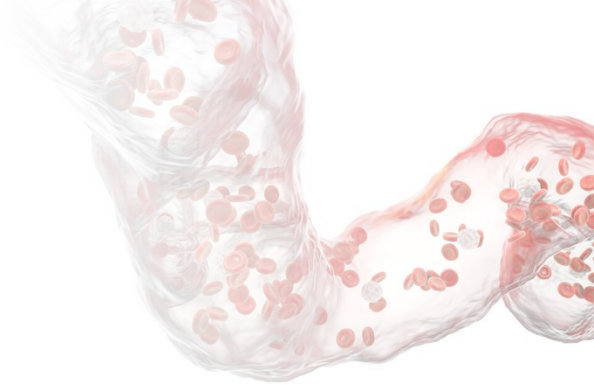

rose^2

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

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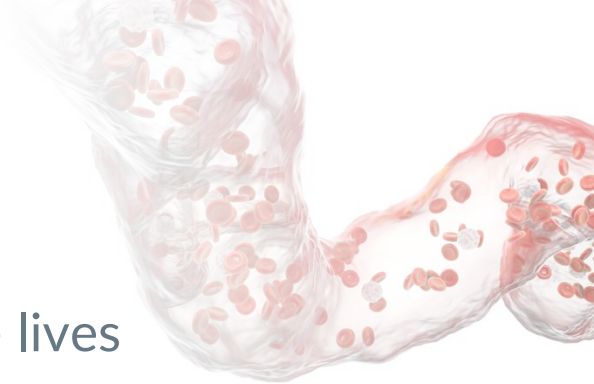
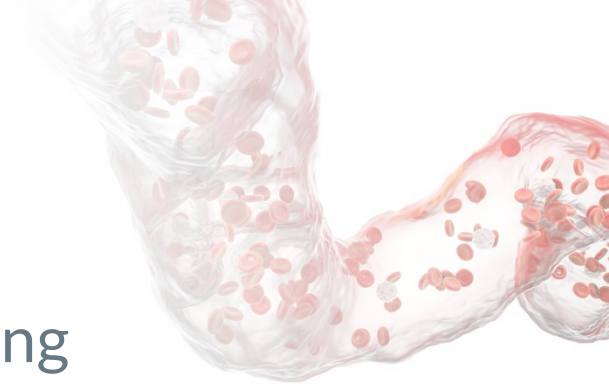
Rationale



- Cardiovascular disease is a leading cause of death worldwide, claiming more lives than cancer and chronic respiratory disease
- CVD deaths in the United States is on the rise increasing from 784,454 in 2010 to 928,741 in 2020
- The 2022 ACC Expert Consensus recommends that adults with ASCVD at very high risk on statin therapy:
  - Reduce LDL-C ≥50% on maximally tolerated statin therapy AND
  - Target an LDL-C goal <55 mg/dL
- Less than 25% of ASCVD patients are on high-intensity statin therapy (HIS), and less than 25% of these patients have an LDL-C level <70 mg/dL. As a result, there is an ongoing need for effective, safe, convenient therapies that serve as an adjunct to HIS

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)

