Official Protocol Title:	An Open-Label Clinical Study to Evaluate the Pharmacokinetics of MK-0616 Following Administration of a Single Dose to Participants with Moderate Renal Impairment
NCT number:	NCT05070390
Document Date:	22-Feb-2023

Title Page

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Protocol Title: An Open-Label Clinical Study to Evaluate the Pharmacokinetics of MK-0616 Following Administration of a Single Dose to Participants with Moderate Renal Impairment

Protocol Number: 007-02

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	To Be Determined

Approval Date: 22 February 2023

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 02	22-FEB-2023	This study protocol is being amended to modify 1 eligibility criteria (estimated glomerular filtration rate) for the healthy participant's panel in order to support the inclusion of suitable participants.
Amendment 01	17-JUN-2022	The primary reason for this amendment is to add two additional participants to Panel A (Moderate renal impairment panel).
Original Protocol	10-AUG-2021	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendments:

This study protocol is being amended to modify 1 eligibility criteria (eGFR) for the healthy participant's panel in order to support the inclusion of suitable participants.

Because the MDRD equation was used in the original protocol to calculate eGFR for inclusion/exclusion for both Panel A (moderate renal impairment) and Panel B (healthy matched controls), the eGFR for healthy matched controls is likely to be an underestimation as described in reference [Stevens, L. A., et al 2010] [Levey, A.S., et al 2009]. For this reason, the eGFR criteria for enrollment of healthy matched controls (Panel B) was lowered from 90 mL/min/1.73 m^2 to 80 mL/min/1.73 m^2.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
4.1 Overall Design	Change of the term "mild" to "moderate"	This was a typographical error. Only participants with moderate RI are enrolled in this study.
4.1 Overall Design (Table 1 Renal Function Panels) 5.1 Inclusion Criteria (Additional Categories)	Change in eGFR criteria for enrollment of healthy matched controls (Panel B) from 90 mL/min/1.73 m^2 to 80 mL/min/1.73 m^2.	Because the MDRD equation was used in the original protocol to calculate eGFR for inclusion/exclusion for both Panel A (moderate renal impairment) and Panel B (healthy matched controls), the eGFR for healthy matched controls is likely to be an underestimation as described in reference [Stevens, L. A., et al 2010] [Levey, A.S., et al 2009]. For this reason, the eGFR criteria for enrollment of healthy matched controls (Panel B) was lowered from 90 mL/min/1.73 m^2 to 80 mL/min/1.73 m^2.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: An Open-Label Clinical Study to Evaluate the Pharmacokinetics of MK-0616 Following Administration of a Single Dose to Participants with Moderate Renal Impairment

Short Title: MK-0616 Renal Study

Acronym: N/A

Hypotheses, Objectives, and Endpoints:

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

The study will be conducted in male and female (nonchildbearing potential only) participants, 18 to 75 years of age with moderate renal impairment and healthy adults.

Objectives	Endpoints
Primary	
• Objective: To compare the plasma PK of MK-0616 following a single dose in participants with moderate renal impairment to those of healthy matched control participants. • Estimation: MK-0616 AUC0-inf following a single dose of MK-0616 administered to participants with moderate real impairment will be estimated and compared to MK-0616 AUC0-inf when administered to healthy matched control participants.	• Plasma MK-0616 AUC0-inf, AUClast, Cmax, Tmax, t1/2, CL/F and Vz/F
Secondary	
• Objective: To evaluate the safety and tolerability of the administration of a single dose MK-0616 in participants with moderate renal impairment.	• Adverse events, vital signs, 12-lead electrocardiograms, laboratory safety tests

Objectives	Endpoints
• Objective: To compare the urine PK of MK-0616 following a single dose of MK-0616 to participants with moderate renal impairment to those of healthy matched control participants • Estimation: MK-0616 Ae0-24, Fe, and CLr following a single dose of MK-0616 administered to participants with moderate renal impairment, will be estimated and compared to those estimated in healthy matched control participants.	• Urine MK-0616 Ae0-24, Fe, and CLr
Objective: To evaluate the % reduction of free PCSK9 from baseline following administration of a single dose of MK-0616	• Percent reduction in free PCSK9 from baseline

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Hypercholesterolemia
Population	Healthy Participants and Participants with Moderate Renal Impairment
Study Type	Interventional
Intervention Model	Sequential This is a multi-site study.
Type of Control	No Treatment Control, Matched Healthy Participants
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 6 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 18 participants will be allocated such that 16 evaluable participants complete the study as described in Section 9.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<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>Panels A and B</td><td>MK-0616</td><td>10 mg</td><td>Once</td><td>Oral</td><td>Single Dose</td><td>Experimental</td></tr>
</table>
Other current or former name(s) or alias(es) for study intervention(s) are as follows: N/A
</td></tr>
<tr><td>Total Number of Intervention Groups/ Arms</td><td>2</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for approximately 8 weeks from the time the participant provides documented informed consent through the final contact. After a screening phase of approximately 4 weeks, each participant will receive assigned intervention for 1 day. After the end-of-treatment each participant will be followed for 14 days.</td></tr>
</table>

Study Governance Committees:

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

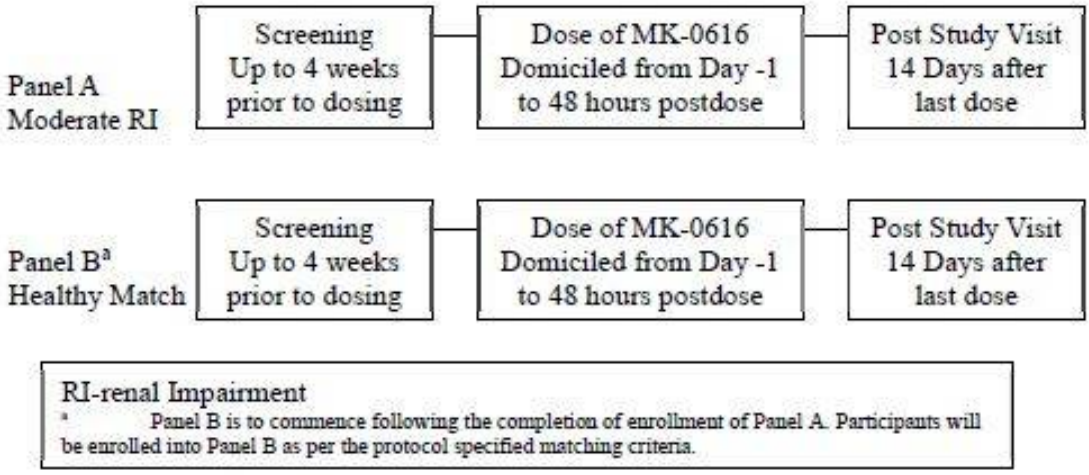
Study Accepts Healthy Volunteers: Yes

A list of abbreviations is in Appendix 11.

1.2 Schema

The study design is depicted in [Figure 1].

