Safety and Efficacy of Obicetrapib in Patients with Heterozygous Familial Hypercholesterolemia

Stephen J. Nicholls, Adam J. Nelson, Marc Ditmarsch, John J.P. Kastelein, Christie M. Ballantyne, Kausik K. Ray, Ann Marie Navar, Steven E. Nissen, Anne C. Goldberg, Liam R. Brunham, Erin Wuerdeman, Annie Neild, Douglas Kling, Andrew Hsieh, Brian A. Ference, Ulrich Laufs, Maciej Banach, Roxana Mehran, Alberico L. Catapano and Michael H. Davidson

MONASH University

MONASH VICTORIAN HEART INSTITUTE

Monash Health Heart

NewAmsterdam Pharma

Disclosures

- Research support: AstraZeneca, Amgen, Anthera, Eli Lilly, Esperion, Novartis, Cerenis, The Medicines Company, Resverlogix, InfraReDx, Roche, Sanofi-Regeneron and LipoScience

- Consulting and honoraria: AstraZeneca, Akcea, Eli Lilly, Anthera, Omthera, Merck, Takeda, Resverlogix, Sanofi-Regeneron, CSL Behring, Esperion, Boehringer Ingelheim, Cyclarity, Daiichi Sankyo, CSL Seqirus, Vaxxinity

Background

- Heterozygous familial hypercholesterolemia (HeFH) is associated with an increased risk of premature CVD.
- Many patients with HeFH fail to achieve LDL-C targets despite use of existing lipid lowering therapies.
- Obicetrapib is a cholesteryl ester transfer protein (CETP) inhibitor which reduces atherogenic lipid parameters and raises HDL-C when added to statins.

Objective

To evaluate the efficacy, safety and tolerability of obicetrapib, as an adjunct to maximally tolerated lipid-modifying therapies, in patients with HeFH and suboptimal LDL-C control.

Study Design

Main Inclusion Criteria

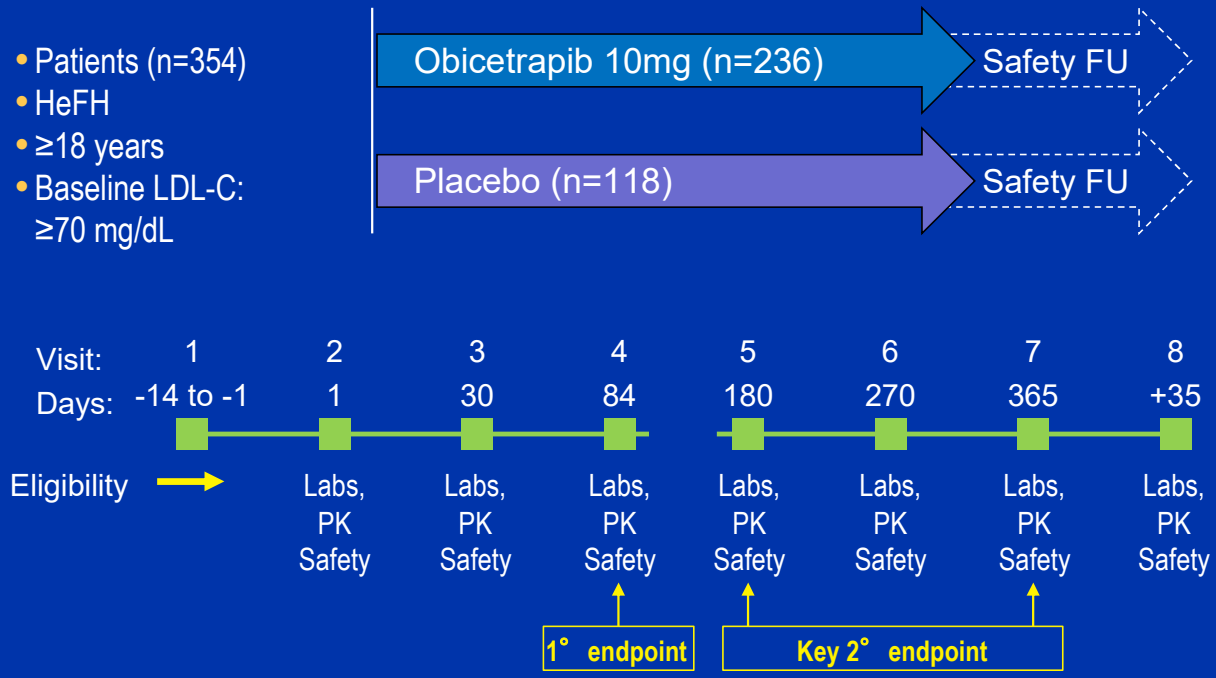
- HeFH diagnosed by
  - Genetic confirmation
  - WHO criteria / Dutch Clinical Network
  - Simon Broome criteria
- On maximally tolerated lipid lowering therapy
- LDL-C ≥ 70mg/dL
- TG ≤ 400mg/dL

Exclusion Criteria

- CV event in the last 3 months
- HoFH
- Uncontrolled hypertension

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

- Patients (n=354)
- HeFH
- ≥18 years
- Baseline LDL-C: ≥70 mg/dL



Primary endpoint: percent change in LDL-C from baseline to day 84
Secondary endpoints: change in LDL-C at day 365 and changes in other lipid parameters and percent of patients achieving a LDL-C <100 mg/dL at day 84