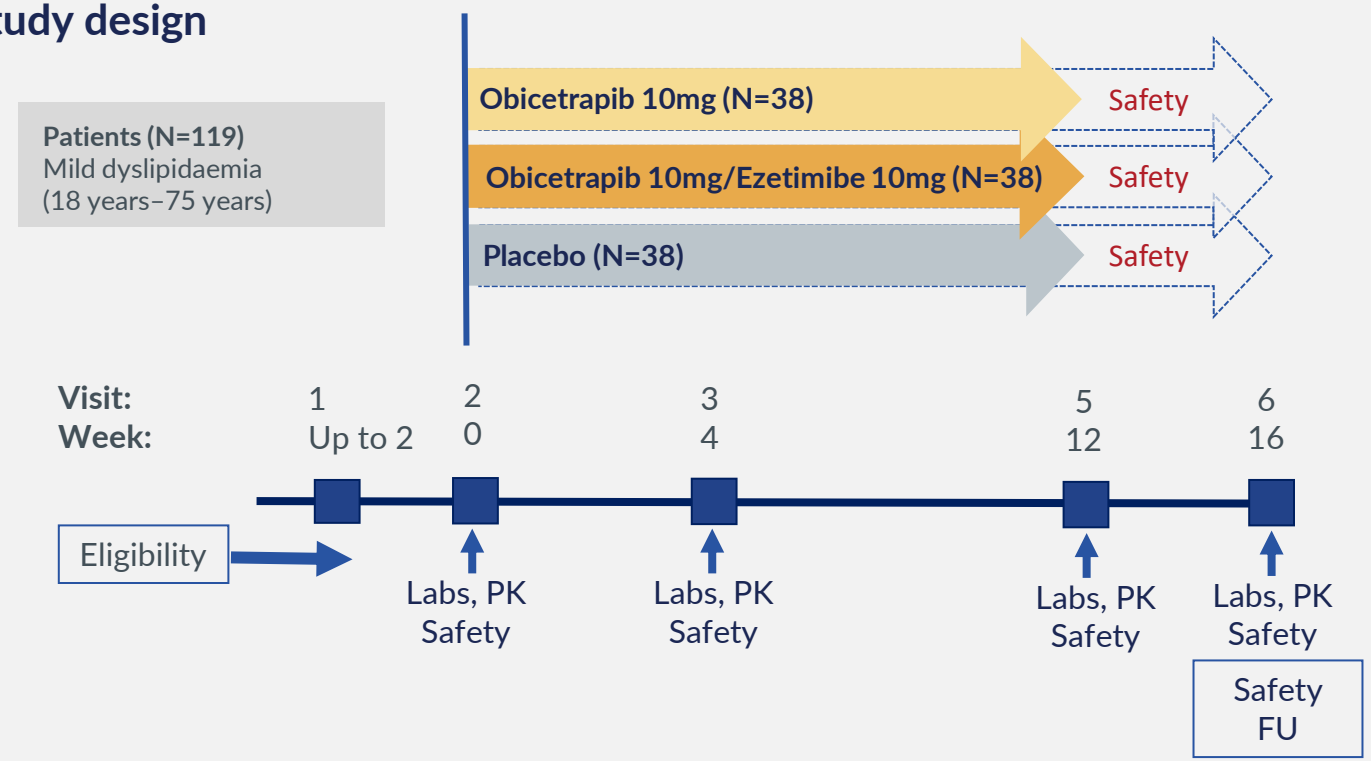
Exclusion criteria

- 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



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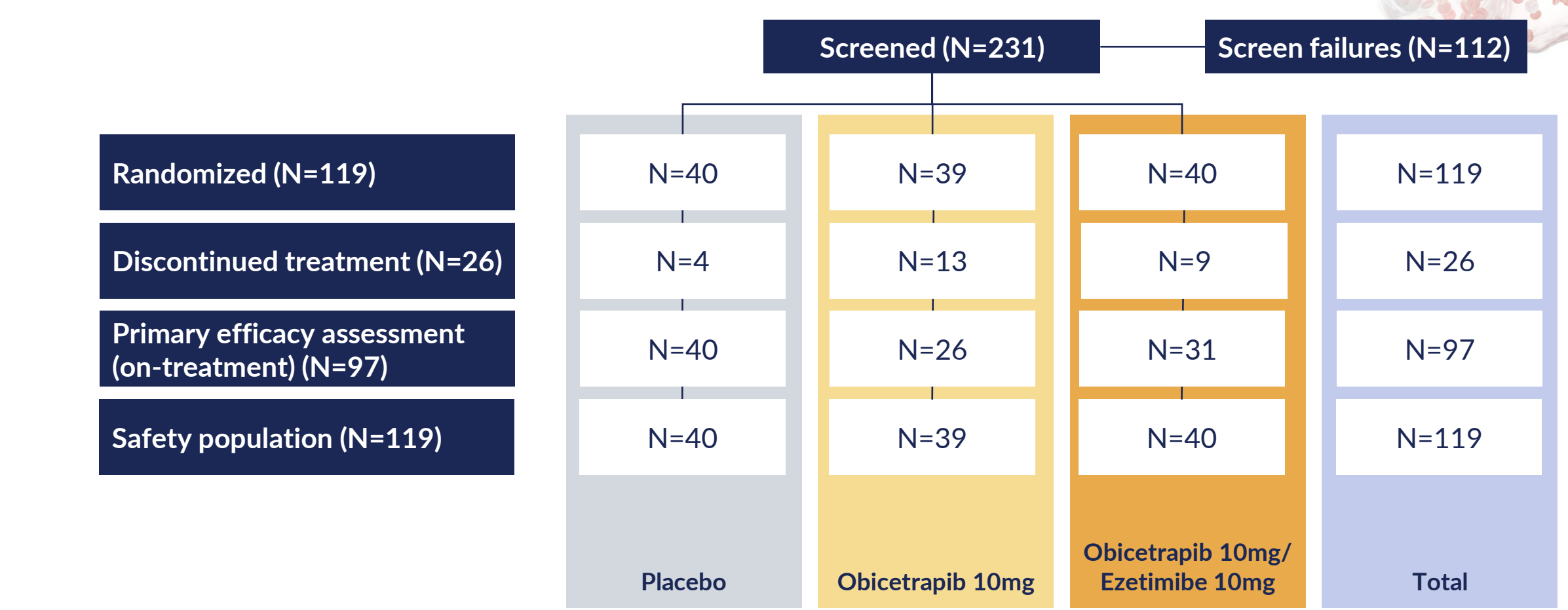
Patient disposition