Figure 1 Study Schema



1.3 Schedule of Activities

Panels A and B																							
Study Period:	**Screening**		**Intervention**																				
Scheduled Hour	**Screening**	**Day -1 [a]**	**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**8**	**12**	**24**	**36**	**48**	**72**	**120**	**168**	**240**	**Post-study[b]**	**Notes**
Administrative Procedures																						
Informed Consent	X																					Obtained prior to any study mandated procedures (Sec. 8.1.1)
Informed Consent for FBR	X																					Sec. 8.1.1.2
Participant Identification Card	X																					Sec. 8.1.3
Inclusion/ Exclusion Criteria[c]	X	X	X																			Sec. 5.1 and 5.2
Medical History	X																					Includes any Substance use: Drugs, alcohol, tobacco, and caffeine (Sec. 8.1.4)
Prior/Concomitant Medication Review	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	Sec. 5.2, 6.5 and 8.1.5
Assignment of a Screening Number	X																					Sec. 8.1.6
Assignment of Randomization Number			X																			Sec. 8.1.7

Panels A and B																						
Study Period:	**Screening**		**Intervention**																			
Scheduled Hour	**Screening**	**Day -1 [a]**	**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**8**	**12**	**24**	**36**	**48**	**72**	**120**	**168**	**240**	**Post-study[b]**	**Notes**
MK-0616 Administration				X																		Sec. 8.1.8, and 8.10.2
Standard Meals[d]										X	-	-	-	-	-	X						Sec. 5.3.1
Domiciling in the CRU[e]			X	-	-	-	-	-	-	-	-	-	-	-	-	X						Sec. 8.1.11
Safety Procedures																						
Full physical examination	X		X											X							X	Sec. 8.3.1
Height	X																					Sec. 8.3.1
Weight	X																				X	BMI to be taken only at Screening
Orthostatic VS (BP and HR)	X		X					X						X							X	Sec. 8.3.2.2
Semirecumbent VS (BP and HR)[f]	X		X					X						X							X	Sec. 8.3.2.1
Body Temperature	X		X					X						X							X	Sec. 8.3.2.1
Respiratory Rate	X		X					X						X							X	Sec. 8.3.2.1
12-lead ECG[g]	X		X					X						X							X	Sec. 8.3.3
Serum FSH	X																					Postmenopausal women only. See Appendix 2 and 5.
HIV, hepatitis B and C screen	X																					Sec. 5.2

Panels A and B																							
Study Period:	**Screening**		**Intervention**																				
Scheduled Hour	**Screening**	**Day -1 [a]**	**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**8**	**12**	**24**	**36**	**48**	**72**	**120**	**168**	**240**	**Post-study[b]**	**Notes**
UDS/BDS	X	X																				Screening UDS/BDS is mandatory, any additional assessments are conducted per site SOP
Alcohol Screen	X		X																			Any additional alcohol screen may be conducted per site SOP.
Laboratory Safety: Hematology, Chemistry, Urinalysis	X	X												X							X	Sec 8.3.4 & Appendix 2
AE/SAE review	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	Sec. 8.4
Pharmacokinetics																						
Blood for Plasma MK-0616 and/or Metabolites Assay			X			X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	Sec. 8.6.1 & Operations Manual
Urine for MK-0616 and/or Metabolites Assay			X	X	-	-	-	-	-	X	-	X	X	X	X	X						Collected predose, 0-4, 4-8, 8-12, 12-24, 24-36, and 36 - 48 hr postdose. (Sec. 8.6.2) & Operations Manual

Panels A and B																						
Study Period:	**Screening**		**Intervention**																			
Scheduled Hour	**Screening**	**Day -1 [a]**	**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**8**	**12**	**24**	**36**	**48**	**72**	**120**	**168**	**240**	**Post-study[b]**	**Notes**
Pharmacodynamics and Target Engagement																						
Blood for Plasma for PCSK9 (free) Assay			X			X	X	X	X		X	X	X	X	X	X					X	Sec. 8.7 & Operations Manual
Blood for Genetic Analysis			X																			Collect predose from enrolled participants only. See Sec. 8.1 & Operations Manual

AE=adverse event; BDS=blood drug screen; BP=blood pressure; CRU=clinical research unit; ECG=electrocardiogram; FBR=future biomedical research; FSH=follicle stimulating hormone; HIV=human immunodeficiency virus; HR=heart rate; ID=identification; PCSK9=proprotein convertase subtilisin kexin 9; RR=respiratory rate; SAE=serious adverse event; SOP=standard operating procedure; UDS=urine drug screen; VS=vital signs.

[a] Day -1 procedures may occur predose

[b] Participants will be required to return to clinic approximately 14 days after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less than 14 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 14 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

[c] Review of inclusion/exclusion criteria will occur at Screening and after predose procedures (if applicable). Based on IC/EC, only specific criteria will be reviewed at predose prior to randomization.

[d] Standardized meals/snacks to be provided after procedure completion at Day 1: ~ 4 (lunch), ~ 7 (snack), ~ 10 (dinner) and ~ 13 (snack) ~ 24 (breakfast Day 2) hrs postdose. After the 24-hour postdose procedures have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition, and timing.

[e] Domiciling beginning on the evening of Day -1 followed by discharge after completion of 48-hrs postdose (Day 3) procedures.

[f] Predose vital signs (HR/BP) to be measured in triplicate on Day 1, within 3 hours predose of study medication. All other measurements will be single measurements.

[g] ECG measurements obtained in triplicate on Day 1 predose. All other measurements will be single measurements.

2 INTRODUCTION

2.1 Study Rationale

MK-0616 is a cyclic peptide inhibitor of PCSK9 being developed for reduction of LDL-C. MK-0616 is a low clearance drug which is excreted as unchanged parent peptide in rat and cynomolgus monkeys predominately by renal clearance. As such, this study is being conducted to assess the impact of moderate renal insufficiency on the PK of MK-0616.

2.2 Background

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

2.2.1 Pharmaceutical and Therapeutic Background

MK-0616 is a cyclic peptide inhibitor of PCSK9 being developed for reduction of LDL-C.

2.2.2 Ongoing Clinical Studies

Preliminary Summary (PN005)

This study consists of two panels (Panel A and B). Panel A is single-dose in healthy adult males and Panel B is multiple-dose in statin-treated male and WONCBP participants. In Panel A 24 participants are randomized to receive a total of three formulations of MK-0616 in an open-label, six-sequence, 3 period crossover design. Panel A is evaluating the PK of two test formulations of MK-0616 CCI [redacted] and compared to a reference formulation CCI [redacted] Panel B is a double-blind, placebo-controlled, single-group panel which is evaluating the PK and PD of a 5-mg dose of MK-0616 administered once-daily for 14 days. Panel A and Panel B are being run concurrently (ie, data from Panel A are not required to initiate/perform Panel B).

Preliminary Safety

The first part of the study completed clinical conduct on 23-Jul-2021. Based upon preliminary safety data, administration of 10 mg MK-0616 in capsules containing CCI [redacted] (single dosing), or 5 mg MK-0616 in capsules containing CCI [redacted] (multiple dosing once-daily for 14 days) was generally well tolerated. All AEs were considered mild by the investigator, with the exception of one severe AE (lower back pain, considered unrelated to treatment). The most commonly reported AEs were headache and abdominal discomfort. There have been no deaths and no serious adverse experiences. There was one discontinuation due to an AE after single dosing (erectile dysfunction, which was considered unrelated to study drug by the investigator). Another participant in the single dosing Panel only completed two of the three periods due to severe lumbago (considered unrelated to study drug by the investigator).

2.3 Benefit/Risk Assessment

Participants in clinical studies will not receive direct benefit from treatment during participation as clinical studies are designed to provide information about the safety and properties of an investigational medicine.

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.

The study will be conducted in male and female (nonchildbearing potential only) participants, 18 to 75 years of age with moderate renal impairment and healthy adults.

