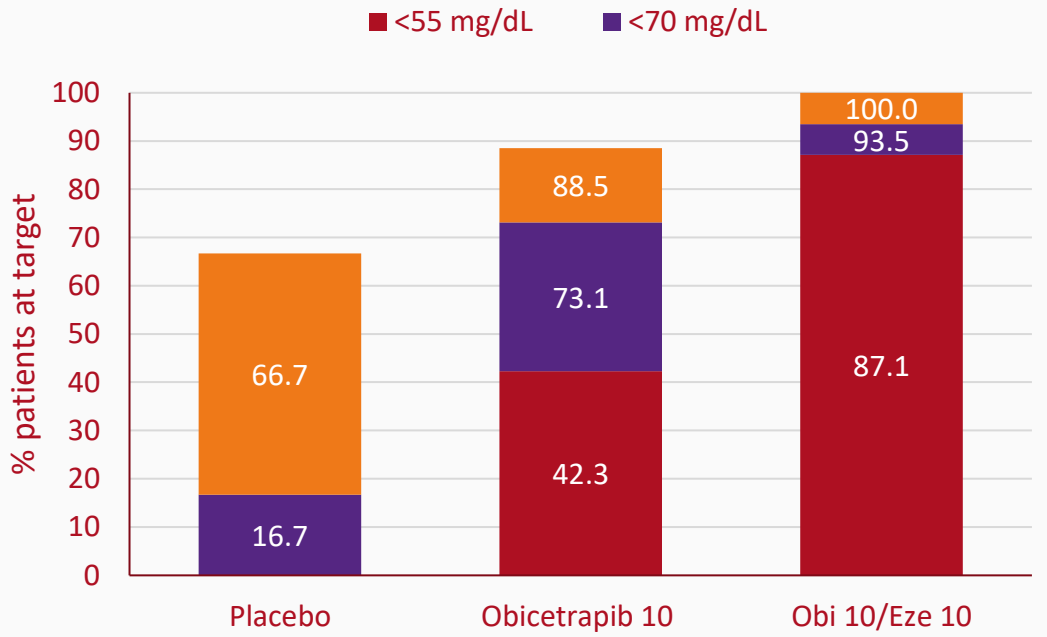


Median (min, max) non-HDL-C levels (mg/dL) at baseline and EoT

Time	Placebo	Obicetrapib 10mg	Obi 10/Eze 10
Baseline Median	125.5 (73, 227) (N=40)	121.5 (57, 209) (N=26)	116.0 (77, 189) (N=31)
EoT Median	113.0 (82, 231) (N=36)	78.5 (48, 164) (N=26)	61.5 (25, 118) (N=31)
% Change from Baseline (median)	-5.6 (-34.9, 83.6) (N=36)	-37.5 (-59.2, 20.0) (N=26)	-55.6 (-76.2, 30.8) (N=31)
% change from baseline LS mean (95% CI)	-0.84 (-6.78, 5.10)	-33.82 (-40.88, -26.77)	-54.02 (-60.49, -47.56)
P-value	-	<0.0001	<0.0001

Ballantyne CM, et. Al., Obicetrapib plus ezetimibe as an adjunct to high-intensity statin therapy: A randomized phase 2 trial. J Clin Lipidol. 2023 May 31:S1933-2874(23)00186-1. doi: 10.1016/j.jacl.2023.05.098. Epub ahead of print. PMID: 37277261

