Official Protocol Title:	A Single-Dose Clinical Trial to Study the Safety, Tolerability, Pharmacokinetics, and Anti-Retroviral Activity of MK-8527 Monotherapy in Anti-Retroviral Therapy (ART)-Naïve, HIV-1 Infected Participants
NCT number:	NCT03615183
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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-8527 Monotherapy in Anti-Retroviral Therapy (ART)-Naïve, HIV-1 Infected Participants

Protocol Number: 002-00

Compound Number: MK-8527

Sponsor Name:

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

Legal Registered Address:

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Regulatory Agency Identifying Number(s):

EudraCT	2018-001861-18

Approval Date: 07-JUN-2018

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:

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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-8527 Monotherapy in Anti-Retroviral Therapy (ART)-Naïve, HIV-1 Infected Participants

Short Title: MK-8527 Single Dose Trial in HIV-1 Infected Participants

Acronym:

Hypotheses, Objectives, and Endpoints:

Study Population: Treatment naïve HIV-1 infected participants

Primary Objectives	Primary Endpoints
- To evaluate the antiretroviral activity of MK-8527 in HIV-1 infected participants relative to placebo. Hypothesis: At a dose that is sufficiently safe and generally well tolerated, MK-8527 has superior antiretroviral activity compared to placebo, as measured by change from baseline in plasma HIV-1 RNA (log10 copies/mL) at 168 hours postdose. That is, the true mean difference in the plasma HIV -1 RNA reduction from baseline between MK-8527 and placebo is at least 1.0 log10 copies/mL.	- Plasma HIV-1 RNA (log10 copies/mL) reduction from baseline
- To evaluate the safety and tolerability of MK-8527 in HIV-1 infected participants.	- AEs, laboratory tests, vital signs (VS), ECGs

Secondary Objectives	Secondary Endpoints
- To evaluate the intracellular PK of MK-8527-TP in PBMC after administration of single oral doses to HIV-1 infected participants. Hypothesis: At a dose that is sufficiently safe and generally well tolerated, the true GM C168hr MK-8527-TP in PBMC is at least 0.2 pmol/106 cells	- MK-8527-TP AUC0-168, AUC0-last, AUC0-inf, Tmax, Cmax, C168hr, and apparent terminal t1/2 in PBMC.
- To evaluate plasma PK of MK-8527 after administration of single oral doses to HIV-1 infected participants.	- MK-8527 plasma AUC0-168, AUC0-last, AUC0-inf, Tmax, Cmax, C168hr, and apparent terminal t1/2.
- To evaluate the PK-PD association of plasma MK-8527 and intracellular MK-8527-TP with viral load reduction.	- PK (MK-8527-TP in PBMC, MK-8527 plasma)/PD (Plasma HIV-1 RNA) correlation
Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
- To evaluate the relationship between dose and antiretroviral activity of MK-8527.	- Dose-response (Plasma HIV-1 RNA) relationship
- To evaluate the potential for long term exposure of PBMC MK-8527-TP at potentially efficacious levels	- PBMC MK-8527-TP C336H, C672H
- To explore the relationship between genetic variation and response to the treatment 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
Study Type	Interventional
Intervention Model	Sequential This is a single-site study.
Type of Control	Historical control
Study Blinding	Unblinded Open-label
Masking	No Masking
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 11 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 30 participants will be allocated.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin.	Regimen/ Treatment Period	Use
Panel A	MK-8527	10 mg	Once	Oral	Single Dose	Experimental
Panel B	MK-8527	25 mg	Once	Oral	Single Dose	Experimental
Panel C	MK-8527	≤50 mg	Once	Oral	Single Dose	Experimental
Panel D	MK-8527	≤50 mg	Once	Oral	Single Dose	Experimental
Panel E	MK-8527	≤50 mg	Once	Oral	Single Dose	Experimental

Abbreviations:

Total Number	30 participants (5 panels of 6 participants each).
Duration of Participation	Each participant will participate in the study for approximately 8 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 assigned intervention. After drug administration, each participant will be followed for 28 days.

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 10.

1.2 Schema

The study design is depicted in Table 1.

Table 1 Dose Escalation Scheme for MK-8527

Panel[a]	Dose of MK-8527[b]				
A	10 mg				
B		25 mg			
C[c]			≤50 mg		
D[c]				≤50 mg	
E[c]					≤50 mg

[a] In each panel, 6 participants will receive a single dose of MK-8527.

[b] The decision to proceed to the next panel will be made following review of safety and viral load data out to at least Day 8 (i.e., 7 days post-dose) from the preceding panel.

[c] A decision to enroll Panel C and the dose to be administered will be based on the results of safety, PK and viral load data out to at least Day 8 in Panels A and B. Enrollment of Panels D and E and the doses to be administered will be based on the results of safety, PK, and viral load data from all prior panels.

1.3 Schedule of Activities (SoA)

All Panels[a]																										
	Pre-trial	Treatment																							Post-study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1	Pre-dose	0	0.25	0.5	1	2	3	4	6	8	12	24	48	72	96	120	144	168	192	240	336	504	672 [l]	Post-study[k]	
Administrative Procedures																										
Informed Consent	X																									
Informed Consent for Future Biomedical Research	X																									
Inclusion/Exclusion Criteria	X	X																								Recheck clinical status before 1st dose of study intervention
Participant Identification Card	X																									
Medical History (includes substance usage)	X																									Substances: Drugs, alcohol, tobacco, and caffeine
Prior/Concomitant Medication Review	X----------																								X	
Intervention Allocation		X																								
Clinic Procedures and Assessments																										
MK-8527 Administration			X																							
Standard Meals[c]									X----------				X													
Safety Procedures																										
Full physical examination	X	X											X						X						X	
Height	X																									
Weight	X																								X	
Vital Signs (heart rate, blood pressure)	X	X[m]				X							X						X						X	
Vital Signs (respiratory rate, body temperature)	X	X				X							X						X						X	

All Panels[a]																										
	Pre-trial	Treatment																							Post-study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1	Pre-dose	0	0.25	0.5	1	2	3	4	6	8	12	24	48	72	96	120	144	168	192	240	336	504	672[l]	Post-study[k]	
Orthostatic Vital Signs (heart rate, blood pressure)	X	X				X							X						X						X	
12-lead ECG	X	X[m]				X							X						X						X	
Urine/Serum β-Human Chorionic Gonadotropin (β-hCG; WOCBP only)[e]	X	X[d]																								
Serum Follicle Stimulating Hormone (FSH) - (WONCBP only)[f]	X																									
HIV, hepatitis B and C screen (per site SOP)	X																									
Urine Drug Screen (per site SOP)[g]	X	X																								
Hematology, Urinalysis, Chemistry	X	X[d]											X						X						X	
AE/SAE review	X----------																								----------X	
Pharmacokinetics																										
Blood for Plasma MK-8527 Assay[h]		X			X	X	X	X	X	X	X	X	X	X	X	X			X							
Blood for MK-8527 PBMC Assay[i]		X							X			X	X			X	X	X	X		X	X	X	X	X	
Pharmacodynamics																										
Blood for HIV RNA, viral resistance[j]	X	X							X			X	X			X	X	X	X	X	X	X	X	X	X	
CD-4 cell count	X																									
Biomarkers																										
Blood (DNA) for Genetic Analysis[b]		X																								Collected from randomized participants only – See Section 8.8 and 8.9.

All Panels[a]																											
	Pre-trial	Treatment																								Post-study	Notes
Scheduled Hour, Day, Week, etc.	Screening 1	Pre-dose	0	0.25	0.5	1	2	3	4	6	8	12	24	48	72	96	120	144	168	192	240	336	504	672[l]	Post-study[k]	

a. Panels will be conducted sequentially with review of data from prior panel before proceeding. Panel B and C will occur after completion and review of safety, pharmacokinetic, and viral dynamic data from Panels A and B, respectively. Panel D and E will occur after completion and review of safety, pharmacokinetic, and viral dynamic data from prior panels.
b. 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 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 (FBR) if the participant signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.
c. Standardized meals will be provided at ~4 and ~10 hours post-dose. A snack will be offered at ~ 7 and 13 hours post-dose. After the 24 hour postdose procedures have been completed, subsequent meal and snacks will be unrestricted in terms of caloric content, composition and timing.
d. Can be conducted on admission (within 24 hours before dosing).
e. For female participants of childbearing potential only. Urine pregnancy test can be performed at predose.
f. For postmenopausal women only.
g. Screening UDS is mandatory; any additional UDS are conducted per site SOP.
h. Leftover plasma samples will be stored for future biomedical research at the end of the study, if the participant signs the Future Biomedical Research consent.
i. For all panels, PBMC samples may be collected up to the post-trial visit regardless of initiation of ART.
j. For all panels, blood for HIV-1 viral RNA and viral resistance may be collected up to the post-trial visit if a participant does not start ART.
k. The post-trial visit will occur approximately 28 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-trial visit occurs prior to 28 days following the last dose of study drug. For confirmation of viral load return to baseline, additional data from viral load samples collected during routine follow-up visits may be transmitted to the sponsor for those participants who do not begin ART and who provide appropriate informed consent.
l. The 672 hour sample may be collected at the post-trial visit.
m. Predose ECGs and VS (heart rate and blood pressure) will be obtained in triplicate approximately 1-2 minutes apart within 3 hours prior to dosing MK-8527.