Objectives	Endpoints
Primary	
• Objective: To compare the plasma PK of MK-0616 following a single dose in participants with moderate renal impairment to those of healthy matched control participants. • Estimation: MK-0616 AUC0-inf following a single dose of MK-0616 administered to participants with moderate real impairment will be estimated and compared to MK-0616 AUC0-inf when administered to healthy matched control participants.	• Plasma MK-0616 AUC0-inf, AUClast, Cmax, Tmax, t1/2, CL/F and Vz/F
Secondary	
• Objective: To evaluate the safety and tolerability of the administration of a single dose MK-0616 in participants with moderate renal impairment.	• Adverse events, vital signs, 12-lead electrocardiograms, laboratory safety tests

Objectives	Endpoints
• Objective: To compare the urine PK of MK-0616 following a single dose of MK-0616 to participants with moderate renal impairment to those of healthy matched control participants • Estimation: MK-0616 Ae0-24, Fe, and CLr following a single dose of MK-0616 administered to participants with moderate renal impairment, will be estimated and compared to those estimated in healthy matched control participants.	• Urine MK-0616 Ae0-24, Fe, and CLr
Objective: To evaluate the % reduction of free PCSK9 from baseline following administration of a single dose of MK-0616	• Percent reduction in free PCSK9 from baseline
Tertiary/Exploratory	
• Objective: To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study	• Germline genetic variation and association to clinical data collected in this study

4 STUDY DESIGN

4.1 Overall Design

This is an open-label, single-dose study in participants with moderate renal impairment and healthy matched control participants. The study will consist of two panels (Panels A and B) [Table 1].

Panel A will include participants with moderate RI. Screening of participants will occur within 28 days prior to the first dose. Up to 10 adult, male and female (nonchildbearing potential only) participants with moderate RI will be enrolled with a minimum of 2 participants of each sex. Participants in Panel A will receive a single 10-mg dose of MK-0616/[redacted] Plasma samples will be taken at prespecified time points up to 240 hours and urine samples will be taken at prespecified time points up to 48 hours postdose, where possible, for PK assessment of MK-0616.

Enrollment in Panel B will commence following the completion of enrolment of Panel A. Screening of participants will occur within 28 days prior to the first dose. Panel B will be made up of 8healthy participants. There should be a minimum of 2 participants of each sex in Panel B. Participants in Panel B will have a mean age (± 15 years) and BMI (± 10%) of participants with the moderate RI. Participants in Panel B will receive a single 10-mg dose of MK-0616/[redacted] Plasma samples will be taken at prespecified time points up to 240 hours and urine samples will be taken at prespecified time points up to 48 hours postdose, where possible, for PK assessment of MK-0616.

Table 1 Renal Function Panels

Panel	Renal Function	N	eGFR mL/min/1.73 m^{2a}
A[b]	Moderate	10	30≤ eGFR <60[b]
B	Healthy Matched Control	8	eGFR ≥80

eGFR=estimated glomerular filtration rate; MDRD=Modification of Diet in Renal Disease.

[a] eGFR based on MDRD equation at screening. Panel A baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 3-month period prior to screening. If no historical measurement is available, a second baseline eGFR sample will be taken during the screening period (≥72 hours apart) and the mean of the 2 values will be used for group assignment; the second baseline eGFR sample may be obtained at the time of check-in.

[b] Reasonable efforts will be made to enroll at least 4 participants with eGFR values ≤ 45 mg/min/1.73 m^2, with at least 1 participant with eGFR ≤37.5 mL/min/1.73 m^2.

Because this is a Phase 1 assessment of MK-0616 in humans, the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is therefore written with flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Refer to Section 8.10.6 for examples of modifications permitted within the protocol parameters.

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

MK-0616 is likely to be used in patients with varying degrees of RI. The primary purpose of this trial is to understand the impact of moderate RI on the PK of MK-0616. From data obtained in nonclinical studies, renal clearance is expected to be the major route of elimination of MK-0616. Results from this preliminary study of the impact of moderate RI on MK-0616 pharmacokinetics will be used to design a comprehensive evaluation of MK-0616 in RI patients.

Given the limited developmental and reproductive toxicity data available for MK-0616, enrollment shall be restricted to adult males and females of nonchildbearing potential who meet the study's eligibility criteria.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

No efficacy endpoints will be evaluated.

4.2.1.2 Safety Endpoints

Safety will be assessed by monitoring AEs, physical examinations, VS, 12-lead ECGs, and laboratory safety tests (chemistry, hematology, urinalysis). Based on the data from preclinical safety studies and clinical studies to date, no specific concerns or target organ toxicities have been identified. Therefore, standard safety monitoring has been deemed adequate.

4.2.1.3 Pharmacokinetic Endpoints

Pharmacokinetic parameters selected for evaluation in this study will effectively inform the pharmacokinetic profile of MK-0616 and include the following: AUC0-inf, AUClast, Cmax, Tmax, t1/2, CL/F, Vz/F, CLr (renal clearance), Ae (amount excreted).

4.2.1.4 Pharmacodynamic Endpoints

Reduction of free PCSK9 relative to baseline will be included as an exploratory endpoint. Inhibition of PCSK9 results in reduction of plasma LDL-C, therefore the percent reduction of plasma LDL-C from baseline/pre-dose levels will be used as a pharmacodynamic endpoint.

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 DNA specimens for which consent was provided during this clinical study.

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 participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR are presented in Appendix 6.

4.2.2 Rationale for Control

Healthy participants with normal renal function, matched by mean age, mean BMI, and sex, will serve as the control group. Comparison of data from participants with renal impairment to data from healthy participants will effectively inform the differences of safety and PK between the 2 groups.

4.3 Justification for Dose

The methods used in calculating doses and estimated exposures are detailed in Section 4.3.1 and Section 4.3.2.

As this is a Phase 1 assessment of MK-0616 in humans, and the PK, pharmacodynamic and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.11.6.

The projected clinical/therapeutic dose of MK-0616 is anticipated to lie between 10 and 18 mg. The 10-mg dose selected for this study therefore serves as a meaningful dose level to evaluate in moderate RI. Because renal clearance is thought to be the primary route of elimination for MK-0616, the exposure of MK-0616 in moderate RI is anticipated to be approximately 2-fold higher than in healthy controls (anticipated healthy Cmax 6 nM, AUC0-inf 258 uM*hr; anticipated moderate RI Cmax ~6 nM, AUC0-inf <516 uM*hr). The highest anticipated Cmax and AUC exposure in this study are 25-fold and 4.4-fold below the highest single dose exposure experienced in previous clinical trials (300-mg dose administered in Protocol 001; Cmax 150 nM, AUC0-inf 2290 uM*hr), and CCI below the NOAEL exposures observed in 1-month GLP toxicity studies in nonhuman primates CCI

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).

A study may be paused during review of newly available preclinical/clinical safety, PK, pharmacodynamic, efficacy, or biologic data or other items of interest, prior to a final decision on continuation or termination of the study. It may be necessary to keep the study open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the study. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. If the decision has been made to end the study following this review period, the study end will be defined as the date of the Sponsor decision, and this end of study date supersedes the definitions outlined above. The Competent Authority(ies) and IRB(s)/IEC(s) will be apprised of the maximum duration of the study beyond the last participant out and the justification for keeping the study open.

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

Male/female participants with moderate renal impairment and healthy matched participants between the ages of 18 and 75 years (inclusive) will be enrolled in this study.

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:

Type of Participant and Disease Characteristics

1. Is in good health based upon medical history, physical examination, VS measurements, and ECGs performed before randomization.

2. Is in good health based on laboratory safety tests obtained at the screening visit and before administration of the initial dose of study intervention. Appendix 2 provides a table of laboratory safety tests to be performed. Appendix 10 provides an algorithm for the assessment of out-of-range laboratory values.

Demographics

3. Is male or female, from 18 years to 75 years of age inclusive, at the time of providing informed consent.

   Healthy Matched Controls (Panel B): Age must be within ± 15 years of the mean age of participants within the RI panel(s) to which the participant is matched.

4. Has a BMI ≥18 kg/m^2 and ≤40 kg/m^2. See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height (m)^2.

   Healthy Matched Controls (Panel B): BMI must be within ± 10% of the mean BMI of participants within the moderate RI (panel A) to which the participant is matched.