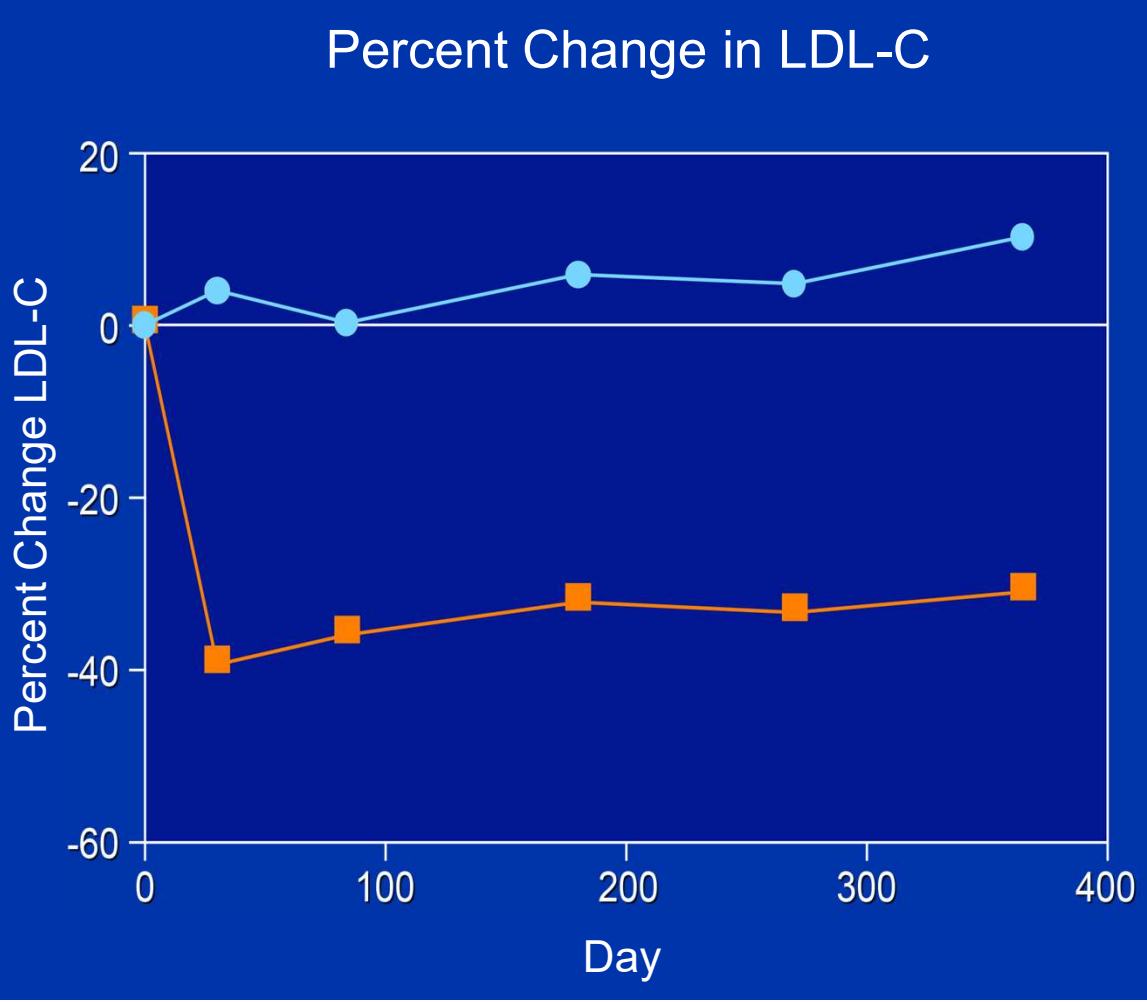
Demographics

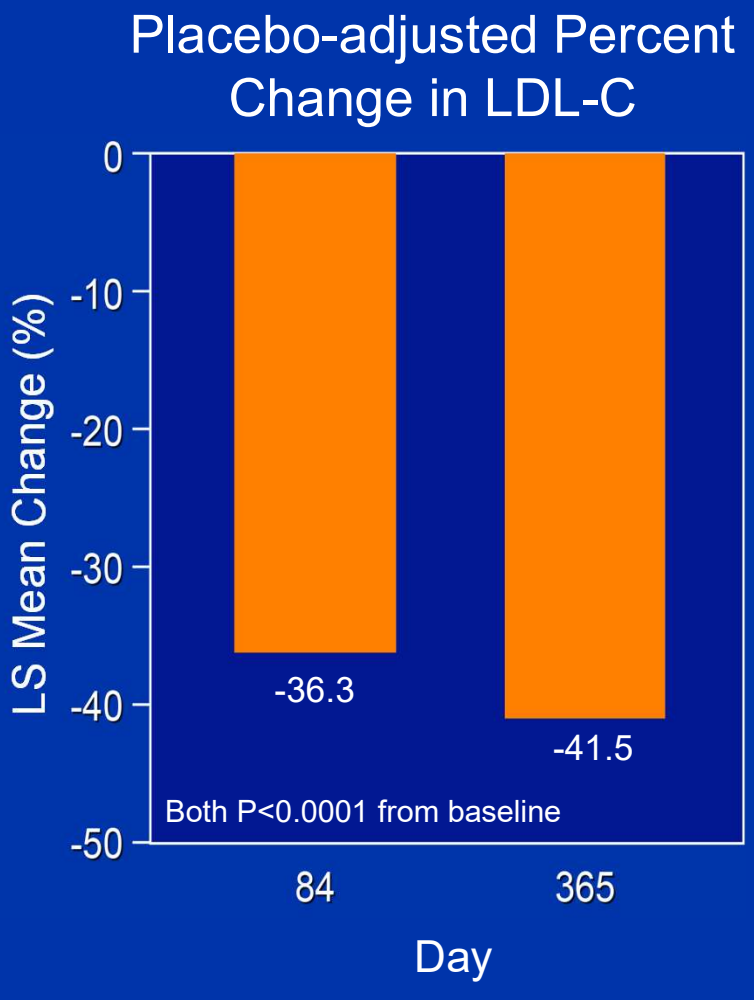
Parameter	Placebo (N=118)	Obicetrapib (N=236)
Age (yrs)	56.6	57.0
Females (%)	55.1	53.0
White (%)	93.2	92.8
BMI (kg/m^2)	29.6	29.3
Diabetes (%)	22.0	19.9
Statin use(%)	83.9	88.6
High intensity statin use (%)	67.8	78.8
Ezetimibe use (%)	50.0	53.8
PCSK9 inhibitor use (%)	22.6	14.0

Baseline Lipid Parameters

Parameter	Placebo (N=118)	Obicetrapib (N=236)
LDL-C (mg/dL)	119.9	123.4
Non-HDL-C (mg/dL)	146.7	148.4
Apolipoprotein B (mg/dL)	105.3	107.2
HDL-C (mg/dL)	50.2	53.2
Triglycerides (mg/dL)	139.9	133.6
Lp(a) (nmol/L)	34.9	45.8

