Fixed-dose Combination of Obicetrapib and Ezetimibe for Reduction of LDL-Cholesterol (TANDEM Trial)

A Phase 3 Randomised, Double-Blind, Placebo-Controlled Trial

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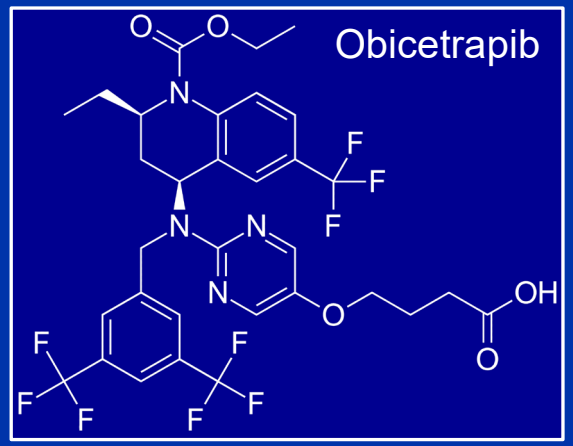
Disclosure

Clinical Trials: AbbVie, Arrowhead, AstraZeneca, Bristol Myers Squibb, Crispr Therapeutics, Eli Lilly, Esperion, Kardigan, Medtronic, New Amsterdam Pharma, Novartis, and Silence Therapeutics. Companies are directed to pay any honoraria, speaking or consulting fees directly to charity

Background

- Reducing low density lipoprotein (LDL) cholesterol is the cornerstone for cardiovascular prevention.
- Despite the availability of multiple classes of drugs, many ASCVD patients do not achieve target LDL cholesterol levels.
- Obicetrapib is an orally administered, selective CETP inhibitor that significantly reduced LDL cholesterol in phase 2 studies
- The phase 3 TANDEM trial assessed the fixed dose combination (FDC) of obicetrapib with ezetimibe in participants with elevated LDL-cholesterol despite maximally tolerated lipid lowering therapies.

