Efficacy and Safety of the Oral PCSK9 Inhibitor, MK-0616, a Macrocyclic Peptide, in the Treatment of Hypercholesterolemia: A Phase 2b Randomized Placebo-Controlled Clinical Trial

Speaker: Christie M. Ballantyne, MD[1]

on behalf of Puja Banka, MD[2]; Gustavo Mendez, MD[3]; Raymundo Garcia, MD[4]; Julio Rosenstock, MD[5]; Anthony Rodgers, MS[2]; Geraldine Mendizabal, MD[2]; Yale Mitchel, MD[2]; Alberico L. Catapano, MDhc, PhD[6,7]

[1]Baylor College of Medicine, Houston, Texas, USA; [2]Merck & Co., Inc., Rahway, NJ, USA; [3]Hospital Angeles Xalapa, Xalapa, Veracruz, México; [4]Unidad Biomedica Avanzada Monterrey, Monterrey, Nuevo León, Mexico; [5]Velocity Clinical Research at Medical City, Dallas, TX, USA; [6]University of Milan; [7]IRCCS Multimedica, Milan, Italy

Speaker Twitter Handle: @CBallantyneMD

ACC.23 TOGETHER WITH WCC

AMERICAN COLLEGE of CARDIOLOGY

WORLD HEART FEDERATION

Disclosures

Dr. Ballantyne has received grant/research support through his institution from Abbott Diagnostic, Akcea, Amgen, Arrowhead, Esperion, Ionis, Merck & Co., Inc, New Amsterdam, Novartis, Novo Nordisk, Regeneron, and Roche Diagnostic and has been a consultant for 89Bio, Abbott Diagnostics, Alnylam Pharmaceuticals, Althera, Amarin, Amgen, Arrowhead, Astra Zeneca, Denka Seiken, Esperion, Genentech, Gilead, Illumina, Ionis, Matinas BioPharma Inc, Merck & Co., Inc, New Amsterdam, Novartis, Novo Nordisk, Pfizer, Regeneron, and Roche Diagnostic

This trial was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA

Background

- Elevated low density lipoprotein cholesterol (LDL-C) is a primary causative factor for atherosclerotic cardiovascular disease (ASCVD)
- Despite effective treatments (e.g., statins), a large proportion of patients fail to achieve guideline-recommended LDL-C levels
- Injectable treatments targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) have demonstrated large reductions in LDL-C and decreased risk of ASCVD events, but access barriers and need for repeat injections have led to poor adoption
- An oral PCSK9 inhibitor may widen access and improve attainment of guideline-recommended treatment goals

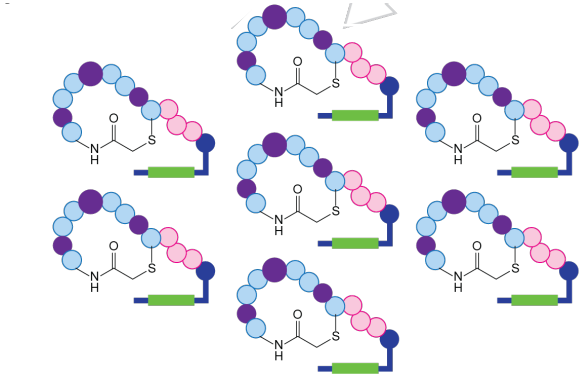
Development of MK-0616: An oral PCSK9i

Large diffuse/flat surface of PCSK9/LDL-receptor interaction difficult to disrupt with typical small molecules

- *Macrocyclic peptides can bind PCSK9 with monoclonal antibody-like affinity at 1/100th molecular weight*

Macrocycle Library

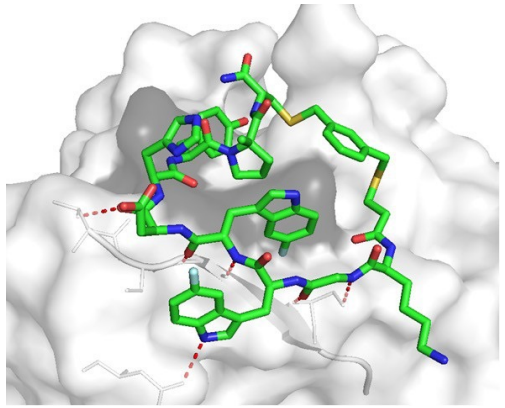
Macrocyclic peptides displayed on mRNA



Hit-finding platform

mRNA display

Screening of ultra-large libraries (10^{14} potential compounds)



