Official Protocol Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK0616 in Adults With Heterozygous Familial Hypercholesterolemia
NCT Number:	NCT05952869
Document Date:	21-Aug-2024

TITLE PAGE

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Protocol Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-0616 in Adults With Heterozygous Familial Hypercholesterolemia

Protocol Number: 017-03

Compound Number: MK-0616

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

Legal Registered Address:

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Regulatory Agency Identifying Number(s):

NCT	NCT05952869
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WHO	Not applicable
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IND	152853

Approval Date: 21 August 2024

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 3 Country-specific Amendment	21-AUG-2024	The purpose of this amendment is to provide country-specific requirements for participants in Czechia, Finland, Hungary, Netherlands, Norway, and Spain.
Amendment 2 Global Amendment	06-JUN-2024	The purpose of this amendment is to CCI [redacted]
Amendment 1/ Country-Specific Amendment	31-AUG-2023	The purpose of this amendment is to provide country-specific requirements for participants in Czechia, Finland, Hungary, Netherlands, Norway, and Spain.
Original Protocol	20-APR-2023	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendment:

The purpose of this amendment is to provide country-specific requirements for participants in Czechia, Finland, Hungary, Netherlands, Norway, and Spain.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 10.7 Country-specific requirements	Provided clarification on the guidance for resumption of study intervention in participants in Czechia, Finland, Hungary, Netherlands, Norway, and Spain.	Health Authority/Agency request

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 7.1.1 Temporary Interruption of Study Intervention	Added cross-reference notation to Appendix 7 Country-specific Requirements.	To notify the reader of country-specific requirements.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-0616 in Adults With Heterozygous Familial Hypercholesterolemia

Short Title: A Phase 3 Study of MK-0616 in Adults With Heterozygous Familial Hypercholesterolemia

Acronym: CORALreef HeFH

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In adults with HeFH:

Primary Objective	**Primary Endpoint**
To evaluate the efficacy of MK-0616 compared with placebo on mean percent change from baseline in LDL-C at Week 24. H1: MK-0616 is superior to placebo on mean percent change from baseline in LDL-C at Week 24.	LDL-C
To evaluate the safety and tolerability of MK-0616.	-Adverse events -Discontinuation of study intervention due to adverse events
Secondary Objectives	**Secondary Endpoints**
To evaluate the efficacy of MK-0616 compared with placebo on mean percent change from baseline in LDL-C at Week 52. H2: MK-0616 is superior to placebo on mean percent change from baseline in LDL-C at Week 52.	LDL-C

To evaluate the efficacy of MK-0616 compared with placebo on mean percent change from baseline in non-HDL-C at Week 24. H3: MK-0616 is superior to placebo on mean percent change from baseline in non-HDL-C at Week 24.	Non-HDL-C
To evaluate the efficacy of MK-0616 compared with placebo on mean percent change from baseline in ApoB at Week 24. H4: MK-0616 is superior to placebo on mean percent change from baseline in ApoB at Week 24.	ApoB
To evaluate the efficacy of MK-0616 compared with placebo on percent change from baseline in Lp(a) at Week 24. H5: MK-0616 is superior to placebo on percent change from baseline in Lp(a) at Week 24.	Lp(a)
To evaluate the efficacy of MK-0616 compared with placebo on the proportion of participants with LDL-C <70 mg/dL and ≥50% reduction from baseline at Week 24.	LDL-C
To evaluate the efficacy of MK-0616 compared with placebo on the proportion of participants with LDL-C <55 mg/dL and ≥50% reduction from baseline at Week 24.	LDL-C

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Hypercholesterolaemia
Population	Participants ≥18 years of age with heterozygous familial hypercholesterolemia
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Placebo
Study Blinding	Double-blind with in-house blinding
Blinding Roles	Participants or Subjects
	Investigator
	Sponsor
	Outcomes assessor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 25 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 270 participants will be randomized.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Period	Use
Group 1	MK-0616	20 mg	20 mg QD	Oral	52 weeks	Test Product
Group 2	Placebo	0 mg	0 mg QD	Oral	52 weeks	Placebo

QD=once daily
Note: MK-0616 is formulated with CCI of sodium caprate, a permeation enhancer. The placebo formulation does not contain a permeation enhancer.

Total Number of Intervention Groups/Arms	2 (2:1 ratio MK-0616:Placebo)
Duration of Participation	Each participant will participate in the study for approximately 64 weeks from the time the participant provides documented informed consent through the final contact. After a screening phase of up to 30 days, each participant will receive assigned intervention for approximately 52 weeks. After the end of treatment each participant will be followed for 56 days or will be offered the opportunity to participate in a separate OLE study.

Study Governance Committees:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Events Committee	Yes

Study governance considerations are outlined in Appendix 1.

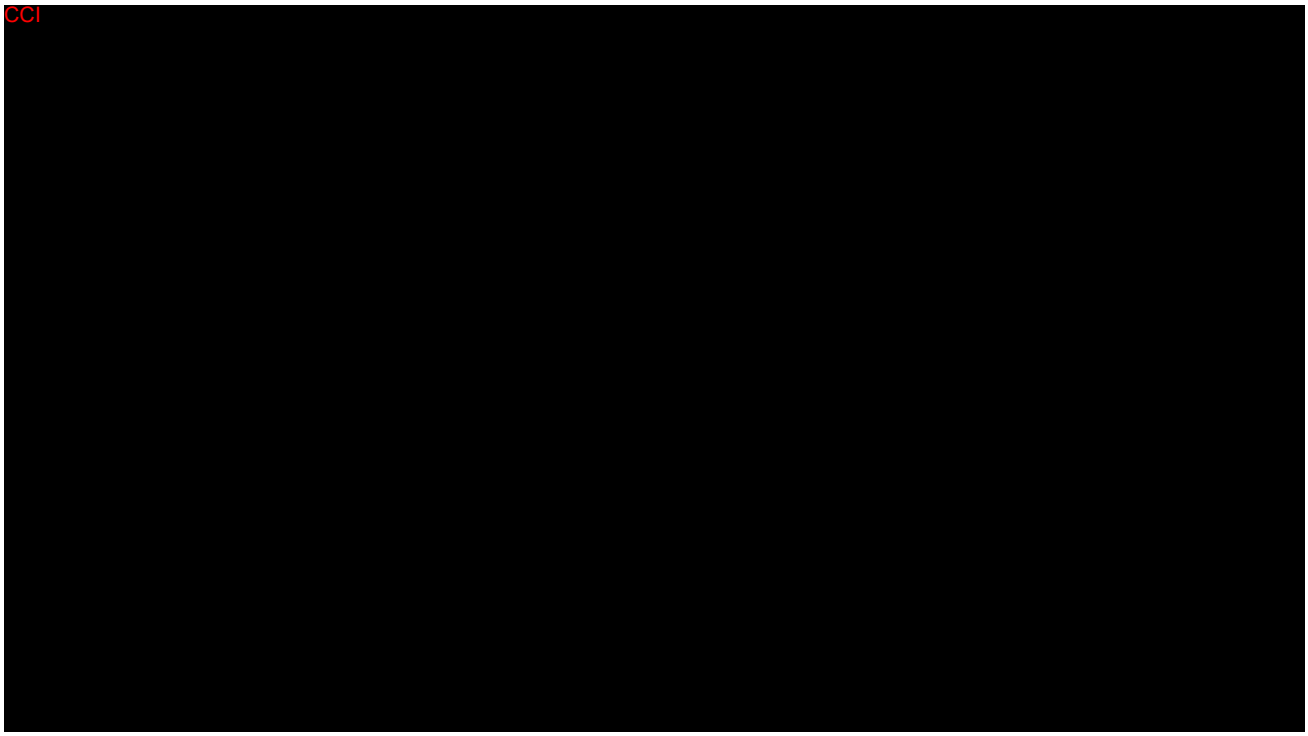
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 9.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



1.3 Schedule of Activities

With IRB/IEC approval and participant consent, this study allows specified screening procedures to be performed under limited screening consent. See Sections 8.1.1.2 and 8.11.2.1.

Study Period:	**Optional Limited Screening**	**Screening**	**Intervention**							**Follow-up TC**		**Notes**
Visit Number:		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**SI Discon**	Optional home health visits can take place at Visits 3, 4, 5 and 7. See Section 8.11.3 Visit 9 not required for participants who enroll in OLE protocol.
Scheduled Day/Week	**Up to 60 days prior to Day 1**	**Up to 30 days**	**Day 1**	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 52**	**Week 60[a]**		
Window (Days)	**N/A**	**N/A**	**N/A**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**+7**	**N/A**	
Administrative Procedures												
Informed Consent for Optional Limited Screening	X											Participants who undergo Optional Limited Screening must provide documented consent for a blood draw before the Screening Visit (Section 8.11.2.1).
Informed Consent for Optional Familial Hypercholesterolemia Genetic Panel	X	X										Refer to Section 8.1.5.
Informed Consent		X										
Informed Consent for FBR		X										Participants remain eligible for the main study if they opt out of FBR.
Inclusion/Exclusion Criteria		X	X									

Study Period:	**Optional Limited Screening**	**Screening**	**Intervention**							**Follow-up TC**		**Notes**
Visit Number:		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**SI Discon**	Optional home health visits can take place at Visits 3, 4, 5 and 7. See Section 8.11.3 Visit 9 not required for participants who enroll in OLE protocol.
Scheduled Day/Week	**Up to 60 days prior to Day 1**	**Up to 30 days**	**Day 1**	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 52**	**Week 60[a]**		
Window (Days)	**N/A**	**N/A**	**N/A**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**+7**	**N/A**	
Participant Identification Card	X	X	X									Add randomization number at Visit 2/Day 1.
Medical History		X	X									
Optional Familial Hypercholesterolemia Genetic Panel	X	X										Optional testing. See Section 8.1.5.
Prior/Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X	
Dietary Counseling			X			X		X				See Section 5.3.1
IRT Visit Registration	X	X	X		X	X	X	X			X	Refer to IRT manual for details
Intervention Randomization			X									
Study Intervention Dispensing			X		X	X	X	X				
Witnessed Dose			X	X			X	X				Only on days with PK sampling
Study Intervention Accountability				X	X	X	X	X	X		X	See Section 6.4 for details
Background Lipid-lowering Therapy Review		X	X	X	X	X	X	X	X	X	X	See Section 6.4.1 for details.

Study Period:	**Optional Limited Screening**	**Screening**	**Intervention**							**Follow-up TC**		**Notes**
Visit Number:		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**SI Discon**	Optional home health visits can take place at Visits 3, 4, 5 and 7. See Section 8.11.3 Visit 9 not required for participants who enroll in OLE protocol.
Scheduled Day/Week	**Up to 60 days prior to Day 1**	**Up to 30 days**	**Day 1**	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 52**	**Week 60[a]**		
Window (Days)	**N/A**	**N/A**	**N/A**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**+7**	**N/A**	
Fasting Accountability			X	X	X	X	X	X	X		X	Participants' compliance with fasting guidelines relative to administration of study intervention will be assessed (Section 6.4.2).
Efficacy Procedures												
Lipid panel		X	X	X	X	X	X	X	X		X	Lipid panel parameters are listed in Appendix 2.
LDL-C	X											Specimen may be processed by local or central laboratory. See Appendix 2.
ApoB / Lp(a) / hs-CRP			X				X		X		X	
Clinical Events Assessment			X	X	X	X	X	X	X	X	X	Can be requested at any time during the study
Vital Status			X	X	X	X	X	X	X	X	X	Can be requested at any time during the study

Study Period:	**Optional Limited Screening**	**Screening**	**Intervention**							**Follow-up TC**		**Notes**
Visit Number:		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**SI Discon**	Optional home health visits can take place at Visits 3, 4, 5 and 7. See Section 8.11.3 Visit 9 not required for participants who enroll in OLE protocol.
Scheduled Day/Week	**Up to 60 days prior to Day 1**	**Up to 30 days**	**Day 1**	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 52**	**Week 60[a]**		
Window (Days)	**N/A**	**N/A**	**N/A**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**+7**	**N/A**	
Safety Procedures												
Full physical examination			X						X		X	
Directed physical examination					X		X	X				
Height			X									
Weight			X				X		X		X	
Vital Signs (pulse rate, blood pressure)		X	X	X	X	X	X	X	X		X	
12-lead ECG (local)		X							X		X	
Chemistry		X	X		X		X		X		X	
TSH		X										
Hematology		X	X		X		X		X		X	
A1C		X	X		X		X	X	X		X	
Urine or Serum hCG (POCBP only)		X	X	X	X	X	X	X	X		X	A serum test will be performed if a urine test is not acceptable per local regulations (Section 8.3.6 for details). Refer to Appendix 7 for country-specific requirements.

