Official Protocol Title:	A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-0616 in Adults With Hypercholesterolemia
NCT number:	NCT05261126
Document Date:	24-May-2022

Title Page

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Protocol Title: A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-0616 in Adults With Hypercholesterolemia

Protocol Number: 008-04

Compound Number: MK-0616

Sponsor Name:

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

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	152853
EudraCT	2021-005221-24

Approval Date: 24 May 2022

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 04	24-MAY-2022	To update Sponsor's entity name and address change and to add clarifications and minor updates.
Amendment 03	10-MAR-2022	United Kingdom-specific amendment created to fulfill health authority request.
Amendment 02	14-FEB-2022	South Korea-specific amendment created to fulfill health authority request.
Amendment 01	04-FEB-2022	Germany-specific amendment created to fulfill health authority request.
Original Protocol	03-NOV-2021	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 4

Overall Rationale for the Amendments:

To update Sponsor's entity name and address change and to add clarifications and minor updates.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page Section 10.1.1 Code of Conduct for Clinical Trials	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
1.3 Schedule of Activities	Clarification on timing of visit added to Visits 4 and 5.	To ensure study participants have access to study intervention.
1.1 Synopsis 6.1 Study Intervention Administered	'Test product' replaced 'Experimental' in the Study Intervention Table 'Use' column.	To align with Japan regulatory requirements.
5 Study Population	Clarified the collection, use, and confidentiality of demographic data provided by participants.	Clarification
8 Study Assessments and Procedures	Updated maximum amount of blood needed for collection.	To reflect additional blood volume required for beta quantification LDL samples and for select countries with an additional clinic visit based on country-specific amendments.

Section # and Name	Description of Change	Brief Rationale
8.2 Efficacy Assessments 9.4.1 Efficacy Endpoints 10.2 Appendix 2: Clinical Laboratory Tests	Updated description of LDL-C measurement.	To clarify method of LDL-C measurement.
Section 10.7 Appendix 7: Country-specific Requirements	Country-specific amendments for Germany, South Korea, and the United Kingdom were added to this amendment. Changes are outlined in Section 10.7 and referenced in Sections 1.2 Schema, 1.3 Schedule of Activities, 4.3 Justification for Dose, 5 Study Population, 5.1 Inclusion Criteria, 5.2 Exclusion Criteria, 5.3.1 Meals and Dietary Restrictions, 6.5 Concomitant Therapy, 7.1 Discontinuation of Study Intervention, 8 Study Assessments and Procedures, 8.3.7 Pregnancy Testing, 8.4.7 Events of Clinical Interest, 8.11.1 Visit Reminders, 8.11.7 Post-treatment, 10.2 Appendix 2: Clinical Laboratory Tests, and 10.5 Appendix 5: Contraceptive Guidance.	To consolidate country-specific amendments 1, 2, and 3 into this global amendment.
Throughout the document	Minor editorial changes	Editorial changes.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-0616 in Adults With Hypercholesterolemia

Short Title: A Phase 2b Study of MK-0616 in Adults With Hypercholesterolemia

Acronym: Not Applicable

Hypotheses, Objectives, and Endpoints:

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

In adults with hypercholesterolemia:

Objectives	Endpoints
Primary	
• Objective: To compare the effect of MK-0616 with the effect of placebo on percent change from baseline in LDL-C at Week 8. • Hypothesis: At least 1 of the 4 doses of MK-0616 is superior to placebo on percent reduction from baseline in LDL-C at Week 8.	• LDL-C
• Objective: To evaluate the safety and tolerability of each dose of MK-0616.	• AEs • Discontinuation of study intervention due to AEs
Secondary	
• Objective: To compare the effect of MK-0616 with the effect of placebo on percent change from baseline in ApoB and non-HDL-C at Week 8.	• ApoB and non-HDL-C
• Objective: To compare the effect of MK-0616 with the effect of placebo on the proportion of participants with LDL-C value at goal at Week 8.	• LDL-C (LDL-C goals are defined in Section 9.4.1)

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Hypercholesterolemia
Population	Male and female participants ≥18 and ≤80 years of age with 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
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 13 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 375 participants will be randomized.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>Study intervention will be administered in the fasted state, as described in Section 5.3.1.
<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Adminis-tration</th><th>Treatment Period</th><th>Use</th></tr>
<tr><td>Group 1</td><td>MK 0616</td><td>6 mg</td><td>QD</td><td>oral</td><td>8 weeks (V2 to V5)</td><td>Test Product</td></tr>
<tr><td>Group 2</td><td>MK 0616</td><td>12 mg</td><td>QD</td><td>oral</td><td>8 weeks (V2 to V5)</td><td>Test Product</td></tr>
<tr><td>Group 3</td><td>MK 0616</td><td>18 mg</td><td>QD</td><td>oral</td><td>8 weeks (V2 to V5)</td><td>Test Product</td></tr>
<tr><td>Group 4</td><td>MK 0616</td><td>30 mg</td><td>QD</td><td>oral</td><td>8 weeks (V2 to V5)</td><td>Test Product</td></tr>
<tr><td>Group 5</td><td>Placebo</td><td>0 mg</td><td>QD</td><td>oral</td><td>8 weeks (V2 to V5)</td><td>Placebo</td></tr>
<tr><td colspan="7">Abbreviations: QD once daily; V visit
Note: Each dose of MK 0616 is formulated with CCI of sodium caprate, a permeation enhancer.</td></tr>
</table></td></tr>
<tr><td>Total Number of Intervention Groups/ Arms</td><td>5</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for approximately 19 weeks from the time the participant provides documented informed consent through the final contact. After an up-to 21-day screening phase, each participant will receive assigned intervention for 8 weeks. After the end-of-treatment, each participant will be followed for 8 weeks for safety.</td></tr>
</table>

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

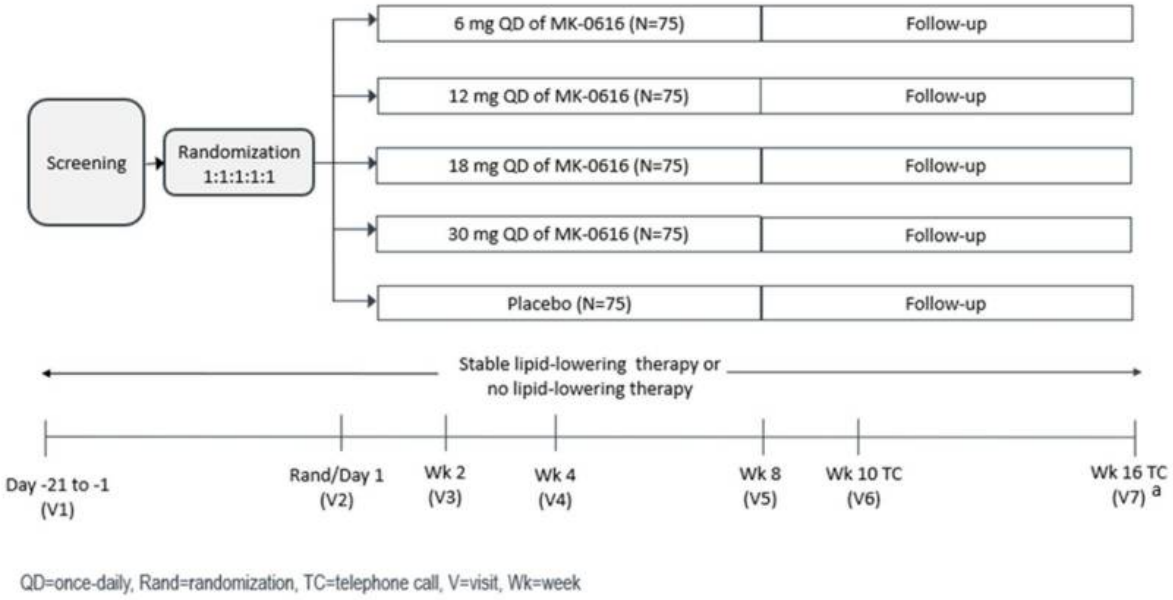
Study Accepts Healthy Volunteers: No

A list of abbreviations is in Appendix 10.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



a. Country specific requirements are in Appendix 7.

1.3 Schedule of Activities

Study Period:	Screening	Treatment				Post-Treatment Follow-up			Notes
Visit Number/Title:	1	2	3	4	5	6 (TC)	7 (TC)[a]	SI Discon	Participants who discontinue study intervention prematurely will have an SI Discon Visit. These participants will be encouraged to remain in the study despite discontinuation of study intervention (Section 7.1).
Week/Day:	Day -21 to -1	Day 1	Wk 2	Wk 4	Wk 8	Wk 10	Wk 16	N/A	
Visit Windows (Days):	N/A	N/A	+5	±5[b]	±5[b]	+7	+7	N/A	
Administrative Procedures									
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							
Participant Identification Card	X	X							Add randomization number at V2/Day 1.
Medical History	X								
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	
Dietary Counseling/Monitoring	X	X	X	X	X				See Section 5.3.1.
IRT Visit Registration	X	X		X	X			X	
IRT Randomization		X							
Dispense Study Intervention		X		X					

Study Period:	Screening	Treatment				Post-Treatment Follow-up		SI Discon	Notes
Visit Number/Title:	1	2	3	4	5	6 (TC)	7 (TC)[a]		Participants who discontinue study intervention prematurely will have an SI Discon Visit. These participants will be encouraged to remain in the study despite discontinuation of study intervention (Section 7.1).
Week/Day:	Day -21 to -1	Day 1	Wk 2	Wk 4	Wk 8	Wk 10	Wk 16	N/A	
Visit Windows (Days):	N/A	N/A	+5	±5[b]	±5[b]	+7	+7	N/A	
Witnessed Dose		X		X					
Study Intervention Accountability (overall population)			X	X	X			X	See Section 6.4 for details.
Background Lipid-lowering Therapy Accountability	X	X	X	X	X			X	Only applicable for participants on background lipid-lowering therapy. See Section 6.4.1 for details.
Fasting Accountability (overall population)			X	X	X			X	Participants' compliance with fasting guidelines (Section 5.3.1) relative to administration of study intervention will be assessed (Section 6.4.2).

Study Period:	Screening	Treatment				Post-Treatment Follow-up		SI Discon	Notes
Visit Number/Title:	1	2	3	4	5	6 (TC)	7 (TC)[a]		Participants who discontinue study intervention prematurely will have an SI Discon Visit. These participants will be encouraged to remain in the study despite discontinuation of study intervention (Section 7.1).
Week/Day:	Day -21 to -1	Day 1	Wk 2	Wk 4	Wk 8	Wk 10	Wk 16	N/A	
Visit Windows (Days):	N/A	N/A	+5	±5[b]	±5[b]	+7	+7	N/A	
Provide or Configure Electronic Device for Fasting Log and Train on Completion of Fasting Log (subset)		X							Between V2/Day 1 and V5/Wk 8 (or SI Discon Visit), a subset of participants will complete a daily Fasting Log (Section 8.1.15). Use of a personal or Sponsor-provided device for the Fasting Log will be determined at V1/Screening. Compliance with the Fasting Log should be reinforced at each visit.
Collect Electronic Device From Participant (subset)					X			X	For participants who received an electronic device for the Fasting Log.

Study Period:	Screening	Treatment				Post-Treatment Follow-up			Notes
Visit Number/Title:	1	2	3	4	5	6 (TC)	7 (TC)[a]	SI Discon	Participants who discontinue study intervention prematurely will have an SI Discon Visit. These participants will be encouraged to remain in the study despite discontinuation of study intervention (Section 7.1).
Week/Day:	Day -21 to -1	Day 1	Wk 2	Wk 4	Wk 8	Wk 10	Wk 16	N/A	
Visit Windows (Days):	N/A	N/A	+5	±5[b]	±5[b]	+7	+7	N/A	
Dispense Urine Pregnancy Test Kits (WOCBP only)					X			X	WOCBP will perform a urine pregnancy test approximately 4 and 8 weeks after the last dose of study intervention. A serum test will be performed if a urine test is not acceptable per local regulations (Section 8.3.7).
Efficacy Assessments									
Lipid Panel	X	X	X	X	X			X	Lipid panel parameters are listed in Appendix 2.
VLDL-C, ApoB, ApoA1, Lp(a), hsCRP		X			X			X	
Safety Assessments									
Full Physical Examination[a]		X			X			X	
Directed Physical Examination				X					
Height		X							
Weight		X			X			X	

Study Period:	Screening	Treatment				Post-Treatment Follow-up			Notes
Visit Number/Title:	1	2	3	4	5	6 (TC)	7 (TC)[a]	SI Discon	Participants who discontinue study intervention prematurely will have an SI Discon Visit. These participants will be encouraged to remain in the study despite discontinuation of study intervention (Section 7.1).
Week/Day:	Day -21 to -1	Day 1	Wk 2	Wk 4	Wk 8	Wk 10	Wk 16	N/A	
Visit Windows (Days):	N/A	N/A	+5	±5[b]	±5[b]	+7	+7	N/A	
Temperature	X								
Vital Signs (blood pressure, pulse rate)	X	X	X	X	X			X	
12-lead ECG (local)[a]		X			X			X	
Chemistry (including CK)	X	X	X	X	X			X	
A1C	X	X			X			X	A1C will only be assessed in participants with a history of diabetes mellitus.
Hematology	X	X	X	X	X			X	
Urine or Serum hCG, (WOCBP only, per local requirements)	X	X		X	X			X	In addition to the visits shown here, WOCBP will perform urine pregnancy tests approximately 4 and 8 weeks after the last dose of study intervention using site-provided kits. A serum test will be performed if a urine test is not acceptable per local regulations (Section 8.3.7 for details).

