Safety and Efficacy of Obicetrapib in Patients at High Cardiovascular Risk

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Disclosures

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

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Background

- LDL-C lowering is a cornerstone of treatment of patients at high risk of cardiovascular events.
- Many high risk patients 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 at high risk of cardiovascular events and suboptimal LDL-C control.

Study Design

Main Inclusion Criteria

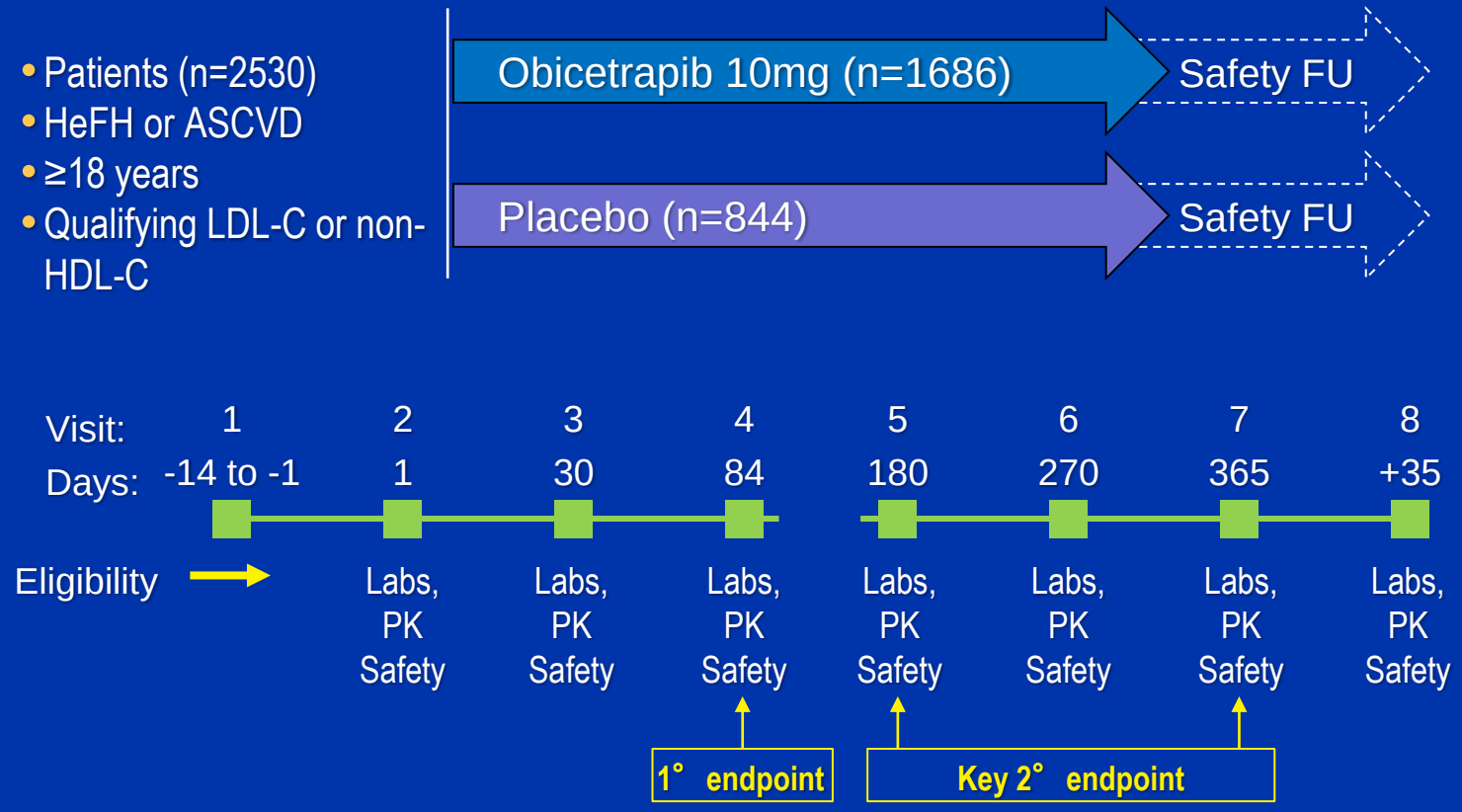
- High CV risk
  - –HeFH
  - –Atherosclerotic CVD
- On maximally tolerated lipid lowering therapy
- Suboptimal lipid control
  - –LDL-C ≥100mg/dL or non-HDL-C ≥130 mg/dL without enhancing risk factors
  - –LDL-C 55-100mg/dL or non-HDL-C 85-130 mg/dL with an enhancing risk factor
- TG ≤ 400mg/dL