2 INTRODUCTION

2.1 Study Rationale

The purpose of this study is to assess the activity of single doses of MK-8527 in antiretroviral therapy (ART)-naïve human immunodeficiency type 1 virus (HIV-1) infected participants. This study will assess the short term antiretroviral activity of MK-8527 monotherapy, and data from this study will aid dose selection in future studies.

2.2 Background

Refer to the Investigator's Brochure (IB) for detailed background information on MK-8527.

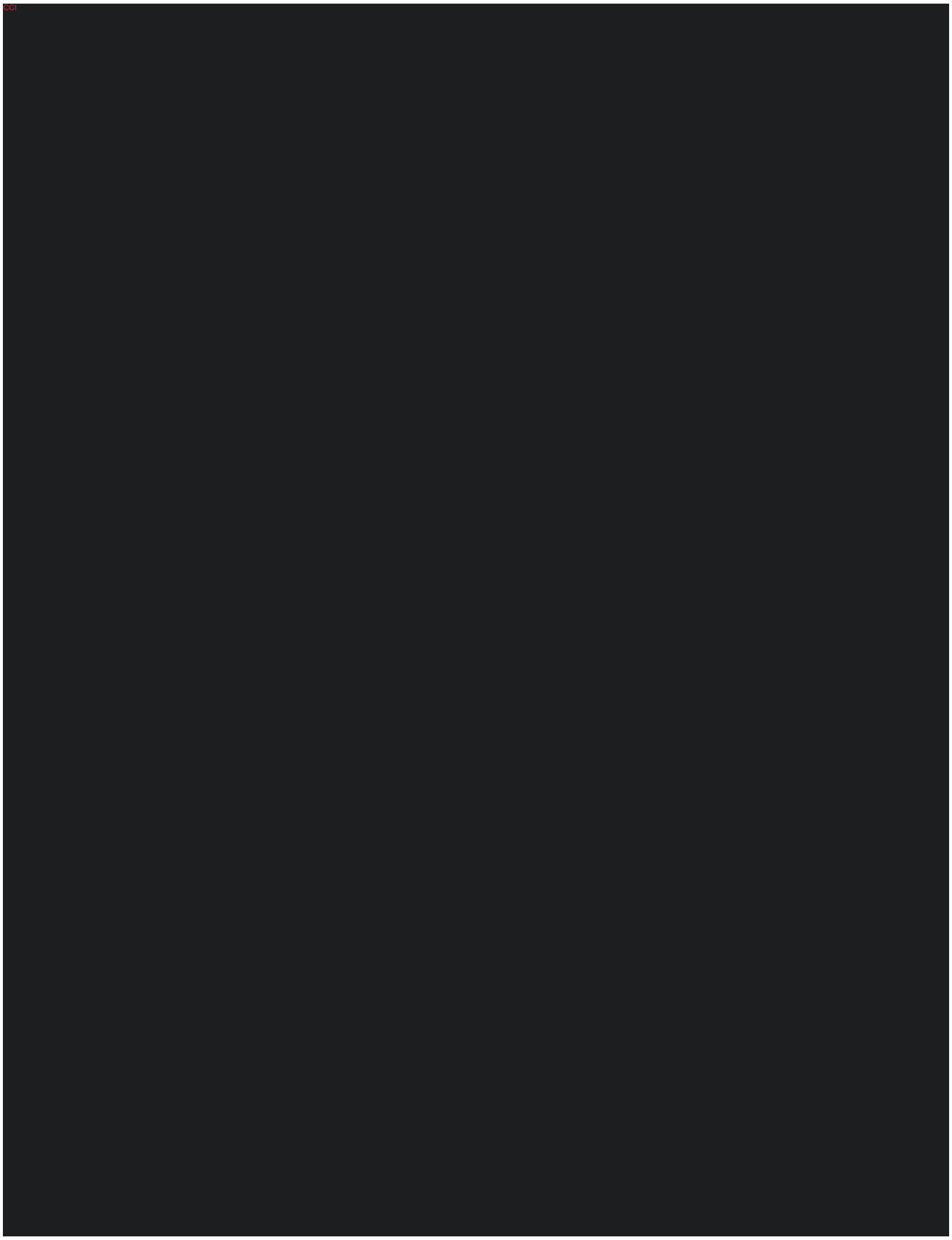
2.2.1 Pharmaceutical and Therapeutic Background

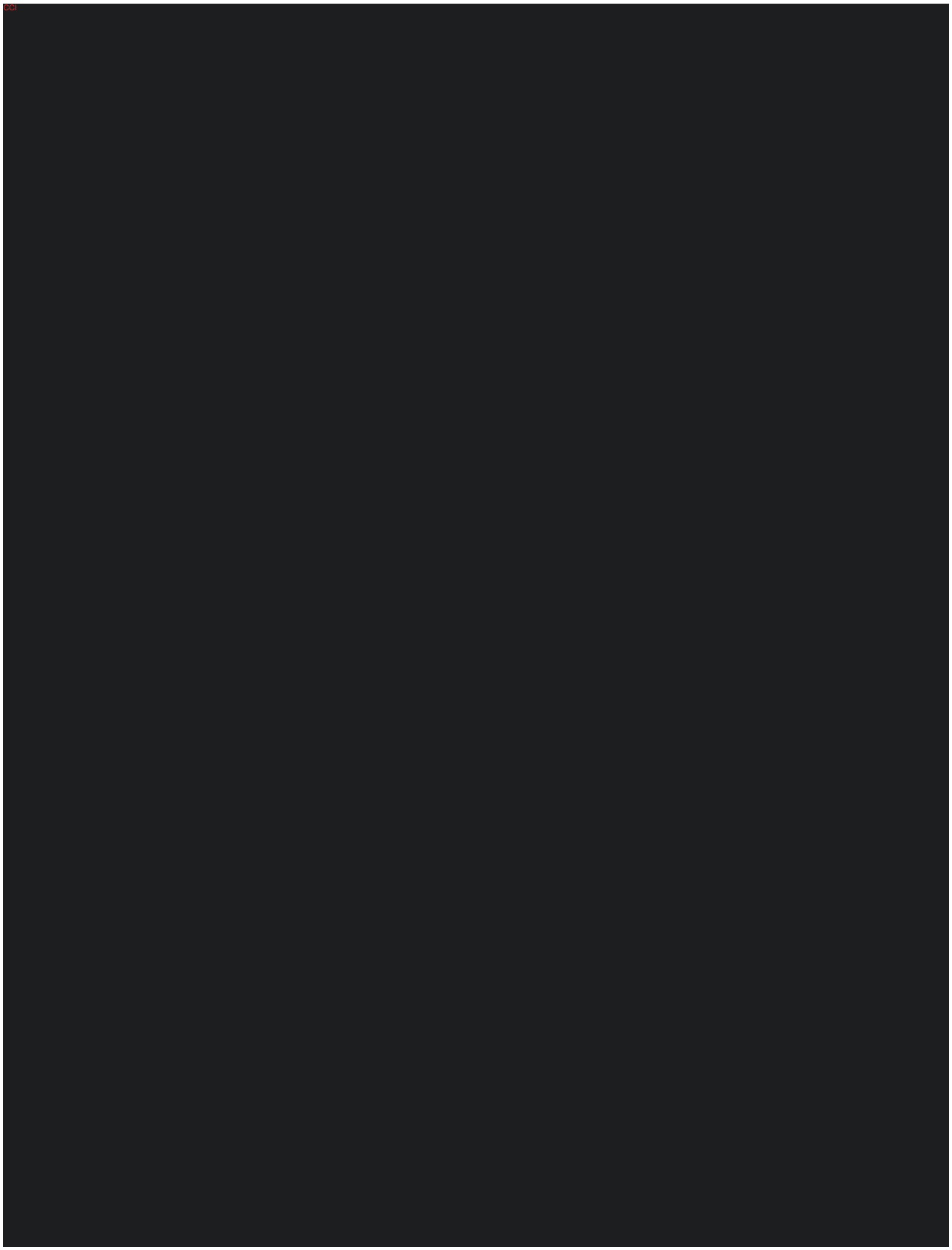
As treatment for Human Immunodeficiency Virus type 1 (HIV-1) has improved, HIV-1 infection has become less of an acute disease with almost fatal outcome to a chronic, manageable disease. There is now clear medical need for new treatment regimens and dosing strategies that are both highly effective and with improved tolerability than previous treatments. In particular, increased tolerability and convenience of administration have become areas where significant improvements can be made to increase adherence and improve long term treatment outcomes. A highly potent nucleoside reverse transcriptase inhibitor (NRTI) with improved tolerability and ease of administration would be a valuable addition to the HIV-1 treatment armamentarium.

