Universitätsklinikum Leipzig

Klinik und Poliklinik für Kardiologie

Herzmedizin im Herzen Leipzigs

New oral LDL-c lowering therapies on the horizon: CETP inhibitors

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ZENTRUM FÜR SPORT- UND BEWEGUNGSMEDIZIN

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New LDL-lowering drugs in advanced clinical programs

PCSK9-Inhibitor MK-0616, oral

PCSK9-Adnectin Lerodalcibep, s.c.

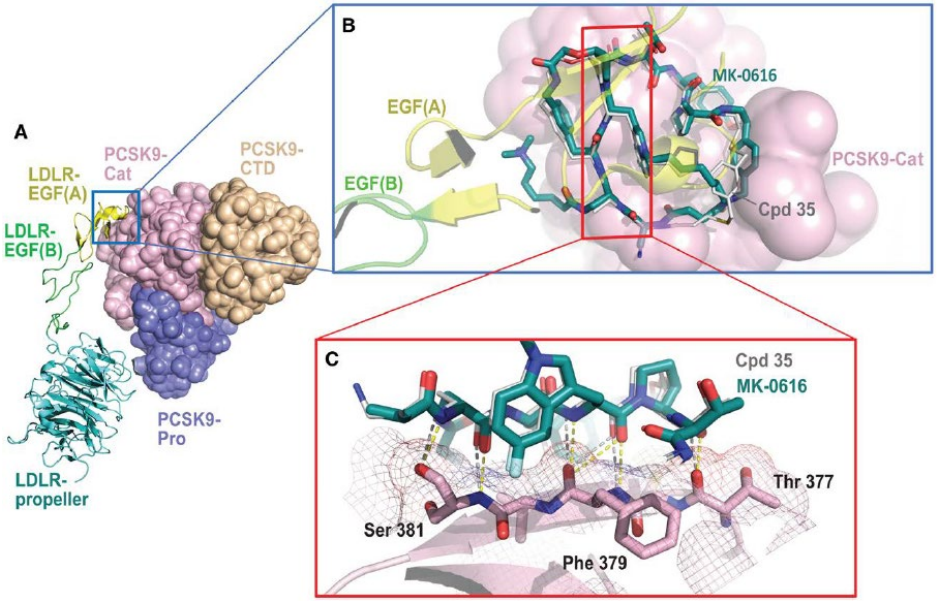
CETP-Inhibitor Obicetrapib, oral

New LDL-lowering drugs in advanced clinical programs

Oral PCSK9-Inhibitor MK-0616

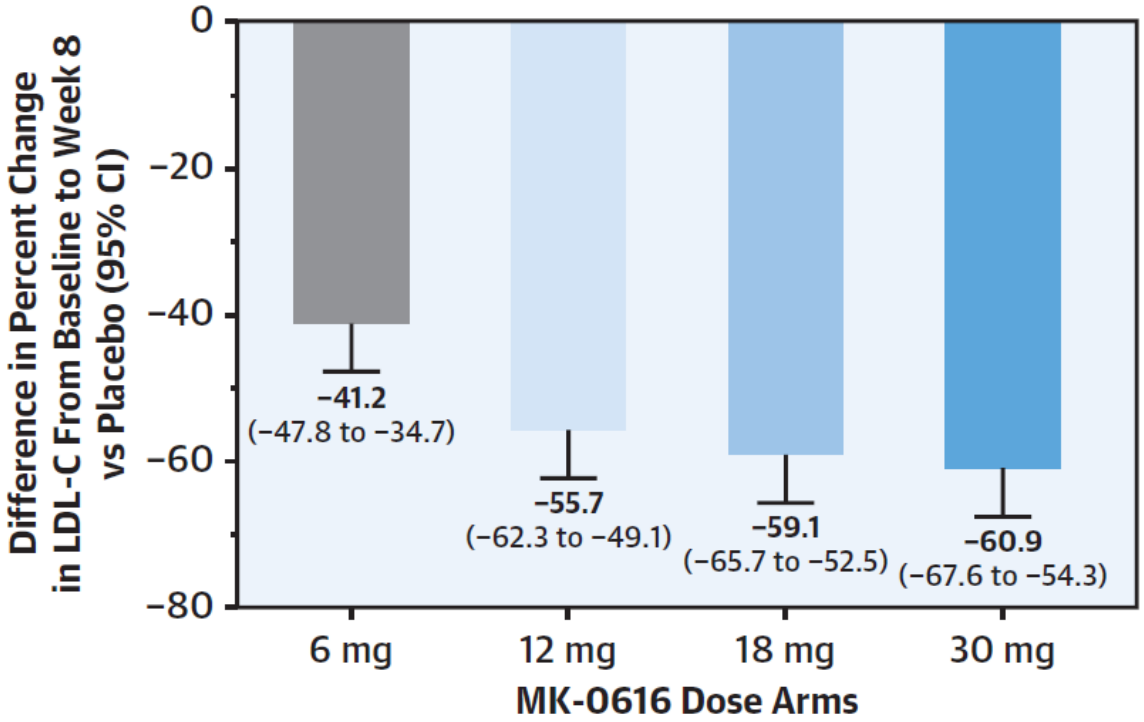
PCSK9-Adnectin Lerodalcibep

CETP-Inhibitor Obicetrapib



Johns et al., Circ 2023;148:144–58

Phase 2b Randomized Trial of the Oral PCSK9 Inhibitor MK-0616



Key Points

- All doses of MK-0616 demonstrated statistically superior reductions in LDL-C vs placebo with up to 60.9% placebo-adjusted reduction from baseline values
- MK-0616 was well tolerated with no overall trends in AEs across treatment groups

Ballantyne et al., JACC 2023;81:1553–64

New LDL-lowering drugs in advanced clinical programs

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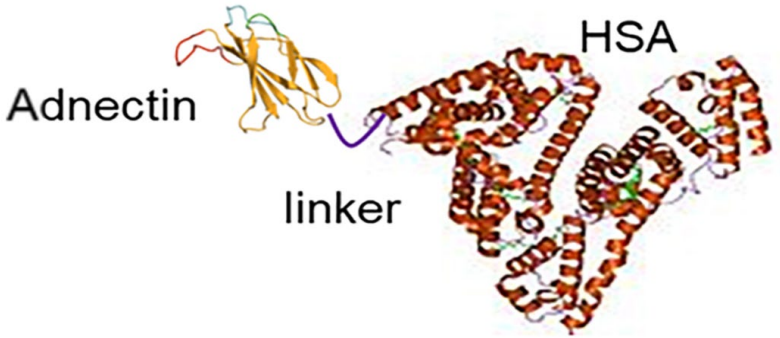
PCSK9-Adnectin Lerodalcibep