Study Period:	Screening	Treatment				Post-Treatment Follow-up		SI Discon	Notes
Visit Number/Title:	1	2	3	4	5	6 (TC)	7 (TC)[a]		Participants who discontinue study intervention prematurely will have an SI Discon Visit. These participants will be encouraged to remain in the study despite discontinuation of study intervention (Section 7.1).
Week/Day:	Day -21 to -1	Day 1	Wk 2	Wk 4	Wk 8	Wk 10	Wk 16	N/A	
Visit Windows (Days):	N/A	N/A	+5	±5[b]	±5[b]	+7	+7	N/A	
FSH	X								FSH may be measured to confirm postmenopausal state (Appendix 5). Testing requirements for FSH are in Section 8.3.7.1.
TSH	X								
FT4	X								Only in participants with hypothyroidism.
AE Monitoring	X	X	X	X	X	X	X	X	
PK, PD, and Biomarkers									
PK Sample Collection		X		X	X			X	Refer to Appendix 2 and the laboratory manual for details on collection of PK samples, and Section 8.9 for details on FBR.
Plasma PCSK9 Sample Collection		X		X	X			X	Refer to Appendix 2 and the laboratory manual for details on collection of PCSK9 samples, and Section 8.9 for details on FBR.

Study Period:	Screening	Treatment				Post-Treatment Follow-up		SI Discon	Notes
Visit Number/Title:	1	2	3	4	5	6 (TC)	7 (TC)[a]		Participants who discontinue study intervention prematurely will have an SI Discon Visit. These participants will be encouraged to remain in the study despite discontinuation of study intervention (Section 7.1).
Week/Day:	Day -21 to -1	Day 1	Wk 2	Wk 4	Wk 8	Wk 10	Wk 16	N/A	
Visit Windows (Days):	N/A	N/A	+5	±5[b]	±5[b]	+7	+7	N/A	
Blood for Genetic Analysis		X							Collect predose at V2/Day 1. See Section 8.8.1.
Plasma for FBR		X			X			X	Collect predose at V2/Day 1.

A1C glycosylated hemoglobin, AE adverse event, ApoA1 apolipoprotein A1, ApoB apolipoprotein B, CK creatine kinase, FBR future biomedical research, FSH follicle stimulating hormone, FT4 free T4 test, hCG human chorionic gonadotropin, hsCRP high-sensitivity C-reactive protein, IRT interactive response technology, Lp(a) lipoprotein (a), N/A not applicable, PCSK9 protein convertase subtilisin/kexin type 9, PD pharmacodynamic, PK pharmacokinetic, QD once daily, SI Discon study intervention discontinuation, TC telephone call, TSH thyroid stimulating hormone, V visit, VLDL-C very low-density lipoprotein cholesterol, Wk week, WOCBP woman of childbearing potential.

a. Country-specific requirements are in Appendix 7.
b. The maximum time between on-treatment visits must not exceed 35 days since study intervention supplies contain 35 capsules to be taken QD.

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]. Despite the availability of several proven LDL-C-lowering therapies (eg, statins, ezetimibe, bile acid sequestrants, PCSK9 inhibitors), a substantial proportion of patients with hypercholesterolemia are not at guideline-recommended LDL-C targets [Fox, K. M., et al 2018]. This information supports the need for additional LDL-C-lowering therapies for the treatment of hypercholesterolemia.

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 PCSK9 inhibitors have received regulatory approval for the treatment of hypercholesterolemia. Unlike these injectable therapies, MK-0616 is an orally administered PCSK9 inhibitor for the treatment of hypercholesterolemia. An oral PCSK9 inhibitor, that can achieve equivalent LDL-C-lowering as the injectable PCSK9 inhibitors, offers potential advantages in simplicity of dosing, patient preference, and access.

The principal objectives of this Phase 2b study are to evaluate the LDL-C-lowering efficacy and safety of MK-0616 in participants with hypercholesterolemia. This study will also be used to support dose selection of MK-0616 for future development.

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 cyclic 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.

2.2.2 Preclinical and Clinical Studies

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

MK-0616 is formulated with sodium caprate to enhance intestinal absorption and oral bioavailability. Sodium caprate is the sodium salt of capric acid that is ubiquitously present in dairy products, particularly milk [Ceballos, L.S., Morales, E.R., et al. 2009], and is an FDA-approved food additive [U.S. Food & Drug Administration 2019]. CCI [redacted]

Three Phase 1 clinical studies of MK-0616 are complete. These consist of a single ascending-dose PK/PD study in healthy participants (P001), a multiple ascending-dose PK study in participants on background statin therapy (P003), and a single-dose PK formulation study of MK-0616 in healthy participants (P004).

In Study P003, treatment with MK-0616 resulted in a reduction in LDL-C that is similar in magnitude to that observed with injectable PCSK9 inhibitors (~65% reduction from baseline in LDL-C after 14 days of once-daily dosing). Safety data from the Phase 1 studies, which included approximately 130 participants who received up to 300 mg of MK-0616, showed that MK-0616 is generally well-tolerated in both healthy participants and in those on background statin therapy. No SAEs were reported, and most AEs were mild or moderate in intensity. The most commonly reported treatment emergent AEs (occurring in more than 1 participant) were diarrhea, dyspepsia, gastroenteritis, gastroesophageal reflux, dry mouth, impaired fasting glucose, nasopharyngitis, skin irritation, back pain, dizziness, and headache. There were no clinically meaningful trends observed for laboratory safety tests, vital signs, or ECGs.

CCI [redacted] Results from P003 showed an accumulation ratio of 1.3 to 2.3 for AUC0-24, Cmax, and C24 with 10 to 20 mg QD dosing, with steady state reached by Day 7. These results support QD dosing of MK-0616. PK results from Phase 1 studies show that MK-0616 CCI [redacted]

Food significantly decreases the bioavailability of MK-0616 and delays its absorption. Therefore, participants in the current study will be instructed to administer study intervention in the fasted state (Section 5.3.1).

2.2.3 Ongoing Clinical Studies

Two Phase 1 studies of MK-0616 are ongoing, including a formulation study and a study in Japanese participants.

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. Several injectable PCSK9 inhibitors have demonstrated adequate safety and LDL-C lowering efficacy to receive regulatory authority approval for the treatment of hypercholesterolemia.

In the preclinical development program, CCI [redacted] CCI [redacted] CCI [redacted] Additionally, robust LDL-C lowering was observed following single-dose administration of MK-0616 in monkeys.

Results from a complete Phase 1 multiple ascending-dose study in participants on background statin therapy (P003) showed that MK-0616 treatment leads to clinically meaningful reductions in LDL-C (Section 2.2.2). MK-0616 was generally well-tolerated in the 3 complete Phase 1 studies at doses up to 300 mg. No SAEs were reported, and most AEs were mild or moderate in intensity.

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 participating 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 hypercholesterolemia:

Objectives	Endpoints
Primary	
• Objective: To compare the effect of MK-0616 with the effect of placebo on percent change from baseline in LDL-C at Week 8. • Hypothesis: At least 1 of the 4 doses of MK-0616 is superior to placebo on percent reduction from baseline in LDL-C at Week 8.	• LDL-C

Objectives	Endpoints
• Objective: To evaluate the safety and tolerability of each dose of MK-0616.	• AEs • Discontinuation of study intervention due to AEs
Secondary	
• Objective: To compare the effect of MK-0616 with the effect of placebo on percent change from baseline in ApoB and non-HDL-C at Week 8.	• ApoB and non-HDL-C
• Objective: To compare the effect of MK-0616 with the effect of placebo on the proportion of participants with LDL-C value at goal at Week 8.	• LDL-C (LDL-C goals are defined in Section 9.4.1)
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	
CCI [redacted]	• Germline genetic variation and association to clinical data collected in this study

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2b, randomized, double-blind, placebo-controlled, multi-site study of MK-0616 in participants with hypercholesterolemia. Participants with a range of ASCVD risk are eligible for the study, including those who are not on any lipid-lowering therapy (including participants who stopped prior treatment and treatment naïve participants), as well as those on 1 or more lipid-lowering therapies, and those with or without heterozygous FH.

CCI [redacted]

CCI [redacted] Participants with homozygous FH and those on treatment with a PCSK9 inhibitor are not eligible for the study.

This study consists of an up-to 21-day screening period (Visit 1 [Screening] to Visit 2 [Day 1]), an 8-week treatment period (Visit 2 [Day 1] to Visit 5 [Week 8]), and an 8-week post-treatment follow-up period (Visit 5 [Week 8] to Visit 7 [Week 16]) for safety assessment. Participants who discontinue study intervention prematurely will be encouraged to continue in the study off-treatment and to complete all remaining visits as outlined in the SoA.

After completing the screening period, approximately 375 participants meeting eligibility criteria will be randomized in a 1:1:1:1:1 ratio to treatment with either 1 of 4 doses of MK-0616 (6, 12, 18, or 30 mg) or placebo. Randomized participants will administer 1 capsule of study intervention daily (Table 2) in the fasted state according to the guidelines provided in Section 5.3.1.

Randomization will be stratified by renal function (eGFR ≥60 or <60 ml/min/1.73 m^2) at Visit 1 (Screening) and by dose of background statin therapy (Sections 4.2 and 6.3.2), with an aim to enroll approximately one-third of participants in each of the following statin

categories: no statin therapy, low- to moderate-intensity statin therapy, or high-intensity statin therapy (Appendix 9). A randomization cap may be applied in IRT if the number of participants randomized in any statin category is disproportional relative to the other statin categories.

The Sponsor's siDMC will evaluate the accruing unblinded safety data on a regular basis.

Two database locks are planned for this study in order to facilitate program planning. The first will occur after the efficacy cutoff date, defined as the date when all randomized participants complete Visit 5 [Week 8] (or otherwise discontinue the study prematurely). The second database lock will occur after all participants complete their participation in the study through Visit 7 (Week 16) (or otherwise discontinue the study prematurely). All study objectives will be addressed based on the first database lock, which will include complete efficacy, PK, and PD data. Analyses of safety based on the first database lock will include all available data (including post-Visit 5 [Week 8]). Additional safety analyses will be performed using the comprehensive data in the second database lock.

The Sponsor will be unblinded to participants' treatment assignments after the first database lock. Participants and investigators will remain blinded to participants' treatment assignments until after the second database lock.

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 2b study are to test the hypothesis that MK-0616 reduces LDL-C in participants with hypercholesterolemia, 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 lipid-lowering therapies (details on the rationale for use of placebo are in Section 4.2.2). Eligibility criteria for this study will support the enrollment of a range of participants with ASCVD risk, including those who are not on any lipid-lowering therapy (including participants who stopped prior treatment and treatment naïve participants), as well as those on 1 or more lipid-lowering therapies, and those with or without heterozygous FH.

Since [redacted] those with eGFR <45 mL/min/1.73 m^2 are not eligible to participate. Additionally, stratification by renal function will be employed to support balanced randomization of participants with eGFR values ≥60 or <60 ml/min/1.73 m^2 at Visit 1 (Screening) across the 5 treatment groups. Since statin treatment can increase PCSK9 levels and potentially affect dose-response and efficacy, stratification by statin therapy will also be employed in this study to support balanced randomization of participants on no statin therapy, low- to moderate-intensity statin therapy, or high-intensity statin therapy across the 5 treatment groups.