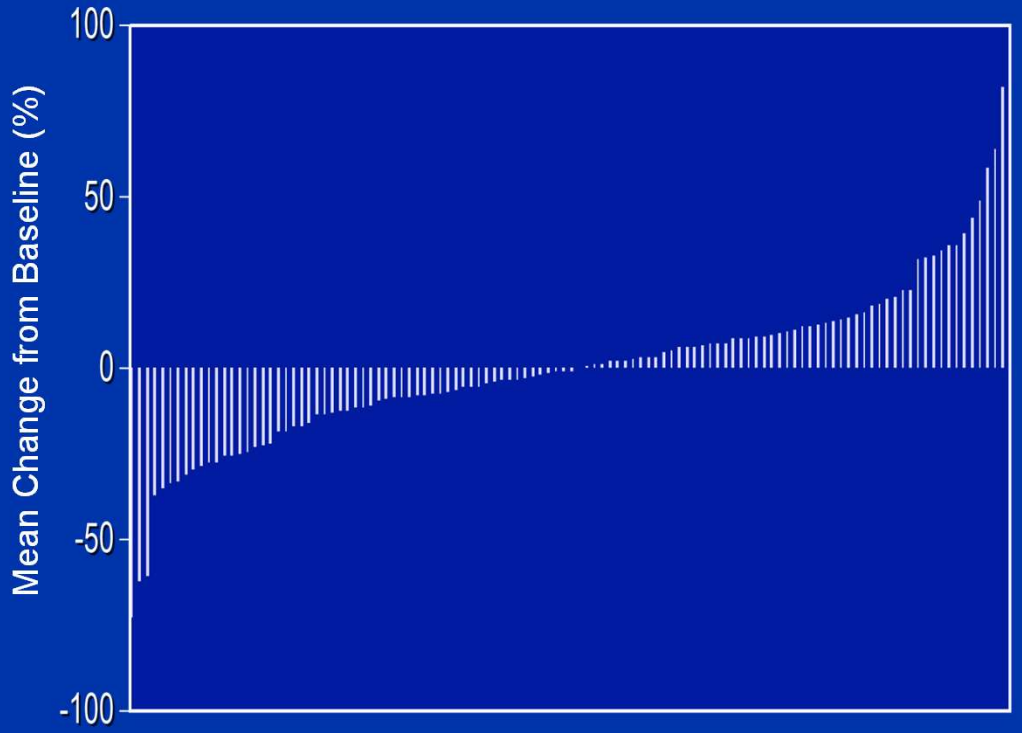
Percent Change in LDL-C with Obicetrapib





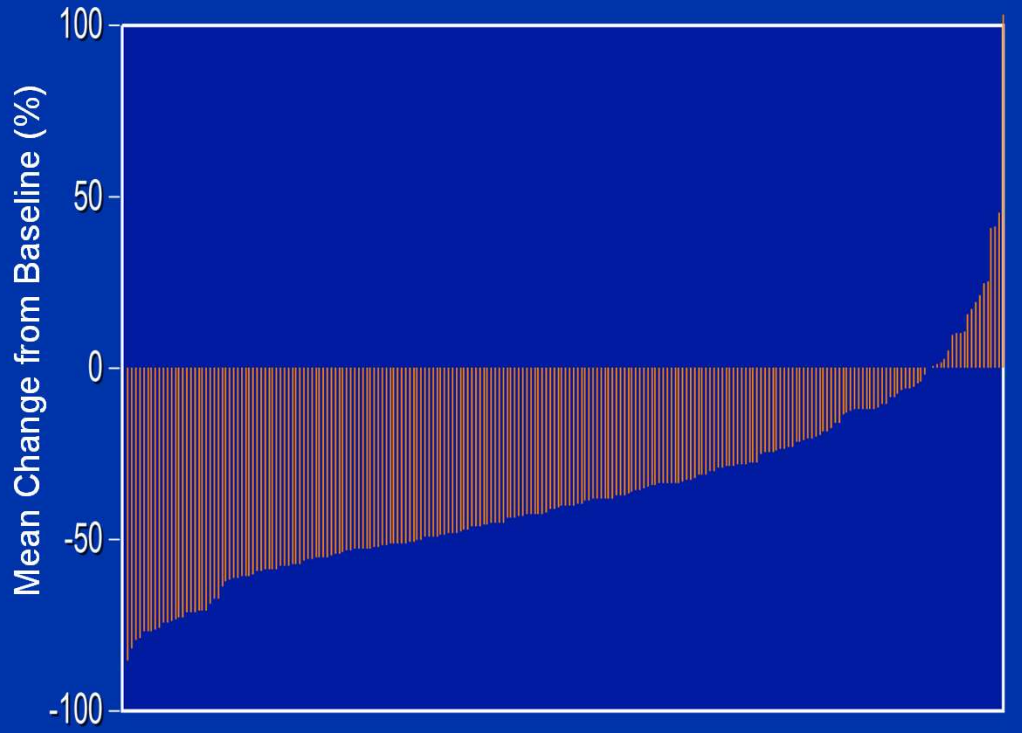
Individual Changes in LDL-C with Placebo and Obicetrapib at Day 84

