Official Protocol Title:	A Single-Dose Clinical Trial to Study the Safety, Tolerability, Pharmacokinetics, and Anti-Retroviral Activity of MK-8558 Monotherapy in Anti-Retroviral-Naïve HIV-1 Infected Participants
NCT number:	NCT03859739
Document Date:	22-AUG-2019

Title Page

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Protocol Title: A Single-Dose Clinical Trial to Study the Safety, Tolerability, Pharmacokinetics, and Anti-Retroviral Activity of MK-8558 Monotherapy in Anti-Retroviral-Naïve HIV-1 Infected Participants

Protocol Number: 002-03

Compound Number: MK-8558

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

One Merck Drive

P.O. Box 100

Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

EudraCT	2018-003904-37

Approval Date: 22 August 2019

Sponsor Signatory

Typed Name: Date
Title:

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: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
002-00	04-JAN-2019	Original protocol
002-01	16-APR-2019	This amendment is being written to submit safety and pharmacokinetic (PK) data from an ongoing study (Protocol 001) to support the administration of up to 900 mg as a single dose within the current study (Protocol 002).
002-02	13-JUN-2019	This study protocol is being amended to refine and clarify some of the eligibility criteria in order to support the inclusion of suitable participants. [redacted]
002-03	22-AUG-2019	This amendment is being written to increase the maximum proposed dose of MK-8558 to be administered in Panels C and D and to submit safety and pharmacokinetic (PK) data from an ongoing study (Protocol 001) to support the proposed increase in maximum dose within the current study (Protocol 002).

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendments:

This amendment is being written to increase the maximum proposed dose of MK-8558 to be administered in Panels C and D and to provide safety and pharmacokinetic (PK) data from an ongoing study (Protocol 001) to support the proposed dose increase.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 2.2.1 Pharmaceutical and Therapeutic Background 4.3 Justification for Dose 4.3.2 Maximum Dose/Exposure for This Study 4.3.3 Rationale for Dose Interval and Study Design 6.1 Study Intervention(s) Administered 6.3.1 Intervention Assignment 6.6 Dose Modification (Escalation/Titration/Other)	Increase in maximum proposed dose in Panels C and D from 900 mg to 1600 mg. Adjustment of exposure multiples for embryofetal development (EFD) data to support dosing of ≤1600 mg.	[redacted]

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities 4.1 Overall Design 4.2 Scientific Rationale for Study Design 4.3 Justification for Dose 4.3.2 Maximum Dose/Exposure for This Study 4.3.3 Rationale for Dose Interval and Study Design 5.3.1.1 Dietary Restrictions 6.3.1 Intervention Assignment	Modification of administration instructions for Panel D: MK-8558 is to be administered following a standard breakfast to participants in this panel.	[redacted]
2.2.1 Pharmaceutical and Therapeutic Background 2.2.2 Ongoing Clinical Studies	Addition of updated data on clinical exposure, safety, and PK from the ongoing FIH study, Protocol 001.	These updated clinical safety and PK data support the proposed dose increase within Amendment 03.

Section # and Name	Description of Change	Brief Rationale
4.2 Scientific Rationale for Study Design 6.5 Concomitant therapy	cci [redacted]	cci [redacted]
Throughout	Minor editorial changes and correction of typographical errors.	

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Single-Dose Clinical Trial to Study the Safety, Tolerability, Pharmacokinetics, and Anti-Retroviral Activity of MK-8558 Monotherapy in Anti-Retroviral-Naïve HIV-1 Infected Participants

Short Title: MK-8558 Single Dose Trial in HIV-1 Infected Participants

Acronym:

Hypotheses, Objectives, and Endpoints:

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

Study Population: Treatment naïve HIV-1 infected participants

Primary Objectives	Primary Endpoints
- Objective: To evaluate the anti-retroviral activity of MK-8558 in HIV-1 infected participants relative to historical placebo. [redacted]	- Plasma HIV-1 RNA (log10 copies/mL) reduction from baseline
- Objective: To evaluate the safety and tolerability of MK-8558 in HIV-1 infected participants.	- AEs, laboratory safety assessments, vital signs, and 12-lead ECGs

Secondary Objectives	Secondary Endpoints
- Objective: To evaluate plasma PK of MK-8558 after administration of single oral doses to HIV-1 infected participants. CCI [redacted]	- MK-8558 plasma AUC0-168, AUC0-last, AUC0-inf, Tmax, Cmax, C168hr, CL/F, Vz/F, and terminal t1/2.
Exploratory Objectives	Exploratory Endpoints
- Objective: To evaluate the PK-PD association of plasma MK-8558 with viral load reduction.	- PK (MK-8558 plasma)/PD (Plasma HIV-1 RNA) relationship
- Objective: To evaluate the relationship between dose and anti-retroviral activity of MK-8558.	- Dose-response (Plasma HIV-1 RNA) relationship
- 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 this study.	- Germline genetic variation

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Treatment of HIV-1 Infection
Population	HIV-1 Infected Participants, Naïve to Anti-Retroviral Therapy
Study Type	Interventional
Intervention Model	Sequential This is a multi-site study.
Type of Control	Historical placebo control
Study Blinding	Unblinded Open-label
Masking	No Masking
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 8 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 24 participants will be allocated.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Panel A	MK-8558	400 mg	Once	Oral	Single Dose	Experimental
Panel B	MK-8558	≤900 mg	Once	Oral	Single Dose	Experimental
Panel C	MK-8558	≤1600 mg	Once	Oral	Single Dose	Experimental
Panel D	MK-8558	≤1600 mg	Once	Oral	Single Dose	Experimental

Total Number	24 participants (4 panels of 6 participants each)
Duration of Participation	Each participant will participate in the study for approximately 9 weeks from the time the participant signs the Informed Consent Form (ICF) through the final contact. After a screening phase of 4 weeks, each participant will receive the assigned intervention (single dose MK-8558). After study drug (MK-8558) administration, each participant will be followed for approximately five weeks.

Study Governance Committees:

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

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 11.

1.2 Schema

The study design is depicted in Table 1.

Table 1 Dosing Scheme for MK-8558

Panel[a]	**Dose of MK-8558**			
A	400 mg			
B[b]		≤900 mg		
C[b]			≤1600 mg	
D[b,c]				≤1600 mg with food

a. In each panel, 6 participants will receive a single dose of MK-8558.
b. The decision to proceed to the next panel, and the selection of dose will be made following review of data from the preceding panel.
c. Optional panel. If the study objectives are met by Panels A-C, Panel D may not be required.

1.3 Schedule of Activities (SoA)

All Panels (Panels A-D)[a]																						
Study Period	**Screening[b]**	**Intervention**																				**Post-study[c]**
Scheduled Hour		**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**24**	**48**	**72**	**120**	**168**	**240**	**336**	**504**	
Administrative Procedures																						
Informed Consent	X																					
Informed Consent for Future Biomedical Research	X																					
Inclusion/Exclusion Criteria	X	X																				
Participant Identification Card	X																					
Medical History (includes substance usage)[d]	X																					
Prior/Concomitant Medication Review	X	----------																				X
Participant Domiciling in Clinical Research Unit (CRU)[e]		X	----------											X								
Intervention Allocation		X																				
Clinical and Safety Procedures																						
MK-8558 Administration			X																			
Standard Meal[f]									X	----------				X								
Standard Breakfast[g]		X																				
Full physical examination	X	X[h]												X				X				X
Height	X																					
Weight	X	X																				X
Vital Signs (heart rate, blood pressure)[i]	X	X[j]							X					X				X				X
Vital Signs (respiratory rate, body temperature)	X	X							X					X				X				X
Orthostatic Vital Signs (heart rate, blood pressure)[j]	X	X							X					X								X
12-lead ECG[k]	X	X[l]							X					X				X				X
Serum Follicle Stimulating Hormone (FSH)[m]	X																					

All Panels (Panels A-D)[a]																					
Study Period	**Screening[b]**	**Intervention**																			**Post-study[c]**
Scheduled Hour		**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**24**	**48**	**72**	**120**	**168**	**240**	**336**	**504**	
HIV/Hepatitis screen (per site SOP)	X																					
Urine Drug Screen (per site SOP)[n]	X	X[h]																				
Clinical and Safety Procedures- Continued																						
Hematology, Urinalysis, Chemistry[o]	X	X[h]												X				X				X
CD-4 cell count	X																					
Serum C-reactive protein (CRP)		X																				
Urine/serum β-hCG[p]	X	X																				X
AE/SAE review	X	----------																				X
Pharmacokinetics																						
Blood for Plasma MK-8558 Assay[q]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacodynamics																						
Blood for HIV RNA, viral resistance[r]	X	X							X				X	X	X	X	X	X	X	X	X	X
Biomarkers																						
Blood for Genetic Analysis[s]		X																				