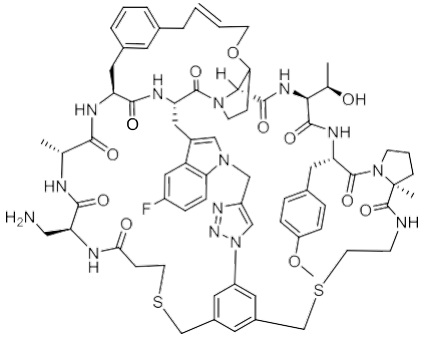
Medicinal Chemistry

Structure-Based Drug Discovery

Improve structure-activity relationship, PK and stability

Macrocyclic Peptide

Predecessor to MK-0616

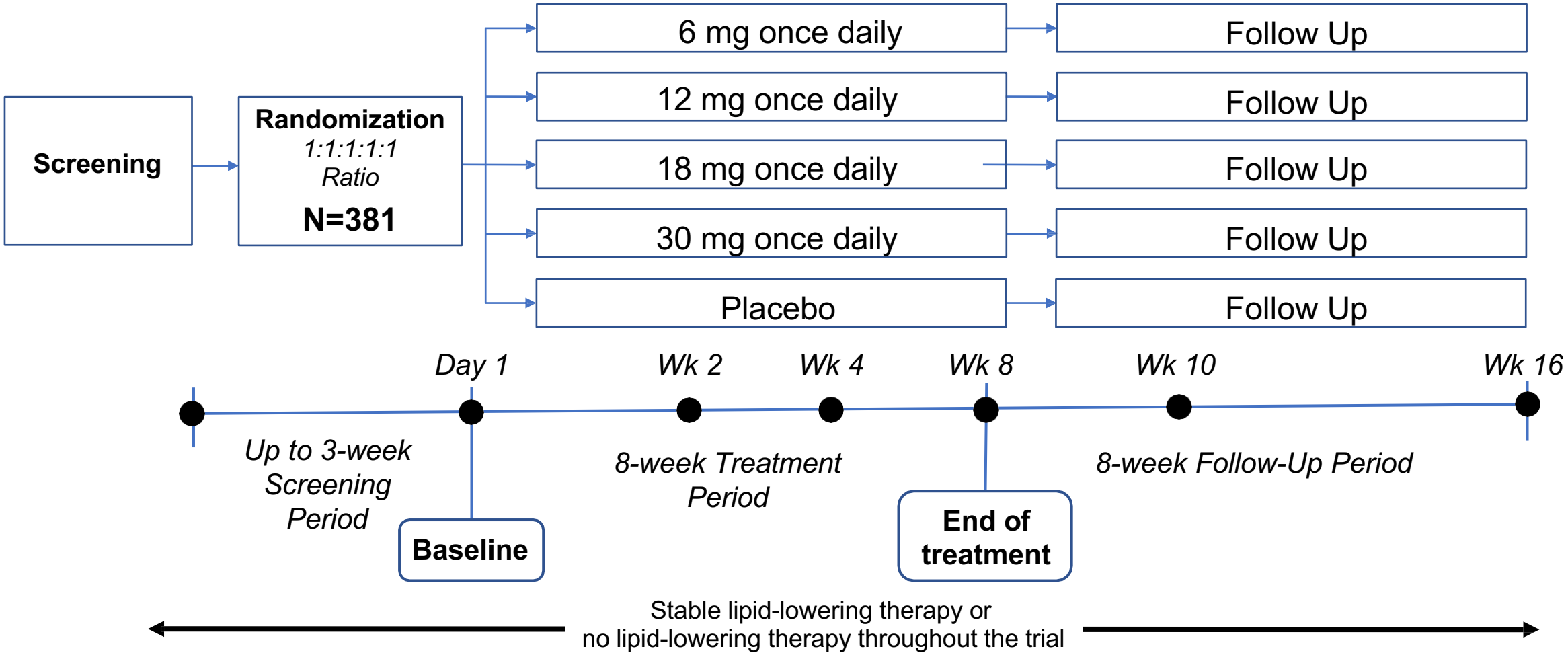


MW = ~1500 g/mol

Ki = 2-5 pM

J Med Chem 63(22):13796-13824, 2020;
doi.org/10.1021/acs.jmedchem.1c01599

Study Design: Phase 2b, Multicenter, Randomized, Controlled Trial of MK-0616



Objective and Hypothesis

Primary Objective

To evaluate the effect of the oral, macrocyclic peptide PCSK9 inhibitor, MK-0616, vs. placebo on % change from baseline in LDL-C at Week 8 in participants with hypercholesterolemia