An 8-week treatment period was selected to provide adequate time to observe the potential effects of MK-0616 on LDL-C (primary endpoint). An 8-week post-treatment safety follow-up period was selected [redacted] Additionally, this study will evaluate 4 different doses of MK-0616 (6, 12, 18, and 30 mg) to support dose selection of MK-0616 for future development.

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 lipid-lowing therapies, will be determined by its effect on LDL-C relative to placebo, with the primary endpoint of percent change from baseline in LDL-C at Week 8, a secondary endpoint of the proportion of participants with LDL-C goal attainment at Week 8 (LDL-C goals are defined in Section 9.4.1), and [redacted]

Like LDL-C, ApoB and non-HDL-C are predictors of ASCVD risk. Therefore, the effects of MK-0616 relative to placebo on percent change from baseline in ApoB and non-HDL-C at Week 8 will be evaluated as secondary endpoints.

[redacted] to further evaluate the effects of MK-0616 relative to placebo on the lipid profile of participants with hypercholesterolemia. [redacted] at Week 8.

4.2.1.2 Safety Endpoints

AEs, physical examination findings, vital signs, ECGs, and laboratory safety tests (chemistry [including CK], hematology, A1C in participants with diabetes mellitus, and pregnancy tests in WOCBP) will be assessed to provide a comprehensive safety evaluation of MK-0616 relative to placebo in participants with hypercholesterolemia. Potential DILI events will be captured as ECIs per the standard requirement of Sponsor studies (Section 8.4.7). 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

Trough concentrations of MK-0616 will be summarized to inform on MK-0616 exposure in participants.

4.2.1.4 Pharmacodynamic Endpoints

PCSK9 inhibition reduces free plasma PCSK9 concentrations. In the Phase 1 single ascending-dose study, all doses of MK-0616 led to maximum mean reductions of >90% from baseline in free plasma PCSK9. The effects of MK-0616 on free plasma PCSK9 will be measured in the current study to inform on dose selection for the Phase 3 program.

4.2.1.5 Planned Exploratory Biomarker Research

4.2.1.5.1 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.

4.2.1.6 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 short study duration, the frequent evaluation of participants at scheduled visits, and because higher-risk participants with ASCVD or ASCVD risk-equivalents are expected to be on stable treatment with background LDL-C-lowering therapy (per local guidelines) and to continue this therapy throughout the study.

4.3 Justification for Dose

Four doses of MK-0616 (6, 12, 18, and 30 mg) will be tested in this study. In the Phase 1 multiple ascending-dose study in participants on background statin therapy (P003), the mean reduction from baseline in LDL-C at Day 14 was >50% with both the 10 and 20 mg fasting doses of MK-0616. Although a lower dose could not be tested, a 10 mg fed dose, which is presumed to behave like a 5 mg fasted dose given the food effect (Section 2.2.2), did not attain similar LDL-C reductions. CCI

CCI

In the current study of MK-0616, the planned doses will allow for refinement of the exposure-response relationship and selection of a Phase 3 dose by populating the ascending and descending phases of the exposure-response curve and characterizing EC50 and the Emax plateau, and will also ensure that there is an adequate safety margin for the anticipated clinical dose in the projected patient population.

Additional country-specific justification for dose is in Appendix 7.

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 (ie, the participant is unable to be contacted by the investigator).

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/clinical endpoints 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 due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1) our studies include people of varying age, race, ethnicity, and sex. The collection and use of these demographic data are to follow all local laws and guidelines in keeping with the needs for participant confidentiality while supporting the study of the disease, its related factors, and the IMP under investigation.

Male and female participants ≥18 and ≤80 years of age with hypercholesterolemia and a range of ASCVD risk, including those who are not on any lipid-lowering therapy (including participants who stopped prior treatment and treatment naïve participants), as well as those on 1 or more lipid-lowering therapies, and those with or without heterozygous FH will be enrolled in this study.

Participants with an exclusionary laboratory value (see Sections 5.1 and 5.2) may have 1 repeat determination performed if the investigator considers the Visit 1 (Screening) result to be inconsistent with prior determinations. Only the laboratory test not meeting entry criterion should be repeated (not the entire panel). The last laboratory draw/result should be used to assess eligibility.

Country-specific inclusion and exclusion criteria are in Appendix 7.

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

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Meets 1 of the following ASCVD status/risk categories AND has a fasted LDL-C value in the corresponding LDL-C range at Visit 1 (Screening) (Table 1).

   Note 1: ASCVD status/risk categories are mutually exclusive, therefore, the highest applicable ASCVD status/risk category should be used to determine participant eligibility and corresponding LDL-C range.

   Note 2: See Appendix 7 for additional eligibility requirements for participants in Japan.

Table 1 ASCVD Status/Risk Categories and Corresponding LDL-C Ranges for Inclusion

ASCVD Status/Risk Category	Corresponding LDL-C Range	
	(mg/dL)	(mmol/L)
Has clinical ASCVD[1]	≥70 and ≤160	≥1.81 and ≤4.14
Has an ASCVD risk equivalent[2] and/or a 10-year risk of having an ASCVD event that is ≥7.5%[3]	≥100 and ≤200	≥2.59 and ≤5.18
Has a 10-year risk of having an ASCVD event that is ≥5.0% and <7.5%[3]	≥130 and ≤250	≥3.37 and ≤6.48

[1] Clinical ASCVD is defined as having a history of 1 or more of the following: acute coronary syndrome, myocardial infarction, angina pectoris, coronary revascularization, arterial revascularization, stroke, transient ischemic attack, peripheral arterial disease [Grundy, S. M., et al 2019].

[2] ASCVD-risk equivalents include diabetes mellitus and heterozygous FH. The diagnosis of heterozygous FH should be definitive and based on an established diagnostic algorithm (eg, US MEDPED, Simon Broome, Dutch Lipid Network, or Japanese Atherosclerosis Society Guidelines) [McGowan, M. P., et al 2019] [Kinoshita, M., et al 2018].

[3] The 10-year risk percentage for having an ASCVD event will be determined using an ASCVD risk calculator (Appendix 8).

2. Is either on a stable dose of 1 or more lipid-lowering therapies for ≥30 days before Visit 1 (Screening) or has not received treatment with any lipid-lowering therapy for ≥30 days before Visit 1 (Screening). Those who are not on a lipid-lowering therapy at Visit 1 (Screening) can either have been previously treated or be treatment naïve.

   Note 1: Lipid-lowering therapies include medications (eg, statins, ezetimibe, bempedoic acid, niacin, fibrates) and supplements (eg, omega-3 fatty acids) that can affect cholesterol levels.

   Note 2: For all participants, there should be no planned lipid-lowering therapy additions or dose changes during the study (Visit 1 [Screening] to Visit 7 [Week 16]).

   Country-specific requirements for inclusion criterion #2 are in Appendix 7.

Demographics

3. Is male or a female, ≥18 years and ≤80 years of age, at the time of providing documented informed consent.

Female Participants

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

- Not a WOCBP

  OR

- A WOCBP and:

  - Uses an acceptable contraceptive method, or be abstinent from heterosexual 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 8 weeks 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 women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies

  - Has a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 72 hours 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 8.3.7.

  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

  Country-specific contraception requirements are in Appendix 7.

Informed Consent

5. The participant (or legally acceptable representative) provides documented informed consent for the study. The participant may also provide consent for FBR. However, the participant may participate in the study without participating in FBR.

   Country-specific information for participants in Germany is provided in Appendix 7.

Additional Categories

6. 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

The participant must be excluded from the study if the participant 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].

2. Has a history of nephrotic syndrome.

3. Has any clinically significant malabsorption condition.

4. Had unstable angina, a myocardial infarction, percutaneous transluminal coronary angioplasty, transient ischemic attack, or stroke within 3 months before Visit 1 (Screening).

5. Has a planned coronary revascularization procedure within the next 3 months after Visit 1 (Screening).

6. Has poorly controlled diabetes mellitus, defined as A1C ≥9.0%, at Visit 1 (Screening).

7. Has a known allergy or intolerance to any of the ingredients in the study intervention.

8. 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).

9. Has a severe, acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or administration of study intervention or may interfere with the interpretation of study results and, in the opinion of the investigator, would make the participant inappropriate for entry into this study.

Prior/Concomitant Therapy

10. Is undergoing or previously underwent an LDL-C apheresis program within 3 months before Visit 1 (Screening).

11. Is receiving treatment with oral semaglutide at Visit 1 (Screening).

12. Meets 1 or more of the following criteria:

    - Is on treatment with a PCSK9 inhibitor (siRNA or mAb), an ANGPTL3 inhibitor, or an MTP inhibitor (eg, lomitapide) at Visit 1 (Screening).

    - Was previously treated with an siRNA PCSK9 inhibitor within 1 year before Visit 1 (Screening).

- Was previously treated with a mAb PCSK9 inhibitor within 6 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

13. Is currently participating in or has previously participated 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

14. Has moderate or greater renal insufficiency defined as eGFR <45 mL/min/1.73 m^2 at Visit 1 (Screening); eGFR will be calculated according to Appendix 2. (Germany-specific criterion is in Appendix 7).

15. Has laboratory or clinical evidence of clinically significant hepatic conditions, including 1 or more of the following:

    - ALT or AST >2X ULN at Visit 1 (Screening).
    - 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.

    Country-specific exclusion requirements are in Appendix 7.

16. Has elevated CK >3X ULN at Visit 1 (Screening).

17. Has a fasting triglyceride value ≥400 mg/dL (≥4.52 mmol/L) at Visit 1 (Screening).

18. Has an abnormal TSH value at Visit 1 (Screening) without a history of hypothyroidism. Participants with a history of hypothyroidism are eligible if their treatment for this condition is stable for ≥3 months before Visit 1 (Screening) and their FT4 value at Visit 1 (Screening) is normal.

Other Exclusions

19. Routinely consumes >3 alcoholic drinks per day. One standard drink is defined as any beverage containing 14 g of pure alcohol (ie, 12 oz of beer, 8 to 9 oz of malt liquor, 5 oz of wine, 1.5 oz of distilled spirits).

20. Has a recent history of drug abuse (within the last year) or is a current user of recreational or illicit drugs at the time of Visit 1 (Screening).

21. 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.

22. Country-specific exclusion criterion is in Appendix 7.

23. Country-specific exclusion criterion is in Appendix 7.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Fasting Guidance for Clinic Visits

In order to ensure laboratory parameters are collected in the fasted state, participants will be contacted approximately 3 days before each clinic visit and instructed 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.

Country-specific requirements are in Appendix 7.

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 8.1.10.1.

Fasting Guidance on Days With no Clinic Visit

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

1. Take their dose of study intervention (with water) first thing in the morning following an overnight fast (≥8 hours), and

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

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

Dietary Counseling/Monitoring

At Visit 1 (Screening), participants will receive counseling from a qualified healthcare professional on a diet consistent with local guidelines. At each subsequent visit, 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.

Country-specific requirements are in Appendix 7.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

Participants will be counseled to limit alcohol use to moderate amounts while participating in the study (ie, ≤3 drinks per day and not more than 21 drinks per week). One standard drink is defined as any beverage containing 14 g of pure alcohol (ie, 12 oz of beer, 8 to 9 oz of malt liquor, 5 oz of wine, 1.5 oz of distilled spirits).

Participants should be advised to refrain from nicotine-containing products and ingesting caffeine for at least 30 minutes before blood pressure, pulse rate, and ECG determinations (Sections 8.3.4 and 8.3.5).

5.3.3 Activity Restrictions

Participants will be instructed not to initiate a strenuous exercise program during the study.

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) provided by the Sponsor 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 intervention(s) to be used in this study will be administered in the fasted state (Section 5.3.1) and are outlined in Table 2.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength	Dosage Level(s)	Route of Administration	Regimen/Treatment Period/Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Group 1	Experimental	MK-0616	Drug	Capsule	6 mg	6 mg QD	Oral	8 weeks (V2 to V5)	Test Product	IMP	Central
Group 2	Experimental	MK-0616	Drug	Capsule	12 mg	12 mg QD	Oral	8 weeks (V2 to V5)	Test Product	IMP	Central
Group 3	Experimental	MK-0616	Drug	Capsule	18 mg	18 mg QD	Oral	8 weeks (V2 to V5)	Test Product	IMP	Central
Group 4	Experimental	MK-0616	Drug	Capsule	30 mg	30 mg QD	Oral	8 weeks (V2 to V5)	Test Product	IMP	Central
Group 5	Placebo Comparator	Placebo	Drug	Capsule	0 mg	0 mg QD	Oral	8 weeks (V2 to V5)	Placebo	IMP	Central

EEA European Economic Area; IMP investigational medicinal product; NIMP noninvestigational medicinal product; QD once daily; V visit.