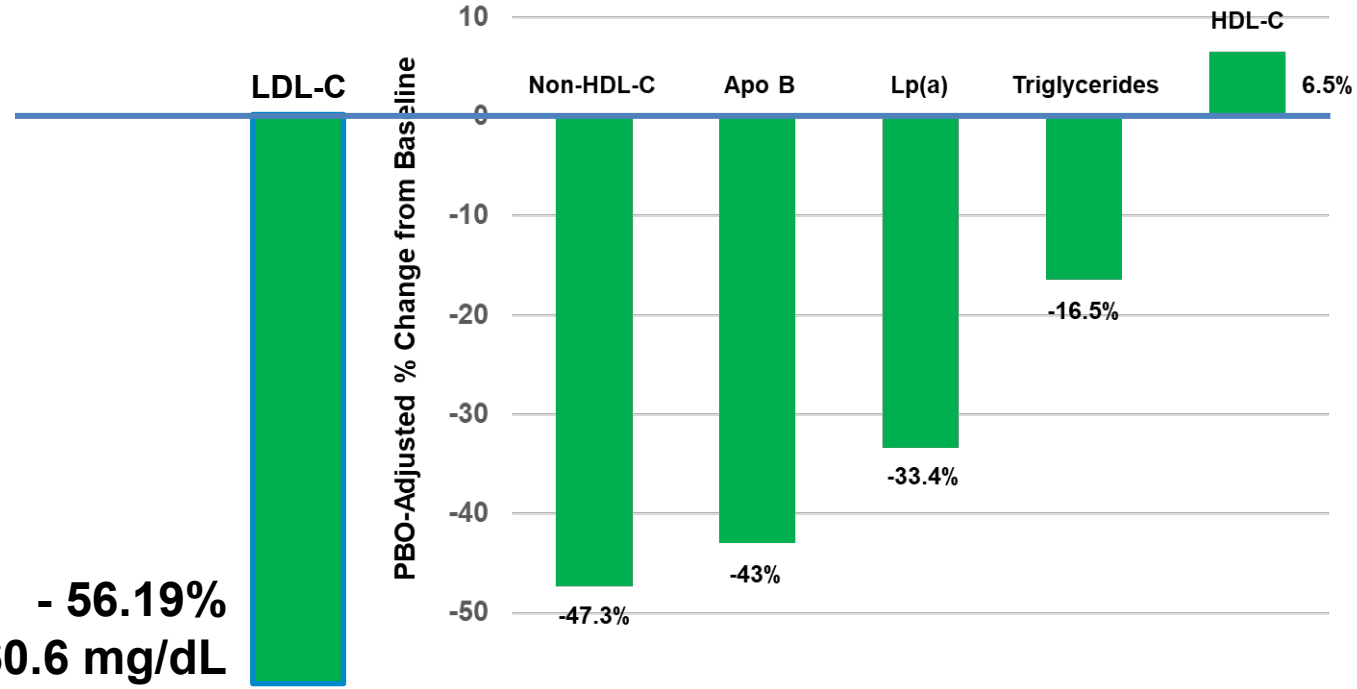
CETP-Inhibitor Obicetrapib



Raal et al., EHJ 2023;44(40):4272-80

Efficacy and Safety of Lerodalcibep in Pt at Very-High and High Risk for CVD
Phase 3, Double-blind Placebo-controlled 52-week trial (LIBerate-HR)

Placebo-adjusted LDL-C Change from Baseline ITT Analysis Week 52



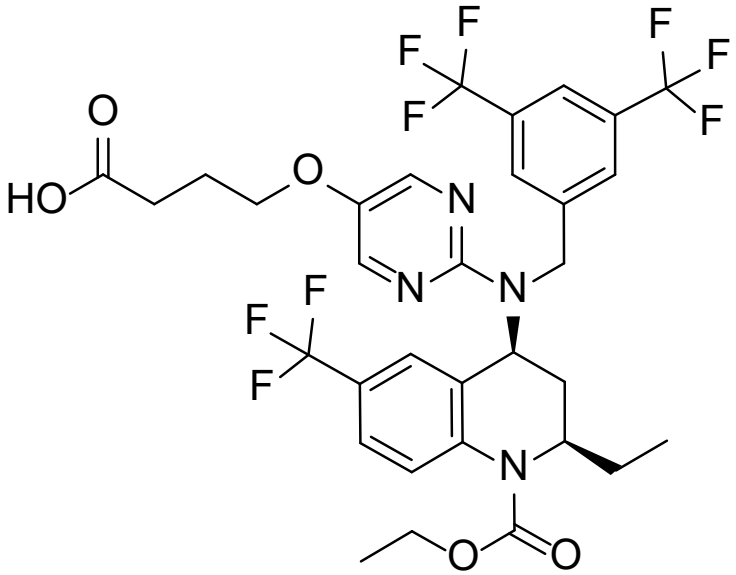
LIBerate-HR; Klug et al., 24-LBCT-21933-ACC, Late-Breaking Clinical Trials II, April 7, 2024

