

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

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Disclosures

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Background

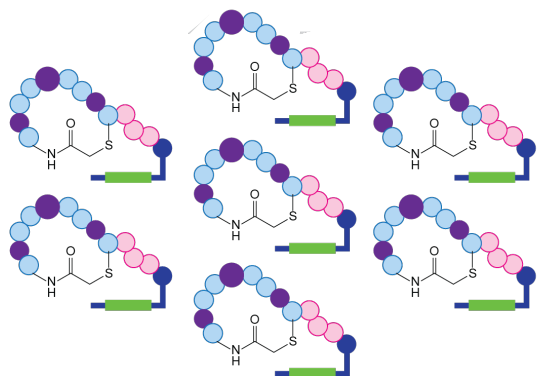
- Elevated low density lipoprotein cholesterol (LDL-C) is a primary causative factor for atherosclerotic cardiovascular disease (ASCVD)
- Despite effective treatments (e.g., statins), a large proportion of patients fail to achieve guideline-recommended LDL-C levels
- Injectable treatments targeting proprotein 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

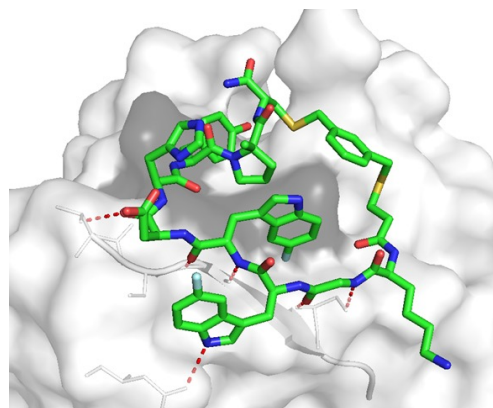
- *Macrocyclic peptides can bind PCSK9 with monoclonal antibody-like affinity at 1/100th molecular weight*

Macrocycle Library
Macrocyclic peptides displayed on mRNA



Hit-finding platform
mRNA display

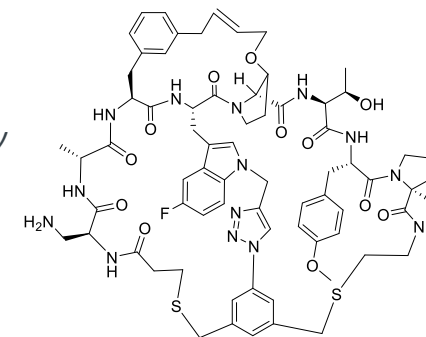
Screening of ultra-large libraries (10¹⁴ potential compounds)