Tandem Trial Randomisation and End Points

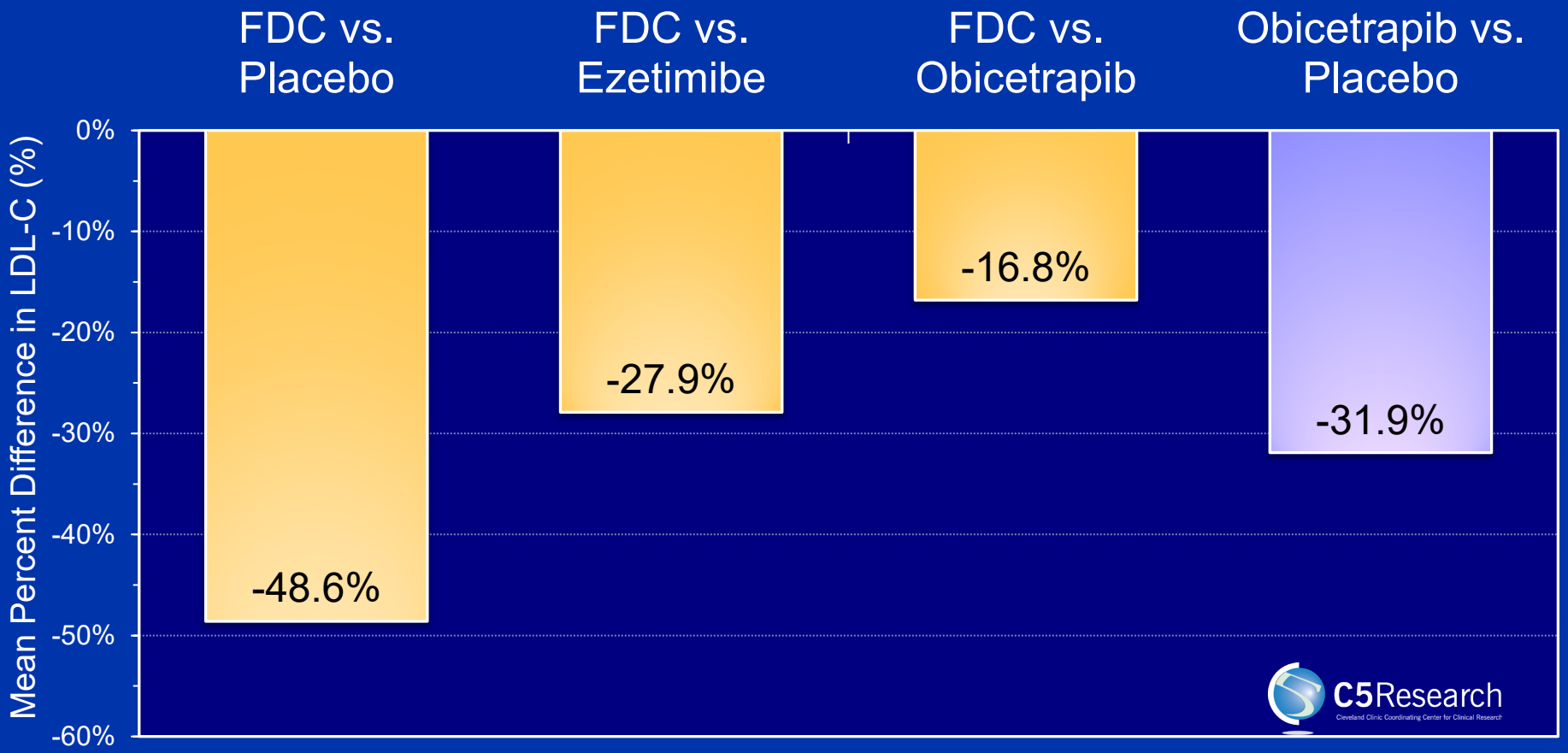


- 407 participants with preexisting ASCVD, HeFH or multiple risk factors with LDL-C >1.8 mmol/L on maximum tolerated therapy.
- Participants randomised 1:1:1:1 to placebo, ezetimibe 10 mg, obicetrapib 10 mg, or FDC.
- LDL-C measured by ß quantification after ultracentrifugation.
- Multiplicity-controlled primary end points: Percent change in LDL-C, baseline to day 84 for FDC compared with 1) placebo 2) ezetimibe 3) obicetrapib and 4) obicetrapib monotherapy vs. placebo

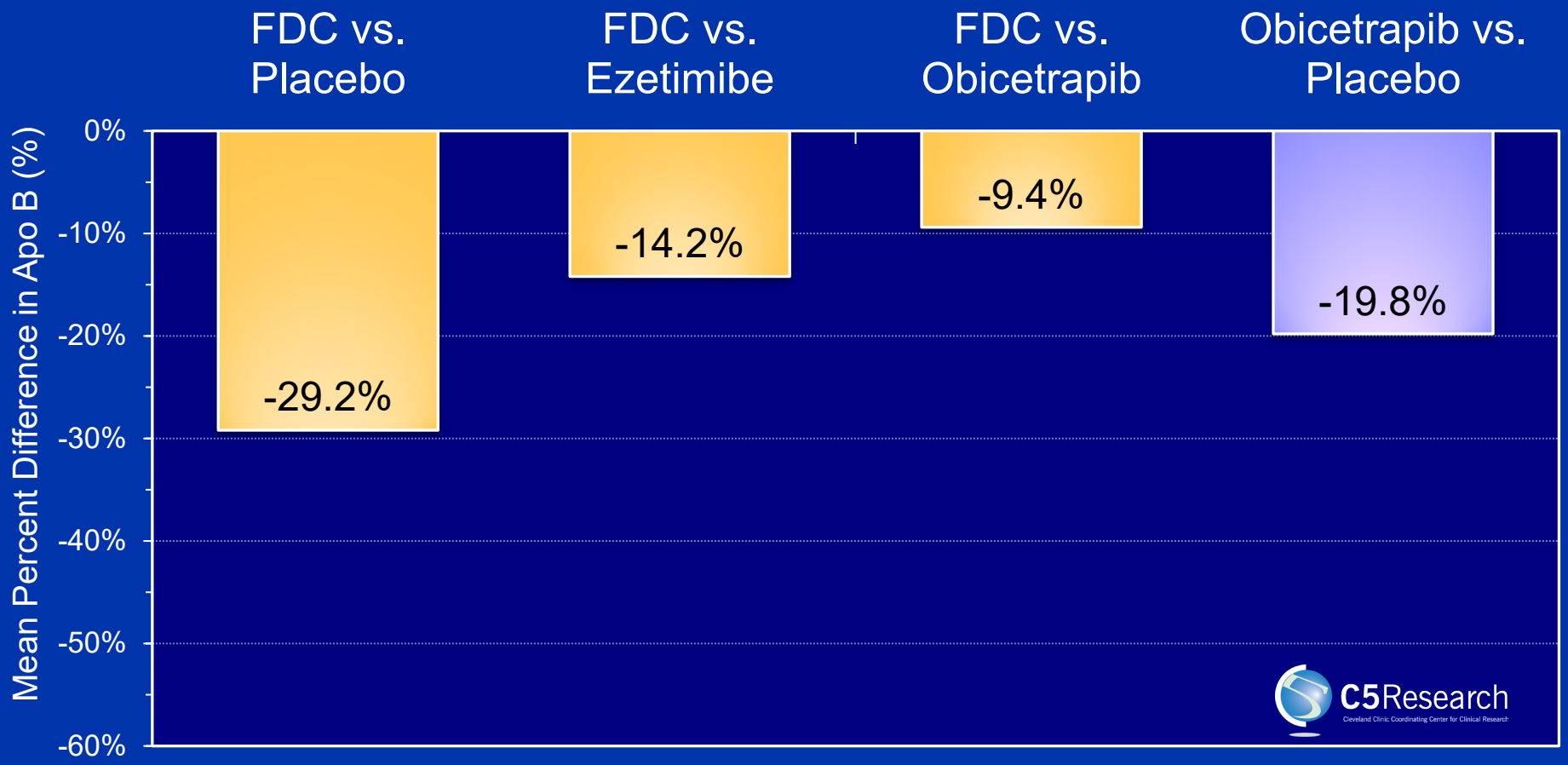
Selected Baseline Characteristics of Participants