New LDL-lowering drugs in advanced clinical programs

Oral PCSK9-Inhibitor MK-0616

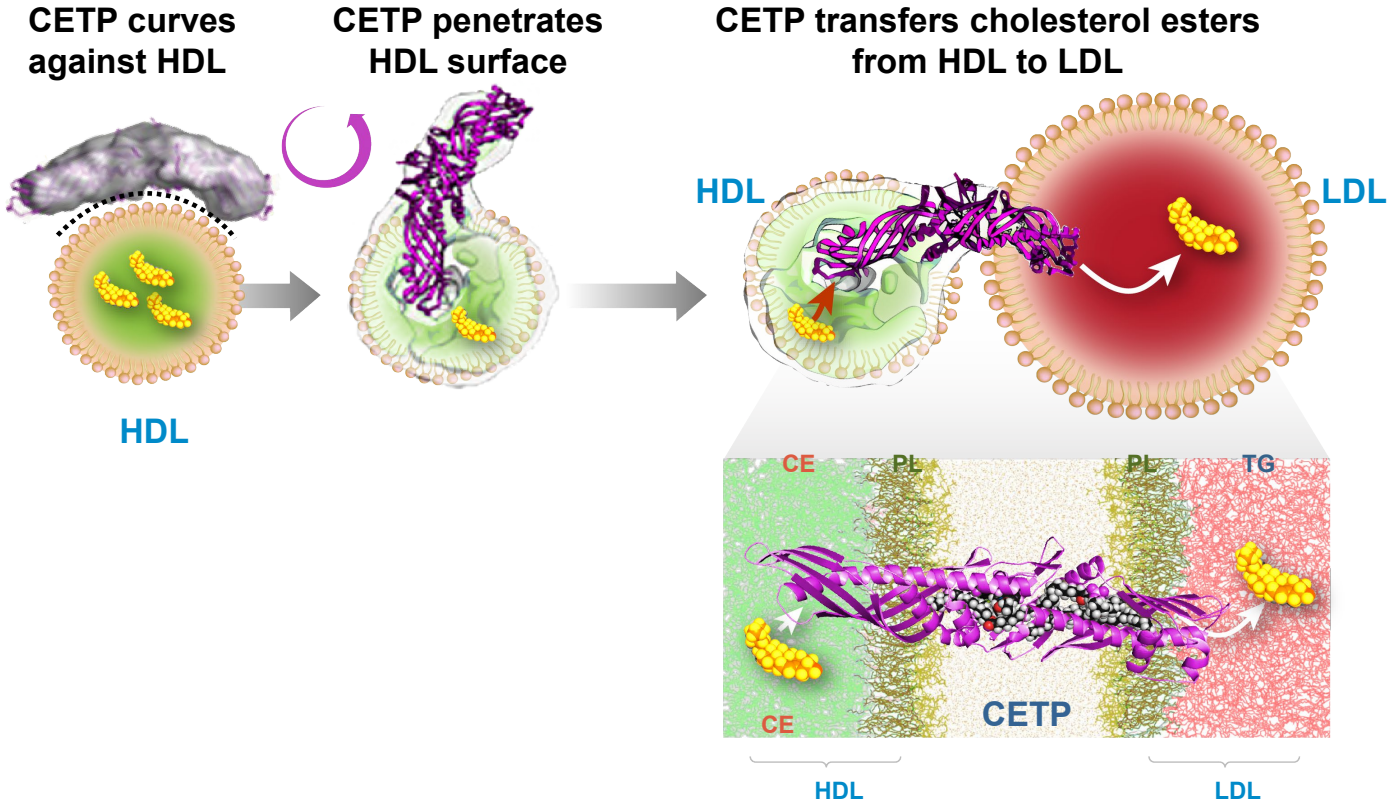
PCSK9-Adnectin Lerodalcibep

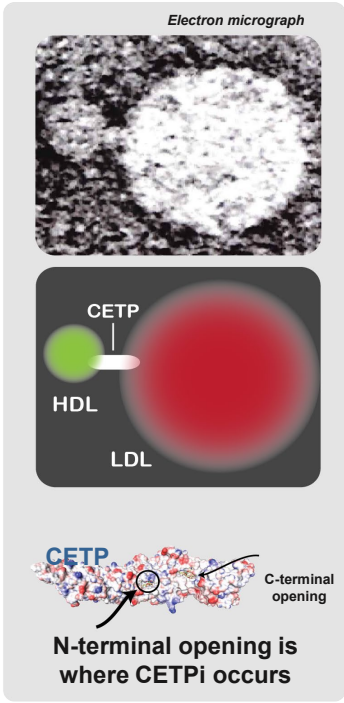
CETP-Inhibitor Obicetrapib



Nicholls et al. Nat Med 2022

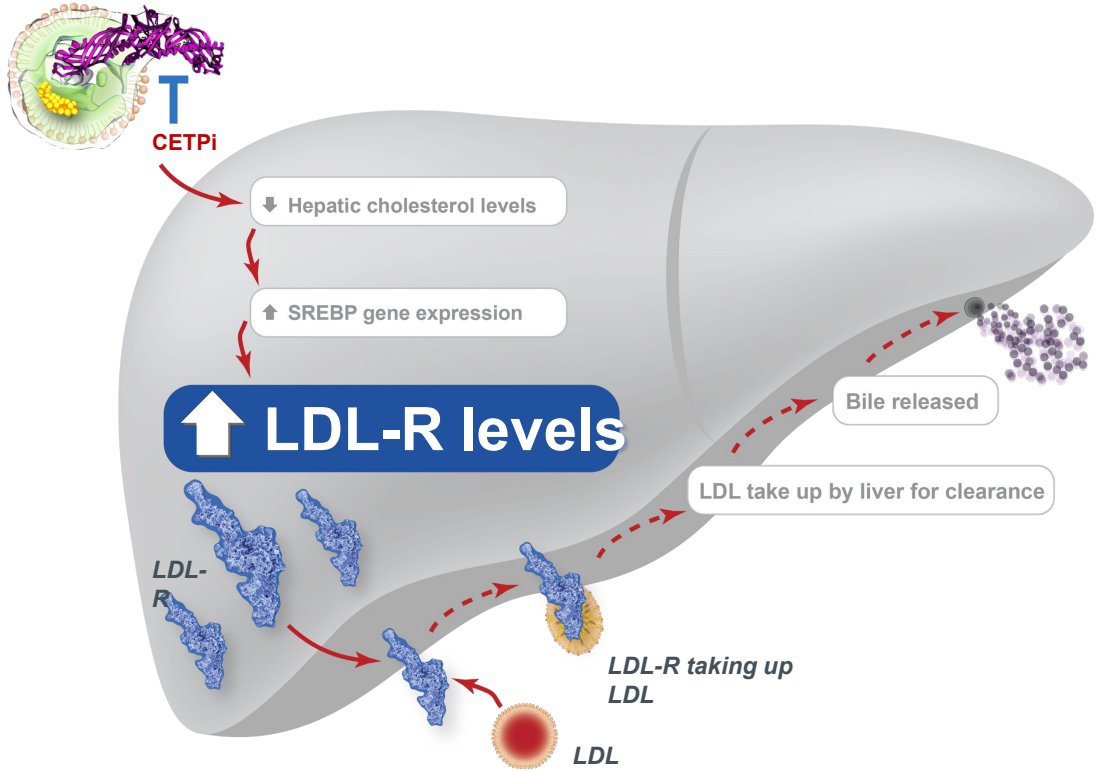
CETP activity increases circulating LDL-C levels





Slide from J. Kastelein. Figures adapted from Meng Z et al., Molecular and Cell Biology of Lipids, 1862(12), 2017, 1606-17, and from Lei D et al., J Biol Chem., 2291(27), 2016, 14034-44

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



Decrease in hepatic cholesterol

Increase in hepatic LDL receptors

Decrease in plasma LDL levels

Slide from J. Kastelein. Adapted from: Millar JS, et al., JCI 2015;125(6):2510-22 and van der Tuin SJ, et al., JLR 2015;56(11):2085-93

Genetically lower CETP associated with lower cardiovascular risks

The Ashkenazi Jewish Longevity Gene Project

Individuals with exceptional longevity had significantly higher (up to 3.6-fold) homozygosity for the 405 valine (I405V) allele of CETP (VV genotype) vs controls

Barzilai et al. JAMA 2003;290(15):2030-40

The Copenhagen City Heart Study

Prospective study, n= 10,261; ~34 years follow-up

Carriers of CETP (inactivating) genotpes had decreased LDL cholesterol levels

and lower cardiovascular risk:

ischemic cardiovascular event: HR 0.7

ischemic heart disease: HR 0.65

ischemic cerebrovascular disease: HR 0.71

Johannsen et al. JACC 2012,60(20):2041–8

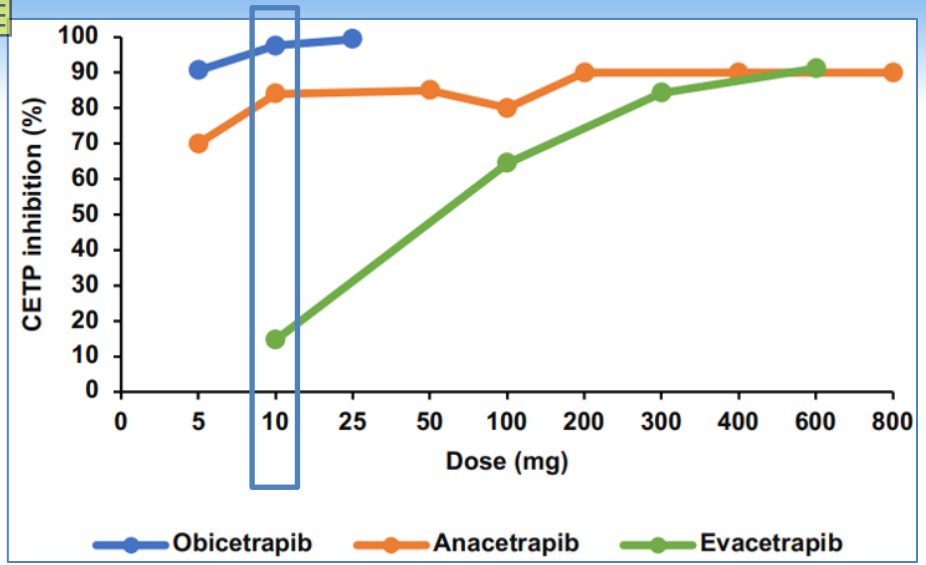
Ultra-short summary of the complex history of pharmacologic CETP inhibition

Torcetrapib, ILLUMINATE: **negative study, off-target effects (e.g. increased BP)**
NEJM 2007; 357:2109-22

Dalcetrapib, dal-OUTCOMES: **neutral study, no LDL-C lowering**
NEJM 2012; 367:2089-99

Evacetrapib, ACCELERATE: **non-significant trends, study underpowered / too short**
NEJM 2017; 376:1933-42

Anacetrapib: REVEAL: **modest effect, insufficient LDL-C lowering (~-11mg/dl)**
NEJM 2017; 377:1217-27



Obicetrapib
Pharmacology

CETP inhibitor	Dose (mg)	LDL-C (mmol/L) % change from baseline	HDL-C (mmol/L) % change from baseline
Torcetrapib	60	–15.7	33.1
Dalcetrapib	600	–5.4	26.4
Anacetrapib	100	–23.4	138.1
Evacetrapib	100	–22.3	94.6
Obicetrapib	5	–45.3	157.1