Baseline characteristics

		Placebo N=40 (%)	Obicetrapib 10mg N=26 (%)	Obicetrapib 10mg/ Ezetimibe 10mg N=31 (%)
	Mean Age (years)	60.6	64.8	63.5
	Female %	35	34.6	38.7
	Mean BMI (kg/m^2)	30.8	29.9	31.8
Race %	White	75	88.5	93.5
	Black/African American	22.5	11.5	6.5
Statin use %	Atorvastatin 40mg/80mg	75	69.2	80.6
	Rosuvastatin 20mg/40mg	25	30.8	19.4
Baseline level (median)	LDL-C (mg/dL)	95	100	87
	HDL-C (mg/dL)	42.5	47	46

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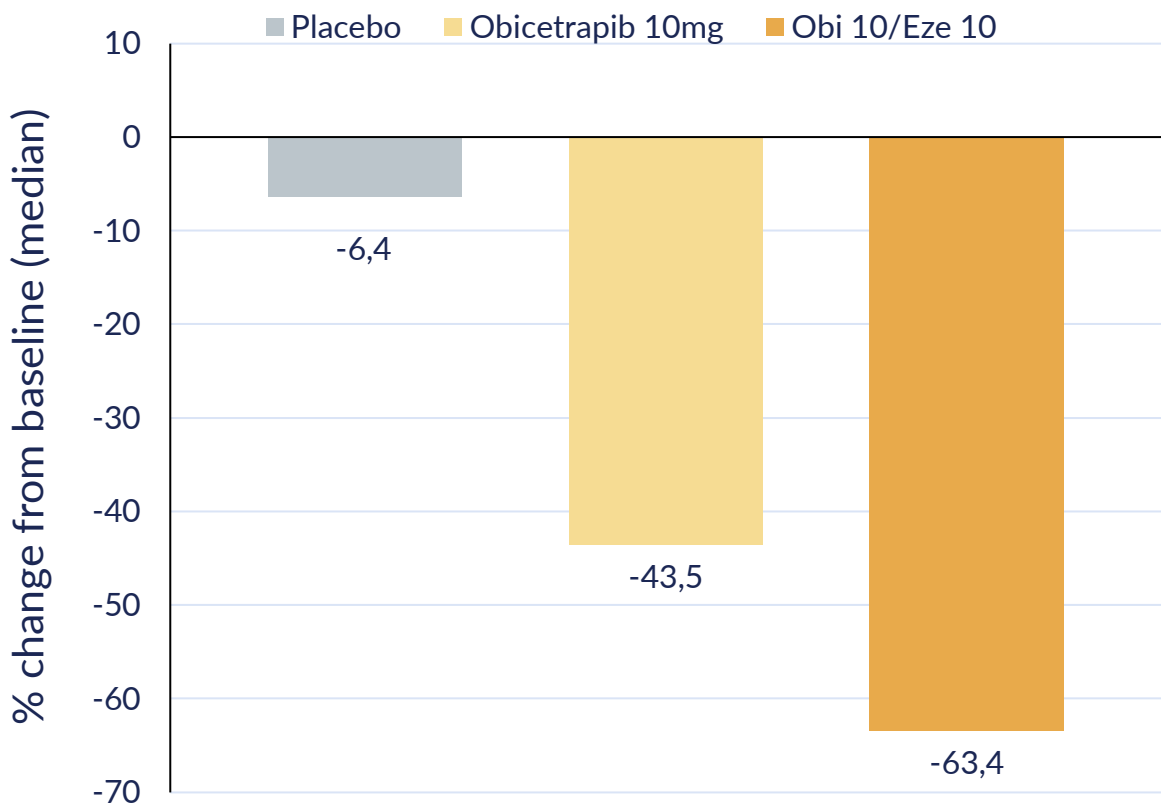
LDL-C in mg/dL and percent change from baseline