All Panels (Panels A-D)[a]																						
Study Period	**Screening[b]**	**Intervention**																				**Post-study[c]**
Scheduled Hour		**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**24**	**48**	**72**	**120**	**168**	**240**	**336**	**504**	

a. Panels A-D will be conducted sequentially. Panels B-D will proceed after review of data from prior panel.
b. Participants will be screened within approx. 4 weeks prior to administration of study drug.
c. The post-study visit will occur approximately 35 days following administration of the study drug. Follow up for any clinical or laboratory adverse experiences should occur by phone or in person if the post-study visit occurs prior to 35 days following the dose of study drug.
d. Substances include: Drugs, alcohol, tobacco, and caffeine.
e. Participants will be admitted to the CRU the evening before scheduled dosing.
f. Standard meals will be given approx. 4 (lunch) and 10 (dinner) hrs post-dose. Snacks will be offered at approximately 8 and 13 hrs post-dose. See Section 5.3.1.
g. A standard breakfast is to be administered approx. 30 minutes prior to dosing in Panel D only. The fat content of this breakfast (i.e., high, moderate, or low) will be determined following the review of emerging safety and PK data from the ongoing studies, Protocols 001 and 002.
h. Pre-dose physical exam, urine drug screen and laboratory assessments may be conducted within 24 hrs prior to dosing.
i. Participants should be resting in the semi-recumbent position for at least 10 minutes prior to obtaining HR and BP.
j. Following measurement of the semi-recumbent HR and BP, participants assume a standing position for approximately 2 minutes and then orthostatic HR and BP will be obtained.
k. ECGs are performed after the participant has remained in a semi-recumbent position for at least 10 minutes.
l. Pre-dose ECGs and VS (HR and BP) will be obtained in triplicate at least 1-2 minutes apart within 3 hrs prior to dosing.
m. For post-menopausal females only.
n. Drug screen at screening and pre-dose are mandatory; any additional drug screens are conducted per site SOP and/or at the investigator's discretion.
o. Safety laboratory samples (hematology, urinalysis, and chemistry) will be collected after at least an 8-hr fast. Screening hematology labs will include PT/INR measurements.
p. Serum/urine (as required by local regulations) β-human chorionic gonadotrophin (β-hCG) to be performed in women of childbearing potential (WOCBP) only.
q. Leftover plasma samples will be stored for future biomedical research if the participant signs the Future Biomedical Research consent.
r. For participants who initiate follow-on anti-retroviral therapy (ART), blood for HIV-1 viral RNA and viral resistance will be collected at timepoints up to the initiation of ART. At the timepoint immediately prior to initiation of ART an additional blood sample collected for viral resistance testing may be taken for extraction of proviral DNA. This proviral DNA will be frozen and analyzed for the presence of viral resistance mutations only if standard Sanger sequencing cannot be performed because plasma viral load is too low at this time point. In addition, ultra-deep sequencing may be performed on this proviral DNA sample in the event that further information on viral resistance is required.
s. This 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 that 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 future biomedical research if the participant signs the future biomedical research consent. If the planned genetic analyses are not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

2 INTRODUCTION

2.1 Study Rationale

[redacted]

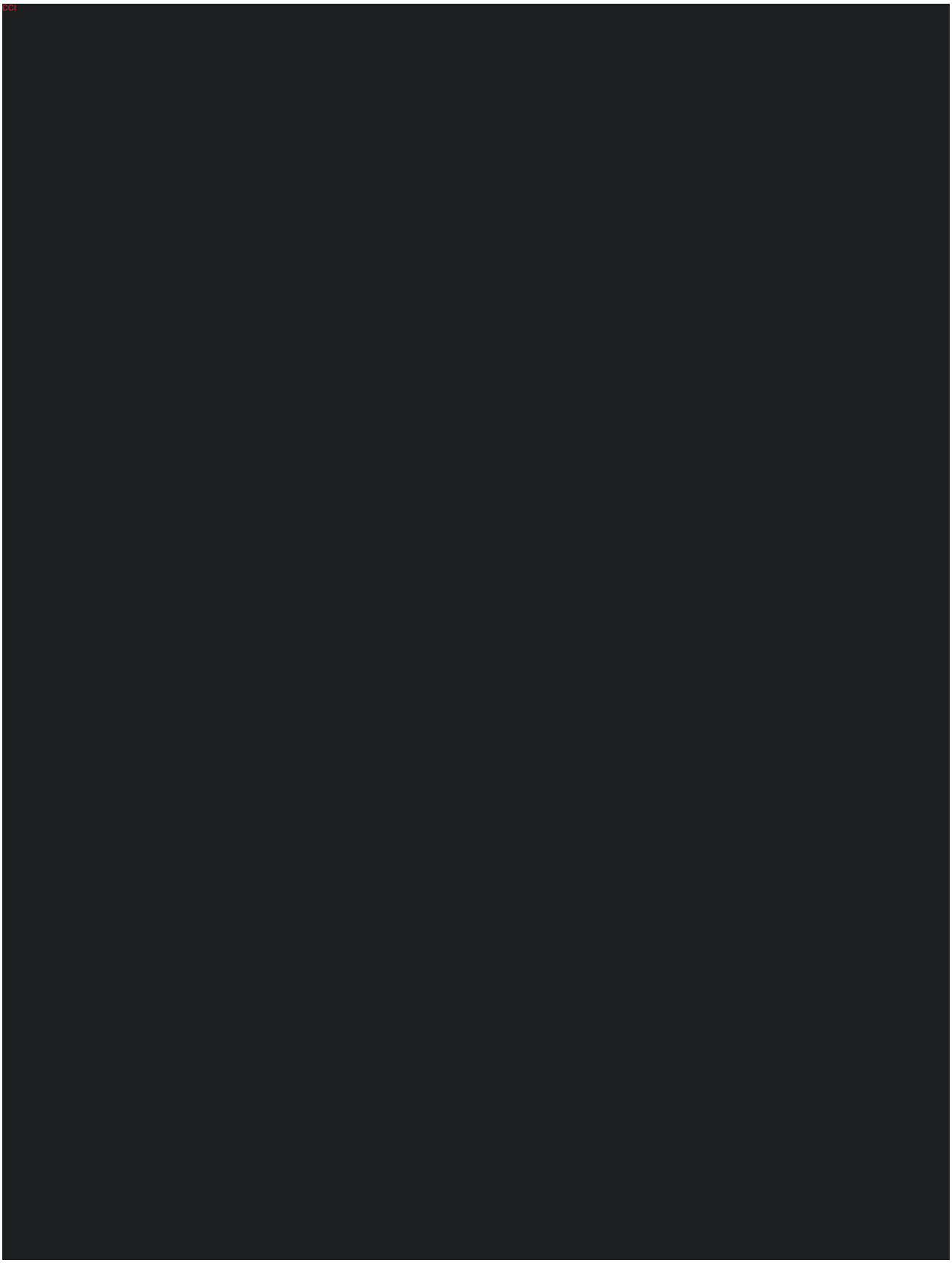
2.2 Background

Refer to the Investigator's Brochure (IB) for detailed background information on MK-8558.

2.2.1 Pharmaceutical and Therapeutic Background

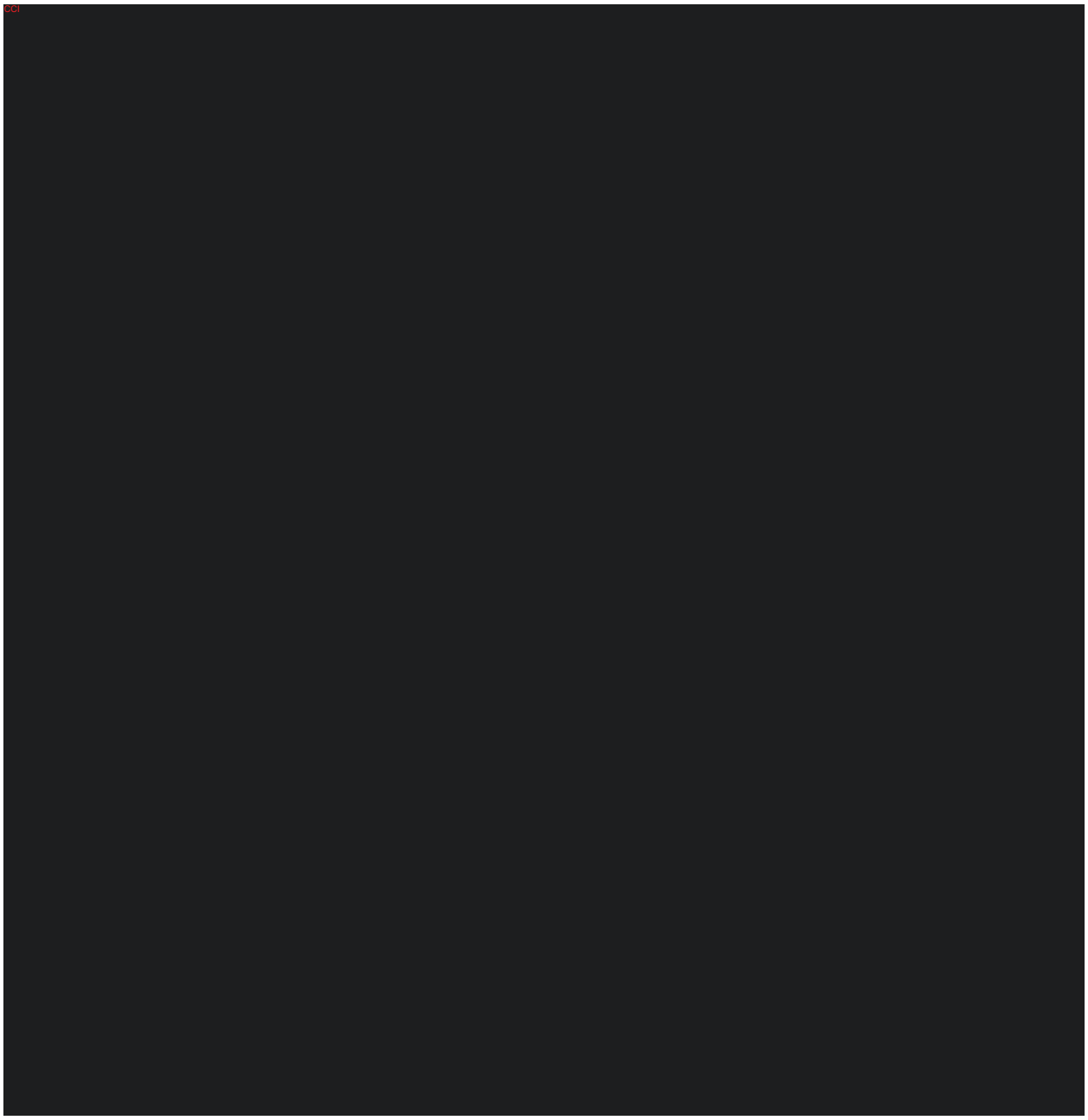
[redacted]