Placebo



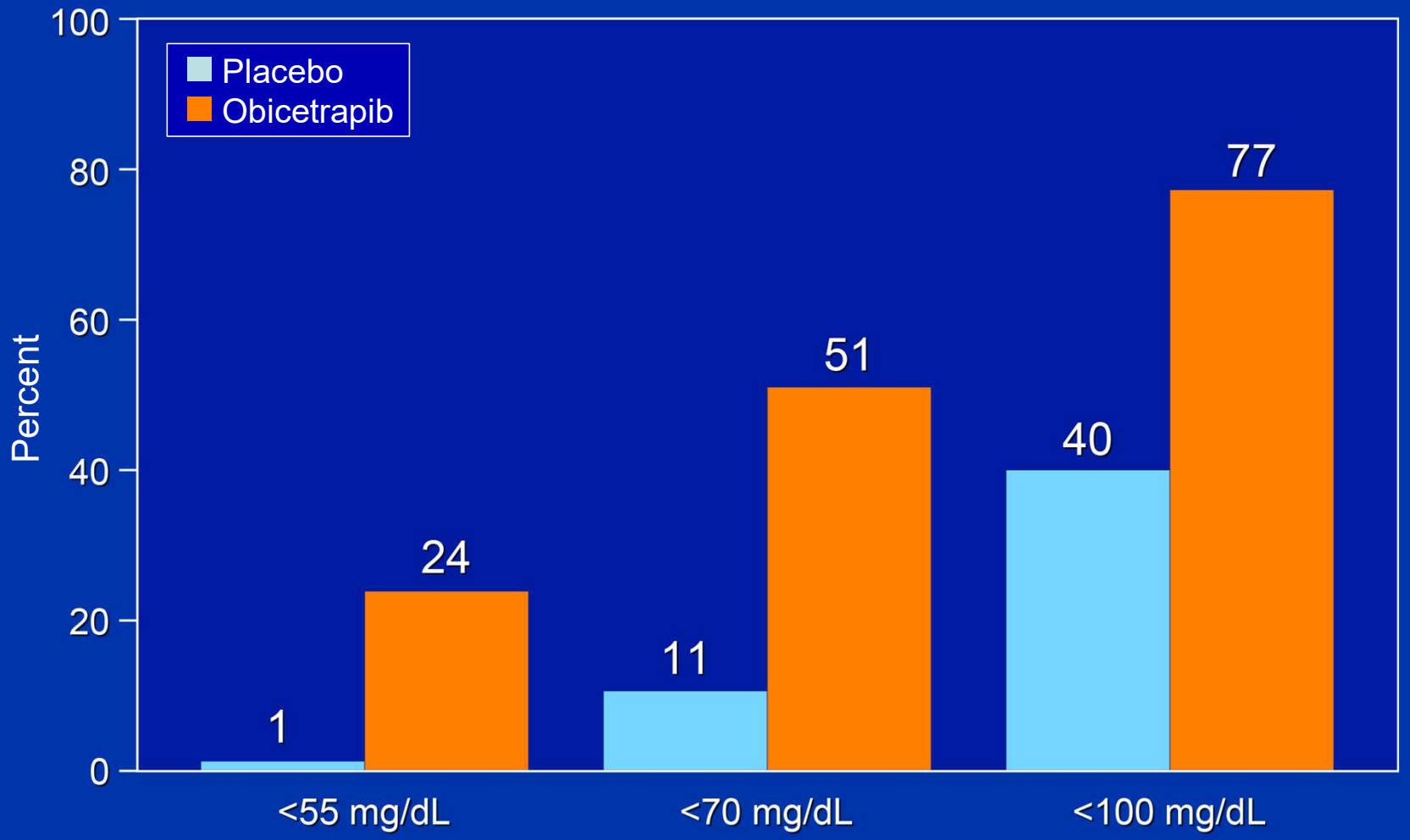
3% achieved LDL-C lowering >50%

Obicetrapib

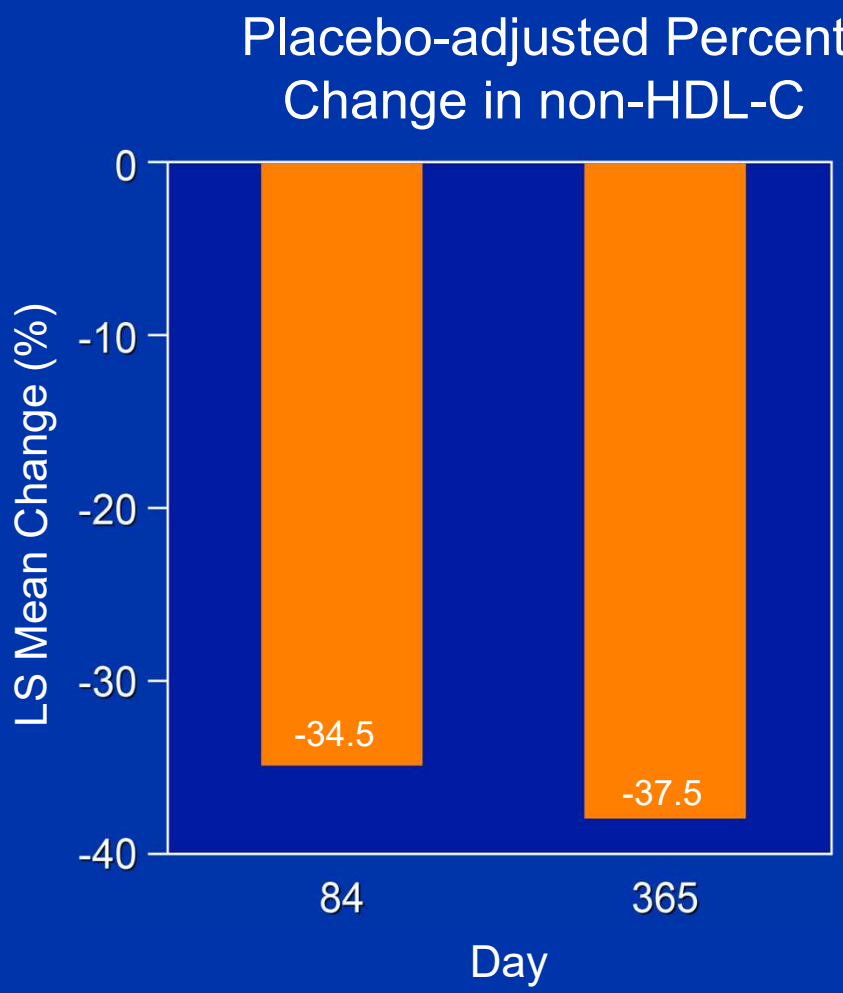