Exclusion Criteria

- CV event in the last 3 months
- HoFH
- Uncontrolled hypertension or diabetes, active liver disease, history of malignancy

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

- Patients (n=2530)
- HeFH or ASCVD
- ≥18 years
- Qualifying LDL-C or non-HDL-C



Primary endpoint: percent change in LDL-C from baseline to day 84
Secondary endpoints: change in LDL-C at day 365, changes in other lipid parameters and percent achieving LDL-C targets

Demographics

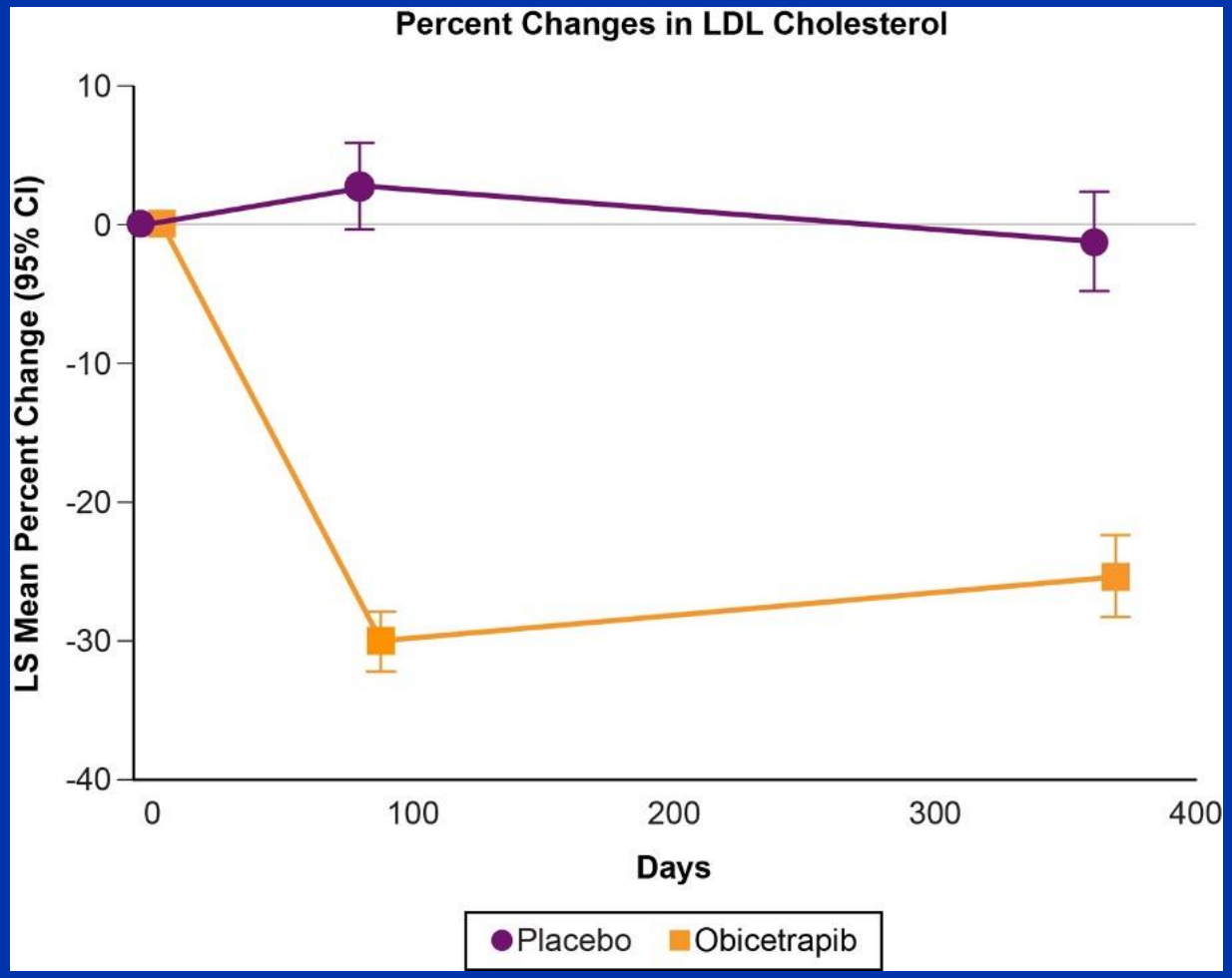
Parameter	Placebo (N=844)	Obicetrapib (N=1686)
Age (yrs)	65.3	65.4
Females (%)	33.2	34.0
White (%)	76.7	73.6
BMI (kg/m^2)	29.7	29.4
Diabetes (%)	39.8	37.0
ASCVD (%)	88.4	89.3
Coronary artery disease (%)	76.4	78.3
Cerebrovascular disease (%)	19.7	20.8
Peripheral arterial disease (%)	7.2	6.5
HeFH (%)	16.9	16.8