Study Period:	**Optional Limited Screening**	**Screening**	**Intervention**							**Follow-up TC**		**Notes**
Visit Number:		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**SI Discon**	Optional home health visits can take place at Visits 3, 4, 5 and 7. See Section 8.11.3 Visit 9 not required for participants who enroll in OLE protocol.
Scheduled Day/Week	**Up to 60 days prior to Day 1**	**Up to 30 days**	**Day 1**	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 52**	**Week 60[a]**		
Window (Days)	**N/A**	**N/A**	**N/A**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**+7**	**N/A**	
FSH		X										FSH only to be performed to confirm postmenopausal state (Appendix 5). Testing requirements for FSH are in Section 8.3.6.1.
AE/SAE review	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetics/Pharmacodynamics/Biomarkers												
Predose PK				X			X	X			X	Collect sample before dose on the day of PK sample (20 to 28 hours post last dose). See Section 8.6.1. Do not collect PK sample at the Study Intervention Discontinuation Visit if this visit occurs >48 hours after the last dose of study intervention.
Postdose PK			X	X			X					Collect sample 1 hour postdose. See Section 8.6.1.
Predose Plasma for Free PCSK9			X				X					Collect sample before dose on the day of PK sample (20 to 28 hours post last dose). Leftover specimens will be stored for FBR. See Section 8.8.

Study Period:	**Optional Limited Screening**	**Screening**	**Intervention**							**Follow-up TC**		**Notes**
Visit Number:		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**SI Discon**	Optional home health visits can take place at Visits 3, 4, 5 and 7. See Section 8.11.3 Visit 9 not required for participants who enroll in OLE protocol.
Scheduled Day/Week	**Up to 60 days prior to Day 1**	**Up to 30 days**	**Day 1**	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 52**	**Week 60[a]**		
Window (Days)	**N/A**	**N/A**	**N/A**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**+7**	**N/A**	
Postdose Plasma for Free PCSK9			X				X					Collect sample 1 hour postdose. Leftover specimens will be stored for FBR. See Section 8.8.
Antibodies to MK-0616			X	X			X	X			X	Sample to be drawn predose.
Blood for Genetic Analysis			X									Collect predose from enrolled participants only. See Section 8.8.1
Plasma for Future Biomedical Research			X				X		X		X	

A1C=glycosylated hemoglobin, AE=adverse event, ApoB=apolipoprotein B, ECG=electrocardiogram; FBR=future biomedical research, FSH=follicle-stimulating hormone, hCG=human chorionic gonadotropin, hs-CRP=high-sensitivity C-reactive protein, IRT=interactive response technology, LDL-C=low-density lipoprotein cholesterol; Lp(a)=lipoprotein (a), N/A=not applicable, OLE=open-label extension, PCSK9=protein convertase subtilisin/kexin type 9, PD=pharmacodynamic, PK=pharmacokinetic, POCBP=participant of childbearing potential, QD=once daily, SAE=serious adverse event; SI Discon=study intervention discontinuation, TC=telephone call, TSH=thyroid-stimulating hormone; V=visit

[a] For participants who will be enrolled in the open-label protocol, Visit 9 (Week 60) is not required.

Refer to Appendix 7 for country-specific requirements.

2 INTRODUCTION

2.1 Study Rationale

Cardiovascular disease, principally ASCVD, is the leading cause of global mortality and a major contributor to disability [Roth, G. A., et al 2021]. Epidemiologic, genetic, and clinical intervention studies have shown that LDL-C is causally associated with ASCVD, and that lifestyle and pharmacologic reductions in LDL-C lower the risk of myocardial infarction, stroke, and death from cardiovascular disease [Ference, B. A., et al 2017].

HeFH is a highly penetrant, autosomal dominant disorder caused by mutations in the LDL receptor, apolipoprotein B100, or PCSK9 genes that affects ~1 in 250 people globally. Since LDL-C is causative in the development of ASCVD [Ference, B. A., et al 2017], adults with HeFH are at increased risk for coronary heart disease and early ASCVD events compared to the general population [Iyen, B., et al 2019]. Data from randomized clinical studies, cohort studies, and mendelian randomization studies all demonstrate that reduction of LDL-C results in reduction of ASCVD events [Ference, B. A., et al 2017].

Despite the availability of several proven LDL-C-lowering therapies (eg, statins, ezetimibe, bile acid sequestrants, injectable PCSK9i), a substantial proportion of patients with hypercholesterolemia, including those with HeFH, are not at guideline recommended LDL-C targets [Fox, K. M., et al 2018] [Cannon, C. P., et al 2021].

PCSK9 is a well-validated target for lowering LDL-C and reducing ASCVD risk, with strong human genetics implicating an important role for PCSK9 in regulating LDL-C. Circulating PCSK9 molecules bind to cell surface LDL receptors and direct the receptors to intracellular lysosomes for degradation instead of back to the surface, resulting in reduced clearance of LDL-C from the circulation. Thus, blockade of the PCSK9-LDL receptor interaction increases steady state levels of cell surface hepatic LDL receptors, which enhances LDL-C clearance and lowers circulating levels of LDL-C.

Several injectable PCSK9i have shown large reductions in LDL-C and have received regulatory approval for the treatment of hypercholesterolemia, including in patients with HeFH. Unlike these injectable therapies, MK-0616 is an orally administered PCSK9i for the treatment of hypercholesterolemia. An oral PCSK9i, that can achieve similar LDL-C-lowering as the injectable PCSK9i, offers potential advantages in simplicity of dosing, patient preference, and access.

The principal objectives of this Phase 3 study are to evaluate the LDL-C-lowering efficacy and safety of MK-0616 in participants with HeFH.

2.2 Background

Refer to the IB for detailed background information on MK-0616.

2.2.1 Pharmaceutical and Therapeutic Background

MK-0616 is a macrocyclic peptide that binds to human PCSK9 and prevents interaction of PCSK9 with the LDL receptor. This action results in a reduction in PCSK9-mediated degradation of the LDL receptor and a resultant increase in clearance of LDL particles and reduction in plasma LDL-associated cholesterol. MK-0616 is formulated with sodium caprate to enhance intestinal absorption and oral bioavailability.

Refer to the IB for additional information.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

PCSK9 is a well-validated target for lowering LDL-C, with strong human genetics implicating an important role for PCSK9 in regulating LDL-C, a key risk factor for ASCVD events. Additionally, cardiovascular outcomes studies have demonstrated that treatment with antiPCSK9 mAbs reduce the risk of cardiovascular events such as myocardial infarction and ischemic stroke [Sabatine, M. S., et al 2017] [Schwartz, G. G., et al 2018].

In the preclinical development program, no clinically relevant safety findings associated with MK-0616, or its permeation enhancer (sodium caprate), have been observed in any species studied. Additionally, robust LDL-C lowering was observed following single-dose administration of MK-0616 in monkeys.

In Phase 1 studies, multiple-dose administration of MK-0616 was associated with reduction in LDL-C similar to that observed with injectable PCSK9i (~65% reduction of LDL-C from baseline following 14 days of once-daily dosing).

In the Phase 2b study, results showed that the reduction in LDL-C at Week 8 was both statistically significant and clinically meaningful for all doses of MK-0616 (6 mg, 12 mg, 18 mg, 30 mg) versus placebo ranging from 41.2% to 60.9%, respectively.

MK-0616 has been generally well tolerated in clinical studies to date. CCI [redacted] The Phase 2b study in participants with hypercholesterolemia collected safety data over 16 weeks in ~300 participants assigned to 1 of 4 MK-0616 dose levels (6 mg, 12 mg, 18 mg, 30 mg). In these clinical studies, AEs were generally of mild to moderate intensity and there were no clinically meaningful trends as a function of study intervention on AEs, laboratory parameters, vital signs or ECGs.

Based on the available preclinical and clinical data, the benefit/risk assessment for MK-0616 is considered favorable.

Additional details regarding specific benefits and risks for participants enrolling in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In adults with HeFH:

Primary Objective	**Primary Endpoint**
To evaluate the efficacy of MK-0616 compared with placebo on mean percent change from baseline in LDL-C at Week 24. H1: MK-0616 is superior to placebo on mean percent change from baseline in LDL-C at Week 24.	LDL-C
To evaluate the safety and tolerability of MK-0616.	-Adverse events -Discontinuation of study intervention due to adverse events
Secondary Objectives	**Secondary Endpoints**
To evaluate the efficacy of MK-0616 compared with placebo on mean percent change from baseline in LDL-C at Week 52. H2: MK-0616 is superior to placebo on mean percent change from baseline in LDL-C at Week 52.	LDL-C
To evaluate the efficacy of MK-0616 compared with placebo on mean percent change from baseline in non-HDL-C at Week 24. H3: MK-0616 is superior to placebo on mean percent change from baseline in non-HDL-C at Week 24.	Non-HDL-C
To evaluate the efficacy of MK-0616 compared with placebo on mean percent change from baseline in ApoB at Week 24. H4: MK-0616 is superior to placebo on mean percent change from baseline in ApoB at Week 24.	ApoB

To evaluate the efficacy of MK-0616 compared with placebo on percent change from baseline in Lp(a) at Week 24. H5: MK-0616 is superior to placebo on percent change from baseline in Lp(a) at Week 24.	Lp(a)
To evaluate the efficacy of MK-0616 compared with placebo on the proportion of participants with LDL-C <70 mg/dL and ≥50% reduction from baseline at Week 24.	LDL-C
To evaluate the efficacy of MK-0616 compared with placebo on the proportion of participants with LDL-C <55 mg/dL and ≥50% reduction from baseline at Week 24.	LDL-C

CCI [redacted]

CCI

[redacted]

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, parallel-group, multisite, double-blind study of MK-0616 in participants with HeFH.

Participants with HeFH are eligible for the study. Participants should be receiving optimized treatment (per local guidelines and investigator judgment) with a moderate- or high-intensity statin. Other LLTs such as ezetimibe are also allowed based on local guidelines. LLTs should be stable for ≥30 days before screening and are expected to be unchanged for the duration of the study. To ensure that the majority of participants are treated with a high-intensity statin and ezetimibe (in addition to statin therapy), a randomization cap may be applied on moderate-intensity statin participants or participants not on ezetimibe.

Participants with homozygous FH and those on treatment with a PCSK9i are not eligible for the study.

This study consists of an up to 30-day screening period (Visit 1 [Screening] to Visit 2 [Day 1]), a 52-week treatment period (Visit 2 [Day 1] to Visit 8 [Week 52]), and a 56-day post treatment follow-up period (Visit 8 [Week 52] to Visit 9 [Week 60]) for safety assessment or participants will be offered the opportunity to enter a separate OLE study. Participants who discontinue study intervention prematurely should be encouraged to continue in the study off-treatment and to complete all remaining visits as outlined in the SoA.

A single optional Limited Screening Visit may be performed to assess potential eligibility for participants who do not have a recent (within 3 months) historical assessment of LDL-C level. After providing documented consent for this Limited Screening visit, participants will be assigned a screening number and undergo a blood draw. If, based on LDL-C values, the decision to proceed to Visit 1 (Screening) is made, documented consent for the full study will be obtained and the mandatory Screening Visit will be conducted.

After completing the screening period, approximately 270 participants meeting eligibility criteria will be randomized in a 2:1 ratio to treatment with either MK-0616 or placebo. Randomized participants will take 1 tablet of study intervention daily (Table 1) in the fasted state according to the guidelines provided in Section 5.3.1.

CCI [redacted]

All central lipid panel results and efficacy assessments will be masked after Visit 2 through study completion. Investigators should not evaluate lipid panel at a local laboratory during the study.

CCI [redacted]

CCI [redacted]

Participants who are 1) compliant with taking study intervention, and 2) complete the study (Visit 8, Week 52) while on study intervention will be offered the opportunity to participate in a separate OLE study where all participants receive MK-0616 daily.