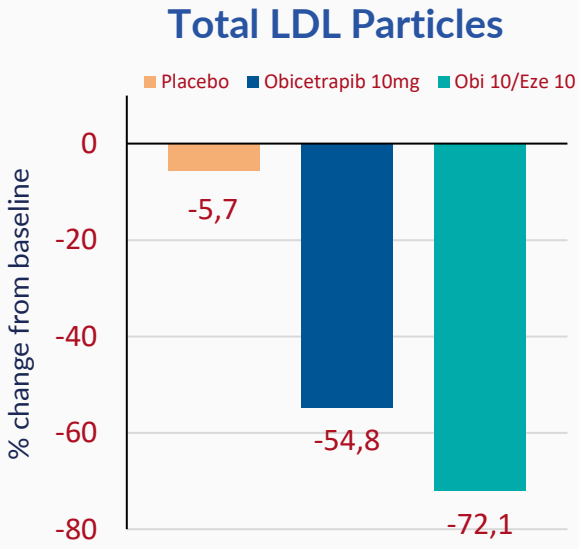
LDL-C target attainment

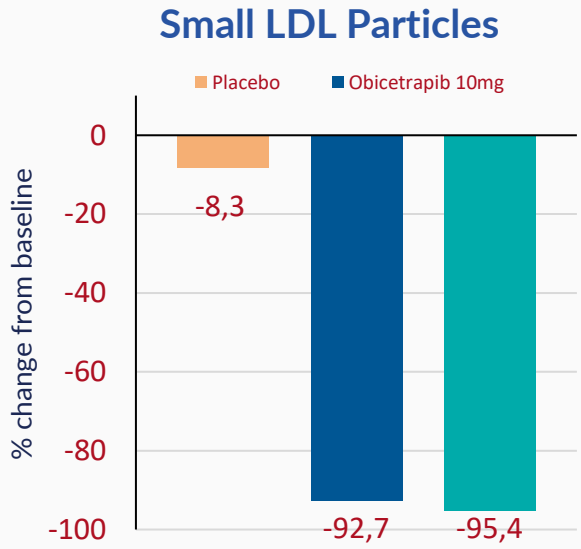


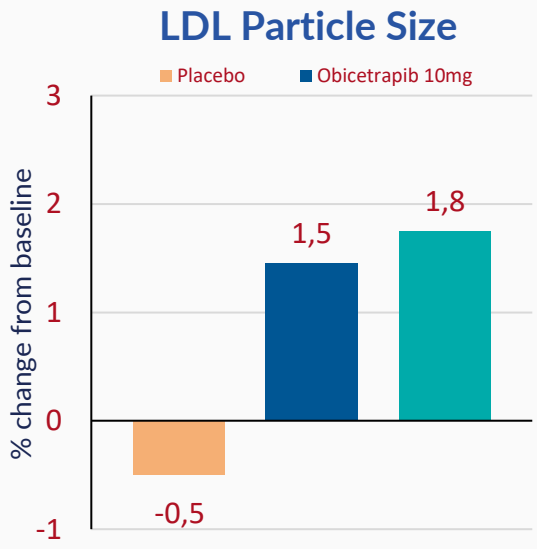
BL	95 mg/dL	100 mg/dL	87 mg/dL

Ballantyne CM, et. Al., Obicetrapib plus ezetimibe as an adjunct to high-intensity statin therapy: A randomized phase 2 trial. J Clin Lipidol. 2023 May 31:S1933-2874(23)00186-1. doi: 10.1016/j.jacl.2023.05.098. Epub ahead of print. PMID: 37277261

Total, small LDL particles and LDL-particle size percent change from baseline

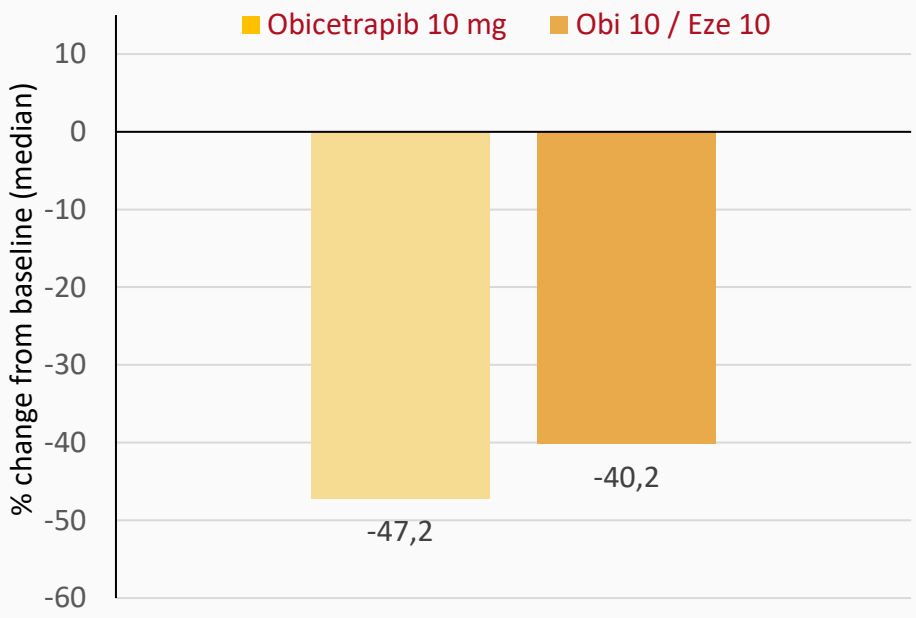






Ballantyne CM, et. Al., Obicetrapib plus ezetimibe as an adjunct to high-intensity statin therapy: A randomized phase 2 trial. J Clin Lipidol. 2023 May 31:S1933-2874(23)00186-1. doi: 10.1016/j.jacl.2023.05.098. Epub ahead of print. PMID: 37277261