Baseline Medication Use and Lipid Parameters

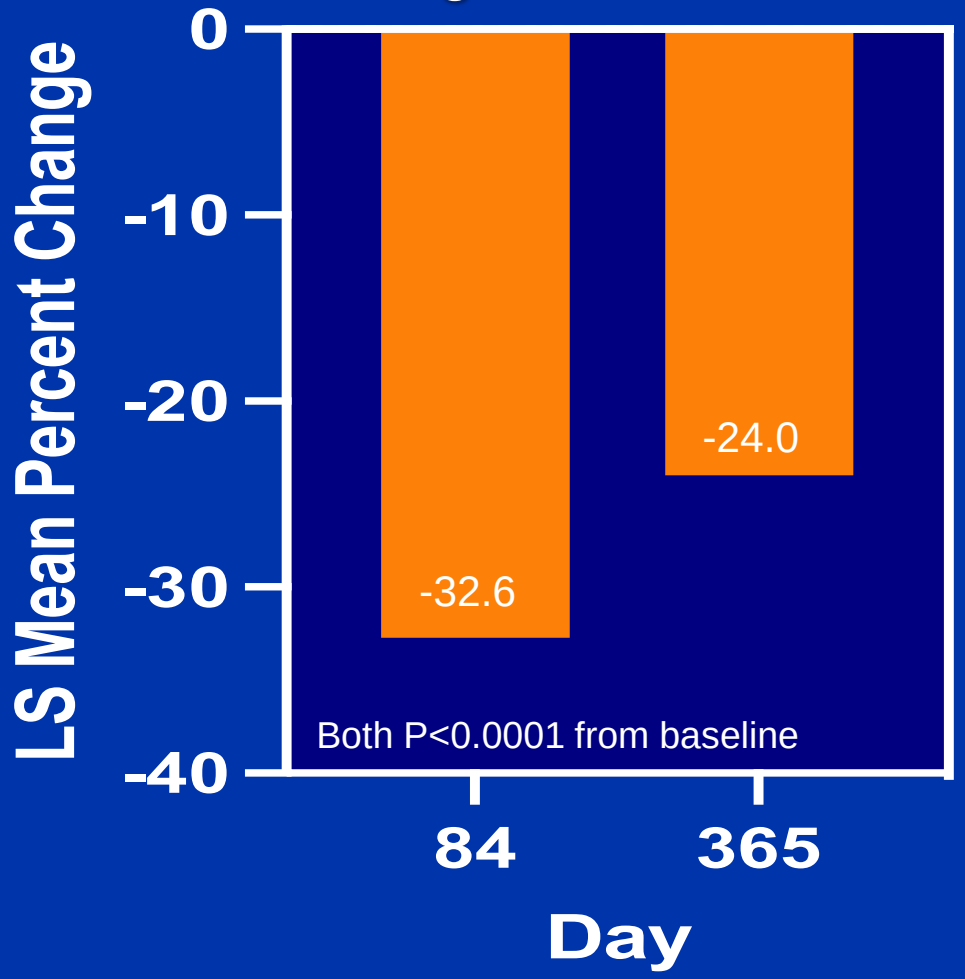
Parameter	Placebo (N=844)	Obicetrapib (N=1686)
Statin use(%)	92.7	90.9
High intensity statin use (%)	70.1	70.1
Ezetimibe use (%)	26.1	26.9
PCSK9 inhibitor use (%)	3.9	3.7
LDL-C (mg/dL)	98.4	98.1
Non-HDL-C (mg/dL)	125.6	124.7
Apolipoprotein B (mg/dL)	91.9	91.6
HDL-C (mg/dL)	49.7	49.5
Triglycerides (mg/dL)	127.0	122.0
Lp(a) (nmol/L)	40.7	39.2