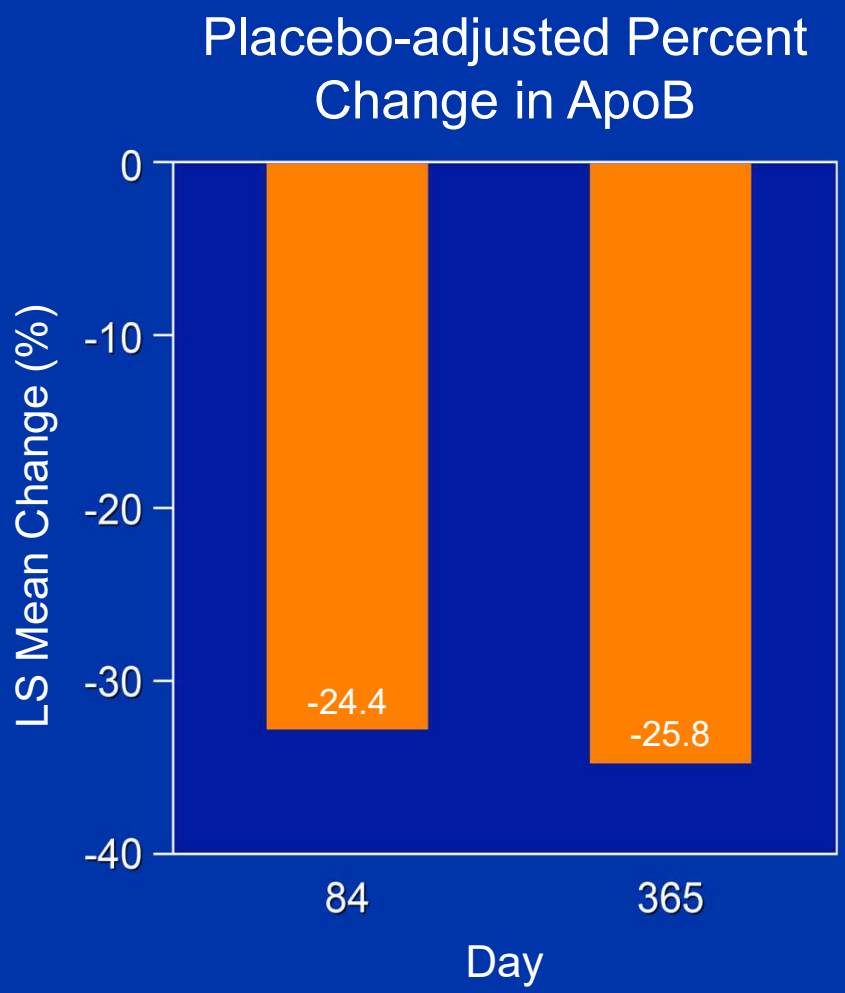
34% achieved LDL-C lowering >50%

Percent of Patients Achieving LDL-C Goals

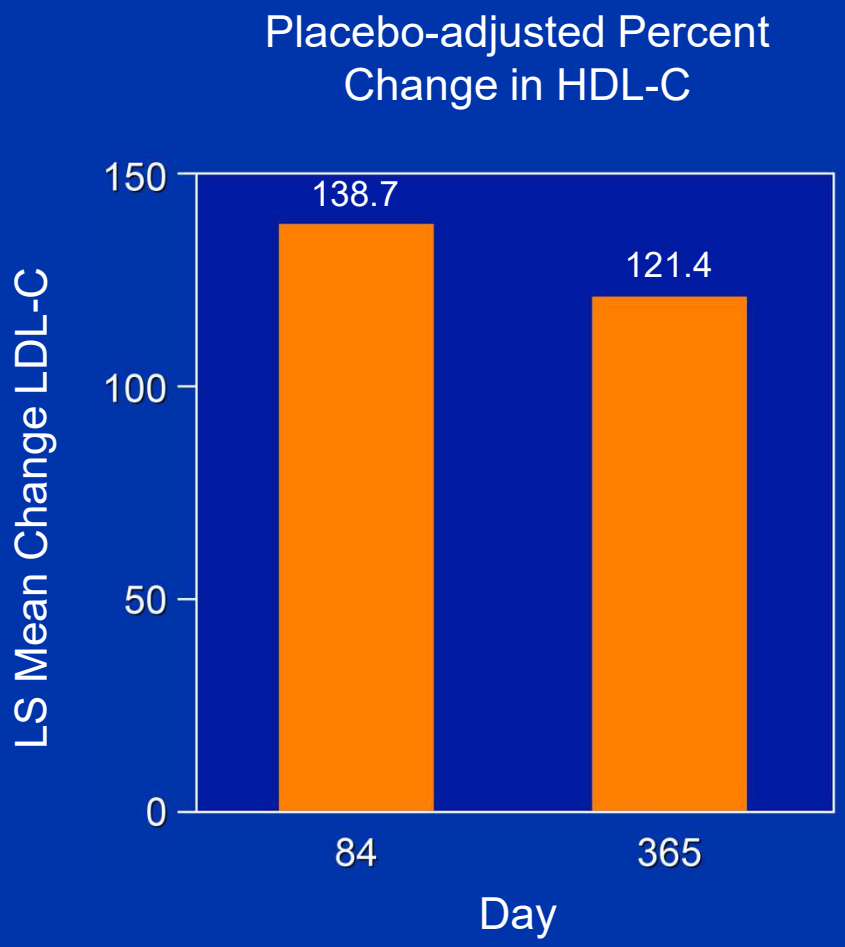