All participants who opt not to enter the OLE study, who are not eligible for the OLE, or who continue in the study after discontinuation of study intervention will have a follow-up contact ~56 days after last study intervention dose for AE monitoring and to assess for the occurrence of endpoint events. Clinical outcome events will be adjudicated by an independent, external CEC. An independent, external DMC will monitor data for safety.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

The goals of this Phase 3 study are to test the hypothesis that MK-0616 reduces LDL-C in participants with HeFH, and to evaluate its safety and tolerability. To do so, this study will use a double-blind, parallel-group design in the assessment of MK-0616 versus placebo, a standard design for studies of LLTs (details on the rationale for use of placebo are in Section 4.2.2). Eligibility criteria for this study will support enrollment of participants with HeFH who require LDL-C reduction despite use of background therapies. A placebo-controlled design will be used in this study to avoid bias in the collection and evaluation of data during its conduct and to assess whether any observed effects are treatment-related or an effect of study participation. Since participants will be on optimized background LLT (according to local guidelines and investigator judgment) with a moderate- or high-intensity statin and given challenges with access to injectable PCSK9i, use of a placebo-controlled design is reasonable. Randomization at a 2:1 ratio (MK-0616:placebo) will increase the number of participants who receive MK-0616 and will allow for greater safety exposure data on MK-0616.

CCI [redacted]

A 52-week treatment period was selected to provide adequate safety data for MK-0616. A sample size of 270 was chosen to allow for sufficient exposure and safety data for MK-0616. A 56-day post treatment safety follow-up period was selected CCI [redacted]

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

LDL-C is causally associated with ASCVD, the most common condition leading to mortality in the world (Section 2.1). Therefore, the efficacy of MK-0616, like that of other LLTs, will be determined by its effect on LDL-C relative to placebo, with the primary endpoint of mean percent change from baseline in LDL-C at Week 24. Secondary endpoints include mean percent change from baseline in LDL-C at Week 52 and proportions of participants with LDL-C <70 mg/dL and ≥50% reduction from baseline and <55 mg/dL and ≥50% reduction from baseline at Week 24. CCI [redacted]

At Visit 2, LDL-C will be calculated based on the Martin/Hopkins calculation and directly measured using beta-quantification. At all other timepoints, LDL-C will be calculated based on the Martin/Hopkins calculation and if the calculated LDL-C is ≤40 mg/dL or triglycerides are ≥400 mg/dL, or calculated LDL-C is missing then LDL-C will be directly measured using beta-quantification.

Like LDL-C, ApoB, non-HDL-C, and Lp(a) are predictors of ASCVD risk. Therefore, the efficacy of MK-0616 compared with placebo on mean percent change from baseline in ApoB, non-HDL-C, and percent change in Lp(a) at Week 24 will be evaluated as secondary endpoints. CCI [redacted]

CCI [redacted]

4.2.1.2 Safety Endpoints

AEs, physical examination findings, vital signs, ECGs, and laboratory safety tests (chemistry, hematology, A1C, and pregnancy tests (in POCBP) will be assessed to provide a comprehensive safety evaluation of MK-0616 relative to placebo in participants with HeFH. Potential DILI events will be captured as ECIs per the standard requirement of Sponsor studies (Section 8.4.7). CCI [redacted] AEs will be evaluated and assessed according to the guidelines in Section 8.4 and Appendix 3. Participants may be asked to return for unscheduled visits to perform additional safety monitoring.

4.2.1.3 Pharmacokinetic Endpoints

Peak and trough concentrations of MK-0616 will be summarized by visit to inform on MK-0616 exposure.

4.2.1.4 Pharmacodynamic Endpoints

Free PCSK9 levels will be summarized to assess pharmacodynamic effects of MK-0616. PCSK9 inhibition reduces free plasma PCSK9 concentrations.

4.2.1.5 Immunogenicity

ADA samples will be collected from all participants during the treatment period and stored as described in the SoA (Section 1.3). These samples may be analyzed for ADA if there is indication of potential immunogenicity (eg, hypersensitivity reactions, loss of efficacy, PK changes) observed. If analyzed, immunogenicity to MK-0616 will be described as the results of the ADA assay from these samples.

4.2.1.6 Planned Exploratory Biomarker Research

4.2.1.6.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug ADME, mechanism of action of the drug, disease etiology, and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to understand study disease or related conditions.

4.2.1.7 Future Biomedical Research

The Sponsor will conduct FBR on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for FBR.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and

identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in Appendix 6.

4.2.2 Rationale for the Use of Placebo

This study will be placebo-controlled in order to avoid bias in the collection and evaluation of data during its conduct and to assess whether any observed effects are treatment-related or an effect of study participation. Use of placebo is considered acceptable in this study given the frequent evaluation of participants at scheduled visits, and because participants are expected to be treated with optimized background LLT (according to local guidelines and investigator judgment) with a moderate- or high-intensity statin. Participants are expected to remain on this optimal background LLT throughout the study and blinded LDL-C monitoring will ensure that participants who have a substantial change to LDL-C during the study will be identified and managed within a time frame that is in line with typical standard of care.

Participants who, in the judgment of the investigator have an indication for and plan to initiate an approved PCSK9i, should not be enrolled in the study.

4.3 Justification for Dose

The 20 mg dose of MK-0616 was chosen for evaluation in the study based on a popPK analysis of data from Phase 1 and 2 studies, exposure-response and dose-response analyses of data from the Phase 2 study, and results from a relative bioavailability study. CCI

[redacted]

MK-0616 will be administered after an overnight fast (≥8 hours) and at least 30 minutes before the first food or beverage of the day in order to maintain optimal MK-0616 concentrations.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped as described in Appendix 1.10.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Participants with an exclusionary laboratory value, blood pressure measurement and/or ECG findings (see Sections 5.1 and 5.2) may have 1 repeat determination performed if the investigator considers the result to be inconsistent with prior determinations. Only the laboratory tests/procedures not meeting entry criteria should be repeated. The last laboratory draw/result should be used to assess eligibility.

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Has possible or definite diagnosis of HeFH based on a locally accepted diagnostic algorithm (eg, AHA algorithm, US MEDPED, Simon Broome, Dutch Lipid Network, or Japanese Atherosclerosis Society Guidelines) [Gidding, S. S., et al 2015] [McGowan, M. P., et al 2019] [Kinoshita, M., et al 2018].
   Refer to Appendix 7 for country-specific requirements.
2. Has fasted lipid values (evaluated by the central laboratory) at Visit 1 (Screening) as follows:
   - History of a major ASCVD event: LDL-C ≥55 mg/dL (≥1.42 mmol/L). Note: history of a major ASCVD event is defined as having a history of 1 or more of the following: acute coronary syndrome, myocardial infarction, coronary revascularization, cerebrovascular arterial revascularization, ischemic stroke, or peripheral arterial disease with a history of acute limb ischemia, peripheral arterial revascularization, or major amputation
   - No history of a major ASCVD event: LDL-C ≥70 mg/dL (≥1.81 mmol/L)
3. Is treated with a moderate- or high-intensity statin (± non-statin LLT) (See Appendix 8) at Visit 1 (Screening).
   Participants must be on optimized LLT based on local guidelines, standard of care, and investigator judgment.
4. Is on a stable dose of all background LLTs for at least 30 days before Visit 1 (Screening) with no medication or dose changes planned during the participation in the study.

Demographics

5. Is an individual of any sex/gender from 18 years of age inclusive, at the time of providing the informed consent.

Male Participants

Note: No contraceptive measures are required for participants assigned male sex at birth.

Female Participants

6. A participant assigned female sex at birth is eligible to participate if not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a POCBP
  OR

- Is a POCBP and:
  - Uses an acceptable contraceptive method, or is abstinent from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 56 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed. Refer to Appendix 7 for country-specific requirements.
  - Has a negative highly sensitive pregnancy test (urine or serum) as required by local regulations within 24 hours (for a urine test) or 72 hours (for a serum test) before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.6.
  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

Informed Consent

7. The participant (or legally acceptable representative) has provided documented informed consent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR.

Additional Categories

8. Is willing and considered able by the investigator to comply with study procedures, including adherence with study intervention, fasting guidelines (Section 5.3.1), and visit schedule.

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

Medical Conditions

1. Has a history of homozygous FH based on genetic or clinical criteria [Cuchel, M., et al 2014], compound heterozygous FH, or double heterozygous FH.

Cardiac Conditions

2. Had a heart failure hospitalization within 3 months before Visit 1 (Screening), has New York Heart Association class IV heart failure or has a last known left ventricular ejection fraction ≤25% by any imaging method.
3. Has recurrent episodes of ventricular tachycardia within 3 months prior to randomization that is not controlled by medication or ablation.
4. Has QTc ≥500 ms (in the absence of intraventricular conduction delay and/or a bundle branch block including etiologies due to ventricular paced rhythms) based on an ECG performed within 6 months before or at Visit 1 (Screening).
5. Has uncontrolled hypertension defined as sitting SBP >160 mm Hg or DBP >100 mm Hg at Visit 2 (Randomization) despite stable antihypertensive treatment.
6. Has unstable angina, a myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, transient ischemic attack, or stroke within 3 months before Visit 1 (Screening).
7. Has a planned arterial revascularization procedure within 24 weeks after randomization.

Non-Cardiac Conditions

8. Has a history of nephrotic syndrome.
9. Has any clinically significant malabsorption condition based on principal investigator assessment (eg, recurrent vomiting, inflammatory bowel disease with ongoing symptoms, chronic intestinal disease accompanied by a disturbance in digestion and absorption, or a history of extensive resection of the upper GI tract).
10. Has poorly controlled diabetes mellitus, defined as A1C ≥9.0%, at Visit 1 (Screening).

11. Has laboratory or clinical evidence of clinically significant hepatic conditions, including 1 or more of the following:
    - ALT or AST ≥3 × ULN at Visit 1 (Screening)
    - Direct bilirubin >2 × ULN at Visit 1 (Screening) or baseline,
    - A history of hepatitis or liver disease that, in the opinion of the investigator, has been active within the 6 months before Visit 1 (Screening) and may increase the risk associated with study participation or administration of study intervention.
12. Has an abnormal TSH (defined as TSH <LLN or >1.5 × ULN). Participants with a history of hypothyroidism must be on stable treatment for this condition for ≥3 months before Visit 1 (Screening).
13. Has a known allergy or intolerance to any of the ingredients in the study intervention.
14. Is actively receiving chemotherapy for malignancy or has a history of malignancy ≤3 years before Visit 1 (Screening), except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer, which have no timeframe limitations relative to Visit 1 (Screening).
15. Has a life expectancy of <2 years based on investigator judgment.

Prior/Concomitant Therapy

16. Is undergoing or previously underwent an LDL-C apheresis program within 3 months before Visit 1 (Screening) or plans to initiate an LDL-C apheresis program.
17. Meets 1 or more of the following criteria:
    - Is on treatment with a PCSK9i (siRNA or mAb), an ANGPTL3 inhibitor, or an MTP inhibitor (eg, lomitapide) at Visit 1 (Screening) or such treatment is planned.
    - Was previously treated with an siRNA PCSK9i within 18 months before Visit 1 (Screening).
    - Was previously treated with a mAb PCSK9i within 3 months before Visit 1 (Screening).
    - Was previously treated with an ANGPTL3 inhibitor within 6 months before Visit 1 (Screening).
    - Was previously treated with an MTP inhibitor (eg, lomitapide) within 1 month before Visit 1 (Screening).

Prior/Concurrent Clinical Study Experience

18. Is currently participating in or plans to participate in any other interventional clinical study, or was previously participating in an interventional clinical study within 3 months (or 5 half-lives for agents in the previous study, whichever is longer) before Visit 1 (Screening).

Diagnostic Assessments

19. Criterion has been removed.
20. Has elevated creatine kinase >3 × ULN at Visit 1 (Screening).
21. Has a fasting triglyceride value ≥400 mg/dL (≥4.52 mmol/L) at Visit 1 (Screening).

Other Exclusions

22. Routinely consumes >3 alcoholic drinks per day. One standard drink is defined as any beverage containing 14 g of pure alcohol (ie, 12 oz [355 ml] of beer, 8 to 9 oz [237 to 266 ml] of malt liquor, 5 oz [148 ml] of wine, 1.5 oz [44 ml] of distilled spirits).
23. Has a recent history of drug abuse (within the last year) or is a current user of illicit drugs at the time of Visit 1 (Screening)
24. Has a medical disorder, condition, or history thereof that in the opinion of the investigator would impair the participant's ability to participate in or complete the study.
25. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

Participants should be encouraged to follow a low cholesterol diet and a medically appropriate and consistent exercise regimen per local guidelines if applicable.

5.3.1 Meals and Dietary Restrictions

Fasting Guidance for Clinic Visits

To ensure laboratory parameters are collected in the fasted state, it is recommended to contact participants approximately 3 days before each clinic visit and instruct them to fast (ie, no food, study intervention [if applicable], or beverages, except small amounts of water) for ≥8 hours before the visit. Non-study medications should be taken as prescribed.