Lp(a) in nmol/L & percent change from baseline



Median (min, max) Lp(a) levels (nmol/L) at baseline and E0T

Time	Obicetrapib 10 mg	Obi 10 / Eze 10
Baseline Median	44.0 (0.8, 372.4) (N=24)	27.6 (0.2, 479.9) (N=31)
EoT Median	13.8 (0.9, 329.9) (N=24)	8.6 (0.1, 520.8) (N=31)
% Change from Baseline (median)	-47.2 (-97.5, 214.5) (N=24)	-40.2 (-92.4, 702.0) (N=31)

Ballantyne CM, et. Al., Obicetrapib plus ezetimibe as an adjunct to high-intensity statin therapy: A randomized phase 2 trial. J Clin Lipidol. 2023 May 31:S1933-2874(23)00186-1. doi: 10.1016/j.jacl.2023.05.098. Epub ahead of print. PMID: 37277261

Conclusions

- Obicetrapib 10 mg and the combination of obicetrapib 10 mg and ezetimibe 10 mg were observed to reduce median LDL-C levels by -43.5% and -63.4%, respectively, on top of HIS therapy
- The combination of obicetrapib 10 mg and ezetimibe 10 mg was observed to reduce total LDL particles and small LDL particles by 72.1% and 95.4%, respectively
- 87.1% of patients taking the combination of obicetrapib 10 mg and ezetimibe 10 mg were observed to achieve an LDL-C level <55mg/dL
- Obicetrapib 10 mg and the combination of obicetrapib 10 mg and ezetimibe 10 mg on top of HIS therapy were well tolerated
- These data support the continued development of a fixed dose combination of obicetrapib 10 mg plus ezetimibe 10 mg

Pooled Safety

Safety: TEAEs, TESAEs, and withdrawal overview (safety population)

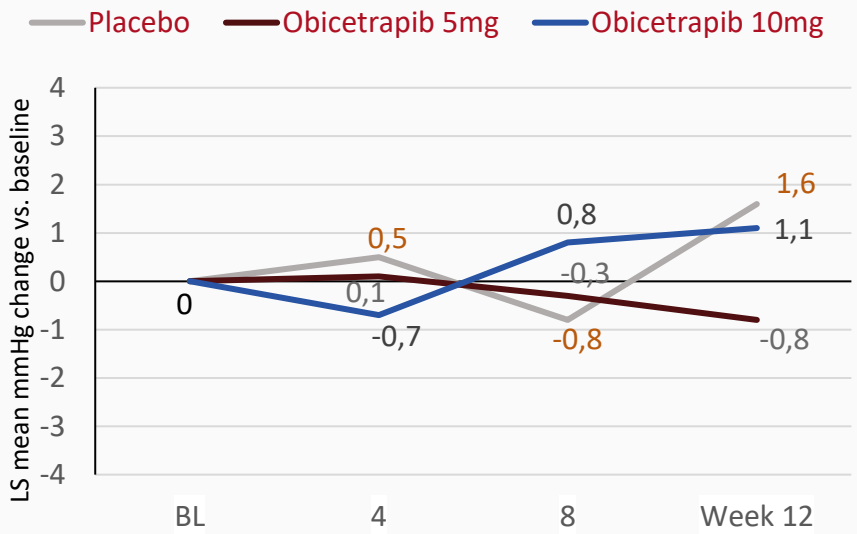
	Placebo N= 40, N (%)	Obicetrapib 10 mg N= 39, N (%)	Obi 10 mg / Eze 10 mg N= 40, N (%)
TEAEs (%)			
TEAEs	16 (40)	8 (20.5)	11 (27.5)
Related TEAEs	2 (5.0)	4 (10.3)	5 (12.5)
Severe TEAEs	2 (5.0)	1 (2.6)	0 (0)
TESAEs			
TESAEs, total	1 (2.5)	1 (2.6)	0 (0)
Deaths	0	0	0
Withdrawal's study / medication			
TEAEs leading to discontinuation of study drug	2 (5.0)	2 (5.1)	1 (2.5)

N=total number of subjects in each treatment group.
n=number of subjects who experienced an event.
%=100 x n/N.