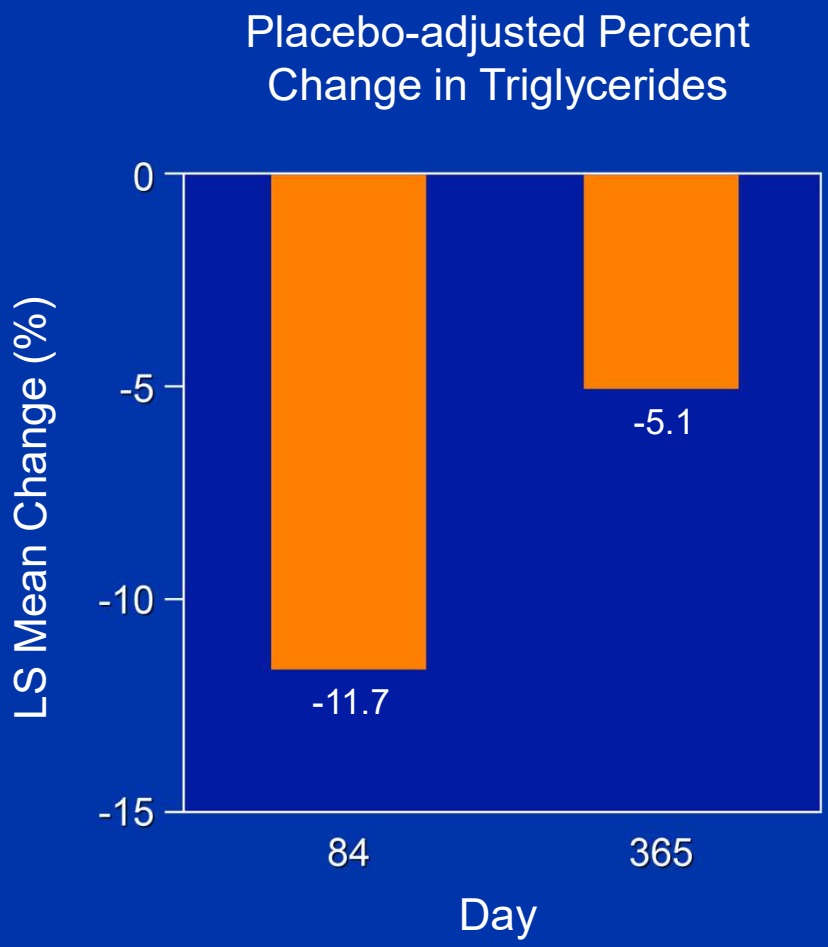
Percent Change in non-HDL-C and ApoB





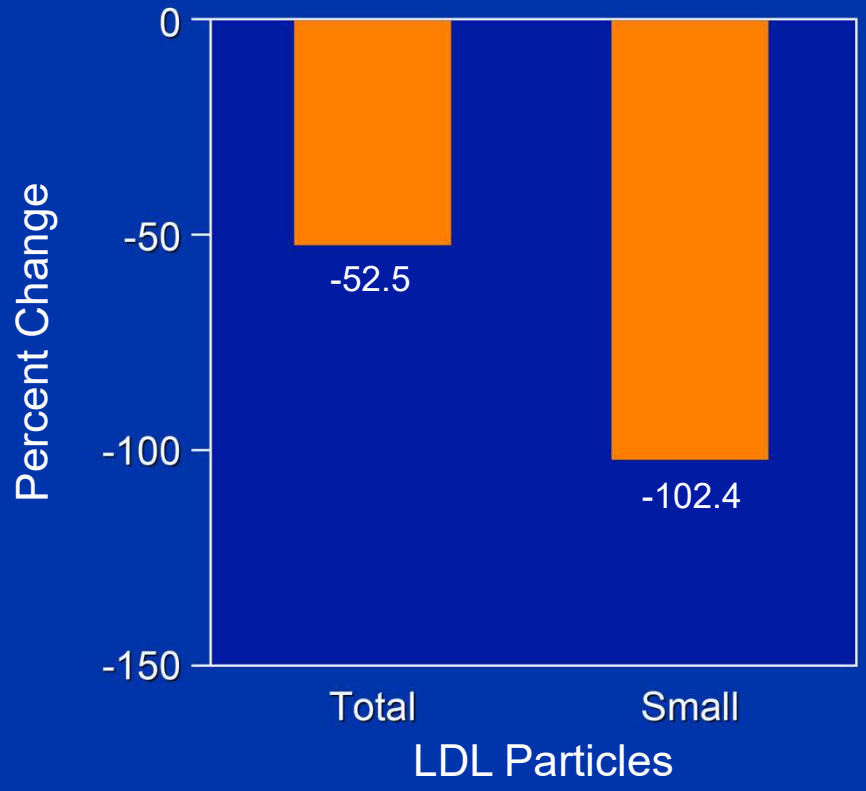
Percentage Change in HDL-C and Triglycerides



