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ORIGINAL INVESTIGATIONS

Phase 2b Randomized Trial of the Oral PCSK9 Inhibitor MK-0616

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ABSTRACT

BACKGROUND MK-0616 is an oral macrocyclic peptide inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9) in development for the treatment of hypercholesterolemia.

OBJECTIVES This Phase 2b, randomized, double-blind, placebo-controlled, multicenter trial aimed to evaluate the efficacy and safety of MK-0616 in participants with hypercholesterolemia.

METHODS This trial was planned to include 375 adult participants with a wide range of atherosclerotic cardiovascular disease risk. Participants were assigned randomly (1:1:1:1:1 ratio) to MK-0616 (6, 12, 18, or 30 mg once daily) or matching placebo. The primary endpoints included percentage change from baseline in low-density lipoprotein cholesterol (LDL-C) at Week 8 and the proportion of participants with adverse events (AEs) and study intervention discontinuations due to AEs; participants were monitored for AEs for an additional 8 weeks after the 8-week treatment period.

RESULTS Of the 381 participants randomized, 49% were female, and the median age was 62 years. Among 380 treated participants, all doses of MK-0616 demonstrated statistically significant ($P < 0.001$) differences in least squares mean percentage change in LDL-C from baseline to Week 8 vs placebo: -41.2% (6 mg), -55.7% (12 mg), -59.1% (18 mg), and -60.9% (30 mg). AEs occurred in a similar proportion of participants in the MK-0616 arms (39.5% to 43.4%) as placebo (44.0%). Discontinuations due to AEs occurred in 2 or fewer participants in any treatment group.

CONCLUSIONS MK-0616 demonstrated statistically significant and robust, dose-dependent placebo-adjusted reductions in LDL-C at Week 8 of up to 60.9% from baseline and was well tolerated during 8 weeks of treatment and an additional 8 weeks of follow-up. (A Study of the Efficacy and Safety of MK-0616 [Oral PCSK9 Inhibitor] in Adults With Hypercholesterolemia [MK-0616-008]; NCT05261126) (J Am Coll Cardiol 2023;81:1553-1564) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The causative association of low-density lipoprotein cholesterol (LDL-C) with atherosclerotic cardiovascular disease (ASCVD) is well known, and treatment with LDL-C-lowering therapies, particularly statins, has demonstrated lower risk of myocardial infarction, stroke, and death from cardiovascular disease.[1] Despite available treatments, a large proportion of patients fail to achieve

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

AE = adverse event

ApoB = apolipoprotein B

ASCVD = atherosclerotic cardiovascular disease

HDL-C = high-density lipoprotein cholesterol

LDL-C = low-density lipoprotein cholesterol

Lp(a) = lipoprotein (a)

LS = least squares

PCSK9 = proprotein convertase subtilisin/kexin type 9

VLDL-C = very low-density lipoprotein cholesterol

guideline-recommended LDL-C levels, resulting in residual cardiovascular risk and a global unmet need.[2-6] Limiting factors for currently available treatments may include tolerability concerns with statin therapy, limited incremental efficacy with available add-on oral therapies, patient reluctance for repeat injections with injectable treatments, and cost or access barriers. Thus, novel oral therapies that are effective, well tolerated, and accessible to a majority of patients are needed.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a relatively recent target for LDL-C-lowering therapies.[7,8] PCSK9 binds to LDL receptors in the liver and directs the receptors to intracellular lysosomes for degradation, impeding their normal recycling to the cell surface and resulting in reduced clearance of LDL from circulation.[9,10] Injectable treatments targeting PCSK9 have demonstrated large reductions in LDL-C and decreased risk of ASCVD events. An oral PCSK9 inhibitor that can achieve robust reductions in LDL-C and is well tolerated may offer potential advantages over injectable PCSK9 inhibitors in terms of simplicity of dosing, patient preference, and access.

MK-0616 is an orally bioavailable, renally excreted, macrocyclic peptide that binds to PCSK9. In early studies, treatment with single doses of MK-0616 resulted in >90% reduction in free PCSK9, and treatment with multiple doses during 14 days resulted in a decrease of plasma LDL-C by >60%.[11] This Phase 2b study was designed to evaluate LDL-C lowering and safety of MK-0616 in a diverse population of participants with hypercholesterolemia and a broad range of cardiovascular risk.

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METHODS

This Phase 2b, randomized, double-blind, placebo-controlled study (Sponsor Protocol #008, Clinical Trials Registry, NCT05261126) was conducted at 63 sites in 8 countries. The study was performed in accordance with applicable federal regulations and principles of Good Clinical Practice. All sites received approval from Institutional Review Boards or independent ethics committees (Supplemental Appendix), and all participants provided written informed consent before enrollment.

PARTICIPANTS. Eligible male and female participants aged ≥18 years and ≤80 years were to be in one of the following risk categories with corresponding fasted LDL value:

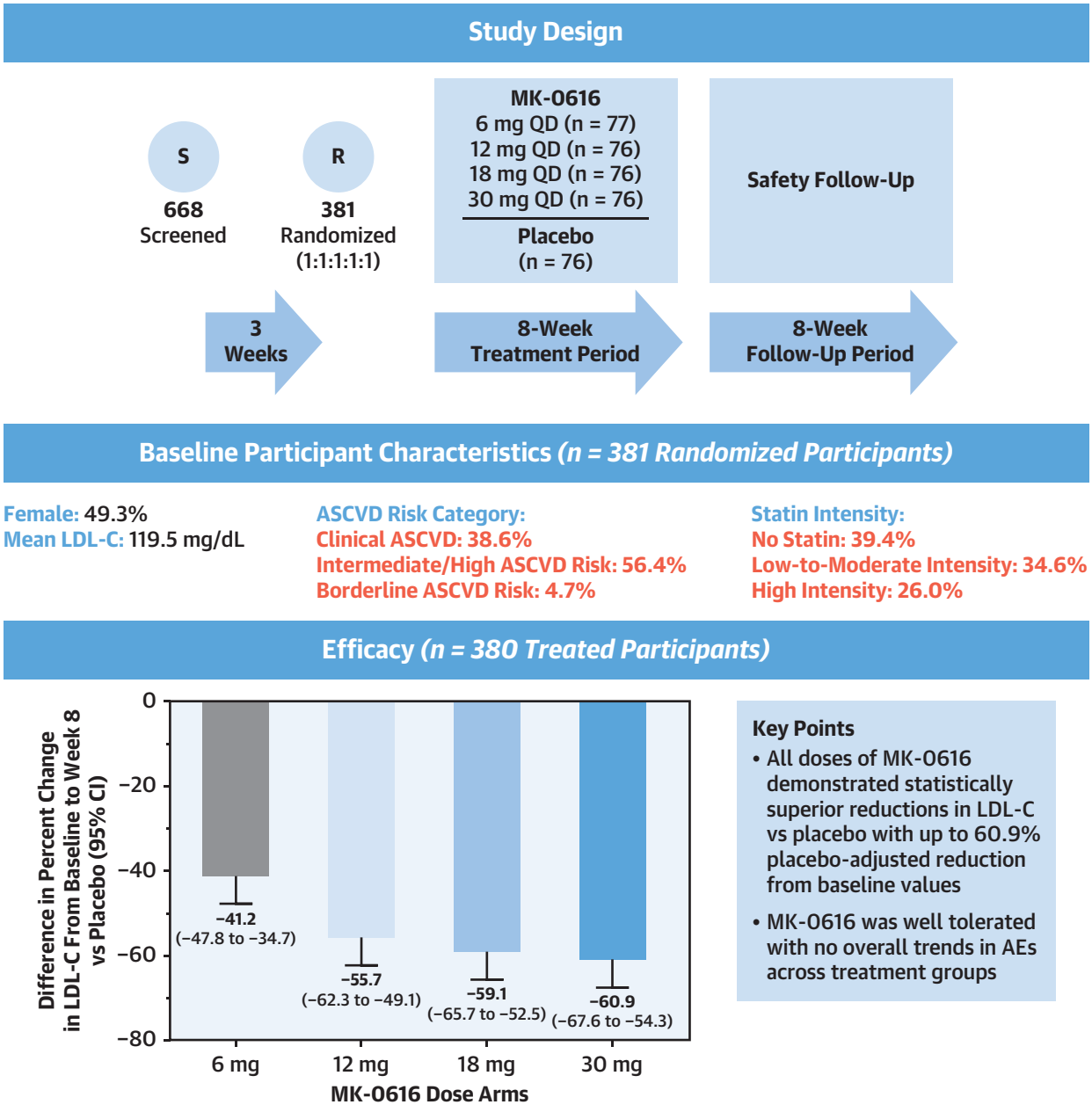
1) Clinical ASCVD: LDL-C range = ≥70 and ≤160 mg/dL (≥1.81 and ≤4.14 mmol/L);
2) Intermediate or higher risk for ASCVD: participants without clinical ASCVD with a 10-year risk of having an ASCVD event that is ≥7.5% (determined using an ASCVD risk calculator such as the ASCVD Risk Estimator[12] or locally acceptable equivalent) and/or an ASCVD-risk equivalent (eg, diabetes mellitus or heterozygous familial hypercholesterolemia); LDL-C range = ≥100 and ≤200 mg/dL (≥2.59 and ≤5.18 mmol/L); and
3) Borderline risk for ASCVD: participants without clinical ASCVD with a 10-year risk of having an ASCVD event that is ≥5.0% and <7.5%; LDL-C range = ≥130 and ≤250 mg/dL (≥3.37 and ≤6.48 mmol/L).

Participants were also either on a stable dose of 1 or more lipid-lowering therapies for ≥30 days before the screening visit or had not received treatment with any lipid-lowering therapy for ≥30 days before the screening visit.

Participants who were diagnosed with homozygous familial hypercholesterolemia were excluded from this study. Other cardiovascular factors that led to exclusion included unstable angina, myocardial infarction, transient ischemic attack, stroke, a fasting triglyceride value ≥400 mg/dL (≥4.52 mmol/L) at the screening visit, or percutaneous transluminal coronary angioplasty within 3 months of the study, as well as a planned coronary revascularization procedure within the 3 months after the screening visit. Participants with a history of nephrotic syndrome, moderate or greater renal insufficiency (ie, estimated glomerular filtration rate <45 mL/min/1.73 m^2), poorly controlled diabetes mellitus (ie, A1C ≥9.0%), or a history of malignancy 3 or fewer years before the study were also excluded. Female participants of child-bearing potential were not included if they were pregnant or breastfeeding or did not agree to abstain from heterosexual activity or use acceptable contraceptives. Additionally, participants who had previously used a PCSK9 inhibitor without adequate washout (ie, 6 months for a monoclonal antibody or 1 year for a small interfering RNA PCSK9 inhibitor) were not included.