Primary Hypothesis

At least 1 of the 4 doses of MK-0616 (6 mg, 12 mg, 18 mg, and 30 mg) is superior to placebo on % reduction from baseline in LDL-C at Week 8

Methods

Participants

- Male and female participants aged 18-80 years
- Range of stable background statin therapy
  - No statins, low to moderate intensity statin, high intensity statin
- Range of ASCVD risk with corresponding LDL-C criteria:
  - Clinical ASCVD
    - LDL-C range: ≥70 and ≤160 mg/dL (≥1.81 and ≤4.14 mmol/L)
  - Intermediate/High ASCVD Risk
    - LDL-C range: ≥100 and ≤200 mg/dL (≥2.59 and ≤5.18 mmol/L)
  - Borderline ASCVD Risk
    - LDL-C range: ≥130 and ≤250 mg/dL (≥3.37 and ≤6.48 mmol/L)

Methods

Efficacy Evaluation at Week 8	Safety Evaluation at Week 16
Primary endpoint • LDL-C percent change from baseline **Secondary endpoints** • ApoB percent change from baseline • non-HDL-C percent change from baseline • % participants with LDL-C value at protocol-defined goals	**Primary endpoints** • Proportion of participants with adverse events (AE) • Discontinuations due to AEs

Statistical Methods

Efficacy Endpoints: Differences in LS Means and the associated 95% CIs and p-values provided and based on a constrained longitudinal data analysis model

Multiplicity Adjustment: Hypothesis testing for the primary efficacy endpoint performed in order of descending randomized dose and planned to stop with the first comparison that has a one-sided p-value ≥0.025