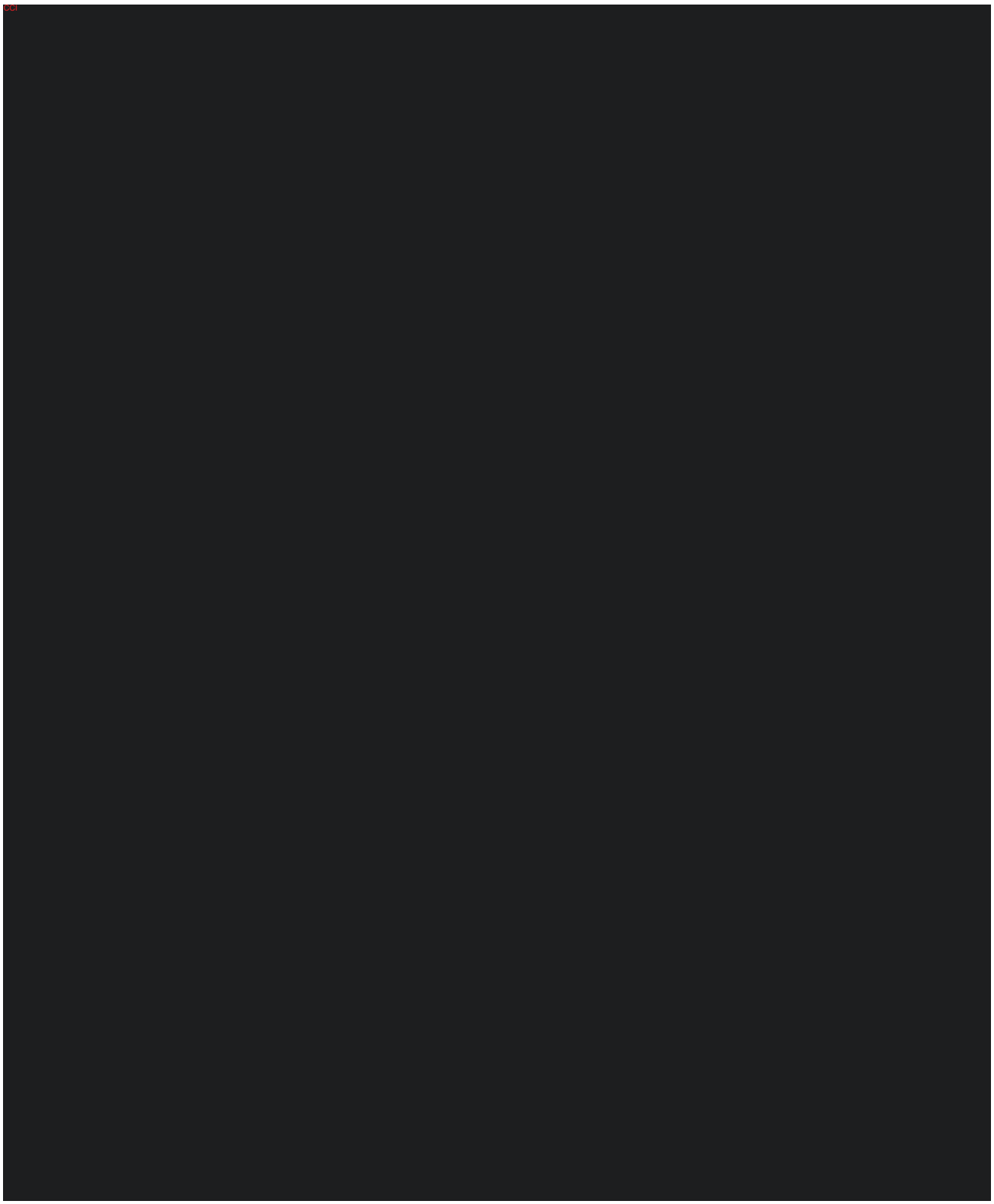
CCI

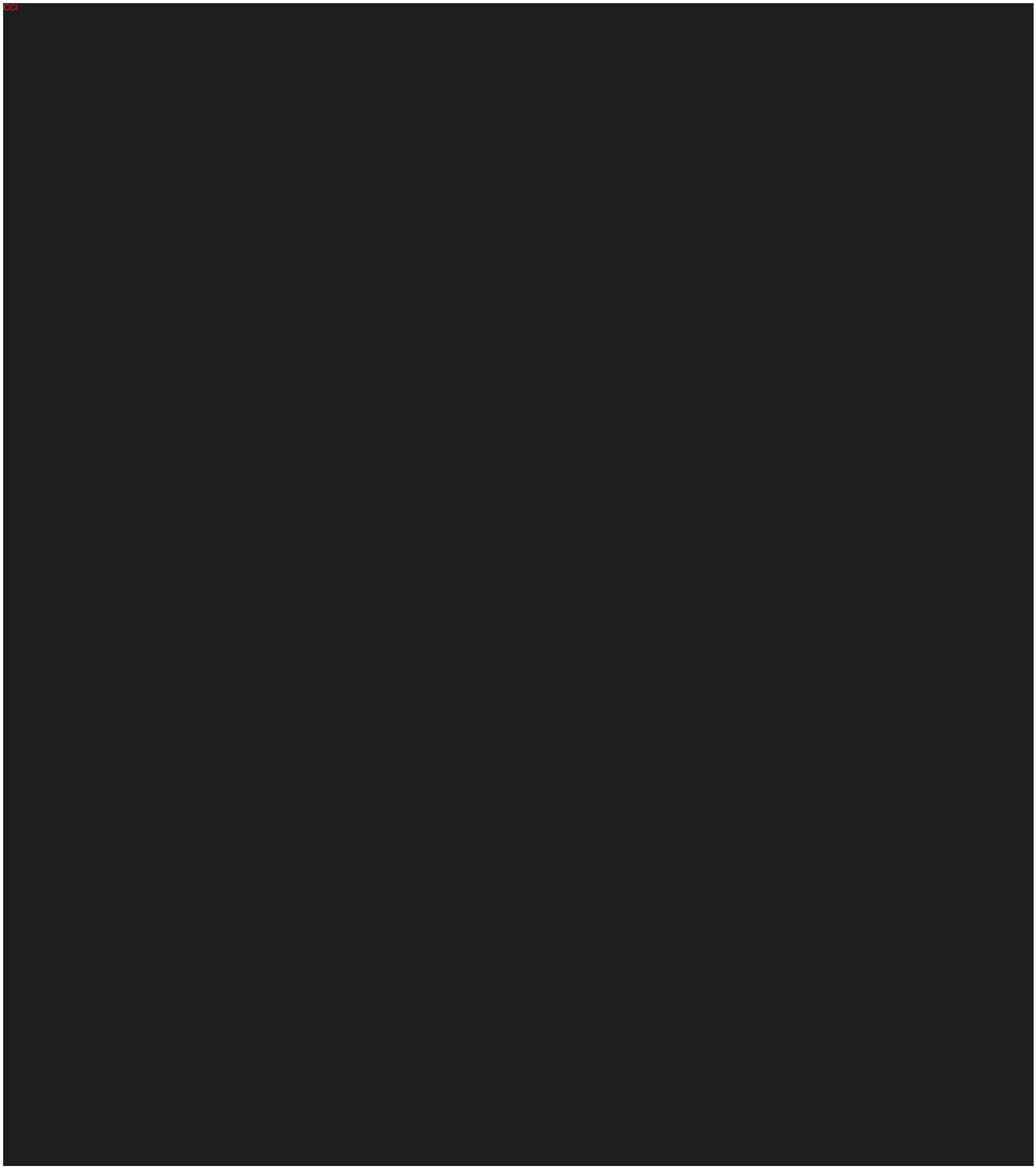


2.2.2 Ongoing Clinical Studies

[redacted]







[redacted]

2.3 Benefit/Risk Assessment

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

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.

Study Population: Treatment naïve HIV-1 infected participants

Study Population: Treatment naïve HIV-1 infected participants

Objectives	Endpoints
Primary	
• Objective: To evaluate the anti-retroviral activity of MK-8558 in HIV-1 infected participants relative to historical placebo. • [redacted]	• Plasma HIV-1 RNA (log10 copies/mL) reduction from baseline
• Objective: To evaluate the safety and tolerability of MK-8558 in HIV-1 infected participants.	• AEs, laboratory safety assessments, vital signs, and 12-lead ECGs
Secondary	
• Objective: To evaluate plasma PK of MK-8558 after administration of single oral doses to HIV-1 infected participants. • [redacted]	• MK-8558 plasma AUC0-168, AUC0-last, AUC0-inf, Tmax, Cmax, C168hr, CL/F, Vz/F, and terminal t1/2.
Exploratory	
• Objective: To evaluate the PK-PD association of plasma MK-8558 with viral load reduction.	• PK (MK-8558 plasma)/PD (Plasma HIV-1 RNA) relationship
• Objective: To evaluate the relationship between dose and anti-retroviral activity of MK-8558.	• Dose-response (Plasma HIV-1 RNA) relationship

Objectives	Endpoints
• 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 this study.	• Germline genetic variation

4 STUDY DESIGN

4.1 Overall Design

This is an open-label, single-dose, historical placebo-controlled, multiple panel trial of MK-8558 in participants with HIV-1 infection.

Up to four panels (Panels A-D), consisting of 6 participants per panel, will be enrolled. In each panel, participants will receive a single oral dose of MK-8558 (as outlined in Table 1) and undergo safety assessments and blood sampling for PK and viral load analysis.

Panels will be enrolled in a sequential manner, i.e., Panel B will initiate, and its dose level selected, following the review of safety, tolerability, viral dynamics, and PK data from Panel A (to at least 7 days post-dose). Similarly, selection of Panel C and D dose levels will occur following review of safety, tolerability, and viral dynamics data from Panels B and C, respectively, within this trial, and of emerging data from Protocol 001.