At Visit 1 (Screening), the fast may be broken after laboratory samples are collected. For other clinic visits, the fast may be broken 30 minutes after administration of study intervention. Timing of dosing study intervention is described in Section 8.1.11.1.

Fasting Guidance on Days With no Clinic Visit

After Visit 2 (Day 1), on days with no clinic visit, participants should:

- Take their dose of study intervention (with small amounts of water) first thing in the morning following an overnight fast (≥8 hours). Note: Other dosing times may be considered based on investigator judgment provided participant can follow fasting instructions.

  AND

- Withhold food and beverages (except small amounts of water) until 30 minutes after administration of study intervention.

If a participant misses a dose of study intervention, the participant should fast as long as possible, preferably at least 4 hours before dosing, and withhold food and beverages (except water) until 30 minutes after administration of study intervention. Participants should not take 2 doses of study intervention on the same day.

Note: Non-study medications should be taken as prescribed.

Dietary Counseling

Participants will receive counseling from a qualified healthcare professional on a diet consistent with local guidelines. At designated subsequent visits, participants will be asked about their diet and exercise, and further counseling should be provided, as appropriate. Detailed dietary information will not be captured in the database but recorded in the source documents.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

No restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention or withdraws from the study will not be replaced.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies (MK-0616 and matching placebo) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study will be administered in a fasted state (Section 5.3.1) and are outlined in Table 1.

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Group 1	Experimental	MK-0616	Drug	Tablet	20 mg	20 mg QD	Oral	52 weeks	Test Product	IMP	Central
Group 2	Placebo Comparator	Placebo	Drug	Tablet	0 mg	0 mg QD	Oral	52 weeks	Placebo	IMP	Central

EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product: QD=once daily.
The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

Note: MK-0616 is formulated with CCI of sodium caprate, a permeation enhancer. The placebo formulation does not contain a permeation enhancer.

All supplies indicated in Table 1 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.11 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is in Section 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 2:1 ratio to MK-0616 study intervention or placebo study intervention, respectively.

6.3.2 Stratification

CCI

[redacted]

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. MK-0616 and placebo will be packaged identically. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

6.4 Study Intervention Compliance

Study intervention compliance will be monitored. Participants with interruptions from the protocol-specified treatment plan that result in <80% compliance with study intervention will receive additional counseling by site staff to optimize compliance.

- Compliance with study intervention will be assessed by counting returned tablets, corroborated with participant reporting. To facilitate this, participants will be instructed to bring unused study intervention and empty bottles to each clinic visit after Visit 2 (Day 1). Those who are non-compliant with study intervention will receive additional counseling by site staff.
- Any discrepancies between the actual and expected amount of unused study intervention will be discussed with the participant at the time of the visit, and any explanation will be documented in the source records. Intervention start and stop dates, will be recorded in the eCRF.
- A record of the number of study intervention tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records.

6.4.1 Background Lipid-lowering Therapy Review

Adherence to LLT (medications and/or supplements), will be reviewed at every visit by direct questioning and will be documented in source documents throughout the study. Those who report noncompliance with their LLT in the screening or double-blind treatment period should receive additional counseling by site staff.

6.4.2 Fasting Compliance

Participants will be instructed to fast before and after administration of study intervention according to the guidance provided in Section 5.3.1. Compliance with the fasting guidance during the period before each visit will be assessed by direct questioning. Those who report noncompliance with fasting during the period before each visit will receive additional counseling by site staff.

6.5 Concomitant Therapy

Medications specifically prohibited in the exclusion criteria are discouraged during the ongoing study. If there is a clinical indication for any medications specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Any LLTs (medications and/or supplements the participant was receiving within 30 days before Visit 1 (Screening) should be recorded on the concomitant therapy CRF. See Table 2 for examples of LLTs. Participants should be receiving optimized treatment (per local guidelines, standard of care, and investigator judgment) and as such, no LLT additions or dose changes are expected during the study (Visit 1 [Screening] to Visit 9 [Week 60]), unless clinically mandated.

Acceptable LLTs include, but are not limited to the following:

Table 2 Examples of Accepted Lipid-lowering Therapies

Statins	Niacin
ATP citrate lyase inhibitors (eg, bempedoic acid)	Fibrates
Cholesterol absorption inhibitors (eg, ezetimibe)	Omega-3 fatty acids (eg, ethyl eicosapentaenoic acid)
Bile acid sequestrants	

ATP= adenosine triphosphate

Treatment with any non-study PCSK9i is prohibited during the study concomitantly with study intervention (Visit 1 [Screening] to Visit 9 [Week 60]); there are no other prohibited medications for this study. Participants who initiate treatment with commercially available PCSK9i must discontinue study intervention and should continue in the study for follow-up (Section 7.1). The PCSK9i should be recorded as a concomitant medication.

Additionally, any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that

the participant is receiving at the time of enrollment (Visit 1 [Screening]) or receives during the study must be recorded on the concomitant therapy CRF.

The Sponsor Clinical Director should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.6 Dose Modification (Study Intervention Interruptions)

No modifications to study intervention dose are permitted.

6.6.1 Study Intervention Interruption

A participant must interrupt study intervention for any of the reasons outlined in Section 7.1.1.

6.7 Intervention After the End of the Study

Participants who are 1) compliant with taking study intervention, and 2) complete the study (Visit 8, Week 52) while on study intervention will be offered the opportunity to participate in a separate OLE study where all participants receive MK-0616 daily.

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.17). If the emergency unblinding call center is not available for a given site in this study, the central electronic intervention randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in the study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.11.3 unless the participant has withdrawn from the study (Section 7.2).

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study intervention, but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- After prolonged study intervention interruption that prohibits restarting study intervention if agreed upon with the Sponsor.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
  Note: A positive urine pregnancy test during the double-blind treatment period requires immediate interruption of study intervention until a serum test can be performed. If the serum test is positive, the participant must be discontinued from study intervention and followed per Section 8.4.
- The participant begins treatment with commercially available PCSK9i.
- The participant enrolls in another interventional clinical trial.

For participants who are discontinued from study intervention, but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

Participants may be allowed to begin study intervention again if deemed medically appropriate, after consultation with the Sponsor.

7.1.1 Temporary Interruption of Study Intervention

A participant must interrupt study intervention for any of the following reasons:

- The participant has an ALT or AST result ≥5 × ULN or symptoms of hepatic dysfunction.
- Has a potential DILI event defined as an elevated AST or ALT laboratory value that is greater than or equal to 3 × the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2 × the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2 × the ULN, without any other immediately apparent cause for the abnormalities.

Participants with transient alterations in hepatic enzymes may resume study intervention (based on investigator's judgment) once specified criteria are no longer met.

Refer to Appendix 7 for country-specific requirements.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant or a participant's legally acceptable representative requests to withdraw consent from the study, the investigator will clarify whether the participant wishes to withdraw completely from study (eg, no further site contact) or whether the participant is willing to be contacted for additional follow-up by phone. If the participant is willing to be contacted about their health status at a future timepoint, then the participant is not withdrawn from study follow-up.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

For participants who have withdrawn consent from further study follow-up, collection of clinical event and vital status data will be completed by review of medical or public records in accordance with participant informed consent and local regulations.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.16. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- At any time that a participant's vital status is in question, the investigator should explore all possible options to locate the participant per local regulations (unless the participant has explicitly withdrawn his/her consent to any type of follow-up). The site must document all attempts to try to contact the participant in the medical records/source documents. The vital status will be collected for all randomized participants who have not withdrawn consent, irrespective of completion of study procedures.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before providing documented informed consent may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- The maximum amount of blood collected from each participant over the duration of the study will not exceed the volume mentioned in the operations/Laboratory Manual.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.1.2 Consent for Optional Limited Screening

If allowed by the IRB/IEC and local regulations, this study allows specified optional screening activities to be conducted under limited consent, before the participant has provided full consent under the main ICF. A separate ICF will be used for participants who consent to limited screening.

The specific screening activities that the Sponsor allows to be conducted under optional limited consent are identified in Section 1.3. No other study activities can be conducted unless the participant has provided full consent under the main ICF. See also 8.11.2.2.

8.1.1.3 Consent for Optional Familial Hypercholesterolemia Genetic Panel

This study allows for commercially available HeFH genetic panel testing to aid in the diagnosis of familial hypercholesterolemia for participants without prior diagnostic testing. If the participant opts to undergo this testing, a separate ICF will be required and the testing will be conducted before randomization (at the Optional Limited Screening or Screening visit). This familial hypercholesterolemia genetic panel testing is optional and not required for participation in the study.

8.1.1.4 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant ID card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee at Visit 1 (Screening) and Visit 2 (Day 1).

Clinically significant findings in physical examination, laboratory tests, ECGs, or other evaluations during the screening period will be recorded in the participant's medical history.

8.1.5 Optional Familial Hypercholesterolemia Genetic Panel

Familial hypercholesterolemia diagnostic genetic panel testing can be offered to participants who have not had prior familial hypercholesterolemia genetic testing. This can be performed at either the Optional Limited Screening or Screening visit. Results of this testing will not impact study eligibility based on clinical criteria.

The site investigator should follow local guidance to disclose any commercially available genetic results to participants who opt to take the optional test.

8.1.6 Prior and Concomitant Medications Review

8.1.6.1 Prior Medications

The investigator (or qualified designee) will review and record any prior LLTs (medications and/or supplements) the participant was receiving within 30 days before Visit 1 (Screening). Other prior medications/vaccines taken by the participant at the time of enrollment (Visit 1 [Screening]) will also be recorded.

Participants treated with 1 or more of the excluded therapies in Section 5.2 are not eligible for the study.

8.1.6.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study. No LLT additions or dose changes are expected during the study (Visit 1 [Screening] to Visit 9 [Week 60]) unless clinically mandated. Treatment with any non-study PCSK9i is prohibited during the study (Visit 1 [Screening] to Visit 9 [Week 60]); there are no other prohibited medications for this study.

8.1.7 Dietary Counseling

Refer to Section 5.3.1 for guidance on dietary counseling.

8.1.8 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any individual who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.2.

8.1.9 Assignment of Randomization Number

All eligible participants will be randomly allocated and will receive a randomization number. The randomization number identifies the participant for all procedures occurring after randomization. Once a randomization number is assigned to a participant, it can never be reassigned to another participant.

A single participant cannot be assigned more than 1 randomization number.

8.1.10 IRT Visit Registration, IRT Randomization, and Study Intervention Dispensing

The investigator (or designee) will register the participant in IRT at the visits specified in the SoA. Participants who satisfy all entry criteria will be assigned a randomization number via IRT at Visit 2 (Day 1). Participants who do not meet eligibility criteria will be entered into IRT as screen failures. IRT will also be used to identify the study intervention supplies that will be dispensed to participants at the visit specified in the SoA. Refer to the IRT user manual for details about the IRT system.

Study intervention could be dispensed at the clinical site or via home delivery to the participant at visits indicated in the SoA (Section 1.3) or at unscheduled visits if approved locally. Only authorized site staff may arrange shipment of study intervention from the site to the participant following Sponsor process to ensure temperature control, full traceability, participant data privacy, and that the study blind is preserved where applicable.

8.1.11 Study Intervention Administration

Study intervention will be dispensed as oral tablets. At Visit 2 (Day 1), participants will be educated by a trained member of the site staff on appropriate dosing (Section 8.1.11.1) and fasting instructions (Section 5.3.1), and the requirement to bring all remaining study intervention supplies to each clinic visit to assess compliance (Section 6.4). Documentation of participant training will be filed with the participant's source documents.

Details on appropriate handling, storage, and accountability of study intervention are provided in Section 6.2.2.

8.1.11.1 Timing of Dose Administration

Except for days with scheduled clinic visits during the double-blind treatment period, study intervention will be administered by the participant QD at home. Dosing will occur first thing in the morning (with water) following an overnight fast (ie, no food, or beverages, except small amounts of water) of ≥8 hours. Participants will withhold food and beverages (except water) until 30 minutes after administration of study intervention (Section 5.3.1).

Participants will be instructed to fast for ≥8 hours before scheduled clinic visits (Section 8.11.1). Study intervention will be administered as follows on the day of scheduled clinic visits:

- Visit 2 (Day 1): Study intervention will be administered (with water) as a witnessed dose after all visit procedures are complete (except collection of postdose PK/PD samples).
- Visit 3 (Week 4): Study intervention will be administered (with water) as a witnessed dose after laboratory samples are collected (except collection of postdose PK/PD samples).
- Visit 4 (Week 8): Study intervention will be administered (with water) after laboratory samples are collected.