Results – Baseline Participant Characteristics

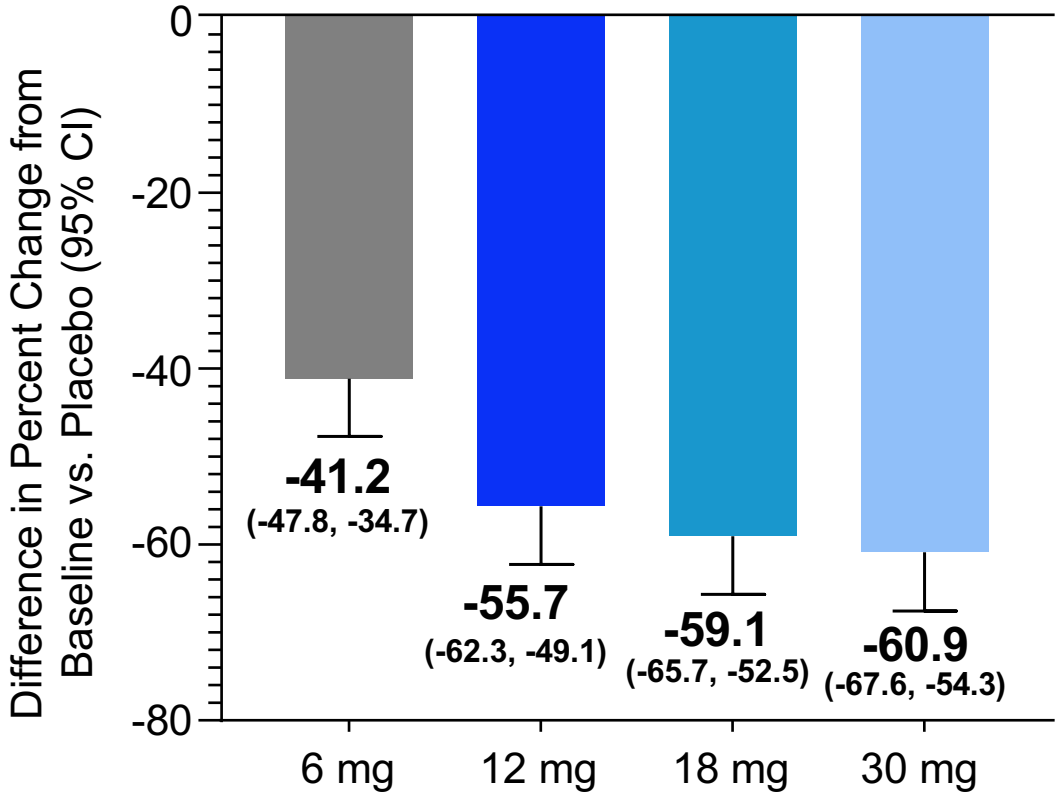
	MK-0616				Placebo	Total
	6 mg (n=77)	12 mg (n=76)	18 mg (n=76)	30 mg (n=76)	(n=76)	(n=381)
Sex (female), n (%)	38 (49.4)	35 (46.1)	39 (51.3)	38 (50.0)	38 (50.0)	**188 (49.3)**
Age, mean ± SD, years	61.7 ±10.3	62.0 ± 9.4	62.0 ± 9.2	60.9 ± 10.2	60.6 ± 9.3	**61.5 ± 9.7**
Type 2 Diabetes, n (%)	39 (50.6)	45 (59.2)	45 (59.2)	37 (48.7)	45 (59.2)	**211 (55.4)**
Race, n (%)						
White	49 (63.6)	48 (63.2)	55 (72.4)	44 (57.9)	54 (71.1)	**250 (65.6)**
Asian	18 (23.4)	13 (17.1)	11 (14.5)	13 (17.1)	8 (10.5)	**63 (16.5)**
Black/African American	4 (5.2)	5 (6.6)	2 (2.6)	9 (11.8)	4 (5.3)	**24 (6.3)**
Multiple	2 (2.6)	5 (6.6)	3 (3.9)	8 (10.5)	5 (6.6)	**23 (6.0)**
Am. Indian/Alaska Native	4 (5.2)	5 (6.6)	5 (6.6)	2 (2.6)	5 (6.6)	**21 (5.5)**
Ethnicity, n (%)						
Hispanic or Latino	26 (33.8)	29 (38.2)	31 (40.8)	31 (40.8)	37 (48.7)	**154 (40.4)**
ASCVD risk category, n (%)						
Clinical ASCVD	30 (39.0)	37 (48.7)	25 (32.9)	30 (39.5)	25 (32.9)	**147 (38.6)**
Intermediate/high ASCVD risk	43 (55.8)	36 (47.4)	47 (61.8)	42 (55.3)	47 (61.8)	**215 (56.4)**
Borderline ASCVD risk	4 (5.2)	3 (3.9)	4 (5.3)	4 (5.3)	3 (3.9)	**18 (4.7)**
Missing	0	0	0	0	1 (1.3)	**1 (0.3)**
LDL-C, mean ± SD, mg/dL	116.5 ± 37.0	117.3 ± 36.4	123.7 ± 35.1	119.4 ± 36.7	120.7 ± 28.3	**119.5 ± 34.8**

Participant Disposition

	MK-0616				Placebo
	6 mg (n=77)	12 mg (n=76)	18 mg (n=76)	30 mg (n=76)	(n=76)
Treated	**77**	**76**	**76**	**76**	**75**
Discontinued, n (%)	**7 (9.1)**	**2 (2.6)**	**4 (5.3)**	**5 (6.6)**	**4 (5.3)**
Adverse Event	2 (2.6)	0 (0.0)	2 (2.6)	2 (2.6)	1 (1.3)
Low eGFR	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Lost To Follow-Up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Non-Compliance With Study Drug	0 (0.0)	2 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol Deviation	3 (3.9)	0 (0.0)	1 (1.3)	2 (2.6)	1 (1.3)
Extended Travel	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Participant Withdrawal	1 (1.3)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)
Completed, n (%)	**70 (90.9)**	**74 (97.4)**	**72 (94.7)**	**71 (93.4)**	**71 (94.7)**