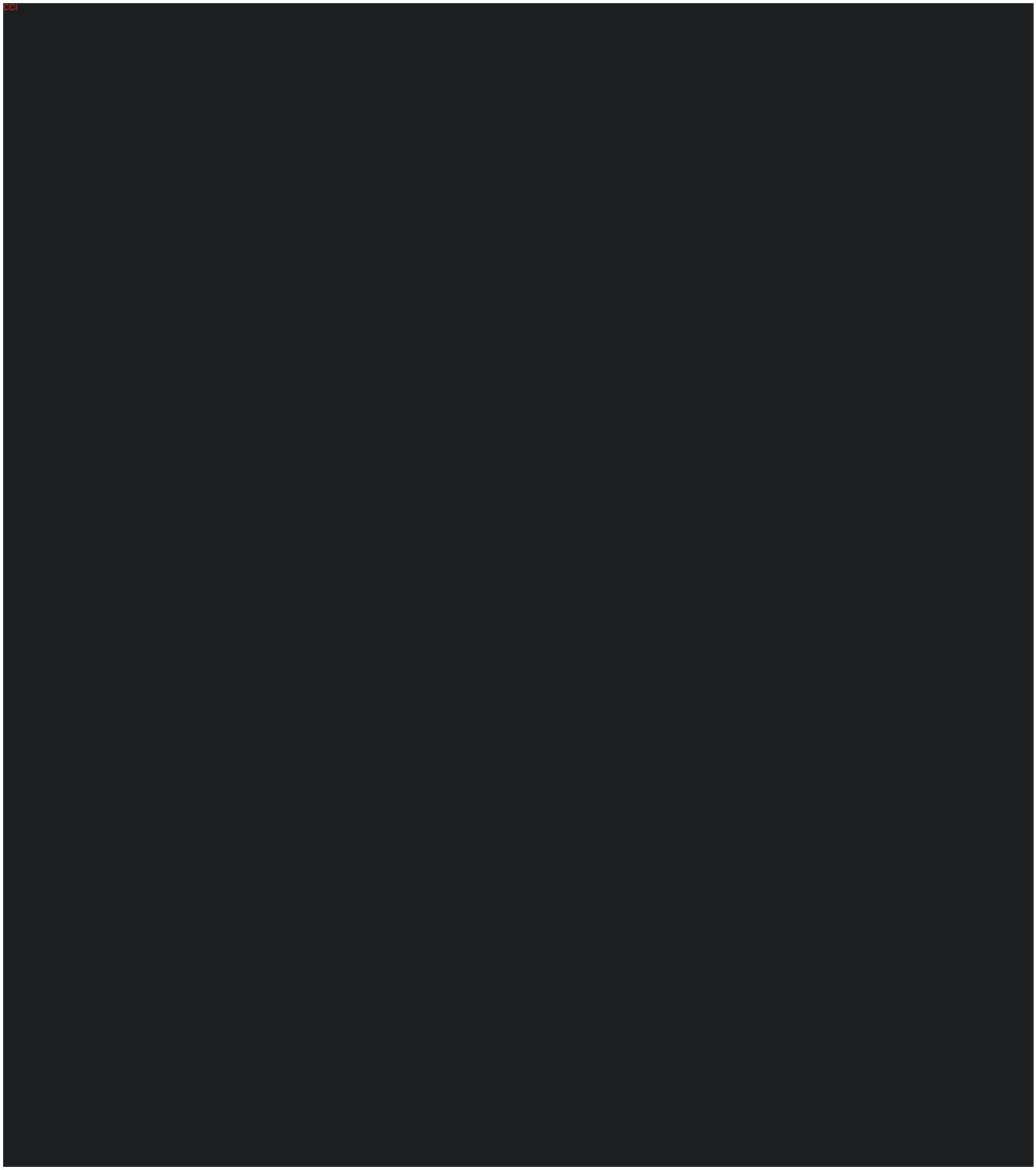
Current recommendations for treatment of HIV infection call for 3 agents, consisting of 2 nucleoside reverse transcriptase inhibitors (NRTIs) in combination with either an integrase strand transfer inhibitor, a protease inhibitor, or a non-nucleoside reverse transcriptase inhibitor. Currently marketed NRTIs include tenofovir disproxil fumarate, lamivudine, emtricitabine, abacavir, didanosine, stavudine, and zidovudine. While the currently approved NRTIs represent a cornerstone of modern ART, there are significant class-associated toxicities, including loss of bone mineral density, new or worsening renal impairment, severe lactic acidosis, and serious hypersensitivity reactions.

MK-8527 is a potent HIV-1 nucleoside reverse transcriptase translocation inhibitor (NRTTI) with a novel mechanism of action that distinguishes it from similar NRTIs. [redacted] Given that tolerability issues are one of the most common reasons for lack of adherence and subsequent treatment failure, a need exists for new NRTIs like MK-8527 that possess an improved safety and tolerability profile.

The parent drug MK-8527 is converted intracellularly to MK-8527 triphosphate (TP), the active moiety, which is a potent and specific inhibitor of HIV-1 RT activity in vitro with an IC50 of 0.21 nM, significantly more potent than marketed nucleosides. [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 obtain 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 ICF documents.

3 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

Study Population: Treatment naïve HIV-1 infected participants

Objectives	Endpoints
Primary	
• To evaluate the antiretroviral activity of MK-8527 in HIV-1 infected participants relative to placebo. Hypothesis: At a dose that is sufficiently safe and generally well tolerated, MK-8527 has superior antiretroviral activity compared to placebo, as measured by change from baseline in plasma HIV-1 RNA (log10 copies/mL) at 168 hours postdose. That is, the true mean difference in the plasma HIV -1 RNA reduction from baseline between MK-8527 and placebo is at least 1.0 log10 copies/mL.	• Plasma HIV-1 RNA (log_{10} copies/mL) reduction from baseline
• To evaluate the safety and tolerability of MK-8527 in HIV-1 infected participants.	• AEs, laboratory tests, vital signs (VS), ECGs
Secondary	
• To evaluate the intracellular PK of MK-8527-TP in PBMC after administration of single oral doses to HIV-1 infected participants. Hypothesis: At a dose that is sufficiently safe and generally well tolerated, the true GM C168hr MK-8527-TP in PBMC is at least 0.2 pmol/10^6 cells	• MK-8527-TP AUC0-168, AUC0-last, AUC0-inf, Tmax, Cmax, C168hr, and apparent terminal t1/2 in PBMC.
• To evaluate plasma PK of MK-8527 after administration of single oral doses to HIV-1 infected participants.	• MK-8527 plasma AUC0-168, AUC0-last, AUC0-inf, Tmax, Cmax, C168hr, and apparent terminal t1/2.
• To evaluate the PK-PD association of plasma MK-8527 and intracellular MK-8527-TP with viral load reduction.	• PK (MK-8527-TP in PBMC, MK-8527 plasma)/PD (Plasma HIV-1 RNA) correlation

Objectives	Endpoints
Tertiary/Exploratory	
• To evaluate the relationship between dose and antiretroviral activity of MK-8527.	• Dose-response (Plasma HIV-1 RNA) relationship
• To evaluate the potential for long term exposure of PBMC MK-8527-TP at potentially efficacious levels	• PBMC MK-8527-TP C336H, C672H
• To explore the relationship between genetic variation and response to the treatment 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, multiple panel trial. This study will be conducted in conformance with Good Clinical Practices (GCP).

Up to five panels of 6 participants each will be enrolled in a sequential manner. In each panel, participants will receive a single dose of MK-8527 up to 50 mg. Panel A will initiate with a dose of 10 mg. The exact dose administered for succeeding panels will be selected following review of the safety, PK data, and viral dynamic data from prior panels. The assumption is made that PK in HIV-infected participants will be comparable to that observed previously in healthy participants (Protocol 001). However, PK data from Panel A will be reviewed prior to Panel B to confirm this assumption. The dose in Panel B may be adjusted downward based on review of safety and viral dynamic data out to 7 -days post-dose from Panel A in addition to the review of PK data. All doses of study drug will be administered following at least an 8-hour fast.