Percent Change in LDL-C with Obicetrapib

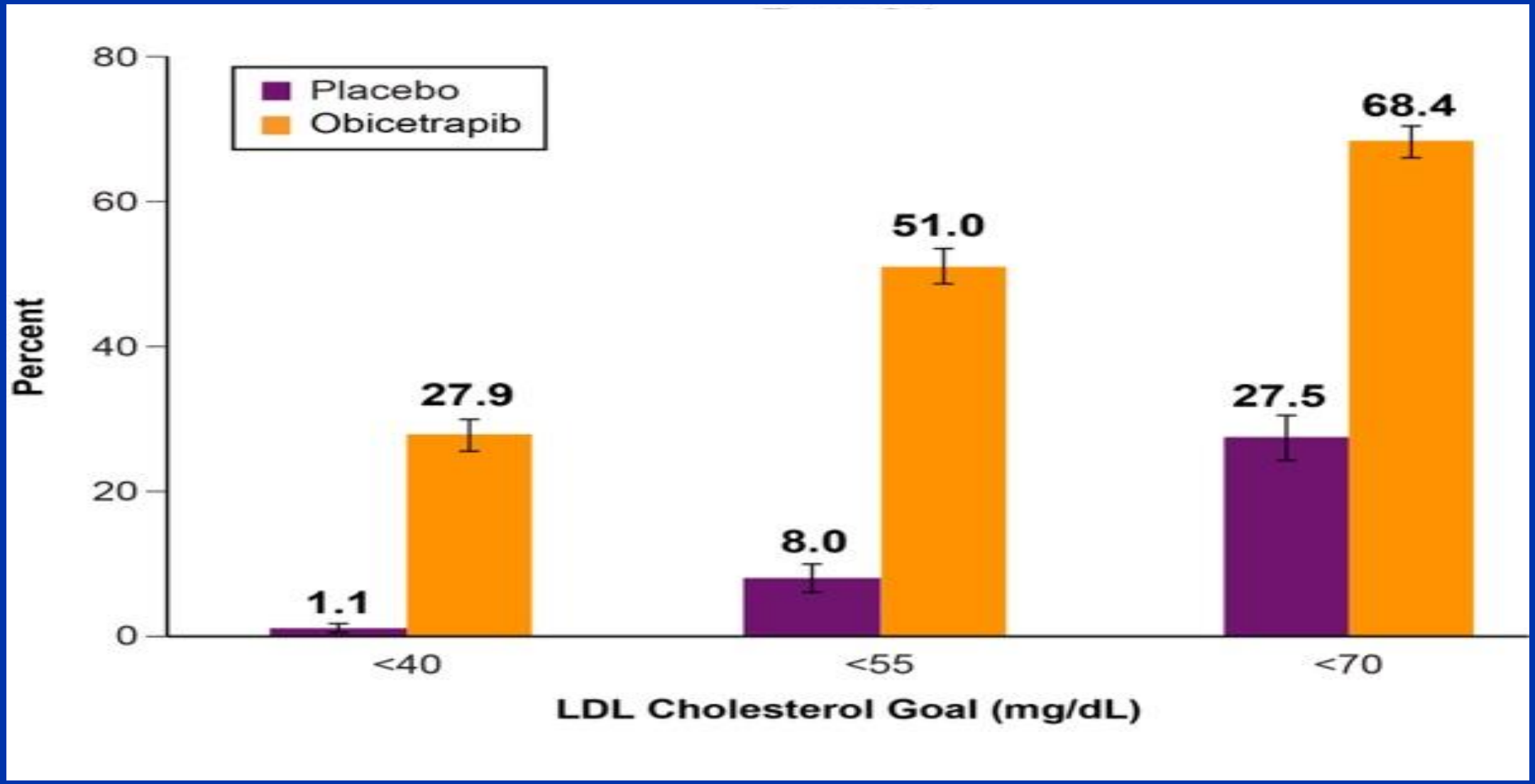
Percent Change in LDL-C



Placebo-adjusted Percent Change in LDL-C

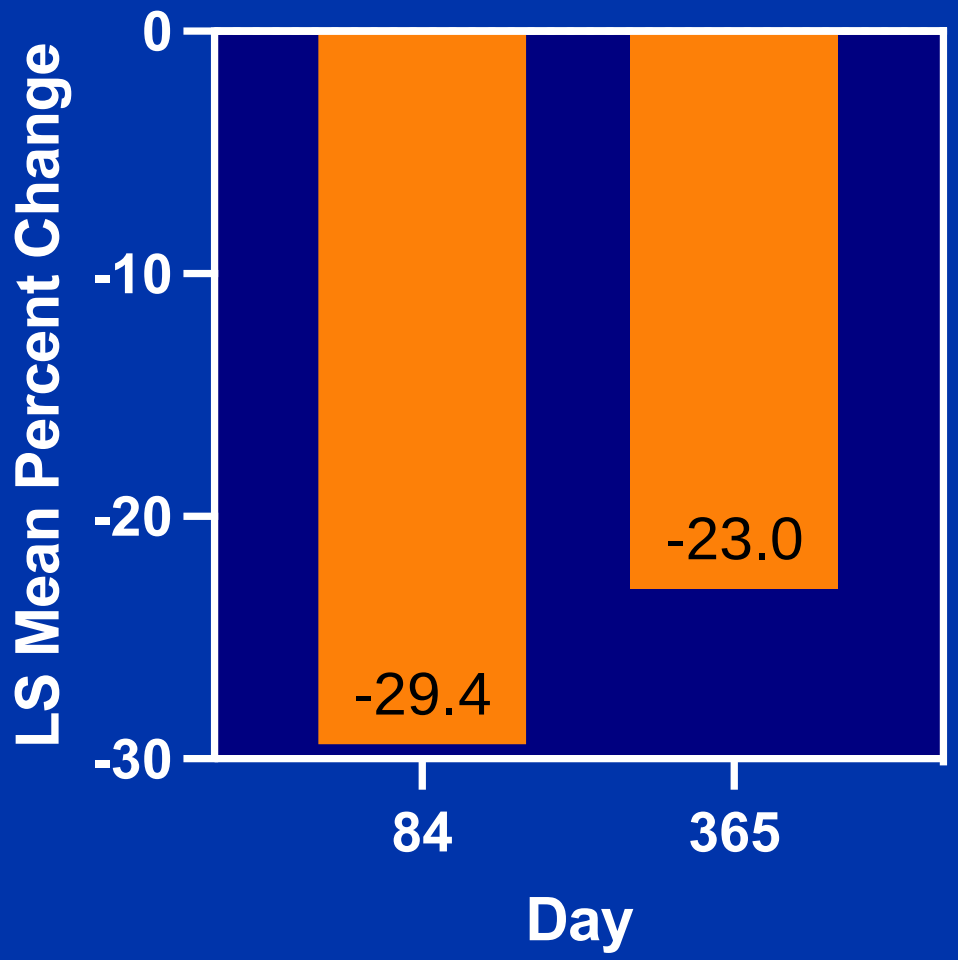


Percent of Patients Achieving LDL-C Goals

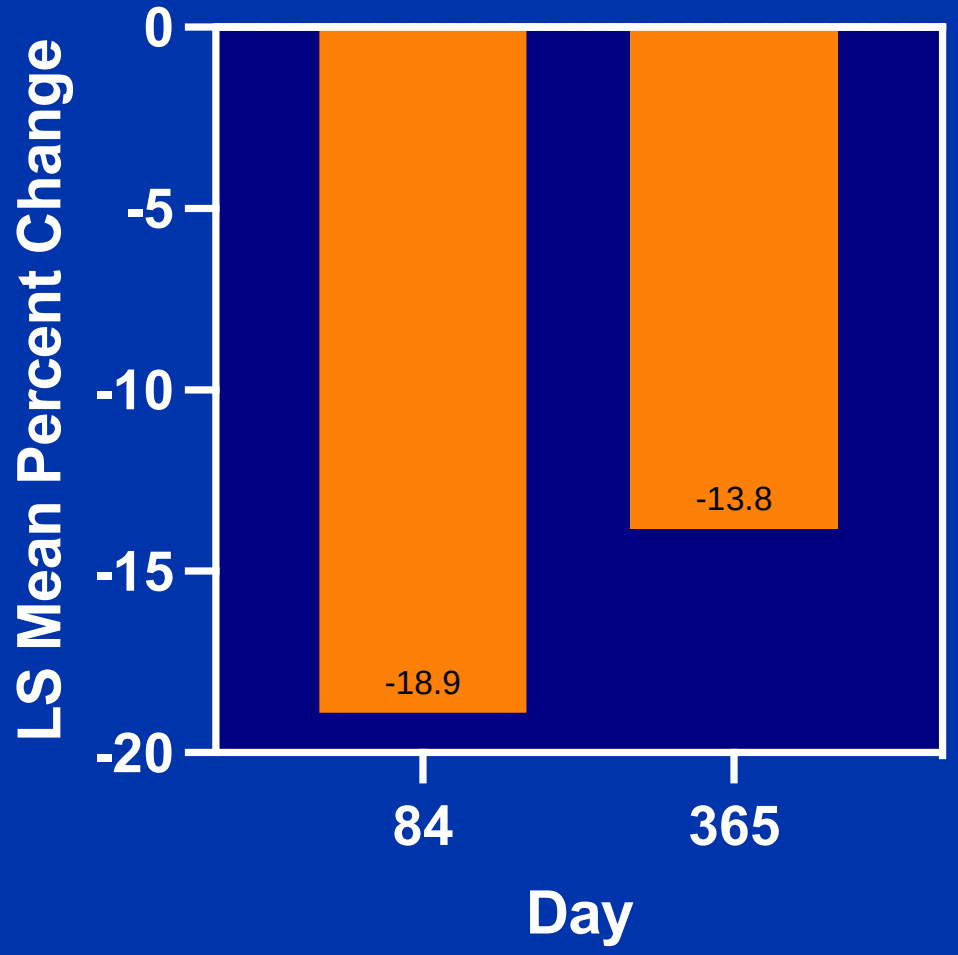


Percent Change in non-HDL-C and ApoB

Placebo-adjusted Percent Change in non-HDL-C

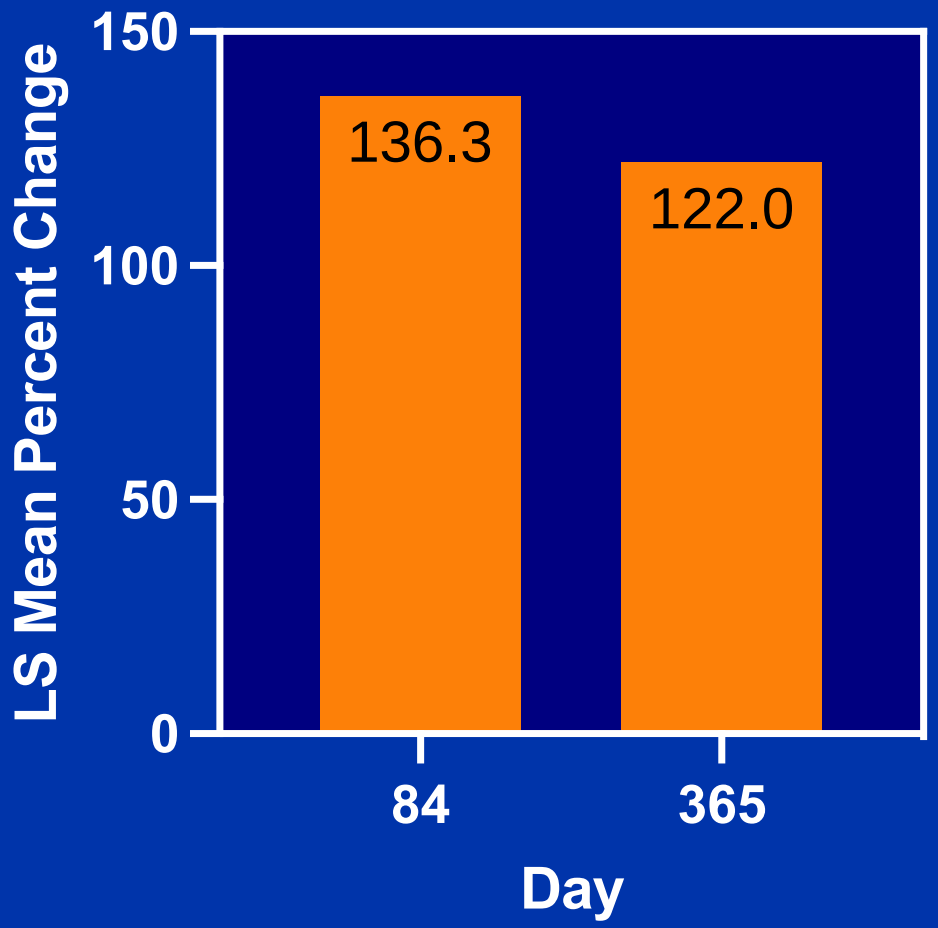


Placebo-adjusted Percent Change in ApoB

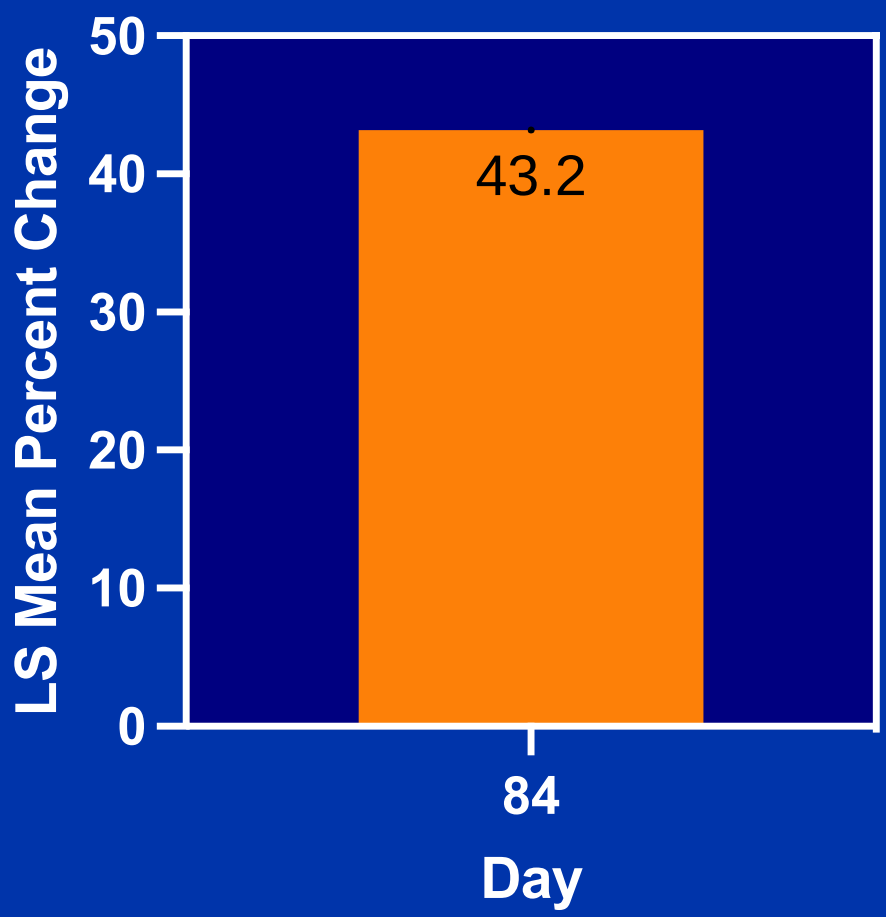