DESIGN. This study consisted of an up-to-21-day screening period (Screening to Day 1), an 8-week treatment period (Visit 2 [Day 1] to Visit 5 [Week 8]), and an 8-week post-treatment follow-up period (Visit 5 [Week 8] to Visit 7 [Week 16]) for safety assessment (**Central Illustration**). Participants who discontinued study intervention prematurely were encouraged to

CENTRAL ILLUSTRATION **A Phase 2b Study of MK-0616, an Oral PCSK9 Inhibitor**



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This Phase 2b, randomized, controlled trial randomized 381 participants for 16 weeks including an 8-week treatment period and an 8-week follow-up period. **(Lower left)** The forest plot shows statistically significant ($P < 0.001$) reductions in LDL-C at Week 8 of treatment for all MK-0616 doses vs placebo. AE = adverse event; ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; QD = once daily.

continue in the study off-treatment and to complete all remaining visits.

After completing the screening period, participants meeting eligibility criteria were randomized in a 1:1:1:1:1 ratio to treatment with either 1 of 4 MK-0616 doses (6, 12, 18, or 30 mg) or matching placebo. Each dose of MK-0616 was formulated with sodium caprate, a permeation enhancer; the placebo

formulation did not contain permeation enhancer. Because food decreases the bioavailability of MK-0616 and delays its absorption, randomized participants were advised to take 1 capsule of study intervention daily in a fasted state. Guidance for fasting included taking study medication with water after an overnight fast of ≥8 h and to withhold food and beverages (except water) until 30 min after taking study medication.

Randomization was stratified by renal function (estimated glomerular filtration rate ≥60 or <60 mL/min/1.73 m^2) and by intensity of background statin therapy (ie, no statin therapy vs low- to moderate-intensity statin therapy vs high-intensity statin therapy[13]).

Participants were randomized using a computer-generated allocation schedule that was implemented using interactive response technology. A double-blinding technique with in-house blinding was used. MK-0616 and placebo were packaged identically so that blinding was maintained. The participant, the investigator, the site personnel, and the sponsor personnel or delegates who were involved in the study were blinded to the intervention assignments.

EFFICACY EVALUATION. The primary hypothesis was that at least 1 of the 4 doses of MK-0616 is superior to placebo for the primary endpoint of percentage change from baseline in LDL-C at Week 8.

LDL-C was calculated based on the Friedewald formula,[14] except in cases where the calculated LDL-C was ≤40 mg/dL or missing, or triglycerides were ≥400 mg/dL. In these cases, LDL-C was directly measured using beta quantification. For analysis, LDL-C was based on the beta-quantification method whenever it was available, or based on the Friedewald formula when no beta quantification was available. LDL-C values <20 mg/dL by beta quantification were reported and analyzed as 20 mg/dL (n = 23 over 8 weeks; n = 7 at Week 8).

Secondary endpoints evaluated at Week 8 included the effect of MK-0616 relative to placebo on percentage change from baseline in apolipoprotein B (ApoB), the percentage change from baseline in non-high-density lipoprotein cholesterol (non-HDL-C), and the proportion of participants who attained LDL-C goals. The LDL-C goals were 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 intermediate or higher ASCVD risk; and LDL-C <130 mg/dL (<3.37 mmol/L) in participants with borderline ASCVD risk. Percentage change from baseline in other lipid parameters including HDL-C, total cholesterol, triglycerides, very low-density lipoprotein cholesterol (VLDL-C), and lipoprotein(a) (Lp[a]) at Week 8 were assessed as exploratory endpoints.

SAFETY EVALUATION. Assessments of adverse events (AEs) and premature discontinuations of study intervention due to AEs were primary endpoints in this study. AEs were assessed by investigators with regard to seriousness, intensity, relation to study medication, and need for study intervention discontinuation due to an AE. Other study parameters, including vital signs, physical examination, and laboratory safety tests, were also evaluated.

STATISTICAL ANALYSIS. The sample size for this Phase 2b trial was driven primarily by safety and exposure considerations. Based on an assumed SD of 25%, a -50% treatment difference (MK-0616 minus placebo) with respect to mean percentage change from baseline in LDL-C at Week 8, and a discontinuation rate of <2% at or before Week 8, a sample size of 75/arm would provide >99% power at a 1-sided alpha of 0.025 for each of the treatment comparisons.

The population for efficacy analyses included all randomized participants who received at least 1 dose of double-blind study intervention, had at least 1 observation for the analysis endpoint, and had baseline data for those analyses that require baseline data. The population for safety included all randomized participants who received at least 1 dose of double-blind study intervention.

For the primary and secondary endpoints of percentage change from baseline in LDL-C (primary), ApoB, and non-HDL-C at Week 8, the differences in least squares (LS) means and the associated 95% CIs and *P* values were provided (MK-0616 minus placebo; 4 pairwise comparisons per endpoint) based on a constrained longitudinal data analysis model. The constrained longitudinal data analysis model assumes a common baseline mean across treatment groups and a different mean for each treatment group at post-baseline time points. In this model, the response vector consists of the baseline value and the percentage change observed at the post-baseline time points. To control for multiplicity for testing of hypotheses with respect to the primary endpoint, hierarchical testing was performed in order of descending randomized dose and was to stop with the first comparison with a 1-sided *P* value ≥0.025.

For the secondary endpoint of proportion of participants with LDL-C value at goal at Week 8, 95% CIs (based on the stratified Miettinen and Nurminen method[15]) and nominal *P* values were provided for between-treatment differences. For the exploratory

endpoint of percentage change in HDL-C, total cholesterol, triglycerides, VLDL-C, and Lp(a) at Week 8, differences in mean percentage change from baseline with associated 95% CIs vs placebo are provided.

RESULTS

PARTICIPANTS. Of 668 participants screened, 381 were randomized, with 380 treated and included in both efficacy and safety analyses (**Figure 1**): 77, 76, 76, 76, and 75 participants treated with MK-0616 6 mg, MK-0616 12 mg, MK-0616 18 mg, MK-0616 30 mg, and placebo, respectively. There were 358 (94.2%) participants who completed the 8-week treatment period and the 8-week safety follow-up period.