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

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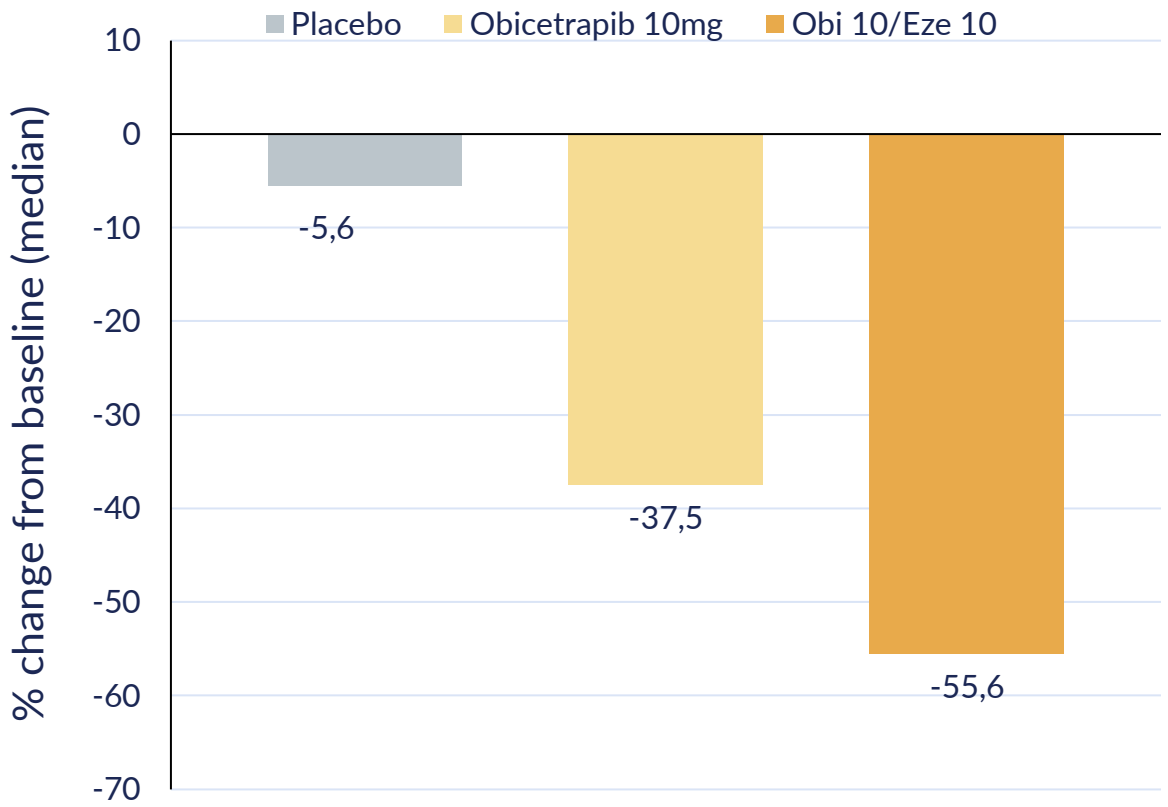
Non-HDL-C in mg/dL and percent change from baseline



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

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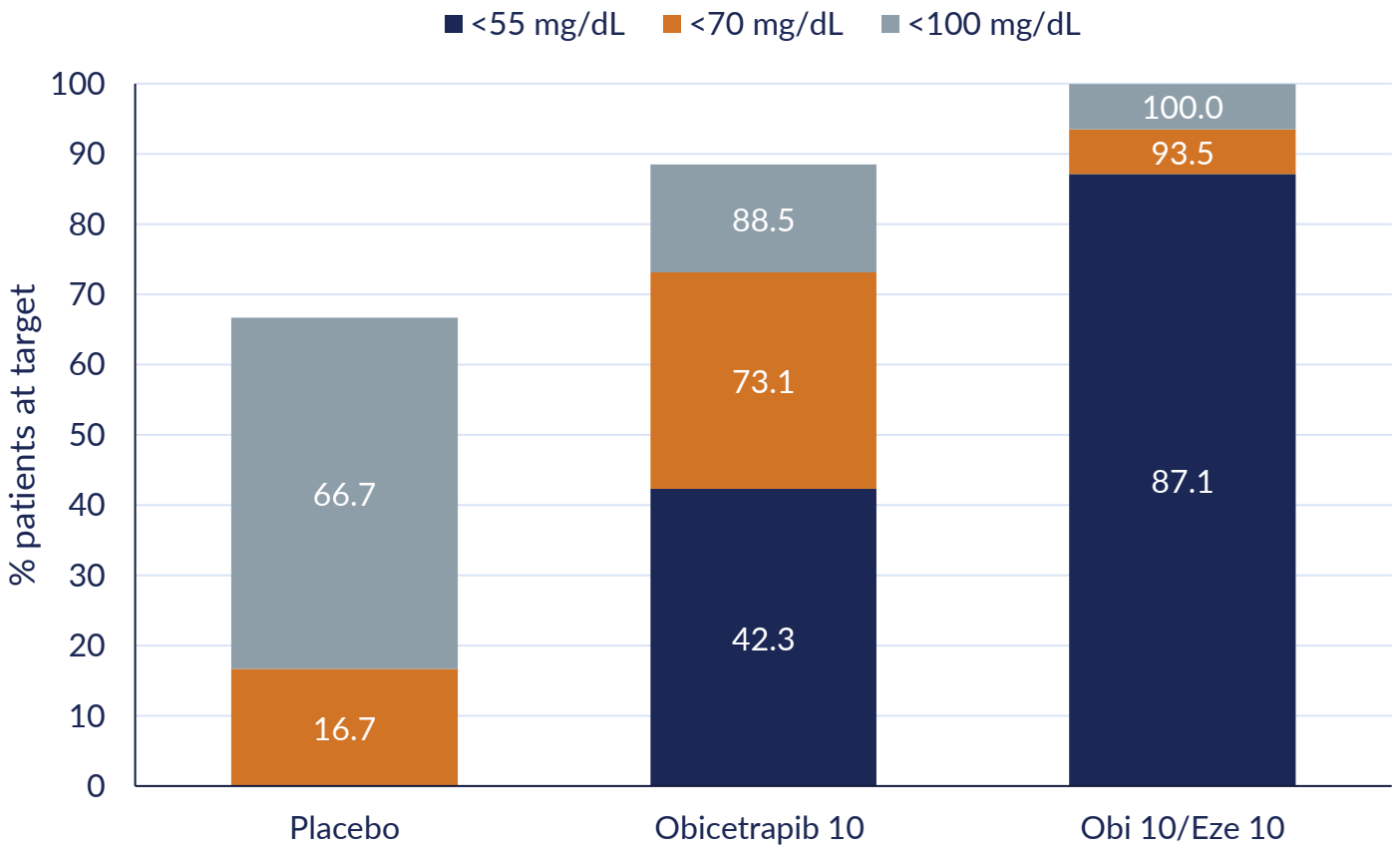
LDL-C target attainment