[redacted] initiation of follow-on ART is not a requirement for participation in the study and is ultimately a decision of the participant and PI/his/her physician. The exact timing and regimen will be decided by the participant in consultation with PI/his/her physician, [redacted] The Sponsor will

provide the site guidance as to the time when PBMC MK-8527-TP concentrations fall below ~1 nM regarding recommendations for ART initiation. The recommendation of the Sponsor on when to start ART will be documented in an official memo. The Sponsor will not provide this therapy. All participants will be followed for safety monitoring for a maximum of approximately 28 days after dosing of MK-8527. If participants start ART as planned, on Day 10 through 14 after dosing, the final blood draw for viral load (VL) and viral resistance will occur on the day of ART initiation (prior to receiving the first dose of ART). If participants do not initiate ART, the Investigator may ask to continue regular blood draws for PK assessments, VL changes, and viral resistance for up to ~28 days post-dose. Participants choosing to forgo follow-on ART may also be asked if they wish to continue to participate in monitoring of VL and viral resistance beyond 28 days. The timing of these blood draws beyond Day 28 will first be discussed with the Sponsor.

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.

Because this is a Phase 1 assessment of MK-8527 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 8.12 for examples of modifications permitted within the protocol parameters.

4.2 Scientific Rationale for Study Design

This protocol is designed with five sequential panels and will primarily assess the short-term antiretroviral activity of MK-8527 monotherapy in ART-naïve HIV-1 infected participants. Data from this study will aid dose selection in future studies. The goals of this study will be achieved by enrolling a minimum number of participants using the shortest treatment duration possible. [redacted] The time intervals between dosing allows for careful review of emerging data to permit a decision on advancing to the next panel at an appropriate dose to fully explore the dose-response profile of the compound.

The doses to be tested in this study are designed based on preclinical predictions and observations in the single ascending dose (SAD) study, to achieve exposures expected to be effective against the virus and produce significant VL reduction, but not exceed the maximum dose tested in Protocol 001. The projected plasma MK-8527 AUC0-168 is anticipated to be below the safety margin limits established in preclinical monkey toxicity studies (NOAEL).

This study will evaluate the efficacy and kinetics by which MK-8527 reduces HIV-1 RNA VL over time. The doses tested in this study will evaluate the effectiveness of MK-8527 in suppressing viral replication and assess any potential for differentiation with respect to safety, tolerability, and efficacy.

The study is specifically designed with an emphasis on collecting single dose viral dynamic data. This is consistent with HIV study guidelines, and VL dynamics observation after single dose is generally predictive of long term efficacy. MK-8527 is intended for the treatment of participants with wild-type strains of HIV-1; therefore, infected participants who are therapy naïve will be enrolled in this study. Although antiretroviral agents are usually administered in combination to minimize the risk for resistance, MK-8527 will be given as monotherapy in order to evaluate the effect of this agent alone on HIV-1 VL. Since only a single dose will be administered, risk of resistant strain emergence is minimal. Prior to enrollment, participants will be screened for the presence of common NRTI resistance mutations to set a baseline standard for MK-8527 sensitivity to the viral variants present in each participant [Johnson, V. A., et al 2013]. Participants identified with a common NRTI mutation (e.g., M184V or M184I) will be excluded from the study.

Blood samples will be collected pre-dose on Day 1, and after dosing through Day 10 and potentially up to Day 28 or longer for HIV viral RNA quantification. Blood samples will also be collected prior to initiation of ART to assess the potential for resistant variants; initiation of ART will not depend on the results of this screening. Should unanticipated nonresponders or viral breakthrough be observed despite this pre-screening process, a portion of the screening blood sample will be archived for phenotyping and/or genotyping of any previously unidentified clinically meaningful resistance variants.

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

The safety and tolerability of MK-8527 will be monitored by standard clinical assessments, including AEs, laboratory tests, VS and ECGs which is deemed sufficient based on the preclinical and clinical safety profile known to date. This will build upon the observations in Protocol 001.

4.2.1.2 Pharmacokinetic Endpoints

One objective of this study is to evaluate the initial plasma MK-8527 and intracellular MK-8527-TP PK profile in HIV-1 infected males and females. This study will establish if the anticipated target concentration can be achieved safely following single doses of MK-8527 to HIV-1 infected participants. [redacted]

For the PK assessment, active MK-8527-TP in PBMCs may be determined for up to 28 days following single dose administration. Plasma concentrations of unchanged MK-8527 will be determined for up to 7 days. These will enable determination of attainment of predicted target required for significant viral load reduction on a weekly dosing regimen and exposures below the safety margins established from the monkey NOAEL.

This study will establish whether achieving the efficacy target is associated with a commensurate VL reduction worthy of continued clinical development. Hence, assessment of this primary pharmacokinetic parameter will be conducted 7 days after administration of the MK-8527 dose. Additional assessments beyond 7 days (e.g., 14, 21 or 28 days) may also be performed.

4.2.1.3 Viral Pharmacodynamic Endpoints

A pharmacodynamic (PD) endpoint of a >1.0 log10 suppression of HIV-1 RNA from baseline on Day 7, relative to historical placebo data, will be used. A 70% posterior probability of achieving the target viral load reduction for at least one dose level that also exhibits an acceptable safety and tolerability profile will satisfy the primary pharmacodynamic hypothesis. The 70% posterior probability was chosen as a reasonable level of certainty in the results to ensure that the appropriate dose(s) that can achieve the PD target is taken into subsequent studies in the patient population with a reasonable chance of achieving the desired therapeutic effect in VL reduction. This target is consistent with previous observations with NRTI drugs which have produced VL reduction of 0.5log 10 as well as results with some newer compounds which have demonstrated potential to lower VL below 1.0log10, and also with past feedback from regulatory agencies that limit NRTI monotherapy studies to 7-10 days in duration. A decrease of this magnitude supports potential activity with long term administration in the target population.

Participants with a baseline HIV-1 RNA load of at least 5,000 copies/mL will be enrolled to ensure an adequate dynamic range by which changes in HIV RNA can be quantified. Periodic blood samples will be collected to assess MK-8527 associated changes in absolute VL over time and will be compared relative to historical placebo data. Based on the long half-life of MK-8527-TP, changes in VL may be assessed through 28 days for participants who do not initiate follow-on ART. For these participants, any VL data that are further collected as part of routine follow-up may be transmitted to the Sponsor, provided the participant gave appropriate consent. These extra data would only be reviewed to determine when the participant's VL returned to baseline to provide an exploratory and preliminary understanding of the long term effect of MK-8527.

Evaluation of VL 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 VL. Furthermore, given the overall favorable safety profile of MK-8527 in preclinical and clinical testing to date, the need for a placebo control to minimize investigator and participant bias with respect to adverse experiences was deemed not necessary.

Additionally, the kinetics of VL reduction vs. dose and exposure will also be determined.

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 will be used for research related to the study intervention(s), the disease under study, and related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate).

DNA samples will be analyzed for variation across the entire genome. Analyses 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 5.

4.3 Justification for Dose

As this is a Phase 1 assessment of MK-8527 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.

4.3.1 Starting Dose for This Study

The ongoing Phase 1 study in healthy participants (Protocol 001) is exploring the safety, tolerability and PK of MK-8527. The goal is to establish the safety of MK-8527 in humans and to determine if the projected PK target for MK-8527 could be achieved at a dose that is well tolerated in humans.

The study has explored single doses up to 100 mg. It has been generally well tolerated with only mild AEs reported and no serious AEs observed. [redacted]

This study is intended to evaluate the VL reduction potential of MK-8527 in ART-naïve HIV infected individuals. The PK profile of MK-8527 in this target participant population is unknown at this time and it is unclear if it is similar to the profile in healthy participants. To avoid the potential of underdosing in the participant population, a starting dose of 10 mg is being proposed. In Protocol 001, the PK target was achieved in healthy participants who received a dose of 5 mg. This minimizes the risk of exposing HIV-1 infected participants to drug levels below what are predicted to provide adequate VL reduction.

4.3.2 Maximum Dose/Exposure for This Study

The maximum dose to be administered in this study will be ≤50 mg and will be based on review of emerging data from the initial doses but will not exceed the maximum exposure observed in Protocol 001 in healthy participants. The safety, tolerability, PK and VL data from this study will be reviewed and decisions on subsequent doses will be based on the emerging profile. The goal will be to establish a dose that is sufficiently safe yet provides adequate VL suppression for a minimum of one week to support a weekly dosing regimen. A dose that provides longer duration of VL suppression may be explored.