Medicinal Chemistry
Structure-Based Drug Discovery

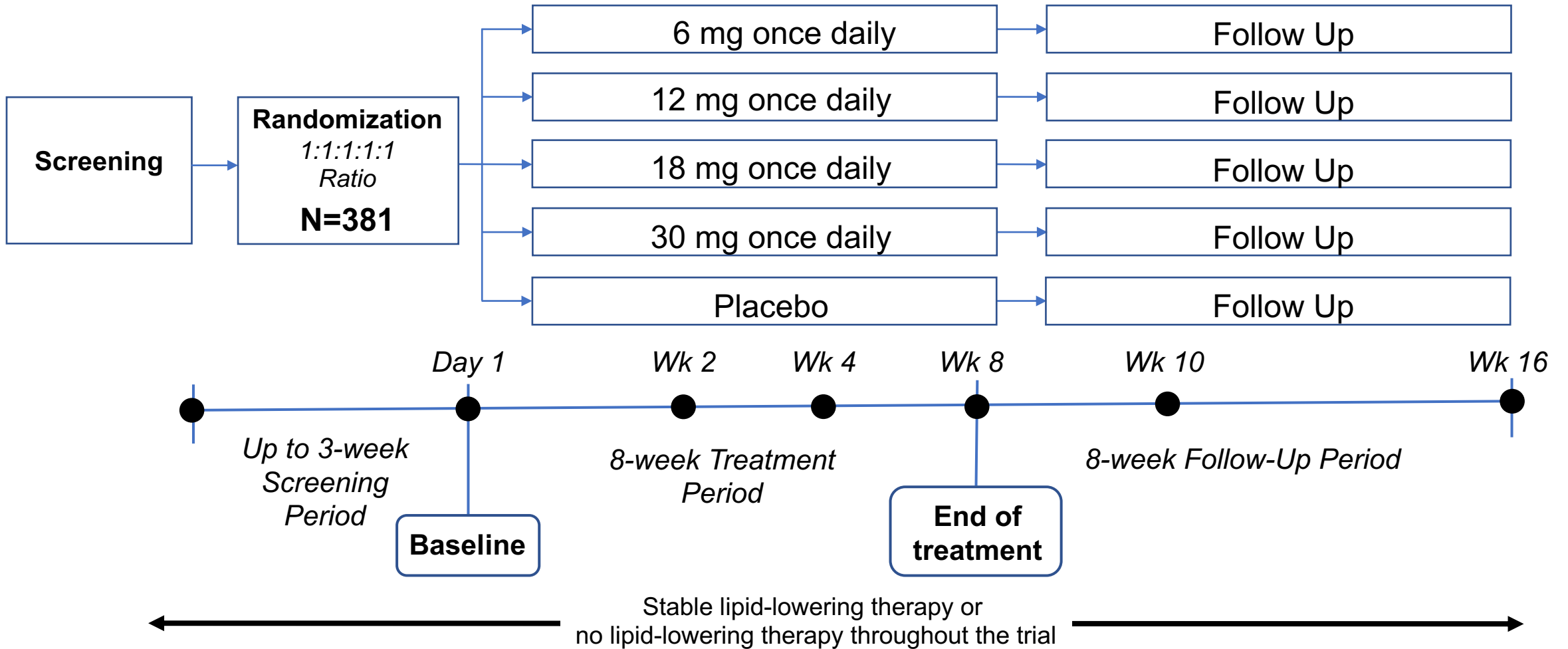
Improve structure-activity relationship, PK and stability

Macrocyclic Peptide
Predecessor to MK-0616



MW = ~1500 g/mol
Ki = 2-5 pM

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
<p>Primary endpoint</p> <ul style="list-style-type: none">• LDL-C percent change from baseline <p>Secondary endpoints</p> <ul style="list-style-type: none">• ApoB percent change from baseline• non-HDL-C percent change from baseline• % participants with LDL-C value at protocol-defined goals	<p>Primary endpoints</p> <ul style="list-style-type: none">• Proportion of participants with adverse events (AE)• Discontinuations due to AEs