Results – Primary Endpoint

LDL-C at Week 8

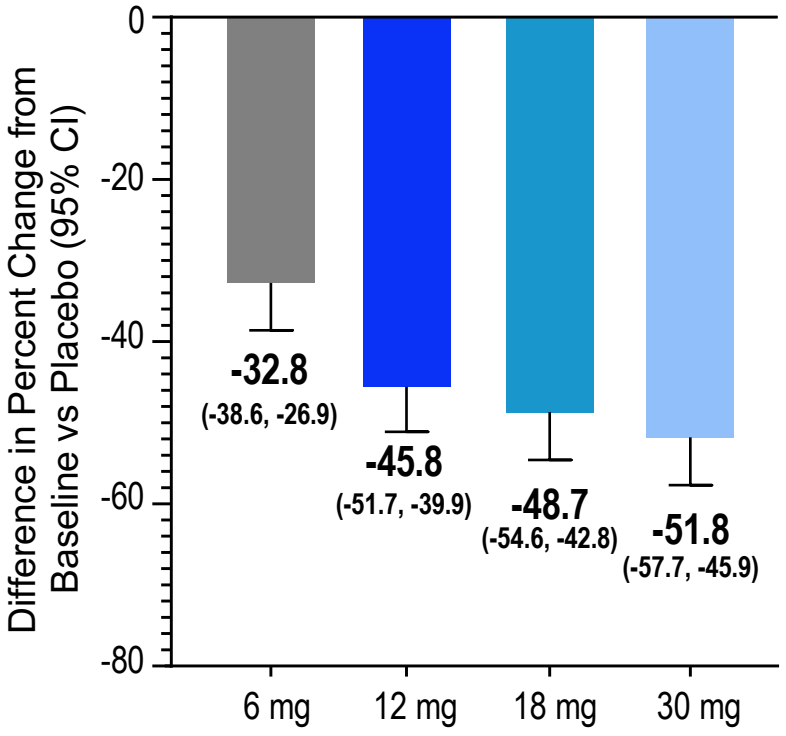


- LDL-C reduction from Baseline to Week 8 superior to placebo ($p<0.001$) for all doses of MK-0616
- Near-complete efficacy achieved by 2 weeks with persistent effect over the 8-week treatment period
- Results generally consistent across prespecified subgroups

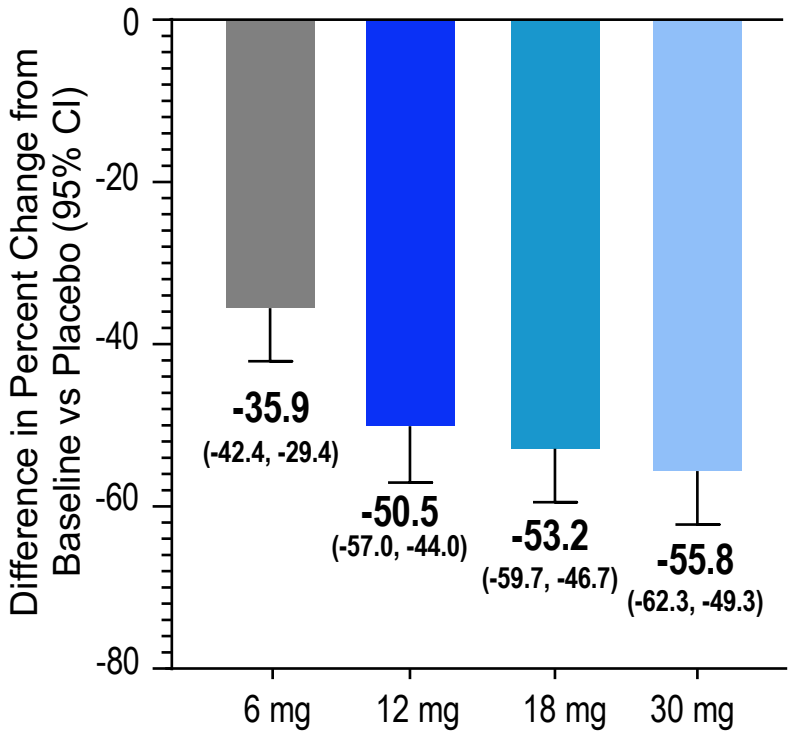
Efficacy Population: All participants who received ≥1 dose, had ≥1 observation for the analysis endpoint, and had baseline data for those analyses that require baseline data.