Ballantyne CM, et. Al., Obicetrapib plus ezetimibe as an adjunct to high-intensity statin therapy: A randomized phase 2 trial. J Clin Lipidol. 2023 May 31:S1933-2874(23)00186-1. doi: 10.1016/j.jacl.2023.05.098. Epub ahead of print. PMID: 37277261

Pooled Analysis of TULIP, OCEAN, ROSE, ROSE2 & TA-8995-203

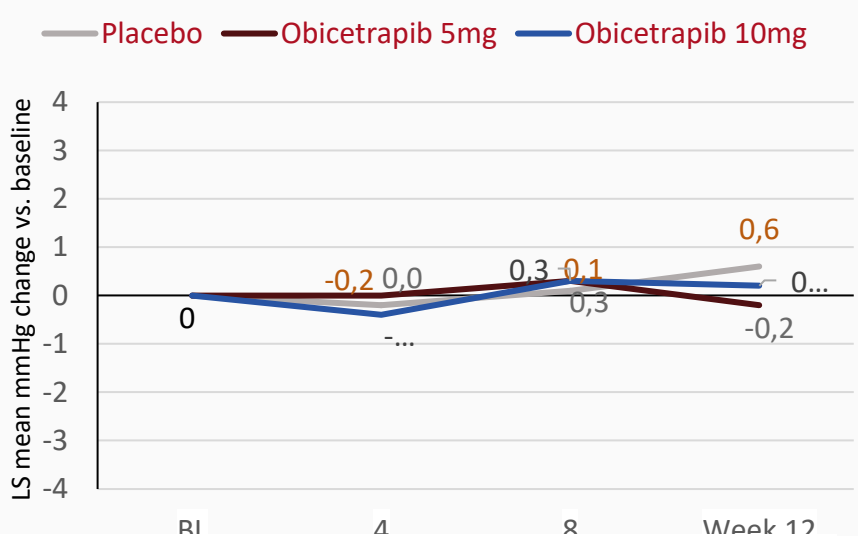
Systolic



Placebo (N)	255	248	206	157
Obi 5 mg (N)	160	159	155	63
Obi 10 mg (N)	266	263	181	188