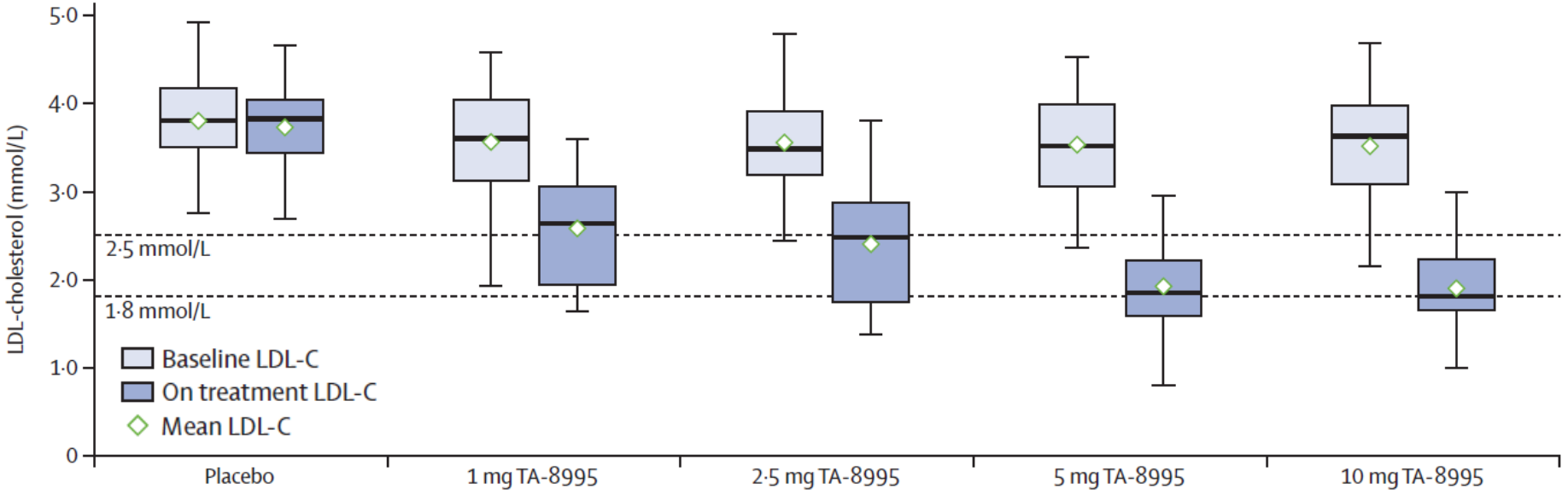
less lipophilic

Nurmohamed et al. CVR 2022;118(14):2919-2931

Ford et al. Br J Clin Pharmacol 2014; de Grooth et al. Circulation. 2002; Teramoto et al. Am J Cardiol 2014; Krishna et al. Lancet. 2007; Pharmacology & Therapeutics 2017

LDL-C in Phase 2 Study TULIP

N=364, 12 wk, no SAE



- 45 %

- 45 %

Hovingh GK et al., Lancet 2015; 10.1016/S0140-6736(15)60158-1

ROSE study: Obicetrapib in combination with high-intensity statins

Inclusion criteria

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

Exclusion criteria

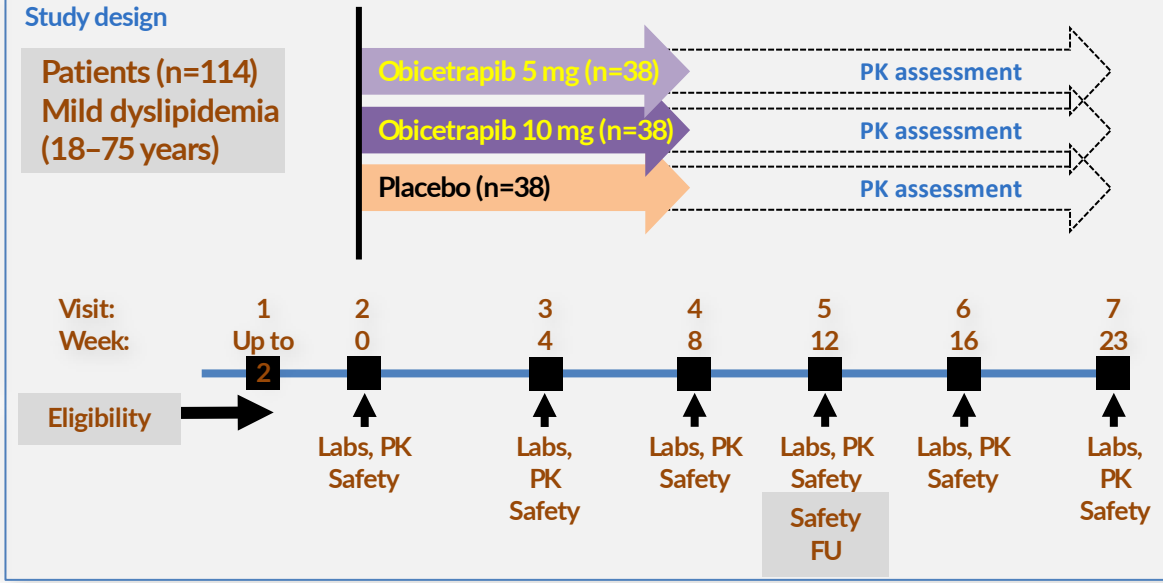
- significant CV disease
- diabetes mellitus
- uncontrolled hypertension

Primary efficacy endpoint

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

Study design

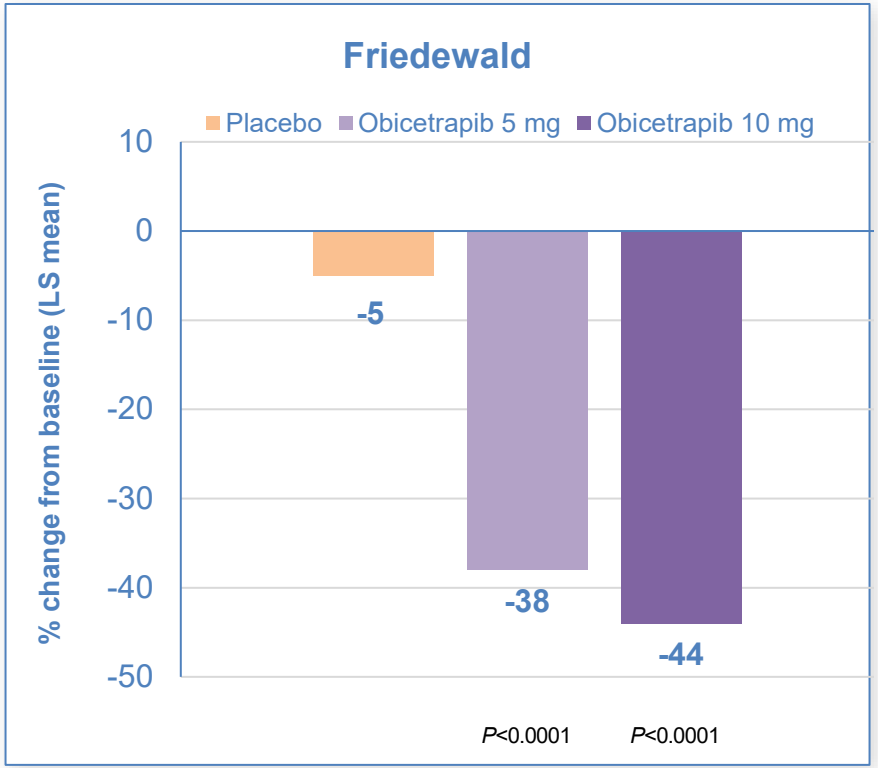
Patients (n=114)
Mild dyslipidemia
(18–75 years)

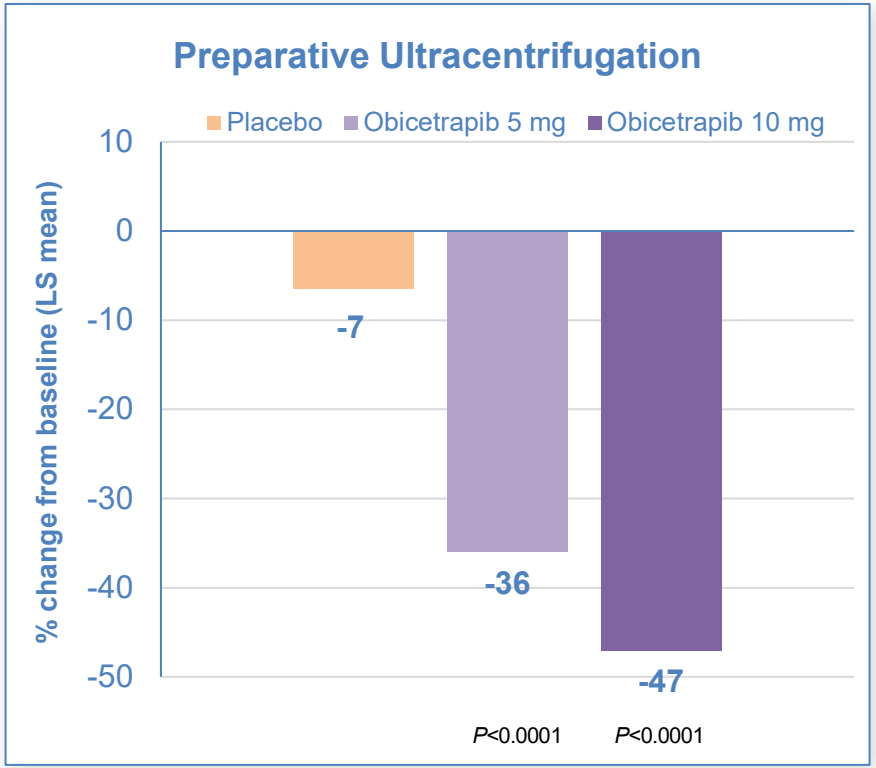


Pre-specified assessment of LDL-C levels by preparative ultra-centrifugation and Friedewald