Results – Secondary Endpoints

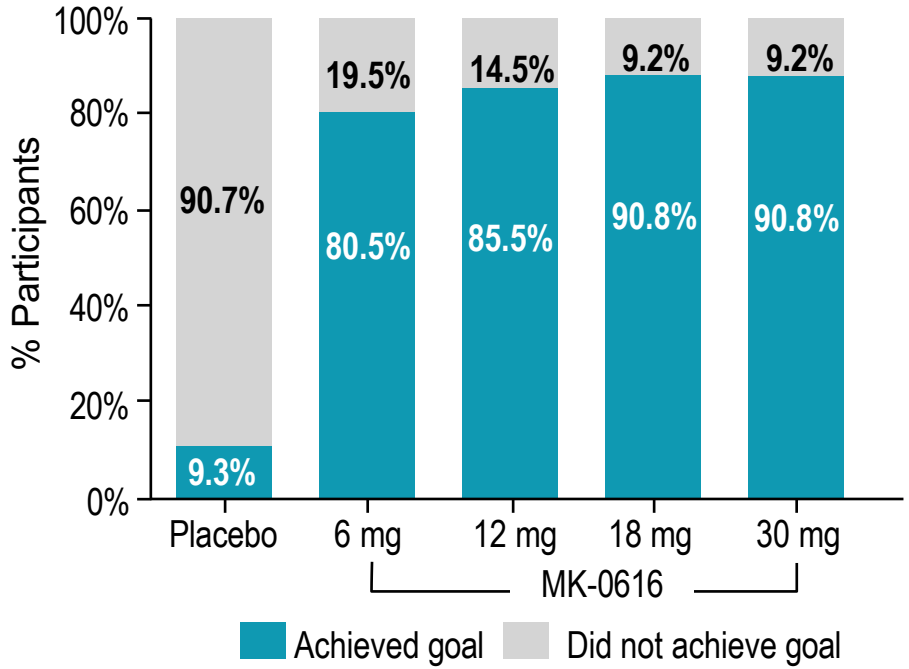
ApoB at Week 8



Non-HDL-C at Week 8



Achievement of Protocol-Defined Goals†



†Defined as:
LDL-C <70 mg/dL (<1.81 mmol/L) in participants with clinical ASCVD;
LDL-C <100 mg/dL (<2.59 mmol/L) in participants with high/intermediate ASCVD risk
LDL-C <130 mg/dL (<3.37 mmol/L) in participants with borderline ASCVD risk

Efficacy Population: All participants who received ≥1 dose, had ≥1 observation for the analysis endpoint, and had baseline data for those analyses that require baseline data.

Results – Safety and Tolerability Over 16 Weeks

	MK-0616				Placebo
	6 mg (n=77)	12 mg (n=76)	18 mg (n=76)	30 mg (n=76)	(n=75)
n (%) of participants with:					
≥1 AE	34 (44.2)	30 (39.5)	33 (43.4)	32 (42.1)	33 (44.0)
Discontinued Intervention due to an AE	2 (2.6)	0 (0.0)	2 (2.6)	2 (2.6)	1 (1.3)
Serious AEs	1 (1.3)	3 (3.9)	2 (2.6)	2 (2.6)	0 (0.0)
Moderate or severe AEs	10 (13.0)	9 (11.8)	10 (13.2)	12 (15.8)	11 (14.7)
Study intervention-related AEs*	6 (7.8)	11 (14.5)	11 (14.5)	8 (10.5)	8 (10.7)
Deaths**	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)

AE = Adverse Event
* Deemed by the investigator to be possibly, probably, or definitely related to study intervention
** There was one death that was the result of a traffic accident

Safety Populations: All randomized participants who received ≥1 dose

Conclusions

- **In this Phase 2b randomized controlled trial in a diverse population of hypercholesterolemia patients:**
  - All doses of MK-0616 demonstrated statistically superior reductions in LDL-C vs. placebo with up to 60.9% placebo-adjusted reduction from baseline to Week 8; results were consistent across subgroups
  - Improvements in ApoB and non-HDL-C were consistent with those observed for LDL-C with up to a 51.8% reduction in ApoB and up to 55.8% reduction in non-HDL-C
  - MK-0616 was well tolerated with no overall trends in AEs across treatment groups
- **These data support further development of MK-0616, an oral PCSK9 inhibitor that may improve access to effective LDL-C-lowering therapies and improve attainment of guideline-recommended LDL goals aimed at reducing cardiovascular risk**

- **Thank you for your interest in this trial. The authors also thank the participants, the investigators, and site personnel who made this trial possible.**

- **The full trial results are now published in the *Journal of the American College of Cardiology.***

JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

The full trial results are available here:

To download today's presentation:
https://bit.ly/3j8y2oh