4.3.3 Rationale for Dose Interval and Study Design

MK-8527, an NRTTI, is not considered a compound with a high degree of uncertainty related to the potential risk of harm to participants according to the publication "Guideline on Strategies to Identify and Mitigate Risks for First-in-Human and Early Clinical Trials with Investigational Medicinal Products" (European Medicine Agency [EMA] guidance released July 2017). The degree of uncertainty was determined by careful evaluation of the following: mode of action of MK-8527, presence or absence of biomarkers, the nature of the target, the relevance of available animal models and/or findings in non-clinical safety studies, single dose safety/PK data in healthy volunteers, and the study population. Furthermore, it acts via a well-established mechanism (inhibition of HIV-1 viral replication), for which multiple marketed agents act similarly (tenofovir disproxil fumarate, lamivudine, emtricitabine, abacavir, didanosine, stavudine, and zidovudine). Safety assessment toxicity studies, ancillary pharmacology studies, and first-in-human data with MK-8527 provide no contraindications to clinical investigation. [redacted] study (Protocol 002) proposes to study sequential panels of 6 participants each (all 6 active treatment). For each panel, all 6 participants are planned to be administered a single dose of MK-8527 on the same day in spaced time intervals according to Phase 1 clinical research standards for compounds not considered to be of high risk. The study design is such that the next panel will be dosed after careful review of the safety, tolerability, and viral dynamic data from the previous dose and panel. At the subsequent dose panels (C, D, and E), PK data will be reviewed from prior panels. Based on these results, the appropriate dose (increase or decrease) will be determined to fully explore the dose response profile of MK-8527. Sufficient time (~ at least 30 days) is allowed between dosing in subsequent panels to allow for the analysis and review of these data. There will be frequent, careful assessments of adverse events (AEs) throughout the postdose 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, pharmacokinetic, 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, PD, 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 (e.g., PK, PD, 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(s) or program being stopped for non-safety 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.

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

1. One participant 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 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 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 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 drug.

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.

5 STUDY POPULATION

Male/Female participants with HIV-1 infection who are 18 to 60 years (inclusive) will be enrolled in this trial.

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

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Other than HIV infection, is in good health based on medical history, physical examination, VS measurements performed at the prestudy (screening) visit and/or prior to administration of the single dose of study drug.

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

3. Was diagnosed with HIV-1 infection ≥ 3 months prior to screening or perform the French 2008 HAS Algorithm to confirm chronic HIV.

4. Has a screening plasma HIV-1 RNA ≥ 5,000 copies/mL within 30 days prior to the treatment phase of this study.

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

6. Is ART-naïve which is defined as having never received any antiretroviral agent **OR** the following:

   ≤30 consecutive days of an investigational antiretroviral agent, excluding an NRTI,

   OR

   ≤60 consecutive days of combination ART not including an NRTI

7. Has not received an investigational agent or marketed ART within 30 days of study drug administration.

8. Is willing to receive no other ART for the monitoring period of this study.

9. Has no evidence at screening for mutations conferring resistance to NRTIs (including but not limited to M184V, M184I) as previously defined.

10. Has the following laboratory values at screening: direct bilirubin ≤ 1.0 mg/dL, AST (SGOT) and ALT (SGPT) ≤ 2 x upper limit of normal.

Demographics

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

12. Has a Body Mass Index (BMI) ≤35 kg/m^2, inclusive. See Section 8.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height $(m)^2$.

13. Is Male or Female with the following requirements:

Male Participants

a. If the male participant has a female partner(s) of childbearing potential, he must agree to use a medically acceptable method of contraception during the study and for 120 days after the last dose of study drug. If their partner is pregnant, males must agree to use a condom and no additional method of contraception is required for the pregnant partner.

   NOTE: Spermicides alone are not an acceptable method of contraception. Their partner must additionally be using one of the following methods: hormonal contraception, intra-uterine device, diaphragm with spermicide, cervical cap with spermicide.

Female Participants

b. If the participant is a female with reproductive potential, she must demonstrate a serum β-human chorionic gonadotropin (β-hCG) level consistent with the nongravid state at the prestudy (screening) visit and agree to use (and/or have their partner use) 2 acceptable methods of birth control beginning at the prestudy (screening) visit, throughout the study (including washout intervals between treatment periods/panels) and until 28 days after the last dose of study drug. Acceptable methods of birth control are defined in Section 5.3.4.1.

c. If the participant is a postmenopausal female: she is without menses for at least 1 year and have a documented follicle stimulating hormone (FSH) level in the postmenopausal range at prestudy (screening).

AND/OR

d. If the participant is a surgically sterile female: she is status posthysterectomy, or oophorectomy.

   These procedures must be confirmed with medical records. In the absence of documentation, hysterectomy may be confirmed by pelvic exam or if necessary by ultrasound; oophorectomy may be confirmed by hormone levels, particularly FSH in the post-menopausal range. Information must be captured appropriately within the site's source documents.

Informed Consent

14. 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.

Additional Categories

15. Is willing to comply with the trial restrictions (see Section 5.3 for a complete summary of trial restrictions).

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Has a history of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, 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 (eg, uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma) may be enrolled in the study at the discretion of the investigator.

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

3. Has a history of cancer (malignancy). Exception: participants, who, in the opinion of the study investigator, are highly unlikely to sustain a recurrence for the duration of the study.

4. 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 CrCl, as determined by a 24-hour urine collection, may be used in place of, or in conjunction with, the estimate of the CrCl.

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

5. 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.

6. Is positive for hepatitis B surface antigen.

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

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

Prior/Concomitant Therapy

9. 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 poststudy visit. There may be certain medications that are permitted (see Section 6.5).

Prior/Concurrent Clinical Study Experience

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

Diagnostic Assessments

11. Has a clinically significant abnormality on the ECG performed at the prestudy (screening) visit and/or prior to administration of the initial dose of study drug. Appendix 7 provides a table of the 12-Lead ECG Abnormality Criteria.

Other Exclusions

12. Is under the age of legal consent.

13. Consumes greater 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.

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

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

16. Has a positive urine drug screen (except for cannabis) at screening and/or predose; rechecks are allowed.

17. 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.

18. 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

Participants will fast from all food and drinks, except water, for at least 8 hours prior to trial drug administration (and laboratory safety tests). Participants will fast from all food and drinks except water between trial drug administration and the first scheduled meal. Meals and snack(s) will be provided by the site at timepoints indicated in the trial flowchart.

During the domiciled period, 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 for all participants. After the 24-hour postdose procedures have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition and timing.

Water will be provided during trial drug administration. Water will be restricted 1 hour prior to and 1 hour after trial drug administration.

Instructions on whether to take MK-8527 with or without food and/or drink may be modified during the trial 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 poststudy 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 prestudy and poststudy 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 (1 unit = 120 mg of caffeine).

5.3.2.2 Alcohol Restrictions

Participants will refrain from consumption of alcohol 24 hours prior to the prestudy and poststudy 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 (i.e., weight lifting, running, bicycling, etc.) from the prestudy (screening) visit until the poststudy visit.

5.3.4 Contraception and Pregnancy Testing

5.3.4.1 Contraception

Women of childbearing potential can be enrolled. However, a highly effective method of contraception must be used with a failure rate of <1%. Acceptable methods of birth control (to be used during the period as specified in Section 5.1.2) are the following: intrauterine device (IUD without local hormone release), and vasectomy of partner having occurred >3 months prior to screening with a confirmatory negative sperm count. Surgical sterilization of the male partner or the female participant must be documented with medical records. Oral contraceptives are not allowed as a method of birth control in this trial.

Participants must be completely informed of the unknown risks of pregnancy and agree not to become pregnant during the time they are participating in this trial.

Male participants with female partner(s) of child-bearing potential must agree to use a medically acceptable method of contraception during the trial and for 90 days after the last dos e of trial drug. Males should use a condom. Female partners must additionally use one of the following methods if they are not pregnant: hormonal contraception, intra-uterine device, diaphragm, or cervical cap. If their partner is pregnant, males must agree to use a condom and no additional method of contraception is required for the pregnant partner. Male participants must also agree to not donate sperm during the study and for a period of 90 days after the last dose of study drug.

If there is any question that a participant will not be reliable in the use of appropriate contraceptive methods, he/she should not be entered into the trial.

5.3.4.2 Pregnancy Testing

Female participants of childbearing potential will be tested for serum β-human chorionic gonadotropin (hCG) at pretrial. Serum or urine β-hCG will be tested at predose and at the last trial visit. In the case of a positive or borderline serum β-hCG pregnancy test at the pretrial visit, the participant must not enter the trial; in the case of a positive or borderline serum or urine β-hCG pregnancy test during the trial, the pregnancy test should be repeated and confirmed positive. If the pregnancy has been confirmed the participant must be discontinued from the trial immediately and the pregnancy must be reported to the Spon sor as outlined in Section 8.4.5.

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 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 intervention(s) to be used in this study are outlined in Table 5.

Table 5 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
Panel A	Experimental	MK-8527	Drug	Capsule	10 mg 1 mg 0.5 mg	10 mg	Oral	Single Dose	Experimental	IMP	Sponsor
Panel B	Experimental	MK-8527	Drug	Capsule	10 mg 1 mg 0.5 mg	25 mg	Oral	Single Dose	Experimental	IMP	Sponsor
Panel C	Experimental	MK-8527	Drug	Capsule	10 mg 1 mg 0.5 mg	≤50 mg	Oral	Single Dose	Experimental	IMP	Sponsor
Panel D	Experimental	MK-8527	Drug	Capsule	10 mg 1 mg 0.5 mg	≤50 mg	Oral	Single Dose	Experimental	IMP	Sponsor
Panel E	Experimental	MK-8527	Drug	Capsule	10 mg 1 mg 0.5 mg	≤50 mg	Oral	Single Dose	Experimental	IMP	Sponsor

All supplies indicated in Table 5 will be provided per the "Sourcing" row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number

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 6.