- Visit 5 (Week 16): Study intervention will be administered (with water) after laboratory samples are collected.
- Visit 6 (Week 24): Study intervention will be administered (with water) as a witnessed dose after laboratory samples are collected (except collection of postdose PK samples).
- Visit 7 (Week 36): Study intervention will be administered (with water) as a witnessed dose after laboratory samples are collected.
- Visit 8 (Week 52): The last dose of study intervention will be taken on the day of Visit 8 (Week 52) at the clinic.

If a participant misses a dose of study intervention, the participant should fast as long as possible, preferably at least 4 hours before dosing, and withhold food and beverages (except water) until 30 minutes after administration of study intervention. Participants should not take 2 doses of study intervention on the same day.

8.1.12 Witnessed Dose

Administration of study intervention will be witnessed by a member of the site staff at Visit 2 (Day 1), Visit 3 (Week 4), and Visit 6 (Week 24), and Visit 7 (Week 36) for collection of PK/PD samples. The time of dosing will be recorded.

8.1.13 Study Intervention Accountability

Accounting for compliance with study intervention is described in Section 6.4.

8.1.14 Background Lipid-lowering Therapy Review

Review of compliance with background LLT is described in Section 6.4.1.

8.1.15 Fasting Accountability

Accounting for compliance with fasting guidelines relative to administration of study intervention is described in Section 6.4.2.

8.1.16 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.16.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.17 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Before contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study intervention, the reason thereof, etc, in the medical record. If it is not possible to record this assessment in the medical record before the unblinding, the unblinding should not be delayed.

If unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician may be allowed to continue study intervention with Sponsor consultation and should continue to be monitored in the study.

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. If the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding if this is required for participant safety.

At the end of the study, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

8.1.18 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

8.2.1 Lipid Assessments

Lipid parameters (LDL-C, HDL-C, non-HDL-C, total cholesterol, triglycerides, ApoB, Lp[a]), and hs-CRP will be measured at the visits specified in the SoA. The rationale for efficacy endpoints is provided in Section 4.2.1.1.

At Visit 2 (Day 1), LDL-C will be calculated based on the Martin/Hopkins calculation and directly measured using beta-quantification. At other timepoints, LDL-C will be calculated based on the Martin/Hopkins calculation and if the calculated LDL-C is ≤40 mg/dL or triglycerides are ≥400 mg/dL, or calculated LDL-C is missing then LDL-C will be directly measured using beta-quantification.

Participants must be fasting for ≥8 hours before obtaining lipid panel assessments.

Because the effects of study intervention on efficacy endpoints could inform on participants' treatment assignments, efficacy results will be masked by the central laboratory after Visit 2 (Day 1) through the end of the study. Investigators should not evaluate efficacy endpoints locally during the study.

An LDL-C Monitoring Plan is implemented to address elevations in a participant's LDL-C during the trial (Section 4.1).

8.2.2 Clinical Events Assessment

Participants will be assessed for the occurrence of potential study endpoint events described in Section 10.1.4.3. Assessment for endpoint events will occur at each study visit as outlined in Section 1.3. Investigators will also assess potential study endpoints they learn of between scheduled study visits. Potential endpoints events will be submitted to the CEC for review AND reported as an AE/SAE (Section 8.4).

8.2.3 Vital Status Assessments

The vital status assessment is included at every visit and in the final contact and may be conducted at any time during the study. This assessment can be conducted by review of medical records or public records when vital status is in question in accordance with local regulations, unless the participant has specifically withdrawn consent for collection of vital status data.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the Laboratory Manual.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A full physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements), per institutional standard, at the visits specified in the SoA.

A directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements), per institutional standard, at the visit specified in the SoA.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Height and Weight

Height and body weight will be measured at the visits specified in the SoA.

Height measurements should be rounded to the nearest inch/centimeter (without shoes).

Body weight will be measured using a standardized scale and should be rounded to the nearest pound/kilogram. Participants' weight should be measured after voiding and while wearing light clothing (eg, no coats or heavy sweatshirts). The site should follow their local procedures to ensure the body weight scale is working properly.

8.3.3 Vital Signs

Vital signs (blood pressure and pulse rate) will be assessed at the visits specified in the SoA.

- Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest with the participant in the seated position. Measurements should be performed using a completely automated device. Manual techniques may be used if an automated device is not available. Blood pressure measurement should be done in triplicate, approximately 1 to 3 minutes apart.
- Whenever possible, blood pressure measurements should be obtained using the same arm, the same blood pressure monitoring device, and the same examiner at each visit.
- The participant should be asked to remove all clothing that covers the location of the cuff placement.
- The examiner should ensure that the middle of the cuff on the upper arm is at the level of the right atrium (the midpoint of the sternum).
- When performed manually, pulse rate must be measured in the brachial/radial artery for at least 30 seconds.

8.3.4 Electrocardiograms

ECG measurements will be performed at the visits specified in the SoA.

- Single 12-lead ECGs will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- ECGs should be performed after the participant has rested quietly for at least 10 minutes.

8.3.5 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol-specified laboratory assessments (with the exception of efficacy laboratory assessments) performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation In the study or within 56 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.
- If a participant is found to have a triglyceride value (evaluated by the Central Laboratory) that is ≥1000 mg/dL (≥11.3 mmol/L), the investigator will receive a triglyceride-specific alert and should follow-up with the participant accordingly.

8.3.6 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Refer to Appendix 7 for country-specific requirements.

8.3.6.1 Pretreatment Confirmation of Postmenopausal State

Participants whose postmenopausal status is in question are required to have 2 pretreatment FSH measurements (approximately 2 weeks apart with a minimum interval of 10 days) in the postmenopausal range or adhere to contraception guidelines in Appendix 5. The first FSH measurement will be obtained at Visit 1 (Screening). Participants whose first FSH measurement is in the postmenopausal range, but who cannot have a second measurement within approximately 2 weeks of Visit 1 (Screening), should be excluded if they are unwilling to adhere to the contraception guidelines in Appendix 5. These participants may be rescreened based on investigator judgment (Section 8.11.2.2.1).

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment; if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

If the participant undergoes any protocol-specified procedure or intervention under limited screening consent, eg, a blood draw, the participant is first required to provide consent to limited screening, and AEs will be captured according to guidelines for standard AE reporting.

Participants who do not enter the separate OLE:

From the time of intervention randomization through 56 days after cessation of treatment, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside the period specified in the previous paragraph must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

Participants who enter the separate OLE:

All new AEs, SAEs, (including those considered related to study intervention) and other reportable safety events that occur after the last dose of study intervention at Visit 8 (Week 52) in this protocol will be collected in the OLE study.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 3.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 3 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period: Limited Screening Consent to Full Consent/Full Consent to Randomization**	**Reporting Period: Randomization/ Allocation Through Protocol-specified Follow-up Period**	**Reporting Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor**
NSAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Report if: – drug/ related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: – participant has been exposed to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (requiring regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI – requiring regulatory reporting	Not required	Within 24 hours of learning of event

Type of Event	**Reporting Period: Limited Screening Consent to Full Consent/Full Consent to Randomization**	**Reporting Period: Randomization/ Allocation Through Protocol-specified Follow-up Period**	**Reporting Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor**
ECI (does not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The

Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Note: To meet EU CTR requirements, the Sponsor will report SUSARs to the Eudravigilance database via E2B(R3) electronic ICSR form in compliance with CTR 536/2014.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding (spontaneously reported to the investigator or their designee) that occurs in a participant during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

There are no disease-related events or disease-related outcomes that do not qualify as an AE or SAE.

8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

CCI

[redacted]

8.5 Treatment of Overdose

In this study, an overdose is any dose that exceeds the prescribed daily dose of study intervention in Section 6.1 (ie, >1 tablet/day of study intervention is an overdose).

The Sponsor does not recommend specific treatment for an overdose.

Decisions regarding dose interruptions will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

8.6.1 Blood Collection for Plasma MK-0616

PK samples will be collected at the timepoints specified in the SoA. Blood samples collected may be stored and further analysis may be performed, if required. When possible, Visit 3 (Week 4), Visit 6 (Week 24), and Visit 7 (Week 36) (or the Study Intervention Discontinuation Visit) should be scheduled at a time that facilitates trough PK sample collection.

For the 1-hour postdose PK sample, a window of 0.5 to 3 hours is allowed. For the predose sample, it would be best to be 20 to 28 hours post last dose, but more importantly, it needs to be before the dose on the day the PK sample is taken.

For participants who prematurely discontinue study intervention, do not collect PK samples at the Study Intervention Discontinuation Visit if this visit occurs >48 hours after the last dose of study intervention.

Blood samples may be stored for further analysis, if required. Sample collection, storage, and shipment instructions for PK samples will be provided in the Laboratory Manual.

8.6.2 Immunogenicity Assessment

Samples for ADA will be collected from all participants as specified in the SoA prior to administration of study intervention and stored. These samples may be analyzed for ADA if there is indication of potential immunogenicity (eg, hypersensitivity reactions, loss of efficacy, PK changes) observed.

Sample collection, storage, and shipment instructions for serum samples will be provided in the Laboratory Manual.

8.7 Pharmacodynamics

Free PCSK9 samples will be collected at the timepoints specified in the SoA. Blood samples may be stored for further analysis, if required.

Sample collection, storage, and shipment instructions for free PCSK9 samples will be provided in a Laboratory Manual.

8.8 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants as specified in the SoA:

- Blood (DNA) for genetic analysis
- Plasma for Free PCSK9

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

The planned genetic analysis sample should be obtained predose on Day 1 but may be collected at the next scheduled blood draw, if needed. Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

- Leftover samples listed in Section 8.8
- Plasma for FBR

8.10 Health Economics or Medical Resource Utilization and Health Economics

Health Economics or Medical Resource Utilization and Health Economics are not evaluated in this study.

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.11.1 Visit Reminders

Approximately 3 days before scheduled clinic visits, site staff will be encouraged to contact participants and remind them to do the following:

- *On the days without clinic visits (applicable after Visit 2 [Day 1])*: Take their daily dose of study intervention (with small amounts of water) first thing in the morning following an overnight fast (≥8 hours), and to withhold food and beverages (except small amounts of water) until 30 minutes after dosing.
- *On the day of the clinic visits (applicable to all scheduled clinic visits)*: Fast for ≥8 hours before the visit. At Visit 1 (Screening), the fast may be broken after laboratory samples are collected. For other clinic visits, the fast may be broken 30 minutes after administration of study intervention (Section 5.3.1).

While fasting, participants should not eat any food, take study intervention, or drink any beverages, except small amounts of water. Non-study medications should be taken as prescribed.

8.11.2 Screening Procedures

8.11.2.1 Optional Limited Screening

If approved by the IRB/IEC, and the participant consents, a single Optional Limited Screening Visit may be performed to assess potential eligibility for participants who do not have a recent (within 3 months) historical assessment of LDL-C level. After providing documented consent for this optional limited screening, participants will be assigned a screening number and undergo a blood draw. If the decision based on the LDL-C value to proceed to study screening is made, documented consent for the full study will be obtained and Visit 1 (Screening) will be conducted.

Those who qualify for randomization will have Visit 2 (Day 1) within 60 days after the Limited Screening (Optional)Visit. The optional limited screening LDL-C test can be performed by either a local or central laboratory.

See Section 1.3 and Section 8.1.1.2 for additional information on limited screening.

8.11.2.2 Screening

Procedures and assessments at Visit 1 (Screening) will be performed per the SoA to determine if potential participants satisfy all eligibility criteria listed in Section 5. Those who qualify for randomization will have Visit 2 (Day 1) within 30 days after Visit 1 (Screening). Participants with an exclusionary laboratory/procedure value may have 1 repeat determination performed if the investigator considers the Visit 1 (Screening) result to be inconsistent with prior determinations (see Section 5 for details). Participants who have not fasted before Visit 1 (Screening) should have all blood collections rescheduled and completed before Visit 2 (Day 1). Pregnancy tests (serum or urine), Screening (Visit 1) hematology tests, familial hypercholesterolemia genetic panel, and Optional Limited

Screening LDL-C tests may be performed locally. All other tests detailed in Table 7 will be performed by the central laboratory.

Site staff will reinforce participant compliance with background LLT (medications and/or supplements), if applicable, at Visit 1 (Screening) (Section 6.4.1).

8.11.2.2.1 Rescreening

If a participant screen-fails (Section 5.4), the participant may be rescreened once based on investigator judgment. Participants who are rescreened will retain the same screening number assigned at the Screening Visit (Section 8.1.8).