	Placebo (N=102)	Ezetimibe 10 mg (N=101)	Obicetrapib 10 mg N=102)	Fixed Dose Combination (N=102)
Median age (years)	67.5	68.0	67.0	68.0
Male	50%	55%	68%	53%
White (%)	82%	81%	83%	84%
Mean LDL-C (mmol/L)	2.5	2.6	2.5	2.3
Statin use	91%	92%	85%	89%
High Intensity statin	73%	70%	65%	61%
Preexisting ASCVD	64%	66%	75%	71%

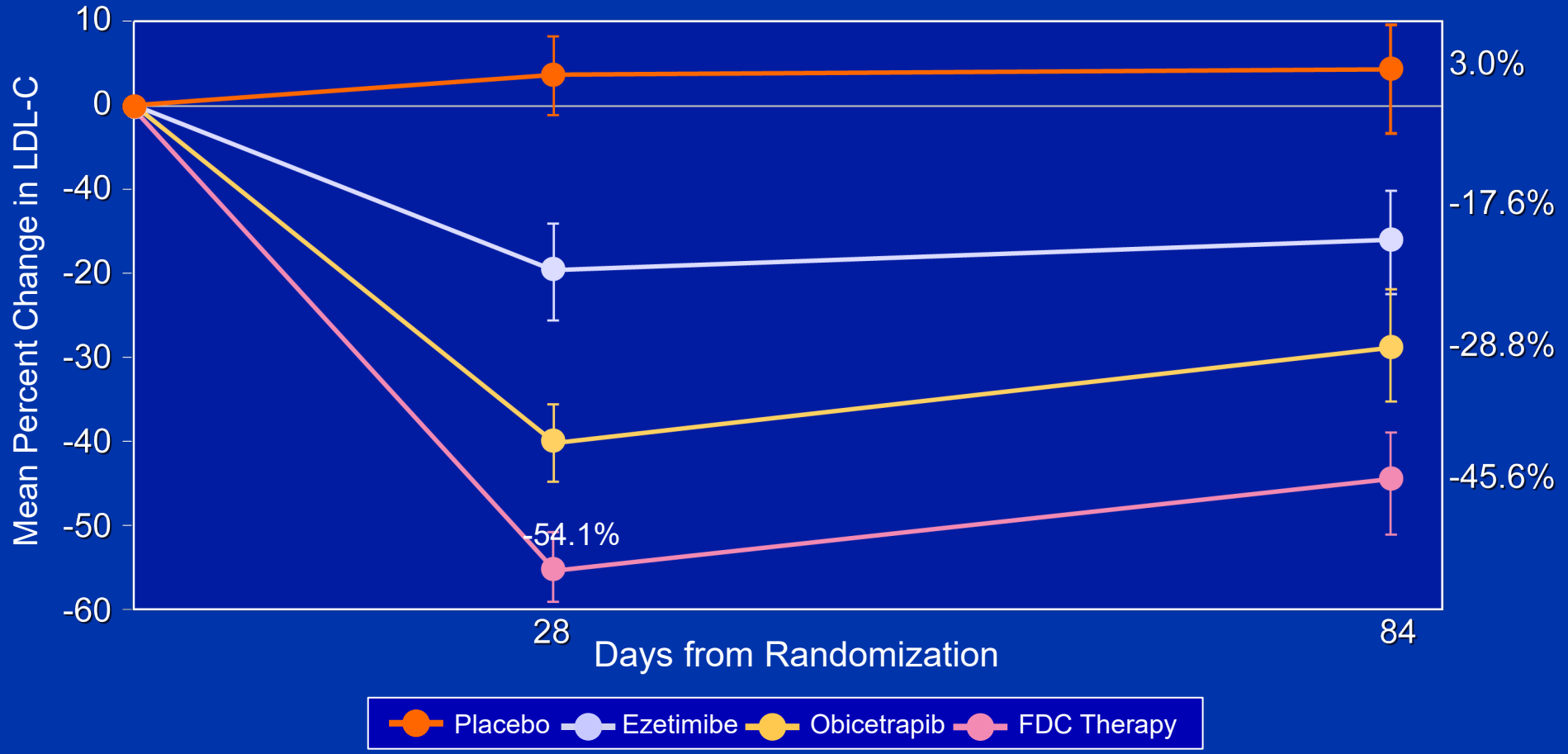
Least Square Mean Difference in LDL-C at Day 84