Rose study. Nicholls SJ et al. Nat Med 2022;28(8):1672-8

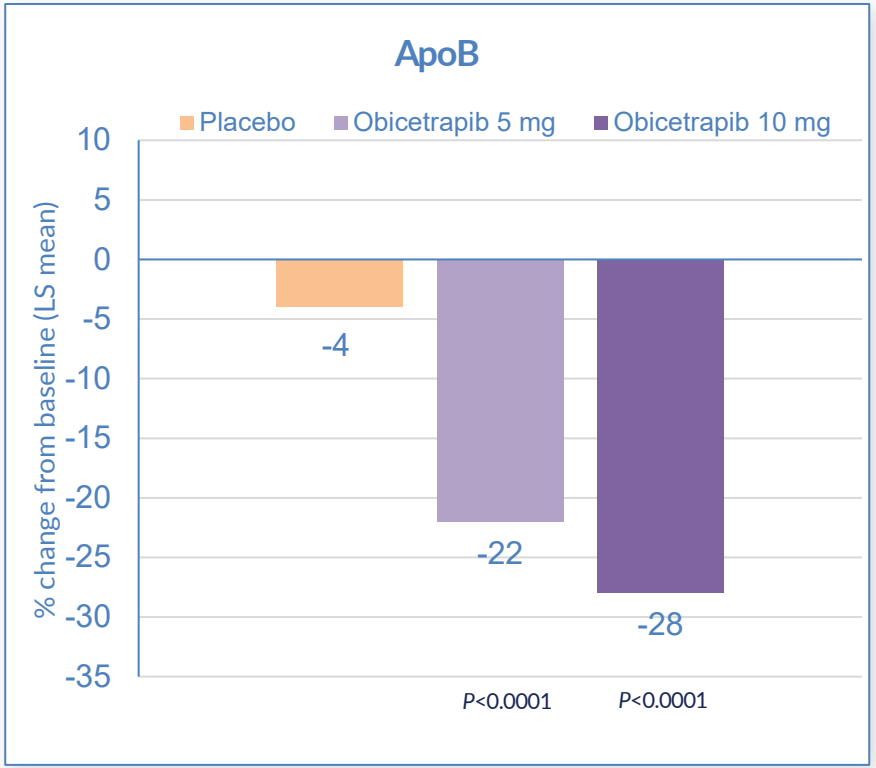
ROSE study: LDL-Cholesterol Lowering

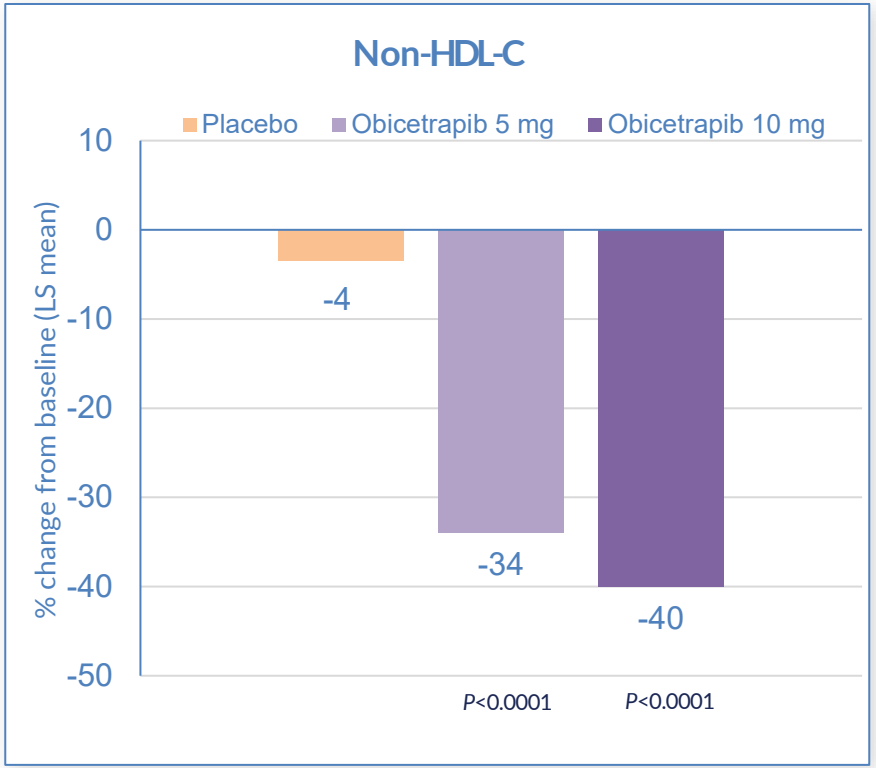




Nicholls SJ et al. Nat Med 2022;28(8):1672-8

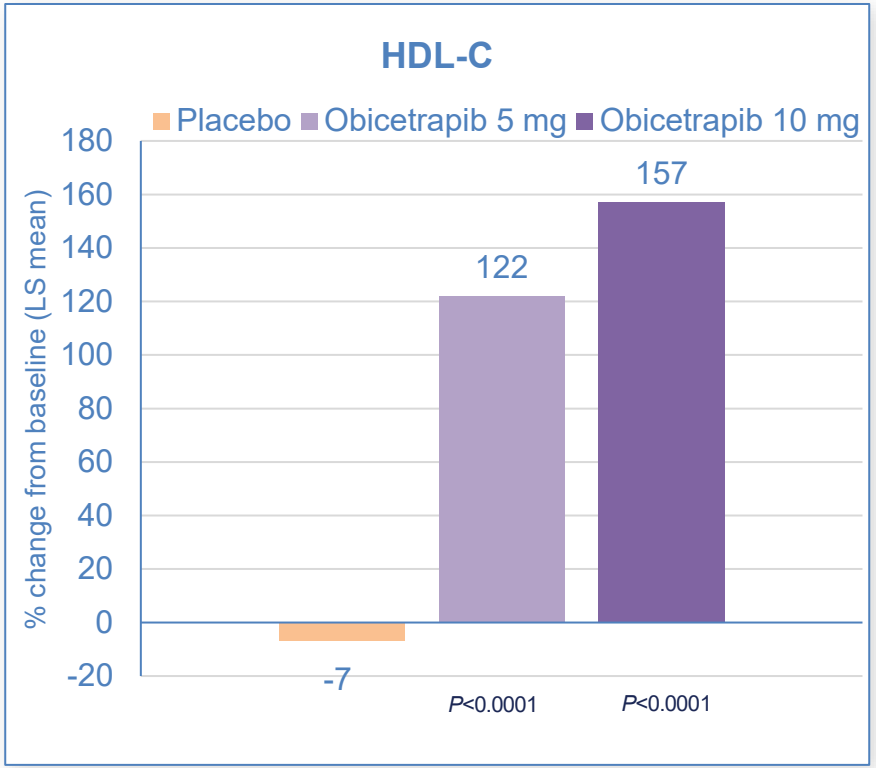
ROSE study: ApoB and Non-HDL-C Lowering

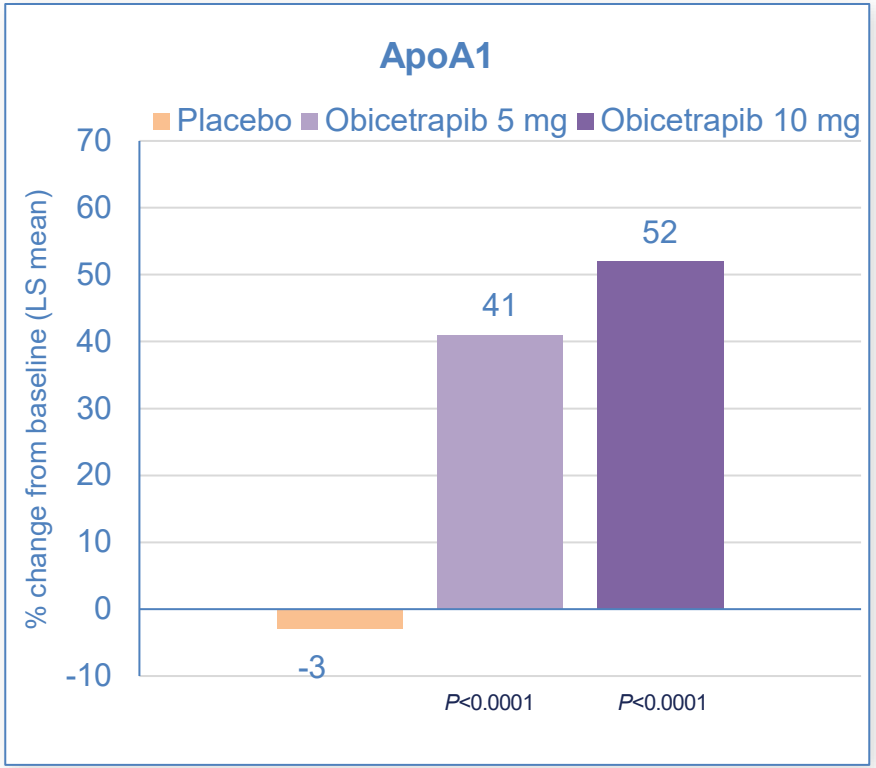