Baseline participant characteristics were generally balanced between the treatment groups (**Table 1**). At baseline, median age was 62 years, 49% of participants were female, and mean LDL-C level was 119.5 ± 34.8 mg/dL. Of randomized participants, 38.6% were categorized as having clinical ASCVD, 56.4% were categorized as intermediate/high risk for ASCVD, and 4.7% were categorized as borderline risk for ASCVD. Additionally, 39.4%, 34.6%, and 26.0% of participants were on no statin, low- to moderate-intensity therapy, and high-intensity therapy, respectively.

EFFICACY. There were statistically significant differences for all MK-0616 dose groups vs placebo for the primary efficacy endpoint (**Central Illustration, Table 2**), with differences in LS means for percentage change from baseline in LDL-C at Week 8 -41.2%, -55.7%, -59.1%, and -60.9% for MK-0616 6 mg, MK-0616 12 mg, MK-0616 18 mg, and MK-0616 30 mg vs placebo, respectively ($P < 0.001$ for all comparisons) (**Table 2**). Near complete efficacy was reached by Week 2 and the effect was persistent during the 8-week treatment period (**Figure 2**). The effect of MK-0616 relative to placebo on the percentage change from baseline at LDL-C at Week 8 was generally consistent across the prespecified subgroups (Supplemental Figure 1).

The secondary endpoints, mean percentage change in ApoB and non-HDL-C, supported the findings for the primary efficacy endpoint. The differences in LS means from placebo for percentage change from baseline at Week 8 were -32.8%, -45.8%, -48.7%, and -51.8% for ApoB and -35.9%, -50.5%, -53.2%, and -55.8% for non-HDL-C with MK-0616 6 mg, 12 mg, 18 mg, and 30 mg, respectively (**Table 2**). The proportion of participants at protocol-defined goals for LDL-C reduction was 80.5%, 85.5%, 90.8%, and 90.8% with MK-0616 6 mg, 12 mg, 18 mg, and 30 mg, respectively, compared with 9.3% with placebo (**Table 2**).

For the exploratory endpoint of percentage change from baseline in Lp(a) at Week 8, the mean differences vs placebo were -12.2% (6 mg), -21.3% (12 mg), -21.7% (18 mg), and -23.7% (30 mg) with MK-0616 6 mg, MK-0616 12 mg, MK-0616 18 mg, and MK-0616 30 mg, respectively (**Table 3**). Results for the other exploratory lipid endpoints including HDL-C, total cholesterol, triglycerides, and VLDL-C are provided in Supplemental Table 1.

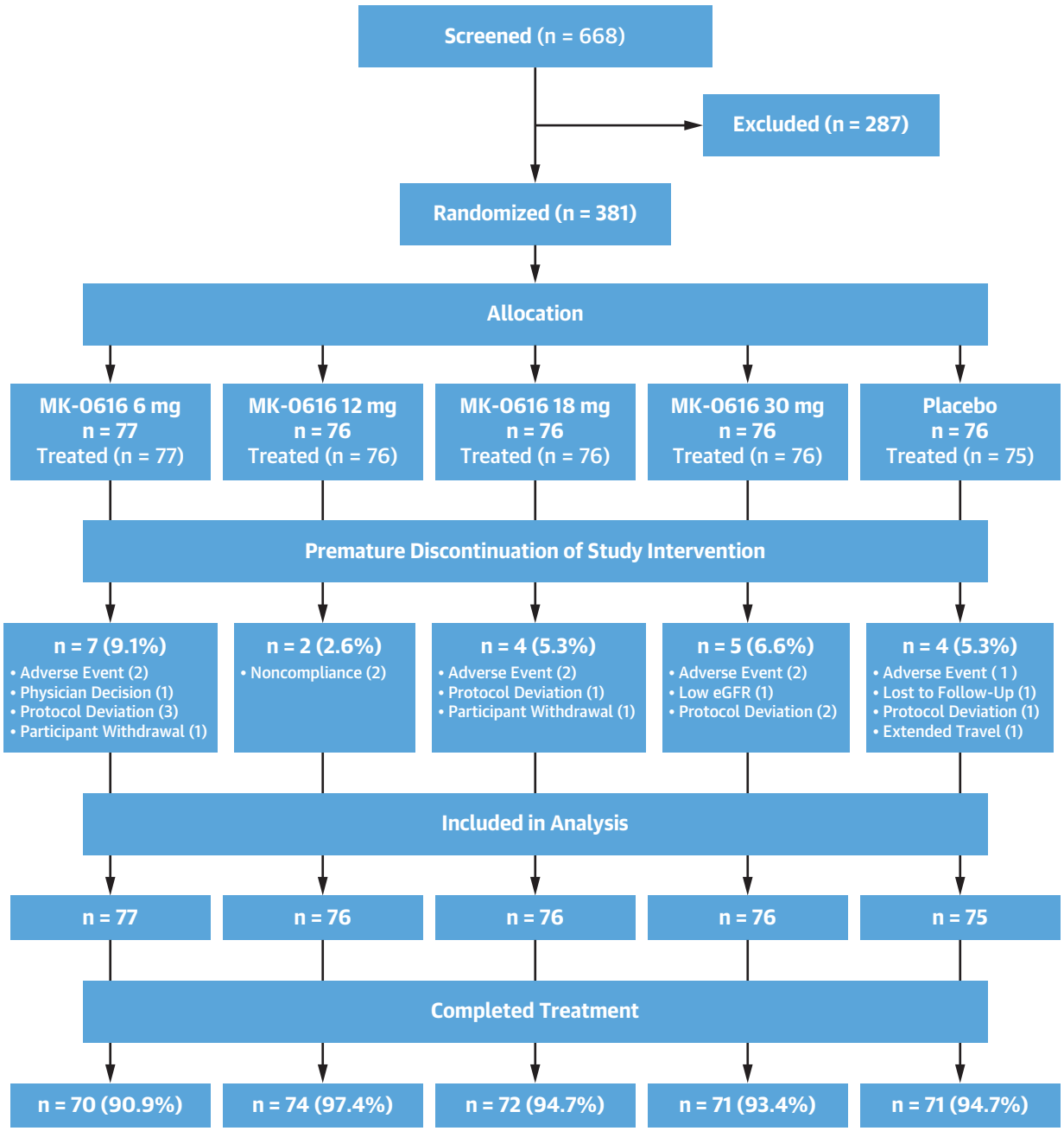
SAFETY. During the 16-week study, including the 8-week treatment period and the 8-week safety follow-up period, the proportion of participants with AEs was similar in all arms: 34 (44.2%), 30 (39.5%), 33 (43.4%), 32 (42.1%), and 33 (44.0%) participants randomized to MK-0616 6 mg, MK-0616 12 mg, MK-0616 18 mg, MK-0616 30 mg, and placebo, respectively (**Table 4**). The proportion of participants who discontinued study intervention due to AEs was similar between treatment groups with no more than 2 participants discontinuing within a single group. Participants with serious AEs were also uncommon, with 3 or fewer in the MK-0616 groups and none in the placebo group. None of the serious AEs were deemed related to study intervention by the investigator. There was 1 death in the MK-0616 18 mg group that was the result of a motor vehicle accident and deemed unrelated to study medication.