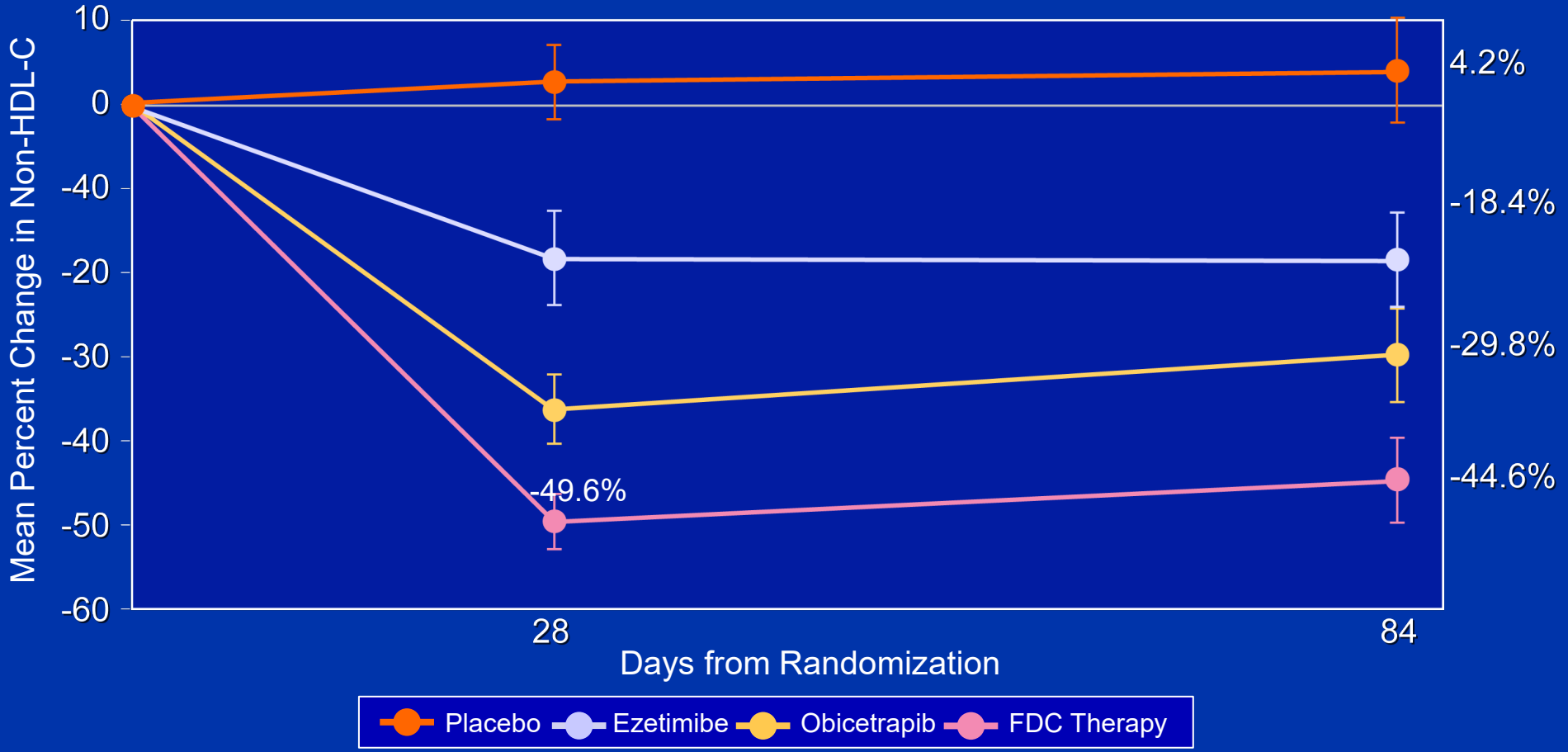
Least Square Mean Difference in Apo B at Day 84