Male Participants

5. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 90 days after the last dose of study intervention:

   Refrain from donating sperm

   PLUS either:

   Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

   OR

   Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:

Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female Participants

6. A female participant is eligible to participate if:

   She is a WONCBP, as defined in Appendix [5].

Informed Consent

7. The participant (or legally acceptable representative) has provided 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.

Additional Categories

8. **Moderate RI (Panel A):** Has a baseline eGFR ≥30 and <60 mL/min/1.73 m^2 based on the MDRD equation. Reasonable efforts will be made to enroll at least 4 participants with

eGFR values ≤45 mL/min/1.73 m^2 and at least 1 participant with eGFR ≤ 37.5 mL/min/1.73 m^2.

9. **Moderate RI (Panel A):** Has had no clinically significant change in renal status at least 1 month prior to dosing and is not currently receiving or has not previously been on hemodialysis.

10. **Healthy Matched Controls (Panel B):** Has an eGFR ≥80 mL/min/1.73 m^2 based on the MDRD equation.

MDRD Equation:

eGFR (mL/min/1.73 m^2) =

175 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 [if female]) x (1.212 [if Black or African American])

Moderate RI (Panel A): Baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 3-month period prior to screening. If no historical measurement is available, a second baseline eGFR sample will be taken during the screening period (≥72 hours apart) and the mean of the 2 values will be used for group assignment; the second baseline eGFR sample may be obtained at the time of check-in.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. **Moderate RI (Panel A):** Has a history of any clinically significant concomitant disease or condition (including treatment for such conditions) or diseases whose current condition is considered clinically unstable that, in the opinion of the investigator, could either interfere with the study drug, compromise interpretation of study data, or pose an unacceptable risk to the patient.

   Healthy Matched Controls (Panel B): Has a history of clinically significant endocrine, GI, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases. Participants with a remote history of uncomplicated medical events (eg, uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma) may be enrolled in the study at the discretion of the investigator.

2. Is mentally or legally incapacitated, has significant emotional problems at the time of prestudy (screening) visit or expected during the conduct of the study or has a history of clinically significant psychiatric disorder of the last 5 years. Participants who have had situational depression may be enrolled in the study at the discretion of the investigator.

3. Has a history of cancer (malignancy).

   Exceptions: (1) Adequately treated nonmelanomatous skin carcinoma or carcinoma in situ of the cervix or; (2) Other malignancies that have been successfully treated with appropriate follow up and therefore unlikely to recur for the duration of the study, in the opinion of the investigator and with agreement of the Sponsor (eg, malignancies that have been successfully treated ≥10 years prior to the prestudy screening visit).

4. Has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (ie, systemic allergic reaction) to prescription or nonprescription drugs or food.

5. Is positive for HBsAg, hepatitis C antibodies or HIV.

6. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the prestudy (screening) visit.

Prior/Concomitant Therapy

7. **Moderate RI (Panel A):** Is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies as indicated in Section 6.5 for the prohibited time period.

8. **Healthy Matched Controls (Panel B):** Is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of study intervention, throughout the study (including washout intervals between treatment periods), until the poststudy visit. There may be certain medications that are permitted (see Section 6.5).

9. Has received any nonlive vaccine starting from 14 days prior to study intervention or is scheduled to receive any nonlive vaccine through 30 days following study intervention.

   Exception:

   - COVID-19 vaccine may be administered. Study intervention must be given at least 72 hours following or at least 48 hours prior to any COVID-19 vaccination.

     Investigational COVID-19 vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

Prior/Concurrent Clinical Study Experience

10. Has participated in another investigational study within 4 weeks (or 5 half-lives, whichever is greater) prior to the prestudy (screening) visit. The window will be derived from the date of the last visit in the previous study.

Diagnostic Assessments

11. Has a QTc interval ≥470 msec (for males) or ≥480 msec (for females).

Other Exclusions

12. **Moderate RI (Panel A):** Does not agree to follow the smoking restrictions as defined by the CRU.

    Healthy Matched Controls (Panel B): Is a smoker and/or has used nicotine or nicotine-containing products (eg, nicotine patch and electronic cigarette) within 3 months of screening.

13. Is under the age of legal consent.

14. Consumes greater than 3 servings of alcoholic beverages (1 serving is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Participants who consume 4 servings of alcoholic beverages per day may be enrolled at the discretion of the investigator.

15. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.

16. Is a regular user of cannabis, any illicit drugs or has a history of drug (including alcohol) abuse within approximately 3 months. Participants must have a negative UDS prior to randomization.

17. Is unwilling to comply with study restrictions.

18. Presents any concern by the investigator regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.

19. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Diet Restrictions

Fasting requirements for study procedures, such as but not limited to laboratory safety evaluations are specified in Appendix 2.

In each treatment period, participants will fast from all food and drinks, except water, for at least 8 hours before study intervention administration. Participants will fast from all food and

drinks, except water, between study intervention administration and the first scheduled meal. Meals and snack(s) will be provided by the investigator at time points indicated in the study flowchart. Participants will fast from all food and drinks, except water, between meals and snacks. The caloric content and composition of meals will be the same in each treatment period. After the 24-hour postdose procedures have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition, and timing.

Instructions on whether to take MK-0616 with or without food and/or drink may be modified during the study based on newly available data.

Water will be provided during study intervention administration. Water will be restricted 1 hour before and 1 hour after study intervention administration.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

Participants will refrain from consumption of caffeinated beverages or xanthine-containing products from 12 hours before the prestudy and poststudy visits and from 12 hours before and after study intervention administration in each treatment period. At all other times, caffeinated beverages or xanthine-containing products will be limited to no more than 6 units per day (1 unit = 120 mg of caffeine).

5.3.2.2 Alcohol Restrictions

Participants will refrain from consumption of alcohol 24 hours before the prestudy and poststudy visits and from 24 hours before and after study intervention administration in each treatment period. At all other times, alcohol consumption is limited to no more than approximately 3 alcoholic beverages or equivalent servings (1 serving is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day.

5.3.2.3 Tobacco Restrictions

Healthy Matched Controls (Panel B): Smoking (and/or the use of nicotine/nicotine-containing products) is not permitted during the study.

Moderate RI (Panel A): Participants will follow the smoking restrictions (and if applicable, the use of nicotine/nicotine-containing products) defined by the CRU.

5.3.3 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (ie, weight lifting, running, bicycling, etc) from the prestudy (screening) visit and until the poststudy visit.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen-failure information may be included, as outlined in the eCRF entry guidelines. Minimal information may include demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements.

5.5 Participant Replacement Strategy

If a participant discontinues from study intervention OR withdraws from the study a replacement participant may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement participant will generally receive the same intervention or intervention sequence (as appropriate) as the participant being replaced. The replacement participant will be assigned a unique treatment/randomization number.

The replacement participant may begin dosing at the subsequent dose level for that panel, based on investigator and Sponsor review and discussion.

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 study intervention(s) provided by the Sponsor will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted before dosing the replacement participant. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention to be used in this study is outlined in [Table 2].

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
All Participants	Experimental	MK-0616	Drug	Capsule	10 mg/ CCI [redacted]	10 mg	Oral	Panels A and B	Experimental	IMP	Provided Centrally by the Sponsor

EEA =European Economic Area; IMP=investigational medicinal product; NIMP=noninvestigational medicinal product.

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. In these circumstances, local legislation is followed.

The CCI [redacted] capsule presentation of MK-0616 drug product contains a granulated powder blend consisting of MK-0616 CCI [redacted]

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 (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Specific calculations or evaluations required to be performed to administer the proper dose to each participant are outlined in a separate document provided by the Sponsor. 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

Participants in this study will be allocated by nonrandom assignment.

Participants will be assigned an allocation number for a single treatment using the allocation schedule shown in [Table 3].