Nicholls SJ et al. Nat Med 2022;28(8):1672-8

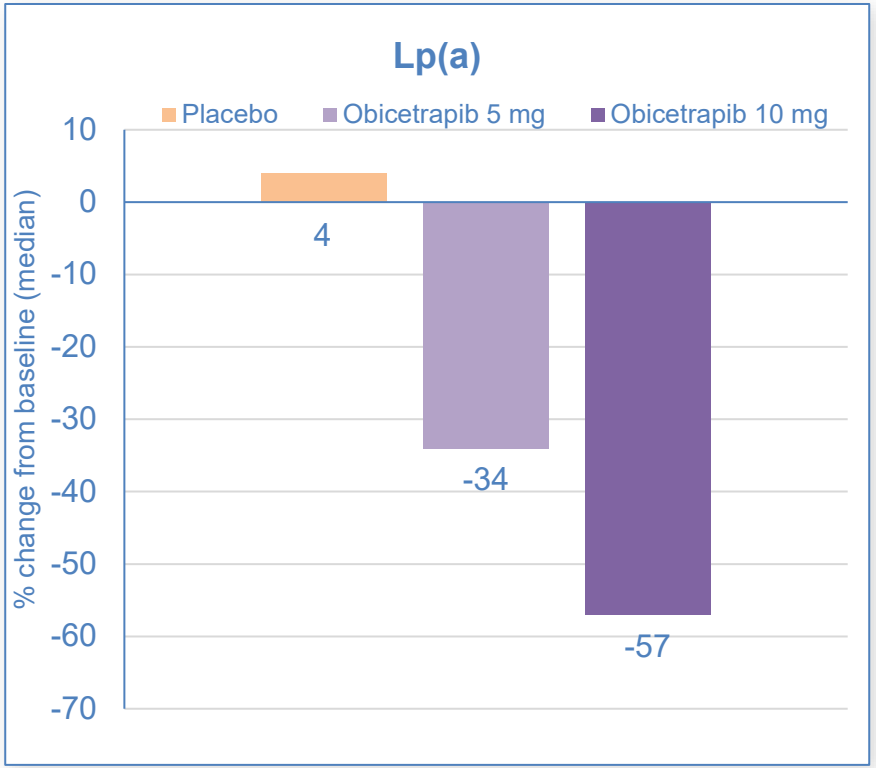
ROSE study: HDL-Cholesterol and ApoA1 increase

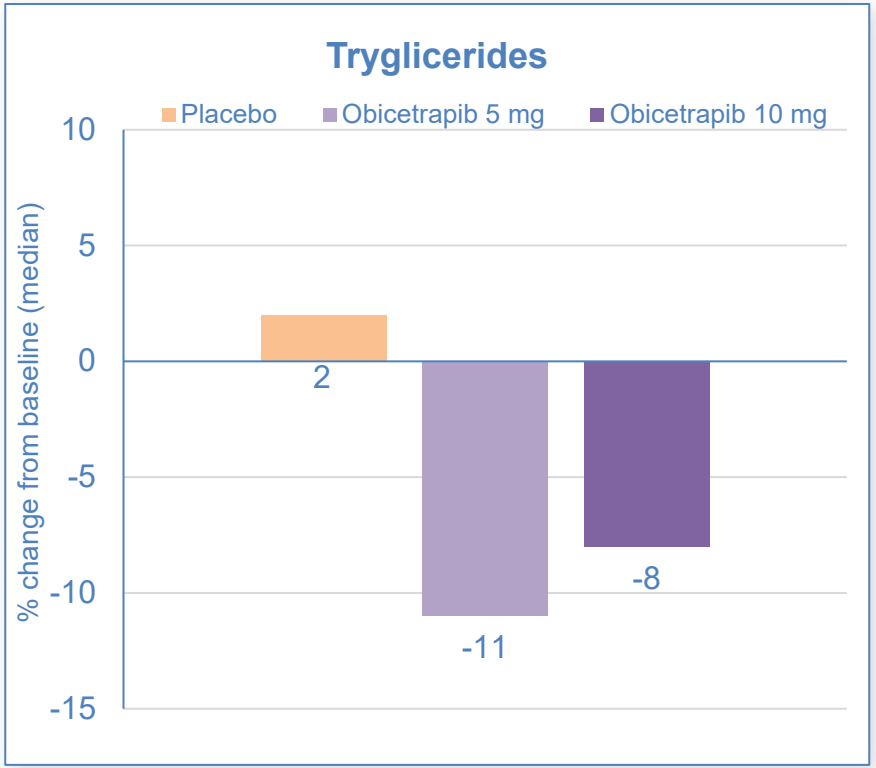




Nicholls SJ et al. Nat Med 2022;28(8):1672-8

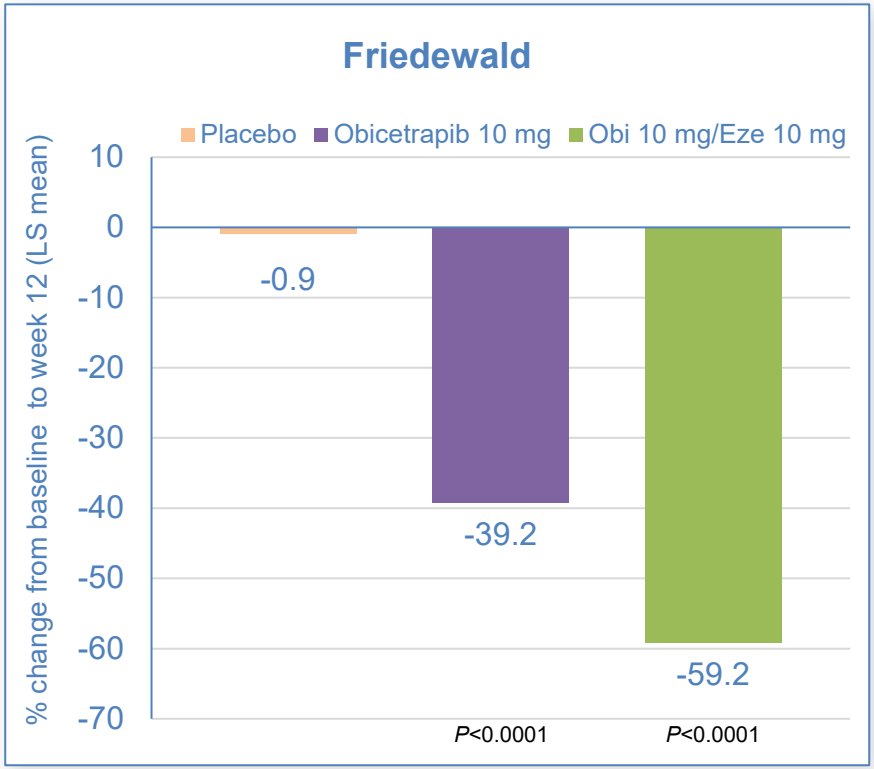
ROSE study: Lipoprotein(a) and Triglyceride Lowering