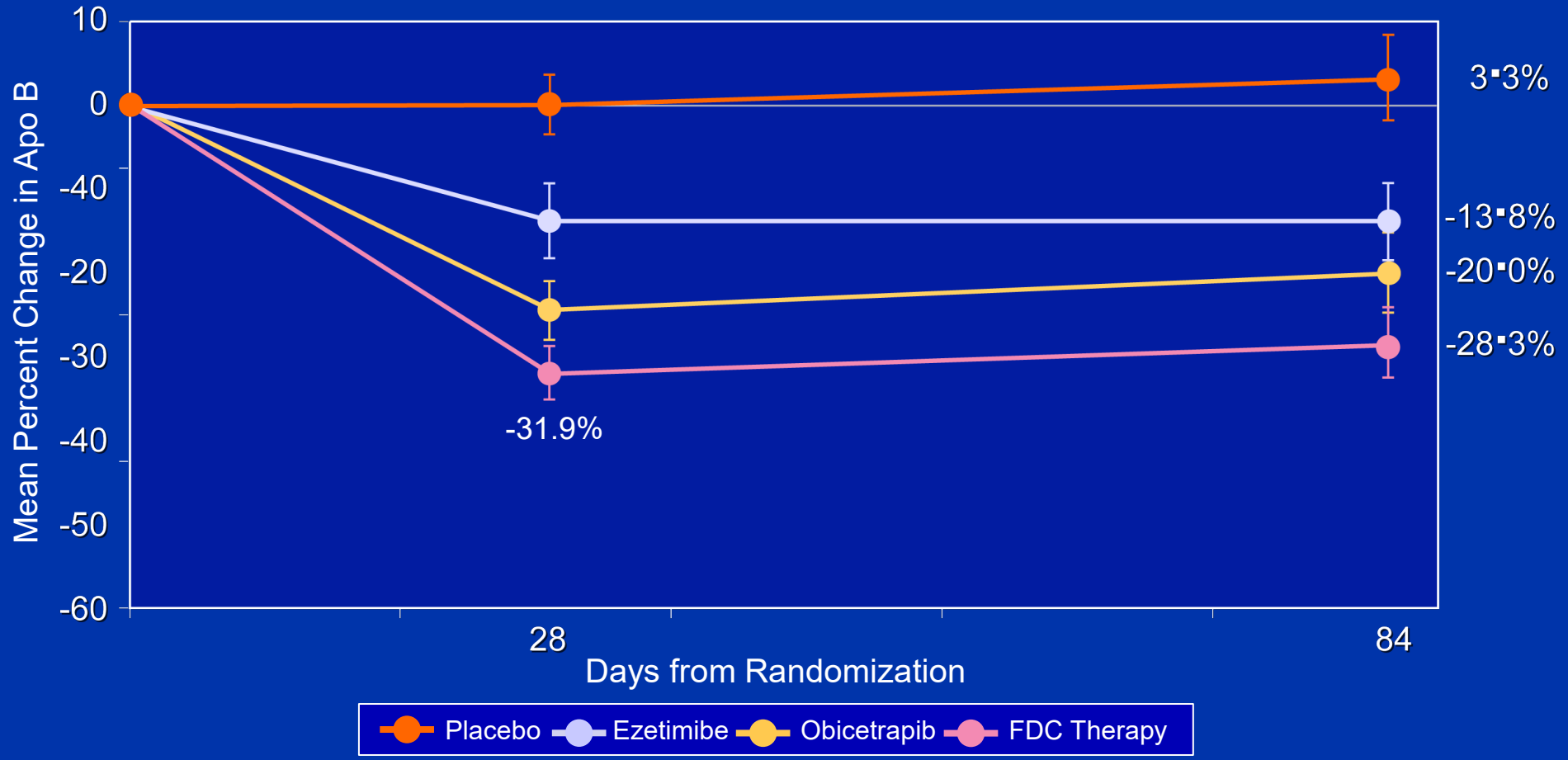
Mean Percent Change in LDL-Cholesterol over Time



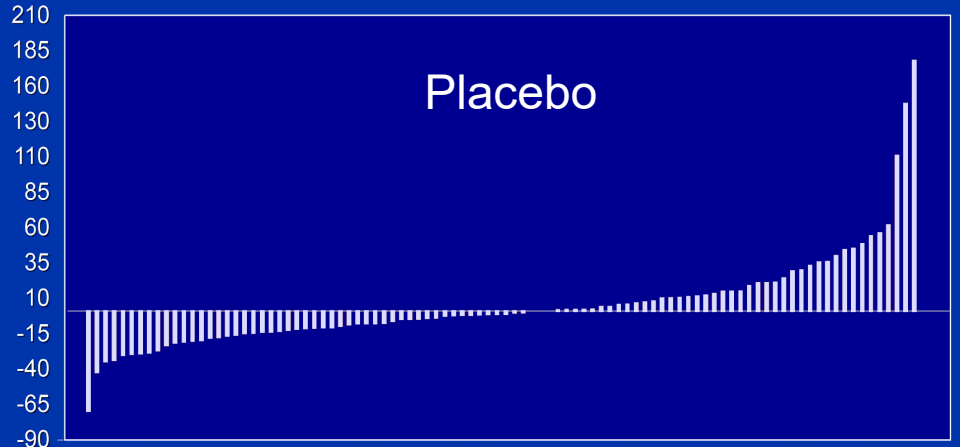
Mean Percent Changes in Non-HDL-C over Time