Data from the ongoing trial, MK-8558 Protocol 001 were used in the selection of the first dose (Panel A) with the inclusion of updated data within a previous substantial amendment (Protocol 002-01) to support the enrollment of Panels B, C and D.

[redacted]

In Panels A through C, study drug will be administered following at least a 10-hour fast. In Panel D, study drug will be administered following a standard breakfast. The fat content of this breakfast (i.e., high/moderate/low) will be determined based on the review of emerging safety and PK data from this study and from Protocol 001 and will be communicated in an official memo prior to dosing.

Following the treatment phase of the trial, participants will be encouraged to initiate an ART regimen [redacted]

[redacted]

Because this is a Phase 1 assessment of MK-8558 in humans, the pharmacokinetic (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, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

In keeping with the EMA Guideline on the Clinical Development of Medicinal Products for the Treatment of HIV Infection [European Medicines Agency 2016], this protocol has been designed to enroll a minimum number of treatment-naïve HIV-infected participants without advanced disease, using the shortest possible treatment duration.

CCI

[redacted]

The design consists of four serially-treated panels of participants receiving treatment in single periods, and allows for the evaluation of safety, tolerability, and viral dynamics, between the dosing of each panel, in order to guide dose selection for subsequent panels. PK data from Panel A will be reviewed prior to commencing Panel B.

This study will evaluate the efficacy and kinetics by which MK-8558 reduces HIV-1 RNA viral load over time. The doses tested in this study will evaluate the effectiveness of MK-8558 in in suppressing viral replication and [redacted]

[redacted]

CCI [redacted]

The study seeks to enroll both male and female participants. Based on the assessment of risk of reproductive and developmental toxicity, appropriate precautionary measures have been included for both male and female participants, as outlined in Section 5.1.

CCI [redacted]

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

The safety and tolerability of MK-8558 will be monitored by standard clinical assessments, including AEs, laboratory tests, VS and ECGs, an approach that is deemed to be sufficient based on the preclinical and clinical safety profile known to date.

4.2.1.2 Pharmacokinetic Endpoints

CCI [redacted]

[redacted]

[redacted]

4.2.1.3 Pharmacodynamic Endpoints

[redacted]

4.2.1.4 Planned Exploratory Biomarker Research

4.2.1.4.1 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 absorption, distribution, metabolism, and excretion; 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) or the disease under study. They may also be used to develop tests/assays including diagnostic tests related to the disease under study 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 multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

4.2.1.5 Future Biomedical Research

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

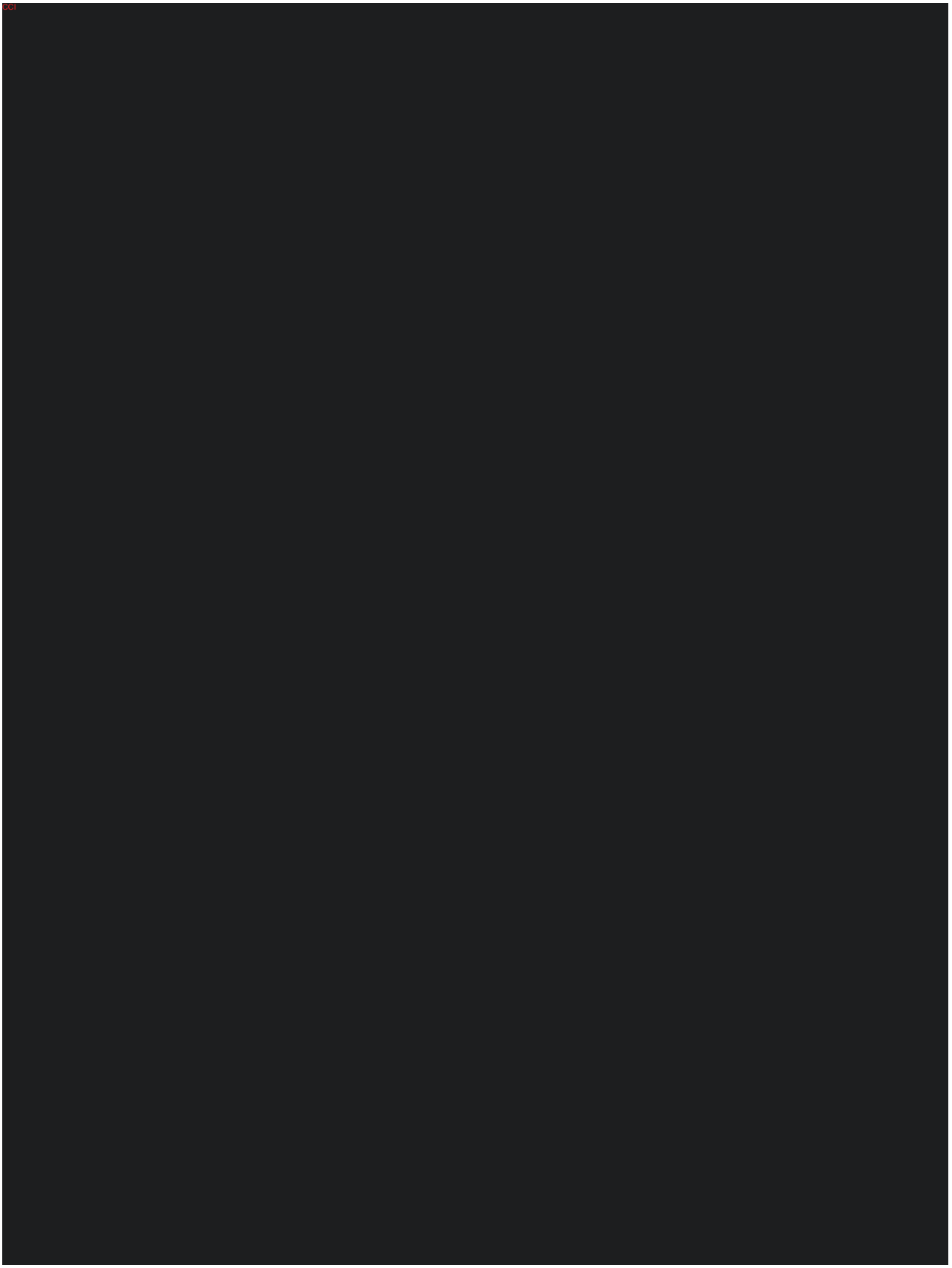
Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of this future biomedical research substudy are presented in Appendix 6.

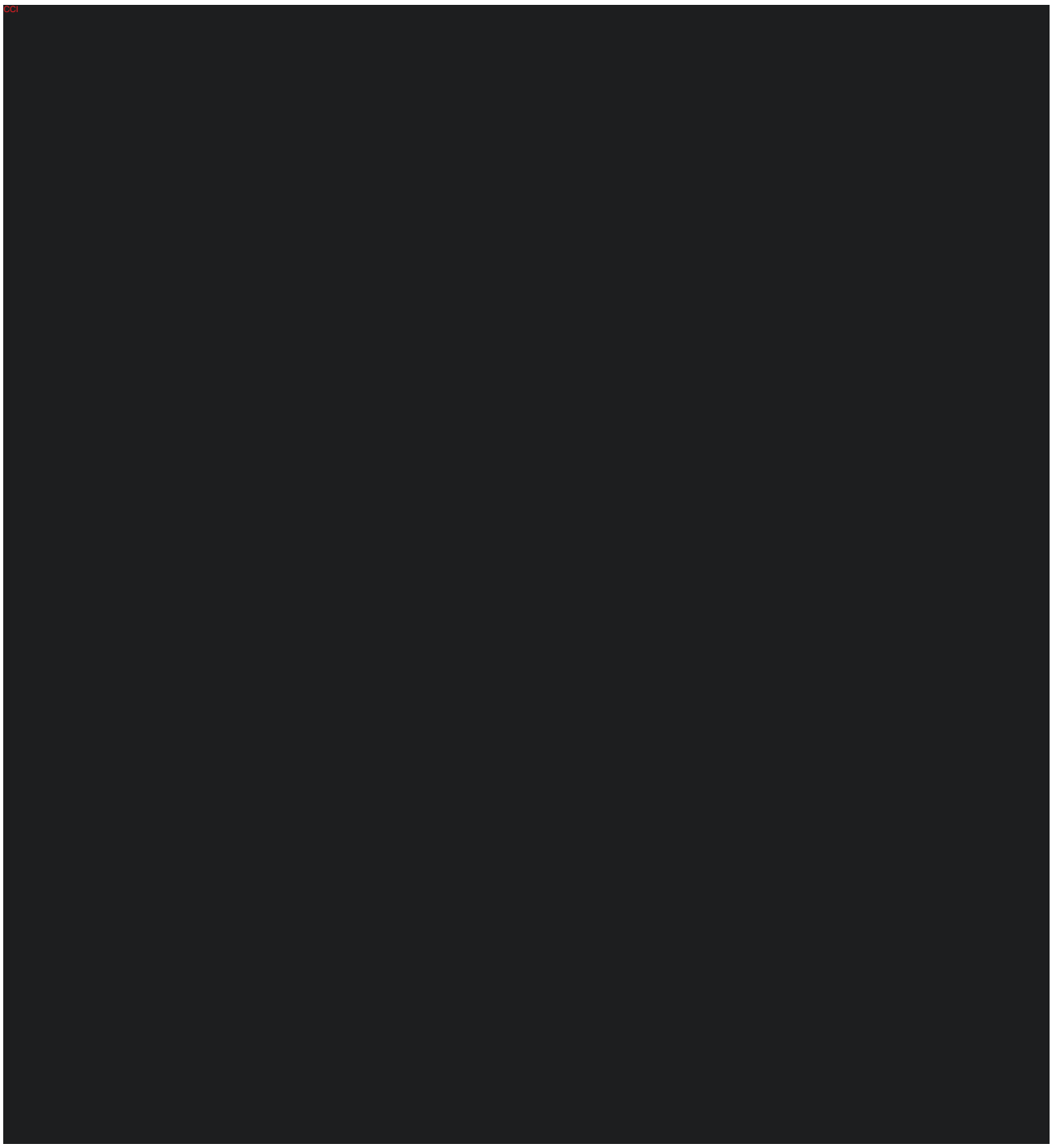
4.2.2 Rationale for the Use of Historical Placebo

The reduction in viral load for each dose level will be compared to historical placebo data from clinical trials previously conducted by the Sponsor. Evaluation of viral load data from other HIV monotherapy studies has indicated that results are consistent between trials and that on average, participants receiving placebo do not exhibit a change from baseline that differs from the anticipated within-participant variability in viral load. cci [redacted]

4.3 Justification for Dose

cci [redacted]





Further, in the event that following the review of data from Panels A to C, additional information is required for the characterization of the dose-PK-response relationship in HIV-1-infected participants, an optional Panel D will be enrolled.