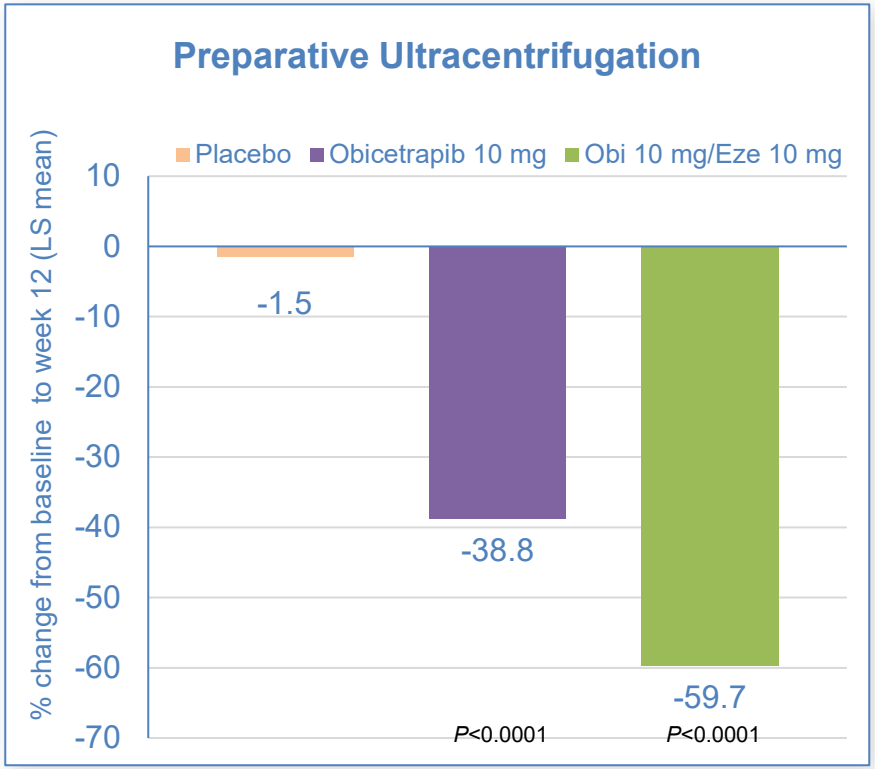




Nicholls SJ et al. Nat Med 2022;28(8):1672-8

Obicetrapib in combination with ezetimibe on top of HIS LDL-C Lowering





ROSE 2; Ballantyne et al. J Clin Lipidol. 2023;17(4):491-503

ROSE: Adverse Events

Adverse events occurring in ≥2 subjects in any treatment arm in the safety population

MedDRA System Organ Class/Preferred Term	Placebo N=40 n (%)	Obicetrapib 5 mg N=40 n (%)	Obicetrapib 10 mg N=40 n (%)
Musculoskeletal and connective tissue disorders	4 (10.0)	4 (10.0)	4 (10.0)
Muscle spasms	2 (5.0)	0	0
General disorders and administration site conditions	4 (10.0)	3 (7.5)	2 (5.0)
Fatigue	2 (5.0)	2 (5.0)	1 (2.5)
Gastrointestinal disorders	4 (10.0)	3 (7.5)	0
Nausea	2 (5.0)	1 (2.5)	0
Nervous system disorders	3 (7.5)	2 (5.0)	2 (5.0)
Investigations	3 (7.5)	2 (5.0)	0
Respiratory, thoracic and mediastinal disorders	3 (7.5)	2 (5.0)	0
Infections and infestations	3 (7.5)	1 (2.5)	0
Injury, poisoning and procedural complications	1 (2.5)	3 (7.5)	1 (2.5)
Metabolism and nutrition disorders	0	2 (5.0)	0
Type 2 diabetes mellitus	0	2 (5.0)	0
Neoplasms benign, malignant and unspecified[a]	2 (5.0)	0	0
Basal-cell carcinoma	2 (5.0)	0	0
Vascular disorders	0	2 (5.0)	0
Hypertension	0	2 (5.0)	0

Nicholls SJ et al. Nat Med 2022;28(8):1672-8

ROSE 2: Treatment Emergent Adverse Events

TEAEs occurring in ≥2 subjects in any treatment arm in the safety population

MedDRA System Organ Class/Preferred Term	Placebo N=40 n (%)	Obicetrapib 10 mg N=39 n (%)	Obi 10 mg/Eze 10 mg N=40 n (%)
Infections and infestations	5 (12.5)	1 (2.6)	4 (10.0)
Urinary tract infection	2 (5.0)	0	1 (2.5)
Gastrointestinal disorders	2 (5.0)	2 (5.1)	4 (10.0)
Nausea	2 (5.0)	0	2 (5.0)
Injury, poisoning and procedural complications	1 (2.5)	3 (7.7)	4 (10.0)
Nervous system disorders	4 (10.0)	3 (7.7)	0
Headache	2 (5.0)	1 (2.6)	0
Investigations[a]	3 (7.5)	1 (2.6)	1 (2.5)
Musculoskeletal and connective tissue disorders	3 (7.5)	0	1 (2.5)
Myalgia	2 (5.0)	0	0
Cardiac disorders	0	3 (7.7)	0

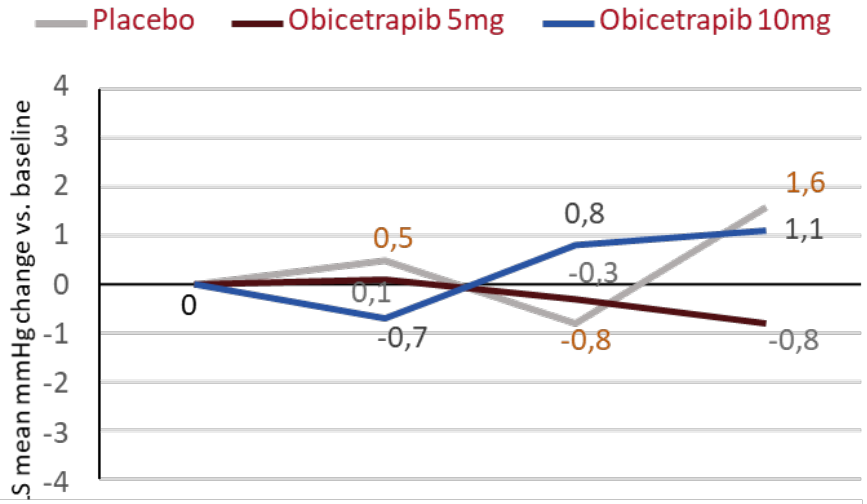
[a]Defined as laboratory tests and other medical investigations that gave an unusual reading.