The most common AE in the study was COVID-19 infection, which occurred in 7.8%, 2.6%, 6.6%, 5.3%, and 9.3% of participants in MK-0616 6 mg, 12 mg, 18 mg, 30 mg, and placebo, respectively. Overall, there was no AE that increased in incidence in a dose-dependent manner and there were no overall trends in AEs across treatment groups (**Table 4**). Supplemental Table 2 presents a summary of AEs during the 8-week treatment period only. Changes from baseline to Week 8 in laboratory parameters, including chemistry and hematology parameters, renal and liver function tests, and hemoglobin A1C, were similar across treatment arms.

DISCUSSION

In this Phase 2b study, treatment with MK-0616, an oral PCSK9 inhibitor, in participants with hypercholesterolemia, led to statistically significant reductions in LDL-C compared with placebo, with >55% placebo-adjusted reduction observed at doses of 12 mg and higher (**Central Illustration**). MK-0616 was well tolerated and there were no overall trends in AEs across treatment groups.

FIGURE 1 **The CONSORT Diagram**



The flow of participants throughout the study is shown including the number screened, excluded, randomized, treated, prematurely discontinued, and completed in this Phase 2b randomized, controlled clinical trial. eGFR = estimated glomerular filtration rate.

This study was designed to evaluate MK-0616 in a population with diverse demographics and a range of cardiovascular risk. Almost half of the population included were women, ~40% were Hispanic, ~40% had clinical ASCVD, and more than one-half were intermediate to high risk for ASCVD. Study participants were also well distributed with respect to background statin therapy, including those on no statin therapy, low- to moderate-intensity therapy, and high-intensity therapy. Within the limits of the

TABLE 1 Baseline Participant Characteristics

	MK-0616 6 mg QD (n = 77)	MK-0616 12 mg QD (n = 76)	MK-0616 18 mg QD (n = 76)	MK-0616 30 mg QD (n = 76)	Placebo (n = 76)
Female	38 (49.4)	35 (46.1)	39 (51.3)	38 (50.0)	38 (50.0)
Age, y	61.7 ± 10.3	62.0 ± 9.4	62.0 ± 9.2	60.9 ± 10.2	60.6 ± 9.3
Race					
White	49 (63.6)	48 (63.2)	55 (72.4)	44 (57.9)	54 (71.1)
Asian	18 (23.4)	13 (17.1)	11 (14.5)	13 (17.1)	8 (10.5)
Black or African American	4 (5.2)	5 (6.6)	2 (2.6)	9 (11.8)	4 (5.3)
Multiple	2 (2.6)	5 (6.6)	3 (3.9)	8 (10.5)	5 (6.6)
American Indian/Alaska Native	4 (5.2)	5 (6.6)	5 (6.6)	2 (2.6)	5 (6.6)
Ethnicity					
Hispanic or Latino	26 (33.8)	29 (38.2)	31 (40.8)	31 (40.8)	37 (48.7)
Not Hispanic or Latino	51 (66.2)	46 (60.5)	45 (59.2)	45 (59.2)	38 (50)
Not reported	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	1 (1.3)
BMI, kg/m^2	29.3 ± 5.6	29.0 ± 5.5	29.9 ± 6.1	28.9 ± 5.9	29.9 ± 5.8
Diabetes					
Type 1	1 (1.3)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)
Type 2	39 (50.6)	45 (59.2)	45 (59.2)	37 (48.7)	45 (59.2)
eGFR ≥60 mL/min/1.73 m^2	71 (92.2)	72 (94.7)	72 (94.7)	71 (93.4)	71 (93.4)
Heterozygous FH	3 (3.9)	5 (6.6)	6 (7.9)	8 (10.5)	7 (9.2)
LDL-C, mg/dL	116.5 ± 37.0	117.3 ± 36.4	123.7 ± 35.1	119.4 ± 36.7	120.7 ± 28.3
ApoB, mg/dL	103.6 ± 25.8	104.3 ± 27.0	108.0 ± 23.6	106.4 ± 25.1	107.7 ± 20.7
Non-HDL-C, mg/dL	145.7 ± 40.8	147.4 ± 44.2	152.4 ± 37.0	150.2 ± 39.4	151.6 ± 32.4
Lp(a), mg/dL	46.5 ± 57.8	45.0 ± 51.8	34.0 ± 41.7	46.0 ± 51.2	41.0 ± 49.6
HDL-C, mg/dL	51.3 ± 14.7	48.9 ± 13.3	49.9 ± 16.3	50.6 ± 14.1	46.9 ± 12.0
Total cholesterol, mg/dL	196.9 ± 43.9	196.4 ± 46.1	202.3 ± 37.8	200.8 ± 38.8	199.4 ± 32.1
Triglycerides, mg/dL	146.0 ± 70.6	149.9 ± 78.1	147.3 ± 85.5	155.0 ± 95.5	157.4 ± 81.7
VLDL-C, mg/dL	29.2 ± 14.2	29.1 ± 14.3	28.3 ± 14.1	28.7 ± 12.1	30.5 ± 14.2
Statin intensity					
No statin	30 (39.0)	29 (38.2)	31 (40.8)	30 (39.5)	30 (39.5)
Low-to-moderate intensity	27 (35.1)	27 (35.5)	26 (34.2)	26 (34.2)	26 (34.2)
High intensity	20 (26.0)	20 (26.3)	19 (25.0)	20 (26.3)	20 (26.3)
Ezetimibe	12 (15.6)	15 (19.7)	6 (7.9)	13 (17.1)	7 (9.2)
ASCVD risk category[a]					
Clinical ASCVD	30 (39.0)	37 (48.7)	25 (32.9)	30 (39.5)	25 (32.9)
Intermediate/high ASCVD risk	43 (55.8)	36 (47.4)	47 (61.8)	42 (55.3)	47 (61.8)
Borderline ASCVD risk	4 (5.2)	3 (3.9)	4 (5.3)	4 (5.3)	3 (3.9)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)