The selected dosing regimen for Panel D is intended to enable the characterization of this dose-PK-response relationship. However, if the objectives of the trial have been met by Panels A-C, the enrollment of Panel D may not be necessary.

As this is a Phase 1 assessment of example 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 6.6.

[redacted]

4.3.1 Starting Dose for This Study

[redacted]

4.3.2 Maximum Dose/Exposure for This Study

[redacted]

[redacted]

Further details of exposure estimates for a range of possible doses are provided in Table 6.

4.3.3 Rationale for Dose Interval and Study Design

[redacted]

Sufficient time is allowed between dosing in subsequent panels to allow for the analysis and review of these data. There will be frequent, careful assessments of AEs throughout the post-dose period. This recommendation is in keeping with the projected safety profile and the ability of the Phase 1 unit to monitor each participant closely.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, 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 Institutional Review Board(s)/Independent Ethics Committee(s) [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.

A primary objective of this early Phase 1 study is to identify the maximum safe and well-tolerated dose and/or dosing regimen that achieve PK, pharmacodynamic, and/or biologic targets in humans based on preclinical or early clinical data. Therefore, it is possible that study participants may not receive all doses specified in the protocol if this objective is achieved at lesser dose levels in this study. This would not be defined as early termination of the study, but rather an earlier than anticipated achievement of the study objective(s). If a finding (eg, PK, pharmacodynamic, efficacy, biologic targets, etc.) from another preclinical or clinical study using the study intervention(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study results in the study(ies) or program being stopped for nonsafety reasons, this also does not meet the definition of early study termination.

Early study termination is defined as a permanent discontinuation of the study due to unanticipated concerns of safety to the study participants arising from clinical or preclinical studies with the study intervention(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study.

5 STUDY POPULATION

Male/Female participants with HIV-1 infection, who are naïve to ART between the ages of 18 and 60 years 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:

1. Other than having HIV infection, is in good health based on medical history, physical examination, vital sign (VS) measurements, and laboratory safety tests (Appendix 2), at the pre-study (screening) visit and/or prior to administration of the study drug.

2. Is documented as being HIV-1 positive, as determined by a positive ELISA or QT-PCR with confirmation (e.g., Western Blot).

3. Has a screening plasma HIV-1 RNA ≥ 2,500 copies/mL within 30 days prior to the treatment phase of this study.

4. Has a screening plasma CD4+ T-cell count of >200/mm^3.

5. Is ART-naïve, which is defined as having never received any antiretroviral agent [redacted]

8. [redacted]

Demographics

10. Is from 18 years to 60 years of age inclusive, at the time of signing the informed consent.

11. Has a Body Mass Index (BMI) ≤35 kg/m^2. BMI = weight (kg)/height (m) ^{2}.

12. May be either male or female, satisfying the sex-specific requirements specified below:

Male Participants

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

Male participants are eligible to participate if they agree to the following during the intervention period and for at least 35 days after the last dose of study medication, corresponding to the time needed to eliminate the study medication (i.e., 5 terminal half-lives):

a. To be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and to remain abstinent.

OR

b. To use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5: Contraceptive Guidance and Pregnancy Testing]) as detailed below:

- To use a male condom, and for the partner to use 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.

Female Participants

- A female participant is eligible to participate if she is not pregnant or breastfeeding AND one of the following conditions applies:

  - She is a woman of nonchildbearing potential (WONCBP), as defined in Appendix [5] OR

  - She is a woman of childbearing potential (WOCBP) and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or is abstinent from heterosexual intercourse as her preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix [5] during the intervention period and for at least 35 days after the last dose of study medication, [redacted] The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relation to the first dose of study intervention.

  - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum, as required by local regulations) within 24 hours before the first dose of study medication.

  - If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

  - -Additional requirements for pregnancy testing during and after study intervention are located in Appendix [2].

  - -The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

13. The participant provides written informed consent/assent for the study. The participant may also provide consent/assent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

5.2 Exclusion Criteria

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

Medical Conditions

1. Has acute (primary) HIV-1 infection.

2. Has a history of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic (with the exception of Gilbert's disease), immunological (outside of HIV-1 infection), renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases. Participants with a remote history of uncomplicated medical events (e.g., 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.

3. Is mentally or legally incapacitated at the time of pre-study (screening) visit or expected during the conduct of the study or has a history of a 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.

4. Has a history of cancer (malignancy).

   Exceptions: Participants with adequately treated disease deemed "cured," who, in the opinion of the trial investigator, are highly unlikely to sustain a recurrence for the duration of the trial may be enrolled at the discretion of the investigator.

5. Participant has an estimated creatinine clearance (CrCl) ≤ 90 mL/min based on the Cockcroft-Gault (CG) Equation.

Cockcroft-Gault Equation:

$$Cl_{Cr} = \frac{(140\text{-age[yr]})(\text{body wt [kg]})}{(72)(\text{serum creat [mg/dL]})}$$

[When creatinine is measured in micromole/litre, use this formula]

$$Cl_{Cr} = \frac{(140\text{-age[yr]})(\text{body wt[kg]})}{(72)(\text{serum creatinine [micromol/L]} \times 0.0113)}$$

For females, multiple the result by 0.85.

At the discretion of the investigator, a measured creatinine clearance, as determined by a 24-hour urine collection, may be used in place of, or in conjunction with, the estimate of the creatinine clearance.

Participants who have a measured creatinine clearance of up to 10% below 90 mL/min may be enrolled in the study at the discretion of the investigator.

6. Has a history of significant multiple and/or severe allergies (e.g., food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (i.e., systemic allergic reaction) to prescription or non-prescription drugs or food; or has hereditary galactose intolerance, lactase deficiency, or glucose-galactose malabsorption.

7. Is positive for hepatitis B surface antigen.

8. Has a history of chronic hepatitis C unless there has been documented cure and/or participant with a positive serologic test for Hepatitis C Virus (HCV) has a negative HCV VL.

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

Prior/Concomitant Therapy

10. 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 drug, throughout the study, until the post-study visit. There may be certain medications that are permitted (see Section 6.5).

Prior/Concurrent Clinical Study Experience

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

Diagnostic Assessments

12. Has a clinically significant abnormality on the ECG performed at the pre-study (screening) visit and/or prior to administration of the initial dose of study drug.

Other Exclusions

13. Is unwilling to comply with the study restrictions (see Section 5.3 for a complete summary of study restrictions).

14. Is under the age of legal consent or not capable of giving consent.

15. Has been committed to an institution by way of official or judicial order.

16. Is an excessive smoker (i.e., more than 10 cigarettes/day) and is unwilling to restrict smoking to ≤10 cigarettes per day.

17. Consumes more than 3 glasses of alcoholic beverages (1 glass 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 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator.

18. Consumes excessive amounts, defined as more 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.

19. Has a positive urine drug screen (except for cannabis) at screening and/or pre-dose; rechecks are allowed.

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

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

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 Section 8.

In each treatment panel (except for Panel D, described separately below), participants will fast from all food and drinks, except water, for at least 10 hours prior to study drug administration. Participants will fast from all food and drinks except water between study drug administration and the first scheduled meal. Meals and snack(s) will be provided by the investigator at time points indicated in the SoA. 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 panel. After the 24-hour post-dose procedures have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition and timing.

In Panel D, following an overnight fast of at least 10 hours, breakfast will be provided to participants approximately 30 minutes prior to study drug administration. Breakfast should be consumed in its entirety within approximately 20 minutes. The start and stop time of the breakfast will be recorded. Within approximately 10 minutes after consuming the breakfast, subjects will be administered trial drug as indicated in Section 8.1.8, and participants will fast from all food and drink, except water, for at least 4 hours following dosing. In Panel D, participants will consume a high-fat, moderate-fat, or low-fat breakfast (to be determined following the review of emerging safety and PK data from the ongoing studies, Protocols 001 and 002). The contents of the breakfasts are listed in Table 8, Table 9, and Table 9.

Table 7 Contents of the Standard, High-Fat Breakfast

2 fried or scrambled eggs
2 strips bacon
2 slices toast with 2 pats of butter
4 oz (113 g) hash browns (fried potato)
240 mL whole milk

The nutritional content of the high-fat breakfast is as follows:

Total fat = 55.6 g
Total carbohydrates = 55 g
Total protein = 31.1 g
Total calories = 500.4 in fat, 220 in carbohydrates, and 124.4 in protein.