The classification of IMP and NIMP 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/NIMP may exist (Appendix 7). In these circumstances, local legislation is followed.

Note: Each dose of MK 0616 is formulated with CCI of sodium caprate, a permeation enhancer.

All supplies indicated in Table 2 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 (not applicable in the case where multiple lots or batches may be required due to the length of the study, etc.).

Refer to Section 8.1.10 for details regarding administration of the study intervention.

All placebos were created by the Sponsor to match the active product.

6.1.1 Medical Devices

No medical devices are tested in this study.

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 5 study intervention arms. Participants will be assigned randomly in a 1:1:1:1:1 ratio to once-daily treatment with 1 of the 4 doses of MK-0616 (6, 12, 18, or 30 mg) or placebo.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. Background statin dose (no statin therapy vs. low- to moderate-intensity statin therapy vs. high-intensity statin therapy [Appendix 9]). Details on enrollment by statin category are in Section 4.1.

2. Renal function (eGFR ≥60 vs <60 mL/min/1.73 m^2) at Visit 1 (Screening); eGFR will be calculated according to Appendix 2.

The rationale for the stratification factors used in this study is in Section 4.2.

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. MK-0616 and placebo will be packaged identically so that blind is maintained. 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.

The Sponsor will be unblinded to participants' treatment assignments after the first database lock. Participants and investigators will remain blinded to participants' treatment assignments until after the second database lock (Section 4.1).

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment plan that result in <80% compliance with study intervention will require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

- Compliance with study intervention will be assessed by counting returned capsules, 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, including dates for intervention delays will be recorded in the eCRF.

6.4.1 Background Lipid-lowering Therapy Compliance

Compliance with lipid-lowering therapy (medications and/or supplements), in those on lipid-lowering therapy at Visit 1 [Screening], will be assessed by direct questioning. Those who report non-compliance with taking their lipid-lowering therapy in the screening or double-blind treatment period will receive additional counseling by site staff.

6.4.2 Fasting Compliance

Participants in the overall population 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 week before each visit will be assessed by direct questioning. Those whose compliance with fasting guidance is <80% during the week before each visit will receive additional counseling by site staff. Compliance with fasting guidance will also be assessed via a Fasting Log in a subset of participants (see Section 8.1.15 for details).

6.5 Concomitant Therapy

Medications specifically prohibited in the exclusion criteria are not allowed 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 lipid-lowering therapies (medications and/or supplements) the participant was receiving within 30 days before Visit 1 (Screening) should be recorded on the concomitant therapy CRF. No lipid-lowering therapy additions or dose changes are permitted during the study (Visit 1 [Screening] to Visit 7 [Week 16]). Acceptable lipid-lowering therapies include, but are not limited to the following (Country-specific requirements are in Appendix 7):

- statins
- bempedoic acid
- ezetimibe
- niacin
- fibrates
- omega-3 fatty acids

Treatment with any nonstudy PCSK9 inhibitor, an ANGPTL3 inhibitor, an MTP inhibitor (eg, lomitapide), LDL-C apheresis, or oral semaglutide is prohibited during the study (Visit 1 [Screening] to Visit 7 [Week 16]); there are no other prohibited medications for this study.

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.

Any licensed COVID-19 vaccine (including for emergency use) in a particular country is permitted in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy. Investigational vaccines (ie, those not licensed or approved for emergency use) are not permitted.

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 (Escalation/Titration/Other)

No dose modifications are permitted.

6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

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 (see Section 8.11.6 for exceptions), 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 that, in the opinion of the investigator and/or Sponsor, places the participant at unnecessary risk from continued administration of study intervention.
- The participant has a 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 permanently discontinued from study intervention and followed per Section 8.4.5.

- The participant has an eGFR consistently <35 mL/min/1.73 m^2; eGFR will be calculated according to Appendix 2.

  Note 1: For eGFR, a consistent value is defined as a repeat measurement performed within 7 days of notification from the central laboratory.

Note 2: If the eGFR value continues to meet discontinuation criterion but demonstrates stability or improvement relative to the prior result, an additional repeat may be performed (within 7 days). If this repeat continues to meet the discontinuation criterion, the participant must be discontinued from study intervention.

- The participant has an ALT or AST result ≥3X ULN, a total bilirubin result ≥2X ULN, and, at the same time, an alkaline phosphatase result <2X ULN (guidance on follow-up of participants with laboratory values meeting this criterion is in the Investigator Study File Binder, or equivalent).

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.

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, they shall not be allowed to restart study intervention.

Country-specific discontinuation requirements are in Appendix 7.

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 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.

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.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

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.

- 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 at scheduled visits over the duration of the study will not exceed approximately 140 mL (see the laboratory documentation). This blood volume does not account for unscheduled visits or the Study Intervention Discontinuation Visit.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Country-specific requirements are in Appendix 7.

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 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).

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

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator (or qualified designee) will review and record any prior lipid-lowering therapies (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.

8.1.5.2 Concomitant Medications

The investigator (or qualified designee) will review and record medications taken by the participant during the study. No lipid-lowering therapy additions or dose changes are permitted during the study (Visit 1 [Screening] to Visit 7 [Week 16]). Treatment with any non-study PCSK9 inhibitor, an ANGPTL3 inhibitor, an MTP inhibitor (eg, lomitapide), LDL-C apheresis, or oral semaglutide is prohibited during the study (Visit 1 [Screening] to Visit 7 [Week 16]); there are no other prohibited medications for this study.

8.1.6 Dietary Counseling/Monitoring

Refer to Section 5.3.1 for guidance on dietary counseling and monitoring.

8.1.7 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 participant 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 Sections 8.11.2 and 8.11.3.

8.1.8 Assignment of Randomization Number

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

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

8.1.9 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.

8.1.10 Study Intervention Administration

Study intervention will be administered as oral capsules. At Visit 2 (Day 1), participants will be educated by a trained member of the site staff on appropriate dosing (Section 8.1.10.1) 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.

8.1.10.1 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 once-daily at home. Dosing will occur first thing in the morning (with water) following an overnight fast (ie, no food, study intervention, 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 post-dose PK/PD samples).
- Visit 3 (Week 2): Study intervention will be administered (with water) after laboratory samples are collected.
- Visit 4 (Week 4): Study intervention will be administered (with water) as a witnessed dose after laboratory samples are collected (except collection of post-dose PK/PD samples).
- Visit 5 (Week 8): No study intervention will be administered. The last dose of study intervention will be taken on the day before Visit 5 (Week 8).

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.

8.1.11 Witnessed Dose

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

8.1.12 Study Intervention Accountability (Overall Population)

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

8.1.13 Background Lipid-Lowering Therapy Accountability

Accounting for compliance with background lipid-lowering therapy (for those on lipid-lowering therapy at Visit 1 [Screening]) is described in Section 6.4.1.

8.1.14 Fasting Accountability (Overall Population)

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

8.1.15 Fasting Log (Subset)

At Visit 2 (Day 1), a subset of participants will either receive an electronic device or have their own electronic device configured (if compatible) to complete a daily Fasting Log. Use of a personal or Sponsor-provided device for the Fasting Log will be determined at Visit 1 (Screening).

At Visit 2 (Day 1), participants will be educated by a trained member of the site staff on how to record the time of study intervention administration and the time of the first meal of the day in the Fasting Log. The Fasting Log will be completed each day up to the day before Visit 5 (Week 8) or Study Intervention Discontinuation Visit. Participants who received an electronic device to complete the Fasting Log will return it at Visit 5 (Week 8) or the Study Intervention Discontinuation Visit.

Site personnel should reinforce compliance with the Fasting Log at each visit.

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 8.11.6.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the Study Intervention Discontinuation 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 should continue treatment and 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

Lipid parameters (LDL-C, HDL-C, non-HDL-C, total cholesterol, triglycerides, VLDL-C, ApoB, and Lp[a]), ApoA1, and hsCRP will be measured at the visits specified in the SoA. The rationale for efficacy endpoints is provided in Section 4.2.1.1. LDL-C will be calculated based on the Friedewald formula; 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. For analysis, LDL-C will be based on the beta-quantification method when available, or calculated based on the Friedewald formula when no beta-quantification is available.

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. Unless clinically urgent, investigators should not evaluate efficacy endpoints locally during the study. Non-study physicians should also be encouraged not to evaluate efficacy endpoints locally during the study.

8.3 Safety Assessments

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

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 (provided by the Sponsor if requested) 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 Temperature

Participant's temperature will be measured at Visit 1 (Screening). It is recommended that individual sites use the same method for measuring temperature (eg, oral, tympanic) in all participants throughout the study

8.3.4 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.
- 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.
- Participants should be advised to refrain from nicotine-containing products and ingesting caffeine for at least 30 minutes before blood pressure and pulse rate determinations (Section 5.3.2).

8.3.5 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 HR and measures PR, QRS, QT, and QTc intervals.
- ECGs should be performed after the participant has rested quietly for at least 10 minutes.
- Participants should be advised to refrain from nicotine-containing products and ingesting caffeine for at least 30 minutes before ECG measurements (Section 5.3.2).

8.3.6 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 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 8 weeks 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.

8.3.7 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 subject's participation in the study.

  - 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 permanently discontinued from study intervention (Section 7.1) and followed per Section 8.4.5.

  - Sites will provide WOCBP urine pregnancy test kits to assess pregnancy status. The tests will be performed approximately 4 and 8 weeks after the last dose of study intervention. Participants will contact the site if the result is either positive or unable to be confirmed as negative. These participants will have a confirmatory serum pregnancy test (locally or centrally). Otherwise, sites will confirm that both urine pregnancy tests were performed during the Visit 7 (Week 16) telephone contact (or post-treatment telephone contact corresponding to 8 weeks after the last dose of

study intervention for participants who discontinued study intervention prematurely). Results from the urine and serum (if applicable) pregnancy tests will be recorded in participants' source files.

- If urine pregnancy tests are not acceptable per local regulations, then a serum pregnancy test will be performed (locally or centrally) for the 4- and 8-week post-treatment pregnancy assessment.

Country-specific Visit 7 pregnancy testing requirements are in Appendix 7.

8.3.7.1 Pretreatment Confirmation of Postmenopausal State

Female 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 after consulting with the Sponsor (Section 8.11.3).

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 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.

All AEs, SAEs, and other reportable safety events must be reported by the investigator from the time of intervention randomization through the final study contact (Visit 7 [Week 16]).

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 he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

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 Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time 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/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
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 (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential DILI - Require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do 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 towards 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 SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

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 in a participant (spontaneously reported to the investigator or their designee), including the pregnancy of a male participant's female partner, that occurs 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:

a. An elevated AST or ALT laboratory value that is greater than or equal to 3X the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2X the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2X 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).

Country-specific requirements are in Appendix 7.

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 capsule/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 Appendix 2 (Table 8). Blood samples may be stored for further analysis, if required.

Sample collection, storage, and shipment instructions for PK samples will be provided in a laboratory manual.

8.7 Pharmacodynamics

Free and total plasma PCSK9 samples will be collected at the timepoints specified in Appendix 2 (Table 8). Blood samples may be stored for further analysis, if required.

Sample collection, storage, and shipment instructions for free and total plasma 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 for genetic analysis

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.

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:

- Plasma for FBR
- Leftover DNA for future research
- Leftover plasma PK samples for future research
- Leftover plasma PCSK9 samples for future research

8.10 Medical Resource Utilization and Health Economics

Not applicable.

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, participants will be contacted and reminded to do the following:

- *On the days before clinic visits (applicable after Visit 2 [Day 1]):* Take their daily dose of study intervention (with water) first thing in the morning following an overnight fast (≥8 hours), and to withhold food and beverages (except water) until 30 minutes after dosing.

- *On the day of the clinic visit (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.

Country-specific Visit 7 requirements are in Appendix 7.

8.11.2 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 21 days after Visit 1 (Screening). Participants with an exclusionary laboratory 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).

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

For participants in the subset who will complete the Fasting Log, site personnel will determine if these participants will either receive an electronic device or have their own device configured to complete the Fasting Log (Section 8.1.15).

8.11.3 Rescreening

If a participant screen-fails (Section 5.4), the participant may be rescreened once based on investigator judgment, and after consultation with the Sponsor. Participants who are

rescreened will retain the same screening number assigned at the initial Screening Visit (Section 8.1.7).