Table 3 Allocation of Participants to Treatment

Panel	Impairment Stage	n	Treatment
A	Moderate RI	10	Single dose of MK-0616 10 mg
B	Healthy Control	8	Single dose of MK-0616 10 mg
RI=renal impairment			

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment plan require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.

Study-site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5 Concomitant Therapy

Healthy Matched Controls (Panel B):

If a participant does not discontinue all prior medications within 14 days or 5 half-lives of the first dose of study intervention, they may be included in the study if the investigator can rationalize that the specific use of a prior medication is not clinically relevant within the context of the study.

Concurrent use of any prescription or nonprescription medication, or concurrent vaccination, during the ongoing study (ie, after intervention allocation) must first be discussed between the investigator and Sponsor before administration, unless appropriate medical care necessitates that therapy or vaccination should begin before the investigator and Sponsor can consult. The participant will be allowed to continue in the study if both the Sponsor and the investigator agree.

Paracetamol/acetaminophen may be used for minor ailments without prior consultation with the Sponsor.

Moderate RI (Panel A): 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.

Participants who are taking certain prescription medications to treat manifestations of renal disease or medications needed to treat stable diseases (eg, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, diuretics) may be allowed to participate in the study at the discretion of the investigator and following consultation with the Sponsor Clinical Monitor. Participants must be on a stable regimen for at least 2 weeks (or 5 half-lives of the concomitant medication, whichever is longer) prior to dosing and be able to withhold the use 4 hours prior to and 4 hours postdose of study drug. If a participant is prescribed prohibited medication, upon discussion between the Sponsor and the investigator, the investigator may substitute the previously prescribed medication to an allowed one for the purpose of this study.

Any medication (including over-the-counter) that would significantly alter eGFR, which, by the determination of the investigator, might interfere with the study (eg, cimetidine) must be discontinued at least 2 weeks (or 5 half-lives of the compound, whichever is longer) prior to dosing.

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 or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

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

Panels A and B:

Listed below are specific restrictions for concomitant therapy or vaccination:

- Nonlive vaccines may only be administered in consultation with the Sponsor prior to or following the receipt of study intervention according to the time frames specified in Exclusion Criteria (Section 5.2).

  Exception: COVID-19 vaccine may be administered. Study intervention must be given at least 72 hours following or at least 48 hours prior to any COVID-19 vaccination.

  Investigational COVID-19 vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

6.5.1 Rescue Medications and Supportive Care

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

CRUs will be staffed with medically trained personnel with appropriate access to full service acute-care hospitals to facilitate rapid institution of medical intervention.

6.6 Dose Modification (Escalation/Titration/Other)

See Section 8.11.6 for modifications permitted within protocol parameters.

6.6.1 Stopping Rules

The following stopping rules will be used during the conduct of this study.

If any of the below stopping rules are met, the study will be paused, and no further dosing will occur until the Sponsor has reviewed the totality of data available. To continue the study (on joint agreement with the Sponsor and investigator), a substantial amendment will be submitted for approval.

1. An individual participant reports an SAE considered related to the study intervention by the investigator.

2. Two (2) or more participants within a Panel (at the same dose level) report Severe Nonserious AEs considered related to the study intervention by the investigator.

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

This study is open-label; therefore, the participant, the study-site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

Not Applicable

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

In clinical studies with a single intervention, discontinuation of study intervention can only occur before the intervention. Therefore, participants who receive a single-dose intervention cannot discontinue study intervention.

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

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 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 8.1.9. 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.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing

may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study will not exceed ~200 mL (Appendix 8).

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

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

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

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

If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent.

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 allocation, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification 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.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 2 weeks before the first dose of study intervention.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study.

8.1.6 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 intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by nonrandom assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation. 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.

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff.

8.1.8.1 Timing of Dose Administration

Study intervention will be administered in the morning.

Approximately 240 mL of water will be provided during study intervention administration. Additional water may be provided in ~50 mL increments if necessary.

8.1.9 Discontinuation and Withdrawal

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study and/or intervention. If a participant discontinues for any reason at any time during the course of the study and/or intervention, the participant may be asked to return to the clinic (or be contacted) for a poststudy visit as per the number of days described in Section 8.10.4 to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.4.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.4.1) to confirm if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 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@merck.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.

8.1.10 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study. The emergency unblinding call center will be available so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.11 Domiciling

Participants will report to the CRU the evening before the scheduled day of study intervention administration for each treatment period and remain in the unit until 48 hours postdose. At the discretion of the investigator, participants may be requested to remain in the CRU longer

8.1.12 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/Immunogenicity Assessments

There are no direct efficacy assessments in this study; surrogate markers of efficacy are outlined in Section 8.7.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood volumes drawn/collected by visit and by sample type per participant, can be found in Appendix 10.8.

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. Height and weight will also be measured and recorded.

BMI

BMI equals a person's weight in kilograms divided by height in meters squared ($BMI=kg/m^2$). BMI will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4 round down and 0.5 to 0.9 round up.

Body weight and height will be obtained with the participant’s shoes off and jacket or coat removed.

8.3.2 Vital Signs

8.3.2.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

Participants should be resting in a quiet setting without distractions in a semirecumbent position for at least 10 minutes before having VS measurements obtained. Semirecumbent VS will include HR, systolic and diastolic BP, RR, and body temperature at timepoints indicated in the SoA. The correct size of the BP cuff and the correct positioning on the participants' arm is essential to increase the accuracy of BP measurements.

The predose (baseline) HR and BP will be triplicate measurements, obtained at least 1 to 2 minutes apart within 3 hours of dosing MK-0616. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Postdose VS measurements will be single measurements.

Participants will continue to rest semirecumbent from dosing until 4 hours postdose except to stand for the measurement of orthostatic VS (if needed) or other study-related procedure.

Body Temperature

Body temperature will be measured. The same method must be used for all measurements for each individual participant and should be the same for all participants.

8.3.2.2 Orthostatic Vital Signs

Orthostatic VS (HR and systolic and diastolic BP) will also be obtained. Participants should be semirecumbent for at least 10 minutes and then stand upright for 2 minutes before measurement of orthostatic VS.

8.3.3 Electrocardiograms

- Triplicate 12-lead ECG will be obtained predose, single measurements will be obtained at postdose timepoints and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and [QTc] intervals. Refer to Appendix 9 for evaluation and potentially significant findings.

- At each time point when triplicate ECG are required, 3 individual ECG tracings should be obtained at least 1 to 2 minutes apart, but no more than 2 minutes apart. The full set of triplicates should be completed in no more than 6 minutes.

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry before lead placement. Participants may need to be shaved to ensure proper lead placement. Female participants may need to remove interfering garments.

Participants should be resting in the semirecumbent for at least 10 minutes before each ECG measurement.

The correction formula to be used for QTc is Fridericia

If repeat ECGs are required, the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the electrodes, 12-lead electrode sites will be marked on the skin of each participant with an ECG skin-marker pen to ensure reproducible electrode placement.

Before each period, predose ECGs will be obtained in triplicate at least 1 to 2 minutes apart within 3 hours before dosing MK-0616. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed).

During each treatment period, if a participant demonstrates an increase in QTc interval ≥60 msec compared with median predose baseline measurement, the ECG will be repeated twice within 5 minutes. The median value of the QTc interval from the 3 ECGs will represent the value at that time point. If the median QTc interval increase from baseline for any postdose time point is ≥60 msec, the participant will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QTc interval is within 60 msec of baseline. If prolongation of the QTc interval ≥60 msec persists, a consultation with a study cardiologist may be appropriate and the Sponsor should be notified.