Table 8 Contents of the Standard, Moderate-Fat Breakfast

Brown bread (70 g)
Butter (15 g)
Cheese (40 g)
Jam (15 g)
240 mL Whole milk

The nutritional content of the moderate-fat breakfast is as follows:

Total fat = 34 g (31% of calories)
Total carbohydrates = 53 g (48% of calories)
Total protein = 22 g (20% of calories)
Total calories = 619 Kcalories

Table 9 Contents of the Standard, Low-Fat Breakfast

2 small bread rolls (60 g)
Light cream cheese (65 g)
Fat free milk (160 mL)

The nutritional content of the low-fat breakfast is as follows:

Total fat = 9 g (8% of calories)
Total carbohydrates = 43 g (37% of calories)
Total protein = 15 g (13% of calories)
Total calories = 312 Kcalories

The exact meal contents may be substituted with agreement between Sponsor and Investigator and must be documented in an administrative letter. The specific nutritional content of the breakfast may be modified during the study based on newly available data.

Instructions on whether to take MK-8558 with or without food and/or drink may be modified during the study based on newly available data.

5.3.1.2 Fruit Juice Restrictions

Participants will refrain from the consumption of grapefruit juice, grapefruits, and grapefruit products beginning approximately 2 weeks prior to administration of the initial dose of study drug, throughout the study, and until the post-study visit.

Participants also will refrain from the consumption of all fruit juices 24 hours prior to and after study drug administration. On all other days during the study, consumption of fruits and fruit juices (except for grapefruit, grapefruit juices, and grapefruit products) is allowed.

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 prior to the pre-study and post-study visits and from 12 hours prior to and after study drug administration. At all other times, caffeinated beverages or xanthine-containing products will be limited to no more than 6 units per day amounts (1 unit = 120 mg of caffeine).

5.3.2.2 Alcohol Restrictions

Participants will refrain from consumption of alcohol 24 hours prior to the pre-study and post-study visits and from 24 hours prior to and after study drug administration. At all other times, alcohol consumption is limited to no more than approximately 3 alcoholic beverages or equivalent (1 glass 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

Smoking (and/or the use of nicotine/nicotine-containing products) should be restricted to ≤10 cigarettes per day and participants will be required to follow the smoking restrictions defined by the CRU while on site.

5.3.3 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (e.g., weight lifting, running, bicycling, heavy gardening, moving heavy objects, etc.) from the pre-study (screening) visit until administration of the initial dose of study drug, throughout the study, and until the post-study visit. Participants will be asked to rest semi-recumbent for 4 hours

post-dose, except to stand for the measurement of orthostatic vital signs (if needed) or any other trial related procedure.

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 electronic case report forms (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 study site should contact the Sponsor for the replacement participant's treatment/randomization number.

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 interventions (MK-8558) 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 prior to dosing the replacement supplies. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 10.

Table 10 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin-istration	Regimen/Treatment Period	Use	IMP/ NIMP	Sourcing
Panel A	Experimental	MK-8558	Drug	Tablet	10 mg 100 mg	400 mg	Oral	Single Dose	Experimental	IMP	Provided centrally by the Sponsor
Panel B	Experimental	MK-8558	Drug	Tablet	10 mg 100 mg	≤900 mg	Oral	Single Dose	Experimental	IMP	Provided centrally by the Sponsor
Panel C	Experimental	MK-8558	Drug	Tablet	10 mg 100 mg	≤1600 mg	Oral	Single Dose	Experimental	IMP	Provided centrally by the Sponsor
Panel D	Experimental	MK-8558	Drug	Tablet	10 mg 100 mg	≤1600 mg	Oral	Single Dose	Experimental	IMP	Provided centrally by the Sponsor
Definition Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.											

All supplies indicated in Table10 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (e.g., 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

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided 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 assigned to panel and treatment according to an allocation schedule. A sample allocation schedule is shown in Table 11.

Table 11 Sample Allocation Schedule

Panel	N	Dose of MK-8558[a]			
A	6	400 mg			
B[b]	6		≤900 mg		
C[b]	6			≤1600 mg	
D[b]	6				≤1600 mg with food

a. Doses may be adjusted downward following review of safety and viral load data from preceding panels.
b. The doses to be administered in Panels B, C and D will be based on the results of safety and viral load data out to at least Day 8 in Panels A, B and C, respectively.

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.

6.5 Concomitant Therapy

If a participant does not discontinue all prior medications within 14 days or 5 half-lives of the first dose of study intervention, he/she 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 (i.e., after randomization or intervention allocation) must first be discussed between the investigator and Sponsor prior to 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 (maximum 4 grams in 24 hours) or ibuprofen (maximum 600 mg in 24 hours) may be used for minor ailments without prior consultation with the Sponsor.

6.5.1 Rescue Medications and Supportive Care

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

6.6 Dose Modification (Escalation/Titration/Other)

Prior to proceeding to the next panel, the following data from at least 4 evaluable subjects from the previous dosing panel will be reviewed:

- key safety data including vital signs, 12-lead ECGs, laboratory safety tests, and AEs from the previous dose levels up to at least 168 hours post dose
- viral dynamic data (out to 168 hours post-dose)

Before proceeding to Panel B, PK data from Panel A (a minimum of 4 evaluable subjects) will be reviewed to compare PK from HIV-infected participants with PK observed in healthy participants in Protocol 001, to ensure that doses selected for Panel B are appropriate from both efficacy and safety standpoints.

In addition, safety, tolerability, and PK data from doses up to 1600 mg (including a food-effect assessment) from the ongoing Protocol 001 have been reviewed and support the proposed dosing for Protocol 002.

Based on the review of data (specified above), modifications to planned dosing may be implemented, including:

- administration to a subsequent panel the same dose level to further evaluate that particular level;
- administration of a lower dose of the study treatment;
- administration of the same or lower dose as a divided dose; or
- administration of the same or a lower dose with or without food.

Or, dosing may be stopped. Participant discontinuation criteria are outlined in Section 7.

6.6.1 Stopping Rules

Enrollment of the trial will be halted in the following circumstances:

1. One participant (cumulatively) reports a serious AE with a potential causal relationship to the study drug or two (2) participants per panel report severe AEs with a potential causal relationship to study drug.

2. Three (3) or more of the enrolled participants (cumulatively) experience the same AE requiring withdrawal from the study, or the same severe AE assessed as having a potential causal relationship to study drug.

3. Two (2) participants (cumulatively) experience severe but not life threatening AEs or severe clinically significant laboratory abnormalities that are similar in nature.

4. One (1) serious AE/laboratory abnormality (cumulatively) is reported that is life threatening, results in persistent or significant disability/incapacity, results in or prolongs an existing inpatient hospitalization, or is another important medical event OR participant death thought to be potentially related to the investigational product.

5. Two (2) or more of the enrolled participants experience confirmed QTcF > 500 ms or QTcF change from baseline > 60 ms in a given panel with a potential causal relationship to study

If one of the above circumstances occurs, enrollment and dosing will be halted, and an internal safety review will be conducted prior to making a decision about terminating the study. The safety of participants will be assessed on an ongoing basis, and while conditions that could warrant early trial termination are not limited to those noted above, these criteria are meant to pre-specify circumstances under which the trial may be terminated early. In the event that the trial is interrupted or safety data suggest that the benefit-to-risk assessment has been meaningfully altered and must be reassessed, the Regulatory Authority will be notified.

6.7 Intervention After the End of the Study

There is no study-specified intervention following 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.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment regimen will still continue to participate in the study as specified in Section 1.3 and Section or if available, a protocol clarification letter.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Sections 8.1.9 and 8.10.3.

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

1. The participant requests to discontinue study intervention.

    - The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued participation in the study.

    - The participant has a positive urine drug screen (excluding cannabis) confirmed upon recheck at any time during the course of the study.

For participants who are discontinued from study intervention all applicable discontinuation activities will be performed according to Section 8.1.9, or if available, a protocol clarification letter.

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

7.2 Participant Withdrawal From the Study

Participants may withdraw from the study at any time for any reason. If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

A participant must be withdrawn from the study if:

- The participant withdraws consent from the study.
- The participant is lost to follow-up.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, 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 (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).

- 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 utilized 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 380.5 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 consent from each potential participant prior to participating in a clinical study or future biomedical research.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 consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant must receive the Institutional Review Board/Independent Ethics Committee's (IRB/IEC's) approval/favorable opinion in advance of use. The participant 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 dated signature.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

The 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 future biomedical research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the future biomedical research substudy. A copy of the informed consent will be given to the participant.

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 written informed consent. At the time of intervention allocation/randomization, 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, including details of substance usage, 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 28 days before the first dose of study medication.

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 prior to intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used 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 re-assigned to another participant.

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

8.1.8 Study Intervention Administration

Administration of study medication will be witnessed by the investigator and/or study staff.

Approximately 240 mL of water will be provided during trial drug administration. Additional water (in increments of 50 mL) may be provided for participants receiving a dose of MK-8558 requiring more than 2 tablets.

Water will be restricted 1 hour prior to and 1 hour after study drug administration. Details on water and dietary restrictions are outlined in Section 5.3.1.

8.1.8.1 Timing of Dose Administration

All doses of MK-8558 will be given in the morning at approximately the same time in each treatment panel.

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 post-study 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 post-study procedures at the time of discontinuation or as soon as possible after discontinuation. If the post-study 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 if any AEs have occurred since the post-study 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 future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main 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 future biomedical research 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 prior to 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.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main 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.

8.1.11 Domiciling

Participants will report to the CRU the evening prior to the scheduled day of study intervention administration and remain in the unit until 24 hours post-dose. 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 pre-study to post-study visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Appendix 8: Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Type.

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) as per institutional standard. Investigators should pay special attention to clinical signs related to previous serious illnesses. The pre-dose physical examination may be performed within 24 hours prior to dosing.

Body Mass Index (BMI)

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

Height and weight will be measured and recorded with the participant’s shoes off and jacket or coat removed.