8.11.4 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 8.1.10) and fasting guidance (Section 5.3.1). A subset of participants will either receive an electronic device or have their own electronic device configured (if compatible) to complete a daily Fasting Log (Section 8.1.15). These participants will be educated by a trained member of the site staff on accurate completion of the Fasting Log.

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 4 (Week 4) for collection of PK/PD samples (Section 8.1.11).

Compliance with study intervention (Section 6.4), background lipid-lowering therapy (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. Compliance with the Fasting Log, in the subset of participants completing this log, will also be reinforced throughout the study (Section 8.1.15).

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 21 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 at Visit 4 (Week 4), and PK/PD sample collections (Visit 4 [Week 4] and Visit 5 [Week 8]) should be rescheduled to occur within the allowable visit window (specified in the SoA).

If there are extenuating circumstances that do not enable the participant to attend a scheduled clinic visit (ie, incapacitating health conditions or local or national emergency situations), a telephone, video, or home visit using site staff or a nursing service may be used, if allowed by local regulations, following consultation with the Sponsor.

8.11.5 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 8.1.5.2) and reinforcement of compliance with background lipid-lowering therapy (medications and/or supplements), if applicable (Section 6.4.1)

- Review and reinforcement of compliance with study intervention (Section 6.4), fasting guidelines (Section 6.4.2), and the Fasting Log (in the subset completing this log; Section 8.1.15)

8.11.6 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 (Visit 4 [Week 4]) and PK/PD sample collection (Visit 4 [Week 4] and Visit 5 [Week 8])

- Study intervention accountability (overall population)

- Fasting accountability (overall population)

- Plasma collection for FBR

Additionally, the subset of participants completing the Fasting Log will no longer complete the log after the Study Intervention Discontinuation Visit. Those using a Sponsor-provided device for the Fasting Log will return it at the Study Intervention Discontinuation Visit (Section 8.1.15).

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 contacts conducted via phone (Section 7.2).

8.11.7 Post-treatment

Participants will be contacted approximately 2 and 8 weeks after the last dose of study intervention to assess safety (Section 1.3). Additionally, WOCBP will perform at-home urine pregnancy tests approximately 4 and 8 weeks after the last dose of study intervention to assess pregnancy status (Section 8.3.7).

Country-specific Visit 7 requirements are in Appendix 7.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to unblinding the database addressing all study objectives (first database lock), changes are made to primary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding the database addressing all study objectives (first database lock), will be documented in an sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Other planned analyses (ie, those specific to the analysis of PK data and FBR) will be documented in separate analysis plans.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 to 9.12.

Study Design Overview	A Phase 2b, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-0616 in Adults with Hypercholesterolemia
Treatment Assignment	Participants will be assigned randomly in a 1:1:1:1:1 ratio to 1 of 4 doses of MK-0616 (6, 12, 18, or 30 mg) or matching placebo. Randomization will be stratified by background statin dose (no statin therapy vs. low- to moderate-intensity statin therapy vs. high-intensity statin therapy) and renal function (eGFR ≥60 vs <60 ml/min/1.73 m^2) at Visit 1 (Screening).
Analysis Populations	Efficacy: FAS Safety: APaT
Primary Endpoint(s)	Percent change from baseline in LDL-C at Week 8
Secondary Endpoints	1. Percent change from baseline in ApoB and non-HDL-C at Week 8 2. Proportion of participants with LDL-C value at goal at Week 8
Statistical Methods for Key Efficacy Analyses	For the primary and secondary endpoints of percent change from baseline in LDL-C (primary), ApoB, and non-HDL-C at Week 8, the differences in means and the associated 95% CIs and *p*-values will be provided (MK-0616 minus placebo; 4 pairwise comparisons per endpoint) based on a cLDA model. For the secondary endpoint of proportion of participants with LDL-C value at goal at Week 8, 95% CIs (based on the M&N method) and *p*-values will be provided for between-treatment differences.
Statistical Methods for Key Safety Analyses	Analyses for which 95% CIs will be provided for between-treatment differences (MK-0616 minus placebo) in the percentage of participants with events will be performed using the M&N method.
Interim Analyses	No interim analyses are planned.

Multiplicity	There are 4 pairwise treatment group comparisons that may be tested to address the primary hypothesis. Testing will be performed in order of descending randomized dose and will stop with the first comparison that has a one-sided *p*-value ≥0.025.
Sample Size and Power	The sample size for this Phase 2b trial is driven primarily by safety and exposure considerations. Based on an assumed standard deviation of 25%, a -50% treatment difference (MK-0616 minus placebo) with respect to mean percent change from baseline in LDL-C at Week 8, and a discontinuation rate of <2% at or before Week 8, a sample size of 75/arm provides >99% power at a one-sided alpha of 0.025 for each of the treatment comparisons.

9.2 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.

The Sponsor will generate the randomized allocation schedule for study intervention assignment for this protocol, and the randomization will be implemented in IRT.

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

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

9.4.1 Efficacy Endpoints

Primary Efficacy Endpoint

- Percent change from baseline in LDL-C at Week 8

LDL-C will be based on the beta-quantification method when available, or calculated based on the Friedewald formula when no beta-quantification is available.

Secondary Efficacy Endpoints

- Percent change from baseline in ApoB and non-HDL-C at Week 8
- Proportion of participants with LDL-C value at goal at Week 8. LDL-C goal is defined as:
  - LDL-C <70 mg/dL (<1.81 mmol/L) in participants with clinical ASCVD

- LDL-C <100 mg/dL (<2.59 mmol/L) in participants with an ASCVD risk-equivalent and/or a 10-year risk of having an ASCVD event that is ≥7.5%

- LDL-C <130 mg/dL (<3.37 mmol/L) in participants with a 10-year risk of having an ASCVD event that is ≥5.0% and <7.5%

Efficacy endpoints are further described in Section 4.2.1.1.

9.4.2 Safety Endpoints

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

9.4.3 Pharmacokinetic Endpoint

The PK endpoint is MK-0616 plasma concentration (Cmin). The PK endpoint is further described in Section 4.2.1.3.

9.4.4 Pharmacodynamic Endpoint

The PD endpoint is MK-0616 free plasma PCSK9 levels. The PD endpoint is further described in Section 4.2.1.4.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

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 at least 1 observation for the analysis endpoint
- 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.

9.5.2 Safety Analysis Population

Safety analyses will be conducted in the APaT population, which consists of all randomized participants who received at least 1 dose of double-blind study intervention. Participants will be included in the treatment group corresponding to the study treatment 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 treatment actually received.

At least 1 laboratory, vital sign, or ECG measurement obtained subsequent to at least 1 dose of double-blind study intervention is required for inclusion in the analysis of the respective safety parameter. To assess change from baseline, a baseline measurement is also required.

9.5.3 Pharmacokinetic Analysis Population

Participants from the active MK-0616 treatment population who received at least 1 dose of active study intervention and complied with the protocol sufficiently will be included in the PK analysis population. Compliance includes exposure to treatment, availability of measurements and documentation of dose and sample collection time, and absence of important protocol deviations.

9.6 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 sSAP.

P-values for the key secondary efficacy endpoints will be provided as an assessment of strength of evidence without intent to make inferential claims.

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

For stratified analyses, the stratification factors used for randomization (background statin dose and renal function at Visit 1 [Screening], Section 6.3.2) will be applied to the analysis. If it is expected that statistical models may not converge on account of small strata, the baseline renal function factor will be dropped from the models. A decision to drop this factor will be based on blinded data and documented in the sSAP prior to database lock.

Two database locks are planned for this study in order to facilitate program planning. The first will occur after the efficacy cutoff date, defined as the date when all randomized participants complete Visit 5 (Week 8) (or otherwise discontinue the study prematurely). The second database lock will occur after all participants complete their participation in the study through Visit 7 (Week 16) (or otherwise discontinue the study prematurely). All study objectives will be addressed based on the first database lock, which will include complete efficacy, PK, and PD data. Analyses of safety based on the first database lock will include all available data (including post-Visit 5 [Week 8]). Additional safety analyses will be performed using the comprehensive data in the second database lock.

The Sponsor will be unblinded to participants' treatment assignments after the first database lock. Participants and investigators will remain blinded to participants' treatment assignments until after the second database lock.

9.6.1 Statistical Methods for Efficacy Analysis

This section describes the statistical methods that address the primary and key secondary objectives related to the efficacy endpoints.

The primary efficacy estimand following the guidance in ICH E9 (R1) [European Medicines Agency 2020] 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.

2. The **population** of participants targeted by the clinical question: adults with hypercholesterolemia.

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 8.

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 study intervention and/or initiation of non-study intervention). No observed data will be excluded from analyses.

5. The **population-level summary** for the endpoint which provides the basis for a comparison between treatment conditions: the difference (MK-0616 - placebo) in the mean percent change from baseline in LDL-C at Week 8.

9.6.1.1 Primary Efficacy Endpoint

To address the primary hypothesis, the percent change from baseline in LDL-C will use a cLDA method proposed by Liang and Zeger [Liang, K-Y and Zeger, S. L. 2000]. This model assumes a common baseline mean across treatment groups and a different mean for each treatment group at post-baseline time points. In this model, the response vector consists of the baseline value and the percent change observed at the post-baseline time points. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The analysis model will include terms for treatment, time, background statin dose (no statin therapy, low- to moderate-intensity statin therapy, or high-intensity statin therapy), baseline renal function (eGFR $\geq$60 vs <60 ml/min/1.73 m^2), and the interaction of treatment by time. The treatment difference for each of the 4 pairwise comparisons of MK-0616 versus placebo in terms of mean percent change from baseline in LDL-C at Week 8 will be estimated and tested from this model. An unstructured covariance matrix will be used to model the correlation among repeated measurements.

Although the baseline measurement is included in the response vector, it is independent of treatment, and hence, the baseline means are constrained to be the same for different treatment groups. Of note, in the event that there are no missing data, the estimated treatment difference from the above cLDA model will be identical to that from a traditional longitudinal ANCOVA model which uses the baseline value as a covariate. However, unlike

longitudinal ANCOVA, the cLDA model accounts for variability in the baseline values, thus providing more accurate standard errors and CIs for individual treatment effects. Details of the model specification, assumptions, and SAS implementation code will be provided in the sSAP.

The cLDA method assumes that the mechanism for missing data is MAR. It is expected that <2% of participants will be missing their LDL-C value at Week 8. Sensitivity analyses to assess the robustness of the MAR-based analysis to deviations from this assumption will be described in the sSAP.

The model-based least squares mean and empirical mean change (with 95% CIs) from baseline for each treatment group and difference between treatment groups at the Week 8 post-baseline time point will be summarized.

9.6.1.2 Secondary Efficacy Endpoints

The analysis of secondary efficacy endpoints regarding percent change from baseline in ApoB and non-HDL-C at Week 8 will follow the same approach as the primary efficacy analysis.

For the secondary endpoint of the proportion of participants with LDL-C value at goal at Week 8, 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 8 assessment will be considered as not being at the LDL-C goal at Week 8.

Table 4 summarizes the key analysis strategies for the primary and key secondary efficacy endpoints.

Table 4 Analysis Strategy for Key Efficacy Endpoints

Endpoint	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint			
Percent change from baseline in LDL-C at Week 8	cLDA	FAS	Model-based
Key Secondary Endpoints			
Percent change from baseline in ApoB and non-HDL-C at Week 8	cLDA	FAS	Model-based
Proportion of participants with LDL-C value at goal at Week 8	M&N	FAS	M=F

ApoB apolipoprotein B, cLDA constrained longitudinal data analysis method, FAS full analysis set, LDL C low density lipoprotein cholesterol, M&N Miettinen and Nurminen, M F: Missing Failure, non HDL C non high density lipoprotein cholesterol

9.6.2 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 8 weeks after last dose of study intervention, if available.

9.6.2.1 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.

9.6.2.2 Assessment of Safety Topics of Special Interest

There are no safety topics of special interest in this study.

Table 5 summarizes analysis strategy for safety endpoints in this study.

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		

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.

9.6.3 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (eg, age, race, gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

No interim analyses are planned. Unblinded safety summaries will be reviewed on a periodic basis by the Sponsor's siDMC (see Section 10.1.4.1) and will be specified in the siDMC charter. These summaries will be provided by an internal unblinded statistician and programmer with no other involvement in the study.

9.8 Multiplicity

There are 4 pairwise treatment group comparisons (MK-0616 vs placebo) that may be tested to address the primary hypothesis. Testing will be performed in order of descending randomized MK-0616 dose and will stop with the first comparison that has a one-sided *p* -value ≥0.025.