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

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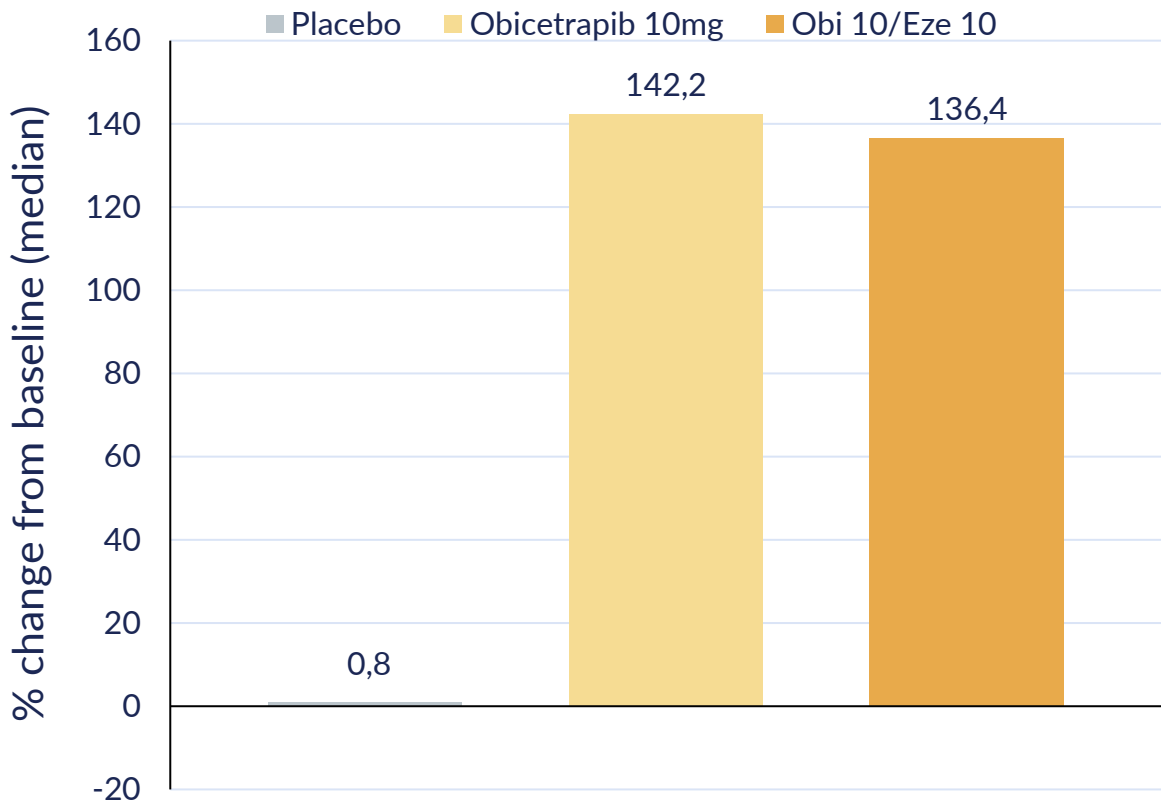
HDL-C in mg/dL and percent change from baseline



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

Time	Placebo	Obicetrapib 10mg	Obi 10/Eze 10
Baseline Median	42.5 (31, 68) (N=40)	47.0 (28, 111) (N=26)	46.0 (26, 76) (N=31)
EoT Median	44.5 (28, 83) (N=36)	120.5 (58, 185) (N=26)	112.0 (52, 184) (N=31)
% Change from Baseline (median)	0.8 (-33.3, 45) (N=36)	142.2 (34.9, 310.7) (N=26)	136.4 (46.5, 261.3) (N=31)