8.3.2 Vital Signs

Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

Participants should be resting in a semi-recumbent for at least 10 minutes prior to having vital sign (VS) measurements obtained. Semi-recumbent VS will include heart rate (HR) and blood pressure (BP). The correct size of the BP cuff and the correct positioning on the participants' arm is essential to increase the accuracy of BP measurements. Measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

The pre-dose Day 1 HR and BP will be in triplicate measurements, obtained at least 1-2 minutes apart within 3 hours prior to dosing MK-8558. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Post-dose VS measurements will be single measurements.

Participants may stand for the measurement of orthostatic VS (if needed) during the 4 hour interval after dosing.

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.

Respiratory Rate

Respiratory rate will be counted per site’s SOP.

8.3.2.1 Orthostatic Vital Signs

Orthostatic VS (HR and BP) will also be obtained. Participants should be semi-recumbent for at least 10 minutes and then stand upright for 2 minutes prior to measurement of orthostatic VS.

8.3.3 Electrocardiograms

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

- Participants should be resting in the semi-recumbent position for at least 10 minutes prior to each electrocardiogram (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.

- Pre-dose ECGs will be obtained in triplicate at least 1-2 minutes apart within 3 hours prior to dosing MK-8558. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Post-dose ECG measurements will be single measurements.

- During each treatment period, if a participant demonstrates an increase in QTcF interval ≥60 msec compared with mean pre-dose baseline measurement, the ECG will be repeated twice within 5 minutes. The mean value of the QTcF interval from the 3 ECGs will represent the value at that time point. If the mean QTcF interval increase from baseline for any post-dose 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 QTcF is within 60 msec of baseline. If prolongation of the QTcF interval ≥60 msec persists, a consultation with a study cardiologist may be appropriate and the Sponsor should be notified.

- If the QTcF interval is 500 msec (confirmed upon recheck and manual measurement), the Sponsor should be notified and the ECGs should be reviewed by a cardiologist. The participant should be telemetry-monitored (until the QTcF is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (e.g., a cardiac or intensive care unit) 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 QTcF is noted, concomitant medications that prolong QTcF should be held until the QTcF is within 60 msec of baseline and the QTcF is <500 msec.

- A study cardiologist will be consulted by the investigator as needed to review ECG tracings with 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 case report form (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 35 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.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), 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, or surrogate).

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 consent form is signed but before intervention allocation/randomization, must be reported by the investigator for randomized participants only if the event is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

From the time of intervention allocation/randomization through 35 days following 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 of the time 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 12.

Table 12 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Time Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
Nonserious Adverse Event (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
Serious Adverse Event (SAE) including Cancer and Overdose	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: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (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

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, events of clinical interest (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: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

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 wth 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 suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as

serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

This section is not applicable to this study.

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

- An overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.

- An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that must trigger 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

In the event that a participant has taken (accidentally or intentionally) any drug administered as part of the protocol that exceeds the dose as 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.

There is no specific guidance available regarding overdose with MK-8558, due to the lack of clinical experience with overdosing. In case of acute over-dosage, standard supportive care should be provided as clinically appropriate. The Sponsor clinical director should be contacted immediately.

8.6 Pharmacokinetics

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

8.6.1 Blood Collection for Plasma MK-8558

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

8.7 Pharmacodynamics

Sample collection, storage, and shipment instructions for pharmacodynamic samples (for HIV RNA measurement and viral resistance testing) will be provided in the Study 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 future biomedical research if the participant signs the future biomedical research consent. If the planned genetic analysis is not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

Sample collection, storage, and shipment instruction for planned genetic analysis samples will be provided in the Study Operations Manual.

8.9 Future Biomedical Research Sample Collection

If the participant signs the future biomedical research consent, the following specimens will be obtained as part of future biomedical research:

- Leftover DNA for future research
- Leftover main study plasma from MK-8558 assay stored 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 prior to 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

Refer to the SoA (Section 1.3) and Administrative and General Procedures (Section 8.1).

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 of the 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 Post-study

Participants will be required to return to clinic approximately 35 days after the last dose of study intervention for the post-study visit. If the post-study visit occurs less than 35 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 35 days post the last dose of study intervention to determine if any AEs have occurred since the post-study clinic visit.

8.10.5 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the blood samples for plasma MK-8558 and HIV-1 viral RNA are the critical procedures.

At any post-dose time point, the blood sample for MK-8558 and the blood sample for viral RNA need 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 prior 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 13.

Table 13 Blood Collection Windows for Plasma PK and HIV RNA

PK/PD Collection	PK/PD Collection Window
0 – <1.0 hr	5 min
1 - <24 hrs	15 min
24 - <48 hrs	2 hrs
48 - <96 hrs	4 hrs
96 – <168 hrs	8 hrs
≥168 hrs	24 hrs

- Pre-dose standard safety evaluations: vital signs and ECG at 3 hours; laboratory safety tests and physical exam at 24 hours
- Post-dose standard safety evaluations: vital signs, ECG, laboratory safety tests, and physical exam
    - <24 hours post-dose may be obtained within 30 minutes of the theoretical sampling time
    - 24 - <48 hours post-dose may be obtained within 2 hours of the theoretical sampling time

- 48 – <96 hours post-dose may be obtained within 4 hours of the theoretical sampling time
- 96 – <168 hours post-dose may be obtained within 8 hours of the theoretical sampling time
- ≥168 hours post-dose may be obtained within 24 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-8558 in humans, and the PK, pharmacodynamic, and safety profiles of the compound is 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.

- Repeat of or decrease in the dose of the study intervention administered in any given period/panel
- Entire period(s) or panel(s) may be omitted
- Adjustment of the dosing interval (e.g., divided doses [QD to BID, TID])
- 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 fed cohort to another panel. In the event that this modification is implemented, the planned dosing and feeding regimen with supporting data will be communicated in an official memo.
- Modification of the PK/pharmacodynamic sample processing and shipping details based on newly available data or for operational reasons

The PK/pharmacodynamic sampling scheme currently outlined in the protocol may be modified during the study based on newly available PK or pharmacodynamic data (e.g., 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 (Section 8).

The timing of procedures for assessment of safety procedures (e.g., 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 employ 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

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 9.2).

Statistical Methods

Primary Objective (Safety):

Incidence of adverse experiences will be descriptively summarized. Summary statistics and plots will be generated for the change from baseline values in the vital signs, ECG parameters, and selected laboratory safety parameters for participants, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline). Summary statistics for the raw laboratory safety tests, ECGs, and/or vital signs may also be computed, as deemed clinically appropriate.

Primary Objective (Pharmacodynamics):

CCI

[redacted]

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 Pharmacology 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 Clinical Study Report.

9.3 Hypotheses/Estimation

CCI

[redacted]

9.4 Analysis Endpoints

Primary Endpoints:

Safety: Primary safety endpoints will include AEs, in addition to laboratory safety tests, ECGs, and VS.

Pharmacodynamics (PD):

The primary PD variables in this study include plasma HIV-1 RNA pre-dose and at the time points listed in the Study Flow Chart up until the time at which ART is initiated.

Secondary Endpoints (PK):

The secondary endpoints in this study include: MK-8558 plasma AUC0-last, AUC0-inf, AUC0-168hr, Tmax, Cmax, C168hr, CL/F, Vz/F, and terminal t1/2.

9.5 Analysis Populations

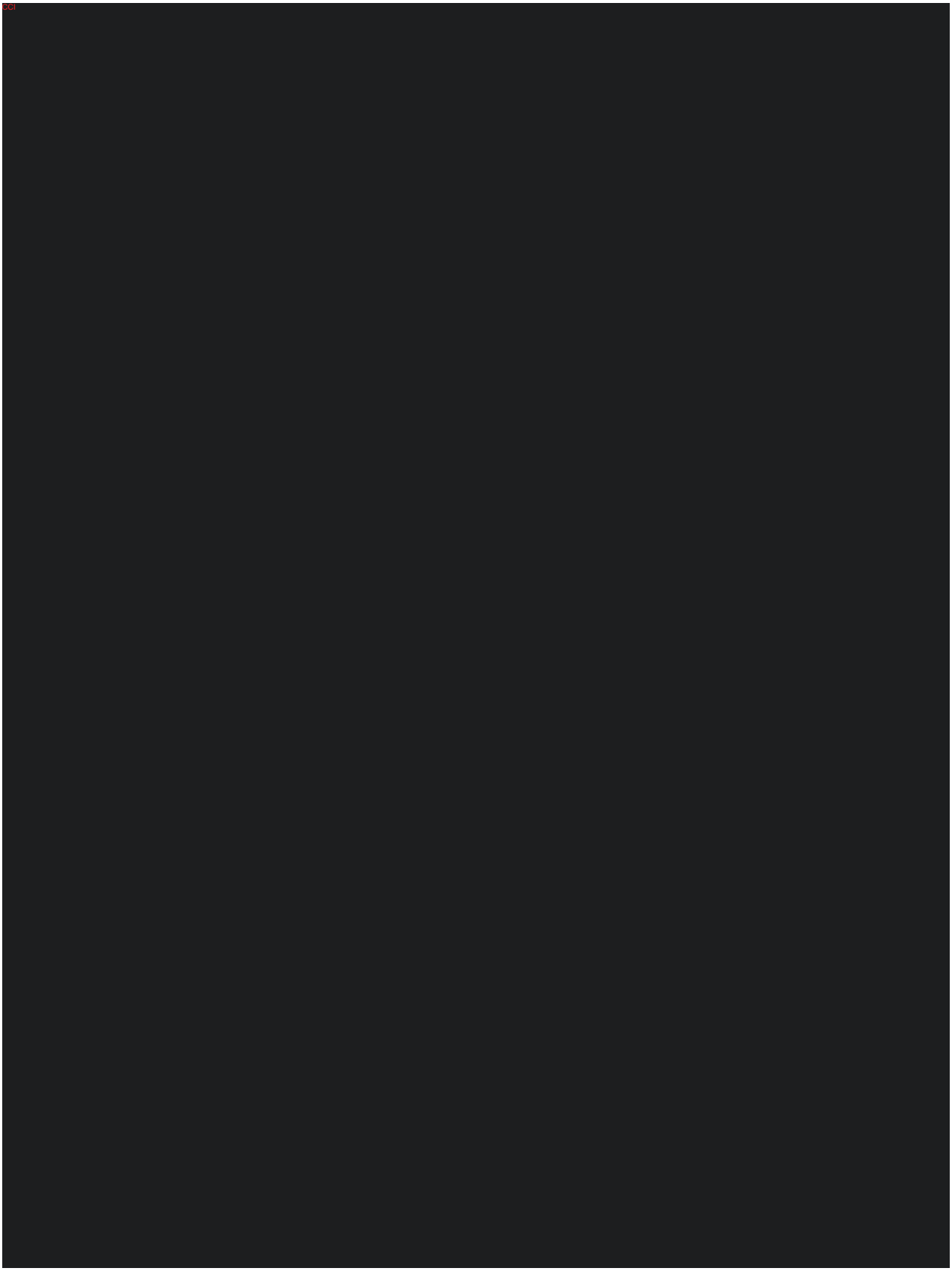
All Participants as Treated (APaT): The All Participants as Treated Population consists of all participants who received at least one dose of treatment. This population will be used for assessments of safety and tolerability.