Values are n (%) or mean ± SD. [a]Intermediate/high risk includes participants with a 10-year risk of having an ASCVD event that is ≥7.5% and/or a risk equivalent (eg, diabetes mellitus or heterozygous familial hypercholesterolemia); borderline risk includes participants with a 10-year risk of having an ASCVD event that is ≥5.0% and <7.5%.

ApoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); QD = once daily; VLDL-C = very low-density lipoprotein cholesterol.

sample size, the results were generally consistent across all prespecified subgroups. Overall, this study demonstrates that MK-0616 has the potential to make a broad, evidence-based impact on a disease that is a leading cause of global mortality across genders, races and ethnicities, and levels of risk.

Currently available PCSK9-targeting therapies, including the monoclonal antibodies, evolocumab and alirocumab, and the small interfering RNA, inclisiran, have demonstrated robust efficacy of approximately 50% to 60% reduction in LDL-C when added to statin therapy, and safety profiles that were similar to placebo with regard to discontinuations due to AEs, serious AEs, or intervention-related AEs.[16-20] However, the injectable route of administration has been a limitation while the development of oral therapies to this target has proven challenging.[21]

Oral therapy with statins has been the long-standing gold standard in the treatment of hypercholesterolemia.[13,22] However, despite guidelines that have focused on use of high-intensity statin

TABLE 2 Summary of Primary and Secondary Efficacy Endpoints

	MK-0616 6 mg QD	MK-0616 12 mg QD	MK-0616 18 mg QD	MK-0616 30 mg QD	Placebo
Primary endpoint					
LDL-C					
Participants evaluated	77	76	76	76	75
Baseline LDL, mg/dL	116.5 ± 37.0	117.3 ± 36.4	123.7 ± 35.1	119.4 ± 36.7	121.3 ± 28.0
Week 8 LDL, mg/dL	69.6 ± 29.2	54.9 ± 28.2	55.0 ± 24.9	48.8 ± 23.3	124.0 ± 34.6
LS mean percentage change from baseline (95% CI) in LDL-C at Week 8	-40.0 (-45.2 to -34.8)	-54.5 (-59.8 to -49.2)	-57.9 (-63.2 to -52.6)	-59.7 (-65.0 to -54.5)	1.2 (-4.1 to 6.5)
Difference in LS means vs placebo (95% CI)	-41.2 (-47.8 to -34.7)[a]	-55.7 (-62.3 to -49.1)[a]	-59.1 (-65.7 to -52.5)[a]	-60.9 (-67.6 to -54.3)[a]	–
Secondary endpoints					
ApoB					
Participants evaluated	77	75	76	76	75
Baseline LDL, mg/dL	103.6 ± 25.8	104.3 ± 27.0	108.0 ±23.6	106.4 ± 25.1	107.7 ± 20.7
Week 8 LDL, mg/dL	70.0 ± 21.1	57.5 ± 21.2	57.3 ± 20.2	52.3 ± 21.2	108.7 ± 26.3
LS mean percentage change from baseline (95% CI) in ApoB at Week 8	-32.8 (-37.6 to -27.9)	-45.8 (-50.7 to -40.9)	-48.7 (-53.6 to -43.8)	-51.8 (-56.7 to -47.0)	0.0 (-4.9 to 4.9)
Difference in LS means vs placebo (95% CI)	-32.8 (-38.6 to -26.9)[a]	-45.8 (-51.7 to -39.9)[a]	-48.7 (-54.6 to -42.8)[a]	-51.8 (-57.7 to -45.9)[a]	–
Non-HDL-C					
Participants evaluated	77	76	76	76	75
Baseline LDL, mg/dL	145.7 ± 40.8	147.4 ± 44.2	152.4 ± 37.0	150.2 ± 39.4	152.5 ± 31.7
Week 8 LDL, mg/dL	95.4 ± 34.2	77.0 ± 36.1	76.0 ± 30.5	69.8 ± 32.3	155.7 ± 41.8
LS mean percentage change from baseline (95% CI) in non-HDL-C at Week 8	-34.4 (-39.6 to -29.2)	-49.0 (-54.3 to -43.7)	-51.8 (-57.1 to -46.4)	-54.3 (-59.6 to -49.1)	1.5 (-3.9 to 6.8)
Difference in LS means vs placebo (95% CI)	-35.9 (-42.4 to -29.4)[a]	-50.5 (-57.0 to -44.0)[a]	-53.2 (-59.7 to -46.7)[a]	-55.8 (-62.3 to -49.3)[a]	–
LDL-C value at goal[b]					
Participants evaluated	77	76	76	76	75
Participants with LDL-C value at goal at Week 8	62 (80.5)	65 (85.5)	69 (90.8)	69 (90.8)	7 (9.3)
Difference in proportion vs placebo (95% CI)	69.2 (56.2 to 79.0)[a]	75.2 (62.9 to 84.0)[a]	79.2 (67.1 to 87.1)[a]	79.5 (67.9 to 87.4)[a]	–