% change from baseline LS mean (95% CI)	-0.32 (-13.66, 13.01)	150.80 (134.62, 166.99)	146.60 (129.16, 158.04)
P-value	-	<0.0001	<0.0001

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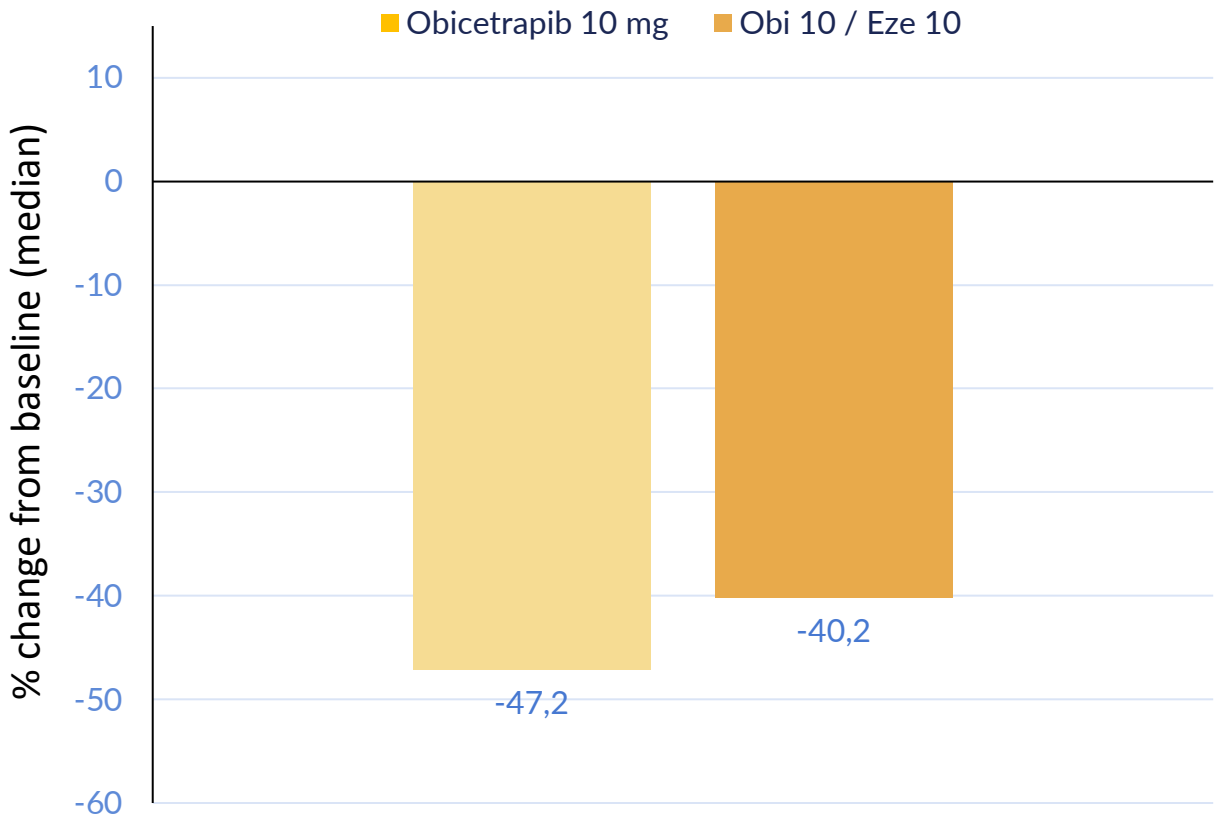
Lp(a) in nmol/L & percent change from baseline



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)