8.11.3 Treatment Period

Each visit should be performed as specified in the SoA. Participants who satisfy all entry criteria will be randomized (via IRT) to double-blind study intervention at Visit 2 (Day 1). Participants will be educated by a trained member of the site staff on appropriate dosing instructions (including missed doses, Section 8.1.11) and fasting guidance (Section 5.3.1).

The first dose of study intervention will be witnessed by a member of the site staff in the clinic at Visit 2 (Day 1) for collection of PK/PD samples. Administration of study intervention will also be witnessed at Visit 3 (Week 4), Visit 6 (Week 24), and Visit 7 (Week 36) for collection of PK/PD samples (Section 8.1.12).

Compliance with study intervention (Section 6.4), background LLT (medications and/or supplements, if applicable) (Section 6.4.1), and fasting guidance (Section 6.4.2) will be assessed and reinforced throughout the study.

Scheduled clinic visits will be conducted at the study site. If a participant has not fasted before Visit 2 (Day 1), the entire visit should be rescheduled to occur within 30 days of Visit 1 (Screening). If a participant has not fasted before any other visits during the double-blind treatment period, all efficacy and safety laboratory collections, the witnessed dose and PK sample collection at Visit 3 (Week 4), the witnessed dose and PK sample collections at Visit 6 (Week 24) and the witnessed dose and PK sample collection at Visit 7 (Week 36) should be rescheduled to occur within the allowable visit window (specified in the SoA).

If there are circumstances that do not enable the participant to attend a scheduled in-person clinic visit at Weeks 4 (Visit 3), 8 (Visit 4), and 16 (Visit 5), and 36 (Visit 7) a home visit using a qualified health care professional may be performed, if allowed by local regulations and agreed to by the participant, following site processes.

8.11.4 Unscheduled Visits

Unscheduled visits may be utilized at any time during the study at the discretion of the investigator. The following should be performed at unscheduled visits:

- AE review and reporting (Section 8.4 and Appendix 3)
- Concomitant medication review (Sections 6.5 and 8.1.6.2) and reinforcement of compliance with background LLT (medications and/or supplements), if applicable (Section 6.4.1)
- Review and reinforcement of compliance with study intervention (Section 6.4) and, fasting guidelines (Section 6.4.2)

8.11.5 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

Participants who prematurely discontinue study intervention will undergo the assessments and procedures outlined in the SoA at the Study Intervention Discontinuation Visit. After this visit, participants should continue to undergo the assessments and procedures outlined in the SoA at all remaining visits, with the following exceptions, which are not applicable after study intervention is discontinued:

- Witnessed dose and PK/PD/ADA sample collection (Visit 3 [Week 4], Visit 6 [Week 24], and Visit 7 [Week 36])
- Study intervention accountability
- Plasma collection for FBR

Participants who agree to continue in the study after discontinuation of study intervention, but who do not agree to attend clinic visits, may have follow-up visits conducted via home health visit to facilitate blood sample collection. If not possible, phone contacts may be conducted (Section 7.1).

8.11.6 Post-treatment

Participants will be contacted approximately 56 days after the last dose of study intervention for the poststudy visit. If the post-treatment contact occurs less than 56 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 56 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

Participants enrolling into the OLE will not have the 56-day follow-up call.

9 KEY STATISTICAL CONSIDERATIONS

This section outlines the principal statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding/final database lock, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to any unblinding/final database lock, will be documented in an amendment of the SAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Other planned analyses (eg, those specific to FBR) are beyond the scope of this document or will be documented in separate analysis/operational plans.

9.1 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study will be conducted as a double-blind study under in-house blinding procedures. The database addressing all study objectives will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Clinical Biostatistics department of the Sponsor will generate the randomized allocation schedule(s) for study treatment assignment, and the randomization will be implemented in the IRT.

There are no further unblinding responsibilities.

9.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.3 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below.

9.3.1 Efficacy/Pharmacokinetics Endpoints

Primary Efficacy Endpoint

- Mean percent change from baseline in LDL-C at Week 24

Secondary Efficacy Endpoints

- Mean percent change from baseline in LDL-C at Week 52
- Mean percent change from baseline in non-HDL-C at Week 24

- Mean percent change from baseline in ApoB at Week 24
- Percent change from baseline in Lp(a) at Week 24
- Proportion of participants with LDL-C < 70 mg/dL and ≥50% reduction from baseline at Week 24
- Proportion of participants with LDL-C < 55 mg/dL and ≥50% reduction from baseline at Week 24

Analyses of percent change and change from baseline in LDL-C will use results from the same method (i.e., either beta-quantification at both baseline and post-baseline or Martin/Hopkins calculation at both baseline and post-baseline). If results from both methods are available, results from beta-quantification will be used.

9.3.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, ECG, laboratory test results, and vital signs. Safety endpoints are further described in Section 4.2.1.2 of the protocol.

9.4 Analysis Populations

Participants discovered to be simultaneously enrolled in more than one interventional study or at more than one site for any individual interventional study will have their data excluded from all analyses.

9.4.1 Efficacy Analysis Populations

The FAS population will serve as the population for the analysis of efficacy data in this study. The FAS population consists of all randomized participants who:

- receive at least 1 dose of double-blind study intervention.
- have baseline data for those analyses that require baseline data.

Participants will be included in the treatment group to which they are randomized for the analysis of efficacy data using the FAS population.

9.4.2 Safety Analysis Populations

Safety analyses will be conducted in the APaT population, which consists of all randomized participants who received at least one dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data. This will be the treatment group to which they are randomized except for participants who take incorrect study intervention for the entire treatment period; such participants will be included in the treatment group corresponding to the study intervention actually received.

Analyses of laboratory test results, vital signs, and ECG measurements will include only participants with at least one measurement obtained after at least one dose of study intervention. If the analysis will assess change from baseline, a baseline measurement is also required.

9.5 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to the exploratory objectives will be described in the SAP.

P-values for efficacy endpoints not controlled for multiplicity may be provided as an assessment of strength of evidence without intent to make inferential claims.

For analysis purposes, the baseline assessment is the one closest to, but before or on the day of randomization prior to the first dose of study medication (Visit 2 [Day 1]).

CCI [redacted] If it is expected that statistical models will not converge on account of small sample sizes within a stratum, a stratification factor will be dropped from the models. A decision to drop the stratification factor due to small strata will be based on blinded data and documented in the SAP prior to database lock.

9.5.1 Estimand(s)

The primary efficacy estimand following the guidance in ICH E9 (R1) has the following 5 attributes:

1. The **treatment** condition of interest and the alternative treatment condition to which comparison will be made: intervention with MK-0616 or placebo added to background lipid-lowering therapy.
2. The **population** of participants targeted by the clinical question: adults with HeFH.
3. The **variable** (or endpoint) to be obtained for each participant that is required to address the clinical question: percent change from baseline in LDL-C at Week 24.
4. The specification of how to account for **other intercurrent events** to reflect the scientific question of interest: a treatment policy approach will be used for intercurrent events (defined as discontinuation of MK-0616 or placebo, and, or other lipid lowering therapy). Consistent with the treatment policy approach, no observed data will be excluded from analyses on account of intercurrent events.
5. The **population-level summary** for the endpoint which provides the basis for a comparison between treatment conditions: the difference (MK-0616 minus placebo) in the mean percent change from baseline in LDL-C at Week 24.

Estimands for the continuous secondary endpoints are analogous to the estimand for the primary endpoint. For the binary secondary endpoints, the treatment, population, and intercurrent event attributes are the same as for the primary estimand. The remaining attributes are as follows:

1. The **variable** (or endpoint) to be obtained for each participant that is required to address the clinical question: whether the Week 24 LDL-C value is at goal (Yes or No) defined as LDL-C<70 or <55 mg/dL and ≥50% reduction from baseline.
2. The **population-level summary** for the endpoint which provides the basis for a comparison between treatment conditions: the difference (MK-0616 minus placebo) in the proportion with Week 24 LDL-C at goal.

9.5.2 Statistical Methods for Efficacy Analyses

For the primary estimand, the treatment group comparison for the LDL-C percent change from baseline at Week 24 will be done using an ANCOVA model with treatment and the stratification factor CCI [redacted] as fixed effects and baseline LDL-C as a covariate.

Data permitting (discussed below), missing data will be imputed using a retrieved dropout (RD) approach which assumes that all missing Week 24 data can be represented by the observed Week 24 data for participants in the same treatment group who discontinued study treatment but remained in the study.

A "retrieved dropout" value is defined as an observed Week 24 value in a participant who discontinued study treatment prior to Week 24 but remained in the study.

For the RD approach, missing Week 24 values will be imputed as follows:

RD imputation will be done within each treatment group (MK-0616 or Placebo). All Week 24 RD values will be used for imputation, regardless of when the participants discontinued from study medication.

The RD imputation analysis steps are as follows:

1. Generate 1000 bootstrap samples from the dataset that includes all observed LDL-C percent change from baseline values.

2. Within each bootstrap sample, do the following:

    a. Impute missing Week 24 values using a normal distribution where the expected percent change from baseline value is set to the estimated mean percent change from baseline value from the RD participants in the same treatment group. The standard deviation will be the root mean squared error derived from the ANCOVA model described above and estimated based on all participants with Week 24 data.

b. Repeat the imputation for a total of 100 imputed datasets, each containing the original non-missing data and the imputed data for those with missing Week 24 values.

c. Analyze each imputed dataset using the ANCOVA model described above to generate 100 ANCOVA-based estimates of the treatment difference.

d. Calculate the average of the 100 ANCOVA-based estimates of the treatment difference – this is the bootstrap parameter estimate.

3. Compute the estimate of the treatment difference for the mean percent change from baseline as the mean of the 1000 bootstrap parameter estimates, and compute the standard error of the treatment difference for the mean percent change from baseline as the standard error of the 1000 bootstrap parameter estimates from step 2d.

4. Using the estimate and standard error in step 3, calculate a 95% confidence interval and p-values assuming a normal distribution.

The RD analysis may not be feasible due to insufficient observed Week 24 data post discontinuation of study treatment. If the number of retrieved dropout participants per group is at least 50% of participants but no fewer than 5 RD participants who discontinue from study medication per arm, then RD will be the primary approach to impute missing data. If at least one group has less than 50% RD participants or fewer than 5 RD participants, then Washout Imputation (WI) will become primary. If the minimum data requirement for the RD method is met, then WI will be implemented as a sensitivity approach. The WI analysis assumes participants who prematurely discontinued from the study or who have an intermittent missing Week 24 value would have a 'washout' of any potential effect of the assigned study medication.

For the WI approach, missing Week 24 values will be imputed using data from participants in the placebo group who have Week 24 data, as follows:

- For participants in the MK-0616 group:
  1. Fit a regression model as $Y_{24} = \beta_0 + \beta_1 * Y_0 + \gamma * X + \text{error}$, where Y_0 and Y_{24} are the observed placebo group LDL-C values at Baseline and Week 24, respectively, and X is a matrix for the fixed covariates (stratification factor).
  2. Impute missing Week 24 LDL-C values for MK-0616 using the estimated mean from the above model and standard deviation equal to the root mean squared error (RMSE) from the model.
- For participants in the placebo group:
  1. Fit models according to the observed LDL-C data pattern from participants in the placebo group who have both a Baseline and a Week 24 value. Selection of the following models will be based on the last available LDL-C value prior to Week 24:
     a. For participants whose last value prior to Week 24 is Baseline:
     $Y_{24} = \beta_0 + \beta_1 * Y_0 + \gamma * X + \text{error}$

b. For participants whose last value prior to Week 24 is Week 4:
$Y_{24} = \beta_0 + \beta_1 * Y_0 + \beta_2 * Y_4 + \gamma * X + \text{error}$

c. For participants whose last value prior to Week 24 is Week 8:
$Y_{24} = \beta_0 + \beta_1 * Y_0 + \beta_2 * Y_8 + \gamma * X + \text{error}$

d. For participants whose last value prior to Week 24 is Week 16:
$Y_{24} = \beta_0 + \beta_1 * Y_0 + \beta_2 * Y_{16} + \gamma * X + \text{error}.$

2. Impute missing Week 24 LDL-C values for placebo using one of the four models above based on the missing data pattern with a mean equal to the mean from the regression model and a standard deviation equal to the RMSE from the model.