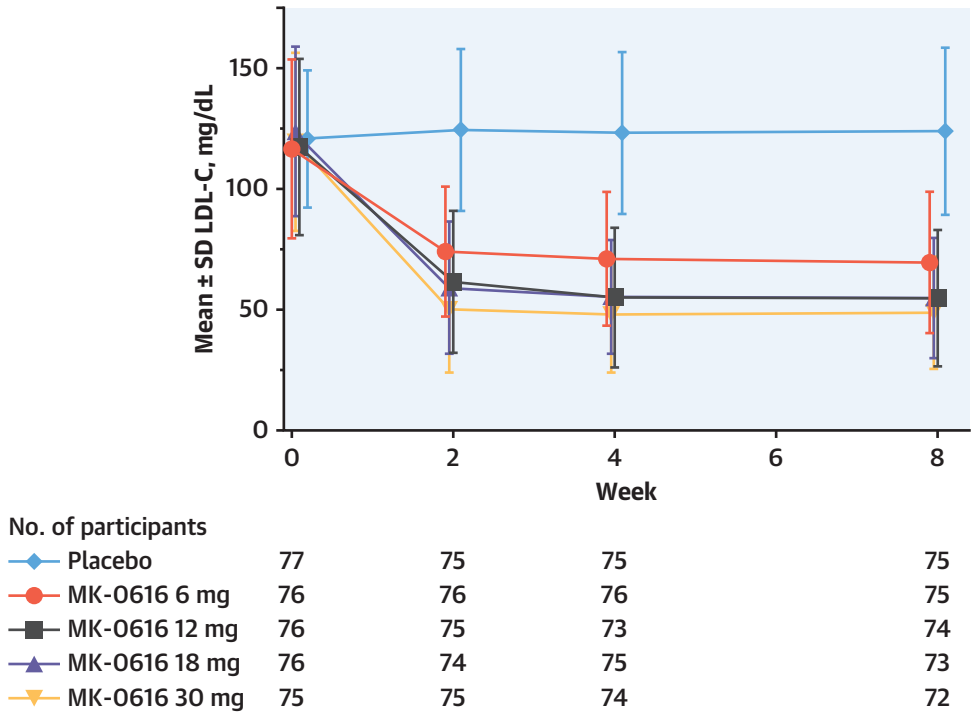
Values are n, mean ± SD, or n (%), unless otherwise indicated. [a]$P < 0.001$ vs placebo (P values for secondary endpoints are nominal). [b]Defined as: LDL-C <70 mg/dL (<1.81 mmol/L) in participants with clinical ASCVD; LDL-C <100 mg/dL (<2.59 mmol/L) in participants with high/intermediate ASCVD risk (ie, risk-equivalent and/or a 10-year risk of having an ASCVD event that is ≥7.5%); LDL-C <130 mg/dL (<3.37 mmol/L) in participants with borderline ASCVD risk (ie, a 10-year risk of having an ASCVD event that is ≥5.0% and <7.5%).

LS = least squares; other abbreviations as in Table 1.

therapy, implementation in clinical practice remains challenging, which may be due in part to adverse events and perceived tolerability associated with statins. Further, even when implementation is successful, high-dose statins often do not achieve treatment goals, particularly in high-risk patients.[23-25] The addition of nonstatin treatments with alternate mechanisms of action is a guideline-recommended strategy; however, many patients remain undertreated.[26-30] Efficacy in lowering LDL-C with available oral add-on therapies is relatively modest with an additional ~12% to 18% reduction on top of statins with bile acid sequestrants, 20% to 25% reduction with ezetimibe, and ~18% with bempedoic acid.[20-22] By contrast, the MK-0616 doses evaluated in this study led to a 41% to 61% placebo-adjusted reduction in LDL-C. Additionally, MK-0616 demonstrated large and clinically meaningful improvements in ApoB (up to 52% placebo-adjusted reduction) and non-HDL-C (up to 56% placebo-adjusted reduction), which are important predictors of atherogenic risk. Important reductions from baseline in the exploratory endpoint of Lp(a) were also observed at Week 8 (up to 24% placebo-adjusted reduction).

MK-0616 was generally well tolerated, with a proportion of participants with AEs comparable with that of placebo for each dose of MK-0616. The incidence of premature discontinuation of study interventions was low and similar between all MK-0616 groups and placebo. The most common AE in this study was

FIGURE 2 **LDL-C During 8 Weeks of Treatment**



LDL-C values are shown at baseline (Week 0), Week 2, Week 4, and Week 8. Near complete efficacy was reached by Week 2 and the effect was persistent during the 8-week treatment period. LDL-C = low-density lipoprotein cholesterol.