Percentage Change in HDL-C and ApoA1

Placebo-adjusted Percent Change in HDL-C

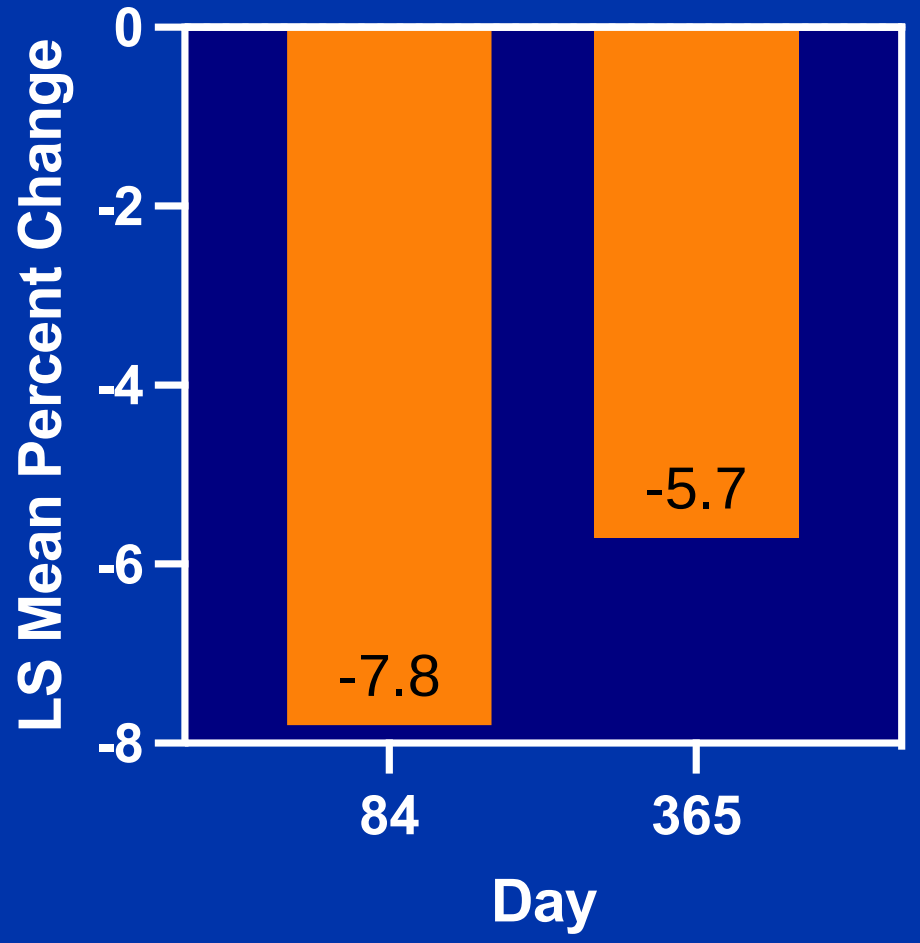


Placebo-adjusted Percent Change in ApoA1

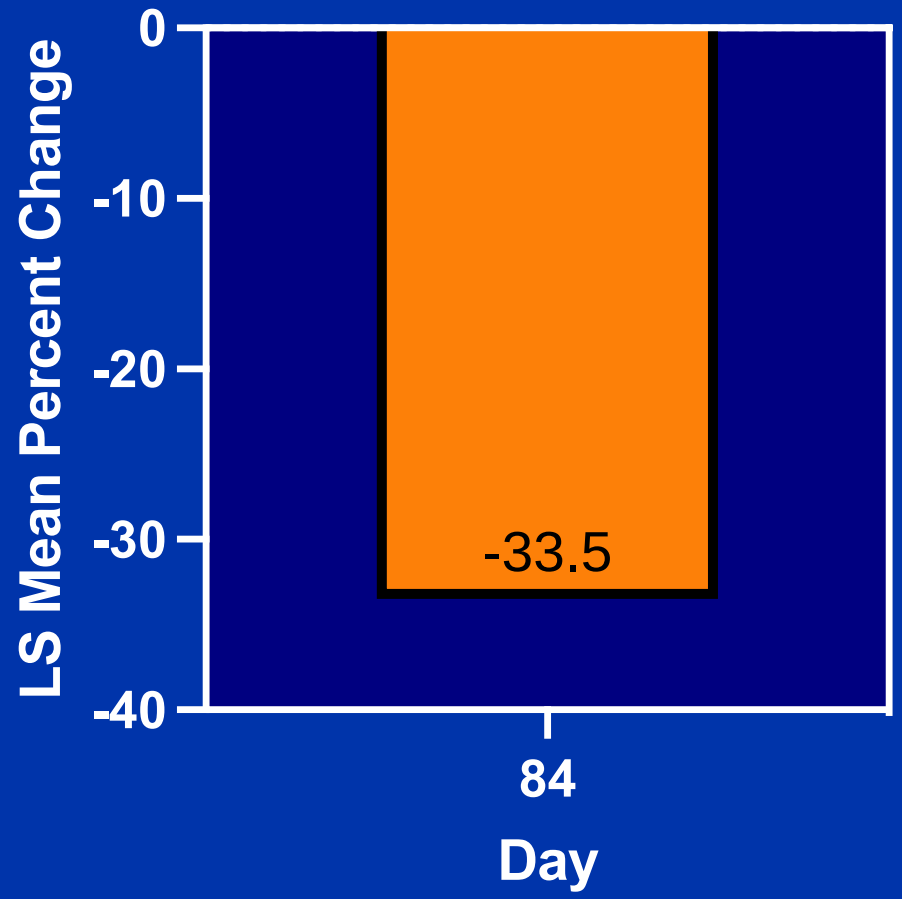


Percentage Change in Triglycerides and Lp(a)

Placebo-adjusted Percent Change in Triglycerides



Placebo-adjusted Percent Change in Lp(a)



Safety and Tolerability

Parameter	Placebo (N=844)	Obicetrapib (N=1686)
Treatment emergent adverse events (%)	60.9	59.8