- The WI analysis will include only participants with a baseline measurement. The WI imputation analysis steps are:

1. Generate 1000 bootstrap samples from the observed LDL-C change from baseline analysis dataset.
2. Within each bootstrap sample, do the following:
   a. Impute Missing Week 24 values using a normal distribution where the expected percent change from baseline value and RMSE will be derived from the WI regression models described above. The WI regression model parameters will be estimated based on all participants with Week 24 data.

   b. Repeat step 2a for a total of 100 imputed datasets, each containing the original non-missing data and the imputed data for those with missing Week 24 values.

   c. Analyze the 100 datasets using the ANCOVA model described above to generate 100 ANCOVA-based estimates of the treatment difference.

   d. Calculate the average of the 100 ANCOVA-based estimates of the treatment difference – this is the bootstrap parameter estimate.

3. Compute the estimate of the treatment difference for the mean percent change from baseline is the mean of the 1000 bootstrap parameter estimates and calculate the standard error of the treatment difference for mean percent change from baseline as the standard error of the 1000 bootstrap parameter estimates from step 2d.

Using the estimate and standard error in step 3, calculate a 95% confidence interval and p-value assuming a normal distribution.

For all analyses involving simulated data, a random seed of 616017 will be used.

Mean percent change and change from baseline for the secondary endpoints except Lp(a) will be analyzed using the methods applied to the primary endpoint.

The percent change and change from baseline in Lp(a) at Week 24 will be analyzed using the aligned rank stratified Wilcoxon test [Hodges, J. L., Jr. and Lehmann, E. L. 1962] [Mehrotra,

D. V., et al 2010] with the randomization stratification factors as strata. In this test, the endpoint values are first aligned across the randomization strata using the stratum-level Hodges-Lehmann location shift estimates, and the aligned values are then analyzed using a Wilcoxon rank sum test. The output from this analysis will be used to provide a 1-sided p-value and corresponding Hodges-Lehmann location-shift estimate of the overall treatment difference with 95% confidence interval (CI). A boxplot of the change from baseline in Lp(a) at Week 24 will be provided for each treatment group. This will be based on the observed data.

For the analysis of percent change and change from baseline with respect to Lp(a), the following primary method will be used if a participant's Week 24 assessment is missing:

For participants who missed an assessment a standard multiple imputation method will be used to impute missing data.

The MAR assumption is made to perform standard Multiple Imputation. It has been shown [Mogg, R. and Mehrotra, D. V. 2007] that MAR-based imputation under non-MAR conditions is unlikely to impact the overall treatment-level mean ranks. For missing data, Fully Conditional Specification (FCS) regression [van Buuren, S., et al 2006] [van Buuren, S. 2007] is used to fill in the missing data in the order of timepoints using measurements calculated at the previous timepoints.

A line plot (Mean ± SEM) of the percent change from baseline in Lp(a) and triglycerides by visit will be provided for each treatment group based on observed data.

For the other secondary endpoints of the proportions of participants with LDL-C < 70 mg/dL and < 55 mg/dL and ≥50% reduction from baseline at Week 24, the 95% CIs and p-values will be provided based on the stratified M&N method (with sample size weighting) for the difference in proportions between treatment groups (MK-0616 minus placebo). Any participant who does not have a Week 24 assessment will be considered as not being at the LDL C goal at Week 24.

The analysis strategy for key efficacy variables is outlined in Table 4.

Table 4 Analysis Strategy for Key Efficacy Endpoints

Endpoint	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint			
Mean percent change from baseline in LDL-C at Week 24	ANCOVA	FAS	RD/WI
Secondary Endpoints			
Mean percent change from baseline in LDL-C at Week 52	ANCOVA	FAS	RD/WI
Mean percent change from baseline in non-HDL-C at Week 24	ANCOVA	FAS	RD/WI
Mean percent change from baseline in ApoB at Week 24	ANCOVA	FAS	RD/WI
Percent change from baseline in Lp(a) at Week 24	ARSW	FAS	Multiple Imputation
Proportion of participants with LDL-C < 70 mg/dL and ≥50% reduction from baseline at Week 24	M&N	FAS	M=F
Proportion of participants with LDL-C < 55 mg/dL and ≥50% reduction from baseline at Week 24	M&N	FAS	M=F

ANCOVA= analysis of covariance; ARSW= aligned rank stratified Wilcoxon test, FAS=full analysis set, RD= retrieved dropout, WI= washout imputation, LDL-C=low-density lipoprotein cholesterol, M&N=Miettinen and Nurminen, M=F: Missing=Failure.

9.5.3 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of AEs and other relevant parameters, including laboratory tests, vital signs, and ECG measurements. The primary assessment of safety will use all data through the efficacy cutoff date including 56 days after last dose of study intervention, if available.

9.5.3.1 Overall Safety Assessment

The overall safety evaluation will include a summary by treatment group of the number and percentage of participants with at least 1 AE, drug-related AE, serious AE, serious drug-related AE, and moderate or severe AE; discontinuation from study intervention due to an AE; and an AE resulting in death. Point estimates and 95% CIs for the differences between treatment groups in the percentages of participants with the event will be provided based on the criteria described below for specific AEs.

The number and percentage of participants with specific AEs will also be provided. Point estimates and 95% CIs for the differences between treatment groups in the percentages of

participants with specific AEs will be provided for AEs that occur in at least 5% of participants in any treatment group.

CIs for between treatment group differences will be provided using the M&N method. These CIs will not be adjusted for multiplicity and should be regarded as helpful descriptive measures for the review of the safety profile and not as a formal method for assessing statistical significance of between-group differences. Rainfall plots with point estimates and 95% CIs will be displayed for AEs that occur in at least 5% participants in any treatment group. Point estimates and 95% CIs will be provided for the percentage of participants with safety parameters that meet predefined limits of change based on the same criteria used above for the specific AEs.

For continuous safety measures, such as change from baseline in laboratory, vital signs, and ECG parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group.

9.5.3.2 Assessment of Safety Topics of Special Interest

The analysis strategy for safety parameters is in Table 5.

Table 5 Analysis Strategy for Safety Parameters

Analysis Part	Safety Endpoint	Descriptive Statistics	95% Between-group CI	Graphical Display
Overall Safety Assessment	Any AE	X	X	
	Any serious AE	X	X	
	Any drug-related AE	X	X	
	Any serious drug-related AE	X	X	
	Any moderate or severe AE	X	X	
	Discontinued study treatment due to AE	X	X	
	Discontinued study treatment due to a drug-related AE	X	X	
	AE that resulted in death	X		
	Specific AEs (≥5% of participants in any treatment group)	X	X[a]	X[a]
	SOCs, PDLCs (≥5% of participants in any treatment group)	X	X[a]	
	Change from Baseline Results (Labs, ECGs, Vital Signs)	X		
CCI [redacted]				

AE=adverse event; CI=confidence interval; ECG=electrocardiogram; PDLC=predefined limit of change; SOC=system organ class.
[a] Threshold for incidence will be applied for CI and graphical display.

9.6 Interim Analyses

No interim efficacy analyses are planned.

The DMC will be responsible for periodic interim safety reviews, to be specified in the DMC charter.

9.7 Multiplicity

CCI [redacted]

The multiplicity strategy strongly controls the Type I error at 0.025 (one-sided).

9.8 Sample Size and Power Calculations

9.8.1 Sample Size and Power for Efficacy Analyses

CCI [redacted] a sample size of 270 in a 2:1 ratio, will provide >99% power at a one-sided alpha of 0.025 for the primary efficacy endpoint treatment comparison (MK-0616 vs. placebo, based on nQuery software version 8). Assumptions of SD and treatment difference are based on LDL-C results from MK-0616-008.

For all secondary endpoints with hypotheses, power at a one-sided alpha of 0.025 is >99% CCI [redacted]

The overall probability of being successful and demonstrating superiority of MK-0616 vs Placebo on all five hypotheses CCI [redacted]

9.8.2 Sample Size and Power for Safety Analyses

Given the sample size of 270 in a 2:1 ratio (180 for MK-0616 and 90 for placebo), Table 6 provides examples of 95% CIs of treatment differences in AEs between MK-0616 and placebo that would have a 95% CI that excludes zero.

Table 6 Examples of Adverse Event Incidences for Which 95% CI for the Difference Would Exclude Zero

MK-0616 n/N (%)	**Placebo n/N (%)**
8/180 (4.4%)	0/90 (0%)
19/180 (10.6%)	3/90 (3.3%)
27/180 (15.0%)	6/90 (6.7%)

AE=adverse event; CI=confidence interval; n=number of participants with an AE; N=population size

Based on M&N method

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Interventional Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), Regulation (EU) 536/2014, the International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and

healthcare providers to ensure operational feasibility. Trial design also includes proactive identification of critical to quality factors utilizing a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial. Individuals involved in trial conduct receive training commensurate with their role prior to their becoming involved in the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations and ICH Guidelines. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed. DMC review of data accumulated during the conduct of the trial is integral to the well-being of trial participants.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on medical record review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for

financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide their financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20), and is self-certified pursuant to the EU-US Data Privacy Framework.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee, affiliated institution, and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this

process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide on any recommendations made by the DMC regarding the study.

10.1.4.2 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.4.3 Clinical Events Committee (CEC)

A CEC will evaluate the following events for the purposes of confirming them according to the criteria in the CEC Charter, as well as evaluating the presence of confounding factors.

1. All-cause mortality (including cardiovascular death and non-cardiovascular death)
2. Potential arterial revascularization - coronary
3. Potential arterial revascularization – cerebrovascular
4. Potential arterial revascularization – peripheral
5. Potential cardiac ischemic events (eg, myocardial infarction, hospitalization for unstable angina)
6. Potential cerebrovascular events (eg, stroke, transient ischemic attack)
7. Potential peripheral ischemic events (eg, acute limb ischemia, chronic limb ischemia, other limb event including amputation)

All personnel involved in the adjudication process will remain blinded to study intervention allocation throughout the study.

10.1.4.4 National Leader Committee

The primary role of the National Leader Committee is to serve as a strong advocate for the program in their respective countries, partnering with the local Sponsor study team to optimize the conduct of the studies, and to facilitate the progress of the study at the regional level. The National Leader Committee is composed of Country Leads selected by the Sponsor with appropriate clinical study experience.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as

Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor’s studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator’s knowledge, threatened.

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i)

the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible,

contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- Pregnancy tests, Screening (Visit 1) hematology tests, familial hypercholesterolemia genetic panel, and Optional Limited Screening LDL-C tests may be performed locally. All other tests detailed in Table 7 will be performed by the central laboratory.
- The Limited Screening Visit LDL-C test can be performed by either local or central laboratory.
- Efficacy results will be masked by the central laboratory after Visit 2 (Day 1) through the end of the study (Section 8.2). The study team and site will be blinded to the data. Investigators should not evaluate efficacy endpoints locally during the study.
- The investigator (or medically qualified designee) must document their review of each laboratory safety report.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 7 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count	RBC Indices: -MCV -MCH -MCHC -RDW		WBC count
	RBC Count			
	Hemoglobin			
	Hematocrit			
		Reticulocytes		
Chemistry	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Bicarbonate	ALT/SGPT	Phosphorus
	Creatinine	Sodium	Alkaline phosphatase	Total protein
	eGFR	Calcium	Chloride	Creatine kinase
	Fasting glucose			
Lipid Panel	LDL-C	HDL-C	Non-HDL-C	Total cholesterol
	Triglycerides			
Other Efficacy Parameters		ApoB	hsCRP	Lp(a)
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (POCBP only)			
PK	• Plasma for PK (Section 8.6)			
PD	• Plasma for Free PCSK9 (Section 8.7)			
Other Tests	• A1C • TSH (Screening only) • FSH (as needed to assess menopausal status) (Screening only) • Familial Hypercholesterolemia genetic panel (Optional) • ADA			

A1C=hemoglobin A_{1c}; ADA=antidrug antibodies; ALT=alanine aminotransferase; ApoB=apolipoprotein B; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; eGFR=estimated glomerular filtration rate; FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; HDL-C=high-density lipoprotein cholesterol; hs-CRP=high-sensitivity C-reactive protein; LDL-C=low-density lipoprotein cholesterol; Lp(a)=lipoprotein (a); MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; MPV=mean platelet volume; PCSK9=protein convertase subtilisin/kexin type 9; PD=pharmacodynamic; PK=pharmacokinetic; POCBP=participant of childbearing potential; RBC=red blood cell; RDW=red cell distribution width; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; TSH=thyroid-stimulating hormone; ULN=upper limit of normal; WBC=white blood cell