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 major protocol deviations. Major protocol deviations will be identified to the extent possible 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 their 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 from at least one treatment will be included in the Per-Protocol dataset. This population will be used for the PK and PD analyses.

9.6 Statistical Methods

Primary (Safety):

Incidence of AEs will be descriptively summarized. Summary statistics and plots will be generated for the change from baseline values in the VS, ECG parameters, and selected laboratory safety parameters for participants, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline). Summary statistics for the raw laboratory safety tests, ECGs, and/or vital signs may also be computed, as deemed clinically appropriate.



[redacted]

Descriptive Statistics:

Individual values will be listed for each PK parameter by treatment, and the following (non-model-based) descriptive statistics will be provided: N (number of participants with non-missing data), arithmetic mean, standard deviation (SD), arithmetic percent coefficient of variation (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).

Exploratory (Pharmacokinetic/Pharmacodynamic):

[redacted]

General

For all analyses, data will be examined for departures from the assumptions of the statistical model(s) as appropriate; e.g., heteroscedasticity, nonnormality of the error terms. Distribution-free methods may be used if a serious departure from the assumptions of the models(s) is observed, or suitable data transformations may be applied.

9.7 Interim Analyses

During the in-life portion of the trial, descriptive summary level results (PK, PD/biomarkers and/or safety (labs, vital signs, ECGs)) will be prepared as needed to support decision-making meetings such as dose escalation meetings. The aggregate summaries and individual participant data will be presented for each dose level as appropriate. There are no planned interim analyses to test any formal hypotheses.

9.8 Multiplicity

No multiplicity adjustment is required here since Bayesian method is used.

9.9 Sample Size and Power Calculations

CCI

[redacted]

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 and Dohme Corp., a subsidiary of Merck & Co., Inc. (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 of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (eg, 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 (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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 to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of 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 fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues

are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified 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. Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

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. Unless required by law, only the investigator, Sponsor (or representative), 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 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 (eg, 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, commonly 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

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 prior to 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 International Committee of Medical Journal Editors authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (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 trial 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, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use 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 Studies.

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 signed ICF, 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 will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 14 will be performed by the local laboratory.
- If the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- 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.
- **Pregnancy testing (for WOCBP only):**
  - Pregnancy testing requirements for study inclusion are described in Section 5.1, and the defined time points for pregnancy testing are included in the SoA.
  - Pregnancy testing (urine or serum, as required by local regulations) should be performed at a minimum at the following time points:
    - At screening, to confirm absence of pregnancy
    - Within 24 hours prior to the first dose of study medication
    - At the Post-Study Visit, corresponding with the end of relevant systemic exposure and the time frame for female participant contraception in Section 5.1 (i.e., 35 days following the last dose of study medication).
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Table 14 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Hemoglobin RBC count Hematocrit	WBC count with Differential (absolute and %): Neutrophils Lymphocytes Monocytes Eosinophils Basophils	Prothrombin Time/ international normalized ratio (PT/INR) (screening only) CD4+ T-cell count (screening only)	
Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin Direct bilirubin (to be performed at screening; at later time points only to be performed if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine*	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose [fasting]	Calcium	Alkaline phosphatase	CRP (pre-dose only)
Routine Urinalysis	• Specific gravity • pH, glucose, protein, and red and white blood cells by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Tests	• Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) • [Serum or urine] β human chorionic gonadotropin (β hCG) pregnancy test (as needed for women of childbearing potential) • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) if applicable • Virology (HIV [redacted] hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)			
NOTES: Laboratory safety tests will be performed after at least an 8-hour fast. Pre-dose laboratory procedures can be conducted up to 24 hours prior to dosing. *Creatinine clearance (at screening) is to be calculated using the Cockcroft-Gault(CG) Equation				

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

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing 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 pre-existing condition that has not worsened is not an SAE. A pre-existing 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 in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

    - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).

    - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).

    - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

- **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

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

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

    - Yes, there is a reasonable possibility of Sponsor's product relationship:

        - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

    - No, there is not a reasonable possibility of Sponsor's product relationship:

        - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

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

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

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (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: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

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

Women 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.

10.5.2 Contraception Requirements

For male participants: refer to Section 5.1.

Requirements for WOCBP:

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• IUD (non-hormonal intra-uterine device) • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
1. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.5.3 Pregnancy Testing

For WOCBP only: pregnancy testing requirements are outlined in Appendix 2.

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 drugs/vaccines may interact with
- 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 the future biomedical research substudy

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 participant' 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 gender, 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 utilizing 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 this substudy. 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 future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main 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 main study use only. If specimens were collected from study participants specifically for future biomedical research, 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 prior to 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.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main 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 main 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 Conference on Harmonization [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: Approximate Blood Volumes Drawn by Trial Visit and by Sample Type

Panels A, B, C and D	Pre-study	Treatment Period	Post-study	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests[a]	1	3	1	5	13	65
Serum β-hCG[b]	1	1	1	3	5	15
PT/INR	1	0	0	1	3	3
Blood for Planned Genetic Analysis	0	1	0	1	8.5	8.5
Blood for MK-8558	0	19	0	19	4	76
Blood for HIV RNA, viral resistance[cd]	1	11	1	13	16	208
Proviral DNA[e]	0	1	0	1	5	5
Approx. Total Blood Volume per Participant for Panels A, B, C and D [f]						380.5 mL

a) Blood volume includes CD4 cell count, HIV/Hepatitis Screen, and FSH.

b) β-human chorionic gonadotrophin (β-hCG) to be performed in women of childbearing potential (WOCBP) only. Volumes provided for serum testing; serum or urine may be performed in accordance with by local regulations.

c) Blood volume includes ultra-deep sequencing which may be performed if needed.

d) For all panels blood for HIV-1 viral RNA and viral resistance may be collected up to the post-study visit if participants do not start ART. The number of collections denoted in this row reflects the maximum quantity required if a participant dose not initiate ART during the trial and the post-study period.

e) At the timepoint immediately prior to initiation of ART an additional blood sample collected for viral resistance testing may be taken for extraction of proviral DNA. This proviral DNA will be frozen and analyzed for the presence of viral resistance mutations only if standard Sanger sequencing cannot be performed because plasma viral load is too low at this timepoint. In addition, ultra-deep sequencing may be performed on this proviral DNA sample in the event that further information on viral resistance is required.

f) 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

Not applicable.

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

For all laboratory values obtained at pre-study (screening) visit and/or pre-dose 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 not clinically significant (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).

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

   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
β-hCG	β-Human Chorionic Gonadotropin
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	Alanine Aminotransferase
ART	Anti-retroviral therapy
AST	Aspartate Aminotransferase
AUC	area under the concentration-time curve
BID	Twice daily
BMI	Body Mass Index
BUN	Blood urea nitrogen
CAC	Clinical Adjudication Committee
CG	Cockcroft-Gault
CI	Confidence interval
Cmax	Maximum concentration in the blood
CrCl	Creatinine clearance
CRF	Case Report Form
CRP	C-reactive protein
CRU	clinical research unit
Ctrough	Trough plasma concentration
CV	Coefficient of variation
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EFD	Embryo-fetal development
EMA	European Medicines Agency
FDAAA	Food and Drug Administration Amendments Act
FIH	First-in-human
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good laboratory practice
HBsAg	hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICMJE	International Committee of Medical Journal Editors
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	international normalized ratio
[redacted]	[redacted]
IP	Inflection point
IRB	Institutional Review Board
IUD	intrauterine device
LDA	longitudinal data analysis

Abbreviation	Expanded Term
MSD	MERCK SHARP & DOHME
NCS	Not clinically significant
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NRTI	nucleoside reverse transcriptase inhibitor
P-gp	P-glycoprotein
PK	pharmacokinetic
PD	Pharmacodynamic
POC	proof-of-concept
PT	Prothrombin Time
QD	Once daily
QTc	Interval of heart beat
QTcF	QTc with Fridericia correction
RNA	ribonucleic acid
SAE	serious adverse event
SD	Standard deviation
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
t1/2	half-life
Tmax	Time to get to maximum concentration in blood
VL	Viral load
VS	Vital sign
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of non-childbearing potential

11 REFERENCES

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		04LBXQ
[European Medicines Agency 2016]	European Medicines Agency. Guideline on the clinical development of medicinal products for the treatment of HIV infection (EMEA/CPMP/EWP/633/02 Rev. 3). London: European Medicines Agency; 2016. 20 p.	04KB08
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[redacted]	[redacted]	04XXZN


PPD