Study drug related adverse events (%)	4.6	4.5
Mild (%)	3.0	3.0
Moderate (%)	1.7	1.4
Severe (%)	0	0.1
Adverse events leading to drug discontinuation (%)	5.1	4.0
Adverse events leading to death (%)	1.4	1.1

AEs experienced by >2% of patients included COVID-19, hypertension, upper respiratory tract infection, nasopharyngitis, arthralgia, urinary tract infection, headache and dizziness with no difference between the treatment groups.

Events of Special Interest

Parameter	Placebo (N=844)	Obicetrapib (N=1686)
AST or ALT >3x ULN (%)	0.9	0.6
Bilirubin >2x ULN (%)	0.5	0.1
CK >5x ULN (%)	0.4	0.3
New diabetes or worsening glycemic control (%)	40.1	35.1
HbA1c increase >0.5% from baseline (%)	15.8	13.9
>25% decrease eGFR (%)	8.3	6.8
Macular degeneration (%)	0	0.1
Change systolic blood pressure (mmHg)	-0.3	0
Change diastolic blood pressure (mmHg)	-0.1	-0.2
Cardiovascular events (%)	5.2	4.2

Limitations

- The study evaluated the effect of obicetrapib for 365 days, the effect of longer treatment requires further evaluation.
- The study lacked diversity in gender and ethnicity encountered in clinical practice, with implications for generalizability.
- 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 32.6% at day 84 and 24.0% at day 365 with 51% of patients achieving a LDL-C <55 mg/dL.
- Obicetrapib resulted in placebo-adjusted reductions in Lp(a) by 33.5%, 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.