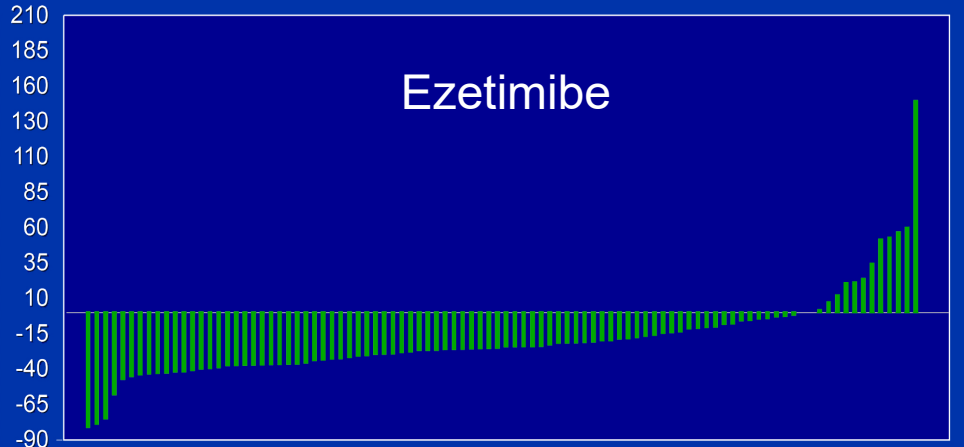


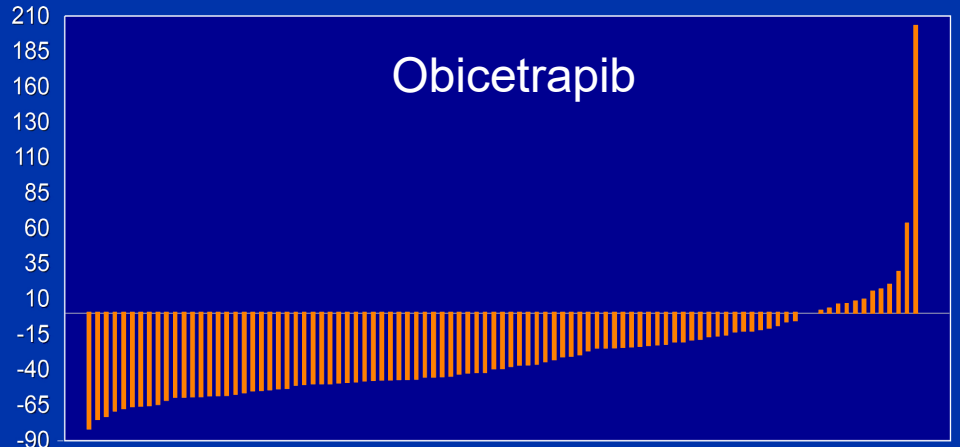
Mean Percent Change in Apolipoprotein B over Time