COVID-19 infection. There were no AEs that increased in a dose-dependent manner. These results are generally in line with the risk profile of injectable PCSK9 inhibitors with the exception that injection-site reactions were not relevant for this oral medication.

STUDY LIMITATIONS. Although these data are promising, there are some limitations to this study that should be considered. Most important, the number of patients and duration of treatment were limited. Larger studies of longer duration will be needed to appropriately assess the efficacy, durability, and safety of MK-0616 in various subgroups in the context of available treatments. Finally, this study was not designed to specifically evaluate the effect of MK-0616 on exploratory endpoints such as reduction in Lp(a).

TABLE 3 **Change From Baseline in Lp(a) (FAS Population)**

	MK-0616 6 mg QD	MK-0616 12 mg QD	MK-0616 18 mg QD	MK-0616 30 mg QD	Placebo
Participants evaluated	77	75	76	76	75
Week 8, mg/dL	41.0 ± 54.0	36.7 ± 46.0	27.3 ± 35.8	33.8 ± 41.9	41.4 ± 51.1
Percentage change from baseline at Week 8	-11.8 ± 17.8	-20.8 ± 22.4	-21.3 ± 22.9	-23.2 ± 25.2	0.5 ± 21.8
Difference in mean percentage change vs placebo (95% CI)	-12.2 (-18.6 to -5.8)	-21.3 (-28.5 to -14.1)	-21.7 (-29.0 to -14.5)	-23.7 (-31.3 to -16.0)	–
Baseline median (IQR)	13 (6 to 71)	19 (7 to 70)	16 (6 to 46)	23.5 (6 to 67.5)	15 (6 to 60)
Median percentage change from baseline (IQR)	-8 (-23.1 to 0.0)	-14.3 (-37.5 to 0.0)	-18.0 (-42.9 to 0.0)	-21.5 (-40.0 to 0.0)	0.0 (-11.6 to 5.0)

Values are n or mean ± SD, unless otherwise indicated.
FAS = Full Analysis Set; other abbreviations as in Table 1.

TABLE 4 Summary of AEs During the Full 16-Week Treatment and Follow-Up Period

Parameter[a]	MK-0616 6 mg QD (n = 77)	MK-0616 12 mg QD (n = 76)	MK-0616 18 mg QD (n = 76)	MK-0616 30 mg QD (n = 76)	Placebo (n = 75)	Total (n = 380)
≥1 AE	34 (44.2)	30 (39.5)	33 (43.4)	32 (42.1)	33 (44.0)	162 (42.6)
Discontinued intervention due to an AE	2 (2.6)	0 (0.0)	2 (2.6)	2 (2.6)	1 (1.3)	7 (1.8)
Serious AEs	1 (1.3)	3 (3.9)	2 (2.6)	2 (2.6)	0 (0.0)	8 (2.1)
Moderate or severe AEs	10 (13.0)	9 (11.8)	10 (13.2)	12 (15.8)	11 (14.7)	52 (13.7)
Intervention-related AEs[a]	6 (7.8)	11 (14.5)	11 (14.5)	8 (10.5)	8 (10.7)	44 (11.6)
Deaths[b]	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.3)
Most common AEs (incidence of >5% within a treatment group)						
Arthralgia	0 (0.0)	4 (5.3)	1 (1.3)	2 (2.6)	1 (1.3)	8 (2.1)
COVID-19	6 (7.8)	2 (2.6)	5 (6.6)	4 (5.3)	7 (9.3)	24 (6.3)
Diarrhea	5 (6.5)	1 (1.3)	3 (3.9)	1 (1.3)	1 (1.3)	11 (2.9)
Dyspepsia	1 (1.3)	5 (6.6)	3 (3.9)	0 (0.0)	1 (1.3)	10 (2.6)
Fatigue	0 (0.0)	3 (3.9)	1 (1.3)	0 (0.0)	5 (6.7)	9 (2.4)
Nausea	1 (1.3)	1 (1.3)	4 (5.3)	2 (2.6)	0 (0.0)	8 (2.1)

Values are n (%). Each dose of MK-0616 was formulated with sodium caprate, a permeation enhancer; the placebo formulation did not contain permeation enhancer. [a]Deemed by the investigator to be possibly, probably, or definitely related to study medication. [b]There was 1 death that was the result of a traffic accident.

AE = adverse event; other abbreviations as in Table 1.

CONCLUSIONS

Oral inhibition of PCSK9 with MK-0616 at doses from 6 mg to 30 mg daily provided clinically meaningful reductions of LDL-C that were superior to placebo in participants with hypercholesterolemia with a wide range of ASCVD risks and background statin therapies. Further, all doses of MK-0616 were well tolerated with a low incidence of serious AEs and discontinuations due to AEs, similar to that of placebo. The data in this trial not only build upon the benefit/risk profile of PCSK9 inhibition established with injectable therapies, but also support further development of MK-0616, an oral PCSK9 inhibitor that may widen access to effective LDL-C-lowering therapies and improve attainment of guideline-recommended LDL goals as a means to reduce cardiovascular risk.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: MK-0616, an oral PCSK9 inhibitor in development for treatment of hypercholesterolemia, reduces LDL-cholesterol to levels consistent with those with injectable monoclonal antibodies.

TRANSLATIONAL OUTLOOK: Larger trials are needed to confirm the safety and efficacy of MK-0616 and its potential to overcome barriers that limit the use of injectable PCSK9 inhibitors in patients with hypercholesterolemia.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.