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

9.9 Sample Size and Power Calculations

9.9.1 Efficacy

The sample size for this Phase 2b study is driven primarily by safety and exposure considerations. Based on an assumed standard deviation of 25%, a -50% treatment difference (MK-0616 minus placebo) with respect to mean percent change from baseline in LDL-C at Week 8, and a discontinuation rate of <2% at or before Week 8, a sample size of 75 per arm (375 total) would provide >99% power at a one-sided alpha of 0.025 for each of the treatment comparisons (MK-0616 vs. placebo, based on nQuery software version 7).

9.9.2 Safety

Given the sample size of 75 per group, Table 6 provides examples of minimum differences in proportions in AEs between each MK-0616 dose and placebo that would have a 95% CI that excludes zero.

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

MK-0616 n/N (%)	**Placebo** n/N (%)
4/75 (5.3%)	0/75 (0%)
10/75 (13.3%)	3/75 (4.0%)
16/75 (21.3%)	7/75 (9.3%)
AE adverse event; CI confidence interval; n number of participants with an AE; N population size. Based on the M&N method	

9.10 Subgroup Analyses

The primary efficacy endpoint will be summarized for each of the following baseline defined subgroups:

- Stratification factor: background statin dose (no statin therapy, low- to moderate-intensity statin therapy, or high-intensity statin therapy)

- Stratification factor: renal function (eGFR ≥60 vs <60 ml/min/1.73 m^2) at Visit 1 (Screening)
- Diagnosis of heterozygous familial hypercholesterolemia (Yes, No)
- Baseline risk category (clinical ASCVD, ASCVD-risk equivalents and/or a 10-year risk of having an ASCVD event that is ≥7.5%, or 10-year risk of having an ASCVD event that is ≥5.0% and <7.5%)
- Baseline BMI (≥30 kg/m^2 vs <30 kg/m^2)
- Diabetes mellitus (Yes, No)
- Region (North America, Western Europe, Eastern Europe, Asia Pacific)
- Age (≥65 vs <65 years)
- Gender (male vs female)

9.11 Compliance (Medication Adherence)

A day within the double-blind treatment period will be considered a compliant day if the participant takes 1 capsule of treatment intervention (MK-0616 or matching placebo).

For each participant, the compliance rate, based on time until study treatment discontinuation, will be calculated using the following formulas:

$$\text{Compliance rate (\%)} = \frac{\text{Number of Compliant Days}}{\text{Number of Days in the Double-blind Treatment Period}} \times 100\%.$$

For each participant the "Number of Days in the Double-blind Treatment Period" is the total number of days from the first dose of double-blind study treatment to the date of the last dose of study treatment.

9.12 Extent of Exposure

The extent of exposure to study treatment will be evaluated by summary statistics and frequencies for the Number of Days on Therapy by treatment group.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, 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 local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH GCP), and also 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. 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.

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. 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. 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.

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.

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 chart 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 his/her 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 his/her 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 his/her 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.

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 Internal Data Monitoring Committee

To supplement the routine monitoring outlined in this protocol, the Sponsor's siDMC will monitor the interim data from this study. The siDMC is comprised of members of Sponsor Senior Management, none of whom are directly associated with the conduct of this study. The siDMC will monitor the study at an appropriate frequency (specified in the siDMC charter) for evidence of adverse effects of study intervention. The siDMC will determine whether the study should continue (or other modifications, prespecified or otherwise, should be made) according to the protocol, considering the overall risk and benefit to study participants. The siDMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both participant safety and the continued ethical integrity of the study.

Specific details regarding responsibilities of the siDMC will be described in a separate charter that is reviewed and approved by the siDMC.

10.1.4.2 Scientific Advisory Committee (SAC)

This study was developed in collaboration with a SAC. The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide input with respect to study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

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 trial Directive 2001/20/EC, 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 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 directive 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 directive, 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.

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

- Except for pregnancy tests, which may be performed locally, the tests in Table 7 will be performed by the 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). Unless clinically urgent, investigators should not evaluate efficacy endpoints locally during the study. Non-study physicians should also be encouraged not to evaluate efficacy endpoints locally during the study.
- Protocol-specific laboratory-based requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol. Country-specific inclusion or exclusion requirements are in Appendix 7.
- The investigator (or medically qualified designee) must document their review of each laboratory safety report.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Country-specific requirements for Visit 7 pregnancy testing are in Appendix 7.

Table 7 Protocol-required Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="4">Parameters</th></tr>
<tr><td rowspan="4">Hematology</td><td>Platelet Count</td><td colspan="2">RBC Indices:
- MCV
- MCH
- MCHC
- MPV
- RDW
- Nucleated RBC</td><td rowspan="4">WBC count with Differential:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils
Immature Granulocyte</td></tr>
<tr><td>RBC Count</td><td colspan="2" rowspan="3">Reticulocytes</td></tr>
<tr><td>Hemoglobin</td></tr>
<tr><td>Hematocrit</td></tr>
<tr><td rowspan="5">Chemistry</td><td>BUN</td><td>Potassium</td><td>AST/SGOT</td><td>Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)</td></tr>
<tr><td>Albumin</td><td>Bicarbonate</td><td>ALT/SGPT</td><td>Phosphorous</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>Alkaline phosphatase</td><td>Total Protein</td></tr>
<tr><td>eGFR</td><td>Calcium</td><td>Chloride</td><td>Creatine Kinase</td></tr>
<tr><td>Glucose</td><td>Potassium</td><td colspan="2">Uric Acid</td></tr>
</table>

Laboratory Assessments	**Parameters**			
Lipid Panel	LDL-C	HDL-C	Non-HDL-C	Total Cholesterol
	Triglycerides			
Other Efficacy Parameters	VLDL-C	ApoB	ApoA1	Lp(a)
	hsCRP			
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (WOCBP only). • WOCBP will be given urine pregnancy test kits to assess pregnancy status approximately 4 and 8 weeks after the last dose of study intervention. • If urine pregnancy tests are not acceptable per local regulations, then a serum pregnancy test will be performed (locally or centrally) for the 4- and 8-week post-treatment pregnancy assessments.			
PK	• Plasma for PK (Section 8.6)			
PD	• Plasma for Free and Total PCSK9 (Section 8.7)			
Other Tests	• A1C (only in participants with diabetes mellitus) • FSH (as needed to assess menopausal status) • TSH • FT4 (only in participants with hypothyroidism)			

A1C hemoglobin A_{1c}, ALT alanine aminotransferase, ApoA1 apolipoprotein A1, 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, FT4 free T4 test, hCG human chorionic gonadotropin, HDL C high density lipoprotein cholesterol, hsCRP 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, 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, VLDL C very low density lipoprotein cholesterol, WBC white blood cell, WOCBP women of childbearing potential

Note 1: eGFR will be calculated using CKD EPI Creatinine or, for participants in Japan, the Japanese 3 variable Equation 4; see Appendix 7.

Note 2: LDL C will be calculated based on the Friedewald formula; 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.

PK and PD Sample Collection

PK and PD samples will be collected at the timepoints shown in Table 8.

Table 8 PK and PD Sample Collection Times

Visit Number/Title:	**Visit 2 (Day 1)**		**Visit 4 (Week 4)**[1]		**Visit 5 (Week 8) or SI Discon Visit**[1, 2, 3]
Time:	Predose	~1.5 hours post-dose	Predose	~1.5 hours post-dose	Unspecified Time[1]
PK samples		X	X	X	X
Free PCSK9 samples	X	X	X	X	X
Total PCSK9 samples	X		X		X

PCSK9=protein convertase subtilisin/kexin type 9, PD=pharmacodynamic, PK=pharmacokinetic, SI Discon=study intervention discontinuation

[1] When possible, Visit 4 (Week 4) and Visit 5 (Week 8) (or SI Discon Visit) should be scheduled at a time that facilitates trough PK sample collection.

[2] Do not collect PK, free PCSK9, or total PCSK9 samples at the Study Intervention Discontinuation Visit if this visit occurs >48 hours after the last dose of study intervention.

[3] For participants who prematurely discontinue study intervention, do not collect PK, free PCSK9, or total PCSK9 samples after the Study Intervention Discontinuation Visit.

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

10.3.1 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 (also referred to as Sponsor's product) 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.

10.3.2 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.

10.3.3 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

10.3.4 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

- 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 Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product 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 Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product 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 Sponsor's product? 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 Sponsor's product 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 Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product 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, or (2) the study is a single-dose drug study; or (3) Sponsor's product(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 SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT 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 Sponsor's product 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 his/her 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 Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship:
    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship:
    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- 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 his/her 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.

10.3.5 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 e-mail 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

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and 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.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female 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, Mullerian 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 female
  - 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 women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal 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 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant[c] • IUS[d] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen- containing) hormonal contraception[c,e] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c,e] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse 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 • Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods).
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect use failure rates (ie, when used consistently and correctly). [c] If locally required, in accordance with CTFG guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation. [d] IUS is a progestin releasing IUD. [e] Country specific contraception requirements are in Appendix 7. Note: The following are not acceptable methods of contraception: Periodic abstinence (calendar, symptothermal, post ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. Male and female condom should not be used together (due to risk of failure with friction).

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 are 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 which 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 utilized 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.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid 45618

2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

10.7.1 Country-specific Requirements for Japan:

Section 5.1

To be eligible for the study, participants in Japan must meet the criteria for Inclusion #1, and must require additional LDL-C reduction according to JAS guideline recommendations [Kinoshita, M., et al 2018].

Sections 5.2, 7.1 and Appendix 2

A 3-variable equation (Equation 4 in [Matsuo, S., et al 2009]) will be used to calculate eGFR for participants in Japan.

Section 6.1

The classification of IMP and NIMP in Section 6.1 is based upon guidance issued by the European Commission and applies to countries in the EEA.

10.7.2 Country-specific Requirements for Germany:

Sections 1.1, 4.4, 5.2, 7.1, 7.2, 8.1.1, 8.1.1.1, 8.1.1.2

In order for a participant to be eligible to participate in Germany, they must be capable of providing documented informed consent; therefore, all references to a participant's "legally acceptable representative" in the protocol are not applicable for participants in Germany.

Section 1.3 Schedule of Activities

For participants in Germany, Visit 7 is an in-person visit and all activities listed in the global SoA for Visit 7 apply.

Additional activities at Visit 7 for participants in Germany are:

- Directed physical examination
- Vital signs (blood pressure, pulse rate)
- Weight
- 12-lead ECG (local)
- Hematology
- Chemistry (including CK)
- A1C (only for participants with history of diabetes mellitus)
- Urine or serum hCG (WOCBP only, per local requirements)

Note: For Visit 7, laboratory samples may be done non-fasting.

Section 5.2

For participants in Germany, the following changes to the global exclusion criteria apply:

- Exclusion criterion # 14: Has moderate or greater renal insufficiency defined as eGFR <60 mL/min/1.73 m^2 at Visit 1 (Screening); eGFR will be calculated according to Appendix 2.
- Exclusion criterion #22 (new): Has uncontrolled hypertension defined as sitting SBP ≥180 mm Hg or DBP ≥110 mm Hg at Visit 1 (Screening).
- Exclusion criterion #23 (new): Has QTcF >450 ms based on an ECG performed within 6 months before Visit 1 (Screening) OR based on the pretreatment ECG at Visit 2 (Day 1) if a prior ECG is not available.

10.7.3 Country-specific Requirements for South Korea

Section 5.1

For participants in South Korea, the following applies:

Clarification for inclusion criterion #2, Note 1:

For participants in South Korea, lipid-lowering therapies include foods, drugs, or supplements that can affect the concentration of lipids during the study (eg, statins, fibrates, bile acid sequestrants, niacin, anti-obesity drugs, steroids intended for systemic action, fish oil, colestine products, fiber-based laxatives, phytosterol margarines, etc) and drugs that affect thyroid function (thyroid preparations or thyroxine administration: except for those on alternative therapy).

Section 5.2

For participants in South Korea, the following addition to the global exclusion criteria applies:

- Exclusion criterion #22 (new): Has uncontrolled hypertension defined as sitting SBP ≥180 mm Hg and/or DBP ≥110 mm Hg at Visit 1 (Screening).

Sections 5.3.1, 6.5

All participants in South Korea, regardless of lipid-lowering therapy use, should be following Total Lifestyle Change, as per local guidelines, for at least 30 days before Visit 1 (Screening).