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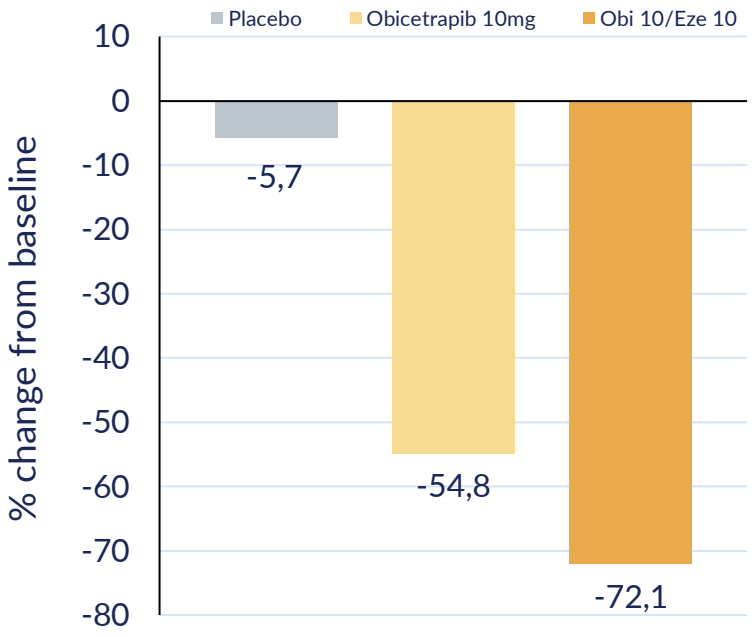
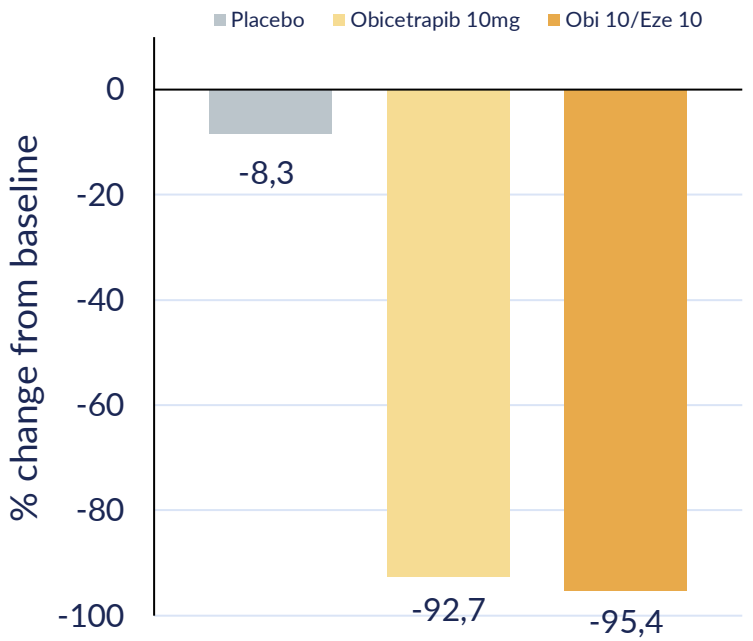
Total, small LDL particles and LDL-particle size percent change from baseline

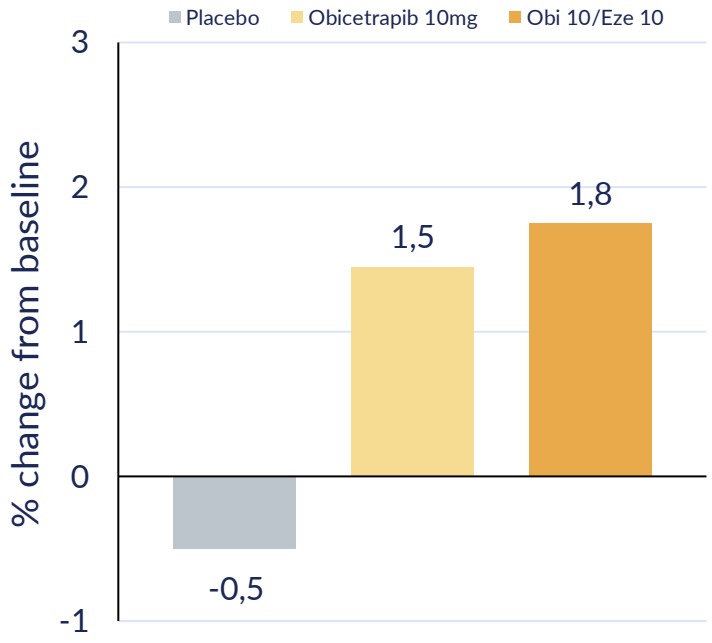
Total LDL Particles



Small LDL Particles



LDL Particle Size



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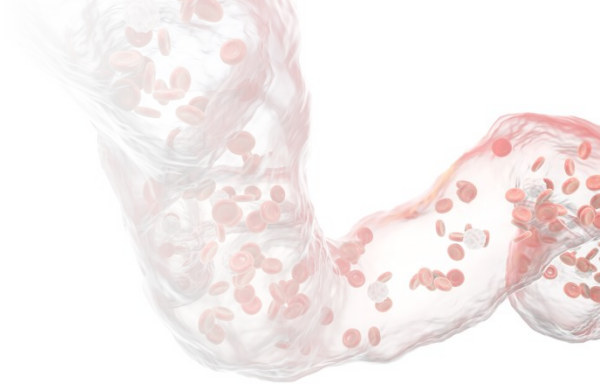
Lipoprotein fractionation, NMR



NMR Relative Risk

Lipoprotein fractionation	Optimal	Moderate	High
LDL-P (nmol/L)	<935	935-1816	>1816
Small LDL (nmol/L)	<467	467-820	>820
LDL Size (nm)	>20.5	N/A	≤20.5

NMR=neuro magnetic resonance.