During each treatment period, if a participant demonstrates a QTc interval ≥500 msec on a postdose ECG, the ECG will be repeated twice within 5 minutes. The median value of the QTc interval from the 3 ECGs will represent the value at that time point. If the median QTc interval is ≥500 msec, the Sponsor should be notified and the ECGs should be reviewed by a cardiologist. The participant should be telemetry monitored (until the QTc is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (eg, a CCU or ICU) is available.

If the participant has unstable hemodynamics, or has any clinically significant dysrhythmias noted on telemetry, the participant should be immediately transferred to an acute care setting for definitive therapy.

If prolongation of the QTc is noted, concomitant medications that prolong QTc should be held until the QTc is within 60 msec of baseline and the QTc is <500 msec.

A cardiologist will be consulted by the investigator as needed to review ECG tracings with significant abnormalities.

8.3.4 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 14 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.5 Pregnancy Testing

This section is not applicable.

8.3.6 Photograph of Rash

Photographs of the rash are highly recommended to be taken immediately, along with any additional information that may assist the investigator to evaluate the skin reaction, skin eruption or rash occurrence in determining etiology and drug relationship.

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

AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation, must be reported by the investigator for randomized participants only 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, placebo, or a procedure.

From the time of intervention allocation through 14 days after cessation of intervention, all AEs, SAEs and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator any time outside the period specified in the previous paragraph also 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 4].

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

Table 4 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation (Randomized participants only)	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
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 24 hours 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 allocated 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

Information in this section is not applicable since participants are WONCBP or males and partner pregnancy/lactation information is not required.

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

Not Applicable

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5.

2. 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).

It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this study.

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose of any drug administered as part of the study exceeding the dose prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

8.6 Pharmacokinetics

The decision as to which plasma and/or urine samples collected will be measured for evaluation of PK/pharmacodynamics will be collaboratively determined by the Sponsor (eg, samples at lower doses may not be measured if samples at higher doses reveal undetectable drug concentrations). If indicated, these samples may also be measured and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

8.6.1 Blood Collection for Plasma MK-0616

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

8.6.2 Urine Collection for Urinary MK-0616

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

For participants with RI, urine samples will be collected whenever possible, as participants may not be able to produce urine at each interval.

8.7 Pharmacodynamics

Sample collection, storage, and shipment instructions for pharmacodynamic samples (PCSK9 free) will be in the Operations 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:

- Leftover DNA for future research

8.10 Visit Requirements

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

8.10.1 Screening

Approximately 4 weeks before intervention allocation/randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

Participants may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures listed in the SoA, including consent review. Rescreen procedures cannot be conducted the day prior to intervention allocation/randomization if there are Day -1 procedures planned per protocol.

8.10.2 Treatment Period Visit

Following confirmation that each participant meets inclusion/exclusion criteria and that all predose procedures have been completed, participants will be assigned a unique allocation number associated with a specific treatment sequence as defined by a computer allocation schedule.

Before each treatment, participants will report to the CRU on Day -1 or at a time specified by the investigator. Participants will fast from all food and drink except for water, for a at least 8 hours before study drug administration and at least 1 hour after study drug administration (refer to Section 5.3.1 for specific dietary restrictions during dosing).

Participants will remain in the CRU up to 48 hours postdose. Participants may be required to remain in the CRU for longer than 48-hours postdose at the discretion of the investigator.

Participants will be administered the assigned treatment in the morning. The exact clock time of dosing should be recorded.

8.10.3 Discontinued Participants Continuing to be Monitored in the Study

At any point if a participant discontinues from treatment but continues to be monitored in the study, all study procedures specified in the SoA may be completed at the discretion of the investigator and with Sponsor agreement. The subset of study procedures completed will be communicated in a PCL.

8.10.4 Poststudy

Participants will be required to return to clinic approximately 14 days after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less than 14 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 14 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

8.10.5 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the blood sample for MK-0616 is the critical procedure.

At any postdose time point, the blood sample for MK-0616 needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Study procedures can be performed before or after the prescribed/scheduled time.

The order of priority can be changed during the study with joint agreement of the investigator and the Sponsor Clinical Director.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

The following variance in procedure collection times will be permitted.

- PK Collection as outlined in [Table 5].

Table 5 Pharmacokinetic (Blood/Urine) Collection Windows

PK Collection	PK Collection Window
0 to <1 h	5 min
1 to <24 h	15 min
24 to <48 h	1 h
48 to 168 h	2 h
>168 h	24 h

Predose standard safety evaluations:

- VS and ECG up to 3 hours predose
- laboratory safety tests and physical exam up to 24 hours predose

Postdose standard safety evaluations:

- VS, ECG, laboratory safety tests, and physical exam
  - Prior to 24-hours postdose may be obtained within 15 minutes of the theoretical sampling time
  - Between 24-hours and 48-hours postdose may be obtained within 1 hour of the theoretical sampling time
  - From 48-hours to 168-hours postdose may be obtained within 2 hours of the theoretical sampling time

8.10.6 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

This is a Phase 1 assessment of MK-0616 in humans, and the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently

outlined may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants.

As such, some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum daily dose may not exceed those currently outlined in the protocol.

- Decrease in the dose of the study intervention administered in any given panel
- Entire panel(s) may be omitted
- Adjustment of the dosing interval (eg, divided doses [bid to qd, qd to bid, tid, or vice versa])
- Remove a planned PK pause if agreed by Sponsor and investigator if no further increases in total daily dose
- Addition of PK pause
- Instructions to take study intervention with or without food or drink may also be modified based on newly available data
- Modification of the PK/pharmacodynamic sample processing and shipping details based on newly available data
- Modification of urine sample collection

The PK/pharmacodynamic sampling scheme currently outlined in the protocol may be modified during the study based on newly available PK or pharmacodynamic data (eg, to obtain data closer to the time of peak plasma concentrations). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

Up to additional 50 mL of blood may be drawn for safety, PK, and/or pharmacodynamic analyses. The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume during his/her participation in the entire study (Appendix 8).

The timing of procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests, etc) may be modified during the study based on newly available data. Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information. These changes will not increase the number of study procedures for a given participant during his/her participation in the entire study.

It is understood that the current study may use some or none of the alterations described above. Any alteration made to this protocol to meet the study objectives must be detailed by the Sponsor in a letter to the Study File and forwarded to the investigator for retention. The letter may be forwarded to the IRB/IEC at the discretion of the investigator.

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

Primary

Pharmacokinetics

Objective:

To compare the plasma PK of MK-0616 following a single dose administration in participants with moderate renal impairment to those of healthy matched control participants.

Separately for each PK parameter, individual values of plasma MK-0616 AUC0-inf and Cmax will be natural log-transformed and evaluated with a linear fixed-effects model containing a categorical effect for populations. The REPEATED statement with the GROUP=Population option will be used in SAS PROC MIXED to estimate separate variances for each population. The Kenward and Roger adjustment will be used to calculate the denominator degrees of freedom for the fixed-effect (DDFM=KR).

Ninety-five percent CIs for the least squares means for each population will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means and their corresponding 95% CIs will yield estimates for the population geometric means and CIs about the geometric means on the original scale.

To compare participants with moderate RI to matching participants with normal renal function, a 2-sided 90% confidence interval for the true difference in means (moderate RI-normal renal function) will be calculated for each PK parameters (AUC0-inf and Cmax) using the mean square error from the model and referencing a t-distribution. The confidence limits will be exponentiated to obtain the 90% CI for the true ratio of geometric means (moderate RI/normal renal function) for each PK parameter.

Figures showing individual PK values with GMs (95% CIs) by population, plotted on the natural log scale, will be provided for AUC0-inf and Cmax.

Secondary

Safety

Objective:

To evaluate the safety and tolerability of the administration of a single dose MK-0616 in participants with moderate renal impairment.