10.7.4 Country-specific Requirements for the United Kingdom

Sections 1.2, 1.3, 5.3.1, 8, 8.3.7, 8.11.1, and 8.11.7

For participants in the United Kingdom, additional activities by visit are:

Visit 1

- 12-lead ECG (local)
- Full physical examination

Visit 3

- 12-lead ECG (local)

Visit 4

- 12-lead ECG (local)

Visit 7

Visit 7 is an in-person visit, and all activities listed in the global SoA for Visit 7 apply.

Additional activities at Visit 7 are:

- Directed physical examination
- Vital signs (blood pressure, pulse rate)
- Weight
- 12-lead ECG (local)
- Hematology
- Chemistry (including CK)
- A1C (only for participants with history of diabetes mellitus)
- In WOCBP, urine or serum hCG (per local requirements)

Note: For Visit 7, laboratory samples may be done non-fasting.

For participants in the United Kingdom, the following change to the global blood collection applies:

The maximum amount of blood collected from each participant at scheduled visits over the duration of the study will not exceed approximately 140 mL (see the laboratory documentation). This blood volume does not account for unscheduled visits or the Study Intervention Discontinuation Visit.

Section 4.3

For participants in the United Kingdom, additional justification for dose is provided below.

The doses for this study were selected to allow identification of the optimal clinical dose.

CCI [redacted]

CCI [redacted] CCI [redacted] This will allow selection of a near-maximal efficacy dose for further development in Phase 3 and ensure sufficient additional safety experience in a heterogenous population with longer treatment duration before the Phase 3 studies. The expected exposures for the doses to be studied are adequately covered by the available clinical and nonclinical data for MK-0616.

Sections 5, 5.1, 5.2, 10.2, and 10.5.2

For participants in the United Kingdom, the following changes to the global inclusion and exclusion criteria apply:

Inclusion criterion #2: Participants who are treatment naïve can only be enrolled if they do not meet NHS guideline criteria for treatment with lipid lowering therapies.

NHS guidelines: https://www.guidelines.co.uk/cardiovascular/nhs-lipid-management-pathway/456226.article.

Inclusion criterion #4: Highly effective methods of contraception must be used by WOCBP. Contraceptive methods that are not considered highly effective are not allowed (see Appendix 5).

Exclusion criterion #15: Has laboratory or clinical evidence of clinically significant hepatic conditions, including 1 or more of the following:

- ALT or AST >2X ULN at Visit 1 (Screening).
- 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.
- Total bilirubin ≥1.5X ULN at Visit 1 (Screening), including those with a history of Gilbert's Syndrome.

Sections 7.1, 8.4.7 and 10.7.4.1

For participants in the United Kingdom, the following changes to the global reasons for study intervention discontinuation apply:

- The participant has an eGFR consistently <35 mL/min/1.73 m^2; eGFR will be calculated according to Appendix 2.

  Note 1: For eGFR, a consistent value is defined as a repeat measurement performed within 7 days of notification from the central laboratory.

  Note 2: Not applicable for participants in the United Kingdom where the participant must be discontinued from study intervention if the eGFR value continues to meet

discontinuation criterion even if it demonstrates stability or improvement relative to the prior result.

- The participant has an ALT or AST result ≥3X ULN, a total bilirubin result ≥2X ULN, and, at the same time, an alkaline phosphatase result <2X ULN (guidance on follow-up of participants with laboratory values meeting this criterion is in Section 10.7.4.1 and in the Investigator Study File Binder, or equivalent).

10.7.4.1 DILI Site Guidance Document for Assessment and Follow-up

10.7.4.1.1 Purpose

The purpose of this document is to provide guidance to enable the investigator/study coordinator to provide clinical follow-up and systematically gather and report data on potential DILI. The data collected will be used by the Sponsor to create narratives for regulatory agency reporting.

10.7.4.1.2 Introduction

Hepatotoxicity is injury or damage to the liver that may be associated with impaired liver function (Navarro and Senior 2006). Drug-induced hepatotoxicity is one of the most common causes of termination of drug development, a major reason for refusal of market authorization and for restricted use, and the single most important cause of the withdrawal of market authorization for products (Björnsson 2006). Thus, drug-induced hepatotoxicity is a major concern during the discovery, development to post-authorization phases of the product life cycle (excerpted from Premarket Evaluation of Hepatotoxicity of Health Products, Ministry of Public Health, Canada, April 2012).

As stated in the United States Food and Drug Administration (FDA) “Guidance for Industry - Drug-Induced Liver Injury: Premarketing Clinical Evaluation”; hepatocellular injury (usually detected by serum aminotransferase elevations [AT]) can be caused by drugs that rarely, if ever, cause severe DILI (e.g., aspirin, tacrine, statins, and heparin), as well as by drugs that do cause such injury. The frequency of serum AT elevations also is not a good indicator of a potential for severe DILI because drugs such as tacrine (not a cause of severe DILI) can cause AT elevations in as many as 50 percent of patients. Very high levels of observed ATs may be a somewhat better indicator of potential for severe DILI, but the most specific indicator is evidence of altered liver function accompanying or promptly following evidence of hepatocellular injury.

The single clearest (most specific) predictor found to date of a drug’s potential for severe hepatotoxicity, is the occurrence of hepatocellular injury (AT elevation) accompanied by increased serum total bilirubin (TBL) not explained by any other cause, such as viral hepatitis or exposure to other hepatotoxins, and without evidence of cholestasis, together with an increased incidence of AT elevations in the overall trial population compared to control. Increased plasma prothrombin time, or its international normalized ratio (INR), a consequence of reduced hepatic production of Vitamin K-dependent clotting factors, is

another potentially useful measure of liver function that might suggest the potential for severe liver injury.

Recognition of the importance of altered liver function, in addition to liver injury, began with Hyman Zimmerman's observation that drug-induced hepatocellular injury (i.e., AT elevation) accompanied by jaundice (i.e., TBL elevation) had a poor prognosis, with a 10 to 50 percent mortality from acute liver failure (in pretransplantation days) (Zimmerman 1978, 1999). This became known as "Hy's Law". This document describes the recommended process for monitoring and evaluation of subjects meeting the laboratory criteria for potential DILI defined as:

- an elevated alanine transaminase (ALT) or aspartate transaminase (AST) lab value that is greater than or equal to three times (3X) the upper limit of normal (ULN) and
- an elevated TBL lab value that is greater than or equal to two times (2X) ULN and
- at the same time, an alkaline phosphatase (ALP) lab value that is less than 2X ULN,

as a result of within-protocol-specific testing or unscheduled testing.

The protocol identifies these laboratory criteria for potential DILI as ECIs. ECIs are selected adverse experiences that must be reported to the Sponsor within 24 hours. The Principal Investigator should record these ECIs on the Adverse Experience Case Report Forms (CRFs) and complete pertinent adverse experience fields as outlined in the Data Entry Guidelines (DEGs).

10.7.4.1.3 Close Observation Recommendations

The following steps should be taken when a subject is observed to have an elevated AST or ALT lab value that is greater than or equal to 3X ULN and an elevated TBL lab value that is greater than or equal to 2X ULN and, at the same time, an ALP lab value that is less than 2X ULN, as a result of within-protocol-specific testing or unscheduled testing.

Initiate **close observation**, defined below, and continue performing **follow-up to resolution**.

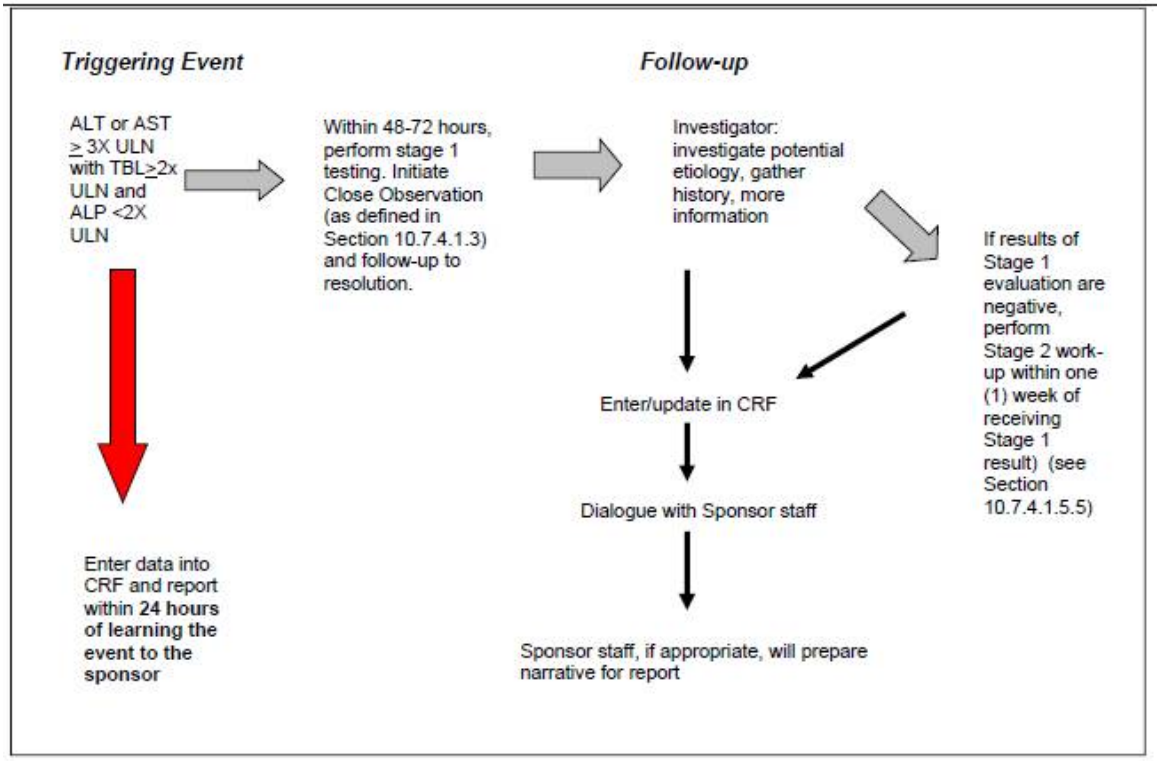
Close observation is defined as follows:

- Repeat liver enzyme and serum bilirubin tests two (2) or three (3) times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or study drug has been discontinued and the subject is asymptomatic.
- Obtain a more detailed history of symptoms and prior or concurrent diseases. (See Section 10.7.4.1.5).
- Obtain a history of concomitant medication use (including prescription and nonprescription medications, herbal and other dietary supplements), alcohol use, recreational drug use and special diets. (See Section 10.7.4.1.5 for details).

- Obtain a history of exposure to chemical agents or other environmental toxins.
- Obtain additional history and complete Stage 1 work-up to attempt to rule out other potential causes of the transaminase elevation, including but not limited to the following: acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; non-alcoholic steatohepatitis (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease (See Section 10.7.4.1.5.5 for details.)
- Consider gastroenterology or hepatology consultation.

In general, treatment with study therapy should be stopped if the laboratory criteria for potential DILI are met. Please refer to the specific discontinuation criteria in the protocol as appropriate.

10.7.4.1.4 Hepatic Assessment Flow Chart



10.7.4.1.5 Factors to Consider in Assessing Potential DILI

When there is a potential DILI, it is important to thoroughly assess the subject's history, hepatic risk factors, clinical condition and hepatic function until resolution (normal or baseline levels).

Answers to the following questions should be recorded in source documents and in appropriate CRFs as outlined in the DEGs.

10.7.4.1.5.1 Study Medication

Considerations should include the following: What was the time interval between administration of study medication and the laboratory abnormality(ies)? What is the status of study medication use- Continuing? Interrupted? Discontinued? Was the subject re-challenged with study medication?

10.7.4.1.5.2 Treatment

Record any concomitant treatments.

10.7.4.1.5.3 Signs and Symptoms (Associated With the Potential DILI Event)

Does the subject have a concomitant illness? Does the subject currently exhibit signs or symptoms of hepatitis/DILI? What are the subject's signs and symptoms (see examples below)? What are the pertinent findings from medical history, physical/laboratory examination (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia > 5%, hepatomegaly, splenomegaly, etc.) that could suggest DILI?