Table 2.1 Pooled Analysis of TULIP, OCEAN, ROSE, ROSE2 & TA-8995-203

Diastolic

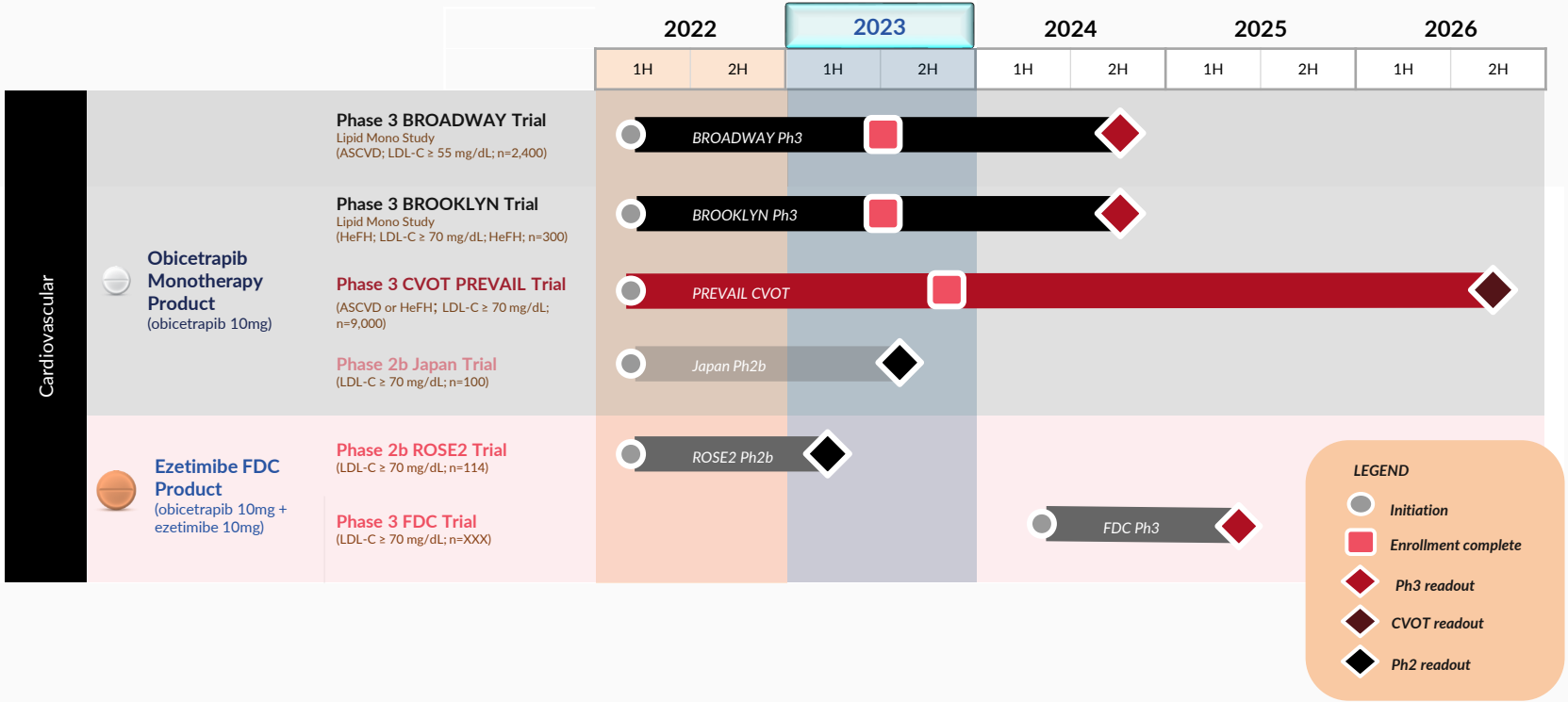


Placebo (N)	255	248	206	157
Obi 5 mg (N)	160	159	155	63
Obi 10 mg (N)	266	263	181	188

Table 2.3 Pooled Analysis TULIP, OCEAN, ROSE, ROSE2 & TA-8995-203

Obicetrapib Clinical Program

Obicetrapib Franchise Projected Clinical Program



Note: Other than as noted, the pipeline represents trials that are currently ongoing. Projections are subject to inherent limitations. Actual results may differ from expectations. The timing of regulatory submissions is subject to additional discussions with regulators.

BROOKLYN

Objective: To evaluate the effects of obicetrapib in patients with heterozygous familial hypercholesterolemia (HeFH)
Status: Protocol updated based on FDA feeback, study start-up ongoing

Main Inclusion criteria

- HeFH by genetic confirmation, and/or WHO Criteria/Dutch Clinical Network, and/or Simon Broome criteria
- 70% of patients on HS
- 10% Statin Intolerant
- Stable lipid lowering therapies with an LDL ≥ 70 mg/dL and TG ≤ 400 mg/dL