Note 1: eGFR will be calculated using CKD-EPI Creatinine 2021

Note 2: At Visit 2 (Day 1), LDL-C will be calculated based on the Martin/Hopkins calculation and directly measured using beta-quantification. At other timepoints, LDL-C will be calculated based on the Martin/Hopkins calculation and if the calculated LDL-C is ≤40 mg/dL or triglycerides are ≥400 mg/dL, or calculated LDL-C is missing then LDL-C will be directly measured using beta-quantification.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death
b. Is life-threatening
   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer.
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:
  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).
  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).
  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the study intervention cause the AE?
- The determination of the likelihood that the study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.
- **The following components are to be used to assess the relationship between the study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
  - **Dechallenge:** Was the study intervention discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)
  - **Rechallenge:** Was the participant reexposed to the study intervention in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

    (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability; (2) the study is a single-dose drug study; or (3) study intervention (s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF REEXPOSURE TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT

RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Participants of Childbearing Potential (POCBP)

A participant assigned female sex at birth is considered fertile following menarche and capable of becoming pregnant until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Participants assigned female sex at birth who are in the following categories are not capable of becoming pregnant and, therefore, not considered POCBP:

- Premenarchal
- Premenopausal with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants assigned female sex at birth who are not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Participants assigned female sex at birth who are on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency[a] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only contraceptive implant[b] • IUS[c] • Nonhormonal IUD • Bilateral tubal occlusion (Tubal occlusion includes tubal ligation)
• Azoospermic partner (vasectomized or secondary to medical cause, confirmed by medical history) – All sexual partner(s) of the POCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception[b] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[b] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with a partner capable of producing sperm, during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Methods That Are Not Considered Highly Effective *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Penile/external or vaginal/internal condom with or without spermicide[d] • Cervical cap, diaphragm, or sponge with spermicide • A combination of penile/external condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)
[a] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly) [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptives are limited to those which inhibit ovulation [c] IUS is a progestin releasing IUD [d] Vaginal/internal condom used for contraceptive purposes Note: The following are not acceptable methods of contraception: • Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM • Penile/external and vaginal/internal condom should not be used together (due to risk of failure with friction)[d]

Refer to Appendix 7 for country-specific requirements.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease, and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research[3, 4]

a. Participants for Enrollment
All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent
Informed consent for specimens (ie, DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens
Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)
Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research[3, 4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history, and intervention outcomes is critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number that does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third-party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research[3, 4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox

(clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens[3, 4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not used in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility, which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population[3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

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10.7 Appendix 7: Country-specific Requirements

10.7.1 Czechia

Sections 1.3 and 8.3.6

Pregnancy testing must be performed monthly during treatment. For participants who do not enter the OLE, pregnancy tests are also required at 4 weeks and 8 weeks after last dose of study intervention.

Section 5.1

Inclusion Criterion 1 has been revised to the following:

Has possible or definite diagnosis of HeFH based on internationally accepted diagnostic algorithm (eg, AHA algorithm, US MEDPED, Simon Broome, Dutch Lipid Network, or Japanese Atherosclerosis Society Guidelines) [Gidding, S. S., et al 2015] [McGowan, M. P., et al 2019] [Kinoshita, M., et al 2018].

Sections 5.1 and 10.5.2

Participants of childbearing potential must use highly-effective contraceptive measures.

Section 7.1.1

Participants with an identified reason for hepatic enzyme elevation that is unrelated to study intervention may resume study intervention (based on investigator's judgment) after consultation with the Sponsor, once the specified criteria are no longer met.

The study-site guidance for assessment and follow-up of potential DILI events (defined as an elevated AST or ALT laboratory value that is greater than or equal to 3 × the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2 × the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2 × the ULN, without any other immediately apparent cause for the abnormalities) can be found in the Investigator Study File Binder (or equivalent).

10.7.2 Finland

Sections 1.3 and 8.3.6

Pregnancy testing must be performed monthly during treatment. For participants who do not enter the OLE, pregnancy tests are also required at 4 weeks and 8 weeks after last dose of study intervention.

Section 5.1

Inclusion Criterion 1 has been revised to the following:

Has possible or definite diagnosis of HeFH based on internationally accepted diagnostic algorithm (eg, AHA algorithm, US MEDPED, Simon Broome, Dutch Lipid Network, or Japanese Atherosclerosis Society Guidelines) [Gidding, S. S., et al 2015] [McGowan, M. P., et al 2019] [Kinoshita, M., et al 2018].

Sections 5.1 and 10.5.2

Participants of childbearing potential must use highly-effective contraceptive measures.

Section 7.1.1

Participants with an identified reason for hepatic enzyme elevation that is unrelated to study intervention may resume study intervention (based on investigator's judgment) after consultation with the Sponsor, once the specified criteria are no longer met.

The study-site guidance for assessment and follow-up of potential DILI events (defined as an elevated AST or ALT laboratory value that is greater than or equal to 3 × the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2 × the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2 × the ULN, without any other immediately apparent cause for the abnormalities) can be found in the Investigator Study File Binder (or equivalent).

10.7.3 Hungary

Sections 1.3 and 8.3.6

Pregnancy testing must be performed monthly during treatment. For participants who do not enter the OLE, pregnancy tests are also required at 4 weeks and 8 weeks after last dose of study intervention.

Section 5.1

Inclusion Criterion 1 has been revised to the following:

Has possible or definite diagnosis of HeFH based on internationally accepted diagnostic algorithm (eg, AHA algorithm, US MEDPED, Simon Broome, Dutch Lipid Network, or Japanese Atherosclerosis Society Guidelines) [Gidding, S. S., et al 2015] [McGowan, M. P., et al 2019] [Kinoshita, M., et al 2018].

Sections 5.1 and 10.5.2

Participants of childbearing potential must use highly-effective contraceptive measures.

Section 7.1.1

Participants with an identified reason for hepatic enzyme elevation that is unrelated to study intervention may resume study intervention (based on investigator's judgment) after consultation with the Sponsor, once the specified criteria are no longer met.

The study-site guidance for assessment and follow-up of potential DILI events (defined as an elevated AST or ALT laboratory value that is greater than or equal to 3 × the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2 × the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2 × the ULN, without any other immediately apparent cause for the abnormalities) can be found in the Investigator Study File Binder (or equivalent).

10.7.4 Netherlands

Sections 1.3 and 8.3.6

Pregnancy testing must be performed monthly during treatment. For participants who do not enter the OLE, pregnancy tests are also required at 4 weeks and 8 weeks after last dose of study intervention.

Section 5.1

Inclusion Criterion 1 has been revised to the following:

Has possible or definite diagnosis of HeFH based on internationally accepted diagnostic algorithm (eg, AHA algorithm, US MEDPED, Simon Broome, Dutch Lipid Network, or Japanese Atherosclerosis Society Guidelines) [Gidding, S. S., et al 2015] [McGowan, M. P., et al 2019] [Kinoshita, M., et al 2018].

Sections 5.1 and 10.5.2

Participants of childbearing potential must use highly-effective contraceptive measures.

Section 7.1.1

Participants with an identified reason for hepatic enzyme elevation that is unrelated to study intervention may resume study intervention (based on investigator's judgment) after consultation with the Sponsor, once the specified criteria are no longer met.

The study-site guidance for assessment and follow-up of potential DILI events (defined as an elevated AST or ALT laboratory value that is greater than or equal to 3 × the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2 × the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2 × the ULN,

without any other immediately apparent cause for the abnormalities) can be found in the Investigator Study File Binder (or equivalent).

10.7.5 Norway

Sections 1.3 and 8.3.6

Pregnancy testing must be performed monthly during treatment. For participants who do not enter the OLE, pregnancy tests are also required at 4 weeks and 8 weeks after last dose of study intervention.

Section 5.1

Inclusion Criterion 1 has been revised to the following:

Has possible or definite diagnosis of HeFH based on internationally accepted diagnostic algorithm (eg, AHA algorithm, US MEDPED, Simon Broome, Dutch Lipid Network, or Japanese Atherosclerosis Society Guidelines) [Gidding, S. S., et al 2015] [McGowan, M. P., et al 2019] [Kinoshita, M., et al 2018].

Sections 5.1 and 10.5.2

Participants of childbearing potential must use highly-effective contraceptive measures.

Section 7.1.1

Participants with an identified reason for hepatic enzyme elevation that is unrelated to study intervention may resume study intervention (based on investigator's judgment) after consultation with the Sponsor, once the specified criteria are no longer met.

The study-site guidance for assessment and follow-up of potential DILI events (defined as an elevated AST or ALT laboratory value that is greater than or equal to 3 × the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2 × the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2 × the ULN, without any other immediately apparent cause for the abnormalities) can be found in the Investigator Study File Binder (or equivalent).

10.7.6 Spain

Sections 1.3 and 8.3.6

Pregnancy testing must be performed monthly during treatment. For participants who do not enter the OLE, pregnancy tests are also required at 4 weeks and 8 weeks after last dose of study intervention.

Section 5.1

Inclusion Criterion 1 has been revised to the following:

Has possible or definite diagnosis of HeFH based on internationally accepted diagnostic algorithm (eg, AHA algorithm, US MEDPED, Simon Broome, Dutch Lipid Network, or Japanese Atherosclerosis Society Guidelines) [Gidding, S. S., et al 2015] [McGowan, M. P., et al 2019] [Kinoshita, M., et al 2018].

Sections 5.1 and 10.5.2

Participants of childbearing potential must use highly-effective contraceptive measures.

Section 7.1.1

Participants with an identified reason for hepatic enzyme elevation that is unrelated to study intervention may resume study intervention (based on investigator's judgment) after consultation with the Sponsor, once the specified criteria are no longer met.

The study-site guidance for assessment and follow-up of potential DILI events (defined as an elevated AST or ALT laboratory value that is greater than or equal to 3 × the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2 × the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2 × the ULN, without any other immediately apparent cause for the abnormalities) can be found in the Investigator Study File Binder (or equivalent).

10.8 Appendix 8: Statin Intensity Chart Based on Total Daily Dose

High intensity	Moderate intensity	Low Intensity *Not allowed per protocol*
Atorvastatin 40 mg or 80 mg Rosuvastatin 20 mg or 40 mg	Atorvastatin 10 mg or 20 mg Rosuvastatin 5 mg or 10 mg Simvastatin 20 mg to 40 mg	Simvastatin 5 mg or 10 mg
	Pravastatin 40 mg or 80 mg Lovastatin 40 mg or 80 mg Fluvastatin 80 mg Pitavastatin 1 mg to 4 mg	Pravastatin 10 mg to 20 mg Lovastatin 10 mg to 20 mg Fluvastatin 20 mg to 40 mg
Adapted from Table 3 in [Grundy, S. M., et al 2019]. Statin intensity categorization may be modified based on country/regional data and guidelines. Consult the Sponsor to determine the appropriate statin intensity category for participants whose daily statin dose is not shown above.		

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
A1C	glycosylated hemoglobin
ADA	antidrug antibodies
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
ANGPTL3	angiopoietin-like 3
APaT	All-Participants-as-Treated
ApoB	apolipoprotein B
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
BMI	body mass index
CBMI	control-based mean imputation
CEC	Clinical Events Committee
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	maximum plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSR	Clinical Study Report
Ctrough	concentration reached by drug immediately before the next dose is administered
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form

Abbreviation	Expanded Term
EDC	electronic data collection
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOC	Executive Oversight Committee
ESRD	end stage renal disease
FAS	Full Analysis Set
FBR	future biomedical research
FCS	Fully Conditional Specification
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FH	familial hypercholesterolemia
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolemia
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
hs-CRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ID	identification
IEC	Independent Ethics Committee
IMP	investigational medicinal product

Abbreviation	Expanded Term
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	interactive response technology
JAPIC-CTI	Japan Pharmaceutical Information Center Clinical Trials Information
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LLN	lower limit of normal
LLT	lipid-lowering therapy
Lp(a)	lipoprotein (a)
mAb	monoclonal antibody
MAR	missing at random
MMRM	mixed-model repeated measures
M&N	Miettinen and Nurminen
MTP	microsomal triglyceride transfer protein
non-HDL-C	non-high-density lipoprotein cholesterol
OLE	open-label extension
PCSK9	protein convertase subtilisin/kexin type 9
PCSK9i	protein convertase subtilisin/kexin type 9 inhibitor
PD	pharmacodynamic
PK	pharmacokinetic
POCBP	participant of childbearing potential
popPK	population pharmacokinetics
QD	once daily
RNA	ribonucleic acid
RR	robust regression
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SEM	standard error of measurement
SGOT	serum glutamic oxaloacetic transaminase

Abbreviation	Expanded Term
SGPT	serum glutamic pyruvic transaminase
SI Discon	study intervention discontinuation
siRNA	small interfering RNA
SLAB	supplemental laboratory test(s)
SoA	schedule of activities
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
UTN	Universal Trial Number
WBC	white blood cell

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