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

Results – Baseline Participant Characteristics

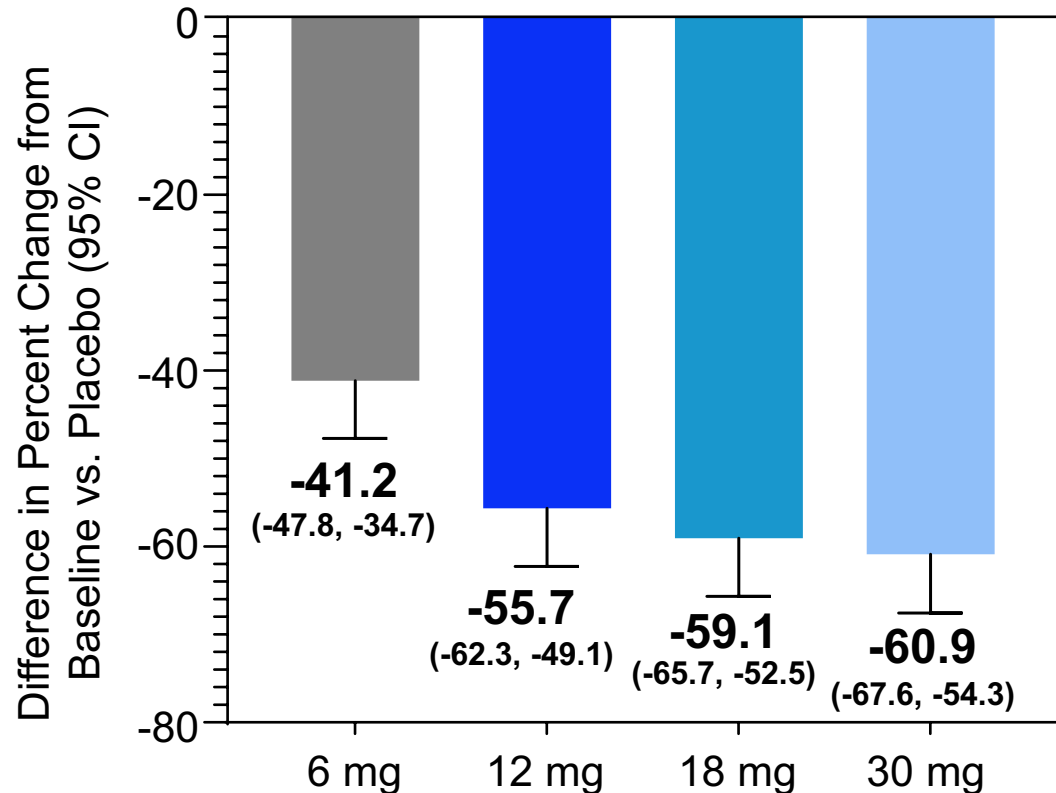
	MK-0616				Placebo (n=76)	Total (n=381)
	6 mg (n=77)	12 mg (n=76)	18 mg (n=76)	30 mg (n=76)		
Sex (female), n (%)	38 (49.4)	35 (46.1)	39 (51.3)	38 (50.0)	38 (50.0)	188 (49.3)
Age, mean ± SD, years	61.7 ± 10.3	62.0 ± 9.4	62.0 ± 9.2	60.9 ± 10.2	60.6 ± 9.3	61.5 ± 9.7
Type 2 Diabetes, n (%)	39 (50.6)	45 (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

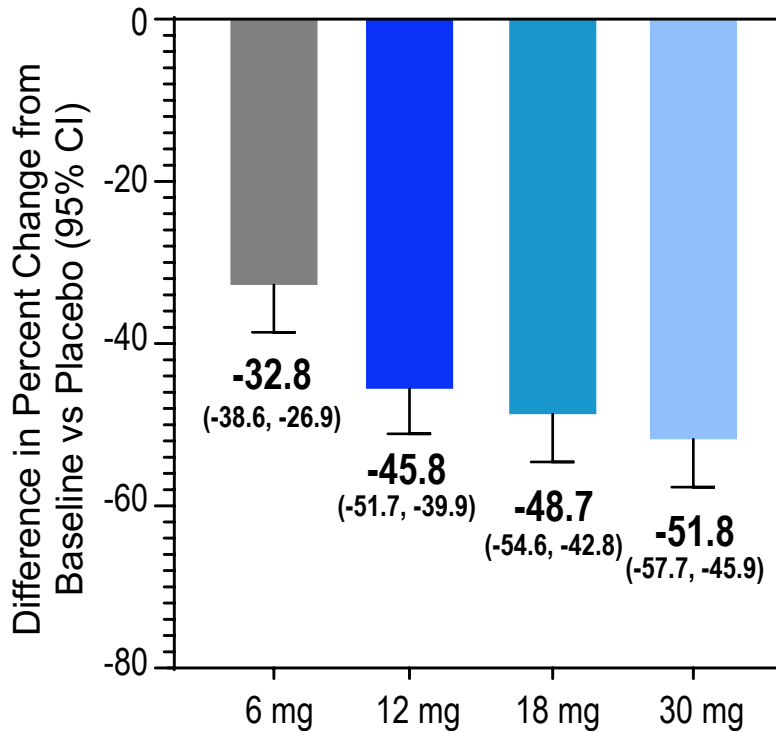


- LDL-C reduction from Baseline to Week 8 superior to placebo ($p < 0.001$) for all doses of MK-0616
- Near-complete efficacy achieved by 2 weeks with persistent effect over the 8-week treatment period
- Results generally consistent across prespecified subgroups