Ballantyne et al. J Clin Lipidol. 2023;17(4):491-503

Systolic and Diastolic Blood Pressure

Pooled TULIP, OCEAN, ROSE, ROSE2 & TA-8995-203 studies

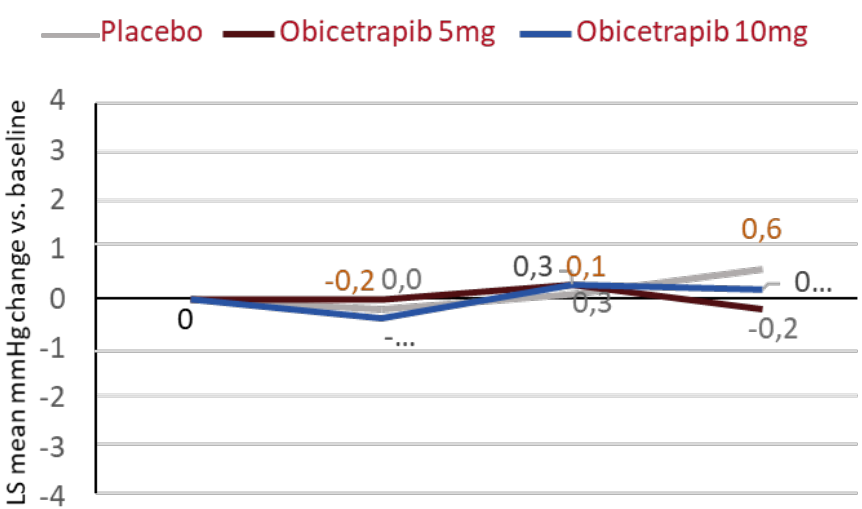
Systolic



	BL	4	8	Week 12
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

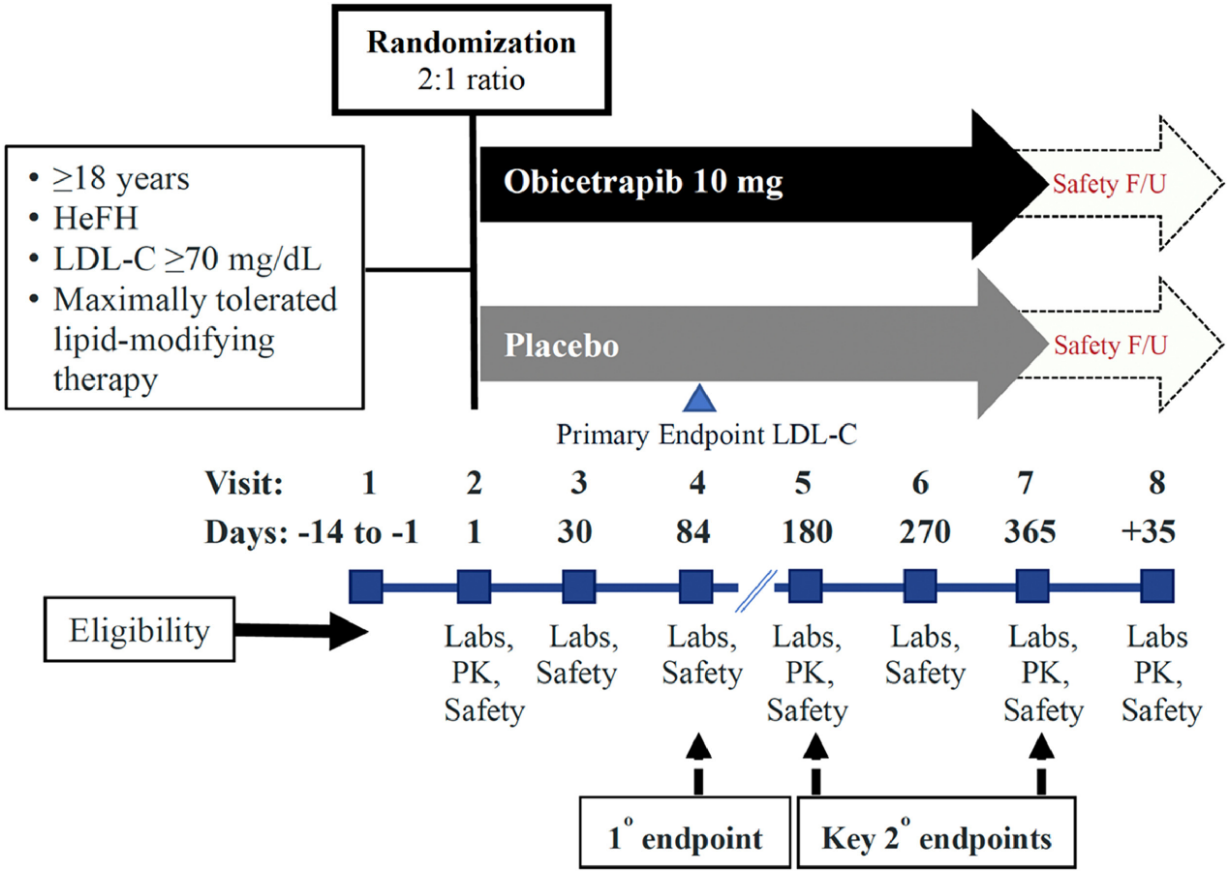


	BL	4	8	Week 12
Placebo (N)	255	248	206	157
Obi 5 mg (N)	160	159	155	63
Obi 10 mg (N)	266	263	181	188

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

1. Hovingh, G. K. et al. Lancet 2015;386:452–60; 2. Ballantyne CM, et al. J Clin Lipidol. 2023;17(4):491-503; 3. Nicholls SJ, et al. Nat Med. 2022;28(8):1672-8; 4. Data on file

Phase 3 BROOKLYN: Obicetrapib in HeFH



N = 354
NCT05425745

Nicholls SJ et al.,
Am Heart J 2024
doi: 10.1016/j.ahj.2024.05.002

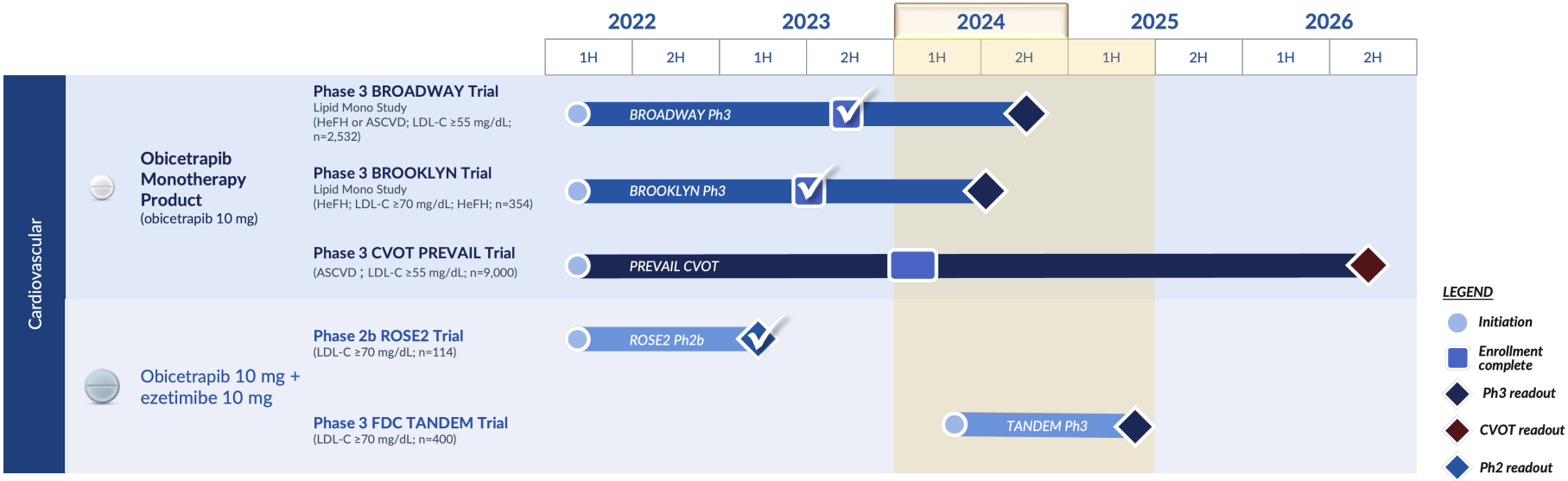
Phase 3 BROOKLYN: top-line results

LDL-C LS mean percentage change:

	% Change from Baseline		Obicetrapib % Change	
	Placebo (n=118)	Obicetrapib (n=236)	Compared to Placebo	p-value
Day 84	+0.3%	-36.1%	-36.3%	<0.0001
Day 365	+10.3%	-31.1%	-41.5%	<0.0001

	Placebo N=118 n (%)	Obicetrapib 10 mg N=234 n (%)	Total N=352 n (%)
Any TEAEs	83 **(70.3)**	149 **(63.7)**	232 **(65.9)**
Any study drug related TEAEs	8 **(6.8)**	10 **(4.3)**	18 **(5.1)**
Any TEAEs leading to discontinuation of study drug	8 **(6.8)**	10 **(4.3)**	18 **(5.1)**
Any TESAEs	8 **(6.8)**	13 **(5.6)**	21 **(6.0)**

Obicetrapib projected clinical studies



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.

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VIELEN DANK