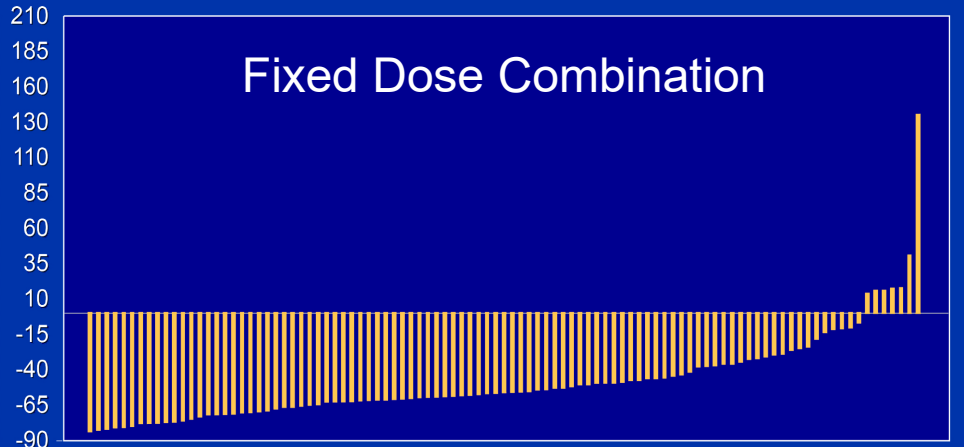


Waterfall Plots: Percent Change in LDL-Cholesterol

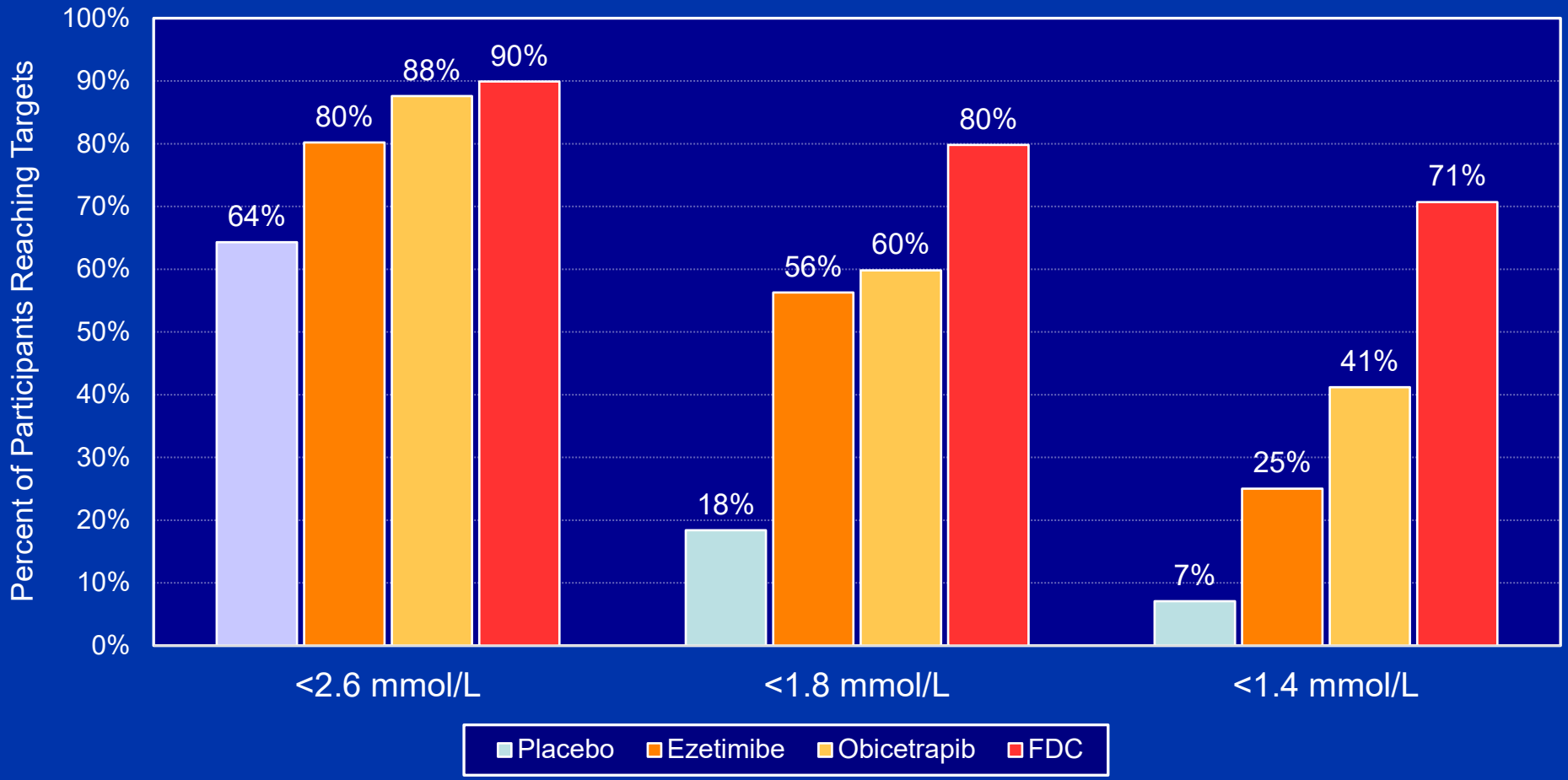




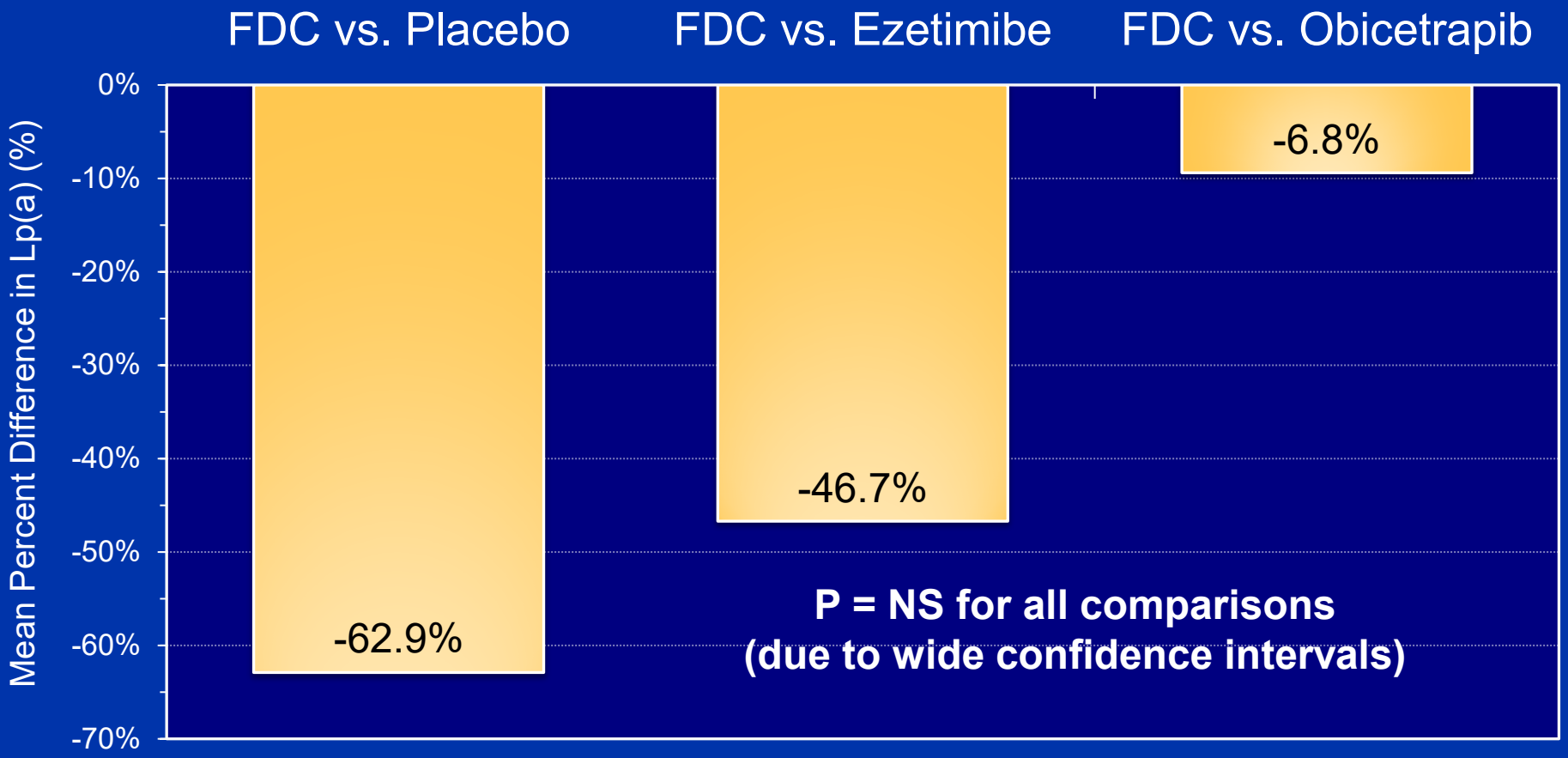




Attainment of LDL-Cholesterol Targets with Therapies



LS Mean Change in Lipoprotein(a): Baseline to Day 84



Adverse Events and Laboratory-Related Safety Findings

	Placebo	Ezetimibe	Obicetrapib	FDC
Any adverse events (AE)	37%	53%	54%	51%
Trial agent related AE	4%	3%	7%	3%
AE leading to treatment withdrawal	4%	7%	9%	5%
Death	0	1%	1%	1%
Increased anti-HTN Therapy	2%	0	4%	5%
Decrease Renal function	5%	6%	5%	7%
Macular Degeneration	0	0	0	0
ALT or AST > 3x ULN	0	1%	2%	0
CK > 5X ULN	0	0	1%	%

Limitations

- The trial was short with a follow up period of 84 days. The Broadway trial provides longer term data out to 365 days.
- The trial enrolled mostly White participants with only 14.5% Black participants.
- Cardiovascular events were not systematically collected but will be assessed in the ongoing 9000 patient PREVAIL trial.

Conclusions

- In participants with LDL-C ≥ 1.8 mmol/L despite maximally tolerated treatment, the fixed dose combination (FDC) of obicetrapib and ezetimibe was well-tolerated during 84 days.
- The FDC reduced LDL cholesterol by nearly 50% with more than 70% of participants achieving levels below 1·4 mmol/L.
- If approved, this fixed dose combination will provide a potentially valuable oral option for treatment of elevated LDL-C in patients on maximally tolerated lipid lowering therapy.

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Summary

Background Reducing LDL cholesterol prevents atherosclerotic cardiovascular disease (ASCVD) events. The aim of this study was to evaluate the LDL cholesterol-lowering efficacy of a fixed-dose combination (FDC) of obicetrapib, a CETP inhibitor, and ezetimibe.

Methods This randomised, double-blind trial across 48 US sites including hospitals, private and group practices, and independent research centres included participants at least 18 years old with pre-existing or high risk for ASVCD or heterozygous familial hypercholesterolaemia with LDL cholesterol concentrations of 1·8 mmol/L (70 mg/dL) or greater despite maximally tolerated lipid-lowering therapy excluding ezetimibe, or having statin intolerance. Participants were randomly assigned (1:1:1:1) to obicetrapib 10 mg plus ezetimibe 10 mg FDC, obicetrapib 10 mg

A Final Thought

Despite the availability of several classes of therapeutic agents that lower LDL cholesterol, a substantial fraction of patients do not achieve target levels with existing therapies.

The fixed dose combination of obicetrapib and ezetimibe offers the potential for an oral therapy that may allow more patients to be treated to goal, support the use of combination therapy for lipid lowering, and add an important additional option to the current therapeutic armamentarium.