ROSE2 Results

Placebo	Obi 10	Obi 10/Eze 10
947	435	286
662	52	34
20.3	21.0	21.0

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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.

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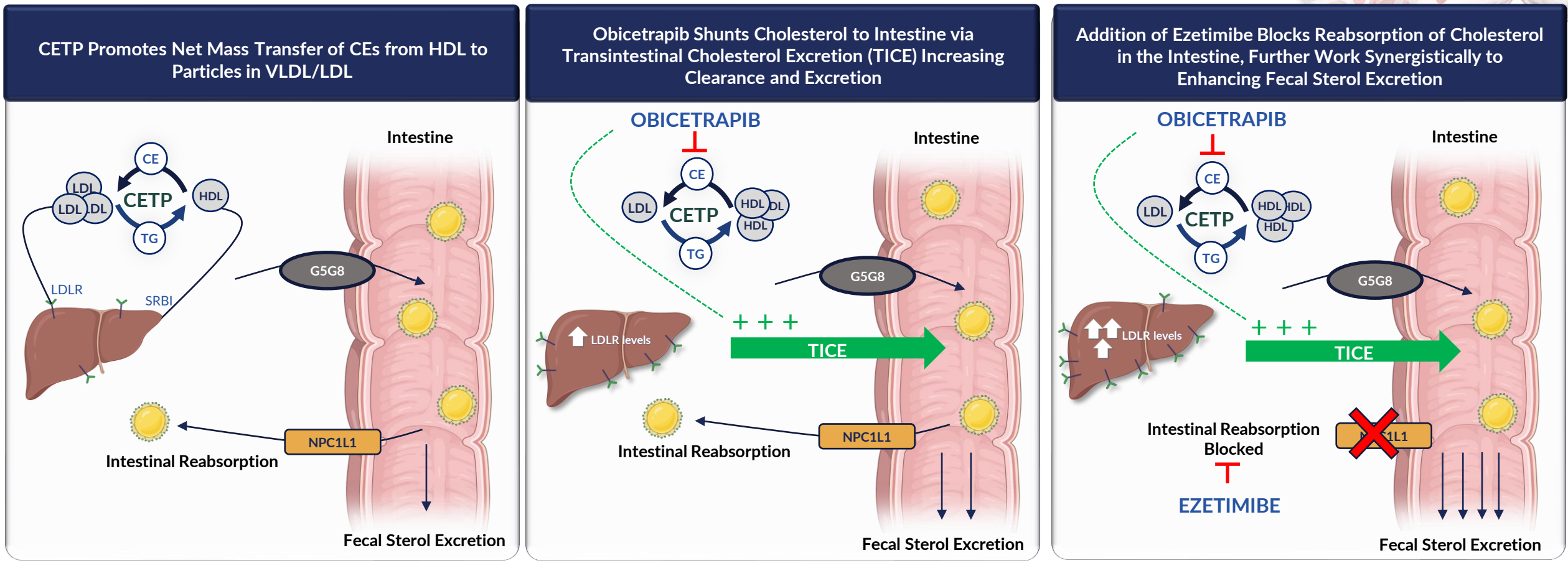
Source: Ballantyne CM, et al. J. of Clinical Lipidology 2023 (to be published June 3, 2023)

NPC1L1 inhibition with ezetimibe potentially resulting in increased net sterol clearance



- CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; MOA, mechanism of action; NPC1L1, Niemann-Pick C1-Like 1; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; TG, triglyceride; VLDL, very low-density lipoprotein.
- NewAmsterdam Pharma Data on File.

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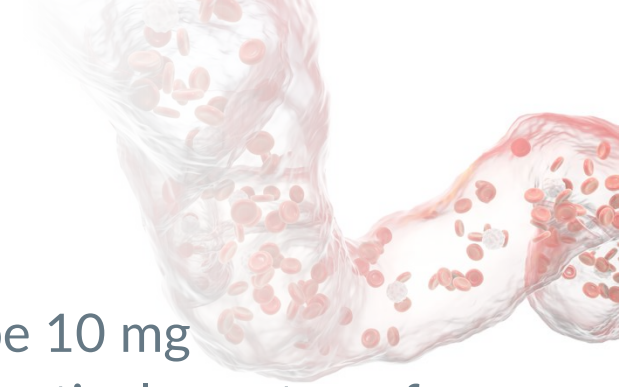
Conclusions



- 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

Publication now available in JCL

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JID: JACL [mNS;May 25, 2023;18:31]

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Journal of Clinical Lipidology

Original Research

Obicetrapib plus Ezetimibe as an adjunct to high-intensity statin therapy: A randomized phase 2 trial

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