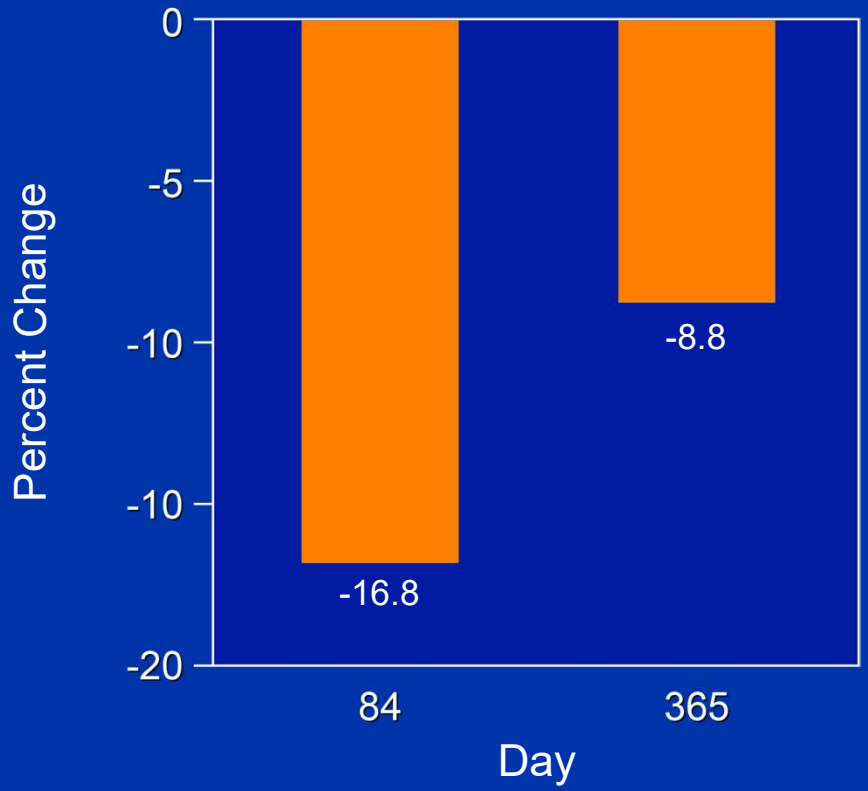


Percent Change in LDL Particles and hsCRP

Placebo-adjusted Percent Change in LDL Particles at Day 180

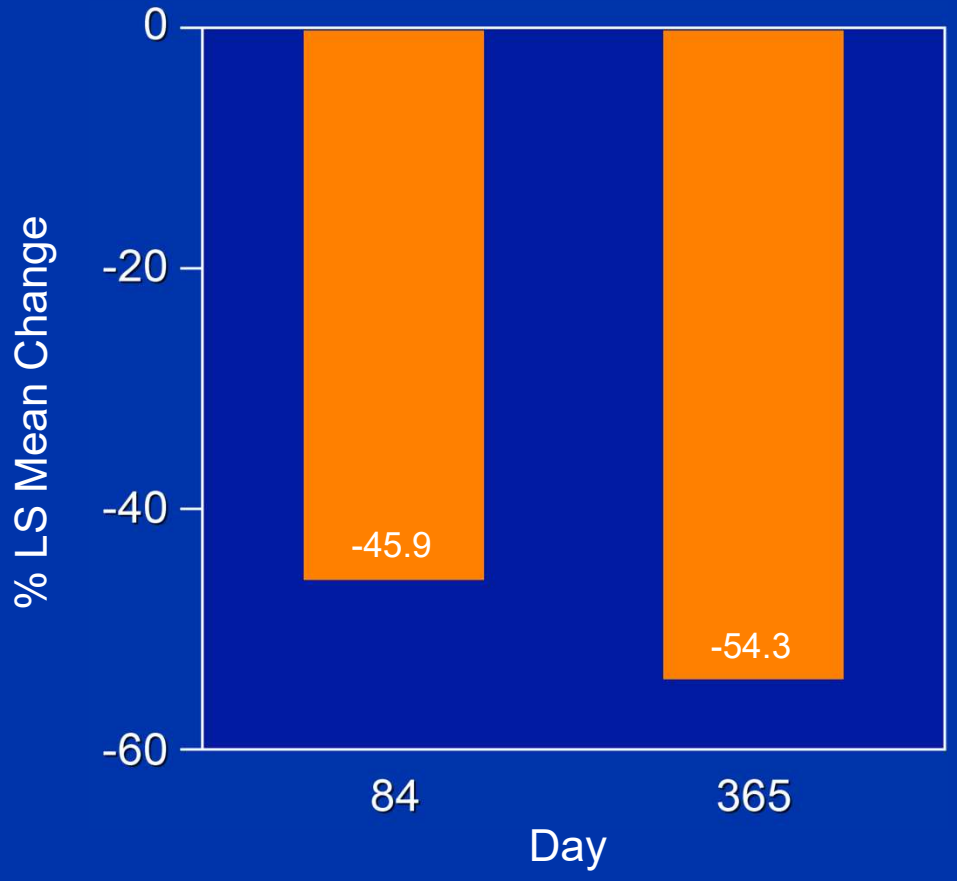


Placebo-adjusted Percent Change in hsCRP

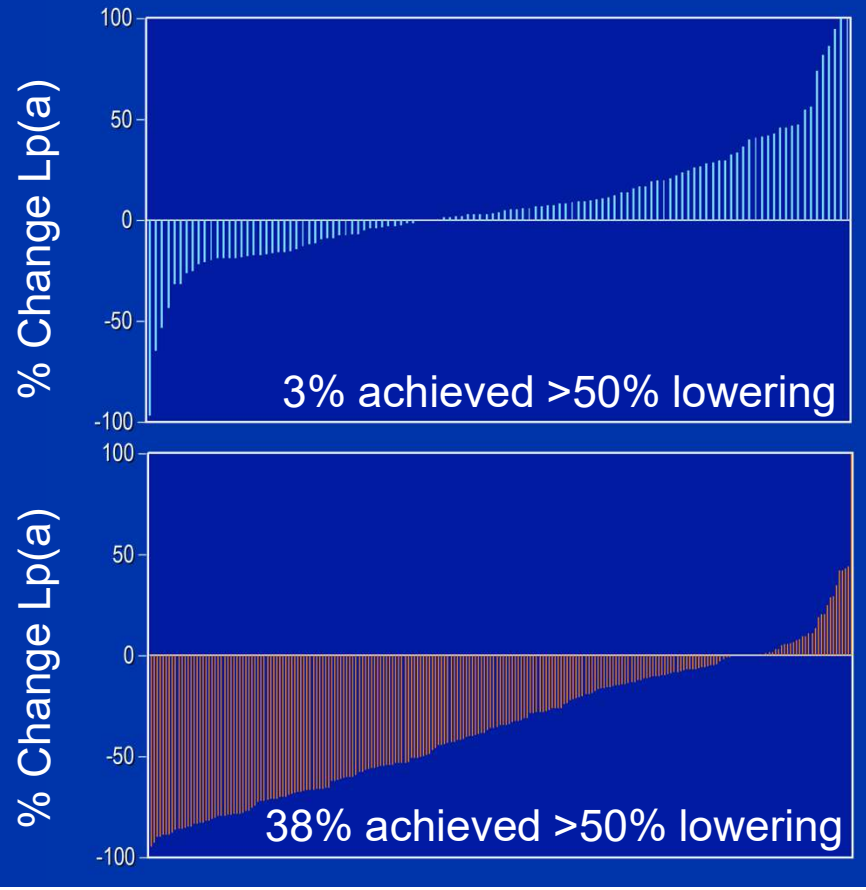


Percent Changes in Lp(a)

Placebo-adjusted Percent Change in Lp(a)



Individual Percent Changes in Lp(a)