The safety and tolerability of MK-0616 will be monitored by clinical assessment of adverse experiences and other safety measurements (eg, labs, vital signs, ECGs).

Urine

Objective:

To compare the urine PK of MK-0616 following a single dose of MK-0616 to participants with moderate renal impairment to those of healthy matched control participants.

MK-0616 Ae0-24, Fe, and CLr following a single dose of MK-0616 administered to participants with moderate renal impairment, will be estimated and compared to those estimated in healthy matched control participants.

Separately for each urine PK parameter, where possible, individual values of Ae0-24, Fe and CLr will be natural log-transformed and evaluated with a linear fixed-effects model, which is described in the primary analysis. Ninety-five percent CIs for the least square means for each population will be constructed. To compare participants with moderate RI to matching participants with normal renal function, a 2-sided 90% CI for the true ratio of means (RI/normal renal function) will be calculated for each urine PK parameter (Ae0-24, Fe and CLr).

% Reduction of Free PCSK9

Objective: To evaluate the % reduction of free PCSK9 from baseline following administration of a single dose of MK-0616

Estimation: The difference between % reduction of free PCSK9 from baseline following administration of a single dose of MK-0616 among participants with moderate renal impairment and in healthy matched control participants will be estimated. 90% CIs will also be reported for this difference.

Sample Size and Power Calculations

The precision of the estimated GMR (moderate renal impairment/normal renal function) of PK parameters obtained from this study can be assessed by calculating the halfwidth of the 90% CIs expected for the given sample size and assumed variability. The pooled between-subject standard deviation (on the natural log scale) for MK-0616 AUC0-inf as estimated from P001 and P004 is 0.29 ln(μM•hr).

Assuming a sample size of 8 participants per population and observed between-subject SDs as given above, then the half width of the 90% CIs of GMRs for MK-0616 AUC0-inf on the log scale will be 0.294. The lower and upper 90% confidence limits for the true GMRs will be given by OBS/1.34 and OBS*1.34 for AUC0-inf, where OBS is the observed GMR. Thus, for example, if the observed GMR for AUC0-inf was 2, then the 90% CI for the GMR would be 1.49 to 2.68.

9.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Early Clinical Development Statistics Department in collaboration

with the Quantitative Pharmacology and Pharmacometrics Department and Translational Medicine Department of the Sponsor.

If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the CSR.

9.3 Hypotheses/Estimation

Pharmacokinetics

Objective:

To compare the plasma PK of MK-0616 following a single dose administration in participants with moderate renal impairment to those of healthy matched control participants.

Estimation: MK-0616 AUC0-inf following a single dose of MK-0616 administered to participants with moderate renal impairment will be estimated and compared to MK-0616 AUC0-inf when administered to healthy matched control participants.

Urine

Objective:

To compare the urine PK of MK-0616 following a single dose of MK-0616 to participants with moderate renal impairment to those of healthy matched control participants.

Estimation: MK-0616 Ae0-24, Fe, and CLr following a single dose of MK-0616 administered to participants with moderate renal impairment, will be estimated and compared to those estimated in healthy matched control participants.

% Reduction of free PCSK9

Estimation: The difference between % reduction of free PCSK9 from baseline caused due to administration of a single dose of MK-0616 among participants with moderate renal impairment and in healthy matched control participants will be estimated. 90% Confidence intervals will also be reported for this difference.

9.4 Analysis Endpoints

The primary PK endpoints are plasma MK-0616 AUC0-inf, AUClast, Cmax, Tmax, t1/2, CL/F, and Vz/F following a single dose of MK 0616 administered to participants with moderate renal impairment or in healthy matched control participants.

The urine MK-0616 Ae0-24, Fe, and CLr following a single MK-0616 dose in participants with moderate renal impairments or in healthy matched control participants.

The secondary safety endpoints are AEs, VS, 12-lead ECGs, and laboratory safety tests.

9.5 Analysis Populations

The following populations are defined for the analysis and reporting of data. All participants will be reported, and their data analyzed, according to the treatment(s) they actually received.

All Participants as Treated (APaT): The All Participants as Treated Population consists of all participants who received at least one dose of treatment. This population will be used for assessments of safety and tolerability.

Per-Protocol (PP): The Per-Protocol Population consists of the subset of participants who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations. Important protocol deviations will be identified to the extent possible prior to unblinding by individuals responsible for data collection/compliance, and its analysis and interpretation. Any participants or data values excluded from analysis will be identified, along with the reason for exclusion, in the CSR. At the end of the study, all participants who are compliant with the study procedure as aforementioned and have available data considered sufficient to exhibit the effect of treatment will be included in the Per-Protocol dataset. This population will be used for the PK analyses.

9.6 Statistical Methods

Primary

Pharmacokinetics:

Separately for each PK parameter, individual values of plasma MK-0616 AUC0-inf and Cmax will be natural log-transformed and evaluated with a linear fixed-effects model containing a categorical effect for populations. The REPEATED statement with the GROUP=Population option will be used in SAS PROC MIXED to estimate separate variances for each population. The Kenward and Roger adjustment will be used to calculate the denominator degrees of freedom for the fixed-effect (DDFM=KR).

Ninety-five percent CIs for the least squares means for each population will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means and their corresponding 95% CIs will yield estimates for the population GMs and CIs about the GMs on the original scale.

To compare participants with moderate RI to matching participants with normal renal function, a 2-sided 90% CI for the true difference in means (RI - normal renal function) will be calculated for each PK parameters (AUC0-inf and Cmax) using the mean square error from the model and referencing a t-distribution. For each population, these confidence limits will be exponentiated to obtain the 90% CI for the true GMRs (RI/normal renal function) for each PK parameter.

Figures showing individual PK values with GMs (95% CIs) by population, plotted on the natural log scale, will be provided for AUC0-inf and Cmax.

Secondary

Safety

The safety and tolerability of MK-0616 will be monitored by clinical assessment of adverse experiences and other safety measurements (eg, labs, VS, ECGs).

Urine PK

MK-0616 Ae0-24, Fe, and CLr following a single dose of MK-0616 administered to participants with moderate renal impairment, will be estimated and compared to those estimated in healthy matched control participants.

Separately for each urine PK parameter, where possible, individual values of Ae0-24, Fe and CLr will be natural log-transformed and evaluated with a linear fixed-effects model, which is described in the primary analysis. Ninety-five percent CIs intervals for the least square means for each population will be constructed. To compare participants with moderate RI to matching participants with normal renal function, a 2-sided 90% CI for the true ratio of means (RI/normal renal function) will be calculated for each urine PK parameter (Ae0-24, Fe and CLr).

% Reduction of free PCSK9

Estimation: The difference between % reduction of free PCSK9 from baseline caused due to administration of a single dose of MK-0616 among participants with moderate renal impairment and in healthy matched control participants will be estimated. Ninety percent CIs will also be reported for this difference.

Summary Statistics using BSA un-normalized eGFR: The participants will be recategorized into different renal categories based on their BSA un-normalized eGFR and non-model based summary statistics by population will be provided for (plasma AUC0-inf, Cmax, Tmax, elimination terminal t1/2, CL/F, and Vz/F, and urine Ae0-24, Fe, and CLr, as applicable).

Individual values will be listed for each PK parameter (plasma MK-0616 AUC0-inf, Cmax, Tmax, elimination terminal t1/2, CL/F, and Vz/F, , and urine MK-0616 Ae0-24, Fe, and CLr) by population, and the following (non-model-based) descriptive statistics will be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the natural log-scale).

9.7 Interim Analyses

Not applicable.

9.8 Multiplicity

There is no prespecified hypothesis; therefore, no multiplicity adjustment is needed.