Category	Examples of Signs and Symptoms
Blood/lymphatic	Eosinophilia, coagulopathy, susceptibility to bleeding/bruising
Circulatory	Varicose veins, edema
Constitutional	Fever, fatigue, malaise, weight gain, other (identify).
Digestive/hepatic	Anorexia, diarrhea, bloody or black stool, light-colored stools, nausea, vomiting, hematemesis, upper quadrant abdominal pain, upper quadrant tenderness, hepatomegaly, jaundice, splenomegaly, ascites, cholestasis
Endocrine/reproductive	Loss of libido
Integumentary	Rash, pruritus
Muscular	Myalgia
Nervous	Changes in mental status or level of consciousness
Urinary	Dark urine

10.7.4.1.5.4 Confounding Variables

What are the relevant medical history and findings? What is the differential diagnosis? What risk factors does the subject have for hepatic injury? (See examples below.) Provide onset of risk factor and duration.

Category	Examples of Confounding Variables
Subject medical history	Autoimmune disorder, cancer, Gilbert's syndrome, obesity, Wilson's disease
Substance use/abuse	Alcohol, illegal drugs, illegal intravenous (IV) drugs
Prior & Concomitant Medications: Review all non-study medications and therapies, including: over-the-counter (OTC), as well as prescription. Ask the subject to bring products/packaging to site and review contents.	History of recent concomitant acetaminophen (APAP)/paracetamol use, excessive nonsteroidal anti-inflammatory drug (NSAID) intake, use of non-study drug or therapy that can cause liver damage or idiosyncratic adverse drug reactions
Herbal and nutritional supplements	Herbal, complementary therapies, and nutritional supplements
Adulteration of products	History of previous exposure to the product or a similar product, and information on potential contamination or adulteration of products
Chemical exposure	Occupational or in other situations
Potential exposure to infectious agents	Infectious hepatitis, transfusion, travel, tattoos, sexually transmitted diseases, new sexual partner, shared needles
Special Diet	Special diet started since randomization
Other	Recent physical trauma, excessive exercise, or other prolonged physical exertion
Family history	Autoimmune disorder, cancer, Gilbert's syndrome, Wilson's disease

10.7.4.1.5.5 Evaluation Algorithm for Potential DILI if There are no Other Clinical Reasons

Note: If clear etiology for the laboratory abnormalities has been confirmed, Stage 1 and 2 testing may not be required. In this case, consultation with the Sponsor is recommended.

Stage 1 work-up should be performed within 48-72 hours:

- ALT
- AST
- Bilirubin: total, direct, indirect
- Alkaline phosphatase (ALP)
- Prothrombin Time (PT)/international normalized ratio (INR)
- Creatine phosphokinase (CPK)
- Manual eosinophil count (if automated count was elevated)

- Toxicology screen for drugs of abuse (including ethanol) and for acetaminophen/paracetamol level should also be sent. Investigators may order additional toxicology tests as clinically indicated.

- Evaluate subject for the following signs and symptoms: fatigue, nausea, vomiting, right upper quadrant abdominal pain or tenderness, fever, rash.

- Obtain the following additional history and assessment for associated risk/confounding factors:

  - More detailed history of symptoms and prior or concurrent illness

  - Aminotransferase values obtained prior to the study or administration of study medication

  - Alcohol consumption (recent and historical)

  - Acetaminophen (APAP)/paracetamol use

  - New prescription, concomitant, or non-prescription (including herbal and other dietary supplements) medications

  - Unusual foods (e.g. mushrooms) or special diets. Consumption of seasonal foods.

  - Recreational drug use

  - Prior history of liver injury or disease, including but not limited to Gilbert's syndrome, autoimmune disorders, cancer, Wilson's disease, NASH, alcoholic or infectious hepatitis, biliary tract disease, hypoxic/ischaemic hepatopathy

  - Obesity/abdominal adiposity (record weight, height, and waist circumference)

  - Occupational history and history of exposure to chemical agents or other environmental toxins

  - Recent travel (last three [3] years)

  - Transfusion history

- Perform the following laboratory tests:

  - Albumin

  - Eosinophils (percentage and absolute; obtain manual count if automated count is elevated)

- Viral hepatitis serologies (obtain appropriate consent prior to testing, if required locally)
    - A (IgG, IgM)
    - B (HepBs Ag, Hep Bs Ab, Hep Bc Ab, Hep Be Ag)
    - C (RNA)
    - D (requires concomitant hepatitis B infection)
- Human Immunodeficiency Virus (HIV) testing (obtain appropriate consent prior to testing, if required locally)
- Evaluation for autoimmune hepatitis:
    - Serum gamma globulin levels/ serum protein electrophoresis
    - Antinuclear antibody (ANA)
    - Anti-mitochondrial antibody (if ALP or TBL >ULN)
- If AST/ALT ratio is greater than one (1) with suspicions of increased alcohol intake, perform the following:
    - Gamma-glutamyl transferase (GGT)

- Obtain a right upper quadrant ultrasound

Stage 2 work-up tests should be drawn within one (1) week of receiving the Stage 1 work-up results and the results of Stage 1 evaluation are negative.

Note: A specific test may be performed earlier if the investigator determines that the clinical presentation leads to a certain diagnosis.

Stage 2 work-up:

- Perform the following laboratory tests:
    - Genetic test for Gilbert's disease if there is a suspicious history. Ensure appropriate subject consent is obtained for this test.
    - Viral hepatitis E (IgG and IgM, obtain appropriate consent prior to testing, if required locally)
    - Anti-smooth muscle antibody
    - Anti-liver-kidney microsomal antibody

- Anti-soluble liver antigen
- Serologies for the following:
  - Cytomegalovirus (CMV) (IgG, IgM)
  - Epstein-Barr Virus (EBV) (IgG, IgM)
  - Herpes simplex
  - Toxoplasmosis
  - Varicella
  - Parvovirus
- Ceruloplasmin
- Serum alpha-1 anti trypsin
- Genetic test for hemochromatosis. Ensure appropriate subject consent is obtained for this test
- Iron Studies:
  - serum ferritin,
  - serum iron,
  - total iron binding capacity

- Consider referral to hepatologist/gastroenterologist
- Consider screen for celiac disease and cystic fibrosis if clinically indicated
- If laboratory tests or ultrasound evidence of biliary tract obstruction, consider obtaining Endoscopic Retrograde Cholangiopancreatography (ERCP) or Magnetic Resonance Cholangiopancreatography (MRCP)

If applicable, request copies of hospital discharge summaries, consultation reports, pathology reports, special studies (e.g. imaging or biopsy), etc.

10.7.4.1.5.6 Potential Diagnosis

What diagnosis do the history, clinical course, and laboratory tests suggest?

10.7.4.1.5.7 Overall Clinical Impression

What are the investigator's overall clinical impressions (e.g., differential diagnosis, potential alternative causes)?

10.7.4.1.5.8 Treatment Plan

What is the plan for treatment and follow-up?

10.7.4.1.6 Preapproved Tests

For the blood volume requirements, please refer to the trial laboratory manual. The following tests have been pre-approved by the Sponsor:

- Anti-liver-kidney microsomal antibody
- Anti-mitochondrial antibody (if alkaline phosphatase or total bilirubin > ULN)
- Antinuclear antibody (ANA)
- Anti-smooth muscle antibody
- Anti-soluble liver antigen
- Ceruloplasmin
- Chemistry Panel (as specified in protocol)
- Complete blood count (CBC), with manual differential if absolute eosinophil count is > ULN
- Hepatitis tests: Hepatitis A IgG AB, Hepatitis A IgM AB, Hepatitis B Core AB, Hepatitis Be AG, Hepatitis B surf AB, Hepatitis B surf AG, Hepatitis C AB, Hepatitis C Qualitative RNA, Hepatitis D AB, Hepatitis E Ab IgM, Hepatitis E IgG (obtain consent prior to testing, if required locally)
- HIV antibody (obtain consent prior to testing, if required locally)
- Genetic test for hemochromatosis
- Iron studies
    - Serum ferritin
    - Serum iron
    - Total iron binding capacity

- Lactic Acid dehydrogenase (LDH)
- PT / INR
- Serum albumin and total protein
- Serum alpha-1 anti trypsin
- Serum creatine kinase (CK)
- Serum gamma globulin levels/ serum protein electrophoresis
- Serum gamma-glutamyl transferase (GGT)
- Toxicology screen (including ethanol and acetaminophen/paracetamol level) - tests not on the standard screen may be ordered, if clinically indicated
- IgM, IgG for both CMV and EBV-VCA Antibody, herpes simplex IgM, toxoplasma AB IgG, IgM, varicella zoster AB IgG, IgM, parvovirus IgM, IgG (if clinically relevant)
- Screen for celiac disease and cystic fibrosis (if clinically indicated and appropriate consent obtained for cystic fibrosis screen)
- UGT1A tests for Gilbert's syndrome (appropriate consent should be obtained)

NOTE: If a test is not listed on the lab requisition form, please contact one of the PPD Central Lab MK-0616-008 Project Managers to obtain information regarding test code and sample collection. In general, the tests should be sent to the Central Lab for analysis whenever possible. However, if tests cannot be performed at the Central Laboratory or in case of emergency, tests may be ordered at a local laboratory.

Additional lab tests and/or procedures The investigator may order additional tests after consultation with the Sponsor.

10.7.4.1.7 Contacts

If you have any questions, please refer to your Sponsor contact list for the following company personnel:

- Clinical Research Associate or Subsidiary Monitor

- Clinical Monitor

- Clinical Scientist

10.7.4.1.8 DILI Site Guidance Document References

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10.8 Appendix 8: ASCVD Risk Calculator

The 10-year risk for an ASCVD event should be calculated using the ASCVD Risk Estimator Plus (or equivalent).

- ASCVD Risk Estimator Plus
    - https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/

Equivalent calculators/algorithms to determine ASCVD risk include the European Association of Preventive Cardiology interactive tool (https://www.heartscore.org), the Suita Score [Kinoshita, M., et al 2018], or any other locally acceptable calculator/algorithm to determine ASCVD risk.

If a participant's demographic information is not compatible with a particular risk calculator (eg, a participant is 80 years old and the calculator is limited to individuals who are 20 to 79 years old), a different risk calculator or algorithm should be used.

10.9 Appendix 9: Statin Intensity Chart Based on Total Daily Dose

High Intensity	Moderate Intensity	Low Intensity
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]. Consult the Sponsor to determine the appropriate statin intensity category for participants whose daily statin dose is not shown above.		

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
A1C	hemoglobin A1C
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANGPTL3	angiopoietin-like 3
APaT	All-Participants-as-Treated
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
AR	adverse reaction
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice-daily
BMI	body mass index
BUN	blood urea nitrogen
C24	concentration at 24 hours
CI	confidence interval
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
cLDA	constrained longitudinal data analysis
Cmax	maximum plasma concentration
Cmin	minimum plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
CTFG	Clinical Trial Facilitation Group
DBP	diastolic blood pressure
DILI	drug-induced liver injury
Discon	discontinuation
DNA	deoxyribonucleic acid
EC50	half maximal effective concentration
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collector
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database

Abbreviation	Expanded Term
FAS	full analysis set
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FH	familial hypercholesterolemia
FSH	follicle stimulating hormone
FT4	free T4 test
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
HDL-C	high-density lipoprotein cholesterol
HR	heart rate
HRT	hormone replacement therapy
hsCRP	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
IND	Investigational New Drug
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IVRS	interactive voice response system
JAS	Japan Atherosclerosis Society
LAM	lactational amenorrhea method
LDL-C	low-density lipoprotein cholesterol
Lp(a)	lipoprotein (a)
mAb	monoclonal antibody
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MEDPED	Make Early Diagnosis to Prevent Early Death
M F:	missing failure
M&N	Miettinen and Nurminen
MPV	mean platelet volume
mRNA	messenger RNA
MTP	microsomal triglyceride transfer protein

Abbreviation	Expanded Term
N	population size
n	number of participants
N/A	not applicable
NIMP	noninvestigational medicinal product
NSAE	nonserious adverse event
PCSK9	protein convertase subtilisin/kexin type 9
PD	pharmacodynamic
PDLC	predefined limit of change
PK	pharmacokinetic
PP	per-protocol
QD	once-daily
RBC	red blood cell
RDW	red cell distribution width
RNA	ribonucleic acid
SAC	scientific advisory committee
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
siDMC	standing internal data monitoring committee
siRNA	small interfering ribonucleic acid
SAC	scientific advisory committee
SLAB	supplemental laboratory test
SoA	schedule of activities
SOC	standard of care
SOP	standard operating procedures
sSAP	supplemental statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
TC	telephone call
TSH	thyroid stimulating hormone
ULN	upper-limit of normal
USA	United States of America
V	visit
VLDL-C	very low-density lipoprotein cholesterol
vs	versus
WBC	white blood cell
Wk	week
WOCBP	woman/women of childbearing potential

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