Table 6 Sample Allocation Schedule

Panel	N	Dose of MK-8527[a]				
A	6	10 mg				
B	6		25 mg			
C[b]	6			≤50 mg		
D[b]	6				≤50 mg	
E[b]	6					≤50 mg

[a] Doses may be adjusted downward following review of safety and viral load data from preceding panels.
[b] A decision to enroll Panel C and the dose to be administered will be based on the results of safety, PK and viral load data out to at least Day 8 in Panels A and B. Enrollment of Panels D and E and the doses to be administered will be based on the results of safety, PK, and viral load data from all prior panels.

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 starting the study, 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 (up to 4 grams/day) may be used for minor ailments without prior consultation with the Sponsor.

All participants will be encouraged to initiate ART some interval after their dose of MK-8527. The exact timing and regimen will be decided by the participant in consultation with PI/his/her physician, but ART initiation will not occur before Day 10 (240 hours post-dose). This timing is required to gather full efficacy data for this novel long-acting anti-retroviral compound and is consistent with prior anti-retroviral monotherapy proof-of-concept (POC) trials, in which low-dose anti-retroviral monotherapy has been administered for as long as 28 days and with European Medicines Agency (EMA) guidance [European Medicines Agency 2016]. If the physician and/or Investigator believe there is a strong indication to start ART before Day 10, this should be discussed with the Sponsor prior to starting, as with other concomitant medications (see above).

To lessen the chance of HIV resistance mutations developing, the Sponsor recommends that ART initiation occur before [redacted] The Sponsor will provide the site with guidance as to the time when this level might be reached. A recommendation from the Sponsor on when to start ART will be documented in an official memo. For participants who choose to initiate ART following the treatment phase of the study, the specific ART regimen selected will be a decision of the participant in consultation with the Investigator and/or the participant's physician.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified to be used in this study.

6.6 Dose Modification (Escalation/Titration/Other)

Prior to each intervention, the clinical and laboratory safety data, VL data, and PK data from the previous dose level will be reviewed by the investigator and discussed with the Sponsor to permit a decision on whether to advance to the next dosing level. No dose modification will occur without the joint agreement of the investigator and the Sponsor.

All dose escalation decisions will be made jointly by the investigator and the Sponsor. Each dose escalation decision will occur after at least 4 evaluable participants have completed the previous dose level.

Dose escalation decisions will be based on key safety data including VS, 12-lead ECGs, laboratory safety tests, and AEs from the previous dose levels up to at least 168 hours. Dose escalation in subsequent panels will also include review of PK data from previous panels. See Section 4.3. If, as judged by the Sponsor and investigator, the safety and tolerability data do not justify dose escalation, the dose will not be increased as planned. Instead, participants may:

- receive the same dose level to further explore safety and tolerability at that level;
- receive a lower dose of the study treatment;
- receive the same or lower dose as a divided dose; or
- receive a lower dose with or without food.

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

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 period will still continue to participate in the study as specified in Section 1.3 and Section 8.1.9, 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 Section 8.1.9.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a confirmed positive serum pregnancy test.
- The participant has a positive UDS at any time during the course of the study, confirmed upon rechecks.

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

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

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 or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Study File Binder (or equivalent).

- 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 approximately 499.5 mL (see Appendix 9).

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 qualified designee must obtain documented consent from each potential participant or each participant's legally acceptable representative 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 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 or by the participant's legally acceptable representative'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 or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative'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 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 sub study. 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 or qualified designee 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 intervention/randomization number to the participant identification card.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the study.

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 non-random assignment, and will receive a treatment number. The treatment number identifies the participant for all procedures occurring after treatment allocation. Once a treatment 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 number.

8.1.8 Study Intervention Administration

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

8.1.8.1 Timing of Dose Administration

All doses of MK-8527 will be given in the morning at approximately the same time in each treatment panel. In each panel, participants will receive a single dose of MK-8527 as a capsule.

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 (approximately 28 days after the last dose of study intervention is given) to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to 28 days after the last dose of study intervention is given, the investigator should perform a follow-up telephone call 28 days after the last dose of study intervention to determine 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 principal 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 clinical research unit (CRU) the evening prior to the scheduled day of study intervention administration for each treatment period and remain in the unit until 24 hours postdose. At the discretion of the investigator, participants may be requested to remain in the CRU longer.

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is 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.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Appendix 9.

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

8.3.1 Physical Examinations

A complete physical examination will be conducted per institutional standard. Height and weight will also be measured and recorded. The pre-dose physical examination may be performed within 24 hour prior to dosing.

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

Body Mass Index (BMI)

Body Mass Index equals a person's weight in kilograms divided by height in meters squared (BMI=kg/m2). 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.

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

8.3.2 Vital Signs

Body temperature, pulse rate, respiratory rate, and blood pressure will be assessed. The same method must be used for all measurements for each individual participant and should be the same for all participants.

8.3.2.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

Participants should be resting in a semi-recumbent position for approximately 10 minutes prior to having 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.

At pre-dose in each Panel, HR and BP will be triplicate measurements obtained approximately 1-2 minutes apart within 3 hours of dosing MK-8527. 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.

8.3.2.2 Orthostatic Vital Signs

Orthostatic VS (HR and BP) will also be obtained. Participants should be semi-recumbent for approximately 10 minutes and then stand upright for approximately 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 garments.

Participants should be resting in the semirecumbent 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.

Predose ECGs in each panel will be obtained in triplicate at least 1-2 minutes apart within 3 hours prior to dosing MK-8527. 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 panel, if a participant demonstrates an increase in QTc interval ≥60 msec compared with mean predose baseline measurement, the ECG will be repeated twice within 5 minutes. The mean value of the QTc interval from the 3 ECGs will represent the value at that time point. If the mean QTc interval increase from baseline for any postdose time point is ≥60 msec, the participant will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QTc is within 60 msec of baseline. If prolongation of the QTc interval ≥60 msec persists, a consultation with a study cardiologist may be appropriate and the Sponsor should be notified.

If the QTc interval is 500 msec, the reading should be repeated. If confirmed prolonged, the Sponsor should be notified and the ECGs should be reviewed by a cardiologist. The participant should be telemetry-monitored (until the QTc is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (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 QTc is noted, concomitant medications that prolong QTc should be held until the QTc is within 60 msec of baseline and the QTc is <500 msec.

A study cardiologist will be consulted by the Principal 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 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 28 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, surrogate, or the participant's legally authorized representative).

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, 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 AE, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

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

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before treatment 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 treatment allocation/randomization through 28 days following cessation of treatment, all AEs, SAEs and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator 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 drug-related.

Investigators are not obligated to actively seek AE or SAE 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 7.

Table 7 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation (Randomized participants only)	Reporting Time Period: Randomization/ Allocation through Protocol-Specified Follow-up Period	Reporting Time Period: After the Protocol Specified Follow-up Period	Timeframe to Report Event and Follow-up Information to SPONSOR:
Non-Serious 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)	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. For vaccine studies only: -any death until participant completion of study (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 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
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 24 hours 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 AE and/or SAE 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 AE, SAE, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECI), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. All AEs will be reported to regulatory authorities, IRB/IECs, and investigators in accordance with all applicable global laws and regulations (ie, per ICH Topic E6 (R2) Guidelines for Good Clinical Practice [GCP]).

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 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:

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

b. 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

The 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.

8.6 Pharmacokinetics

The decision as to which plasma and/or urine samples collected will be assayed for evaluation of PK/PD 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-8527 and PBMC MK-8527-TP

Sample collection, storage, and shipment instructions for plasma and PBMC samples will be provided in the operations/laboratory manual.

8.7 Pharmacodynamics

Sample collection, storage, and shipment instructions for pharmacodynamic samples will be provided in the operations/laboratory manual.

8.8 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:

- DNA for future research
- Leftover main study plasma from MK-8527 assay stored for future research

8.9 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 instructions for Planned Genetic Analysis samples will be provided in the operations/laboratory manual.

8.10 Biomarkers

Biomarkers are not evaluated in this study.

8.11 Health Economics Medical Resource Utilization and Health Economics

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

8.12 Visit Requirements

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

8.12.1 Screening

Approximately 4 weeks prior to treatment allocation, 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 treatment allocation if there are Day -1 procedures planned per protocol.

8.12.2 Treatment Period Visit

8.12.2.1 Predose Procedures (All Panels)

Prior to each treatment, the clinical and laboratory safety data, viral load data, and PK data from the previous dose level/treatment panel will be reviewed by the Investigator and the Clinical Team and a mutual decision on whether to advance to the next dose level will be made. No dose escalation will occur without agreement of the Investigator and the Sponsor.