9.9 Sample Size and Power Calculations

The sample size selected for each population to evaluate the effect of RI on the PK of MK-0616 was not chosen to satisfy any a priori statistical requirement. This sample size (n= 8 participants per panel) has historically been shown to be sufficient for studies of this type and should provide adequate data to support the planned analyses. Nevertheless, estimates of the expected precision of the estimates, based on these sample sizes are presented below.

The precision of the estimated ratios of geometric means (moderate renal impairment / normal renal function) of PK parameters obtained from this study can be assessed by calculating the halfwidth of the 90% CIs expected for the given sample size and assumed variability. The pooled between-subject standard deviation (on the natural log scale) for MK-0616 AUC0-inf after as observed in P001 and P004 is 0.29 ln(μM•hr).

Assuming a sample size of 8 participants per population and observed between-subject SDs as given above, then the half width of the 90% CIs of GMRs for MK-0616 AUC0-inf on the log scale will be 0.294. The lower and upper 90% confidence limits for the true GMRs will be given by OBS/1.34 and OBS*1.34 for AUC0-inf, where OBS is the observed GMR. Thus, for example, if the observed GMR for AUC0-inf was 2, then the 90% CI for the GMR would be 1.49 to 2.68.

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 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.

10.1.5 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.

10.1.6 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.

10.1.7 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.

10.1.8 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.

10.1.9 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

- The tests detailed in [Table 6] will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 6 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count	RBC Indices: MCV MCH Reticulocytes		WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	RBC Count			
	Hemoglobin			
	Hematocrit			
Chemistry	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose (fasting)	Calcium	Alkaline phosphatase	eGFR (CKD-EPI)
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• FSH (as needed in WONCBP only) • Serum or urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) if applicable] • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody)			
ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; HIV=human immunodeficiency virus; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell; WONCBP=women of nonchildbearing potential				

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

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."

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.

Assessment of causality

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 Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

- 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 must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Not Applicable

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

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

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

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

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

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@merck.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

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

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

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

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

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@merck.com.

13. References

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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/

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10.7 Appendix 7: Country-specific Requirements

Not Applicable

10.8 Appendix 8: Blood Volume Table

Panels A and B	Prestudy	Treatment Periods	Poststudy	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests	2	1	1	4	12.5	50
HIV/Hepatitis Screen including FSH (if applicable)	1			1	6	6
Blood for Planned Genetic Analysis		1		1	8.5	8.5
Blood for MK-0616		16		16	3	48
Blood for plasma PCSK9 (free) assay		12		12	3	36
Total Blood Volume per Participant for Panels A, and B[a]						**148.5 mL**

[a] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. Note: never to exceed 50 mL.

10.9 Appendix 9: 12-Lead Electrocardiogram Abnormality Criteria

	Screen Failure Criteria	Potentially Significant Postrandomization Findings (clarification on action to take)
RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥25 bpm from baseline
Sinus Bradycardia	<40 bpm	HR <40 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial Premature Complex	> 1 beat	≥ 3 beats
Ventricular Premature Complex	All	≥ 3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB With LAHB	New Onset LAHB
Right Axis Deviation	RBBB With LPHB	New Onset LPHB
CONDUCTION		
1st Degree AV Block	PR ≥230 ms	PR ≥ 230 ms + Increase of >15 ms; or PR Increase of >25%
2nd Degree AV Block	Mobitz Type II	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB With LAHB/LPHB as Defined Above	New Onset RBBB (Not Including Rate-related)
ICRBBB (QRS <120 ms)	No Exclusion	Nothing
Short PR/Preexcitation Syndrome	Delta Wave + PR <120 ms	Delta Wave + PR <120 ms
Other Intra-Ventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms
QTc (B or F)		
Male	QTc ≥470 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline

	Screen Failure Criteria	Potentially Significant Postrandomization Findings (clarification on action to take)
Female	QTc ≥480 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
HYPERTROPHY		
Atrial Abnormalities	Definite Evidence of P Mitrale or P Pulmonale	Definite Evidence of P Mitrale or P Pulmonale
Ventricular Abnormalities	Voltage Criteria for LVH Plus Strain Pattern	Voltage Criteria for LVH Plus Strain Pattern
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All
ST/T MORPHOLOGY		
ST Elevation Suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST Depression Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Non-specific ST-T Changes (In 2 or More Leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	All	All

AV=atrioventricular; bpm=beats per minute; HR=heart rate: ICRBBB=incomplete right bundle branch block; LAHB=left anterior hemiblock; LPHB=left posterior hemiblock; LVH=left ventricular hypertrophy; mm=millimeter; ms=milliseconds, PR=pulse rate; QTcB=QT correction using Bazett's formula; QTcF=QT correction using Fredericia formula; RBBB=right bundle branch block; ST/T=ST-segment/T wave.
Baseline is defined as Predose Day 1

10.10 Appendix 10: Algorithm for Assessing Out of Range Laboratory Values

For all laboratory values obtained at prestudy (screening) visit and/or predose evaluation:

A. If all protocol-specified laboratory values are normal, the participant may enter the study.

B. If a protocol specified laboratory value is outside of the parameter(s) outlined in the inclusion/exclusion criteria (including a repeat if performed), the participant will be excluded from the study.

C. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:

    a. The participant may be excluded from the study;

    b. The participant may be included in the study if the abnormal value(s) is NCS (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).

    c. The participant may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (eg, elevated eosinophil count in a participant with asthma or seasonal allergies), the medical condition should be annotated on the laboratory report.

    OR

    d. The abnormal test may be repeated (refer items a. and b. below for continuation of algorithm for repeated values).

        a. If the repeat test value is within the normal range, the participant may enter the study.

        b. If the repeat test value is still abnormal, the study investigator will evaluate the potential participant with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the participant may enter the study.

D. If there is any clinical uncertainty regarding the significance of an abnormal value, the participant will be excluded from the study.

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
ADA	anti drug antibodies
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
Ae0-24	amount recovered in urine from 0 to 24 hours
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the curve
BDS	blood drug screen
bid	twice daily
BMI	body mass index
BP	blood pressure
CCU	Cardiac care unit
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
CLr	renal clearance
Cmax	maximum plasma concentration
CrCl	creatinine clearance
CRF	Case Report Form
CRU	clinical research unit
CSR	Clinical Study Report
DDI	drug-drug interaction
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
Fe	fraction of dose recovered in urine
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
GLP	good laboratory practices
HbA1c	hemoglobin A1c
HBcAb	hepatitis B core antibody

Abbreviation	Expanded Term
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgV	immunoglobulin-variable
IHC	immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
ITP	idiopathic thrombocytopenic purpura
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVRS	interactive voice response system
IWG	International Working Group
LDL-C	Low density lipoprotein - cholesterol
LLN	lower limit of normal
LLOQ	lower limit of quantitation
mAb	monoclonal antibody
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger RNA
MTD	maximum tolerated dose
N/A	not applicable
NCI	National Cancer Institute
NCS	not clinically significant
NDA	New Drug Application
NOAEL	no observed adverse effect level
OTC	over-the-counter
PCL	Protocol Clarification Letter
PCSK9	proprotein convertase subtilisin kexin 9
PK	Pharmacokinetic(s)
po	orally

Abbreviation	Expanded Term
PP	per-protocol
PQC	product quality complaint
QP2	Department of Quantitative Pharmacology and Pharmacometrics
RI	renal impairment
RNA	ribonucleic acid
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transminase
SLAB	Supplemental laboratory test(s)
SoA	schedule of activities
SOC	standard of care
SOP	Standard Operating Procedures
SUSAR	suspected unexpected serious adverse reaction
t1/2	half life
Tmax	Time to maximum plasma concentration
UDS	urine drug screen
ULN	upper limit of normal
VS	vital signs
WBC	white blood cell
WONCBP	woman/women of nonchildbearing potential

11 REFERENCES

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