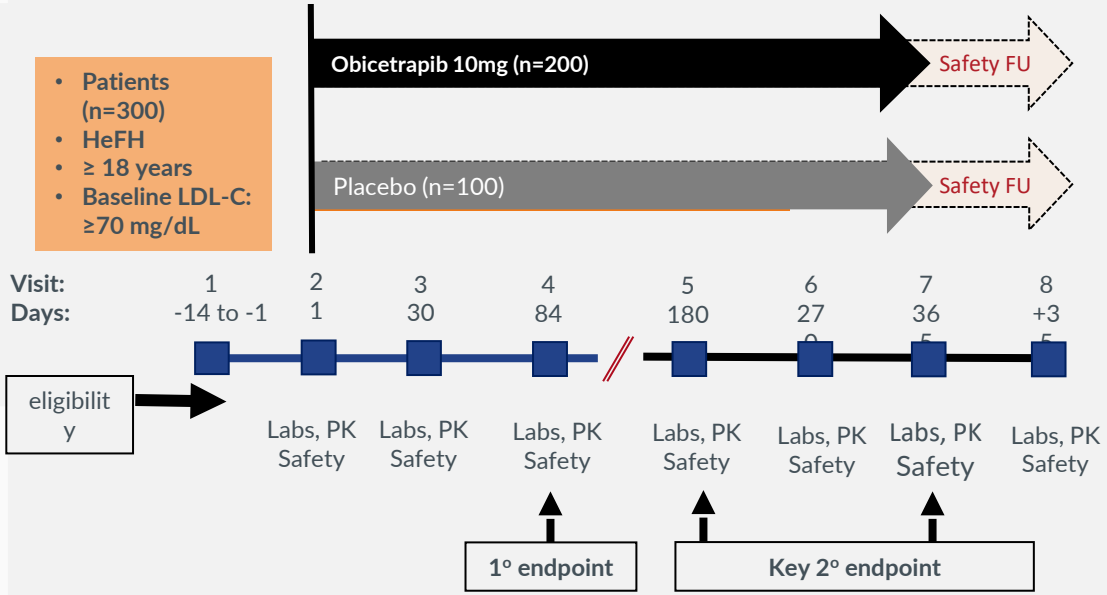
Exclusion criteria

- CV disease < 3 months
- HoFH
- Uncontrolled hypertension

Primary efficacy endpoint

- **Percent change from baseline in LDL-C** compared to the placebo group

Study design: Randomized, double-blind, placebo-controlled



https://clinicaltrials.gov/ct2/show/NCT05425745.

BROADWAY Obicetrapib on Top of Max Tolerated Lipid-Modifying Therapy

Objective To evaluate the effect of obicetrapib on top of max tolerated lipid-modifying therapy in patients with HeFH and or ASCVD

Main inclusion criteria

Have a fasting serum LDL-C at Screening (Visit 1) as follows:

- Have a fasting serum LDL-C ≥ 55 mg/dL (≥ 1.4 mmol/L) to <100 mg/dL (<1.8 mmol/L) OR non-HDL-C ≥ 85 mg/dL (≥ 2.2 mmol/L) to <130 mg/dL (<2.6 mmol/L) with at least 2 risk enhancers

OR

- Have a fasting serum LDL-C ≥ 100 mg/dL (≥ 2.6 mmol/L) OR non-HDL-C ≥ 130 mg/dL (≥ 3.4 mmol/L).

Risk enhancers:

a. Age of >60 years;
b. Recent MI (>3 and <24m prior to Randomization);
c. Type 2 diabetes mellitus;
d. Current cigarette smoking;
e. hsCRP ≥ 2.0 mg/L;
f. TG >150 mg/dL (>1.7 mmol/L);
g. Lp(a) >30 mg/dL (>70 nmol/L);
h. HDL-C <40 mg/dL (<1.0 mmol/L);