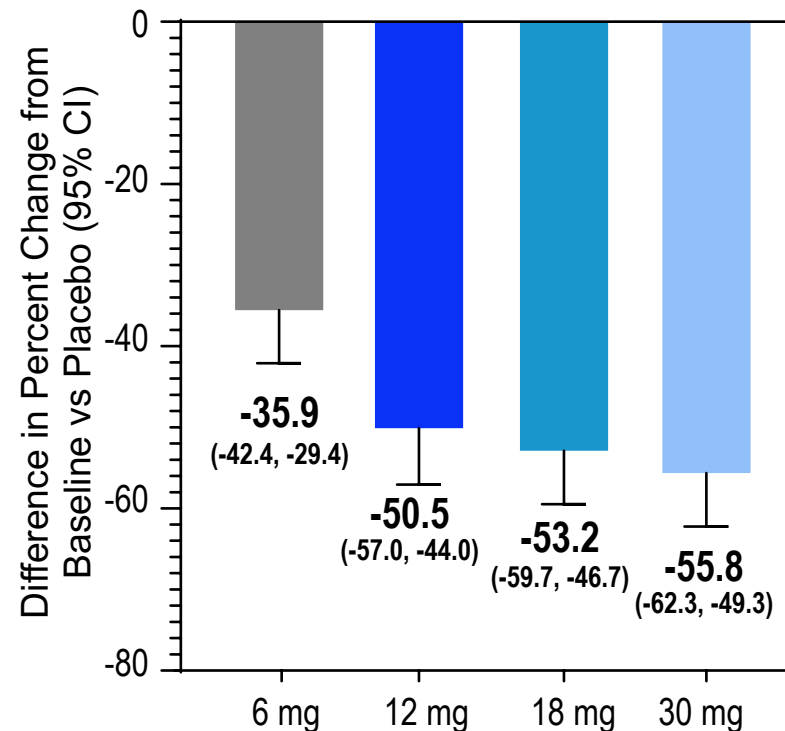
Efficacy Population: All participants who received ≥ 1 dose, had ≥ 1 observation for the analysis endpoint, and had baseline data for those analyses that require baseline data.

Results – Secondary Endpoints

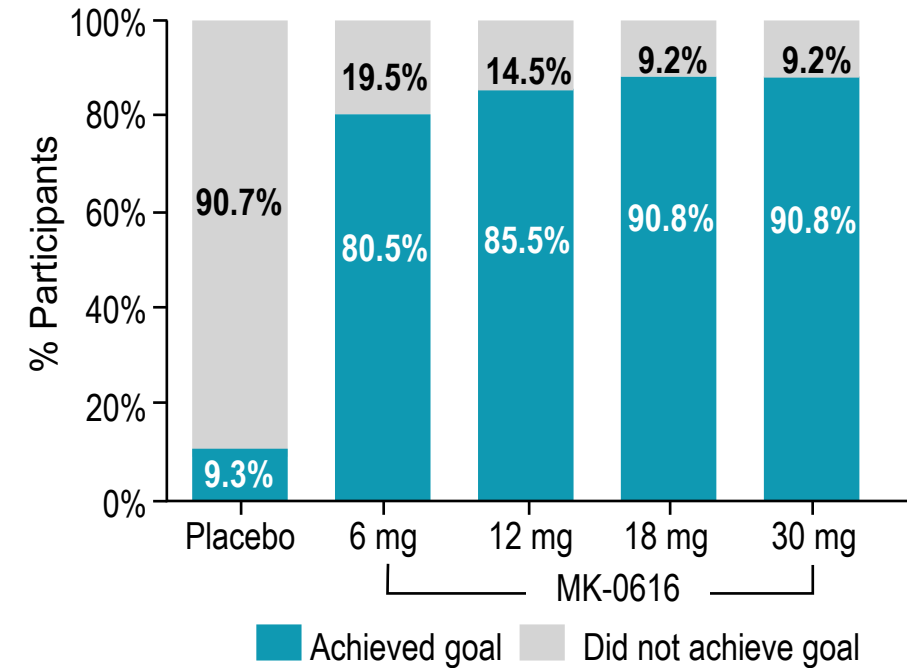
ApoB at Week 8



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 (n=75)
	6 mg (n=77)	12 mg (n=76)	18 mg (n=76)	30 mg (n=76)	
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*.



The full trial results are available here:



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