Safety and Tolerability

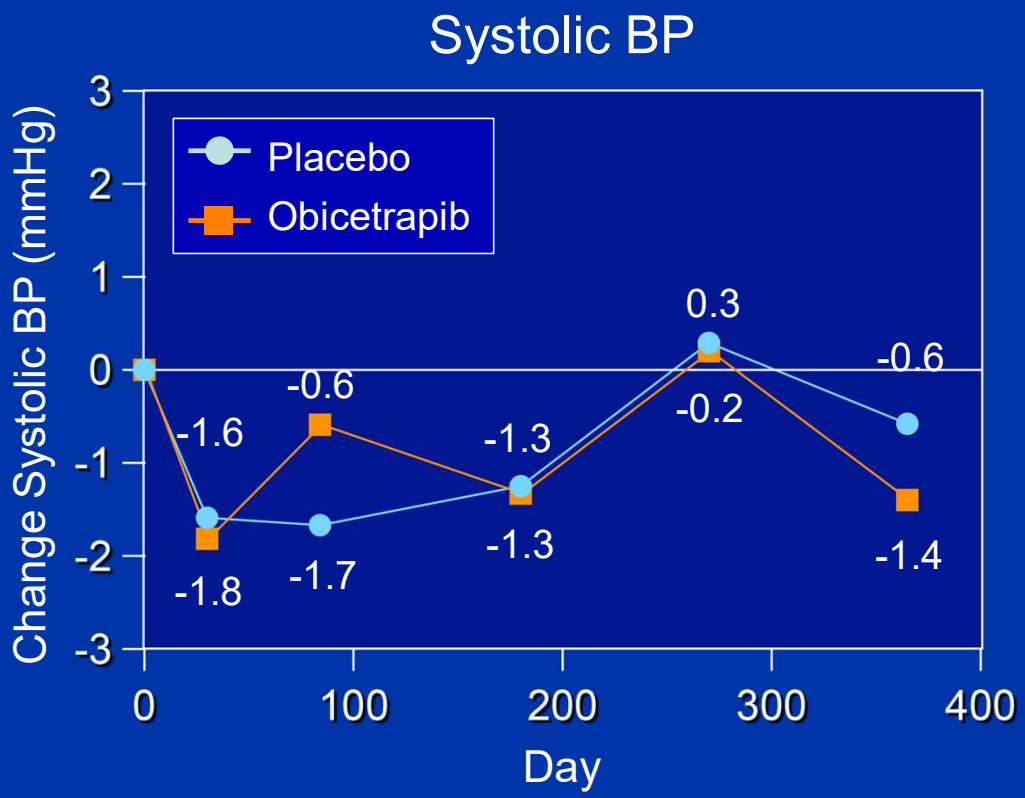
Parameter	Placebo (N=118)	Obicetrapib (N=236)
Treatment emergent adverse events (%)	70.3	63.7
Study drug related adverse events (%)	6.8	4.3
Mild (%)	4.2	2.1
Moderate (%)	2.5	2.1
Severe (%)	0	0
Adverse events leading to drug discontinuation (%)	6.8	4.3
Adverse events leading to death (%)	1.7	1.3

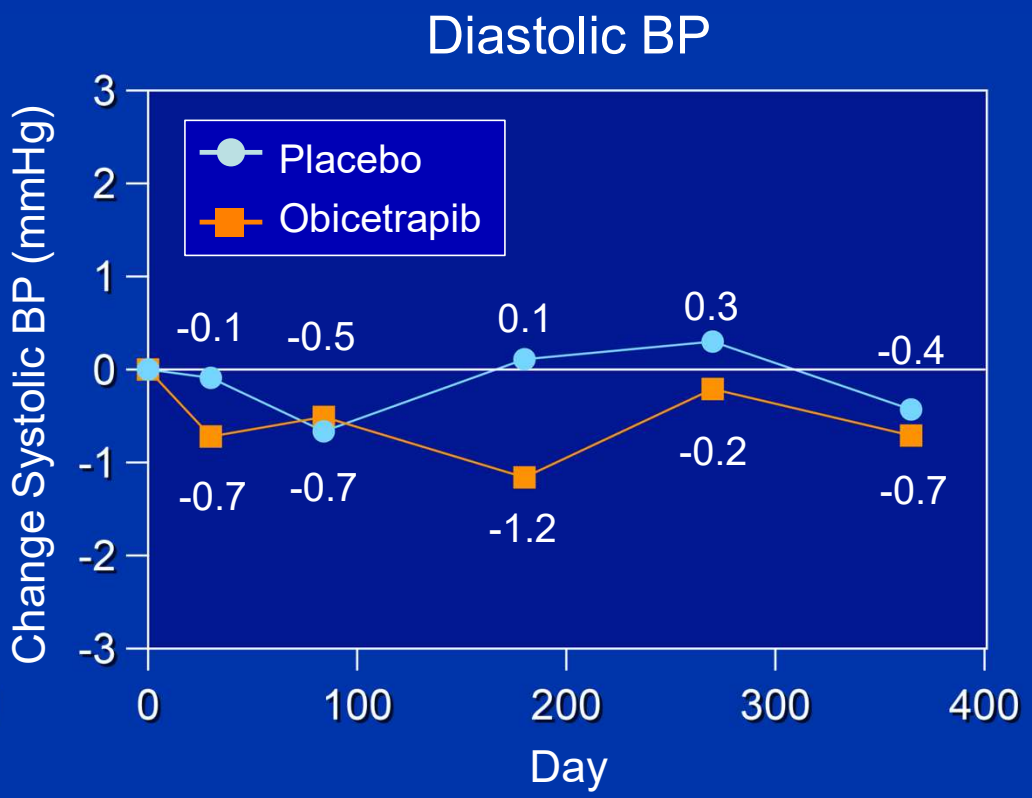
AEs experienced by >5% of patients included influenza, hypertension, nasopharyngitis, diarrhea, upper respiratory tract infection, back pain, headache and fatigue with no difference between the treatment groups.

Events of Special Interest

Parameter	Placebo (N=118)	Obicetrapib (N=236)
AST or ALT >3x ULN (%)	0	0
Bilirubin >2x ULN (%)	1.7	0
CK >5x ULN (%)	3.4	1.3
New diabetes or worsening glycemic control (%)	22.0	20.5
HbA1c increase >0.5% from baseline (%)	5.1	3.4
eGFR <30 or >25% decrease eGFR (%)	8.5	4.3
Macular degeneration (%)	0	0
Cardiovascular events (%)	4.2	2.6

No Significant Change in Blood Pressure with Obicetrapib





Limitations

- The study evaluated the effect of obicetrapib for 365 days, the effect of longer treatment requires further evaluation.
- The Lp(a) lowering was observed in a cohort who were not required to have elevated levels at study entry.
- Additional studies will evaluate the impact of obicetrapib in individuals with elevated Lp(a) levels.
- Whether treatment with obicetrapib results in a reduction in cardiovascular events remains to be determined.

Summary

- Obicetrapib reduced placebo-adjusted LDL-C 36.3% at day 84 and 41.5% at day 365 with >50% reductions observed in 34% of patients
- Obicetrapib resulted in placebo-adjusted reductions in Lp(a) by 54.3%, independent of lowering atherogenic lipid parameters and raising HDL-C.
- Obicetrapib was well tolerated with no safety concerns.
- The longer-term effect of obicetrapib on cardiovascular outcomes is currently being evaluated in the PREVAIL trial.
- The findings suggest that obicetrapib has considerable promise as an approach to more effective lipid control in high CV risk patients.