Main exclusion criteria

- CV disease < 3 months
- HoFH
- Uncontrolled hypertension

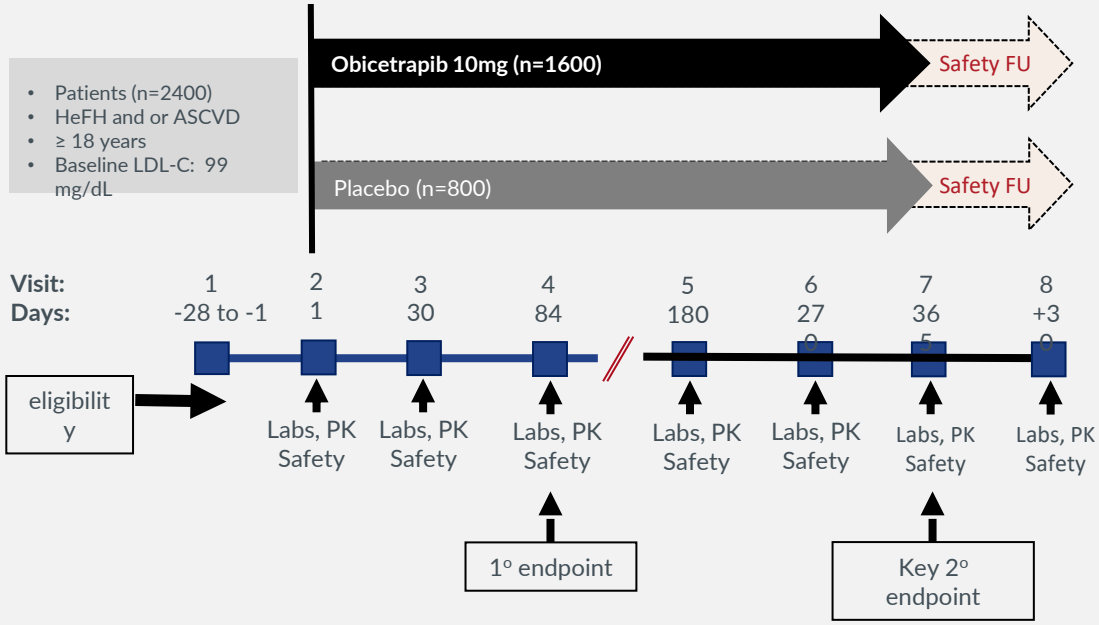
Primary efficacy endpoint

- % change from BL to Day 84 in LDL-C for obicetrapib vs placebo

Key secondary efficacy endpoint

- CV death, MI, stroke, or non-elective coronary revascularization

Study design: Randomized, double-blind, placebo-controlled



https://clinicaltrials.gov/ct2/show/NCT05142722.

PREVAIL

Obicetrapib CV outcome trial is designed to show reduction of cardiovascular morbidity and mortality in patients with established ASCVD

Rationale

Patients with established ASCVD on maximally tolerated lipid-lowering therapy, including high-intensity statins, who are unable to get to their guideline goals, are at high risk for cardiovascular events, have an unmet medical need and therefore require additional lipid-lowering therapy

Objective **To evaluate the potential of Obicetrapib to reduce cardiovascular mortality and morbidity in patients with established ASCVD**

Main inclusion criteria

- Established ASCVD
- Max tolerated lipid-modifying therapy
- LDL-C level ≥ 70 < 100 mg/dL + 1 RF
  - Recent MI (3-12 months)
  - T2DM
  - TG >150 mg/dL
  - HDL-C <40 mg/dL

  Or

  LDL-C ≥ 100 mg/dL

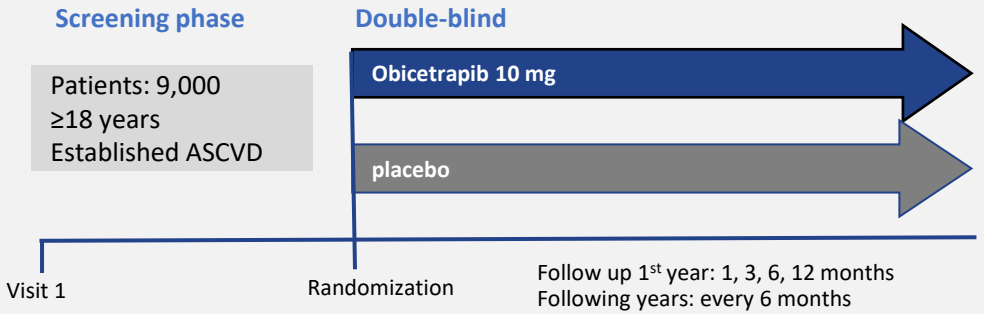
Main exclusion criteria

- Poorly controlled diabetes (HbA1c >10%)
- Hypertension
- Congestive heart failure
- Severe anemia
- Liver disease
- Chronic kidney disease

Strategy

- Duration if 959 primary endpoint events occur or the last randomized patient has been followed for a minimum of 2.5 years

Study design: Randomized, double-blind, placebo-controlled



Primary endpoint

- 4 point MACE (CVD death, non-fatal MI, non-fatal stroke, non-elective coronary revascularization)

Secondary objective

- LDL-c at 1-year
- New-onset diabetes mellitus;

https://clinicaltrials.gov/ct2/show/NCT05202509

Conclusion

CETP Inhibition generates a positive feedback loop of beneficial changes in cholesterol balance- blocks CETP transport from HDL-C to LDL-C, significantly increasing HDL and reducing LDL

CETPi decreases hepatic cholesterol resulting in upregulation of LDL-Receptor levels and improved LDL and ApoB clearance through the liver

Obicetrapib (5 or 10 mg) as an adjunct to high intensity Statin therapy has been shown to be well tolerated and lowers LDL cholesterol and can be a valuable addition to HIS.

Obicetrapib 10mg in combination with ezetimibe 10 mg was also shown to be well tolerated, reduces median LDL significantly, and achieves LDL levels at goal in phase II studies

Large scale clinical outcome programs have been planned and will evaluate the safety and efficacy of Obicetrapib in addition to HIS in patients at risk for CV events