Participants will report to the CRU the day prior to the scheduled day of administration of the study drug or time specified by the investigator. Participants will fast from all food and drink, except for water, for a minimum of 8 hours prior to study drug administration and prior to obtaining samples for laboratory safety tests (refer to Section 5.3).

After the Day 1 predose procedures have been completed, participants will be assigned a unique allocation number associated with a specific treatment sequence as defined by a computer-generated allocation schedule. For details on procedures, please refer to the SoA (Section 1.3), Procedures (Section 8) and/or corresponding appendices.

8.12.2.2 Treatment Procedures (All Panels)

Procedures for study drug administration and postdose procedures are listed in the SoA, Section 1.3 of this protocol.

Participants will be administered a single dose of MK-8527 in the morning. The exact clock time of dosing should be recorded.

8.12.3 Discontinued Participants Continuing to be Monitored in the Study

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

8.12.4 Poststudy

Participants will be required to return to clinic approximately 28 days after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less than 28 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 28 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

8.12.5 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the VL and PBMC blood sample for MK-8527 are the critical procedures.

At any postdose time point, the PBMC blood sample for MK-8527 needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Study procedures can be performed 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 (MK-8527 plasma and MK-8527-TP PBMC) and PD collection (viral load) as outlined in Table 8.

Table 8 PK/PD Blood Collection Window

Blood PK/PD Collection	PK/PD Collection Window
0 – 1.0 hr	5 min
1 - <2hr	10 min
2 - <24 hr	15 min
24 - <48 hr	1 hr
48 - 168 hr	2 hr
>168 - <672 hr	24 hr
672 hr	48 hr

- Predose standard safety evaluations: VS and ECG at 3 hrs; laboratory safety tests, urine drug screen and physical exam at 24 hrs

- Postdose standard safety evaluations: VS, ECG, laboratory safety tests, and physical exam

  a. <24 hr postdose may be obtained within 15 min of the theoretical sampling time

  b. 24 hr - <48 hr postdose may be obtained within 1 hr of the theoretical sampling time

  c. 48 hr – 168 hr postdose may be obtained within 2 hr of the theoretical sampling time

  d. >168 - <672 hr postdose may be obtained within 24 hr of the theoretical sampling time

  e. 672 hr postdose may be obtained within 48 hr of the theoretical sampling time

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

This is a Phase 1 assessment of MK-8527 in humans, and the PK, PD, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants.

As such, some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum daily dose may not exceed that that tested in Protocol 001.

- Repeat of or decrease in the dose of the study intervention administered in any given panel
- Entire panel(s) may be omitted
- Adjustment of the dosing interval (e.g., divided doses [BID to QD, QD to BID, TID, or vice versa])
- Instructions to take study intervention with or without food or drink may also be modified based on newly available data
- Modification of the PK/pharmacodynamic sample timing, processing and shipping details based on newly available data

The PK/PD sampling scheme currently outlined in the protocol may be modified during the study based on newly available PK or PD 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 PD markers.

Up to additional 50 mL of blood may be drawn for safety, PK, and/or PD 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., VS, ECGs, 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) (Sections 9.2-9.9).

Statistical Methods

Primary Objective (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 parameter values, and selected laboratory safety parameter values 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 VS may also be computed, as deemed clinically appropriate.

Primary Objective (Pharmacodynamics): The log10 plasma HIV-RNA (copies/mL) measurements from participants in all panels will be pooled and analyzed based on a longitudinal data analysis model containing fixed effects for dose level, time (pre-dose, 168 hrs post-dose) and dose level by time interaction, and a random effect for participant. The change from baseline for each dose level at 168 hours post-baseline will be estimated from this model. A posterior distribution for the true mean change from baseline at 168 hours will be generated for each dose level using flat priors under a normal likelihood assumption. Historical placebo data from recent monotherapy studies in HIV-1 participants (MK-0518 Protocol 004, MK-1439 Protocol 005, MK-6186 Protocol 007, and MK-1972 Protocol 003) will be separately analyzed based on a longitudinal data analysis model containing fixed effects for study and time (pre-dose, 168 hours post-dose), and a random effect for participant. The change from baseline for placebo at 168 hours post-baseline will be estimated from this model, and a posterior distribution for the true mean change from baseline at 168 hours will be generated using flat priors under a normal likelihood assumption. Using the posterior distributions for each dose level and placebo, the posterior distribution of the true mean difference between each dose level and placebo will be generated, and the posterior probability that the true mean difference in the log10 plasma HIV-1 RNA reduction from baseline between MK-8527 and placebo is at least 1.0 log10 copies/mL will be calculated. A 70% posterior probability for at least one dose level that also exhibits an acceptable safety and tolerability profile will satisfy the primary pharmacodynamics hypothesis. For each dose level, the posterior probability that the true mean log10 plasma HIV-1 RNA reduction from baseline is at least 1.0 log10 copies/mL will also be calculated.

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 Pharmacodynamic 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

Primary

At a dose that is sufficiently safe and generally well tolerated, MK-8527 has superior antiretroviral activity compared to placebo, as measured by change from baseline in plasma HIV-1 RNA (log10 copies/mL) at 168 hours postdose. That is, the true mean difference in the plasma HIV-1 RNA reduction from baseline between MK-8527 and placebo is at least 1.0 log10 copies/mL.

Secondary

At a dose that is sufficiently safe and generally well tolerated, the true GM C168hr MK-8527-TP in PBMC is at least 0.2 pmol/10^6 cells.

9.4 Analysis Endpoints

Primary Pharmacodynamic

The primary pharmacodynamic variables in this study include plasma HIV -1 RNA pre-dose and 4, 24, 96, 120, 144, 168, 240, 336, 504 and 672 hours post-dose.

Primary Safety

The primary safety endpoints in this study include all types of AEs, in addition to laboratory safety assessments, ECGs, and VS.

Secondary Endpoints

The secondary endpoints in this study include AUC0-168hr, Tmax, Cmax, C168hr, apparent terminal t1/2 for both MK-8527 plasma and MK-8527-TP in PBMC following single oral administration of MK-8527 on Day 1.

9.5 Analysis Populations

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

All Participants as Treated (ASasT) – The population includes all participants who received at least one dose of the investigational drug. This population will be used for assessments of safety and tolerability.

Per-Protocol (PP) – The population includes 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 prior to unblinding by individuals responsible for data collection/compliance, and its analysis and interpretation. Any participants or data values excluded from analysis will be identified, along with 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 primary analysis dataset. This population will be used for the primary PD, secondary PK and exploratory 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 parameter values, and selected laboratory safety parameter values 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 backtransformed for reporting (percent change from baseline). Summary statistics for the raw laboratory safety tests, ECGs, and/or VS may also be computed, as deemed clinically appropriate.

Primary (Pharmacodynamics)

The log10 plasma HIV-RNA (copies/mL) measurements from participants in all panels will be pooled and analyzed based on a longitudinal data analysis (LDA) model containing fixed effects for dose level, time (pre-dose, 168 hrs post-dose) and dose level by time interaction, and a random effect for participant. The response vector consists of the baseline and 168 hours post-baseline values. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of means over time. The change from baseline for each dose level at 168 hours post-baseline will be estimated from this model. A posterior distribution for the true mean change from baseline at 168 hours will be generated for each dose level using flat priors under a normal likelihood assumption.

Historical placebo data from recent monotherapy studies in HIV-1 participants (MK-0518 Protocol 004, MK-1439 Protocol 005, MK-6186 Protocol 007, and MK-1972 Protocol 003) will be separately analyzed based on a longitudinal data analysis model containing fixed effects for study and time (pre-dose, 168 hrs post-dose), and a random effect for participant. The change from baseline for placebo at 168 hours post-baseline will be estimated from this model, and a posterior distribution for the true mean change from baseline at 168 hours will be generated using flat priors under a normal likelihood assumption. Using the posterior distributions for each dose level and placebo, the posterior distribution of the true mean difference between each dose level and placebo will be generated, and the posterior probability that the true mean difference in the log10 plasma HIV-1 RNA reduction from baseline between MK-8527 and placebo is at least 1.0 log10 copies/mL will be calculated.

A 70% posterior probability for at least one dose level that also exhibits an acceptable safety and tolerability profile will satisfy the primary pharmacodynamics hypothesis. For each dose level, the posterior probability that the true mean log10 plasma HIV-1 RNA reduction from baseline is at least 1.0 log10 copies/mL will also be calculated. To address the exploratory objective related to antiretroviral activity at 672 hours post-baseline, a similar analysis will be performed using VL measurements at baseline and 672 hours post-baseline. Similar exploratory analyses may be performed at timepoints earlier than 168 hours post-baseline.

Secondary (Pharmacokinetic)

Values of MK-8527 plasma and intracellular MK-8527-TP in PBMC pharmacokinetic parameters C168hr, C336hr, C672hr, AUC0-168hr, AUC0-last, AUC0-inf, and Cmax from participants in all panels will be pooled. Each PK parameter will be analyzed separately for plasma and PBMC. The PK log transformed and analyzed based on a linear model containing a fixed effect for dose level. The 95% confidence intervals for the means will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the means will yield estimates for the population geometric means on the original scale. The secondary hypothesis will be evaluated by calculating the posterior probability that the true GM C168hr MK-8527-TP in PBMC is at least 0.2 pmol/10^6 cells for each dose level using flat priors under a normal likelihood assumption. The secondary hypothesis will be supported for any dose for which the posterior probability is greater than 70%. 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 model(s) is observed, or suitable data transformation may be applied.

Individual values will be listed for each MK-8527 plasma and intracellular MK-8527-TP in PBMC PK parameter (C168hr, C240hr, C336hr, C540hr, C672hr, AUC0-168hr, AUC0-last, AUC0-inf, Cmax, Tmax, and apparent terminal t1/2) by dose level, and the following (non-model-based) descriptive statistics will be provided: N (number of participants with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s2) -1), where s2 is the observed variance on the natural log-scale).

Secondary and Exploratory (Pharmacokinetic/Pharmacodynamic)

The PK-PD and dose-PD association of MK-8527 will be explored. Graphs to visualize the association of the reduction in log10 plasma HIV-1 RNA levels with various plasma and intracellular MK-8527-TP in PBMC parameters (e.g., C168hr, C672hr, AUC0-168hr, AUC0-last, AUC0-inf, and Cmax) and dose will be generated. Exploratory linear and/or non-linear model fits may be considered, as appropriate. Exposure levels and doses that result in various proportions of the population (e.g., 80%, 90%) that have at least 1.0 log10 reduction from baseline in plasma HIV-1 RNA levels with high confidence may be estimated.

The duration of antiretroviral suppression after a single dose of MK-8527 will be evaluated with individual plots across time.

9.7 Interim Analyses

No interim analysis is planned in this study.

9.8 Multiplicity

Since there is only one primary pharmacodynamic hypothesis, no multiplicity adjustment will be made.

9.9 Sample Size and Power Calculations

Pharmacodynamic (Primary): If the true SDs of the log10 reduction from baseline in plasma HIV-RNA at 168 hours postdose are 0.3, 0.4, or 0.5 for this study, there is ~80% power to yield at least 70% posterior probability if the true mean log10 reduction is at least 1.11, 1.12, or 1.13 log10 with N=6 participants in a panel.

PK

Pharmacokinetic (Secondary): If the true SDs of the C168hr triphosphate in PBMC are 0.25, 0.35, or 0.45 for this study, there is ~80% power to yield at least 70% posterior probability if the true mean C168 are at least 0.27, 0.27, or 0.28 pmol/10^6 cells with N=6 participants in a panel.

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 (Institutiona 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 report form 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 Debarmen

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 good clinical practice); 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. 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 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 9 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 9 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit		WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, 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	Gamma GT
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serum/Urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for WOCBP) • Serology (HIV antibody, 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.				

Investigators 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, device, diagnostic agent, or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, 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, or are 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."

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 8.4.7 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

Additional events which require reporting

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

- Is a cancer

- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

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

Assessment of causality

Follow-up of AE and SAE

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

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

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

10.3.5 Reporting of AE, SAE, 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: Contraceptive Guidance and Pregnancy Testing

This appendix is not applicable to this study.

10.5 Appendix 5: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

1. 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.

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

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

4. DNA: Deoxyribonucleic acid.

5. RNA: Ribonucleic acid.

6. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 8.8 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.

7. Summary of Procedures for Future Biomedical Research.

1. Participants for Enrollment

   All participants enrolled in the clinical study will be considered for enrollment in the future biomedical research substudy

2. 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.

3. 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.

4. 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.

5. 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 treatment 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.

6. 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.

7. 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 principal 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.

8. 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.

9. 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.

10. 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.

11. 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.

12. 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.

13. Questions

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

14. References

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

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/

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

10.6 Appendix 6: Country-specific Requirements

This appendix is not applicable to this study.

10.7 Appendix 7: 12-Lead Electrocardiogram Abnormality Criteria

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	Potentially Significant Post-randomization Findings (clarification on action to take)
RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥25 bpm from baseline
Sinus Bradycardia	<40 bpm	HR <40 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial Premature Complex	> 1 beat	≥ 3 beats
Ventricular Premature Complex	All	≥ 3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB With Left Anterior Hemiblock (LAHB)	New Onset LAHB
Right Axis Deviation	RBBB With Left Posterior Hemiblock (LPHB)	New Onset LPHB
CONDUCTION		
1st Degree AV Block	PR ≥230 ms	PR ≥ 230 ms + Increase of >15 ms; or PR Increase of >25%
2nd Degree AV Block	Mobitz Type II	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB With LAHB/LPHB as Defined Above	New Onset RBBB (Not Including Rate-related)
Incomplete Right BBB (ICRBBB) (QRS <120 ms)	No Exclusion	Nothing
Short PR/ Preexcitation Syndrome	Delta Wave + PR <120 ms	Delta Wave + PR <120 ms
Other Intra-Ventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms
QTc (B or F)		
Male	QTc ≥470 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
Female	QTc ≥480 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	Potentially Significant Post-randomization Findings (clarification on action to take)
HYPERTROPHY		
Atrial Abnormalities	Definite Evidence of P Mitrale or P Pulmonale	Definite Evidence of P Mitrale or P Pulmonale
Ventricular Abnormalities	Voltage Criteria for LVH Plus Strain Pattern	Voltage Criteria for LVH Plus Strain Pattern
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All
ST/T MORPHOLOGY		
ST Elevation Suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST Depression Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Non-specific ST-T Changes (In 2 or More Leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	All	All
Baseline is defined as Predose Day 1; ms=milliseconds, mm=millimeter		

10.8 Appendix 10.8: Algorithm for Assessing Out of Range Laboratory Values

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

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

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

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

   1. The participant may be excluded from the study;

   2. 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).

   3. 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

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

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

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

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

10.9 Appendix 9: Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

Panels A, B, C, D, E	Pre-trial	Treatment Periods	Post-trial	Total Collections	mL Per Collection	Total mL/ Test
Laboratory safety tests‡	1	3	1	5	13	65
Serum β-Human Chorionic Gonadotropin (β-hCG)/FSH	1	0	0	1	5	5
HIV/Hepatitis Screen	1	0	0	1	5	5
Blood for Planned Genetic Analysis	1	0	0	1	8.5	8.5
Blood for PBMC	0	12	0	12	16	192
Blood for MK-8527	0	14	0	14	3	42
Blood for HIV RNA, viral resistance §	1	13	0	14	13	182%
					Approx. Total Blood Volume Per Participant for Panels A - E†	499.5 mL

† If additional safety analysis is necessary, additional blood (up to 50 mL) may be obtained. Note: never to exceed 50 mL

‡ Blood for CD4 cell count are included in the Laboratory Safety blood draw volume.

§ For all panels blood for HIV-1 viral RNA and viral resistance may be collected up to the post-trial visit if participants do not start ART.

% An additional 4 mLs of blood may be drawn at 168 hours post-dose if ultra-deep sequencing is needed.

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
AE	Adverse experiences
ART	Anti-retroviral therapy
BSEP	Bile salt export pump
BMI	Body Mass Index
CRF	Case Report Form
CRU	Clinical research unit
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECI	Event of clinical interest
eCRF	Electronic Case Report Form
EDC	Electronic data collection
EM	Exposure multiple
EMA	European Medicines Agency
FBR	Future Biomedical Research
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GM	Geometric mean
GMR	Geometric mean ratio
HED	Human equivalent dose
HIV-1	Human immunodeficiency virus type-1
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
NOAEL	No observed adverse effect level
NRTI	Nucleoside reverse transcriptase inhibitor
NRTTI	Nucleoside reverse transcriptase translocation inhibitor
OAT1	Organic anion transporter 1
OAT3	Organic anion transporter 3
OATP1B1	Organic anion transporting polypeptide 1B1
OCT2	Organic cation transporter 2
PD	pharmacodynamics
PK	Pharmacokinetic
POC	Proof-of-concept
QP2	Department of quantitative pharmacology and pharmacometrics
RNA	Ribonucleic acid
SAD	Single ascending dose
SAE	Serious adverse event
SoA	Schedule of activities
SUSAR	Suspected unexpected serious adverse reaction
TP	Triphosphate
UDS	Urine drug screen
VL	Viral load
WOCBP	Woman/women of childbearing potential

11 REFERENCES

[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
[Johnson, V. A., et al 2013]	Johnson VA, Calvez V, Gunthard HF, Paredes R, Pillay D, Shafer RW, et al. Update of the drug resistance mutations in HIV-1: March 2013. Top Antivir Med. 2013 Feb-Mar;21(1):6-14. Erratum in: Top Antivir Med. 2013 Apr-May;21(2):46.	04CJW4